

Physiology and Pathophysiology of Purinergic Neurotransmission

GEOFFREY BURNSTOCK

Autonomic Neuroscience Centre, Royal Free and University College Medical School, London, United Kingdom

I. Introduction	660
II. Background	660
A. Autonomic neuromuscular transmission	661
B. Autonomic ganglia	662
C. Central nervous system	662
D. Purinergic receptor subtypes	664
E. ATP storage, release, and breakdown	667
F. Plasticity of purinergic signaling	668
III. ATP as a Cotransmitter	670
A. Sympathetic nerves	670
B. Parasympathetic nerves	672
C. Sensory-motor nerves	672
D. Intrinsic nerves in the gut and heart	672
E. Peripheral motor nerves	673
F. Nerves in the brain and spinal cord	673
IV. Neurotransmission and Neuromodulation in Autonomic Ganglia	674
A. Sympathetic ganglia	674
B. Adrenal chromaffin cells	675
C. Parasympathetic ganglia	676
D. Enteric ganglia	676
V. Sensory Neurons	679
A. Dorsal root ganglia	680
B. Nodose ganglia	681
C. Trigeminal ganglia	681
D. Petrosal ganglia	682
E. Retinal ganglia	682
F. Sensory nerve fibers and terminals	682
VI. Neurotransmission and Neuromodulation in the Central Nervous System	685
A. Cortex	686
B. Hippocampus	687
C. Cerebellum	688
D. Basal ganglia	689
E. Midbrain	690
F. Thalamus	690
G. Habenula	690
H. Behavioral studies	690
VII. Central Control of Autonomic Function	693
A. Ventrolateral medulla	693
B. Trigeminal mesencephalic nucleus	693
C. Area postrema	694
D. Locus coeruleus	694
E. Nucleus tractus solitarius	694
F. Motor and sensory nuclei	695
G. Hypothalamus	696
H. Spinal cord	697
VIII. Neuron-Glia Interactions	698
A. P1 and P2 receptors on glial cells	698
B. Neuron-astrocyte interactions	700
C. Interactions of axons with Schwann cells and oligodendrocytes	702
D. Interactions between neurons and microglia	703

IX. Purinergic Neuroeffector Transmission	704
A. Exocrine glands	704
B. Endocrine and neuroendocrine cells	705
C. Endothelial cells	707
D. Secretory epithelial cells in visceral organs	707
E. Immune cells	709
F. Bone cells, joints, and keratinocytes	710
G. Choroid plexus	711
H. Interstitial cells of Cajal	711
I. Sensory epithelia	711
X. Ontogeny and Phylogeny of Purinergic Neurotransmission	712
A. Pre- and postnatal development and aging	712
B. Purinergic neurotransmission in invertebrates and lower vertebrates	722
XI. Neuropathology	729
A. Peripheral nervous system	729
B. Central nervous system	740
XII. Concluding Comments and Future Directions	749

Burnstock G. Physiology and Pathophysiology of Purinergic Neurotransmission. *Physiol Rev* 87: 659–797, 2007; doi:10.1152/physrev.00043.2006.—This review is focused on purinergic neurotransmission, i.e., ATP released from nerves as a transmitter or cotransmitter to act as an extracellular signaling molecule on both pre- and postjunctional membranes at neuroeffector junctions and synapses, as well as acting as a trophic factor during development and regeneration. Emphasis is placed on the physiology and pathophysiology of ATP, but extracellular roles of its breakdown product, adenosine, are also considered because of their intimate interactions. The early history of the involvement of ATP in autonomic and skeletal neuromuscular transmission and in activities in the central nervous system and ganglia is reviewed. Brief background information is given about the identification of receptor subtypes for purines and pyrimidines and about ATP storage, release, and ectoenzymatic breakdown. Evidence that ATP is a cotransmitter in most, if not all, peripheral and central neurons is presented, as well as full accounts of neurotransmission and neuromodulation in autonomic and sensory ganglia and in the brain and spinal cord. There is coverage of neuron-glia interactions and of purinergic neuroeffector transmission to nonmuscular cells. To establish the primitive and widespread nature of purinergic neurotransmission, both the ontogeny and phylogeny of purinergic signaling are considered. Finally, the pathophysiology of purinergic neurotransmission in both peripheral and central nervous systems is reviewed, and speculations are made about future developments.

I. INTRODUCTION

It is nearly 35 years ago that I published a paper entitled “Purinergic Nerves” in *Pharmacological Reviews* (241). It was a new hypothesis backed by some good evidence for ATP as a neurotransmitter in nonadrenergic, noncholinergic nerves supplying the gut and bladder and included every hint that I could find to support the possible involvement of purinergic signaling in different parts of the nervous system. However, it was regarded with skepticism by a large number of people over the next 20 years. So this current review of purinergic neurotransmission, with a huge and rapidly growing body of evidence for purinergic involvement in both physiological and pathophysiological neural mechanisms, is for me, a rather emotional vindication of my life’s work. It is a comprehensive account, and therefore, I hope I will be forgiven for its length and for the long list of papers, although reference to review articles is made wherever possible to cover some of the earlier literature.

II. BACKGROUND

Extracellular actions of purine nucleotides and nucleosides were first described in a seminal paper by Drury and Szent-Györgyi in 1929 (481) in the cardiovascular system, and later in the uterus (451) and intestine (642). Studies of the effects of purines on the nervous system followed the early emphasis on their cardiovascular actions. There was early recognition for a physiological role for ATP at the skeletal neuromuscular junction. Buchthal and Folkow (226) injected ATP into the sciatic artery supplying the gastrocnemius muscle of the frog and reported tetanus-like contractions; they also observed that the sensitivity of the preparation to ACh was greatly increased by previous application of ATP (227, 228). Parts of the spinal cord were shown to be sensitive to ATP (225). Emmelin and Feldberg (518) found complex effects initiated by intravenous injection of ATP into cats affecting peripheral, reflex, and central mechanisms. Injection of ATP into the lateral ventricle of the cat produced muscular weakness, ataxia, and a tendency of the animal to sleep (538). The application of adenosine or ATP to

various regions of the brain produced biochemical or electrophysiological changes (74, 610, 1563). ATP and related nucleotides were shown to have anti-anesthetic actions (981). The first hint that ATP might be a neurotransmitter in the peripheral nervous system (PNS) arose when it was proposed that ATP released from sensory nerves during antidromic nerve stimulation of the great auricular nerve caused vasodilatation in the rabbit ear artery (755, 756). The purinergic nerve hypothesis, with ATP as the transmitter responsible for nonadrenergic, noncholinergic (NANC) transmission to the smooth muscle of the gut and bladder, was proposed by Burnstock in 1972 (241). A brief historical review about the development of the concept of ATP as a neurotransmitter has been published recently (277).

A. Autonomic Neuromuscular Transmission

There was early recognition of atropine-resistant responses of the gastrointestinal tract to parasympathetic nerve stimulation (999, 1138, 1321). However, it was not until the early 1960s that autonomic transmission other than adrenergic and cholinergic was established. In 1963, electrical activity was recorded in the guinea pig taenia coli using the sucrose-gap technique, and after stimulation of the intramural nerves in the presence of adrenergic and cholinergic blocking agents, an inhibitory hyperpolarizing potential was observed (282, 283). The hyperpolarizing responses were blocked by tetrodotoxin (TTX), a neurotoxin that prevents the action potential in nerves without affecting the excitability of smooth muscle cells (233; Fig. 1A), indicating their neurogenic nature and establishing them as inhibitory junction potentials (IJPs) in response to NANC nerves. This work was extended by an analysis of the mechanical responses to NANC nerve stimulation of the taenia coli (284). NANC mechanical responses were also observed by Martinson and Muren in the cat stomach upon stimulation of the vagus nerve (1112), and NANC inhibitory innervation of the portal vein was also demonstrated (780).

The excitatory response of the mammalian urinary bladder to parasympathetic nerve stimulation was shown very early to be only partially antagonized by antimuscarinic agents (731, 1000). It was speculated that the subjunctional receptors, at which the endogenous ACh acts, were inaccessible to atropine (42, 420) or that atropine was displaced from these receptors by the high local concentrations of ACh released during parasympathetic nerve stimulation (781). However, it was later postulated that the atropine-resistant response may be due to the release of a noncholinergic excitatory transmitter, probably norepinephrine (NE) (43, 348).

By the end of the 1960s, evidence had accumulated for NANC nerves in the respiratory, cardiovascular, and

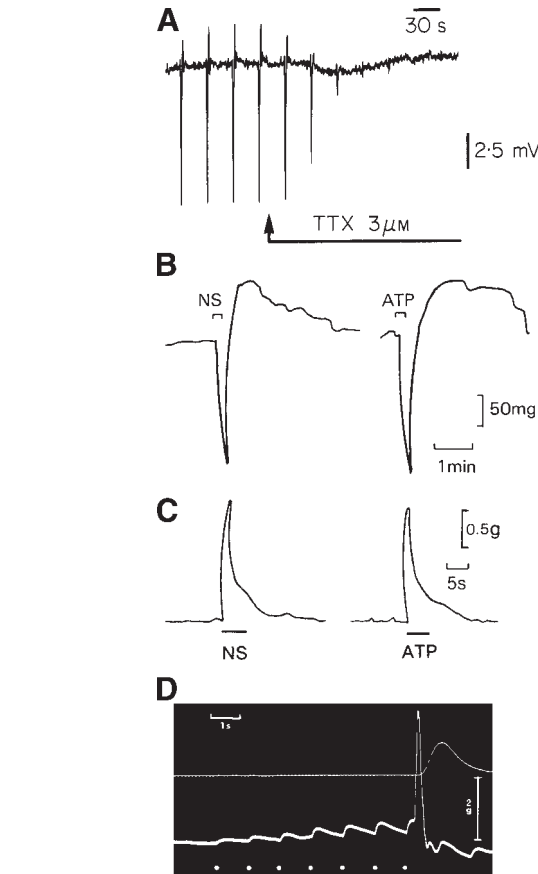


FIG. 1. Early experiments. A: sucrose gap recording of membrane potential changes in smooth muscle of guinea pig taenia coli in the presence of atropine (0.3 μM) and guanethidine (4 μM). Transmural field stimulation (0.5 ms, 0.033 Hz, 8 V) evoked transient hyperpolarizations, which were followed by rebound depolarizations. Tetrodotoxin (TTX, 3 μM) added to the superfusing Krebs's solution (applied at arrow) rapidly abolished the responses to transmural field stimulation, indicating that they were inhibitory junction potentials in response to stimulation of nonadrenergic noncholinergic (NANC) inhibitory nerves. [From Burnstock (249), with kind permission of Blackwell Publishing.] B: mechanical responses of the guinea pig taenia coli to intramural nerve stimulation (NS: 1 Hz, 0.5-ms pulse duration, for 10 s at supramaximal voltage) and ATP (2 × 10⁻⁶ M). The responses consist of a relaxation followed by a "rebound contraction." Atropine (1.5 × 10⁻⁷ M) and guanethidine (5 × 10⁻⁶ M) were present. [From Burnstock and Wong (294), with kind permission of the Nature Publishing Group.] C: a comparison of the contractile responses of the guinea pig bladder strip to intramural nerve stimulation (NS: 5 Hz, 0.2 ms pulse duration and supramaximal voltage) and exogenous ATP (8.5 μM). Atropine (1.4 μM) and guanethidine (3.4 μM) were present throughout. [From Burnstock et al. (286), with kind permission of the Nature Publishing Group.] D: excitatory junction potentials in response to repetitive stimulation of sympathetic nerves (white dots) at 1 Hz in the guinea pig vas deferens. The top trace records the tension, and the bottom trace is the electrical activity of the muscle recorded extracellularly by the sucrose gap method. Note both summation and facilitation of successive junction potentials. At a critical depolarization threshold, an action potential is initiated which results in contraction. [From Burnstock and Costa (287), with kind permission of Springer Science and Business Media.]

urinogenital systems as well as in the gastrointestinal tract (239). The existence of NANC neurotransmission is now firmly established in a wide range of peripheral and

central nerves, and fuller accounts of the development of this concept are available (see Refs. 248, 279, 288).

In the late 1960s, systematic studies were undertaken in an attempt to identify the transmitter utilized by the NANC nerves of the gut and urinary bladder. Several criteria, which must be satisfied before establishing a substance as a neurotransmitter (503), were considered (241, 285). First, a putative transmitter must be synthesized and stored within the nerve terminals from which it is released. Once released it must interact with specific postjunctional receptors, and the resultant nerve-mediated response must be mimicked by the exogenous application of the transmitter substance. Also, enzymes that inactivate the transmitter and/or uptake systems for the neurotransmitter or its derivatives must also be present, and finally, drugs that affect the nerve-mediated response must be shown to modify the response to exogenous transmitter in a similar manner.

Many substances were examined as putative transmitters in the NANC nerves of the gastrointestinal tract and bladder, but the substance that best satisfied the above criteria was the purine nucleotide ATP (285; Fig. 1, *B* and *C*). Nerves utilizing ATP as their principal transmitter were subsequently named "purinergic" (240), and a tentative model of storage, release, and inactivation of ATP for purinergic nerves was proposed (241; Fig. 2). Since then a great deal of evidence followed in support of

the purinergic hypothesis (see Refs. 257, 260, 292, 488, 661, 1278, 1977), although there was considerable opposition to this idea in the first decade or two after it was put forward (see Refs. 242, 643). I believe that this was partly because biochemists felt that ATP was established as an intracellular energy source involved in various metabolic cycles and that such a ubiquitous molecule was unlikely to be involved in extracellular signaling. However, ATP was one of the biological molecules to first appear and, therefore, it is not surprising that it should have been used for extracellular, in addition to intracellular, purposes early in evolution (258). The fact that potent ectoATPases were described in most tissues in the early literature was also a strong indication for the extracellular actions of ATP. In more recent studies, transient clusters of receptors for ATP have been shown to accumulate on smooth muscle membranes opposite autonomic nerve varicosities in close contact with them (707, 1782).

B. Autonomic Ganglia

An effect of ATP on autonomic ganglia was first reported in 1948 when Feldberg and Hebb (537) demonstrated that intra-arterial injection of ATP excited neurons in the cat superior cervical ganglia (SCG). Later work from de Groat's laboratory showed that in the cat vesical parasympathetic ganglia and rat SCG, purines inhibited synaptic transmission through adenosine receptors, but high concentrations of ATP depolarized and excited the postganglionic neurons (1699, 1700). The earliest intracellular recordings of the action of ATP on neurons were obtained in frog sympathetic ganglia (24, 1566). ATP produced a depolarization through a reduction in K^+ conductance. ATP was shown to excite mammalian dorsal root ganglia (DRG) neurons and some neurons from the dorsal horn of the spinal cord (819, 966). These responses were associated with an increase in membrane conductance (see sects. *vA* and *viiH*).

C. Central Nervous System

Following the early studies of Feldberg and Sherwood (538), there were reports that showed that adenosine acted via adenylate cyclase to produce cAMP in cerebral cortex slices and that this was antagonized by the methylxanthines, theophylline and caffeine (1504). Electrically evoked release of nucleotides and nucleosides from both brain slices and synaptosomes prepared from cerebral cortex raised the possibility that they may participate in intercellular transmission (983, 1384). These *in vitro* experiments were extended to the intact cerebral cortex (1665). It was shown that iontophoretic application of adenosine and several adenine nucleotides depressed the excitability of cerebral cortical neurons including identified Betz cells; cAMP, adenine, and

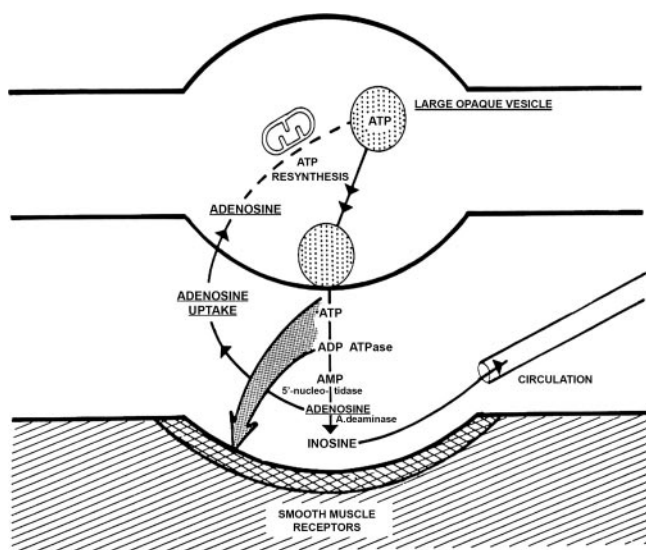


FIG. 2. The purinergic neurotransmission hypothesis (1972). Purinergic neuromuscular transmission is shown depicting the synthesis, storage, release, and inactivation of ATP. ATP, stored in vesicles in nerve varicosities, is released by exocytosis to act on postjunctional receptors for ATP on smooth muscle. ATP is broken down extracellularly by ATPases and 5'-nucleotidase to adenosine, which is taken up by varicosities to be resynthesized and reincorporated into vesicles. Adenosine is broken down further by adenosine deaminase to inosine and hypoxanthine and removed by the circulation. [From Burnstock (241), with permission from the American Society for Pharmacology and Experimental Therapeutics.]

inosine were less effective, whereas ATP caused an initial excitation followed by depression (1347). Adenosine and ATP also depressed firing in cerebellar Purkinje cells (959). About the same time microiontophoretic application of adenine nucleotides was shown to depress the spontaneous firing of corticospinal and other unidentified cerebral cortical neurons, although ATP had an additional excitant action on some neurons (1344, 1648). In other studies, adenosine and adenine nucleotides were shown to have an inhibitory action on the N-wave (a postsynaptic potential) amplitude in neurons of guinea pig olfactory cortex slices, but not on postsynaptic potentials in superior colliculus (1274, 1518). Schubert and Kreutzberg (1521) showed that after injections of tritiated adenosine into the visual cortex of rabbits, it was taken up and converted to radioactive nucleotides, which subsequently appeared in the thalamocortical relay cells of the lateral geniculate nucleus, consistent with synaptic transmission. This was supported by similar experiments in the somatosensory cortex (1875).

ATP was shown to activate units of the emetic chemoreceptor trigger zone of the area postrema of cat brain (174). Premature arousal of squirrels from periods of hibernation was evoked by adenosine nucleotides, but not by other purine nucleotides, and it was suggested that this effect was due to their action on neurons in the central nervous system (CNS) (1744). The infusion of cAMP into the hypothalamus of fowl induced behavioral and electrophysiological sleep, whereas dibutyryl cAMP produced arousal (1107). Local or systemic administration of adenosine in normal animals produced electroencephalogram (EEG) and behavioral alterations of the hypnogenic type (714). Cornforde and Oldendorf (385) demonstrated two independent transport systems across the rat blood-brain barrier, one for adenine and the other for adenosine, guanosine, inosine, and uridine. High levels of 5'-nucleotidase were demonstrated histochemically in the substantia gelatinosa of mouse spinal cord (1672). Early studies of the actions of purines on the CNS were reviewed by Burnstock (245), and important papers about the excitatory actions of ATP on subpopulations of spinal dorsal horn neurons were published in the early 1980s (608, 819, 1490) and excitation of single sensory neurons in the rat caudal trigeminal nucleus by iontophoretically applied ATP (1486). Although most of the early emphasis was about the neuromodulatory roles of adenosine, it was later recognized that fast synaptic transmission involving ATP was widespread in the CNS (see sects. VI and VII).

Early observations of mentally ill patients suggested that purines may play a role in the brain of man (see also sect. XI B5). Thus adenine nucleotides were implicated in depressive illness (7, 708, 1189). In the hypothesis proposed for the mechanism of depression by Abdulla and McFarlane (7), the effect of adenine nucleotides on prostaglandin biosynthesis was implicated. Blood levels of ATP and/or adenosine and urinary cAMP excretion were

significantly elevated in patients diagnosed as schizophrenic or in psychotic and neurotic depression (6, 219, 709, but see also Ref. 830). Inherited disorders of purine metabolism in the brain were related to psychomotor retardation, athetosis, and self-mutilation (Lesch-Nyhan syndrome) (133, 1020, 1534). Antidepressant drugs such as imipramine and amitriptyline potentiated the suppression of neuronal firing in rat cerebral cortex by adenosine (1342, 1648). It was claimed that depressive symptoms in patients relate to hypoxanthine levels in the cerebrospinal fluid (1245). Competitive interactions between adenosine and benzodiazepines in cerebral cortical neurons were reported, and evidence was presented to suggest that morphine releases ATP, and that after breakdown to adenosine, depresses neurotransmission in the cortex (1350). It was suggested that adenosine was involved in the initial phase of seizure-induced functional hyperemia in the cortex (1519).

The majority of studies of the extracellular actions of ATP have been concerned with the short-term events that occur in neurotransmission and in secretion. However, there is increasing awareness that purines and pyrimidines can have potent long-term (trophic) roles in cell proliferation and growth and in disease and cytotoxicity (see Ref. 4; Table 1). An example of synergism between purines and trophic factors comes from studies of the transplantation of the myenteric plexus into the brain (1695, 1696). In these studies, which were originally designed to explore enteric nerves as a possible source for replacement of missing messengers such as dopamine for Parkinson's disease, the myenteric plexus was shown to cause a marked proliferation of nerve fibers in the corpus striatum. An analysis, using coculture of striatal neurons with various elements of the myenteric plexus and enteric neurotransmitters, showed that a growth factor released by enteric glial cells works synergistically with nitric oxide (NO) and ATP (via adenosine) released from NANC inhibitory nerves to promote nerve regeneration (760).

TABLE 1. *Examples of short-term and long-term (trophic) purinergic signaling*

Purinergic Signaling	
<i>Short-term</i>	
Neurotransmission	
Neuromodulation	
Secretion	
Chemoattraction	
Acute inflammation and nociception	
<i>Long-term (trophic)</i>	
Cell proliferation, differentiation, motility, and death in:	
Development	
Regeneration	
Neuroprotection	
Wound healing	
Epithelial cell turnover in mature skin and viscera	
Chronic inflammation (granuloma) and neuropathic pain	
Aging	

D. Purinergic Receptor Subtypes

Implicit in the concept of purinergic neurotransmission is the existence of postjunctional purinergic receptors, and the potent actions of extracellular ATP on many different cell types also implicates membrane receptors. Purinergic receptors were first defined in 1976 (244), and 2 years later a basis for distinguishing two types of purinoceptor, identified as P1 and P2 (for adenosine and ATP/ADP, respectively), was proposed (246). At about the same time, two subtypes of the P1 (adenosine) receptor were recognized (1069, 1766), but it was not until 1985 that a proposal suggesting a pharmacological basis for distinguishing two types of P2 receptor (P2X and P2Y) was made (291). A year later, two further P2 purinoceptor subtypes were identified, namely, a P2T receptor selective for ADP on platelets and a P2Z receptor on macrophages (661). Further subtypes followed, perhaps the most important being the P2U receptor, which could recognize pyrimidines such as UTP as well as ATP (1265, 1536). In 1994 Mike Williams made the point at a meeting that a classification of P2 purinoceptors based on a "random walk through the alphabet" was not satisfactory, and Abbracchio and Burnstock (3), on the basis of studies of transduction mechanisms (486) and the cloning of nucleotide receptors (194, 1080, 1763, 1843), proposed that purinoceptors should belong to two major families: a P2X family of ligand-gated ion channel receptors and a P2Y family of G protein-coupled receptors. This nomenclature has been widely adopted, and currently seven P2X subunits and eight P2Y receptor subtypes are recognized, including receptors that are sensitive to pyrimidines as well as purines (see Refs. 163, 275, 521, 1392). Receptors for diadenosine polyphosphates have been described on C6 glioma cells and presynaptic terminals in rat midbrain, although they have yet to be cloned (444).

1. P1 receptors

Four subtypes of P1 receptors have been cloned, namely, A₁, A_{2A}, A_{2B}, and A₃ (see Refs. 370, 423, 582, 1392). All P1 adenosine receptors couple to G proteins and, in common with other G protein-coupled receptors, they have seven putative transmembrane (TM) domains of hydrophobic amino acids, each believed to constitute an α -helix of ~21–28 amino acids (see Fig. 3A). The NH₂ terminus of the protein lies on the extracellular side, and the COOH terminus lies on the cytoplasmic side of the membrane. Typically, the extracellular loop between TM4 and TM5 and the cytoplasmic loop between TM5 and TM6 are extended. The intracellular segment of the receptor interacts with the appropriate G protein, with subsequent activation of the intracellular signal transduction mechanism. It is the residues within the transmembrane regions that are crucial for ligand binding and specificity and, with

the exception of the distal (carboxyl) region of the second extracellular loop, the extracellular loops, the COOH terminus, and the NH₂ terminus do not seem to be involved in ligand recognition (1275). Site-directed mutagenesis of the bovine A₁ adenosine receptor suggests that conserved histidine residues in TM6 and TM7 are important in ligand binding. Specific agonists and antagonists are available for the P1 receptor subtypes (817; Table 2). For a specific review of P1 receptors in the nervous system, the reader is referred to Reference 1423.

2. P2X receptors

Members of the existing family of ligand-gated non-selective cation channel P2X₁₋₇ receptor subunits show a subunit topology of intracellular NH₂ and COOH termini possessing consensus binding motifs for protein kinases; two transmembrane-spanning regions (TM1 and TM2), the first involved with channel gating and the second lining the ion pore; a large extracellular loop, with 10 conserved cysteine residues forming a series of disulfide bridges; hydrophobic H5 regions close to the pore vestibule, for possible receptor/channel modulation by cations (magnesium, calcium, zinc, copper, and proton ions); and an ATP-binding site, which may involve regions of the extracellular loop adjacent to TM1 and TM2 (see Fig. 3B). The P2X₁₋₇ receptors show 30–50% sequence identity at the peptide level. The stoichiometry of P2X₁₋₇ receptor subunits is thought to involve three subunits that form a stretched trimer (see Refs. 109, 891, 1155, 1240).

It has become apparent that the pharmacology of the recombinant P2X receptor subtypes expressed in oocytes or other cell types is often different from the pharmacology of P2X receptor-mediated responses in naturally occurring sites. This is partly because heteromultimers as well as homomultimers are involved in forming the trimer ion pores (see below). Spliced variants of P2X receptor subtypes might play a part (334, 1578). For example, a splice variant of the P2X₄ receptor, while it is nonfunctional on its own, can potentiate the actions of ATP through the full-length P2X₄ receptors (1721). Third, the presence in tissues of powerful ectoenzymes that rapidly break down purines and pyrimidines is not a factor when examining recombinant receptors, but is *in vivo* (1979).

P2X₇ receptors are predominantly localized on immune cells and glia, where they mediate proinflammatory cytokine release, cell proliferation, and apoptosis. P2X₇ receptors, in addition to small cation channels, upon prolonged exposure to high concentrations of agonist, large channels, or pores are activated that allow the passage of larger molecular weight molecules. The possible mechanisms underlying the transition from small to large channels have been considered (508, 621).

The P2X receptor family shows many pharmacological and operational differences (634; see Table 2). The

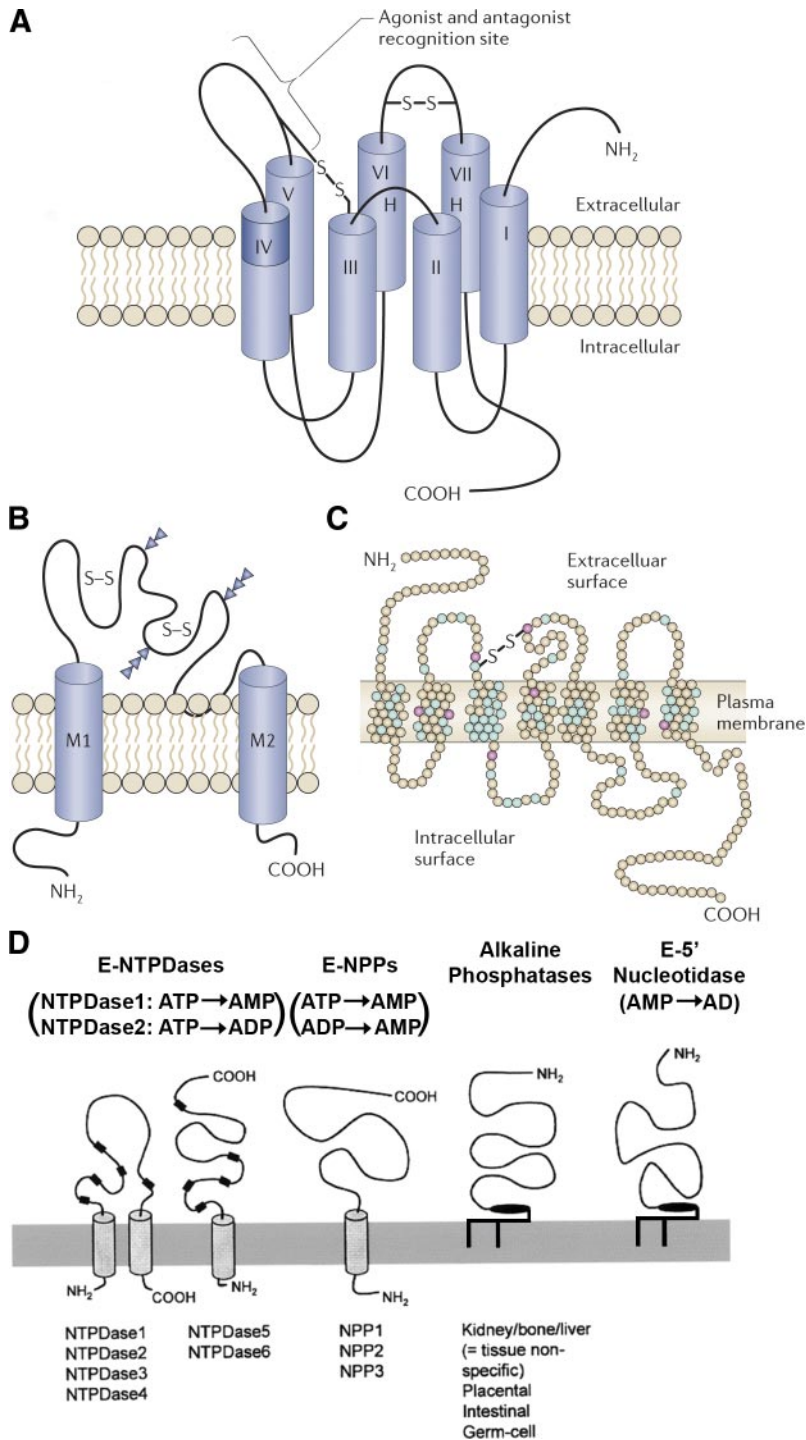


FIG. 3. Membrane receptors for extracellular adenosine and ATP. *A*: the P1 family of receptors for extracellular adenosine are G protein-coupled receptors (S-S; disulfide bond). [From Ralevic and Burnstock (1392), with permission from the American Society for Pharmacology and Experimental Therapeutics.] *B*: the P2X family of receptors are ligand-gated ion channels (S-S; disulfide bond; M1 and M2, transmembrane domains). [From Brake et al. (194), with permission from Nature.] *C*: the P2Y family of receptors are G protein-coupled receptors (S-S; disulfide bond; green circles represent amino acid residues that are conserved between P2Y₁, P2Y₂, and P2Y₆ receptors; fawn circles represent residues that are not conserved; and red circles represent residues that are known to be functionally important in other G protein-coupled receptors). [Modified from Barnard et al. (103), with permission from Elsevier.] *D*: predicted membrane topography of ectonucleotidases, consisting of the ectonucleoside triphosphate diphosphohydrolase (E-NTPDase) family, the E-NPP family, alkaline phosphatases, and ecto-5'-nucleotidase. [From Zimmerman (1978), with permission from John Wiley and Sons, Inc.]

kinetics of activation, inactivation, and deactivation also vary considerably among P2X receptors. Calcium permeability is high for some P2X subunits and Cl⁻ permeability for others, properties that are functionally important. For more specific reviews of the molecular physiology of the P2X receptor, the reader is referred to Khakh et al. (891), North (1257), Egan et al. (508), Stojilkovic et al. (1645), and Roberts et al. (1429).

3. P2Y receptors

Metabotropic P2Y receptors (P2Y₁, P2Y₂, P2Y₄, P2Y₆, P2Y₁₁, P2Y₁₂, P2Y₁₃, and P2Y₁₄) are characterized by a subunit topology of an extracellular NH₂ terminus and intracellular COOH terminus, the latter possessing consensus binding motifs for protein kinases; seven transmembrane-spanning regions, which help to form the li-

TABLE 2. *Characteristics of purine-regulated receptors*

Receptor	Main Distribution	Agonists	Antagonists	Transduction Mechanisms
P1 (adenosine)				
A ₁	Brain, spinal cord, testis, heart, autonomic nerve terminals	CCPA>R-PIA=S-ENBA>NECA; CVT-510	DPCPX, N-0840, MRS1754, N-0840, WRC-0571	G _i /G _o ↓ cAMP
A _{2A}	Brain, heart, lungs, spleen	NECA>CGS 21680=CVT-3146	KF17837, SCH58261, ZM241385, KW 6002	G _s ↑ cAMP
A _{2B}	Large intestine, bladder	NECA (nonselective)	Enprofylline, MRE2029-F20, MRS17541, MRS1706	G _s ↑ cAMP
A ₃	Lung, liver, brain, testis, heart	IB-MECA>NECA>2-Cl-IB-MECA; DBXRM; VT160	MRS1220, L-268605, MRS1191, MRS1523, VUF8504	G _i /G _o , G _i /G ₁₁ , ↓ cAMP, PLC-β activation
P2X				
P2X ₁	Smooth muscle, platelets, cerebellum, dorsal horn spinal neurons	ATP = 2-MeSATP≥α,β-meATP=L-β,γ-meATP (rapid desensitization)	TNP-ATP, IP ₅ I, NF023, NF449	Intrinsic cation channel (Ca ²⁺ and Na ⁺)
P2X ₂	Smooth muscle, CNS, retina, chromaffin cells, autonomic and sensory ganglia	ATP≥ATPγS≥2-MeSATP>>α,β-meATP (pH + zinc sensitive)	Suramin, isoPPADS, RB2, NF770, NF279	Intrinsic ion channel (particularly Ca ²⁺)
P2X ₃	Sensory neurons, NTS, some sympathetic neurons	2-MeSATP≥ATP≥α,β-meATP≥Ap ₅ A (rapid desensitization)	TNP-ATP, PPADS, A317491, NF110, Ip ₅ I, phenol red	Intrinsic cation channel
P2X ₄	CNS, testis, colon	ATP>>α,β-meATP=2-MeSATP=CTP; Ivermectin potentiation	TNP-ATP (weak), BBG (weak), phenolphthalein	Intrinsic ion channel (especially Ca ²⁺)
P2X ₅	Proliferating cells in skin, gut, bladder, thymus, spinal cord	ATP=2-MeSATP=ATPγS>α,β-meATP	Suramin, PPADS, BBG	Intrinsic ion channel
P2X ₆	CNS, motor neurons in spinal cord	(Functions poorly as a homomultimer)		Intrinsic ion channel
P2X ₇	Apoptotic cells in, for example, immune cells, pancreas, skin	BzATP≥2-MeSATP≥ATP>>α,β-meATP	KN62, KN04, MRS2427, O-ATP Coomassie brilliant blue G, RN6189, Az11645373, A-740003	Intrinsic cation channel and a large pore with prolonged activation
P2Y				
P2Y ₁	Epithelial and endothelial cells, platelets, immune cells, osteoclasts	MRS2365>2-MeSADP =ADPβS>2-MeSATP =ADP>ATP	MRS2179, MRS2500, MRS2279, PIT	G _i /G ₁₁ ; PLC-β activation
P2Y ₂	Immune cells, epithelial and endothelial cells, kidney tubules, osteoblasts	2-thio-UTP>UTP=ATP>UTPγS; INS 37217; INS 365	Suramin > RB2, AR-C126313	G _i /G ₁₁ and possibly G _i /G _o ; PLC-β activation
P2Y ₄	Endothelial cells	UTP>ATP>Up ₄ U>UTPγS; INS 37217	RB2 > suramin	G _i /G ₁₁ and possibly G _i , PLC-β activation
P2Y ₆	Some epithelial cells, placenta, T cells, thymus	3-Phenacyl-UDP>UDPβS >UDP>UTP>>ATP	MRS2578	G _i /G ₁₁ ; PLC-β activation
P2Y ₁₁	Spleen, intestine, granulocytes	AR-C67085MX>BzATP=ATPγS>ATP; NF546	Suramin>RB2, NF157, 5'-AMPS, NF340	G _i /G ₁₁ and G _s ; PLC-β activation
P2Y ₁₂	Platelets, glial cells	2-MeSATP≥2-MeSADP >ADP>ATP	CT50547, AR-C69931MX, INS49266, AZD6140, PSB0413, ARL66096, 2-MeSAMP	G _{α_i} , inhibition of adenylate cyclase
P2Y ₁₃	Spleen, brain, lymph nodes, bone marrow	ADP=2-MeSADP>>2-MeSATP>ATP	MRS2211, 2-MeSAMP	G _i /G _o
P2Y ₁₄	Placenta, adipose tissue, stomach, intestine, discrete brain regions	UDP glucose≥UDP-galactose		G _i /G _o

Shown are receptor subtypes for purines and pyrimidines: distribution, agonists, antagonists, and transduction mechanisms. BBG, Brilliant blue green; BzATP, 2'- & 3'-O-(4-benzoyl-benzoyl)-ATP; CCPA, chlorocyclopentyl adenosine; CPA, cyclopentyladenosine; CTP, cytosine triphosphate; IP₃, inosine triphosphate; Ip₅I, di-inosine pentaphosphate; 2-MeSADP, 2-methylthio ADP; 2-MeSATP, 2-methylthio ATP; NECA, 5'-N-ethylcarboxamido adenosine; PLC, phospholipase C; RB2, Reactive blue 2. P2X receptor subtype agonist potencies are based on rat preparations, while P1 and P2Y receptor subtype agonist potencies are based on human preparations. [Updated from Burnstock (271) with permission from Elsevier.]

gand-docking pocket; a high level of sequence homology between some transmembrane-spanning regions, particularly TM3, TM6, and TM7; and a structural diversity of intracellular loops and COOH terminus among P2Y subtypes, so influencing the degree of coupling with $G_{q/11}$, G_s , G_i , and $G_{i/o}$ proteins (5; see Fig. 3C). Each P2Y receptor binds to a single heterotrimeric G protein ($G_{q/11}$ for P2Y_{1,2,4,6}), although P2Y₁₁ can couple to both $G_{q/11}$ and G_s , whereas P2Y₁₂ and P2Y₁₃ couple to G_i and P2Y₁₄ to $G_{i/o}$. Many cells express multiple P2Y subtypes (see Refs. 5, 1800). P2Y receptors show a low level of sequence homology at the peptide level (19–55% identical) and, consequently, show significant differences in their pharmacological and operational profiles. Some P2Y receptors are activated principally by nucleoside diphosphates (P2Y_{1,6,12}), while others are activated mainly by nucleoside triphosphates (P2Y_{2,4}). Some P2Y receptors are activated by both purine and pyrimidine nucleotides (P2Y_{2,4,6}), and others by purine nucleotides alone (P2Y_{1,11,12}). In response to nucleotide activation, recombinant P2Y receptors either activate phospholipase C (PLC) and release intracellular calcium or affect adenylyl cyclase and alter cAMP levels. In recent years P2Y G protein-coupled receptors in neurons have been found to modulate the activity of voltage-gated ion channels in the cell membrane through certain actions of activated G proteins. For example, P2Y receptor subtypes that act via $G_{i/o}$ proteins can involve N-type Ca^{2+} channels, while the M-current K^+ channel can be inhibited through the activation of $G_{q/11}$ -linked P2Y receptor subtypes (5). There is little evidence to indicate that P2Y₅, P2Y₉, and P2Y₁₀ sequences are nucleotide receptors or affect intracellular signaling cascades and consequently have been dropped from International Union of Pharmacology (IUPHAR) P2Y receptor nomenclature and have been termed “orphans.”

2-Methylthio ADP (2-MeSADP) is a potent agonist of mammalian P2Y₁ receptors and N^6 -methyl-2'-deoxyadenosine 3',5'-bisphosphate (MRS2179), MRS2269 and MRS2286 have been identified as selective antagonists (221). At P2Y₂ and P2Y₄ receptors in the rat, ATP and UTP are equipotent, but the two receptors can be distinguished with antagonists, that is, suramin blocks P2Y₂, while Reactive blue 2 blocks P2Y₄ receptors (165, 1862). P2Y₆ is UDP selective, while P2Y₇ turned out to be a leukotriene receptor (1936). P2Y₈ is a receptor cloned from frog embryos, where all the nucleotides are equipotent (164), but no mammalian homolog has been identified to date, apart from a report of P2Y₈ mRNA in undifferentiated HL60 cells (13). The P2Y₁₂ receptor found on platelets was not cloned until more recently (754), although it has only 19% homology with the other P2Y receptor subtypes. It seems likely to represent one of a subgroup of P2Y receptors, including P2Y₁₃ and P2Y₁₄, for which transduction is entirely through adenylyl cyclase (2). It has been suggested that P2Y receptors can be subdivided into two subgroups,

namely, one that includes P2Y_{1,2,4,6,11}, the other includes P2Y_{12,13,14}, largely on the basis of structural and phylogenetic criteria (see Ref. 5).

For a recent review of P2Y receptor molecular biology, pharmacology, cell distribution, and physiology, the reader should refer to Reference 5. The structure and properties of current P2Y receptor subtypes and the current status of P2 receptor subtype agonists and antagonists are summarized in Table 2.

4. Heteromultimeric receptors

The pharmacology of purinergic signaling is complicated because P2X receptor subunits can combine to form either homomultimers or heteromultimers (see Refs. 1257, 1800). Heteromultimers are clearly established for P2X_{2/3} receptors in nodose ganglia (1027, 1388), P2X_{4/6} receptors in CNS neurons (1006), P2X_{1/5} receptors in some blood vessels (699, 1718), and P2X_{2/6} receptors in the brain stem (916). P2X₇ receptors do not form heteromultimers, and P2X₆ receptors will not form a functional homomultimer without extensive glycosylation (1717).

P2Y receptor subtypes can also form heteromeric complexes (5, 1206), and most recently, adenosine A₁ receptors have been shown to form a heteromeric complex with P2Y₁ receptors (see Refs. 1381, 1941). Dopamine D₁ and adenosine A₁ receptors have also been shown to form functionally interactive heteromeric complexes (645).

E. ATP Storage, Release, and Breakdown

1. ATP storage and release

The cytoplasm of most neurons contains ~2–5mM ATP, and higher concentrations of ATP (up to 100 mM) are stored in synaptic vesicles. Synaptic vesicles also contain other nucleotides such as ADP, AMP, Ap₄A, Ap₅A, and GTP, but at lower concentrations. Sperm, tumor cells, and the epithelial cells of the lens of the eye have exceptionally high intracellular levels of ATP and granules in adrenal chromaffin cells, Merkel cells, platelets, and pancreatic insulin-containing β -cells also contain significant amounts of ATP (see Refs. 1260, 1627). A recent paper has shown that ATP transport into brain synaptic vesicles can be distinguished from other neurotransmitter transport systems in terms of its mechanism and energy requirements (1947).

Release of ATP from exercising human forearm muscle was reported by Tom Forrester and colleagues (569) and from the perfused heart during coronary vasodilation in response to hypoxia was reported by Paddle and Burnstock (1288). However, until recently, it was usually assumed that the only source of extracellular ATP acting on purinoceptors was damaged or dying cells, but it is now

recognized that ATP release from healthy cells is a physiological mechanism (see Refs. 160, 487, 1004, 1529). ATP is released from both peripheral and central neurons (285, 755, 881, 1302, 1652, 1855, 1857, 1889), but also from many nonneuronal cell types during mechanical deformation in response to shear stress, stretch, or osmotic swelling, as well as hypoxia and stimulation by various agents (160, 179).

ATP release by mechanical distortion of urothelial cells during distension of the bladder was first demonstrated by Ferguson and colleagues in 1997 (544) and later by Vlaskovska et al. (1797). ATP release by distension was demonstrated from urothelial cells in ureter (932) and from mucosal epithelial cells of the colorectum (1895). It is also released from osteoblasts (1441); astrocytes (373); epithelial cells in the tongue (1444), lung (56, 466), and kidney (127); keratinocytes in the skin; and glomus cells in the carotid body.

There is an active debate about the precise transport mechanism(s) involved in ATP release. There is compelling evidence for exocytotic vesicular release of ATP from nerves, but for ATP release from nonneuronal cells, various transport mechanisms have been proposed, including ATP-binding cassette (ABC) transporters, connexin, or pannexin hemichannels or possibly plasmalemmal voltage-dependent anion and P2X₇ receptor channels, as well as vesicular release (see Refs. 160, 417, 439, 1004, 1475, 1529, 1631). Perhaps surprisingly, evidence was presented that the release of ATP from urothelial cells in the ureter is also largely vesicular, since monensin and brefeldin A, which interfere with vesicular formation and trafficking, inhibited distension-evoked ATP release, but not gadolinium, an inhibitor of stretch-activated channels, or glibenclamide, an inhibitor of members of the ABC protein family (932). Exocytotic vesicular release of ATP from endothelial cells (160, 261), osteoblasts (1441), fibroblasts (179), and astrocytes (373, 1169) has also been reported. There is increased release of ATP from endothelial cells during acute inflammation (159).

ATP released from nerves, or by autocrine and paracrine mechanisms from nonneuronal cells, is involved in a wide spectrum of physiological and pathophysiological activities, including synaptic transmission and modulation, pain and touch perception, vasomotor effects, platelet aggregation, endothelial cell release of vasorelaxants, immune defense, epithelial ion and water transport, as well as cell proliferation, migration, differentiation, and death.

Local probes for real-time measurement of ATP release in biological tissues have been developed recently (583, 1061, 1203, 1329).

2. ATP breakdown

ATP released from cells is regulated by a number of proteins that have their catalytic site on the outer side of

the plasma membrane (121, 976, 1978). A recent review focuses on ectonucleotidases in the nervous system (1980). Extracellular nucleotides can be hydrolyzed by nonspecific enzymes, such as glycosylphosphatidylinositol-anchored ectoalkaline phosphatases and ecto-5'-nucleotidases or ectonucleotidases with more distinct characteristics that are now classified into two families (see Fig. 3D). E-NTPDases (CD39) family are ecto-nucleoside triphosphate diphosphohydrolases that hydrolyze nucleoside 5'-tri- and diphosphates. Another family of enzymes, E-NPP (with 3 subtypes), are ecto-nucleotide pyrophosphatase/phosphodiesterases with a broad substrate specificity. These can hydrolyze phosphodiester bonds of nucleotides and nucleic acids and pyrophosphatase bonds of nucleotides and nucleotide sugars, e.g., cleavage of ATP to AMP and PP_i and conversion of cAMP to AMP. Some of these ectonucleotidases have distinct patterns of distribution in different cell types and are regulated during physiological and pathophysiological processes, probably in association with purine and pyrimidine signaling. The catalytic site of ectonucleotidases faces the extracellular medium, but some isoforms can be cleaved or released in a soluble form, in which case they can be regarded as ectonucleotidases. There are also other ectoenzymes that contribute to levels of extracellular nucleotides, such as interconversion of nucleotides by ectonucleoside diphosphokinase (ecto-NDPK) and ectoadenylate cyclase, possibly a production of ATP by F₀-F₁ ATP synthase, and use of ATP as a phosphate donor for ectoprotein kinase reactions. Ectoenzymes can act to regulate synaptic activity, controlling ATP and adenosine levels, depending on the synaptic plasticity developed in both physiological and pathophysiological conditions (171, 657). Excellent reviews are available summarizing the current status of extracellular ATP breakdown (see Refs. 1978, 1980; see also the recent Special Issue of "Purinergic Signaling" devoted to Ecto-nucleotidases, volume 2, number 2, 2006).

F. Plasticity of Purinergic Signaling

There was early recognition that the expression of purinergic cotransmitters and of receptors in the autonomic nervous system shows marked plasticity during development and ageing, in the nerves that remain following trauma or surgery, under the influence of hormones and in various disease situations (see Refs. 4, 254, 292). For plasticity of purinergic signaling in development and aging, see section xA1, and in disease, see section xi. Examples of neuronal plasticity occurring in healthy adults during pregnancy or following surgical interventions in visceral organs and the CNS follow.

Plasticity of purinergic signaling has been observed in the urinary bladder. Suppressed bladder contractility

during pregnancy is associated with decreased muscarinic receptor density, while the affinity of purinergic receptors for ATP is increased (1716). The amplitude of NANC transmission in detrusor strips from mature female rats was diminished in ovariectomized animals (509). Pregnancy substantially increases the purinergic components of the response of the rabbit bladder to field stimulation (1022). In contrast, there was a decrease in excitatory junction potentials (EJPs), probably mediated by ATP, in guinea pig uterine artery (1686).

Capsaicin treatment of newborn rats leads to selective degeneration of some sensory nerve fibers. In a study of rat bladder in 3-mo-old rats treated at birth with capsaicin, contractions evoked by electrical field stimulation were significantly larger than those of control (vehicle-treated) animals, an effect which preferentially involves the cholinergic component of the response, although there was some increase, too, in the purinergic component (1975). However, since contractions in response to exogenous carbachol or ATP were not significantly different, this suggested that the changes involve prejunctional mechanisms. Capsaicin treatment, causing selective sensory denervation of the rat ureter, leads to increased sympathetic innervation (1496), perhaps involving an increase in release of both NE and ATP.

The urinary bladder of the rat, deprived of its motor innervation, increases severalfold in weight in response to distension; this increase in weight is due to both hyperplasia and hypertrophy of the smooth muscle (514). Since it is now known that distension of the bladder leads to substantial release of ATP from urothelial cells (see sect. *uE1*) and ATP is known to have proliferative actions (4), purines seem likely to participate in the trophic changes that occur in the bladder. Incorporation of bowel tissue into the bladder wall has been used to increase bladder capacity and/or decrease bladder pressure; after 4–12 wk, the contractile response of the transplanted rabbit intestine underwent a partial change in the response to nerve stimulation and ATP from that of intestine towards that of detrusor (116).

Following chemical sympathectomy produced by long-term treatment with guanethidine and subsequent loss of the cotransmitter ATP in the vas deferens and spleen, there is an increase in density of P2X receptor sites, although there was a decrease in receptor affinity (1966).

Chronic food restriction alters P2Y₁ receptor mRNA expression in the nucleus accumbens of the rat (969). Cerebellar lesion upregulates P2X₁ and P2X₂ receptors in the precerebellar nuclei of the rat, perhaps related to the survival of injured neurons (563). In vitro studies of organotypic cultures and in vivo experiments on hippocampus from gerbils subjected to bilateral common carotid occlusion showed that P2X₂ and P2X₄ receptors were upregulated by glucose/oxygen deprivation (321, 322). It was

speculated that the changes in P2X receptor expression might be associated with ischemic cell death. There are data indicating a trophic role for ATP in the hippocampus (1584). It was shown that ATP and its slowly hydrolyzable analogs strongly inhibited neurite outgrowth and also inhibited aggregation of hippocampal neurons; it was suggested that the results indicate that extracellular ATP may be involved in synaptic plasticity through modulation of neural cell adhesion molecule (NCAM)-mediated adhesion and neurite outgrowth. Utilization of green fluorescent protein (GFP)-tagged P2X₂ receptors on embryonic hippocampal neurons has led to the claim that ATP application can lead to changes in dendritic morphology and receptor distribution (891).

Propagation of intercellular Ca²⁺ waves between astrocytes depends on the diffusion of signaling molecules through gap junction channels (see sect. *viiiA*). Deletion of the main gap junction protein connexin-43 (Cx43) by homologous recombination results in a switch in mode of intercellular Ca²⁺ wave propagation to a purinoceptor-dependent mechanism. This compensatory mechanism in Cx43 knockout mice for intercellular Ca²⁺ wave propagation is related to a switch from P2Y₁ to a UTP-sensitive P2Y₄ receptor in spinal cord astrocytes (1654). Trophic effects of purines on neurons and glial cells have been reviewed (4, 1226, 1398).

Following chronic constriction injury to the sciatic nerve, the number of P2X₃ receptor-positive small- and medium-diameter neurons increased in DRG, compared with sham-operated animals (1261, 1734). In addition, spinal cord immunoreactivity increased on the side ipsilateral to the ligated nerve, consistent with upregulation of purinergic receptors on presynaptic terminals of the primary sensory nerves. A decrease in P2X₃ immunoreactivity and function in DRG of rats occurs after spinal nerve ligation (854). Changes in gene expression of multiple subtypes of P2X receptors on DRG neurons (L5) after spinal nerve ligation have been reported (904). After nerve injury, the mRNA for P2X₅ receptors was increased, those for the P2X₃ and P2X₆ receptors were decreased, and those for P2X₂ and P2X₄ receptors were unchanged. However, immunostaining for receptor protein showed an increase from 23 to 73% P2X₂ receptor-positive DRG neurons after nerve ligation. Two days following unilateral section of the cervical vagus nerve, there was a dramatic ipsilateral increase in P2X₁, P2X₂, and P2X₄ receptor immunoreactivity in the cell soma of vagal efferent neurons in the dorsal vagal motor nucleus, but not in the nucleus ambiguus (72). Following surgical sympathectomy, 28% of the spontaneously active afferent fibers in sciatic nerve responded to ATP, compared with none in intact rats (343). After nerve injury, P2X₄ receptor expression increased strikingly in hyperactive microglia, but not in neurons or astrocytes, in the ipsilateral spinal cord; this

appears to be associated with tactile allodynia (1731 and see sect. XI B9).

The interactions of tyrosine kinase and P2Y₂ receptor signaling pathways provide a paradigm for the regulation of neuronal differentiation and suggest a role for P2Y₂ as a morphogen receptor that potentiates neurotrophin signaling in neuronal development and regeneration (64). P2Y₂ receptors, which mediate the mitogenic effects of extracellular nucleotides on vascular smooth muscle, are upregulated in the synthetic phenotype in the neointima after balloon angioplasty (763).

III. ATP AS A COTRANSMITTER

The idea that neurons can synthesize, store, and release a single substance became known as "Dale's principle," although Dale never explicitly suggested this; rather, he speculated that the same neurotransmitter would be stored and released from all the terminals of a single neuron. He was thinking in particular of primary afferent nerve fibers releasing the same transmitter in the spinal cord as from peripheral terminals in the skin during antidromic impulses in collaterals (419). It was only later that Eccles (502) introduced the term *Dale's principle*, and the notion that neurons utilize a single transmitter then dominated thinking until the late 1970s. However, there were a number of hints in the literature that this might not be universally true, and this together with the appeal of the general idea that neurons contain genes capable of producing more than one transmitter, but that during development and differentiation certain genes are triggered and others suppressed, led to a commentary by Burnstock introducing the cotransmitter hypothesis in 1976 (243). Judging from the increasing number of reviews that have appeared on this subject (252, 273, 329, 407, 604, 750, 982, 1077, 1282, 1371), it seems that this hypothesis is now widely accepted and that few neuroscientists today would venture to suggest that any neuron only utilizes one transmitter, albeit that a principal transmitter might dominate for much of its life-span. There is now a substantial body of evidence to show that ATP is a cotransmitter with classical transmitters in most nerves in the PNS and CNS, although the proportions vary between tissues and species as well as in different developmental and pathophysiological circumstances (see Refs. 112, 252, 273, 636). The spectrum of physiological signaling variations offered by cotransmission are discussed in these reviews.

In keeping with the concept of purinergic cotransmission, there was early recognition that ATP and adenosine modulated presynaptic inhibition of ACh release from the skeletal neuromuscular junction (647, 1424) and of NE release from peripheral sympathetic nerves in a wide variety of tissues, including rabbit kidney, canine

adipose tissue, guinea pig vas deferens (367, 724), and rabbit central ear artery, saphenous vein, portal vein, and pulmonary artery (1651, 1780). Presynaptic modulation of ACh release from peripheral cholinergic nerves by purines was observed in the isolated guinea pig ileum and the myenteric plexus longitudinal muscle preparation (1170, 1507, 1795). Clear evidence for this was presented by De Mey et al. (436) who showed that the presynaptic actions of purine nucleotides in canine saphenous vein were mediated largely by adenosine following the rapid breakdown of ATP, since slowly degradable analogs of ATP were ineffective. More recently, evidence has been presented for a presynaptic modulatory action by ATP itself, as well as adenosine, in the iris (589), rat vas deferens (1802), and tail artery (1560).

Purine nucleotides and nucleosides can also act on postsynaptic receptors to modulate cholinergic and adrenergic neurotransmission. Purines were reported to increase ACh receptor activity in various preparations, including the rat diaphragm muscle (528), frog skeletal muscle (23), and rabbit iris sphincter (695). The interactions are Ca²⁺ dependent and may involve interaction with the allosteric site of the receptor-ion channel complex. Purine nucleotides and nucleosides were shown to interact with NE postsynaptically in vitro in the guinea pig seminal vesicles (1204), rabbit kidney (724), guinea pig and mouse vas deferens (751, 1589, 1877), rabbit mesenteric artery (965), and rat mesenteric bed (1391). These neuromodulatory actions of purines have been extensively reviewed (1319, 1420, 1635).

A. Sympathetic Nerves

It was recognized early that ATP was costored with catecholamines in adrenal medullary chromaffin cells (150, 741). Subsequently, ATP was shown to be coreleased with epinephrine from chromaffin cells (313, 468). The 1976 cotransmitter hypothesis included the suggestion that NE and ATP might be cotransmitters in sympathetic nerves, following the earlier demonstration that ATP was contained together with NE in sympathetic nerve terminals in a molar ratio estimated to be from 7:1 to 12:1, NE:ATP (627, 988, 1522, 1642). The first evidence for sympathetic cotransmission involving ATP together with NE came from studies of the taenia coli (1652). It was shown that stimulation of periaortic sympathetic nerves led to release of tritium from guinea pig taenia coli preincubated in [³H]adenosine (which is taken up and converted largely to [³H]ATP) and that the release of both tritium and NE was blocked by guanethidine. Soon after, the possibility that ATP might be coreleased with NE in chemical transmission from the hypogastric nerve to the seminal vesicle of the guinea pig was raised and that the substantial residual NANC responses of the cat nictitating

membrane following depletion of NE by reserpine might be due to the release of ATP remaining in sympathetic nerves (998, 1204).

The most extensive evidence for sympathetic cotransmission, however, came from studies of the vas deferens, initially by Westfall and colleagues (536, 1853). Although it was not realized at the time, when EJPs were first recorded in smooth muscle cells of the vas deferens in response to stimulation of sympathetic nerves (289, 290; Fig. 1D), they were due to ATP rather than to NE. We were puzzled at the time that EJPs were not abolished by adrenoceptor antagonists; however, since they were abolished by the sympathetic neuron blocking agents bretylium and guanethidine (which are drugs that prevent nerve-mediated release of transmitter), we were correct in assuming they were produced by transmitter released from sympathetic nerves. Subsequent studies showed that EJPs are blocked by the ATP receptor antagonists arylazido aminopropionyl-ATP (ANAPP₃) and suramin and also following selective desensitization of the ATP receptor with the stable analog of ATP, α,β -methylene ATP (α,β -meATP) (872, 1593), but not by depletion of NE with reserpine (919, 1596). Furthermore, injection of ATP mimicked the EJP, whereas NE did not (1595). Direct evidence for concomitant release of ATP with NE and neuropeptide Y (NPY) from sympathetic nerves supplying the vas deferens was later presented (873). ATP has also been shown recently to be a cotransmitter with NE in sympathetic nerves supplying the human vas deferens (89). Sympathetic cotransmission to the seminal vesicles, epididymis, and prostate were also described (1777, 1778).

Evidence that soluble ectonucleotidases were released together with ATP and NE in the vas deferens was proposed (1711), although some later studies have contested this proposal. NTPDase1 was identified in cardiac synaptosomes (1543). The mechanisms underlying the synergistic postjunctional actions of NE and ATP on smooth muscle of the vas deferens have been explored (189, 1589). NPY is also colocalized in sympathetic nerve varicosities, but when released acts largely as a postjunctional neuromodulator, potentiating both the responses to NE and ATP in rat vas deferens (516), rat tail artery (189), and bovine chromaffin cells (1041), as well as acting as a prejunctional modulator of release of NE and ATP. Figure 4A is a schematic illustrating sympathetic cotransmission.

Sympathetic purinergic cotransmission has also been clearly demonstrated in many different blood vessels (see Refs. 250, 253, 1594, 1651 for full accounts). The proportion of NE to ATP is extremely variable in the sympathetic nerves supplying the different blood vessels. The purinergic component is relatively minor in rabbit ear and rat tail arteries, is more pronounced in the rabbit saphenous artery, and has been claimed to be the sole transmitter in sympathetic nerves supplying arterioles in the mesentery

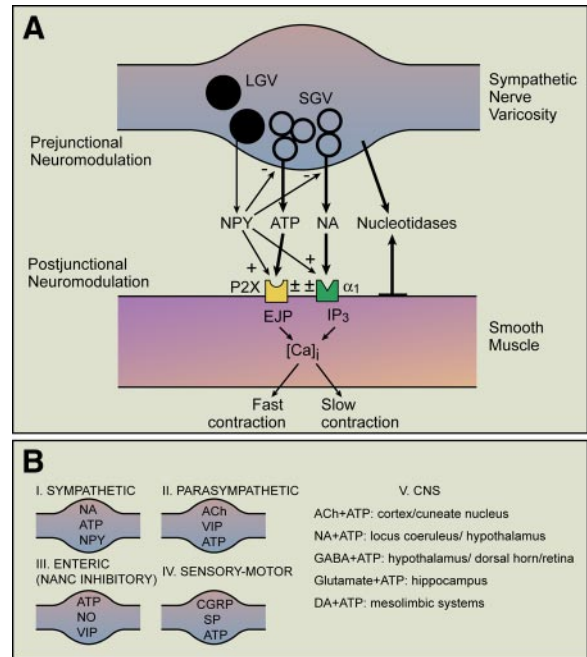


FIG. 4. Cotransmission. *A*: schematic of sympathetic cotransmission. ATP and norepinephrine (NA) released from small granular vesicles (SGV) act on P2X and α_1 -receptors on smooth muscle, respectively. ATP acting on inotropic P2X receptors evokes excitatory junction potentials (EJPs), increase in intracellular calcium ([Ca²⁺]_i), and fast contraction; while occupation of metabotropic α_1 -adrenoceptors leads to production of inositol trisphosphate (IP₃), increase in [Ca²⁺]_i, and slow contraction. Neuropeptide Y (NPY) stored in large granular vesicles (LGV) acts after release both as a prejunctional inhibitory modulator of release of ATP and NA and as a postjunctional modulatory potentiator of the actions of ATP and NA. Soluble nucleotidases are released from nerve varicosities and are also present as ectonucleotidases. [From Burnstock (280), with permission from Elsevier.] *B*: schematic diagram of the principal cotransmitters with ATP in the nervous system. Nerve terminal varicosities of *i*) sympathetic, *ii*) parasympathetic, *iii*) enteric (NANC inhibitory), *iv*) sensory-motor neurons, and *v*) central nervous system (CNS). NO, nitric oxide; VIP, vasoactive intestinal polypeptide; CGRP, calcitonin gene-related peptide; SP, substance P. [Modified from Burnstock (259), with permission from Elsevier.]

and the submucosal plexus of the intestine, whereas NE release from these nerves acts as a modulator of ATP release (527, 1394). ATP is a prominent sympathetic cotransmitter in guinea pig vein, but not artery (1591). Sympathetic purinergic vasoconstriction of canine cutaneous veins is involved in thermoregulation (561, 944). Sympathetic cotransmission involves activation of vasoconstrictive P2X₁ (and/or P2X₃) and P2Y₆-like receptors in mouse perfused kidney and short-term pretreatment with α,β -meATP (acting as a P2X₁ and P2X₃ agonist) potentiated P2Y₆-like receptor-mediated vasoconstriction (1807). Decentralized rat tail arteries were hypersensitive to α,β -meATP (1932). β -Nicotinamide adenine dinucleotide (NAD) was shown recently to be released from sympathetic nerve terminals in canine mesenteric artery and proposed as a putative neurotransmitter or neuromodulator (1592).

The contributions of NE and ATP to postjunctional responses depend on the parameters of nerve discharge. For example, in the central ear artery, short pulse bursts (1 s) at low frequency (2–5 Hz) favor the purinergic component of the response, while long stimulation bursts at higher frequencies favor the noradrenergic component (889). Neurites from cultured sympathetic neurons can use local mechanisms for ATP synthesis that do not depend on a functional connection to the cell body (1712). ATP and NE are released from sympathetic nerves supplying the heart (440). In the pithed rat, there is selective blockade by nifedipine of the purinergic rather than adrenergic component of nerve-mediated vasopressor responses (236). Coreleased ATP can act both as a prejunctional modulator (mostly after breakdown to adenosine) and a postjunctional potentiator of sympathetic neurotransmission. The different prejunctional effects of agents such as PGE₂, ANG II, and calcitonin gene-related peptide (CGRP) on the release of ATP and NE suggest that they are not stored in the same vesicles in the sympathetic nerve terminals (517). Full accounts of the progression of evidence in support of sympathetic cotransmission of ATP and NE are available (253, 1643, 1803). In addition, there is evidence that the preganglionic terminals on neurons in the SCG release ACh and ATP as cotransmitters (1796).

B. Parasympathetic Nerves

Parasympathetic nerves supplying the urinary bladder utilize ACh and ATP as cotransmitters, in variable proportions in different species (265, 286, 766, 786) and by analogy with sympathetic nerves, ATP again acts through P2X ionotropic receptors, whereas the slow component of the response is mediated by a metabotropic receptor, in this case muscarinic. There is also evidence to suggest that there is parasympathetic, purinergic cotransmission to resistance vessels in the heart and airways (802, 1476). Colocalization of P2X and nicotinic ACh receptors has been shown in rat vagal preganglionic nerves (1198).

C. Sensory-Motor Nerves

Since the seminal studies of Lewis (1028), it has been well established that transmitters released following the passage of antidromic impulses down sensory nerve collaterals during “axon reflex” activity produce vasodilatation of skin vessels. The early work of Holton (756) showing ATP release during antidromic stimulation of sensory collaterals taken together with the evidence for glutamate in primary afferent sensory neurons suggests that ATP and glutamate may be cotransmitters in these nerves. We know now that “axon reflex” activity is widespread in autonomic effector systems and forms an important phys-

iological component of autonomic control (1456). CGRP and substance P (SP) are well established as coexisting in sensory-motor nerves, and in some subpopulations, ATP is also likely to be a cotransmitter (255). Concurrent release of ATP and SP from guinea pig trigeminal ganglionic neurons *in vivo* has been described (1120).

D. Intrinsic Nerves in the Gut and Heart

Intrinsic neurons exist in most of the major organs of the body. Many of these are part of the parasympathetic nervous system, but certainly in the gut and perhaps also in the heart, some of these intrinsic neurons are derived from neural crest tissue that differs from those that form the sympathetic and parasympathetic systems and appear to represent an independent local control system.

A subpopulation of intramural enteric nerves provides NANC inhibitory innervation of gastrointestinal smooth muscle. Three major cotransmitters are released from these nerves: 1) ATP producing fast IJPs; 2) NO also producing IJPs, but with a slower time course; and 3) vasoactive intestinal polypeptide (VIP) producing slow tonic relaxations (see Refs. 124, 266). The proportions of these three transmitters vary considerably in different regions of the gut and in different species. For example, in some sphincters, the NANC inhibitory nerves primarily utilize VIP, in others they utilize NO, and in nonsphincteric regions of the intestine, ATP is more prominent (see Ref. 266).

ACh and ATP are the major fast excitatory neurotransmitters to the distal colon myenteric ganglia of guinea pig (1263). In the intestinal myenteric plexus, all enteric neurons, except for the nitric oxide synthase (NOS)-immunoreactive inhibitory neurons supplying muscle, are choline acetyltransferase (ChAT) immunoreactive. Therefore, the authors suggest that purinergic inputs of myenteric origin come from neurons that utilize ACh and ATP as cotransmitters in presynaptic fibers. Fast excitatory postsynaptic potentials (EPSPs) with a purinergic component were found in myenteric neurons throughout the length of the guinea pig gut, but they were most prominent in the ileum and rare in the gastric corpus (1018). Fast synaptic transmitters, ACh and ATP, are released from the same nerve endings in the myenteric plexus of guinea pig ileum (1019).

In guinea pig submucosal and myenteric neurons, activation of 5-hydroxytryptamine (5-HT) and P2X receptors are interdependent (181), again raising the possibility that ATP and 5-HT are cotransmitters in presynaptic nerve terminals.

In the heart, subpopulations of intrinsic nerves in the atrial and intra-atrial septum have been shown to contain ATP as well as NO, NPY, ACh, and 5-HT. Many of these nerves project to the coronary microvasculature and produce potent vasomotor actions (252, 1476).

E. Peripheral Motor Nerves

In addition to the studies of Buchthol and Folkow (226, 227) mentioned earlier, there was later evidence that ATP was released together with ACh from cholinergic nerves in various tissues, including the electric organ of elasmobranch fish (470, 1976) and the phrenic nerve endings in rat diaphragm (1572), although there is also some release of ATP from muscle (1498).

Although it was accepted that ATP was stored in and released together with ACh from motor nerve terminals, it was not recognized at the time as a cotransmitter, but was considered rather as a molecule involved in the vesicular uptake and storage of the neurotransmitter ACh. ³¹P-NMR analysis of synaptic vesicles from *Torpedo* electric organ showed that they store ATP together with ACh associated in free solution at an acid pH (596).

Application of ATP or adenosine was shown to inhibit the release of ACh (647, 1424). The effect of ATP was dependent on hydrolysis to adenosine, which then acted on presynaptic receptors (1422, 1568). ATP was also shown to act postsynaptically to facilitate the action of ACh (1419). ATP facilitates both spontaneous and agonist-activated ACh channel opening. It was also shown that in early development of the neuromuscular junction, released ATP acted on P2X receptor ion channels as a genuine cotransmitter with ACh acting on nicotinic receptors, while in mature animals, ATP no longer acted as a cotransmitter, but rather as a modulator at both prejunctional and postjunctional sites (950, 1424). Later papers confirmed these findings, showing that ATP itself is involved in these postjunctional actions (see Refs. 727, 732, 1073, 1571). ACh and ATP release from *Torpedo* electric organ are both inhibited by the removal of extracellular Ca²⁺ or by the addition of the calmodulin antagonist trifluoperazine, suggesting that ACh and ATP are both released by exocytosis from synaptic vesicles (1526). However, it is interesting that ATP release (in contrast to ACh) is not blocked by botulinum toxin type A, and Ω -conotoxin also differentially blocks ACh and ATP release (1108). A high-affinity adenosine uptake system has been demonstrated in the synaptosomes for reconstitution of stored ATP. Isolated synaptic vesicles from *Torpedo* electric organ contain ~200,000 molecules of ACh and ~24,000 molecules of ATP; small amounts of ADP are also present (10% of ATP content) as well as traces of AMP. Direct postjunctional responsiveness to ATP reappears after denervation of chick skeletal muscle (1849). Corelease of ATP with ACh, prejunctional modulation of transmitter release by adenosine, and postjunctional potentiation of ACh release by ATP have also been demonstrated at the frog neuromuscular junction (see sect. ixB2c).

Recent papers have added some further details about the mechanisms underlying release of ATP from motor

nerve terminals. For example, excitatory adenosine A_{2A} receptors probably coexist with inhibitory (A₁) receptors at the rat neuromuscular junction, modulating the evoked release of ACh, the balance of inhibition, or facilitation depending on the frequency of motor nerve stimulation (388). Depression of ACh release via presynaptic A₁ receptors is by inhibition of N-type Ca²⁺ channels (1524), but is not the basis of tetanic fade at rat neuromuscular junctions (1095). Tetanic depression is overcome by tonic adenosine A_{2A} receptor facilitation of Ca²⁺ influx through L-type channels at rat motor nerve terminals (1276). A presynaptic facilitating effect of P2 receptor activation on rat phrenic nerve endings was later also recognized (611, 1485), and P2X₇-like receptors have been implicated at the mouse neuromuscular junction (1176). Evidence has been presented that ATP, via P2Y receptors, but not adenosine, inhibits nonquantal spontaneous ACh release at the neuromuscular junction of mouse (433, 678) and quantal release in frog (678).

Much of the evidence for purinergic involvement in skeletal neuromuscular transmission has come from studies of the fish electric organ and frog and chick neuromuscular junctions (see sect. xB2).

F. Nerves in the Brain and Spinal Cord

Evidence for purinergic cotransmission in the CNS has lagged behind that presented for purinergic cotransmission in the periphery. However, in the last few years a number of such studies have been reported.

Release of ATP from synaptosomal preparations and slices from discrete areas of the rat and guinea pig brain including cortex, hypothalamus, medulla, and habenula has been measured (97, 1626, 1855). In cortical synaptosomes, a proportion of the ATP appears to be coreleased with ACh, and a smaller proportion with NE (1372). In preparations of affinity-purified cholinergic nerve terminals from the rat caudate nucleus, ATP and ACh are coreleased (1426). There is also evidence for corelease of ATP with catecholamines from neurons in the locus coeruleus (1360) and hypothalamus (235, 1626). Purinergic and adrenergic agonist synergism for vasopressin and oxytocin release from hypothalamic supraoptic neurons is consistent with ATP cotransmission in the hypothalamus (867, 1605).

Corelease of ATP with GABA has been demonstrated in the rabbit retina (1334) and in dorsal horn and lateral hypothalamic neurons (835, 837). Possible mechanisms that underlie the balance between P2X receptor-mediated excitation and GABA_A receptor-mediated inhibition were discussed in a *Nature News and Views* article (1488). P2X and GABA receptors are also colocalized in subpopulations of rat postnatal DRG neurons and their central terminals laminae I-III (986). The intracellular loop of

GABA_B subunits and the COOH-terminal domain of P2X₂/P2X₃ receptors are necessary for cross-talk between ATP and GABA-gated channels (182). There is evidence for corelease of ATP with glutamate in the hippocampus (1182) as well as widespread and pronounced modulatory effects of ATP on glutamatergic mechanisms (795). A recent study has shown that in central neuronal terminals, ATP is primarily stored and released from a distinct pool of vesicles and that the release of ATP is not synchronized either with the cotransmitters GABA or glutamate (1302). Cooperativity between extracellular ATP and *N*-methyl-D-aspartate (NMDA) receptors in long-term potentiation (LTP) induction in hippocampal CA1 neurons (592) is consistent with ATP/glutamate cotransmission. Colocalization of functional nicotinic and ionotropic nucleotide receptors have also been identified in isolated cholinergic synaptic terminals in midbrain (455). Interactions between P2X₂ and both $\alpha 3\beta 4$ and $\alpha 3\beta 2$ nicotinic receptor channels has been shown in oocyte expression studies (892).

There is indirect evidence supporting the possibility that dopamine and ATP are cotransmitters in the CNS (968). After cerebellar lesions in rats producing axotomy of mossy and climbing fiber systems, nitrergic and purinergic systems were activated with similar time courses on precerebellar stations (1792). This raises the possibility that, as in a subpopulation of neurons in the gut, NO and ATP are cotransmitters.

It is speculated that postsynaptic selection of coreleased fast transmitters is used in the CNS to increase the diversity of individual neuronal outputs and achieve target-specific signaling in mixed inhibitory networks (489). Figure 4B summarizes current knowledge of purinergic cotransmission in the peripheral and central nervous systems.

IV. NEUROTRANSMISSION AND NEUROMODULATION IN AUTONOMIC GANGLIA

An earlier review, published in 2001, of purinergic signaling in autonomic ganglia is available (496).

A. Sympathetic Ganglia

Purinergic synaptic transmission was not demonstrated in sympathetic ganglia until the early 1990s (526, 1569). A number of subsequent studies have characterized the receptors present on sympathetic neurons, and it is now clear that there is a species difference between rat and guinea pig. In the guinea pig, α, β -meATP is an effective agonist on SCG (1404, 1968) and celiac ganglion neurons (896). In contrast, α, β -meATP evoked only a small slowly desensitizing response in a subpopulation of

neurons from rat SCG (369, 896). In a study of rat and mouse celiac ganglion neurons, no responses to α, β -meATP were detected (1969). Most of the properties described for P2X receptors in rat sympathetic neurons (kinetics, agonist and antagonist profile, effect of Zn²⁺ and pH) are consistent with those of the recombinant P2X₂ receptor. The presence of a small slowly desensitizing α, β -meATP response in rat SCG neurons can most easily be explained by the coexistence of some heteromeric P2X_{2/3} receptors (496).

A number of studies have demonstrated the presence of P2X receptors in sympathetic ganglia by immunohistochemistry. Immunoreactivity for P2X₁, P2X₂, P2X₃, P2X₄, and P2X₆ receptors was detected in SCG and celiac ganglia of the rat (1896). In a study of cultured SCG neurons, P2X₂ was the most highly expressed receptor; lower, although detectable, levels of all the other subunits, except P2X₄, were present (1035). However, the extent to which the expression of P2X receptors may be influenced by tissue culture conditions is at present unclear. In a study of the guinea pig SCG, P2X₂ and P2X₃ immunoreactivity was detected (1968). P2X₁-GFP has been used to study the time course of P2X₁ receptor clustering (~1 μ m diameter) in plasma membranes of cultured sympathetic neurons from rat SCG and internalization of receptors following prolonged exposure to ATP (1035). In keeping with the histochemical evidence, mRNA for most P2X subunits has been detected in sympathetic neurons. P2X₅ and P2X₆ receptors were first isolated by PCR for celiac and SCG mRNAs, respectively (378). Fragments of P2X₃ and P2X₄ receptors have also been cloned from a rat SCG cDNA library (230, 1027). Three splice variants of the rat P2X₂ receptor have been cloned, and all three were detected in SCG neurons by in situ hybridization (1578). Other in situ hybridization studies have detected P2X₁, P2X₄, and P2X₆ mRNA in rat SCG neurons (230, 378).

Studies of the release and metabolism of endogenous ATP in rat SCG suggested that ATP and ACh were released simultaneously in response to stimulation of preganglionic nerve terminals, although release of ATP or ACh varies with stimulation frequency and temperature (1796), perhaps reflecting different vesicular storage. Endogenous adenosine can inhibit both posttetanic potentiation and LTP in rat SCG (748). Both excitatory P2X receptors (probably P2X₂) (161) and inhibitory P2Y receptors (probably P2Y₂) (162) have been described on presynaptic sympathetic nerve terminals. P2X₇ receptors have also been claimed to be present on presynaptic terminals, but their function is unclear (34). From a study using P2X₁ receptor knockout mice, at least three broad categories of SCG neurons were revealed: neurons with a P2X₂ phenotype, α, β -meATP-sensitive neurons that suggested a P2X₁ heteromeric receptor, and neurons that have no detectable P2X receptor expression (308).

P2Y receptors are also expressed on sympathetic neurons (162, 307). P2Y₂ receptors on SCG neurons were shown to mediate inhibition of both N-type Ca²⁺ and M-type K⁺ currents (162, 557). Studies of sympathetic neurons cultured from thoracolumbal paravertebral ganglia show that while ATP release of NE is mediated by P2X receptors, UDP-induced release of NE is entirely due to generation of action potentials followed by calcium influx through voltage-gated channels (1801), perhaps mediated by P2Y₆ receptors. A P2Y₆ receptor was later shown to be expressed in SCG neurons and, like P2Y₂ receptors, couples to both N-type Ca²⁺ and M-type K⁺ channels (1256). In a later study, P2Y₄ receptors expressed in rat sympathetic neurons were shown to couple much more effectively to M-type K⁺ channels than to Ca²⁺ channels, in contrast to P2Y₁, P2Y₂, and P2Y₆ receptors (556). Evidence for P2Y₁, P2Y₂, P2Y₆ receptors and an atypical UTP-sensitive receptor in mouse cultured SCG neurons and glia has been presented (307).

B. Adrenal Chromaffin Cells

Chromaffin cells of the adrenal medulla can be regarded as a highly specialized form of sympathetic neuron. Although the P2X₂ receptor was originally cloned from PC12 cells, which are a rat pheochromocytoma cell line, adrenomedullary chromaffin cells have received relatively little attention.

In one of the first immunohistochemical studies of P2X receptors, using antibodies raised against P2X₁ and P2X₂ receptors, Vulchanova et al. (1809) observed both P2X₁ and P2X₂ immunoreactivity in both differentiated PC12 cells and chromaffin cells of the adrenal medulla. This observation is not consistent with functional studies (see below) and was not substantiated in more recent immunohistochemical studies (14, 15) in which only limited expression of P2X₅ and P2X₇ was detected in rat chromaffin cells, while P2X₆ immunoreactivity was detected in the guinea pig.

Brake et al. (194) cloned the P2X₂ receptor from PC12 cells and detected weak expression of the mRNA in the adrenal gland by Northern blotting. P2X₄ mRNA has also been detected (155). However, in both studies, it was not certain whether the mRNA was present in the medullary or cortical cells.

ATP can produce at least three different effects on adrenal chromaffin cells: inhibition of voltage-gated Ca²⁺ channels (411, 461, 1046), release of Ca²⁺ from internal stores (1407), and activation of a nonselective cation channel (1285). While the first two effects are most probably mediated by P2Y receptors, the third effect has the characteristics for the activation of P2X receptors.

Functional studies have demonstrated the presence of P2X receptors on bovine (1407) and guinea pig (1056,

1285) chromaffin cells. However, these receptors appear to be absent in the rat (753, 1056). The P2X receptor present on chromaffin cells can be activated by ATP and 2-methylthio ATP (2-MeSATP), but is much less sensitive or insensitive to α,β -meATP (1056, 1407). To date, the only detailed pharmacological study of P2X receptors on chromaffin cells has been carried out on the guinea pig. Here, the receptor is antagonized by pyridoxalphosphate-6-azonphenyl-2',4'-disulfonic acid (PPADS), but suramin and Cibacron blue are quite weak antagonists. The response is potentiated by low pH, but inhibited by Zn²⁺. Thus while this receptor has some properties in common with the rat P2X₂ receptor (agonist profile, effect of pH), the lack of potentiation by Zn²⁺ and the low sensitivity to the antagonists suramin and Cibacron blue are not. Although three spliced variants of the guinea pig P2X₂ receptor have been cloned, and some pharmacological characterization has been carried out, there is at present insufficient information to identify the native P2X receptor present on guinea pig chromaffin cells. The pharmacological properties of the P2X receptor present on guinea pig chromaffin cells are very similar to that of the α,β -meATP-insensitive receptor found on pelvic ganglion neurons. It therefore seems likely that it is in fact the homomeric P2X₂ receptor. ATP and catecholamines are released in parallel from adrenal chromaffin cells in response to stimulation by ACh, K⁺, or Ba²⁺ (871). Evidence has been presented that voltage-dependent Ca²⁺ channels are regulated in a paracrine fashion by ATP acting on P2X receptors in porcine adrenal chromaffin cells (1270).

Ecto-nucleotidases have been localized and characterized in pig adrenal glands (132, 1720). ARL 67156 is an effective inhibitor of ecto-nucleotidase activity in bovine chromaffin cells (475). Diadenosine polyphosphates are stored and released with ATP from chromaffin cells (825).

P2Y receptors mediate inhibition of exocytotic release of catecholamines from adrenal chromaffin cells by modulation of voltage-operated Ca²⁺ channels, rather than by a direct effect on the secretory machinery (1375, 1755). Exposure of bovine chromaffin cells to NPY results in a long-lasting increase in subsequent stimulation of inositol phosphate formation by ATP acting on P2Y receptors (476). P2Y₂ receptors have been identified immunohistochemically on rat chromaffin cells (16), which is consistent with this effect. ATP stimulation also appears to act through adenylate cyclase to stimulate cAMP formation in bovine chromaffin cells (1956), so it is interesting that P2Y₁₂ receptors that use this second messenger system have since been demonstrated in these cells (520).

Interaction between ATP and nerve growth factor signaling participates in the survival and neuritic outgrowth of PC12 cells (415) probably via P2Y receptors (1365).

C. Parasympathetic Ganglia

Prior to the cloning of P2X receptors, ATP was found to produce excitation in the vesical parasympathetic ganglion of the cat (1700). Responses to ATP have been recorded from dissociated neurons from the chick ciliary ganglia (10), rabbit vesical parasympathetic ganglion (1249), intramural ganglia from the guinea pig and cat urinary bladder (281, 1450), and guinea pig and rat cardiac neurons in culture (32, 511). In general, the results are very similar to those obtained in sympathetic neurons. Thus application of ATP evokes a rapid depolarization or inward current through the activation of P2X receptors. Although 2-MeSATP and ATP are approximately equipotent, α,β -meATP evoked only small responses when applied at high concentrations to rat neurons.

The neurons providing motor innervation to the bladder and other pelvic organs originate in the pelvic plexus. In the rat and mouse, this plexus consists of a pair of major pelvic ganglia and a number of small accessory ganglia. In the guinea pig and human, there are additional intramural ganglia within the wall of the bladder (404, 405). The pelvic ganglia receive sympathetic and parasympathetic inputs from preganglionic axons within the hypogastric and pelvic nerves, respectively.

Since they are smaller and have a more diffuse location, parasympathetic ganglia are much harder to study. Consequently, there is less immunohistochemical or molecular biological information about the presence of P2X receptors in these neurons. Although many neurons showed low levels of staining, a small percentage showed strong and specific staining. In keeping with these observations, P2X₂ but not P2X₁ receptor immunoreactivity was detected in axons and nerve terminals in the vas deferens (1809). High levels of P2X₂ mRNA and protein have been identified in rat pelvic ganglion neurons (1971). Although some P2X₄ message was also detectable, no staining was observed using probes directed against P2X₁ and P2X₃ receptor mRNA. P2X₂ and heteromultimer P2X_{2/3} receptors are also dominant in mouse pelvic ganglion neurons (1969). In contrast, at least three P2X receptors are present in guinea pig pelvic neurons, P2X₂, P2X₃, and P2X_{2/3} receptors (1970).

In a study of ATP-evoked currents in parasympathetic neurons dissociated from rat submandibular ganglia, it was shown that the inorganic and organic cation permeability of the ATP-gated P2X receptor channel was similar to that of the cloned P2X₂ receptor with a minimum pore diameter of 0.7 μm (1052). In the intact submandibular ganglia, ATP inhibits neurotransmitter release via presynaptic P2Y receptors but had no effect on postsynaptic neurons. However, upregulation of postsynaptic P2X receptors occurred in dissociated neurons (1586). In addition to P2X receptors, P1 and P2Y receptors are coexpressed postsynaptically in hamster submandib-

ular ganglion neurons, and both receptors mediate inhibition of N- and P/Q-type voltage-dependent Ca²⁺ channels (9). In hamster submandibular ganglion neurons, ATP caused both depolarization and hyperpolarization: the depolarization was mediated via P2X receptors, the hyperpolarization via P2Y₂ receptors (519).

In a comparative study of different parasympathetic ganglia, it was shown that neurons from intracardiac and paratracheal ganglia were insensitive to α,β -meATP, while all the neurons in otic and some neurons in sphenopalatine and submandibular ganglia responded (1085). Immunohistochemistry revealed strong staining for P2X₂ receptors in all five ganglia and strong P2X₃ staining in otic, sphenopalatine, and submandibular ganglia, suggesting that the receptor subtypes involved are homomeric P2X₂ and heteromeric P2X_{2/3} receptors. Combined calcium imaging and immunohistochemistry indicated that both P2X₃ and P2Y₄ receptors were expressed in neurons from cat bladder intramural ganglia (1450; Fig. 5, A–C). It was shown that 100, 49, and 97% of P2X₃ receptor immunopositive neurons coexpressed ChAT, NOS, and neurofilament 200 (NF200), respectively, while 100, 59 and 98% of P2Y₄ immunopositive neurons coexpressed ChAT, NOS, and NF200, respectively. Application of α,β -meATP and UTP elevated intracellular Ca²⁺ in a subpopulation of dissociated cultured neurons. Immunohistochemistry revealed strong and specific staining for the P2X₂ receptor subunit on rat parasympathetic neurons of the otic, sphenopalatine submandibular, intracardiac, and paratracheal ganglia (1085). Strong P2X₃ receptor staining was seen on otic, sphenopalatine, and submandibular ganglia, but neurons in intracardiac and paratracheal ganglia were insensitive to α,β -meATP. The predominant P2 receptor subtypes are homomeric P2X₂ and heteromeric P2X_{2/3} receptors. Thus P2X₃ receptors are expressed in parasympathetic ganglia, in contrast to the widely held view that P2X₃ and P2X_{2/3} receptor subtypes are restricted to sensory neurons. P2Y₂ receptors have been identified on rat intracardiac neurons that mediate increases in intracellular Ca²⁺ and generation of inositol trisphosphate (IP₃) (1053).

Adenosine was reported to mediate a slow hyperpolarizing synaptic potential in cat vesical parasympathetic ganglia by stimulating preganglionic nerves (25). In a later study of rat pelvic ganglion neurons, it was shown that adenosine inhibited N-type Ca²⁺ currents by activation of A₁ receptors via a voltage-dependent and pertussis toxin (PTX)-sensitive pathway, which may explain how adenosine acts as an inhibitory modulator of ganglionic transmission in the pelvic plexus (1311).

D. Enteric Ganglia

Katayama and Morita (878) were the first to study the effects of ATP on single myenteric neurons from guinea

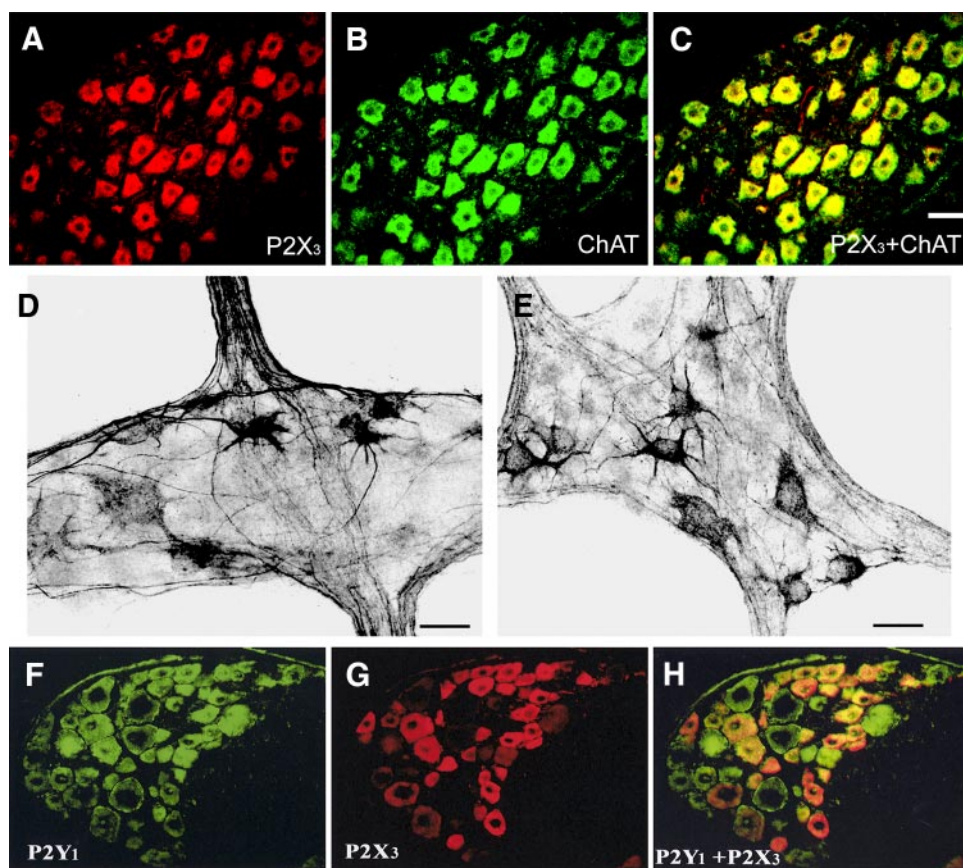


FIG. 5. Immunolocalization of P2 receptors. *A–C*: double staining to show colocalization (yellow/orange) of P2X₃ receptor immunoreactivity (red) with ChAT (green), in intramural ganglia of the cat urinary bladder. Scale bar = 50 μm. [From Ruan et al. (1450), with permission from the American Physiological Society.] *D* and *E*: P2Y₆ receptor immunoreactivity (black) in myenteric plexus of the jejunum (*D*) and distal colon (*E*) of the guinea pig. Scale bars = 25 μm. [From Xiang and Burnstock (1903), with permission of Springer-Verlag.] *F–H*: colocalization (yellow/orange) of P2Y₁ receptor immunoreactivity (green) with P2X₃ receptor immunoreactivity (red) in the rat dorsal root ganglion (DRG). Scale bar = 100 μm. [From Ruan and Burnstock (1451), with permission of Springer-Verlag.]

pig small intestine using the intracellular electrophysiological recording technique. Myenteric neurons are classified into two groups electrophysiologically, and ATP elicited hyperpolarization in 80% of AH (type II) neurons and depolarization in 90% of S (type I) neurons in a dose-dependent manner. Quinidine reversibly depressed both the ATP-induced responses.

Several laboratories have extended these studies of purinergic signaling in the guinea pig myenteric and submucous neurons (see Refs. 266, 613, 771, 1168, 1411). Elegant whole cell and outside-out patch-clamp recordings were used to characterize the physiological and pharmacological properties of P2X receptors on myenteric neurons of the guinea pig ileum (95, 175). ATP and analogs evoked rapid inward currents in over 90% of the neurons studied.

P2X receptors and nicotinic cholinergic receptors are linked in a mutually inhibitory manner in guinea pig myenteric neurons (1972). Mulholland's group carried out studies of purinergic signaling in dispersed primary cultures of guinea pig myenteric plexus. Extracellular ATP was shown to mediate Ca²⁺ signaling via a PLC-dependent mechanism (911). Enteric neurons differed from one another in their ability to respond to combinations of ATP with ACh, ATP with SP, ATP with ACh, ATP with ACh and SP, ATP with bombesin, or ATP with ACh and bombesin.

Evidence was presented from the laboratory of Christofi, Wood, and colleagues that two distinct types of P2 receptors are linked to a rise in [Ca²⁺]_i in guinea pig intestinal myenteric neurons of both AH and S neuronal phenotypes and are not restricted to calbindin immunoreactive sensory neurons.

ATP regulates synaptic transmission by pre- as well as postsynaptic mechanisms in guinea pig myenteric neurons, i.e., ATP augments nicotinic fast depolarization produced by ACh, but inhibits muscarinic and SP-mediated depolarizations in both AH and S neurons (860). α,β-MeATP-sensitive P2X receptors (P2X₂, P2X₃, and P2X_{2/3} receptors) are prejunctional modulators of cholinergic neurotransmission between the myenteric plexus and longitudinal smooth muscle of the guinea pig intestine (130).

Exogenous and endogenous ATP, released during increase in intraluminal pressure, inhibits intestinal peristalsis in guinea pig via different apamin-sensitive purine receptor mechanisms. Exogenous ATP depresses peristalsis mostly via suramin- and PPADS-insensitive P2 receptors, whereas endogenous purines act via P2 receptors sensitive to both suramin and PPADS (729). Evidence has been presented that ATP plays a major role in excitatory neuroneuronal transmission in both ascending and descending reflex pathways to the longitudinal and circular muscles of the guinea pig ileum triggered by mucosal

stimulation (1018, 1167, 1622). Distending inhibitory reflexes involve P2X receptor-mediated transmission from interneurons to motor neurons in guinea pig ileum (140). It has been proposed that ATP is a sensory mediator via P2X₃ receptors on intrinsic sensory neurons in the enteric plexuses (138, 267). P2X₃ receptor immunoreactivity has also been shown on sensory neurons in the human myenteric plexus (1935). Experiments with P2X₂ and P2X₃ receptor knockout mice showed that peristalsis is impaired in the small intestine, indicating that P2X₃ and P2X_{2/3} receptors participate in the neural pathways underlying peristalsis, and it was suggested that these receptors may contribute to the detection of distension or intraluminal pressure increases and initiation of reflex contractions (139, 1411). Intraganglionic laminar nerve endings, which are prominently associated with myenteric ganglia, particularly in the stomach, express both P2X₂ (317) and P2X₃ receptors (1899). P2X₃ receptors are dominant on neurons in the submucosal plexus of the rat ileum and distal colon, and ~50% of the neurons express calbindin, a marker for enteric sensory neurons (1898).

Nicotinic ACh and P2X receptors play a central role in fast synaptic excitatory transmission in the myenteric plexus (615). Nicotinic receptors on S-type neurons on the guinea pig intestine are composed of at least the α 3- and β 4-subunits, while P2X receptors in S-type neurons are composed of P2X₂ subunits (1411), and ATP acting on the receptors is the predominant fast excitatory neurotransmitter in the descending pathways. The P2X₃ receptor subtype predominates in AH-type neurons (139) and probably participates in mechanosensory transduction (138, 1399). Fast EPSPs (fEPSPs) occur in bursts in the myenteric plexus during evoked motor reflexes in the guinea pig ileum. The amplitude of fEPSPs declines with repetitive stimulation. It is suggested that this synaptic "run-down" is not due to nicotinic or P2X receptor desensitization, but rather to depletion of a readily releasable pool of neurotransmitter (1412). Physical and functional interactions between P2X₂ receptor channels and serotonin-gated 5-HT₃ channels have been proposed as a basis for ionotropic cross-talk and a potential mechanism for regulating neuronal excitability and synaptic plasticity within the myenteric plexus (181).

Synaptosomal preparations from the guinea pig ileum myenteric plexus were first described by Dowe et al. (471) and Briggs and Cooper (207). ATP and adenosine were equipotent in their ability to inhibit the nicotine-induced release of [³H]ACh; the inhibition by both ATP and adenosine was reversed by theophylline, indicating that a P1 receptor was involved (1406). However, high concentrations of ATP caused a marked increase in the release of [³H]ACh, presumably mediated by a prejunctional P2 receptor.

Intracellular recordings from submucosal neurons in guinea pig small intestine showed that ATP induced fast

transient depolarization of most AH-type neurons and fast transient depolarization followed by slower onset, longer lasting depolarization of S-type neurons (92, 1168). When whole cell patch recordings were employed, superfusion of ATP and analogs evoked rapidly desensitizing inward current, and ATP-induced single-channel currents were also recorded. In a whole cell patch-clamp study of ATP-induced membrane currents in guinea pig small intestinal submucosal neurons by another group (655), the currents activated by ATP were not blocked by suramin and were often enhanced by Reactive blue 2. This could indicate the involvement of P2X₄ or possibly P2X₆ receptors. The functional interaction, between nicotinic and P2X receptors, has been investigated in freshly dissociated guinea pig submucosal neurons in primary culture: whole cell currents induced by ATP were blocked by PPADS and showed some interdependence on ACh-induced nicotinic currents blocked by hexamethonium (93, 1972). Inhibitory interactions between 5-HT₃ and P2X channels in submucosal neurons have been described (94). Evidence has also been presented for two subtypes of P2X receptor in neurons of guinea pig ileal submucosal plexus (654). Slow EPSPs (sEPSPs) were mediated by P2Y₁ receptors in neurons in the submucosal plexus of guinea pig small intestine (771, 1168). The purinergic excitatory input to these neurons came from neighboring neurons in the same plexus, from neurons in the myenteric plexus, and from sympathetic postganglionic neurons. ATP-mediated EPSPs occurred coincident with fast nicotinic synaptic potentials with noradrenergic IPSPs.

Immunohistochemical studies have demonstrated P2X₂ receptors (318, 1898), P2X₃ receptors (1364, 1769, 1898), and P2X₇ receptors (770) in subpopulations of guinea pig and rat myenteric and submucosal ganglion neurons (see Table 3). Enteric glial cells also express P2 receptors (910, 1773). P2X₂ and P2X₅ receptors have also been immunolocalized on interstitial cells of Cajal (ICCs) (293). P2X₂ receptors were localized on smooth muscle in the mouse colon (637) and P2X₅ receptors on nerve fibers that enveloped ganglion cell bodies and possibly glial cell processes in the mouse gastrointestinal tract (1452). ATP plays a major excitatory role, probably largely via P2X₂ receptors, in rat myenteric neurons, whether sensory, motor, or interneurons (1271). Cross-inhibitory interactions between GABA_A and P2X receptor channels in myenteric neurons of guinea pig small intestine have been described recently (869).

There is growing evidence for the expression of P2Y receptors on enteric neurons in addition to P2X receptors (1885). Fast and slow depolarizations and Ca²⁺ responses of cultured guinea pig ileal submucosal neurons to ATP were mediated by P2X and P2Y receptors, respectively (91). In the mouse gastrointestinal tract, P2Y₁ receptors on NANC myenteric neurons appear to mediate relaxation through NO and ATP (637). Slow excitatory synaptic

TABLE 3. Neuron types in the guinea pig ileum that express P2X₂, P2X₃, or both receptor subunits

Neuron Type	Chemical or Morphological Identifier	P2X Receptor Type(s)
Excitatory longitudinal muscle motor neuron	Calretinin IR	P2X ₃
Ascending interneuron	Calretinin IR	P2X ₃
Inhibitory muscle motor neurons and descending interneurons	NOS IR	P2X ₂ /P2X ₃ , some NOS neurons may also express only one of the subunits
Intrinsic primary afferent neuron (both myenteric and submucosal)	Dogiel type II; NeuN and/or calbindin IR	P2X ₂ (P2X ₃ in rat and mouse)
Noncholinergic secretomotor neuron	VIP IR	P2X ₃
Cholinergic secretomotor/vasodilator neuron	Calretinin IR	P2X ₃
Cholinergic secretomotor neuron	NPY IR	P2X ₃ (13% of this population have the subunit)

IR, immunoreactivity; NOS, nitric oxide synthase; VIP, vasoactive intestinal polypeptide; NPY, neuropeptide Y. [From Poole et al. (1364), with permission from Elsevier.]

transmission is mediated by P2Y₁ receptors in the guinea pig enteric nervous system (771). A P2Y₁ receptor has been cloned and characterized recently from guinea pig submucosa (618). P2Y₂ receptors are widely distributed on S-type (Dogiel type 1) neurons in the myenteric and submucosal plexuses throughout the guinea pig gut (1901). About 40–60% of P2X₃ receptor immunoreactive neurons were immunoreactive for P2Y₂ receptors in the myenteric plexus, and all P2X₃ receptor immunoreactive neurons expressed P2Y₂ receptors in the submucosal plexus. It seems likely that the S-type neurons with fast P2X receptor-mediated and slow P2Y receptor-mediated depolarizations are these neurons coexpressing P2X₃ and P2Y₂ receptor subunits. It has been shown recently that 30–36% of the ganglion cells in the myenteric, but not submucosal, plexus of the guinea pig gastrointestinal tract are labeled with P2Y₆ receptor-immunoreactive neurons (see Fig. 5D), while ~42–46% of the neurons in both myenteric and submucosal plexuses are immunoreactive for P2Y₁₂ receptors (1903). About 28–35% of P2Y₆ receptor-immunoreactive neurons coexist with NOS, but not with calbindin, while all P2Y₁₂ receptor-immunoreactive neurons were immunopositive for calbindin and appear to be AH intrinsic primary afferent neurons. In a recent study of the rat distal colon, P2Y₁ and P2Y₆ immunoreactivity was found on smooth muscles, P2Y₄ and P2Y₆ receptor immunoreactivity on glial cells in both plexuses, P2Y₄ receptors on ICCs, while P2Y₂ and P2Y₁₂ receptors were demonstrated on enteric neurons (1770, 1771). Some of the P2Y₂ immunoreactive neurons, but none of the P2Y₁₂ immunoreactive neurons exhibited neuronal (n)NOS.

Differential gene expression of A₁, A_{2A}, A_{2B}, and A₃ receptors in human enteric neurons have been reported (366), and fine-tuning modulation of myenteric motoneuron activity by endogenous adenosine has been claimed (387). Adenosine has dual effects on ACh release from myenteric motor neurons: prejunctional facilitating A_{2A} and extrajunctional inhibitory A₁ receptors (485). This group also showed that adenosine activation of A_{2A} receptors downregulates nicotinic autoreceptor function at

rat myenteric nerve terminals. Adenosine suppresses slow EPSPs in AH neurons via A₁ receptors (see Ref. 1886). In the mouse distal colon, A_{2B} receptors are located on enteric NANC inhibitory neurons (1983).

V. SENSORY NEURONS

Sensory neurons of the DRG share with neurons of the sympathetic, parasympathetic, and enteric ganglia, along with adrenomedullary chromaffin cells, a common embryological origin in the neural crest. In contrast, cranial sensory neurons are derived from the placodes. Although these sensory and autonomic neurons exhibit some common properties, they also show very diverse phenotypes commensurate with their diverse physiological roles.

There have been many reports characterizing the native P2X receptors in sensory neurons, including those from dorsal root, trigeminal, nodose, and petrosal ganglia. DRG and trigeminal ganglia contain primary somatosensory neurons, receiving nociceptive, mechanical, and proprioceptive inputs. Nodose and petrosal ganglia, on the other hand, contain cell bodies of afferents to visceral organs.

All P2X subtypes, except P2X₇, are found in sensory neurons, although the P2X₃ receptor has the highest level of expression (both in terms of mRNA and protein). P2X_{2/3} heteromultimers are particularly prominent in the nodose ganglion. P2X₃ and P2X_{2/3} receptors are expressed on isolectin B₄ (IB₄) binding subpopulations of small nociceptive neurons (188). Species differences are recognized.

RT-PCR showed that P2Y₁, P2Y₂, P2Y₄, and P2Y₆ mRNA is expressed on neurons of DRG, nodose, and trigeminal ganglia, and receptor protein for P2Y₁ is localized on over 80% of mostly small neurons (1451). Double immunolabeling showed that 73–84% of P2X₃ receptor positive neurons also stained for the P2Y₁ receptor (see Fig. 5, F–H), while 25–35% also stained for the P2Y₄ receptor. Patch-clamp studies of cultured neurons from

DRG were consistent with both P2X₃ and P2Y₁ receptors being present in a subpopulation of DRG neurons.

It has been shown that the sensory neurons have the machinery to form purinergic synapses on each other when placed in short-term tissue culture (1948). The resulting neurotransmitter release is calcium dependent and uses synaptotagmin-containing vesicles; the postsynaptic receptor involved is a P2X subtype. Experiments are needed to find out whether purinergic synapses form between sensory neurons *in vivo*, whether this is more common after nerve injury, and whether this has physiological or pathophysiological significance.

Comprehensive reviews of P2X receptor expression and function in sensory neurons in DRG, nodose, trigeminal and petrosal ganglia are available (262, 496). An account of the roles played by both adenosine and ATP in nociception can be found in section XI, A8 and B9).

A. Dorsal Root Ganglia

The P2X₃ subunit that was first cloned using a cDNA library from neonatal rat DRG neurons shows a selectively high level of expression in a subset of sensory neurons, including those in DRG (335, 378, 1027). In DRG ganglia, the level of P2X₃ transcript is the highest, although mRNA transcripts of P2X₁₋₆ have been detected. Green fluorescence has been used to quantitate P2X receptor RNA in DRG (1751). The expression pattern of P2X₃ receptors in sensory ganglia has also been studied by immunohistochemistry at both the light microscope (99, 188, 1261, 1811, 1812, 1896) and electron microscope (1062) levels. In DRG, intensive P2X₃ immunoreactivity is found predominantly in a subset of small- and medium-diameter neurons, although it was absent from most large neurons. The P2X₃ subunit is predominantly located in the nonpeptidergic subpopulation of nociceptors that binds the IB₄ and is greatly reduced by neonatal capsaicin treatment (1812). The P2X₃ subunit is present in an approximately equal number of neurons projecting to skin and viscera, but in very few of those innervating skeletal muscle (188). P2X₃ receptors are strongly represented in sensory ganglia during rat embryonic neurogenesis (353; see sect. xA2).

P2X₂ receptor immunoreactivity is observed in many small and large DRG neurons, although the level is lower than that of P2X₃ (985, 1811). Some neurons seem to contain both P2X₂ and P2X₃ immunoreactivity. Although P2X₃ immunoreactivity is the predominant type detected, variable levels of immunoreactivity for P2X₁, P2X₂, P2X₄, P2X₅, and P2X₆ receptors have also been detected in DRG neurons (1338, 1896). These receptors are arranged in clusters 0.2–0.5 μm in diameter and rarely appear to colocalize (99). Both transient and sustained responses to P2 receptor agonists occur in DRG neurons (see Ref. 496).

The transient response in DRG neurons is activated by ATP, α,β-meATP, and 2-MeSATP. The pharmacological evidence to date generally supports the hypothesis that this rapid desensitizing transient response is mediated by homomeric P2X₃ receptors.

P2X receptors on the cell bodies of the sensory neurons have been studied extensively using voltage-clamp recordings from dissociated neurons of the DRG (238, 683, 1031, 1432). Rapid application of ATP evokes action potentials, and under voltage clamp, a fast-activating inward current, as well as depolarization and an increase in intracellular Ca²⁺ concentration.

mRNA for an orphan G protein-coupled receptor TGR7, which is specifically responsive to β-alanine, claimed to participate in synaptic transmission, is coexpressed in small-diameter neurons with P2X₃ and vanilloid type 1 (VR1) receptors in both rat and monkey DRG (1559). Ca²⁺/calmodulin-dependent protein kinase II, upregulated by electrical stimulation, enhances P2X₃ receptor activity in DRG neurons, and it is suggested that this may play a key role in the sensitization of P2X receptors under inflammatory conditions (1909). Rapid reduction of the excitatory action of ATP on DRG neurons by GABA, probably via GABA_A anionic receptors, and slow inhibition of ATP currents via metabotropic GABA_B receptors appear to be additional mechanisms of sensory information processing (986, 1600). Fibers project from DRG to the superficial lamina of the dorsal horn of the spinal cord where the receptors may function to modulate transmitter release near their central terminals. Oxytocin inhibits ATP-activated currents in DRG neurons (1921). In contrast, neurokinin B potentiates ATP-activated currents in DRG neurons (1827). 17β-Estradiol attenuates α,β-meATP-induced currents in rat DRG neurons (326, 1084). Ω-Conotoxin GVIA, known as a selective blocker of N-type calcium channels, potently inhibits the currents mediated by P2X receptors in rat DRG neurons (992), while neurokinin B potentiates ATP-activated currents (1827). Pentobarbital suppressed the fast-type current mediated by P2X₃ receptors in rat DRG neurons and may contribute to its anesthetic and analgesic actions (922).

There are species differences in the responses of DRG neurons to ATP. Transient responses are the predominant type evoked by P2X agonists from DRG neurons of rat and mouse, with persistent and biphasic types seen less frequently (238, 683). In contrast, only sustained inward currents have been reported on DRG neurons from bullfrog (120, 1032). It is possible that distinct P2X receptors may be differentially distributed at cell soma and nerve terminals of the same neuron. The physiological significance of the heterogeneity in P2X receptor expression in sensory neurons is not yet clear.

Neurons and glial cells differentially express P2Y receptor subtype mRNA in rat DRG (939). P2Y₁ and P2Y₂ receptor mRNA was expressed in ~20% of neurons;

Schwann cells expressed P2Y₂ mRNA, and nonneuronal satellite cells expressed P2Y₁₂ and P2Y₁₄ mRNA. ATP and UTP produce slow and sustained excitation of sensory neurons in DRG via P2Y₂ receptors (1164). Colocalization P2Y₁ and P2X₃ immunoreactivity has been described in a subpopulation of DRG neurons (177, 1451). P2Y receptors contribute to ATP-induced increase in intracellular Ca²⁺ and subsequent release of CGRP from DRG neurons (1493). ATP and UTP were equipotent in increasing axonal transport in cultured DRG neurons, probably via P2Y₂ receptors (1483). RT-PCR and immunohistochemistry studies have identified P2Y₁ and P2Y₄ mRNA and protein in DRG as well as nodose and trigeminal ganglia of the rat (1451). Other nucleoside triphosphates, including NTP, GTP, and CTP, and the diphosphates NDP, GDP, UDP, and CDP were also active in modulating sodium currents in DRG neurons (1313). Bradykinin and ATP, acting via P2Y receptors, accelerate Ca²⁺ efflux from rat sensory neurons via protein kinase C (PKC) and the plasma membrane Ca²⁺ pump isoform 4 and represent a novel mechanism to control excitability and augment their sensitivity to other stimuli (773, 1760). Inhibition of N-type voltage-activated calcium channels in DRG neurons by P2Y receptors has been proposed as a mechanism of ADP-induced analgesia (631). P2Y₂ and P2Y₄ receptors were strongly expressed in DRG of the cat, as well as P2X₃ receptors (1449). Other P2X and P2Y receptor subtypes were also present in cat DRG, but there was low expression of P2Y₁ receptors compared with >80% of P2Y₁ receptor-positive neurons in rat DRG. Metabotropic P2Y₁ receptors inhibit P2X₃ receptor channels in rat DRG neurons via G protein activation (632). Extracellular ATP upregulated the TTX-resistant Na⁺ current recorded in cultured rat and mouse DRG neurons, consistent with P2Y receptor activation; the activation of PKC appears to be a necessary step in the GTP-dependent upregulation process (80). GFP studies have shown that there is ADP-induced endocytosis and internalization of P2Y receptors in DRG neurons (1825). An orphan G protein-coupled receptor, localized in rat DRG, has been proposed to be an adenine receptor (129).

Some nicotinic ACh receptor antagonists, such as α -bungarotoxin and (+)-tubocurarine, appear to be potent blockers of fast P2X receptor ATP-gated currents in DRG neurons (993). Adenosine-5'-O-(3-thiotriphosphate) (ATP γ S) enhances nerve growth factor (NGF)-promoted neurite formation in DRG neurons, perhaps via its ability to increase NGF-promoted TrkA activation (63). NTP-Dase2 has been shown to be present in satellite glial cells in DRG (202), consistent with evidence for a functional role for ATP in satellite glial cells (705). Functional expression of P2X₇ receptors on nonneuronal glial cells, but not on small-diameter neurons from rat DRG, has been reported (1960).

B. Nodose Ganglia

P2X₂ and P2X₃ receptors were shown to be expressed immunohistochemically in rat nodose ganglia (1811). ATP, α,β -meATP, and 2-MeSATP evoke sustained currents in rat nodose neurons. These responses are inhibited by suramin, PPADS, Cibacron blue, trinitrophenyl (TNP)-ATP, and Ca²⁺ (896, 1703, 1790), but not by di-inosine pentaphosphate (Ip₅I) (495). Therefore, the α,β -meATP-sensitive persistent responses in nodose neurons resemble the recombinant P2X_{2/3} receptors (1027). Neurons of the mouse nodose ganglion give persistent responses to both ATP and α,β -meATP similar to those seen in the rat and guinea pig (372, 1617, 1970). In P2X₃ receptor-deficient mice, no nodose neurons respond to α,β -meATP at concentrations up to 100 μ M, while the response to ATP is significantly reduced. The residual persistent responses to ATP have all the characteristics of recombinant P2X₂ homomers. Thus the pharmacological evidence is consistent with the notion that both heteromeric P2X_{2/3} and homomeric P2X₂ receptors are present in significant amounts in nodose neurons, although the proportions may vary from cell to cell (371). Most neurons in the rat nodose ganglia showed colocalization of P2X₃ receptors and the IB₄ from *Griffonia simplicifolia* type one (GS-IB₄). Subpopulations of neurons expressed P2X_{1/3} and P2X_{2/3} heteromultimers (778). RT-PCR showed P2X₁, P2X₂, P2X₄, and P2X₇ receptors were expressed in rat nodose ganglia (71). Sensory neurons from nodose ganglia express, in addition to P2X₃ receptor mRNA, significant levels of P2X₁, P2X₂, and P2X₄ receptor mRNAs, and some of these mRNAs are present in the same cell. P2X₂ and P2X₃ receptor immunoreactivities are both present and are colocalized in the same neurons (1027, 1896).

P2Y₁ receptors have been demonstrated immunohistochemically in rat and human nodose ganglia (565). Coexistence of functional P2Y receptors (acting via the IP₃ pathway) and ryanodine receptors and their activation by ATP has been demonstrated in vagal sensory neurons from the rabbit nodose ganglion (747). RT-PCR has shown P2Y₁, P2Y₂, P2Y₄, and P2Y₆ receptor mRNA in rat nodose ganglia (1451). P2Y₁ receptor immunoreactivity was found in >80% of the sensory neurons, particularly small diameter (neurofilament-negative neurons), while P2Y₄ receptors were expressed in more medium- and large-diameter neurons. About 80% of the P2X₃ receptor immunoreactive neurons also stained for P2Y₁ receptors, while ~30% of the neurons showed colocalization of P2Y₄ with P2X₃ receptors.

C. Trigeminal Ganglia

Most of the facial sensory innervation is provided by nerve fibers originating in the trigeminal ganglion, com-

prised of neurons that transduce mechanical, thermal, and chemical stimuli, probably including odorant molecules. In trigeminal ganglia, P2X₃ receptor immunoreactivity is found in the cell bodies of both small and large neurons (383, 833, 1062, 1896). Lower levels of immunoreactivity to P2X₁, P2X₂, P2X₄, and P2X₆ receptors appear to be present in these neurons. Whole cell patch-clamp studies of trigeminal neurons showed ATP-activated (both fast and slow) desensitizing currents in the majority of cells examined, but outward or biphasic currents also occurred in a small number of cells (688). P2X₃ receptor mRNA increased in trigeminal ganglia (and DRG) after nerve transection, suggesting that they play a role in the pathomechanism of postnerve injury hypersensitivity (1734). A subpopulation of neurons cultured from rat trigeminal ganglia have been identified which lack the typical nociceptive characteristics and express homomeric P2X₂ receptors (1619). The authors speculate that trigeminal neurons are equipped with a repertoire of receptors that fulfill multiple tasks affecting different sensory modulators. Expression of P2X₃ receptors in the rat trigeminal ganglia after inferior alveolar nerve injury decreased by ~35% (522). One day after ischemic insult, the number of P2X₃ receptor immunoreactive neurons in trigeminal ganglia of the Mongolian gerbil decreased by ~67%, and by day 5, only a few neurons showed weak immunoreactivity (782).

P2Y₁ and P2Y₄ receptor mRNA and protein are also expressed in rat trigeminal ganglia with many neurons showing colocalization with P2X₃ receptors (1451). Striking differences between P2X₃ receptors in trigeminal and DRG neurons were highlighted, questioning the validity of extrapolating spinal cord models of P2X₃ function to the craniofacial region (44). In particular, only a small percentage of IB₄-binding neurons express P2X₃ receptors, whereas many peptidergic neurons express P2X₃ receptors.

Evidence has been presented that satellite glial cells in mouse trigeminal ganglia express P2Y receptors (possibly the P2Y₁ subtype), although their precise role is not yet clear (705, 1845; see sect. VIII for further discussion). Recently, single-cell calcium imaging demonstrated that both P2Y₁ and, to a lesser extent, P2Y_{2,4,6,12,13} receptors on satellite glial cells contribute to ATP-induced calcium-dependent signaling in mixed neuron-glia primary cultures from mouse trigeminal ganglia (324).

D. Petrosal Ganglia

The petrosal ganglion provides sensory innervation of the cortical sinus and carotid body through the carotid sinus nerve. P2X receptors have been identified on neurons in the rat petrosal ganglia (1955). ATP activates cat and rabbit petrosal ganglia neurons *in vitro* (29, 31) and

evokes ventilatory reflexes *in situ*, which are abolished after bilateral chemosensory denervation (1613). Dopamine inhibits ATP-induced responses of neurons of the cat petrosal ganglia (30).

E. Retinal Ganglia

Retinal ganglion cells on the eye receive information from both rods and cones, and early papers about purinergic transmission in the retina have been reviewed (1354). P2X₂ receptors have been identified in retinal ganglion cells (198, 675), particularly within cone pathways (1386). Functional studies have also identified P2X_{2/3} heteromultimeric receptors in cultured rat retinal ganglion cells (1687). P2X₂ receptors are expressed on cholinergic amacrine cells of mouse retina (862) and also GABAergic amacrine cells (1386).

It was proposed that ATP, coreleased with ACh from retinal neurons, modulates light-evoked release of ACh by stimulating a glycinergic inhibitory feedback loop (1219). RT-PCR at the single-cell level revealed expression of P2X₂, P2X₃, P2X₄, and P2X₅ receptor mRNA in approximately one-third of the bipolar cells (1854); P2X₇ receptors were identified on both inner and outer retinal ganglion cell layers of the primate (812) and rat (199), and electron microscope analysis suggested that these receptors were localized in synapses, suggesting that purines play a significant role in neurotransmission within the retina and may modulate both photoreceptor and rod bipolar cell responses (1387). Stimulation of P2X₇ receptors elevated Ca²⁺ and killed retinal ganglion cells (1958) and may be involved in retinal cholinergic neuron density regulation (1414).

P2X₃ receptors are present on Müller cells (815). Müller cells release ATP during Ca²⁺ wave propagation (1235). While the potent P2X₇ agonist 3'-O-(4-benzoyl)-benzoyl ATP (BzATP) killed retinal ganglion cells, this was prevented by the breakdown product adenosine via A₃ receptors (1959).

Evidence has been presented recently for the involvement of P2X₇ receptors in outer retinal processing: P2X₇ receptors are expressed postsynaptically on horizontal cell processes as well as presynaptically on photoreceptor synaptic terminals in both rat and marmoset retinas (1387).

F. Sensory Nerve Fibers and Terminals

Sensory nerve terminals express purinoceptors and respond to ATP in many situations (see Ref. 262). However, it has been shown that ATP sensitivity is not necessarily restricted to the terminals; increased axonal excitability to ATP and/or adenosine of unmyelinated fibers in

rat vagus, sural and dorsal root nerves, as well as human sural nerve has been described (810, 1725).

During purinergic mechanosensory transduction, the ATP that acts on P2X₃ and P2X_{2/3} receptors on sensory nerve endings is released by mechanical distortion from urothelial cells during distension of bladder and ureter and from mucosal epithelial cells during distension of the colorectum (see sect. XI A 8). It is probably released from odontoblasts in tooth pulp, from epithelial cells in the tongue, epithelial cells in the lung, keratinocytes in the skin, and glomus cells in the carotid body. Released ATP is rapidly broken down by ectoenzymes to ADP (to act on P2Y₁, P2Y₁₂, and P2Y₁₃ receptors) or adenosine (to act on P1 receptors) (1980).

1. Lung

Pulmonary neuroepithelial bodies (NEBs) (215, 218) and more recently subepithelial receptor-like endings associated with smooth muscle (SMARs) (216) have been shown to serve as sensory organs in the lung, and P2X₃ and P2X_{2/3} receptors are expressed on a subpopulation of vagal sensory fibers that supply NEBs and SMARs with their origin in the nodose ganglia. Quinacrine staining of NEBs indicates the presence of high concentrations of ATP in their secretory vesicles, and it has been suggested that ATP is released in response to both mechanical stimulation during high-pressure ventilation and during hypoxia (1425). NEBs are oxygen sensors especially in early development, before the carotid system has matured (217, 588). In a study of bronchopulmonary afferent nerve activity of a mouse isolated perfused nerve-lung preparation, it was found that C fibers could be subdivided into two groups: fibers that conduct action potentials at <0.7 ms⁻¹ and are responsive to capsaicin, bradykinin, and ATP; and fibers that conduct action potentials on an average of 0.9 ms⁻¹ and respond vigorously to ATP, but not to capsaicin or bradykinin (952). Both the transient receptor potential vanilloid 1 (TRPV1) receptor and P2X receptors mediate the sensory transduction of pulmonary reactive oxygen species, especially H₂O₂ and OH, by capsaicin-sensitive vagal lung afferent fibers (1454).

Vagal C-fibers innervating the pulmonary system are derived from cell bodies situated in two distinct vagal sensory ganglia: the jugular (superior) ganglion neurons project fibers to the extrapulmonary airways (larynx, trachea, bronchus) and the lung parenchymal tissue, while the nodose (inferior) neurons innervate primarily structures within the lungs (1757). Nerve terminals in the lungs from both jugular and nodose ganglia responded to capsaicin and bradykinin, but only the nodose C-fibers responded to α,β -meATP.

Sensory afferent fibers within the respiratory tract, which are sensitive to ATP, probably largely via P2X_{2/3} receptors, have been implicated in vagal reflex activity

(1327), in the cough reflex (858, 859), and in the bradypneic reflex (1455).

2. Gut

ATP and α,β -meATP activated submucosal terminals of intrinsic sensory neurons in the guinea pig intestine (138), supporting the hypothesis of Burnstock (266) that ATP released from mucosal epithelial cells has a dual action on P2X₃ and/or P2X_{2/3} receptors in the subepithelial sensory nerve plexus. ATP acts on the terminals of low-threshold intrinsic enteric sensory neurons to initiate or modulate intestinal reflexes and acts on the terminals of high-threshold extrinsic sensory fibers to initiate pain (see sect. XI A 8c). Further support comes from the demonstration that peristalsis is impaired in the small intestine of mice lacking the P2X₃ subunit (139) and that up to 75% of the neurons with P2X₃ receptor immunoreactivity in the rat submucosal plexus expressed calbindin (1898); calbindin is regarded as a marker for intrinsic sensory neurons, at least in the guinea pig (see Ref. 603). Thirty-two percent of retrogradely labeled cells in the mouse DRG at levels T8-L1 and L6-S1, supplying sensory nerve fibers to the mouse distal colon, were immunoreactive for P2X₃ receptors (1433). Intraganglionic laminar nerve endings are specialized mechanosensory endings of vagal afferent nerves in the rat stomach, arising from the nodose ganglion; they express P2X₃ receptors and are probably involved in physiological reflex activity, especially in early postnatal development (1899).

Purinergic mechanosensory transduction has also been implicated in reflex control of intestinal secretion, whereby ATP released from mucosal epithelial cells acts on P2Y₁ receptors on enterochromaffin cells to release 5-HT, which leads to regulation of secretion either directly or via intrinsic reflex activity (384).

3. Carotid body

The ventilatory response to decreased oxygen tension in the arterial blood is initiated by excitation of specialized oxygen-sensitive chemoreceptor cells in the carotid body that release neurotransmitter to activate endings of the sinus nerve afferent fibers. ATP and adenosine were shown early on to excite nerve endings in the carotid bifurcation (828, 1137) and subsequently α,β -meATP (1623).

Large amounts of adenine nucleotides were localized in glomus cells, stored within specific granules together with catecholamines and proteins (158). Evidence of ATP release from carotid chemoreceptor cells has been reported (300), and corelease of ATP and ACh is the likely mechanism for chemosensory signaling in the carotid body in vivo (see Ref. 1264). ATP coreleased with ACh from type I glomus chemoreceptor cells during hypoxic and mechanical stimulation was shown to act on P2X_{2/3}

receptors on nerve fibers arising from the petrosal ganglion mediating hypoxic signaling at rat and cat carotid body chemoreceptors (1377, 1775, 1955). Immunoreactivity for P2X₂ and P2X₃ receptor subunits has been localized on rat carotid body afferents (1377). These findings were confirmed and extended in a recent study where P2X₂ receptor deficiency resulted in a dramatic reduction in the responses of the carotid sinus nerve to hypoxia in an *in vitro* mouse carotid body-sinus nerve preparation (1444). ATP mimicked the afferent discharge, and PPADS blocked the hypoxia-induced discharge. Immunoreactivity for P2X₂ and P2X₃ receptor subunits was detected on afferent terminals surrounding clusters of glomus cells in wild-type but not in P2X₂ and/or P2X₃ receptor-deficient mice. ATP induces [Ca²⁺]_i rise in rat carotid body cultured glomus cells (1163). Support for this mechanism in hypercapnia, as well as in hypoxia, came from CO₂/pH chemosensory signaling in cocultures of rat carotid body and petrosal neurons (1954).

ATP, acting on P2X₂ receptors, contributed to modified chemoreceptor activity after chronic hypoxia, indicating a role for purinergic mechanisms in the adaptation of the carotid body in a chronic low-O₂ environment (721). It was concluded in recent reviews that ATP is emerging as an important excitatory transmitter for afferent nerve activation by hypoxia, but that further studies are needed to analyze the interactions between putative O₂ sensors and excitatory and inhibitory transmitters in the carotid body (1376). Adenosine also stimulates carotid chemoreceptors, probably via postsynaptic A_{2A} receptors (938, 1463) and presynaptic A_{2B} receptors (381).

4. Heart

An ATP-triggered vagal reflex has been described leading to suppression of sinus mode automaticity and atrioventricular nodal conduction (1326). This is probably mediated by P2X_{2/3} receptors located on vagal sensory nerve terminals in the left ventricle, supporting the hypothesis that ATP released from ischemic myocytes is a mediator of atropine-sensitive bradyarrhythmias associated with left ventricular myocardial infarction (1911).

5. Skin, muscle, and joints

Ca²⁺ waves in human epidermal keratinocytes mediated by extracellular ATP produce [Ca²⁺]_i elevation in DRG neurons, suggesting a dynamic cross-talk between skin and sensory neurons mediated by extracellular ATP (947).

P2 receptors on the endings of thin fiber muscle afferents play a role in evoking both the metabolic and mechanoreceptor components of the exercise pressor reflex (706). PPADS attenuated the pressor response to contraction of the triceps muscle. ATP has been shown to be an effective stimulant of group IV receptors in mechan-

ically sensitive muscle afferents (1038, 1408). Arterial injection of α,β -meATP in the blood supply of the triceps surae muscle evoked a pressor response that was a reflex localized to the cat hindlimb and was reduced by P2X receptor blockade (1038). In this study, ATP was also shown to enhance the muscle pressor response evoked by mechanically sensitive muscle stretch, which was attenuated by PPADS.

Sensory nerve fibers arising from the trigeminal ganglion supplying the temporomandibular joint have abundant receptors that respond to capsaicin, protons, heat, and ATP; retrograde tracing revealed 25, 41, and 52% of neurons supplying this joint exhibited VR1 and P2X₃ receptors, respectively (785).

6. Inner ear

ATP has been shown to be an auditory afferent neurotransmitter, alongside glutamate (see Ref. 765). There are ~50,000 primary afferent neurons in the human cochlear and about one-half express P2X₂ (or P2X₂ variants) and, debatably, P2X₃ receptors. ATP is released from K⁺-depolarized organ of Corti in a Ca²⁺-dependent manner, and an increase in ATP levels in the endolymph has been demonstrated during noise exposure, perhaps released by exocytosis from the marginal cells of the stria vascularis (1194). The P2 receptor antagonist PPADS attenuated the effects of a moderately intense sound on cochlea mechanics (157). NO enhances the ATP-induced [Ca²⁺]_i increase in outer hair cells (1549). Spiral ganglion neurons, located in the cochlear, convey to the brain stem the acoustic information arising from the mechano-electrical transduction of the inner hair cells express P2X receptors (1897) and are responsive to ATP (491, 814).

7. Nasal organ

Odorant recognition is mediated by olfactory receptors predominantly situated on the microvilli of olfactory receptor neurons in the nasal organ. Nucleotides act via purinoceptors on olfactory neurons as well as sustentacular supporting cells (412, 624, 725). Purinergic receptors appear to play an integral role in signaling acute damage in the olfactory epithelium by airborne pollutants. Damaged cells release ATP, thereby activating purinergic receptors on neighboring sustentacular cells, olfactory receptor neurons, and basal cells, initiating a stress-signaling cascade involving heat shock proteins for neuroprotection (726). The majority of nasal trigeminal neurons lacked P2X₃ receptor-mediated currents but showed P2X₂-mediated responses when stimulated by ATP (424).

8. Taste buds

Taste bud cells and associated sensory nerve fibers express P2 receptors, including P2X₂ and P2X₃ receptor

subunits (153) and P2Y₁ receptors (877). ATP is the key transmitter acting via P2X₂ and P2X₃ receptors on taste receptor cells detecting chemicals in the oral cavity (558). These authors showed that genetic elimination of P2X₂ and P2X₃ receptors abolished responses of the taste nerves, although the nerves remained responsive to touching, temperature, and menthol and reduced responses to sweeteners, glutamate, and bitter substances. They also showed that a bitter mixture containing denatonium and quinine stimulated release of ATP from the taste epithelium. Ectonucleotidases are known to be abundantly present in taste buds (110). Dystonin disruption, produced in mutant mice, resulted in a decrease in the number of vagal and glossopharyngeal sensory neurons and in the number of taste buds as well as in the number of P2X₃ receptor-labeled neurons and their peripheral endings in taste bud epithelium (784). Other papers present data that suggest that P2Y₂ and P2Y₄ receptors also play a dominant role in mediating taste cell responses to ATP and UTP (113, 302, 909). NTPDase2 has been shown to have a dominant presence on type 1 cells in mouse taste papillae (111).

VI. NEUROTRANSMISSION AND NEUROMODULATION IN THE CENTRAL NERVOUS SYSTEM

The actions of adenosine in the CNS have been recognized for many years (see review Refs. 497, 1102, 1343, 1350, 1533, 1597, 1866). However, consideration of the role(s) of ATP in the CNS received less attention until more recently (see Refs. 1, 154, 257, 272, 378, 505, 639, 792, 796, 804, 1117, 1258, 1431). In particular, fast purinergic synaptic transmission has been clearly identified in the brain (890). It was first observed in the medial habenula (506) and has now been described in a number of other areas of the CNS, including spinal cord (102), locus coeruleus (1243), hippocampus (1182, 1299), and somatosensory cortex (1301). Electron microscopic immunocytochemical studies support these functional experiments (see Fig. 6). Although adenosine, following ectoenzymatic breakdown of ATP, is the predominant, presynaptic modulator of transmitter release in the CNS (see Refs. 497, 1422), ATP itself can also act presynaptically (409). A strong case is made for coordinated purinergic regulatory systems in the CNS controlling local network behaviors by regulating the balance between the effects of ATP, adenosine, and ectonucleotides on synaptic transmission (879, 1121). Two examples are given: one showing synergistic modulation of excitatory and inhibitory synaptic inputs in the hippocampus, and the other showing diametrically opposite effects on excitatory transmission in the caudal nucleus of the solitary tract.

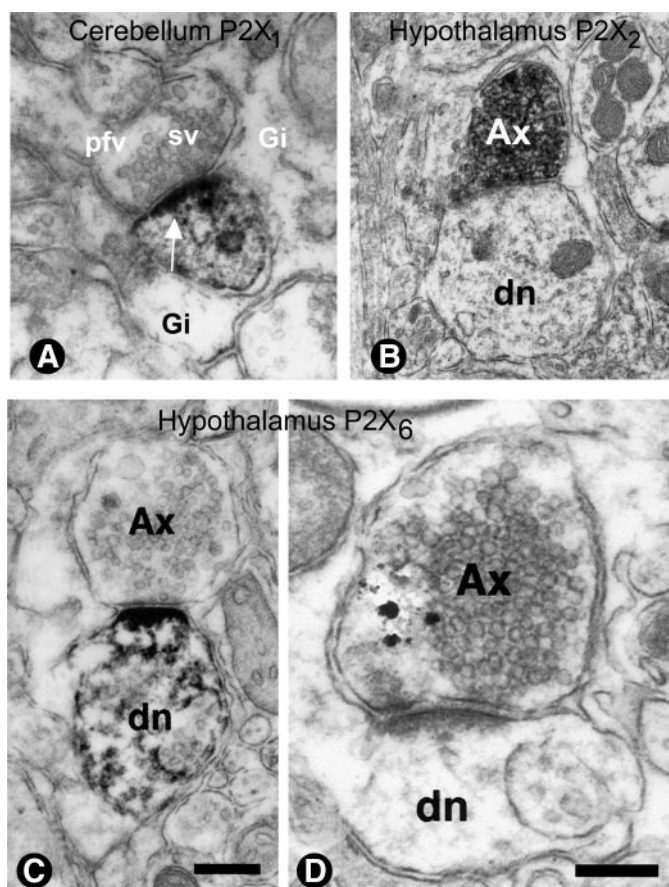


FIG. 6. Electron microscopic immunostaining of P2X receptors in the brain. *A*: molecular layer of rat cerebellum processed for P2X₁ receptor-positive dendritic spines of Purkinje cells involved in the formation of asymmetric axodendritic synapses. A P2X₁ receptor-positive postsynaptic dendritic spine is shown displaying labeling mostly at the postsynaptic density (arrow). Gi, neuroglia processes; pfv, parallel fiber; sv, spherical synaptic vesicles. Magnification $\times 97,000$. [From Loesch and Burnstock (1064) with permission from Springer-Verlag.] *B*: neuropil of supraoptic nucleus (SON) labeled for P2X₂ receptors. Note P2X₂ receptor-labeled presynaptic axon profile adjacent to unlabeled dendrite; also note that obscuring effect of immunoprecipitate in the labeled axon prevents clear identification of synaptic vesicles. Magnification $\times 43,000$. [From Loesch et al. (1067), with permission from Springer-Verlag.] *C*: paraventricular nucleus labeled for P2X₆ receptors by the ExtrAvidin method. An unlabeled axon terminal containing agranular and a few granular vesicles forms a synapse with a P2X₆ receptor-positive dendrite (dn). Note the intense immunodeposit over the postsynaptic density. *D*: paraventricular nucleus labeled for P2X₆ receptors with immunogold-silver method. P2X₆-labeled axon terminal forms an asymmetric synapse with an unlabeled dendrite. dn, dendrite; Ax, axon terminal. Scale bars in *C* and *D* = 0.25 μm . [From Loesch and Burnstock (1066), with permission from Elsevier.]

ATP is present in high concentrations within the brain, varying from ~ 2 mM/kg in the cortex to 4 mM/kg in the putamen and hippocampus (945). Much is now known about the breakdown of ATP released in the CNS (977). Cortex and hippocampus synaptic membranes exhibit higher activities of NTPDase1 and NTPDase2 than cerebellum and medulla oblongata, with ecto-5'-nucleotidases and adenosine deaminase were found in most brain regions.

In situ hybridization of P2 receptor subtype mRNA and immunohistochemistry of receptor subtype proteins have been carried out in recent years to show wide, but heterogeneous, distribution in the CNS of both P2X receptors (292, 864, 1006, 1062, 1064, 1257, 1457, 1896) and P2Y receptors (272, 989, 1172, 1179). P2X₂, P2X₄, and P2X₆ receptors are widespread in the brain and often form heteromultimers. P2X₁ receptors are found in some regions such as cerebellum and P2X₃ receptors in the brain stem. P2X₇ receptors are probably largely prejunctional. P2Y₁ receptors are also abundant and widespread in the brain. The hippocampus expresses all P2X receptor subtypes and P2Y₁, P2Y₂, P2Y₄, P2Y₆, and P2Y₁₂ receptors.

Evidence has been presented that nucleotides can act synergistically with growth factors to regulate trophic events (1228, 1398). However, a recent paper has shown that ATP can also stimulate neurite outgrowth from neuroblastoma cells independent of NGF (991). In addition to P2 receptors and the release of ATP from neurons in the brain, there is abundant evidence for P2 receptors on, and release of ATP from, glial cells, suggesting that both short- and long-term (trophic) neuronal-glial cell interactions are taking place (see sect. vii).

There are many reports of ATP acting as a cotransmitter with classical transmitters in neurons in the CNS (see sect. iiiF). Description of neurotransmission and neuromodulation in the brain stem, hypothalamus, and spinal cord can be found in section vii concerned with CNS control of autonomic function.

A. Cortex

Early studies carried out about purinergic signaling in the cortex have been reviewed in section iiC. Although two earlier papers mentioned some direct excitatory effect of ATP in cortex (1350, 1648), serious attention to these actions rather than those of adenosine did not appear until the 1990s. ATP diphosphohydrolase was shown to be one of the ectoenzymes involved in breakdown of ATP released from rat cortical synaptosomes (117). A novel group of pyrimidine compounds has been shown to act as inhibitors of ATP and ADP hydrolysis by NTPDases in synaptosomes from rat cerebral cortex (323). NTPDases1 and -2 have been purified and characterized from porcine cortex synaptosomes (977).

The expression of P2X₇ receptors in the CNS is hotly debated (see Refs. 45, 1495, 1628). The polymorphic variations in P2X₇ receptor expression might provide an explanation, at least in part, for some of the ambiguous findings (1863). P2X₇ receptors have been identified in rat cortical synaptosomes (1078) and have been claimed to mediate caspase-8/9/3-dependent apoptosis in rat primary cortical neurons (956). A recent study claims that P2X₇ receptors exert a permissive role on the activation of

release-enhancing presynaptic $\alpha 7$ nicotinic receptors coexisting in rat neocortex glutamergic terminals (1322). Evidence has been presented that diadenosine pentaphosphate (Ap₅A) and ATP activate P2X and possibly specific dinucleotide receptors on human cerebrocortical synaptic terminals (1356).

Evidence has also been presented for P2Y receptor-mediated inhibition of NE release in the rat cortex (1802). Release of glutamate from depolarized nerve terminals has been claimed to be inhibited by agonists acting on both P1 and P2Y receptors (131). Release of ATP from cortical synaptosomes is decreased by vesamicol, which also inhibits ACh, but not glutamate release (1484). ATP receptor-mediated Ca²⁺ concentration changes in pyramidal neocortical neurons in rat brain slices from 2-wk-old rats were mediated by both P2X and P2Y receptors (994). Responses of cultured rat cerebral cortical neurons to UTP (1251) indicated the presence of P2Y₂ and/or P2Y₄ receptors. P2Y receptors were identified on synaptosomal membranes from rat cortex (1511). A P2Y receptor from the adult bovine corpus callosum was cloned and characterized and the mRNA identified in the frontal cortex (448). P2Y and muscarinic receptor activation evoke a sustained increase in intracellular calcium in rat neocortical neurons and glial cells, and it was proposed that a common calcium entry pathway was involved (1382). Interaction between P2Y and NMDA receptors in layer V pyramidal neurons of rat prefrontal cortex have been demonstrated (1081). ATP induces postsynaptic gene expression in neuron-neuron synapses via P2Y₁ receptors, which could regulate the acetylcholinesterase (AChE) promoter activity in cultured cortical neurons (1581). P2Y₁ receptors mediate inhibition of both strength and plasticity of glutamatergic synaptic neurotransmission in the rat prefrontal cortex (697). Extracellular ATP upregulates the expression of *egr-1*, *egr-2*, and *egr-3*, members of the early growth response family, in cultured rat primary cortical neurons (1133).

Adenosine has been shown to inhibit release of transmitters from slices of rat and rabbit cerebral cortex, including NE, ACh, GABA, and amino acids, probably involving A₁ and A₃ receptors (197) and for glutamate release A₁ and A_{2A} receptors (1105). Thalamocortical excitation is regulated by presynaptic adenosine (A₁) receptors and provides a mechanism by which increased adenosine levels can directly reduce cortical excitability (566). A high level of endogenous adenosine, which occurs during hypoxia, activates A₃ receptors, which inhibit synaptic potentials in pyramidal cells from the cingulate cortex (733). In vivo imaging of A₁ receptors in the human cortex has been achieved with the use of the selective A₁ antagonist 8-cyclopentyl-3-(3-[¹⁸F]fluoropropyl)-1-propylxanthine (118). Adenosine suppresses GABA_A receptor-mediated responses in rat sacral dorsal commissural neurons (1036). In contrast, P2X receptors can act presynaptically

in olfactory bulbs to enhance the release of glutamate (156). Evidence has been presented for uridine activation of fast transmembrane Ca^{2+} fluxes in rat cortical homogenates (870) and later identification of a uridine-specific binding site in rat cerebrocortical homogenates (962).

B. Hippocampus

There are many papers describing the actions of adenosine via P1 receptors in the hippocampus, including presynaptic modulation with both inhibition and enhancement of transmitter release by acting on A_1 and A_{2A} receptors, respectively (1070, 1421), influencing both LTP and long-term depression (LTD) in CA1 neurons and synaptic plasticity (see Refs. 392, 435, 1421). Presynaptic A_3 receptors have also been implicated in modulation of LTP and LTD (391). Most workers recognize that adenosine is produced following rapid ectoenzymatic breakdown of released ATP in the hippocampus (see Refs. 410, 499). Adenosine inhibits excitatory, but not inhibitory, synaptic transmission by decreasing neurotransmitter release in the rat hippocampus (1937).

A_1 and A_{2A} receptors are coexpressed in pyramidal neurons and colocalized on glutamatergic nerve terminals of the rat hippocampus (1401). Modulation of hippocampal cholinergic, glutamatergic, and GABAergic transmission by ATP is dependent largely on prejunctional A_1 receptors (579, 974, 1116). A_1 receptor-mediated inhibition of glutamate release at rat hippocampal CA3-CA1 synapses is primarily due to inhibition of N-type Ca^{2+} channels (1100). Interactions between adenosine and metabotropic glutamate receptors in rat hippocampal slices have been reported (1545). A_{2A} and mGlu5 receptors are colocalized and mediate synergistic actions and suggest that A_{2A} receptors play a permissive role on mGlu5R receptor-mediated potentiation of NMDA effects in the hippocampus (1690). The physiological features of mossy fiber synapses are due largely to the tonic action of adenosine acting via presynaptic A_1 receptors, which maintain a low basal probability of transmitter release (1174). It has been claimed that A_1 receptors are strategically located on the presynaptic component of the active zone for inhibition of transmitter release as well as in the postsynaptic density to influence NMDA receptor firing and dendritic integration (1401). Activation of A_{2A} receptors facilitates brain-derived neurotrophic factor (BDNF) modulation of synaptic transmission in hippocampal slices (460). Deletion of presynaptic A_1 receptors impairs the recovery for synaptic transmission in the hippocampus after hypoxia (61). Hypoxia leads to a rapid (<90 min) homologous desensitization of A_1 receptor-mediated inhibition of synaptic transmission that is likely to be due to an internalization of A_1 receptors in nerve terminals (374). Lee and Chao (1008) have shown that

purinergic signaling interacts with neurotrophin signaling, by transactivating Trk A and Trk B receptors via A_{2A} receptor stimulation.

In an analysis of the role of ATP as a transmitter in the hippocampus and its role in synaptic plasticity, Wieraszko (1858) concluded that the purinergic system is particularly involved in the long-term maintenance, rather than the initial induction, of LTP. ATP receptor activation can stimulate or inhibit glutamate release from rat hippocampal neurons, and ATP release has been implicated in hippocampal LTP (1859). $P2X_1$, $P2X_{2/3}$, and $P2X_3$ receptors can act presynaptically to facilitate glutamate release, and $P2Y_1$, $P2Y_2$, and $P2Y_4$ receptor activation can inhibit release from hippocampal neurons (1439). Stimulation of Schaffer collaterals of rat and mouse hippocampal slices resulted in release of ATP and an increase in the size of LTP (1859, 1860). There is preferential release of ATP upon high- but not low-frequency stimulation of rat hippocampal slices (410). Acute ATP hydrolysis is required for the regulation of α -amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors at hippocampal synapses; this requirement is selective for AMPA over NMDA receptors and is necessary both for LTP and LTD (1045).

ATP released from presynaptic terminals during burst stimulation (or applied extracellularly) is involved in the induction of LTP and CA1 neurons of guinea pig hippocampus through phosphorylation of extracellular domains of synaptic membrane proteins as the substrate for ectoprotein kinase (591, 1920). Extracellular ATP inhibits release of excitatory glutamate from hippocampal neurons, but stimulates release of inhibitory GABA (799, 805).

Evidence for the presence of a P2Y receptor in hippocampus neurons was presented (790, 1157). ATP inhibited K^+ channels in cultured rat hippocampal neurons through P2Y receptors that showed equipotency to UTP and ATP (1213), suggesting that a $P2Y_2$ or $P2Y_4$ subtype was involved. It was proposed that glutamate releases ATP from hippocampal neurons to act as a neurotransmitter (803). Evidence using P2 receptor antagonists was presented to suggest that both presynaptic and postsynaptic P2 receptors in the hippocampus modulate the release and action of endogenous glutamate (1188). ATP inhibits synaptic release of glutamate by acting on P2Y receptors on pyramidal neurons in hippocampal slices (1143). Presynaptic inhibitory P2 receptors in the hippocampus inhibit calcium oscillations produced by release of glutamate (949). P2 receptor-mediated inhibition of NE release in rat hippocampus has been reported (940). While presynaptic P2Y receptors mediate inhibition of transmitter release, P2X receptors mediate facilitation of transmitter release (409). Activation of $P2Y_1$ receptors induces inhibition of the M-type K^+ current in rat hippocampal pyramidal neurons (555). Examination of the

effect of ATP on the voltage-clamped, dissociated rat hippocampal neurons showed that over 30% possessed P2X receptors (82). ATP can produce facilitation of transmission in rat hippocampal slice neurons, which may require the simultaneous activation of P1 and P2 receptors (1244). Ap₅A enhanced the activity of N-type Ca²⁺ channels in rat CA3 hippocampal neurons (1297).

A purinergic component of the excitatory postsynaptic current (EPSC) was identified mediated by P2X receptors in CA1 neurons of the rat hippocampus; EPSCs, which were blocked by PPADS, were elicited by stimulating the Schaffer collateral at a frequency below 0.2 Hz (1299). Evidence for fast synaptic transmission mediated by P2X receptors in CA3 pyramidal cells of rat hippocampal slice cultures has been reported (1182).

Binding studies have shown mRNA for several P2 receptor subtypes in the hippocampus, including binding to α,β -[³H]meATP (83, 154). Immunolocalization of the P2X₄ receptor was widespread in the hippocampus; immunopositive cells were prominent in the pyramidal cell layer (in interneurons as well as pyramidal cells), scattered through CA1, CA2, and CA3 subfields as well as within the granule cell layer and hilus of the dentate gyrus (1006). P2X₄ receptors are located at the subsynaptic membrane somewhat peripherally to AMPA receptors in the CA1 area of the hippocampus. Experiments with P2X₄ receptor knock-out mice show that LTP at Schaffer collateral synapses is reduced, and ivermectin, which potentiates currents at P2X₄ receptors, had no effect on P2X₄ knock-out mice, but increases LTP in wild-type mice (1575). The authors suggest that calcium entry through subsynaptic P2X₄ receptors during high-frequency stimulation contributes to synaptic strengthening.

Arguments have been presented that ATP may have a role in the protection of the function of the hippocampus from overstimulation by glutamate (799). ATP produces an initial rise and later reduction in serotonin release from perfused rat hippocampus mediated by P2X and P1(A₁) receptors, respectively (1272). Noradrenergic terminals of the rat hippocampus are equipped with presynaptic P2X receptors that facilitate NE release (1307).

There are some exciting data indicating a trophic role for ATP in the hippocampus (1584). It was shown that ATP and its slowly hydrolyzable analogs strongly inhibited neurite outgrowth and also inhibited aggregation of hippocampal neurons; it was suggested that the results indicate that extracellular ATP may be involved in synaptic plasticity through modulation of NCAM-mediated adhesion and neurite outgrowth. Changes in [Ca²⁺]_i during ATP-induced synaptic plasticity in guinea pig hippocampal CA1 neurons have been claimed (1919).

A study of the single-channel properties of P2X receptors in outside-out patches from rat hippocampal granule cells has been carried out that suggests the presence of P2X_{2/4} and/or P2X_{2/6} and/or P2X_{4/6} heteromultimers

(1884). This has been supported by P2X receptor expression studies (1616). P2X₇ receptors have been implicated in the regulation of neurotransmitter release in the rat hippocampus (1628). Activation of presynaptic P2X₇-like receptors depresses mossy fiber-CA3 synaptic transmission through P38 mitogen-activated protein kinase (58). The relatively stable P2X₇ agonist BzATP is enzymatically converted to adenosine in hippocampal slices so that its effects on mossy fiber terminals may be via A₁ rather than P2X₇ receptors (975). A stabilizing effect of extracellular ATP on synaptic efficacy and plasticity has been described in hippocampal pyramidal neurons under hypoxic conditions where there is depletion of intracellular ATP (1109).

ATP-gated presynaptic P2X₂ channels facilitate excitatory transmission onto stratum radiatum interneurons, but not onto CA1 pyramidal neurons (893). This demonstration of preferential expression of functional P2X channels is a novel finding that might have wider physiological implications for purinergic signaling in the brain.

NTPDase2 and functional P2X receptors have been identified on proliferating hippocampal progenitor cells in the dentate gyrus, which may play a role in the control of hippocampal neurogenesis (1565).

ATP-induced [³H]GABA and [³H]glutamate release is absent in P2X₇ receptor knockout mice, suggesting that ATP facilitates GABA and glutamate release by a presynaptic mechanism involving P2X₇ receptors (1308).

C. Cerebellum

A high density of P2X receptor binding was found in the cerebellar cortex (83). Electron-immunocytochemistry showed localization of P2X₁ receptors in subpopulations of synapses on both presynaptic and postsynaptic sites as well as on some astrocyte processes (1064). P2X₄ mRNA was found in the cerebellar cortex in Purkinje, granular, and stellate basket cells and P2X₆ receptor immunoreactivity, which was confined mainly to Purkinje cells (620, 1616). Functional P2X₃ and P2X₇ receptors in rat cerebellar synaptic terminals have also been reported (737). A lack of correlation between glutamate-induced release of ATP and neuronal death in cultured cerebellar neurons was reported (1103).

Cerebellar Purkinje neurons were shown experimentally to have P2Y receptors (918) as well as P2X (probably mainly P2X₂) receptors (620). Patch-clamp studies of dissociated cerebellar neurons revealed P2Y receptor-operated potassium channels (789). There appears to be a molecular interplay between the P2Y₄ receptor and the R1 subunit of the NMDA receptor during glucose deprivation with P2Y₄ receptor involvement in cell death under conditions of metabolism impairment (319).

ATP increased the release of aspartate from cultured cerebellar granule neurons and also potentiated its re-

lease by glutamate; it was concluded that this was consistent with a cotransmitter role of ATP in the cerebellum (1145). This group also showed that a P2 receptor antagonist prevented glutamate-evoked cytotoxicity in these cultured neurons (39).

cDNAs encoding three splice variants of the P2X₂ receptor were isolated from rat cerebellum (1578). Ecto-5'-nucleotidase has been localized on cell membranes in cultures of cerebellar granule cells and also ectophosphorylated protein and ecto-ATPase (1982), consistent with purinergic signaling. Single-channel properties of P2X receptors in rat cerebellar slices suggested that they may be P2X_{4/6} heteromultimer receptors (700). Both ADP and adenosine prevent apoptosis of cultured rat cerebellar granule cells via P2X and A₁ receptors, respectively (1794). In a study by Florenzano et al. (563), it was claimed that cerebellar lesion upregulates P2X₁ and P2X₂ receptors in precerebellar nuclei.

P2Y receptors mediate both short-term presynaptic and long-term postsynaptic enhancement of GABAergic transmission between cerebellar interneurons and Purkinje cells (1481). Coexpression of functional P2X and P2Y receptors has been identified in single cerebellar granule cells (736). Modulation of synaptic activity in Purkinje neurons by ATP has been reviewed recently (442).

ATP γ S recapitulates in cultured cerebellar granule neurons many warning signs of cellular neurodegeneration occurring in vivo, including morphological abnormalities, mitochondrial impairment, free radical generation, and oxidative stress; PPADS can efficiently postpone or prevent the progression of neuronal death in a cell culture model (40).

Both P2Y₁ and P2X₇ receptors induce calcium (calmodulin-dependent protein kinase II) activation in cerebellar granule neurons, although there are differences in subcellular distribution and duration of effects between the two receptor subtypes (1017). The P2X₇ activation was not associated with pore formation, but its abundant presence at synaptic structure suggests a role in synaptic plasticity.

P1(A₁) receptors were identified on cerebellar granule cells (1881), and adenosine was shown to selectively block parallel fiber-mediated synaptic potentials in the rat cerebellar cortex (942) and inhibit Purkinje cell firing and glutamate release from cultured cerebellar neurons (464).

D. Basal Ganglia

In vivo release of adenosine from cat basal ganglia was taken as early support for the existence of purinergic nerves in the brain (96). Autoradiographic labeling of P1(A₂) receptors showed them to be exclusively restricted to the human caudate nucleus, putamen, nucleus

accumbens, and globus pallidus as well as the olfactory tubercle (1111). Adenosine A_{2A} receptor modulation of electrically evoked GABA release from slices of rat globus pallidus was described (1127). A_{2A} receptors also mediate inhibition of the NMDA component of excitatory synaptic currents in rat striatal neurons (1872). However, A_{2A} receptors are located largely outside the active zone at synapses in contrast to the location of hippocampal A_{2A} receptors, which are mostly located in the presynaptic active zone (1402). A_{2A} receptors were also shown to be prominent in dopamine-innervated areas of the basal ganglia (1675), and adenosine-dopamine receptor-receptor interactions have been proposed to be an integrative mechanism for motor stimulation actions in basal ganglia (548). Dopamine D₁, D₂, and D₃ knockout mice showed an increase in A_{2A} receptor binding in the caudate putamen, nucleus accumbens, and olfactory tubercle, while in A_{2A} receptor knockout mice there was an increase in D₂ receptor mRNA in these regions of the basal ganglia (1564). Dopaminergic principal neurons in the ventral tegmental area do not possess somatic P2 receptors, in contrast to peripheral and central noradrenergic neurons (1359).

The extracellular actions of adenosine via P1 receptors on the striatum were the first instance in which active purines were recognized; they were largely involved in presynaptic modulation of release of dopamine, ACh, GABA, and glutamate (607). The P1 receptor subtype involved is predominantly A₁, but A₂ receptors were shown to mediate stimulation of dopamine synthesis (364, 1675). A₁ receptors play a major modulatory role in dopamine and adenosine receptor signaling in the neostriatum (1915). Inactivation of adenosine A_{2A} receptor impairs LTP in the nucleus accumbens without altering basal synaptic transmission (414).

ATP release was demonstrated from affinity-purified rat cholinergic nerve terminals from rat caudate nucleus and adenosine resulting from ectoenzymatic breakdown of ATP, acted on prejunctional A₁ receptors to inhibit ACh release (1426). It was shown that ATP was released from cultured mouse embryonic neostriatal neurons (1952) and that adenosine is produced from extracellular ATP at the striatal cholinergic synapse (822). ATP-evoked potassium current in rat striatal neurons was shown to be mediated by a P2 purinergic receptor (788). ATP increases the extracellular dopamine level in rat striatum through stimulation of P2Y receptors (1963), although it has been claimed to inhibit dopamine release in the neostriatum (1724). Dopamine facilitates activation of P2X receptors by ATP (807). Intra-accumbens injection of 2-MeSATP leads to release of dopamine (928). ATP induces neurotoxicity in vivo in the rat striatum via P2 receptors (1473).

Neostriatal medium-spiny neurons and cholinergic interneurons express P2X₂ and P2Y₁ receptors, but it appears that they only become functional under certain as yet unknown conditions (1512). Accumbal neuronal out-

put, reflected by both dopamine release and neuronal electrical activity, is modulated in a functionally antagonistic manner by P2 and P1 receptor stimulation (968).

E. Midbrain

GABAergic synaptic terminals from rat midbrain exhibit functional P2X and dinucleotide receptors, able to induce GABA secretion (659). Coexistence of ionotropic nucleotidic and nicotinic receptors in isolated synaptic terminals from midbrain has been demonstrated (455). GABA_B receptor-mediated presynaptic potentiation of P2X receptor-mediated responses in rat midbrain synaptosomes has been reported (659). With the use of these synaptosomal preparations, it was also shown that aminergic nerve terminals possess modulatory presynaptic nucleotide and dinucleotide receptors (649). P2X₃ receptors have been identified on rat midbrain presynaptic terminals (455). P2X₇ receptors have been identified immunohistochemically and by Ca²⁺ imaging on midbrain synaptosomes and on axodendritic prolongations of cerebellar granule cells (1156). ATP and the diadenosine polyphosphate Ap₅A induce concentration-dependent glutamate release from synaptosomal populations, which was inhibited by PPADS and Ip₅I, respectively (689). Ap₄A was shown to be active on rat midbrain synaptosomal preparations, probably acting via P2X₁ or P2X₃ receptor subtypes or possibly by another unidentified P2X subtype (1356). Subtypes P2X₁₋₆ were detected in the periaqueductal gray area of the midbrain (1887).

Extracellular ATP increased cytosolic Ca²⁺ concentration on ventral tegmental neurons of rat brain (1611). Stimulation of P2Y₁ receptors in the ventral tegmental area enhances dopaminergic mechanisms *in vivo* (967).

Adenosine mediated presynaptic modulation of glutamatergic transmission in the laterodorsal tegmentum (62). An inhibitory GABAergic feedback projection to the ventral tegmental area is stimulated by adenosine either directly or indirectly via glutamate release (968).

F. Thalamus

Adenosine promotes burst activity in guinea pig geniculocortical neurons (1305). Adenosine can down-regulate inhibitory postsynaptic responses in thalamus and exert antioscillatory effects (1756). Adenosine inhibits synaptic release of GABA and glutamate by stimulation of presynaptic A₁ receptors in the subthalamic nucleus (1550).

P2X receptors have been localized in thalamus using α,β -[³H]meATP binding (154), and P2Y receptors have also been described in thalamic neurons (1157). Nociceptive activity was elicited by electrical stimulation of afferent C-fibers in the sural nerve and recorded from single

neurons in the rat ventrobasal complex of the thalamus; the P2 receptor antagonist Reactive red, administered intrathecally, produced significant reduction of the evoked activity in thalamic neurons (479).

G. Habenula

The first clear demonstration of ATP receptor-mediated fast synaptic currents in the CNS was described in the rat medial habenula (506). These synaptic currents were mimicked by ATP and reversibly blocked by suramin and by α,β -meATP desensitization. The evidence was extended by demonstration of ATP release from an isolated rat habenula preparation during electrical field stimulation (1624, 1796). This group later showed that the projections from the triangular septal and septofimbrial nucleus to the habenula are the major source of ATP in the rat habenula and utilize ATP as a fast transmitter, probably with glutamate as a cotransmitter (1626). It was concluded by another group that the P2X receptor-mediated synaptic currents were the only calcium-permeable fast transmitter-gated currents in these neurons (1430). LTP of glutamatergic synaptic transmission induced by activation of presynaptic P2Y receptors in the rat medial habenula nucleus has also been claimed (1379).

H. Behavioral Studies

While the involvement of purinergic signaling in neurotransmission and neuromodulation in the CNS is now well established, there are relatively few studies of the involvement of purinergic signaling in behavioral pathways, apart from brain stem control of autonomic functions (see sect. vii), although behavioral changes have been reported in pathological situations (see sect. xiB5).

1. Learning and memory

ATP and adenosine are involved in mechanisms of synaptic plasticity and memory formation (410, 1859). ATP coreleased with glutamate induces LTP in CA1 neurons associated with learning and memory (592, 1182, 1929; see also sect. viB). Nanomolar concentrations of ATP induce long-lasting enhancement of LTP in hippocampal neurons; the P2 antagonist suramin inhibited activity of the ectoenzyme apyrase, which has been shown to participate in the mechanisms of memory acquisition (171). It has been suggested that ATP coreleased with glutamate activates CA1 pyramidal hippocampal neurons, allowing calcium to enter postsynaptic cells and thereby inhibiting the effectiveness of NMDA receptors in inducing LTP (1300). Because P2X receptors contribute to synaptic transmission, mainly at low frequencies of stimulation, they may act as a dynamic low-frequency filter,

preventing weak stimuli from inducing LTP and long-lasting changes in synaptic efficacy. Mice lacking the P2X₃ receptor exhibit abnormalities in hippocampal synaptic plasticity, but not in spatial learning (1832).

Large rises in $[Ca^{2+}]_i$ in CA1 neurons induce LTP, but small rises induce LTD (1919). There is expression of functional P2X receptor channels in the axons of CA3 neurons branching to their postsynaptic targets and predominantly in nerve terminals forming synapses with interneurons (893).

It has been shown that ATP analogs can facilitate LTP through P2 receptor activation that triggers adenosine release, leading to activation of P1(A_{2A}) receptors (37), which are claimed to be involved in modulating spatial recognition memory in mice (1823). Activation of adenosine receptors in the posterior cingulate cortex impairs memory retrieval in the rat (1333).

Tetanus-induced heterosynaptic depression in the hippocampus is a key cellular mechanism in neural networks implicated in learning and memory. ATP release from glial cells, degradation to adenosine, and activation of A₁ receptors on Schaffer collaterals appear to underlie heterosynaptic depression (1542). Mice lacking the A₁ receptor have normal spatial learning and plasticity, but they habituate more slowly (644). LTP is impaired in middle-aged rats and provides a possible explanation for memory losses during normal aging and indicate that, with regard to plasticity, different segments of pyramidal neurons age at different rates (1416).

Clearly there are multiple roles for P2 and P1 receptors in relation to learning and memory, but the way that therapeutic manipulation of purinergic mechanisms can be used to improve these functions is still unresolved. Higher order cognitive functions, including learning and memory in the prefrontal cortex, appear to involve P2Y receptor signaling (1874).

2. Sleep and arousal

The hypnotic/sedative (somnogenic) actions of adenosine are well known as are the central stimulant actions of methylxanthine antagonists (see Refs. 114, 500, 538). Adenosine, acting through A₁ receptors, is an endogenous, homeostatic sleep factor, mediating the sleepiness that follows prolonged wakefulness. Perfusion of antisense oligonucleotide to the A₁ receptor in the basal forebrain of the rat confirmed the role of A₁ receptors in promoting sleep (1697), and cyclopentyl-1,3-dimethylxanthine, an A₁ specific antagonist, in wild-type mice inhibited rebound sleep (1638). Sleep deprivation induces an increase in A₁ receptor mRNA in basal forebrain (114). The effect of sleep deprivation on the "righting reflex" in the rat is partially reversed by administration of A₁ and A₂ receptor antagonists (1736). Old rats have higher extracellular levels of adenosine compared with young rats

across the 24-h diurnal sleep cycle, but a reduction and sensitivity of the adenosine receptors may be a contributing factor to the decline in sleep drive in the elderly (1196).

The basal forebrain as well as neurons in the cholinergic laterodorsal tegmental nuclei are essential areas for mediating the sleep-inducing effects of adenosine by inhibition of wake-promoting neurons (60). It has been suggested that adenosine may promote sleep by blocking inhibitory inputs on ventrolateral preoptic area sleep-active neurons (1177). A_{2A} receptors in the subarachnoid space below the rostral forebrain, activating cells in the nucleus accumbens that increase activity of ventrolateral preoptic area neurons, may also play a role in the somnogenic effect of adenosine (1510). The sleep-promoting process induced by the A_{2A} receptor agonist CGS21680 was associated with a decline in the activity of orexin neurons (1503). Direct administration of adenosine into the brain elicits an EEG profile indicative of deep sleep, i.e., an increase in rapid-eye-movement (REM) sleep with a reduction in REM sleep latency, resulting in an increase in total sleep (312). In vivo microdialysis measurements in freely behaving cats showed that adenosine extracellular concentrations in the basal forebrain cholinergic region increased during spontaneous wakefulness and during prolonged wakefulness and declined slowly during recovery sleep (1369). It has been suggested that diurnal and age-related variation of the activity of ecto-5'-nucleotidase in the basal forebrain may underlie the role that adenosine plays in promoting sleep and allowing wakefulness (1089). A functional genetic variation of adenosine deaminase affects the duration and intensity of deep sleep in humans (1415). Adenosine and caffeine modulate circadian rhythms in the Syrian hamster (49), and A₁ receptors regulate the response of the hamster and mouse circadian clock to light (1567).

P2X₂ receptor mRNA and protein are expressed by all hypothalamic hypocretin/orexin neurons and might therefore be involved in the regulation of the functions of orexin associated with arousal and wakefulness (564, 1882). A recent study has identified P2Y₁ and P2Y₄ receptors on histaminergic neurons located on the tuberomammillary nucleus of the posterior hypothalamus that mediate increase firing (1541). These neurons are tonically active during wakefulness, but cease firing during sleep; the authors suggest that excitation of the wake-active tuberomammillary neurons by nucleotides and the lack of adenosine action may be an important factor in sleep-wake regulation.

3. Locomotion

The central inhibitory effects of adenosine on spontaneous locomotor activity of rodents and antagonism by caffeine have been known for some time (e.g., Refs. 105,

1598). Later A_{2A} receptors on the nucleus accumbens were shown to mediate locomotor depression (107). Modulation of striatal A_1 and A_2 receptor-mediated activity induces rotational behavior in response to dopaminergic stimulation in intact rats (1367). Interactions between adenosine and L-type Ca^{2+} channels in the locomotor activity of rat was demonstrated (525). A predominant role for A_1 receptors in the motor-activity effects of acutely administered caffeine in rats has been reported (50). A combination of A_1 and A_{2A} receptor blocking agents induces caffeine-like spontaneous locomotor activity in mice (984).

It has been reported that ATP continuously modulates the cerebellar circuit by increasing the inhibitory input to Purkinje neurons, probably via $P2X_5$ and $P2Y_2$ and/or $P2Y_4$ receptor subtypes, thus decreasing the main cerebellar output activity, which contributes to locomotor coordination (210). $P2X_2$ receptor immunoreactivity in the cerebellum was demonstrated and claimed to be consistent with a role for extracellular ATP acting as a fast transmitter in motor learning and coordination of movement (865). Administration of the P2 receptor agonist 2-MeSATP into the nucleus accumbens of rats raises the extracellular level of dopamine and enhances locomotion (928, 1610). Enhanced motor activity is also produced by the psychostimulant amphetamine, but the P2 receptor antagonist PPADS blocks these motor effects (930). Adult rats trained in a step-down inhibitory avoidance task or submitted to isolated foot-shock showed increased ATP hydrolysis in synaptosomes prepared from the cingulate cortex, suggesting that the ectonucleotidase pathway may be involved in memory consolidation of step-down inhibitory avoidance in the cortex (1332). Inhibitory avoidance training led to decreased ATP diphosphohydrolyase activity in hippocampal synaptosomes, suggesting involvement of this enzyme in the formation of inhibitory avoidance memory (169). Intrahippocampal infusion of suramin, acting either by blocking purinergic neurotransmission or as an inhibitor of ATP degradation, modulated inhibitory avoidance learning in rats (170). The inhibitory avoidance task is associated with a decrease in hippocampal nucleotidase activities in adult male, but not female, rats (1458).

ATP is released during swimming of frog embryos, to activate P2Y receptors and produce an increase in excitability of the spinal motor circuits; while adenosine, produced following the breakdown of ATP, lowers the excitability of the motor circuits (422). It was suggested that a gradually changing balance between the actions of ATP and adenosine underlies the rundown of the motor pattern for swimming in *Xenopus*.

4. Feeding

Adenosine given centrally can result in a decrease in food intake (1024). In a later paper this group showed that

the adenosine agonist N^6 -*R*-phenylisopropyladenosine (*R*-PIA) stimulated feeding in rats; this effect was not blocked by caffeine, but the opioid antagonist naloxone did block *R*-PIA-induced eating (1023).

In the striatum, extracellular ATP and adenosine are involved in the regulation of the feeding-associated mesolimbic neuronal activity in an antagonistic manner (929). The ATP-induced increase in cytosolic Ca^{2+} concentration (1610) and feeding-evoked dopamine release (967) have been demonstrated in the rat nucleus accumbens. PPADS suppresses the feeding-evoked dopamine release in the nucleus accumbens, a brain region regarded as important for the regulation of appetite behavior and reinforcement (928). It has been reported that feeding behavior relies on tonic activation of A_{2A} receptors in the nucleus accumbens in rats (1200). NTPDase3 and 5'-ectonucleotidase regulate the levels of adenosine involved in feeding behavior in rat brain (126). Enhanced food intake after stimulation of hypothalamic $P2Y_1$ receptors in rats has been described recently (927). Expression of $P2Y_1$ receptors in the hypothalamus of the rat is enhanced by reduced food availability (1535).

Neonatal rat handling, a brief separation from the mother in the neonatal period, can lead to increased sweet food consumption in adulthood; this appears to be associated with decreased hydrolysis of AMP in the nucleus accumbens and P1 receptor-mediated modulation of dopamine neurotransmission (1574).

5. Mood and motivation

Adenosine has been reported to interact with the psychotomimetic phencyclidine and with alcohol, both agents being potent mood regulators (see Ref. 1867; see also sect. *xE2*). Striatal A_{2A} receptors appear to be an important mediator of the molecular and behavioral sequelae following administration of the antipsychotic drug haloperidol (1834). There is selective attenuation of psychostimulant-induced behavioral responses in mice lacking A_{2A} receptors (339). Caffeine, a P1 receptor antagonist, has been considered as the most widely used psychologically active drug of benefit for many psychomotor variables, including choice reaction time, mood state, and sensory vigilance (see Refs. 579, 847). Evidence was presented that purinergic stimulation via inosine and hypoxanthine can produce an anxiety response that is related to the benzodiazepine receptor (1814). Mice lacking the A_1 receptor showed signs of increased anxiety (839). Stimulation of $P2Y_1$ receptors causes anxiolytic-like effects, which appear to involve $P2Y_1$ receptor-mediated NO production (926). An antidepressant effect of adenosine has been reported in mice, apparently involving A_1 and A_{2A} receptors (875; see sect. *xIB5*). The inhibitory action of dilazep on clonidine-induced aggressive behavior was claimed to be substantially attributed to central

purinoceptor stimulation (1761). Suramin blocked the conditioned fear response in a rat model, suggesting that P2 receptors might be involved in fear behavior (1986). A₁ receptor activation selectively impairs the acquisition of fear conditioning in rats (386). Reduced adenosinergic activity, mostly at A₁ receptors, is associated with the complex network of changes in neurotransmitter pathways related to manic behavior (1088). An A_{2A} receptor genetic polymorphism has been implicated in "panic disorder."

P2 receptors of the mesolimbic-mesocortical system, probably of the P2Y₁ subtype, are involved in the release of transmitters such as dopamine and glutamate, which are responsible for the generation and pattern of the behavioral outcome after motivation-related stimuli (970). Antagonism of A_{2A} receptors by KW-6002 given systemically enhances motor and motivational responses in the rat (1266). Evidence from A_{2A} receptor knockout mice suggests that A_{2A} receptors are involved in goal-directed behavior (1564).

VII. CENTRAL CONTROL OF AUTONOMIC FUNCTION

Research into the central control of autonomic function by purinergic signaling has attracted particular attention in recent years. Furthermore, since adenosine, rather than ATP, was considered for many years to be the principal receptor present in the brain, the early papers concerned with central autonomic control were largely concerned with the effects of adenosine on P1 receptors, but there are more recent studies of the involvement of P2 receptors (664, 1605, 1926).

While the main areas of the brain concerned with control of autonomic function are the brain stem and hypothalamus, the prefrontal cortex is implicated in the integration of sensory, limbic, and autonomic information (see Ref. 679). However, no studies into the possible involvement of purinergic signaling by the prefrontal cortex appear to have been undertaken yet.

A. Ventrolateral Medulla

The ventrolateral medulla (VLM) contains a network of respiratory neurons that are responsible for the generation and shaping of respiratory rhythm; it also functions as a chemoreceptive area mediating the ventilating response to hypercapnia. Evidence has been presented that ATP acting on P2X₂ receptors expressed in VLM neurons influences these functions (665).

Iontophoretic application of ATP excited the spinal cord-projection neurons in the rostral VLM (RVLM) of the medulla oblongata causing powerful vasopressor actions, a response that was mimicked and then blocked by α , β -

meATP as well as by suramin (1668). A further study suggested that two P2X receptor subtypes might be present in RVLM neurons, one sensitive to both ATP and α , β -meATP and the other sensitive to ATP, but not to α , β -meATP (1393). Activation of P2X receptors in the VLM was shown to be capable of producing marked excitation of both sympathoexcitatory and sympathoinhibitory neurons (761). However, P2Y as well as P2X receptors appear to be involved in neural activity in the RVLM (1393). Evidence was presented to suggest that CO₂-evoked changes in respiration are mediated, at least in part, by P2X receptors in the retrofacial area of the VLM (1705). CO₂-P2X-mediated actions were observed only in inspiratory neurons that have purinoceptors with pH sensitivity (characteristic of the P2X₂ receptor subtype) that could account for the actions of CO₂ in modifying ventilatory activity. Not surprisingly, adenosine was shown to be a neuromodulator in the RVLM (1704). It has been shown that a high percentage of NOS-immunoreactive neurons in the RVLM and supraoptic nucleus (SON) of the hypothalamus are also P2X₂ receptor immunoreactive (1927). During hypoxia, release of ATP in the VLM plays an important role in the hypoxic ventilatory response in rats (664, 667, 668). It was suggested that during sustained hypoxia, the central respiratory drive may partially depend on a balance between the excitatory action of ATP and the inhibiting action of adenosine in the ventral respiratory column. It was proposed that modulation of respiratory output induced by adenosine was due both to a decrease in synaptic transmission in respiration-related neurons via presynaptic A₁ receptors and inactivation, via membrane hyperpolarization of medullary expiratory neurons by postsynaptic A₁ receptors (735). A_{2A} receptor binding studies showed localization in several brain stem regions, including RVLM, nucleus tractus solitarius (NTS), and dorsal vagal motor neurons, involved in autonomic function, consistent with the idea that adenosine acts as a neuromodulator of a variety of cardiorespiratory reflexes (1706). P1(A_{2A}) receptors that are expressed by GABAergic neurons in the ventral and ventrolateral medulla are likely to play a role in mediating adenosine-induced respiratory depression (1946).

Intrathecal application of P2X receptor agonists and antagonists indicate that P2X₃ or P2X_{2/3} receptors on the trigeminal primary afferent terminals in the medullary dorsal horn (trigeminal subnucleus caudalis) enhance trigeminal nociceptive transmission (356, 769), perhaps by increasing glutaminergic neurotransmission (831).

B. Trigeminal Mesencephalic Nucleus

Although the trigeminal mesencephalic nucleus (MNV) is located in the CNS, it contains cell bodies of primary afferent neurons that relay proprioceptive infor-

mation exclusively. The MNV is known to contain mRNA for P2X₂, P2X₄, P2X₅, and P2X₆ subtypes (378, 864). With in situ hybridization studies, higher levels of mRNA for P2X₅ were found in this nucleus than in any other brain area (230). ATP-gated ion channels (P2X receptors) were described in rat trigeminal MNV proprioceptive neurons from whole cell and outside-out patch-clamp recording (895, 1318), possibly mediated by P2X₅ receptor homomultimers and P2X_{2/5} heteromultimers (1318). It has been suggested that in the MNV there is ATP receptor-mediated enhancement of fast excitatory glutamate release onto trigeminal mesencephalic motor nucleus neurons (894).

C. Area Postrema

Injection of adenosine into the area postrema produced decreased heart rate and systolic and diastolic blood pressure. Dense areas of P2X₂ receptor immunoreactivity were demonstrated in the rat area postrema (69).

D. Locus Coeruleus

There were early reports of modulation of neurons in the locus coeruleus (LC) by adenosine (1548, 1689). The first report of the action (depolarization) of ATP on P2 receptors in LC was by Harms et al. (710), and later papers examined the ionic mechanism and receptor characterization of these responses (794, 1115, 1551). α,β -MeATP and α,β -methylene ADP (α,β -meADP) were shown to increase the firing rate of rat LC neurons (1497). Both P2X and P2Y receptors are present on LC neurons (585, 1497). Intracellular recordings from slices of rat LC led to the suggestion that ATP may be released either as the sole transmitter from purinergic neurons terminating in the LC or as a cotransmitter with NE from recurrent axon collaterals or dendrites of the LC neurons themselves (1243), the latter proposal being supported experimentally in a later paper (1360). Microinjection of ATP or α,β -meATP into LC (and periaqueductal gray matter) led to changes in bladder function and arterial blood pressure (1436). Purinergic modulation of cardiovascular function in the rat LC involves a functional interaction between tonically active purinergic and noradrenergic systems (1928).

E. Nucleus Tractus Solitarius

The NTS (particularly neurons in the caudal NTS) is a central relay station for viscerosensory information to respiratory, cardiovascular, and digestive neuronal networks. Extracellular purines have been claimed to be the primary mediators signaling emergency changes in the internal environment in the CNS. NTS is a major integra-

tive center in the brain stem that is involved in reflex control of the cardiovascular system; stimulation of P2X receptors in the NTS evokes hypotension with decreases in both cardiac output and total peripheral resistance (923). Injection of adenosine into the NTS produced dose-related decreases in heart rate and systolic and diastolic blood pressures (108, 1729). NTS A_{2A} receptor activation elicits hindlimb vasodilatation (925). ATP and its slowly degradable analog, β,γ -meATP, also produced dose-related potent vasodepressor and bradycardic effects, suggesting that P2 as well as P1 receptors were involved, although P1 receptor antagonists substantially reduced the cardiovascular effects of both ATP and adenosine. The effects of adenosine were shown to be due to its neuromodulatory actions (1187, 1706). Evidence has been presented implicating an interaction between NO and adenosine in NTS cardiovascular regulation (1063). Stimulation of A_{2A} receptors in NTS decreases mean arterial pressure, heart rate, and renal sympathetic nerve activity (1530). A₁ and A_{2A} receptors have counteracting effects on hindlimb vasculature (1128).

Patch-clamp studies of neurons dissociated from rat NTS revealed P2 receptor-mediated responses (1749) and microinjection of P2 receptor agonists into the subpostremal NTS in anesthetized rats produced reduction of arterial blood pressure (523) probably via a P2X₁ or P2X₃ receptor subtype, since α,β -meATP was particularly potent. It was suggested that the actions of ATP and adenosine in the NTS may be functionally linked to selectively coordinate the regulation of regional vasomotor tone (108).

Purines applied in the NTS have been shown to affect baroreceptor and cardiorespiratory functions (1348, 1530). Microinjections into the caudal NTS of anesthetized spontaneously breathing cats showed α,β -meATP elicited a distinct pattern of cardiorespiratory response, namely, dose-related decrease in tidal volume and respiratory minute volume; at higher doses a pronounced apnea was produced (106). This suggested that a P2X receptor was present, perhaps involved in the processing of sensation from pulmonary receptors related to the Breuer-Hering and pulmonary C-fiber reflexes. Impaired arterial baroreflex regulation of heart rate after blockade of P2 receptors in the NTS has been reported (1530). Microinjection of ATP into caudal NTS of awake rats produces respiratory responses, but not the sympathoexcitatory component of the chemoreflex (51). It has been suggested that caudal commissural NTS P2 receptors play a role in the neurotransmission of the parasympathetic (bradycardic) component of the chemoreceptor reflex (1320).

Activation of P2X and P1(A_{2A}) receptors in the NTS elicits differential control of lumbar and renal sympathetic nerve activity, and in a later paper from this group, it was concluded that the fast responses to stimulation of

NTS P2X receptors were mediated via glutamatergic ionotropic mechanisms, whereas the slow responses to stimulation of NTS P2X and A_{2A} receptors were not (1530).

The immunohistochemical distribution of P2X receptor subtypes in the NTS of the rat has been described (1925). Colocalization of P2X₂ and P2X₃ immunoreactivity has been described in the NTS (1811). At the electron microscope level, P2X₃ receptor-positive boutons have been shown to synapse on dendrites and cell bodies and have complex synaptic relationships with other axon terminals and dendrites (1062). P2X₂ receptors have been localized presynaptically in vagal afferent fibers in rat NTS (70). A whole cell patch-clamp study of neurons in the caudal NTS led to the conclusion that ATP activates 1) presynaptic P1(A₁) receptors after breakdown to adenosine, reducing evoked release of glutamate from the primary afferent nerve terminals, and 2) presynaptic P2X receptors on the axon terminals of intrinsic excitatory caudal NTS neurons, facilitating spontaneous release of glutamate (880).

Purinergic and vanilloid receptor activation releases glutamate from separate cranial afferent terminals in the NTS corresponding to myelinated and unmyelinated pathways in the NTS; ATP probably activates P2X₃ receptors on vagal afferents (834).

It has been shown that microinjection of ATP into NTS of awake rats produced pressor and bradycardic responses by independent mechanisms: activation of the parasympathetic bradycardic component appears to involve interaction of P2 and excitatory amino acid receptors, whereas the pressor response was not affected by blockade of receptors to ATP or adenosine (437). In a later study by this group with awake rats, they showed that microinjection of ATP into different subregions of the NTS produces a diverse pattern of hemodynamic and respiratory responses (52). With low doses of P2X receptor agonist into the NTS, bradycardia is mediated via sympathetic withdrawal, whereas at high doses, both sympathetic and parasympathetic components contribute similarly to bradycardia; only the sympathetic component of bradycardia contributes significantly to the hypotension induced by NTS P2X receptor stimulation (924).

Evidence has been presented that the major mechanism of the NTS network excitation by ATP is by way of triggering Ca²⁺-dependent exocytosis of glutamate, but not that of GABA, by Ca²⁺ entry through presynaptic P2 receptor activation (1555).

F. Motor and Sensory Nuclei

P1(A₁) adenosine receptor agonists presynaptically inhibit both GABAergic and glutamatergic synaptic transmission in periaqueductal gray neurons (77). Adenosine suppresses excitatory glutamatergic inputs to rat hypoglossal motoneurons (128).

The mRNA for P2X₄ and P2X₆ receptors as well as three P2X₂ receptor subunit isoforms has been identified in the hypoglossal nucleus, and this was taken to indicate modulation of inspiratory hypoglossal activity and perhaps a general role in modulatory motor outflow in the CNS (378, 600). A potentially important role for P2 receptor synaptic signaling in respiratory motor control is suggested by the multiple physiological effects of ATP in hypoglossal activity associated with the presence of P2X₂, P2X₄, and P2X₆ receptor mRNA in nucleus ambiguus and the hypoglossal nucleus (378, 600). Presynaptic P2X₇-like receptors mediate enhanced excitatory synaptic transmission to hypoglossal motor neurons (808).

Evidence for multiple P2X and P2Y subtypes in the rat medial vestibular nucleus has been presented (352). A P2Y receptor subtype activated by ADP was identified in medulla neurons isolated from neonatal rat brain (791), perhaps, with hindsight, P2Y₁, P2Y₁₂, or P2Y₁₃ receptors.

The actions of ATP and ACh were examined with patch-clamp recording on dissociated preganglionic neurons in the dorsal motor nucleus of the vagus (DMV); the results suggested that these neurons functionally colocalized nicotinic and P2X receptors (1198). Over 90% of the preganglionic neurons in this nucleus respond to ATP, and RT-PCR showed mRNA in the DMV encoding P2X₂ and P2X₄ receptors; it was suggested that the functional receptors expressed in DMV neurons are characterized mainly by P2X₂ and P2X_{2/6} subtypes (1752). Dense areas of P2X₂ receptor immunoreactivity were described on the dorsal vagal complex (69). An electromicroscope immunocytochemical study has shown P2X₄ receptors expressed by both neurons and glia in the rat dorsal vagal complex (67). The complex effects of ATP on respiratory phrenic motor neuron output, in conjunction with the rich expression of ATP receptors on phrenic motor neurons, suggest that purinergic signaling plays an important role in controlling motor outflow from the CNS (1151).

P2X receptors are expressed in the medial nucleus of the trapezoid body of the auditory brain stem where they act to facilitate transmitter release in the superior olivary complex (1838). Although ATP potentiates release at both excitatory and inhibitory synapses, it does so via different P2X receptor subtypes expressed at different locations: P2X₃ receptors on cell bodies or axons of excitatory pathways and P2X₁ receptors on the presynaptic terminals of inhibitory pathways. A₁ rather than P2X receptors have been implicated during high-frequency glutamatergic synaptic transmission in the calyx of Held (1883). P2 receptors modulate excitability, but do not mediate pH sensitivity of respiratory chemoreceptors in the retrotrapezoid nucleus on the ventral surface of the brain stem (1190).

G. Hypothalamus

ATP and α, β -meATP excite neurosecretory vasopressin cells in the SON, an effect blocked by suramin (430). This was claimed to be the first demonstration of a specific physiological role for central purinergic signaling, i.e., regulation of secretion of the neurohormone vasopressin. Suramin did not block the excitatory effect of locally applied NE on vasopressin cells, but did block excitation produced by vagus nerve stimulation. The magnocellular neurons of the supraoptic and paraventricular nuclei receive a dense plexus of fibers originating from noradrenergic neurons in the VLM. Although NE-containing neurons of the caudal medulla provide a direct excitatory input to supraoptic vasopressin cells, they do not use NE as their primary transmitter; ATP was shown to be acting as a cotransmitter with NE in these neurons (235). Corelease of ATP and NE from superfused rat hypothalamic slices was also demonstrated by Sperlágh et al. (1626), although it was questioned whether they were released from the same nerve endings. However, further support for cotransmitter release of ATP with NE at synapses in the hypothalamus comes from evidence that purinergic and adrenergic agonists synergize when stimulating vasopressin and oxytocin release (867). Candidates for coreleased transmitters in NE-containing neurons include SP and NPY as well as ATP, and it has been proposed that SP and NPY differentially potentiate ATP- and NE-stimulated vasopressin and oxytocin release (868). Purinergic and GABAergic cotransmission has also been claimed in the lateral hypothalamus of the chick embryo (835) with cholinergic modulation of the cotransmitter release (836). Evidence has been presented that ATP may be released from magnocellular neurons (1727).

A study of the effects of ATP in increasing $[Ca^{2+}]_i$ in cultured rat hypothalamic neurons was taken to support the action of ATP as an excitatory neurotransmitter (345). Excitatory effects of ATP via P2X receptors in acutely dissociated ventromedial hypothalamic neurons have also been described (1609). A role for adenosine A_1 receptors in mediating cardiovascular changes evoked during stimulation of the hypothalamic defense area has been postulated (429). Application of ATP and UTP (but not adenosine) produced TTX-insensitive depolarizations accompanied by increases in input conductance in supraoptic magnocellular neurosecretory cells; both P2X and P2Y receptors have been suggested to be involved (744).

Ultrastructural localization of both P2X₂ (1067) and P2X₆ (1066) receptor immunoreactivity at both pre- and postsynaptic sites in the rat hypothalamo-neurohypophysial system has been described. Purinergic regulation of stimulus-secretion coupling in the neurohypophysis has been reviewed (1726). From a study of the expression of P2X receptor subtypes in the SON using RT-PCR, in situ hybridization, Ca^{2+} imaging, and whole cell patch-clamp

techniques, it was concluded that P2X₃ and P2X₄ receptors were predominant, but that P2X₇ receptors were also present (1552). A recent study has shown that P2X₅ receptors are expressed on neurons containing vasopressin and NOS in the rat hypothalamus (1905).

It has been suggested that ATP, cosecreted with vasopressin and oxytocin, may play a key role in the regulation of stimulus-secretion coupling in the neurohypophysis (1625) by acting through P2X₂ receptors increasing arginine vasopressin (AVP) release, and after breakdown to adenosine, acting via P1(A_1) receptors (inhibiting N-type Ca^{2+} channels) to decrease neuropeptide release (1821). Adenosine was also shown to modulate activity in supraoptic neurons by inhibiting N-type Ca^{2+} channels via A_1 receptors (1254). Evidence for the involvement of purinergic signaling in hypothalamus and brain stem nuclei in body temperature regulation has been presented (669).

Early studies of the roles of adenosine in the hypothalamus have been reviewed (272). Presynaptic P1 receptors mediate inhibition of GABA release in suprachiasmatic and arcuate nucleus neurons. Adenosine-induced presynaptic inhibition of inhibitory postsynaptic currents (IPSCs) and EPSCs in rat hypothalamus SON neurons via A_1 receptors indicates inhibition of release of both GABA and glutamate. Release of 3H -labeled nucleosides from [3H]adenine-labeled hypothalamic synaptosomes was first described in 1979. Adenosine deaminase-containing neurons in the posterior hypothalamus innervate mesencephalic primary sensory neurons, perhaps indicating purinergic control of jaw movements.

A hypothalamic role has been suggested for extracellular ATP to facilitate copper uptake and copper stimulation of the release of luteinizing hormone-releasing hormone (LHRH) from median eminence, via an interaction with purinergic receptors (104). The hypothalamic supra-chiasmatic nucleus (SCN) is regarded as the site of the endogenous biological clock controlling mammalian circadian rhythms. Long-term communication between glial cells, reflected by waves of fluorescence indicating Ca^{2+} movements, probably via gap junctions, can be induced by ATP, as well as by glutamate and 5-HT (1767). ATP releases LHRH from isolated hypothalamic granules (297).

ATP injected into the paraventricular nucleus stimulates release of AVP resulting in antidiuretic action through renal AVP (V_2) receptors, and in a later study this group showed that ATP (but not ADP, AMP, or adenosine) injected into the SON also decreased urine outflow (1183). Stimulation of the hypothalamic defense area produces autonomic responses that include papillary dilatation, piloerection, tachypnea, tachycardia, and a marked pressor response.

LHRH is released from the hypothalamus in pulses at hourly intervals, which is essential for the maintenance of

normal reproductive function. Studies of an *in vivo* culture preparation of LHRH neurons show that ATP stimulates LHRH release, probably via P2X₂ and P2X₄ receptor subtypes, and may be involved in synchronization of the Ca²⁺ oscillations that appear to underlie the pulsatile release of LHRH (1694). The authors also speculate that glial cells expressing P2Y₁ and P2Y₂ receptors may also participate in this process.

ATP-stimulated vasopressin release from hypothalamo-neurohypophyseal explants is terminated partly by P2 receptor desensitization and partly by ectoenzyme degradation of ATP to adenosine (1604). ATP and the α_1 -adrenoceptor agonist phenylephrine evoke synergistic stimulation of vasopressin and oxytocin release from the hypothalamo-neurohypophysial systems, and the authors speculate that this allows for a sustained elevation of vasopressin release in response to extended stimuli such as severe hemorrhage, chronic hypotension, or congestive heart failure (1605).

P2X₁₋₆ receptor subunits are present on paraventricular nucleus neurons projecting to the RVLM in the rat, suggesting a role for ATP on the paraventricular nucleus in the regulation of sympathetic nerve activity (327).

H. Spinal Cord

Spinal circuits, spinal afferent influx, and descending influences from brain stem and hypothalamus work together in the integrative activities of the preganglionic sympathetic neurons, which regulate the activity on many organs (824).

There was early identification of dense areas of acid phosphatase and 5'-nucleotidase activity in the substantia gelatinosa of the spinal cords of rats and mice, and the possible implication for purinergic transmission was raised (1672). P1 (A₁ and A₂) receptors on neurons in the dorsal and ventral spinal cord mediate modulation of neuronal activity by adenosine (358, 628, 1330). Adenosine reduces glutamate release from rat spinal synaptosomes (1040).

Excitation of dorsal horn neurons by ATP was also recognized early (see sect. II C) and described in more detail later (1039, 1410, 1489). ATP-evoked increases in intracellular calcium were demonstrated in both neurons and glia of the dorsal spinal cord (1491). It was later shown that the ATP-evoked release of Ca²⁺ from astrocytes was via the PLC- β /IP₃ pathway (1492), suggesting mediation via a P2Y receptor. It was proposed that ATP released in synaptic regions acts as a synaptic modulator by augmenting the actions of excitatory amino acids (1037). ATP was also shown to inhibit slow depolarization via P2Y receptors in substantia gelatinosa neurons (1939). Properties of P2Y receptors in *Xenopus* spinal neurons

related to motor pattern generation have been reported (220). A recent study has identified P2Y₁ and P2Y₄ receptor mRNA in subpopulations of dorsal horn neurons, whereas motor neurons in the ventral horn expressed P2Y₄ and P2Y₆ receptor mRNA (939). In addition, astrocytes in the gray matter expressed P2Y₁ receptor mRNA and microglia throughout the spinal cord expressed P2Y₁₂ receptor mRNA.

mRNA for P2X₂, P2X₄, and P2X₆ receptors have been identified within spinal motor nuclei (378). P2X₃ immunoreactivity is apparent on the axon terminals of DRG neurons that extend across the entire mediolateral extent of inner lamina II of the dorsal horn (188, 686, 1208). The immunolabeled nerve profiles in lamina II for P2X₃ receptors are located largely on terminals with ultrastructural characteristics of sensory afferent terminals (1062). In contrast, although P2X₂ immunoreactivity is most prominent in lamina II, it is also seen in deeper layers, and only rarely overlaps with P2X₃ immunoreactivity (1811). Autoradiography of α, β -[³H]meATP showed strong binding in medulla oblongata and spinal cord of the rat (1743). At central terminals of primary afferent neurons, ATP has been shown to act either presynaptically facilitating glutamate release (687, 1039, 1208) or postsynaptically (102, 608, 1037). ATP facilitates spontaneous glycinergic IPSCs in neurons from rat substantia gelatinosa mechanically dissociated from the dorsal horn (1418), and P2X receptors are also expressed on glycinergic presynaptic nerve terminals (823). Distinct subtypes of P2X receptors have been shown to be functionally expressed at pre- and postsynaptic sites in lamina V neurons in rat dorsal spinal cord, and it was suggested that purinergic signaling in deep dorsal horn neurons becomes more important during postnatal development (1561; see sect. xA1).

ATP has been shown to be released from dorsal and ventral spinal cord synaptosomes (1506, 1856). Morphine and capsaicin release purines from capsaicin-sensitive primary afferent nerve terminals in the spinal cord (1676).

Within the spinal cord, P2X receptors are present in a subpopulation of dorsal horn neurons (102). ATP is coreleased with GABA (837). In addition to acting as a fast excitatory synaptic transmitter, ATP facilitates excitatory transmission by increasing glutamate release and enhances inhibitory neurotransmission mediated by both GABA and glycine (779, 1418). P2X₃ receptors are involved in transient modulation of glutamate release in lamina II of the spinal cord, but a different P2X receptor subtype (perhaps P2X_{1/5} or P2X_{4/6}) was involved in long-lasting modulation in lamina V (1211). The authors concluded that differential modulation of sensory inputs into different sensory regions by P2X receptor subtypes represents an important mechanism of sensory processing in the spinal cord dorsal horn. There is potentiation of inhibitory glycinergic neurotransmission by Zn²⁺ and a syn-

ergistic interplay between presynaptic P2X₂ and postsynaptic glycine receptors (1003).

In the ventral horn, almost all large cholinergic COOH terminals contacting motoneurons (91%) show P2X₇ receptor immunoreactivity, while only ~32% of the motor axon terminals in the ventral horn are P2X₇ receptor immunoreactive (449). This suggests that distinct populations of synapses involved in spinal cord motor control circuits may be differentially regulated by the activation of P2X₇ receptors. Blockade of P2X receptors in the dorsal horn with PPADS attenuates the cardiovascular "exercise pressor reflex" to activation of muscle afferents, while stimulation of P2X receptors enhances the reflex response (619).

VIII. NEURON-GLIA INTERACTIONS

Purinergic signaling is emerging as a major means of integrating functional activity between neurons, glial, and vascular cells in the nervous system. These interactions mediate effects of neural activity in development and in association with neurodegeneration, myelination, inflammation, and cancer (see Refs. 4, 272, 552, 1226 and the recent Novartis Foundation Symposium 276 devoted to "Purinergic Signaling in Neuron-Glia Interactions," 2006).

New findings from purinergic research began to converge with glial research as it became more widely appreciated that ATP was coreleased from synaptic vesicles and thus accessible to perisynaptic glia. Receptor expression and pharmacological studies revealed a broad range of purinergic receptors in all major classes of glia, including Schwann cells in the PNS, oligodendrocytes, astrocytes, and microglia in the CNS. This common currency for cell-cell communication opened the possibility of an intercellular signaling system that could unite glia and neurons functionally.

ATP release from axons, dendrites, cell bodies of neurons, and from glia, by membrane channels and vesicular exocytosis, further expands the potential functional significance of purinergic signaling in the brain. It has also been suggested recently that P2X₇ receptor pores may directly mediate efflux of cytosolic ATP, glutamate, and GABA from glial cells in the CNS (483). In addition to its rapid neurotransmitter-like action in intracellular signaling for neurons and glia, it became evident that ATP could also act as a growth and trophic factor, altering the development of neurons (1158) and glia (1226) by regulating the two most important second messengers: cytoplasmic calcium and cAMP. Moreover, the release of ATP by neural impulse activity provides a mechanism linking functional activity in neural circuits to growth and differentiation of nervous system cells. How development is regulated by changes in expression of purinergic receptors and ectoenzymes controlling ATP availability is only

beginning to be explored. Strikingly different actions such as mitogenesis and apoptosis might be induced depending on the functional state of glial cells, the expression of selective receptor subtypes, and the presence of multiple receptors on the same cells. Interactions between purinergic receptors and growth factor receptors can be synergistic, as in astrocytes (1226), or antagonistic, as in Schwann cells (1639).

P2Y₂ and P2Y₄ receptors are strongly expressed in glial endfeet apposed to blood vessel walls (1289, 1576). Glial cells dilate and constrict blood vessels (1192), and light-evoked vasoactivity was blocked when neuron-to-glia signaling was interrupted by a P2 receptor antagonist (1146). Astrocyte-endothelial cell calcium signals are conveyed by two signaling pathways (191). Presumably activation of P2Y receptors participates in cerebrovascular mechanisms regulating blood-brain barrier, blood flow, metabolic trafficking, or water homeostasis (943, 1576, 1985).

A. P1 and P2 Receptors on Glial Cells

Multiple P1 and P2 receptor subtypes are expressed by astrocytes, oligodendrocytes, microglia, Müller cells, and enteric glial cells (142, 168, 292, 552; Table 4).

Adenosine stimulates glutamate release from astrocytes via A_{2A} receptors (1250). A₃ receptors mediate chemokine CCL2 synthesis in cultured mouse astrocytes (1878).

Astrocytes in the cortex and cerebellum express P2Y₁₃ as well as P2Y₁ and P2X₂ receptors (314). Astrocytes and microglia express many purinergic receptors, but as with myelinating glia, the patterns of expression are complex and can change with physiological and developmental state. Many glial cells coexpress multiple types of P1 and P2 receptors, but there can be considerable heterogeneity in expression patterns among individual cells. NTPDase2 is the dominant ectonucleotidase expressed by rat astrocytes (1871). Electron microscopic immunohistochemistry allows us to distinguish the localization of P2 receptors at pre- and postsynaptic sites as well as on glial cells (see Refs. 1064, 1067).

ATP participates in both short-term calcium signaling events and in long-term proliferation, differentiation, and death of glia (395). Both adenosine and ATP induce astroglial cell proliferation and the formation of reactive astrocytes, as demonstrated by increased expression of the astroglial specific marker glial fibrillary acidic protein (GFAP) and elongation of GFAP-positive processes (1226). It has been suggested that, through the activation of distinct membrane receptors, ATP and basic fibroblast growth factor (bFGF) signals merge at the mitogen-activated protein kinase cascade and that this integration may underlie the synergistic interactions of ATP and bFGF in

TABLE 4. *Purinergic receptors on glial cells*

	Adenosine				ATP (Ionotropic)							ATP (Metabotropic)							
	A ₁	A _{2A}	A _{2B}	A ₃	P _{2X} ₁	P _{2X} ₂	P _{2X} ₃	P _{2X} ₄	P _{2X} ₅	P _{2X} ₆	P _{2X} ₇	P _{2Y} ₁	P _{2Y} ₂	P _{2Y} ₄	P _{2Y} ₆	P _{2Y} ₁₁	P _{2Y} ₁₂	P _{2Y} ₁₃	P _{2Y} ₁₄
Astrocyte	R,P,F	F	F	F	R,P,F	R,P,F	R,P,F	R,P,F	R,F	R,P	R,P	R,P,F	R,F	R,F	R,F		F		F
Müller (eye)					R			R	R										
Enteric glia											P		F	F					
Schwann																			
Myelin											F		F						
Nonmyelin		R,P,F	R								P,F	F	F						
Terminal	F												F						
Oligodendrocyte																			
Progenitor	R	R	R	R							F	F	F	F	F	F		F	
Promyelin																			
Myelin	P,F																		
Microglia	F	F	F	F			R,P,F	P	P	P,F	R,F	F	R,F	R,F			R,F	R	

R, mRNA; P, protein; F, functional evidence. Functional evidence includes calcium imaging, protein kinase activation, responses to selective agonists and antagonists, and electrophysiological studies. Note: Full references to the evidence for mRNA and protein as well as functional evidence for receptor subtypes on the different glial cells can be found in Reference 552. [From Fields and Burnstock (552), with permission of Nature.]

astrocytes. Activation of adenosine A_{2B} receptors in astroglia cells has been shown to increase interleukin (IL)-6 mRNA and IL-6 protein synthesis. Blockade of A_{2A} receptors prevents bFGF-induced reactive astroglia in rat striated primary astrocytes (196). Release of ATP through connexin hemichannels in astrocytes has been reported (1649), although vesicular release was also described in later papers (373, 1169). In a study of nucleotide-mediated calcium signaling in rat cortical astrocytes, it was concluded that the calcium rises are mediated by P_{2Y}₁ and P_{2X}₇ receptors but that additional P₂ receptors (P_{2X}₂, P_{2X}₄, P_{2X}₅, P_{2Y}₂, P_{2Y}₄ and P_{2Y}₁₄) may also contribute (598). It is interesting that a recent study has shown that cultured astrocytes are able to release UTP either at rest or following hypoxia and that P_{2Y}₂ receptor mRNA increased by twofold during glucose-oxygen deprivation (86).

In the human 1321N1 astrocytoma cell line, Cx43 gap junctional communication provides intercellular integration of Ca²⁺ signals generated by P_{2Y}₁ receptor activation (1655). ATP regulates anion channel-mediated organic osmolyte release from cultured rat astrocytes via multiple Ca²⁺-sensitive mechanisms (1166). Nicotinic acid adenine dinucleotide phosphate activates P_{2Y} receptors on astrocytes leading to Ca²⁺ release and is a widespread messenger (1580).

P_{2X}₇ receptor-mediated release of the excitatory amino acid glutamate and aspartate from astrocytes has been described (482, 912). P_{2X}₇ receptors also mediate stimulation of the phosphoinositide 3-kinase (PI3K)/Akt pathway in astrocytes, which is involved in regulation of cell cycle and apoptosis differentiation and glucose metabolism (818). ATP mediates calcium signaling between astrocytes and microglia, and this may be involved in controlling the number and function of microglial cells under pathophysiological conditions (1779). The inflam-

matory cytokine interferon (IFN)- γ increased ATP release from astrocytes and potentiated a P_{2X}₇ receptor-mediated cytolytic effect on microglia. A recent study has shown that P_{2X}₇ receptors, rather than connexin hemichannels, mediate ATP release and amplification of astrocytic intercellular Ca²⁺ signaling (1653).

P_{2X} receptor antagonists were shown to mediate increase in release of GABA from Müller glial cells of rabbit retina (1220). Müller glial cells in the human retina express P_{2X}₇ receptors (1303). More recently using single-cell RT-PCR, immunohistochemically and physiology, P_{2Y}₁, P_{2Y}₂, P_{2Y}₄, and P_{2Y}₆ receptors have been shown to be present on human Müller glial cells (584). P_{2Y}₁ receptors have also been shown to be expressed *in vivo* in rabbit Müller cells (1747). Activation of receptor tyrosine kinases by growth factors causes a resensitization of P_{2Y} receptors on cultured Müller cells previously desensitized by agonist application and may underlie the enhanced responsiveness of P_{2Y} receptors in retinal glial cells in experimental retinal detachment and may contribute to Müller cell proliferation (1846).

Enteric glia may play an important role in nucleotide signaling (see Ref. 1460). They express P_{2X}₇ (1773), P_{2Y}₂ (910), and P_{2Y}₄ (1770) receptors and respond to ATP and UTP with an increase in cytosolic Ca²⁺. Ectonucleotide NTPDase2 has been shown to be exclusively localized to the surface of enteric glial cells, suggesting that enteric glia control the availability of ATP and UTP (202). There is indirect evidence that enteric glia may release ATP, to participate in the intercellular propagation of Ca²⁺ waves between enteric glial cells (1957). Ca²⁺ wave-induced ATP release was shown to elicit neuronal responses (771).

While it is generally accepted that three glial cell types are found in the brain, namely, astrocytes, oligodendrocytes, and microglia, it has been proposed recently

that there may be a further identifiable type, termed "synantocytes" that express NG2 chondroitin sulfate proteoglycan, although they were considered to be oligodendrocyte precursor cells (299). These authors showed that ATP acts on synantocytes to increase intracellular Ca^{2+} .

B. Neuron-Astrocyte Interactions

A pivotal finding in research on neuron-glia interactions was the discovery of glial-glia communication via ATP (394, 696). This finding developed from calcium imaging studies showing calcium waves were propagated among astrocytes across a cell free barrier in culture demonstrating that glial-glia communication was mediated in part by release of intercellular signaling molecules rather than passage of cell-cell signaling molecules through gap junctions joining adjacent cells (Fig. 7, *A* and *B*). Release of ATP from astrocytes was visualized using a luciferase fluorescence assay in parallel with increased intracellular calcium in situ (1238) and in vitro (1833). Calcium-wave propagation could be inhibited by purinergic receptor blockers or an enzyme, apyrase, that rapidly degrades extracellular ATP (798). P2Y₁ receptor-mediated Ca^{2+} signaling is involved in Ca^{2+} wave propagation in dorsal spinal cord astrocytes (532). Focal electrical field stimulation applied to a single astrocyte in mixed cultures of rat forebrain astrocytes and neurons causes a prompt elevation of calcium in the astrocyte that propagated cell to cell (1231). Neurons associated with these astrocytes respond with large increases in cytosolic calcium, and similar effects are seen in brain slice (863, 1664). The cytoplasmic calcium increase stimulated by ATP receptor activation in turn stimulates release of glutamate and other signaling molecules from astrocytes to propagate the calcium wave to other cells (946), perhaps via P2Y₁ receptors (465). Similar intercellular calcium waves in astrocytes mediated by ATP release have been observed in retinal explants (1235) and brain slice (1515). Recent studies indicate that astrocytes propagate calcium signals by two separate mechanisms, depending on the brain region, and that ATP release can propagate within the neocortex independent from calcium waves (698). The finding provided a mechanism that could, in theory, enable astrocytes to detect synaptic function, propagate the information through chains of astrocyte cells, and then influence synaptic function at remote sites. In effect, glial-glia communication could provide a parallel system of intracellular communication in the brain operating in concert with neurons, but acting through an entirely distinct mechanism. Widespread propagation of calcium waves through astrocytes in the intact brain appears to be particularly important in pathological states, such as seizure and brain trauma (see sect. XI, *B1* and *B6*); more physiological stimulation tends to activate more discrete signal-

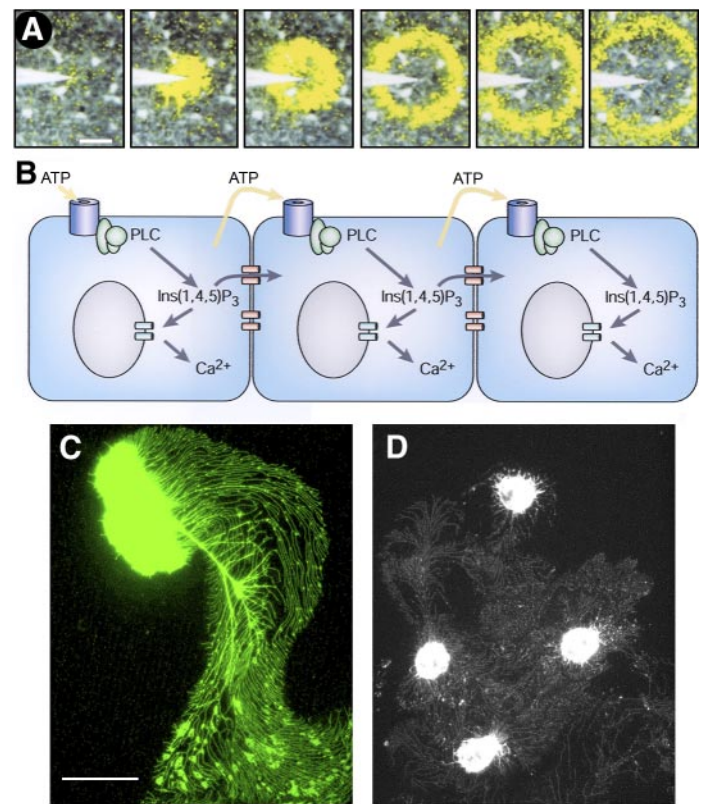


FIG. 7. Glial cells. *A*: stimulation of glial cells from the retina evokes a radially propagating wave of elevated calcium. Mechanical stimulation of a glial cell in the center of the field of view evoked a local elevation of Ca^{2+} . Subsequently, this Ca^{2+} elevation propagated to neighboring cells. In this sequence, images were acquired at 0.93-s intervals, and the yellow overlay image shows the leading edge of the wavefront. *B*: putative mechanism for glial Ca^{2+} wave generation. Ca^{2+} is released from internal stores in response to elevated internal inositol 1,4,5-trisphosphate [Ins(1,4,5) P_3]. Ins(1,4,5) P_3 can diffuse to neighboring cells through gap junctions to cause short-range signaling. Longer-range calcium signaling requires the release of ATP, which causes the regenerative production of Ins(1,4,5) P_3 and further release of ATP from neighboring astrocytes. [From Haydon (719), with permission from Nature.] *C*: the morphological characteristics of N9 microglial cells shown by Biotin-IB₄ and Streptavidin-FITC staining. Resting microglial cell with a long primary process, from which many spinelike processes originate, and many long fine processes branch out from the primary process, spinelike processes, and the cell body. Scale bar = 50 μm . *D*: the morphological changes of N9 microglial cells 1.5 h after stimulation with ATP (3 mM). Note the amoeboid form and that most of the processes have disappeared, although many of the fine processes are still present. Scale bar = 50 μm . [C and D from Xiang et al. (1904), with permission from John Wiley and Sons, Inc.]

ing among fewer numbers of astrocytes (1664). A stochastic two-dimensional model of intercellular Ca^{2+} wave spread in glia, via P2 receptors, has been proposed (783). Intracellular calcium waves can propagate between pia-arachnoid cells and astrocytes, and this can be blocked by octanol or apyrase, indicating involvement of gap-junction communication and extracellular ATP.

ATP, released from astrocytes, acts as an activity-dependent signaling molecule in neuron-glia communication, resulting in astrocyte Ca^{2+} waves and synaptic mod-

ulation (552). Neuron-glia cross-talk may represent an integral part of activity-dependent plasticity of neural networks. Studies of astrocytes in culture (1227) and in brain slices (1370) revealed robust calcium responses in astrocytes to application of ATP or to more selective agonists of specific purinergic receptors. Glia are intimately involved in active control of neuronal activity and synaptic neurotransmission, where glia respond to neural activity releasing ATP leading to increase in $[Ca^{2+}]_i$, which triggers the release of chemical transmitters and, in turn, causes feedback regulation of neuronal activity (see Refs. 539, 554, 1398). The well-established function of glial cells in supporting neurons provides them with effective mechanisms for modulating neuronal communication. Glia help maintain extracellular ion homeostasis, clear neurotransmitter from the synaptic cleft by membrane transporters, provide molecular substrates for neuronal energy requirements and neurotransmitter synthesis, and release many neuromodulatory molecules from growth factors to cytokines, in addition to ATP and adenosine. This allows glial cells to regulate the information flow through neural networks in the brain (660, 1315). Release of cytokines and growth factors can be affected by purinergic signaling and influence cell proliferation.

At the synapses between cerebellar granule cell parallel fibers and Purkinje cells brief bursts of activity can trigger calcium signals in Bergmann glia, unipolar protoplasmic astrocytes (123). The interacting actions of ATP and glutamate are involved in bidirectional astrocyte-neuron communication. Glutamate-stimulated ATP release from spinal cord astrocytes is potentiated by SP (1852). ATP and glutamate released from neurons have powerful synergistic actions in inducing the release of Ca^{2+} from glial stores. In response to receptor activation and Ca^{2+} elevations, astrocytes then release both ATP and glutamate. Released ATP, but not glutamate, significantly contributes to the spread of the interglial Ca^{2+} signal, and both transmitters regulate neuronal excitability. Ca^{2+} -evoked glutamate release activates extrasynaptic neuronal NMDA receptors to increase excitability, an action that is terminated within hundreds of milliseconds. Subsequently, accumulation of adenosine (resulting from breakdown of ATP) both activates neuronal K^+ conductances that hyperpolarize the neuron and reduce neuronal excitability and causes a presynaptic inhibition of release of excitatory neurotransmitters. Thus, on the one hand, the glutamatergic and purinergic signaling systems act synergistically to excite astrocytes, but then have time-dependent distinct and opposing effects on neuronal excitability (540).

Purinergic signaling facilitates glial intervention in synaptic transmission through ATP-mediated intercellular communication and the involvement of ATP in regulating synaptic transmission through purinergic receptors on the pre- and postsynaptic membrane. Purinergic signaling

also interacts with other intracellular signaling molecules [notably neurotransmitters and trophic factors such as epidermal and fibroblast growth factors (EGF and FGF, respectively)], and second messenger systems (notably calcium and cAMP), that are key regulators of synaptic function and plasticity (443, 1226). For example, protein kinase cascades mediate the trophic actions of ATP alone or together with FGF2 (1222). Interactions between $P2Y_2$ and $P2X_7$ receptors and FGF-2 signaling pathways have important implications for CNS development as well as injury and repair (see sect. XI B1). $P2Y_2$ receptors interact with α_V integrin to mediate astrocyte migration; UTP-induced astrocyte migration was inhibited by silencing of $P2Y_2$ receptor expression with $P2Y_2$ receptor siRNA (1826).

By acting on different types of metabotropic glutamate receptors, glutamate released from astrocytes can stimulate (550, 1058) or inhibit (1059) synaptic transmission by hippocampal inhibitory interneurons. Adenosine receptor activation modulates astrocyte calcium fluxes in situ (1370), suggesting involvement of both P1 and P2 receptors in glial regulation of synaptic transmission.

Astrocytes affect both excitatory and inhibitory synaptic transmission in the hippocampus via purinergic signaling. ATP application or electrical stimulation of Schaffer collaterals causes a rise in cytoplasmic calcium in hippocampal astrocytes, which then release ATP activating inhibitory interneurons via $P2Y_1$ receptors to increase synaptic inhibition (186). Both the calcium response in astrocytes, and the activation of interneurons, are blocked by $P2Y_1$ receptor antagonists. ATP released by astrocytes can also mediate glutamatergic activity-dependent heterosynaptic suppression by acting on P2Y receptors and by adenosine produced by ATP degradation (1953).

Heterosynaptic LTD in the hippocampus has been shown to involve purinergic astrocyte-neuronal signaling. In studies selectively blocking ATP release from astrocytes, Pascuale et al. (1315) showed that adenosine, produced from hydrolysis of ATP released from astrocytes, mediates heterosynaptic LTD by activation of A_1 receptors on presynaptic terminals of CA1 hippocampal neurons.

In the retina, endogenous purines are released by potassium depolarization (1335) and by light stimulation (1237). The firing rate of retinal neurons is affected by the passage of glial calcium wave through a mechanism requiring ATP and adenosine release from neurons, most likely from amacrine cells (1235). ATP released by astrocytes can inhibit neuronal transmission by hydrolysis to adenosine and activation of A_1 receptors on retinal ganglion cells; however, several other gliotransmitters are involved in pre- and postsynaptic regulation of synaptic transmission in the retina (1236). Thus glial cells regulate

the information flow through neural networks in the retina (1238).

It was proposed that the effects of ATP released from nerves are mediated by a mechanism involving purinergic receptor-operated calcium channels, phospholipase-linked mobilization of internal calcium, and activation of calcium-dependent protein kinase and phosphatase (1226). Synergistic activation of DNA synthesis in astrocytes by FGFs and extracellular ATP has been demonstrated (1228). Regulated release of ATP from astrocytes has been claimed to lead to depression of synaptic transmission in both hippocampal slices and mixed cultures of neurons and astrocytes (1953) perhaps via P2Y₁ receptors (948).

Evidence has been presented that ATP, released from glial cells in rat hypothalamic paraventricular nucleus in response to activation of α_1 -adrenoceptors, increases postsynaptic efficacy at glutamatergic synapses (660). The increase in quantal efficacy, probably resulting from the insertion of AMPA receptors, is secondary to the activation of P2X₇ receptors, on increase in postsynaptic calcium and the activation of PI3K. Astrocytes undergo anatomical changes, withdrawing processes ensheathing the axon terminals under conditions such as dehydration, parturition, and lactation. When the glial processes are retracted from synaptic contacts following dehydration, NE no longer affects synaptic strength through this mechanism. This morphological remodeling of the synapse also affects transmission by altering the accessibility of transporters on perisynaptic astrocytes and neuromodulatory substances such as taurine, D-serine, and glutamate released by these glial cells (1296). ATP can activate P2X₇ receptors in astrocytes to release glutamate, GABA, and ATP, which regulate the excitability of neurons (1819). There is synergistic action of arachidonic acid and ATP acting via P2X₇ receptors in the regulation of $[Ca^{2+}]_i$ in astrocytes (36).

Changes in purinergic expression in reactive glia following axonal degeneration in the rat optic nerve (i.e., reduced P2Y₁ but increased P2X₁ or P2X₃ and P2Y₂ and/or P2Y₄ receptor expression) suggest a special role for P2X receptors in mediating the glial reactions to CNS injury (821) (see sect. XI B1).

C. Interactions of Axons With Schwann Cells and Oligodendrocytes

Both types of myelinating glia, Schwann cells in the PNS (1125) and oligodendrocytes in the CNS (876), exhibit robust calcium responses to application of ATP, and calcium responses were seen in specialized Schwann cells at the neuromuscular junction activated by purines released during synaptic transmission (1435). There are differences in the sensitivity to purinergic stimulation of

myelinating and nonmyelinating Schwann cells in peripheral human and rat nerve (1125).

Activity-dependent neuron-glia communication by purinergic signaling expanded beyond synapses since axons firing bursts of action potential release ATP (964). Imaging calcium in glia revealed that purinergic receptors enable premyelinating Schwann cells, oligodendrocytes, and astrocytes to detect action potential firing (552).

Neuronal contact was shown to be necessary for ATP-mediated calcium increases in vitro and in situ on Schwann cells and that these responses were independent of myelin formation or maintenance (1083). P2Y₂ receptors were identified in the paranodal Schwann cell membrane of rat spinal root myelinated nerve fibers, although their functional role was unclear (1126). ATP stimulates the release of glutamate and aspartate from cultured rat Schwann cells (829).

Sensory axons become functional late in development when Schwann cells stop proliferating and differentiate into distinct phenotypes. P2 receptors on Schwann cells may contribute to the excitatory effect of ATP observed on unmyelinated, including nociceptive C-fibers (809).

ATP stimulation of P2X₇ receptors activates three different ionic conductances on cultured mouse Schwann cells, which may participate in the regulation of synthesis and release of cytokines in inflammatory processes during nerve injury or peripheral neuropathies (379, 809). The ABC transporter, ABC1, is required for the release of IL-1 β by P2X₇ receptor-stimulated and lipopolysaccharide (LPS)-primed mouse Schwann cells (1114). UTP-stimulated release of ATP from Schwann cells occurs through P2Y₂ receptors, which promote exocytosis of ATP from vesicles as well as anion transport across the cell membranes (1054). Schwann cells in the vas deferens express P2Y receptors, which evoke calcium transients on nerve stimulation, which suggest that Schwann cells may be active participants in junctional transmission in the autonomic nervous system (1048). NTPDase2 is associated with nonmyelinating Schwann cells, whereas NTPDase1 is restricted to blood vessel walls (202). The authors suggest that NTPDase2 plays a role in the dialogue between peripheral neurons and Schwann cells.

Early studies of ATP and adenosine signaling between synapses and perisynaptic Schwann cells were performed at the neuromuscular junction (see Ref. 1710). Specialized Schwann cells (terminal Schwann cells) tightly surround the neuromuscular junction and actively participate in the maintenance and repair of neuromuscular synapses. These Schwann cells respond to nerve stimulation and modulate transmitter release through mechanisms involving ATP and adenosine signaling. Tetanic stimulation of the motor nerve axon elicits rapid calcium transients in terminal Schwann cells at the neuromuscular junction (1409), and similar responses can be

induced by agonists of P2X, P2Y, and A₁ receptors (1437). Suramin blocks 87% of glial calcium response following high-frequency nervous stimulation in frog (1435). In mouse, adenosine A₁ receptors are one of the major means of activating calcium responses in terminal Schwann cells in response to nerve stimulation (380). The effects of adenosine on Schwann cell proliferation depend on the growth factor environment; in the absence of growth factors, adenosine is mitogenic and associated with stimulation of the ERK/mitogen-activated protein kinase pathway in Schwann cells, while in the presence of growth factors (platelet-derived growth factor or neuregulin) adenosine inhibits proliferation (1639).

Myelin, the insulating layers of membrane wrapped around axons by oligodendrocytes in the CNS and Schwann cells in the PNS, is essential for normal impulse conduction. Myelination occurs during late stages of fetal development, but curiously, it continues into early adult life. Evidence from animal studies, cell culture, and human brain imaging indicates that action potentials affect myelination (553). Adenosine is of primary importance in regulating early development of oligodendrocyte progenitor cells, where it stimulates differentiation and myelination, whereas ATP is of primary importance in regulating early development and myelination of Schwann cells, where it inhibits differentiation and myelination (552).

Raising animals in environments with enriched sensory stimulation and social interactions increases CNS myelination and children suffering neglect or abuse show decreased white matter in the corpus callosum. These observations open the possibility that myelinating glia are in some way party to the flow of information through neural circuits and that this may be an overlooked form of plasticity modifying the nervous system according to functional requirements (553). ATP regulates oligodendrocyte progenitor cell migration, proliferation, and differentiation, probably via P2Y₁ receptors (18). P2Y₁₂ receptors have recently been identified on oligodendrocytes in rat brain, and it was speculated that signaling via these receptors might contribute to the migration and adhesion of the glial processes to axons to be myelinated (41).

In contrast to perisynaptic glia, which can detect neurotransmitter escaping the synaptic cleft, activity-dependent communication between axons and myelinating glia occurs in the absence of synapses. Studies showing that ATP is released from axons firing trains of action potentials have revealed that purinergic signaling can enable premyelinating glia to respond to impulse activity in axons, with effects on myelination (1639). Calcium responses in Schwann cells are blocked by electrical stimulation of axons in the presence of apyrase, an enzyme that rapidly degrades extracellular ATP, but responses are only partially blocked in oligodendrocytes (1641). This is consistent with different purinergic receptors expressed in these two cell types. Oligodendrocytes possess all four

adenosine receptor subtypes, but no adenosine receptors coupled to intracellular calcium are detected in premyelinating Schwann cells. Oligodendrocyte progenitor cells also express functional adenosine receptors of all four subtypes, which promote differentiation leading to formation of myelin (1641). A_{2A} receptors have been detected in mouse Schwann cells and found to inhibit proliferation through a different mechanism from the P2 receptor (1640).

Differences in purinergic receptors enable differential responses to impulse activity in peripheral and central myelinating glia on axons of the same DRG neuron (552). Impulse activity in premyelinating axons, acting through ATP activation of P2 receptors, inhibits Schwann cell proliferation, differentiation, and myelination, but impulse activity has the opposite effect on oligodendrocytes, stimulating differentiation of oligodendrocytes from the progenitor stage, and promoting myelination through adenosine (P1) receptor activation.

Purinergic signaling has been found to stimulate myelination by more mature oligodendrocytes through a mechanism involving astrocytes. The cytokine leukemia inhibitory factor is released from astrocytes in response to ATP liberated from axons firing action potentials, which in turn stimulates oligodendrocytes to form myelin (811). This involvement of astrocytes in myelination may explain the puzzling white matter defects seen in Alexander disease, a genetic mutation in astrocytes.

A recent study has shown that Schwann cells in perivascular nerves in mesenteric blood vessels are activated via both P1 and P2 receptors (1049).

D. Interactions Between Neurons and Microglia

Microglial cells are the major cellular elements with immune function in the CNS and play important roles in orchestrating inflammatory brain responses to hypoxia and trauma; their activation, migration, and proliferation play pivotal roles in these responses (see Refs. 535, 1373 and sect. XI, *B1* and *B3*). Microglia respond to a wide range of purine and pyrimidine receptor agonists by increases in intracellular calcium (1044), triggering potassium currents (178) and secretion of inflammatory cytokines, such as IL-1 β , IL-6, tumor necrosis factor (TNF)- α (738, 1554), and plasminogen (806). Rapid changes in morphology (1044) and migration and proliferation (427) are induced in microglia by purinergic receptor activation (see Refs. 452, 1904; see Fig. 7, *C* and *D*). The nature of purinergic responses is dependent on the concentration of ATP; low concentrations of ATP act via P2Y receptors, while high concentrations (>1 mM) activate P2X₇ receptors (1135). With the use of cocultures of rat cortical neurons and microglia, ATP and the more potent P2X₇ agonist BzATP, acting on microglial P2X₇ receptors, cause

neural cell injury (1583). Stimulation of microglial P2X₇ receptors also leads to enhancement of IFN- γ -induced type II NOS activity and perhaps microglial proliferation (141). Astrocyte-derived ATP has been identified as the endogenous factor responsible for microvesicle shedding via P2X₇ receptor activation in microglia and IL-1 β release from these cells (143). Nicotine enhances P2X₇ receptor-mediated TNF release from microglia, which protects neurons while suppressing massive LPS-induced TNF release, which leads to neuroinflammation (1674).

With the use of a combination of RT-PCR, Western blotting, and single-cell calcium imaging, P2 receptor subtypes were assessed in the mouse microglial cell line N9 (142). Interestingly, a different functional profile of P2 receptors was observed in resting or LPS-stimulated N9 cells; overnight exposure to LPS increased P2Y₆ and P2Y₁₄ receptors, decreased P2X₇ receptors, and left unchanged P2Y₁ and P2Y_{2/4} receptor activity.

The roles of microglia in inflammatory pain has attracted strong interest in the past few years (see sect. XI B9). ATP selectively suppresses the synthesis of the inflammatory protein microglial response factor (MRF-1) through Ca²⁺ influx via P2X₇ receptors in microglia. ATP, ADP, and BzATP, acting through P2X₇ receptors, induce release IL-1 β from microglial cells. Activation of P2X₇ receptors enhances IFN- γ -induced NOS activity in microglial cells and may contribute to inflammatory responses. ATP, via P2X₇ receptors, increases production of 2-arachidonoylglycerol, also involved in inflammation by microglial cells. It has been shown that pharmacological blockade of P2X₄ receptors or administration of P2X₄ antisense oligodeoxynucleotide reverses tactile allodynia caused by peripheral nerve injury (see sect. XI B9).

A complex array of responses of microglial cells to P2Y receptor activation have been described, which are reflected by the sensitivity of these cells to nucleotides released from neighboring nerves and astrocytes and by the degree of degradation by ectonucleotides (1793).

IX. PURINERGIC NEUROEFFECTOR TRANSMISSION

It is now recognized that many nonneuronal cells that express purinoceptors are activated by ATP released locally in an autocrine or paracrine manner. However, there are a number of examples where these nonneural, non-muscle cells can also be activated by ATP released as a cotransmitter from autonomic nerves. It is difficult to exclude the possibility that many nonexcitable effector cells are also innervated, albeit transiently, by nerves. This is because the autonomic neuroeffector junction is not a fixed structure with postjunctional specialization as is seen at the skeletal neuromuscular junction or neuronal synapses. Rather, when varicosities in extensive terminal

autonomic nerve fibers, which are actively moving, form close relationships with effector cells, the cotransmitters released are within striking distance of the receptors expressed for these transmitters on effector cells (270, 274). Thus, for example, it is now recognized that mast cells can be transiently innervated by sympathetic nerves that release ATP as a cotransmitter to act on P2 receptors to release histamine (see below).

A. Exocrine Glands

1. Salivary glands

P2 receptors were first identified on parotid acinar cells by Gallacher in 1982 (612), who showed that ATP evokes a marked increase in membrane conductance and amylase secretion. Stimulation of the NANC component of parasympathetic nerves produced increased production of saliva from parotid, submandibular glands (513). P2X₄ and P2X₇ receptor mRNA was identified in parotid acinar cells (1693). These authors also showed that parasympathetic denervation increased the number of cells expressing P2X₄ receptor-mediated responses, the level of P2X₄ mRNA, and the proportion of supersensitive cells. Desensitization of muscarinic receptors by ATP and BzATP acting on P2X₇ receptors in rat parotid acinar cells has been reported (595).

In the rat submandibular gland, P2Y₁ receptor mRNA has been detected with RT-PCR, but as the gland develops, the Ca²⁺ response to P2Y₁ receptor agonists diminishes, having little effect by 4 wk of age (1312). An increase in P2Y₂ receptor activity and mRNA occurs in cultured acinar and ductile components of the rat submandibular gland as well as in parotid and sublingual preparations (1742). Outstanding reviews of the distribution and function of P2 nucleotide receptors in salivary glands are available (1260, 1741). The autonomic innervation of parotid ducts occurs on the basal side of epithelial cells where muscarinic receptors are located; however, P2Y₂ receptors are present on the apical surface (1685), suggesting that the receptors are activated by ATP released from nonneuronal cells.

A novel chloride conductance activated by ATP in mouse parotid acinar cells has been identified (59). The ecto-nucleotidases present on rat submandibular salivary glands have been identified recently and perhaps terminating the action of the sympathetic nerve cotransmitter, ATP, and generating adenosine (734).

2. Exocrine pancreas

The control of pancreatic exocrine function is complex and regulated by both neural and hormonal factors (1252, 1287). Multiple functional P2X and P2Y receptors have been identified in the luminal and basolateral mem-

branes of pancreatic duct cells (850, 1079). However, it is not clear yet whether the source of nucleotides acting on these receptors is autocrine, paracrine, or neuronal. There is evidence that pancreatic acini release ATP in response to cholinergic stimulation (1606). Pancreatic ducts and acini show differential intracellular Ca^{2+} increases to purinergic agonists, indicating different regulatory mechanisms in these two epithelia (1260).

3. Lacrimal glands

Cationic channels sensitive to extracellular ATP have been identified in acinar cells of rat lacrimal glands that play an active role in fluid secretion and the possibility that the ATP is released as a cotransmitter from autonomic nerves was raised (1789). There is a rich innervation of the lacrimal gland by both sympathetic and parasympathetic nerve fibers (680). ATP activates receptor-operated cation channels in mouse lacrimal acinar cells to promote calcium influx (1501), and the ATP-induced inward current in mouse lacrimal acinar cells is potentiated by isoprenaline (1502).

4. Sweat glands

Extracellular ATP can activate autonomic signal transduction pathways in cultured equine sweat gland epithelial cells, and the possibility was raised that purinergic neurotransmission may play a central role in regulating secretory actions in the equine sweat gland and that this process may therefore be an important part of the thermoregulatory response (937). P2Y_1 , P2Y_2 , and P2Y_4 receptors have since been shown to be immunolocalized on human sweat glands and P2Y_2 receptors on equine sweat glands (1050, 1869). The "sympathetic skin response," defined as a transient change of the electrical potential of the skin, may be spontaneous or evoked by a variety of arousal stimuli and has been used as an index of sudomotor function and as an index of arousal-related emotion (see Ref. 1781).

5. Mammary glands

Mammary myoepithelial cells surround the alveoli of secretory epithelial cells. They are contractile cells derived from epithelial stem cells common to secretory epithelial cells, and their contraction compresses alveoli to eject milk into the duct during lactation. Oxytocin released from the posterior pituitary gland following sucking stimulus triggers the contraction of these cells. ATP acts synergistically with oxytocin to increase intracellular Ca^{2+} in mouse mammary myoepithelial cells (1205). P2Y_2 receptors appear to be involved (151). It is not clear whether the source of ATP is neural or paracrine.

B. Endocrine and Neuroendocrine Cells

Purinoceptors are widely expressed in endocrine glands (see Ref. 292).

1. Pituitary

P2X receptors are expressed in all five major pituitary secretory cell types, although the subtype(s) expressed on thyrotrophs and corticotrophs are still to be identified (1644, 1787). ATP receptors mediate the release of luteinizing hormones from gonadotropes. ATP has been shown to act on P2 receptors on pituitary lactotrophs to release prolactin (311, 722, 1262) and on the isolated posterior lobe of the rat hypophysis to regulate vasopressin and oxytocin secretion (1625), probably via a P2X_2 receptor (1726). Extracellular ATP operating via P2X_2 receptors controls the pacemaker activity, voltage-gated Ca^{2+} influx, and basal leuteinizing hormone release from gonadotrophs; ATP also influences gonadotropin-releasing hormone-induced current (1949). In earlier studies, the source of ATP was considered to be pituitary cells (344, 1714). A later experimental paper led to the proposal that, in the neurohypophysis, extracellular ATP released by nerve terminals may act directly on pituicytes (neurohypophysial astrocytes) to induce K^+ efflux via a P2Y receptor (1726). However, the consensus at present appears to be that ATP and adenosine are acting largely as autocrine and/or paracrine agents in the pituitary (see Refs. 723, 1405, 1965). Pituitary folliculo-stellate cells are glialike cells in the anterior pituitary, which are believed to modulate the activity of pituitary endocrine cells via P2Y receptors in response to ATP coreleased with pituitary hormones (1745).

2. Thyroid

The thyroid is extensively innervated by sympathetic, parasympathetic, and sensory nerves (685, 1140), and sympathetic control of thyroid hormone secretion has been reported (674), although there may also be autocrine ATP release from thyroid follicular epithelial cells (941). ATP, presumed to be acting as a neurotransmitter, activated a Ca^{2+} -dependent Cl^- current and evoked DNA synthesis in rat thyroid cell line FRTL-5 (511, 1110). Both ATP and adenosine were shown to stimulate the secretion of endothelin-1 from FRTL-5 cells (1762). Thyroid follicular cells express P2X_3 , P2X_4 , and P2X_7 receptors (653).

3. Thymus

In the thymus, sympathetic nerves run in septa in close connection to subcapsular and perivascular thymic epithelial cells. Cotransmitters NE and ATP from sympathetic nerves have a costimulatory effect on synthesis of IL-6 that is an important factor for thymocyte differenti-

ation and proliferation (1804). Both thymic epithelial cells and phagocytic cell of the thymic reticulum express P2 receptors (38). Medullary epithelial cells, epithelial cells of the thymic septa, and subscapsular epithelial cells are immunopositive for P2X receptors (292).

4. Testis

The testis consists of seminiferous tubules, within which spermatogenesis takes place, and interstitial spaces between these tubules, containing Leydig cells (testosterone-producing cells), as well as supporting tissue and blood or lymphatic vessels. Germ cells and Sertoli cells are the only cell types present within the seminiferous tubules, and they are in close contact with each other. The germ cells migrate within the seminiferous tubules and differentiate from stem spermatogonia, through spermatocytes, to spermatids. The changes in Sertoli cell and germ cell morphology during the repetitive cycle of germ cell development in the rat have been categorized into the 14 different developmental stages. There is sympathetic innervation of the testis with predominant supply to blood vessels; sensory nerve fibers are also present.

There is ultrastructural evidence for sympathetic innervation of Leydig and interstitial cells, which secrete androgens in the testis of various animals and hormones (1380). P2X₂ receptors have been described on Leydig cells (1361), and ATP has been shown to increase testosterone secretion (568). Various P2X receptor subtypes are expressed on germ cells during spermatogenesis (652), but no evidence for a role of sympathetic innervation in the control of sperm development has been presented. Multiple purinergic receptors lead to intracellular calcium increases in rat Sertoli cells (936).

5. Ovary

The mammalian ovary is directly innervated by sympathetic nerves, which appear to play major roles in regulating ovarian functions, such as follicular maturation, steroid secretion, and ovulation. There are also intrinsic neurons in the rat ovary, but it is not known which cells they innervate or whether ATP is a cotransmitter (413). Ovarian sympathetic activity increases during the ovulatory process, but the neuronal content of NE and ATP decreases after ovulation. ATP evokes Ca²⁺ oscillations in isolated human granulosa-luteal cells (1632). Granulosa cells secrete estradiol, and luteal cells secrete both estradiol and progesterone. P2Y receptors are expressed by human and porcine granulosa-luteal cells; ATP has been shown to decrease the production of progesterone and estradiol, and the authors favored a neuronal origin of ATP (1682).

ATP, probably released from sympathetic nerves, has been shown to activate nuclear translocation of kinases (mitogen-activated protein kinases) leading to the induc-

tion of early growth response 1 and Raf expression in human granulosa-luteal cells (1681). At least 99% of follicles in the mammalian ovary undergo follicular atresia, a cellular degeneration that involves apoptosis in both somatic and germinal follicular cells. ATP-induced apoptotic cell death in porcine ovarian theca cells has been shown to be mediated by P2X₇ receptors (1776), which is part of the regulation of folliculogenesis, known to be modulated by sympathetic cotransmitters.

6. Endocrine pancreas

It has been known for more than 40 years that exogenous ATP stimulates insulin release from β -cells in pancreatic islets (1438), and ATP released from nerves was first proposed to regulate insulin secretion in 1979 (1680). There is a rich innervation of pancreatic islets by both sympathetic and parasympathetic nerves (1152). Intrapancratic ganglia are involved in the regulation of periodic insulin secretions (1633). The action of ATP is mediated by P2Y receptors (137). ATP stimulates insulin secretion from rat and mouse endocrine pancreas (397). P2X₇ receptors are expressed on α -glucagon-containing cells (397), perhaps responding to ATP released from β -cells. Studies of insulin release from the perfused pancreas after nerve blockade led to the proposal that the islets communicate via NANC neurotransmission (1633). In the presence of high concentrations of glucose, insulin secretion was significantly greater in islets for P2Y₁ receptor knockout mice, indicating that P2Y₁ receptors play a physiological role in the maintenance of glucose homeostasis, at least in part, by regulating insulin secretion (671, 1015).

7. Pineal

The pineal gland contains neurons, neuroglia, and special secretory cells called pinealocytes, which synthesize, store, and release the hormone melatonin. NE released from sympathetic nerves in the pineal gland triggers the nocturnal peak of melatonin production by activation of arylalkylamine *N*-acetyltransferase, the rate-limiting enzyme that converts 5-HT to the immediate precursor of melatonin, *N'*-acetyl-5-hydroxytryptamine. It has been shown that the rat pineal gland possesses P2 receptors, which, when stimulated, potentiate the effect of NE, and also by themselves, induce, via P2Y₁ receptors, an increase in *N'*-acetyl-5-hydroxytryptamine production (549). The synergistic actions of cotransmitters are well known (see Ref. 273).

8. Adrenal

The adrenal cortex produces corticosteroid hormones. Electron microscopic studies have shown autonomic axons supplying adrenal cortical tissue, which

sometimes penetrate the basal lamina of the cortical cells and come with close (200 nm) contact with their plasma membranes (1434, 1758). It has been suggested that the nerve fibers in the superficial cortex are mainly of extrinsic origin in contrast to a major contribution of intrinsic neurons in the medulla (1281). ATP modulates aldosterone production by adrenal cortex (1678). Extracellular ATP stimulates steroidogenesis in adrenocortical fasciculated cells via P2Y receptors (882), in contrast to adenosine, which inhibits secretion of corticosteroids (1913).

Activation of the splanchnic sympathetic innervation strongly potentiates the steroidogenic action of ACTH from the anterior pituitary, and there is compelling evidence that the innervation normally plays an important part in cortisol secretion (504). Neural release of ATP acting on cortical cells has been considered (851), although the possibility that there is a paracrine nonsynaptic modulatory role for catecholamines and ATP in the regulation of adrenocortical steroid secretion has also been raised (1678). It has been suggested that the supra-chiasmatic nucleus utilizes neuronal pathways to spread its time of the day message, not only to the pineal to control melatonin secretion, but also to the adrenal cortex to influence corticosterone secretion (231).

9. Neuroendocrine cells

The NEBs consist of pulmonary neuroendocrine cells that are usually arranged in innervated clusters in the airway mucosa. They are O₂ sensors, of particular importance in early life before the carotid body O₂ sensory system is fully established. They also appear to mediate reflex activities in response to hyperventilation and noxious substances, by releasing ATP to act on P2X₃ receptors on sensory nerves arising from the nodose ganglia, which innervate NEBs (215, 218). Parasympathetic efferent fibers also innervate NEBs (12).

Merkel cells in the skin are also regarded as neuroendocrine cells. They are innervated largely by sensory nerves, which are likely to be activated by ATP, which is stored in high concentrations and probably released from these cells by mechanical distortion (406).

Rat prostate neuroendocrine cells express both P2X and P2Y receptor subtypes, which mediate marked increase in [Ca²⁺]_i (234, 907). The authors speculate ATP is released as a cotransmitter with NE in sympathetic reviews innervating the prostate.

C. Endothelial Cells

There is dual control of vascular tone by ATP released as a cotransmitter from perivascular sympathetic nerves to act on P2 receptors to mediate smooth muscle contraction and ATP released from endothelial cells during changes in blood flow (shear stress) and hypoxia to

act on endothelial P2X and P2Y receptors to release NO resulting in vasodilatation (269, 1916). In large to small muscular vessels, ATP released from the perivascular nerves would be rapidly degraded by ectonucleotidases before reaching the endothelial cells in the intima. However, in the microvasculature, it is likely that ATP released from nerves would act on endothelial P2 receptors. There are a few examples where this has been experimentally supported. For example, neurally released ATP has been shown to mediate endothelium-dependent hyperpolarization in smooth muscle cells of hamster, rabbit, and chicken small mesenteric arteries (474, 856, 1698). Release of ATP from nerves and astrocytes has been considered to mediate endothelium-dependent vasodilatation of cerebral vessels (28). Diadenosine polyphosphates, which have been shown to be present in rat brain synaptic terminals (1356), have been shown to have antagonist actions on P2Y₁ receptor-mediated effects on rat brain capillary endothelial cells (1786). The possibility that neurally released ATP can influence endothelial cells forming the blood-brain barrier has not been investigated yet, although clearly, these endothelial cells, which express P2X₂ receptors, are closely associated with both nerves and glial cells (1065, 1772). Inhibitory purinergic neurotransmission has been considered to be endothelium dependent in pulmonary (1060) and coronary (1579) vessels.

In addition to control of vascular tone, ATP and its breakdown product, adenosine, and UTP have important long-term (trophic) actions on endothelial and smooth muscle cell proliferation, differentiation, and death (see Refs. 269, 524). However, whether the source for these effects on endothelial cells, which are important in angiogenesis and restenosis, is perivascular nerves and/or endothelial cells has not been addressed yet.

D. Secretory Epithelial Cells in Visceral Organs

Epithelial cells in airways, liver, kidney, gut, gall bladder, adipose tissue, and uterus express multiple purinoceptors, and some cells show differential distribution on basolateral and apical surfaces (see Refs. 292, 1310). Purinergic receptors are involved in cytosolic calcium regulation of chloride and fluid secretion, sodium transport, and ciliary and mucociliary clearance (204). While there is good evidence for autocrine and paracrine mechanisms of regulation of epithelial transport by ATP and adenosine in different organs (see Refs. 224, 1013, 1374, 1520, 1528, 1830), there are some reports discussed below that suggest that nerves may play a part.

1. Airways

A review about P2 receptors in the respiratory system (1844) emphasizes their involvement in epithelial ion transport, mucous secretion, ciliary beat frequency, and

phosphatidylcholine (surfactant) release, as well as the participation of immune cells. Airway epithelium consists of ciliated and nonciliated cells, goblet cells, and basal cells. The beat frequency of ciliary cells is potently increased by ATP, probably via P2X receptors (193, 718, 1086), but whether the ATP arises from adjacent cells or from nerves does not appear to have been addressed. ATP and UTP stimulate mucin secretion via luminal P2Y₂ receptors and goblet cells, which implies that nerves are not involved (8). Surfactant secretion is regulated in alveolar type II cells by ATP acting via P2Y₂ receptors, but there is no evidence for a neuronal source for ATP (1446). However, the possibility that antidromic impulses in sensory-motor nerve fibers in the vicinity of lung epithelial cells influence their activities has been raised (216).

2. Kidney

There is extensive sympathetic innervation of afferent glomerular arterioles, proximal and distal renal tubules, and particularly the ascending limb of Henle's loop (see Refs. 456, 1134). There is a substantial presence of purinoceptors in different regions of the nephron, the glomerulus, and renal vascular system in the kidney, including subtypes involved in the regulation of renin secretion, glomerular filtration, and the transport of water, ions, nutrients, and toxins (79, 1562, 1759). The origin of the purines and pyrimidines involved seems likely to be a combination of neural, autocrine, and paracrine mechanisms. There may be an influence of ATP released as a cotransmitter from sympathetic nerves on the activity of juxtaglomerular cells that highly express P2 receptors (328). The renin-secreting epithelioid juxtaglomerular cells are modified smooth muscle cells that are innervated by sympathetic nerves, the stimulation of which leads to renin secretion (886). The contribution of neurally released ATP to stimulation of renin secretion via P2Y₁₁ receptors has been suggested (1768). Renal vasoconstriction elicited by periarterial sympathetic nerve stimulation is primarily due to release of ATP, at low physiological frequencies of stimulation (1525). Neurally released ATP may also be acting on mesangial cells and podocytes, which have been shown to express P2 receptors, contributing to the regulation of glomerular filtration (559, 1339). Stimulation of periarterial sympathetic nerves led to increased ATP release in perfused rat kidneys (1148), and sympathetic nerve stimulation of superfused human cortical slices also led to release of ATP (1806).

Release of ATP from macula densa cells, which form an epithelial barrier between the luminal fluid that flows through the thick ascending limb of the loop of Henle and filtration of fluid by the glomerulus, has also been implicated in juxtaglomerular function and renin release (127, 953). ATP appears to be the mediator responsible for the propagation of intercellular Ca²⁺ waves in juxtaglomeru-

lar cells induced by mechanical stimulation (1923). ATP has also been found to stimulate proximal tubule cell proliferation, probably via P2Y receptors, but whether the origin of the ATP involved is neural and/or nonneural was not addressed (1012).

3. Gut

The presence of intrinsic neurons in the enteric plexus controlling secretion in mucosal epithelial cells has been recognized for a long time with both cholinergic and noncholinergic secretomotor neurons involved (1531). In general, extrinsic parasympathetic activity increases intestinal secretion, while inhibition occurs with sympathetic stimulation. ATP has been shown to modulate gastric acid and intestinal secretion, and both P2Y and P2X receptors have been identified on mucosal epithelial cells and gastric glands (266, 640, 682, 1764). Extracellular ATP and adenosine have established roles as potent stimulants of fluid and electrolyte secretion in colon, gall bladder, pancreatic duct, and bile duct, where it seems likely to be released from both local cells and nerves (see Refs. 266, 601, 1440). NTPDase has been localized in the gastric mucosa and probably plays a role in the control of acid and pepsin secretion and mucus production, as well as contractility of the stomach (1505).

A relationship between the enteric nervous system and inflammation-induced mucosal transport responses was demonstrated by experiments in which neural blockade abolished the secretory response induced by mast cell degranulation and neutrophil activation (134), and new approaches targeting the enteric nervous system show promise for the treatment of secretory diarrhea (841). ATP-induced contractions of muscularis mucosae evoked colonic epithelial secretion via prostaglandin synthesis and noncholinergic secretomotor nerve stimulation (1331). Intrinsic enteric sensory neurons also provide direct innervation of the mucosa, and stroking the mucosal lining of the guinea pig colon with a brush releases ATP that activates P2Y₁, P2Y₂, and P2Y₄ receptors to trigger an intestinal neural reflex and an increase in short-circuit current, indicative of chloride secretion (365, 635). A recent paper has shown that ATP released as an enteric neurotransmitter acts on P2Y₁ excitatory receptors on intestinal secretomotor neurons in the guinea pig to evoke neurogenic mucosal secretion (533).

Studies with P2Y₂ and P2Y₄ receptor knockout mice indicate that both these receptors are present in the luminal membranes of mouse distal colonic mucosa and that stimulation of these receptors leads to K⁺ secretion (1119). However, luminal purinergic activation of these receptors argues against a neuronal origin of the nucleotides involved. Activation of P2Y receptors may improve

water-soluble and high-molecular-weight compounds from the rat ileum (917).

4. Liver and gall bladder

The liver is supplied by sympathetic, parasympathetic, and sensory nerves, which contribute to the regulation of hepatic carbohydrate metabolism. Infusion of ATP, UTP, and adenosine into perfused rat livers resulted in stimulation of hepatic glycogenolysis (301, 716), and this appears to be mimicked by stimulation of perivascular sympathetic nerves (1917). Activation of P2Y₁ receptors substantially stimulates glycogen phosphorylase in rat hepatocytes (462). The sympathetic cotransmitters NE and ATP also suppress the secretion of very-low-density lipoprotein (1918). ATP-activated cation currents have been recorded in single guinea pig hepatocytes (310). Cholangiocytes, which secrete Cl⁻ and HCO₃⁻, in the intrahepatic bile ducts, are activated by purinergic receptors, although it was assumed that these signals were via autocrine and/or paracrine membranes (1487). In addition to regulation of secretion, ATP activates cell cycle progression and proliferation of rat hepatocytes (1701); the source of ATP is probably hepatocytes during swelling (543). Hepatic stellate cells are the primary fibrogenic cells of the liver; both quiescent and activated forms express P2Y receptors, and stimulation of these receptors on activated cells regulates transcription of the matrix component α_1 -procollagen (478).

ATP is released from guinea pig gall bladder upon nerve stimulation (1683). There is also evidence for local cellular release of ATP contributing to ATP levels using bile surfactant to activate purinoceptors by autocrine and/or paracrine mechanisms (330). ATP appears to be released together with tachykinins from intrinsic neurons in the gallbladder and bile duct, although little is known about their roles, apart from contracting smooth muscle (1317).

Cl⁻ secretion, measured by both electrophysiological and radionucleotide methods, is stimulated through the activation of P2Y₂ receptors in rat bile duct epithelial cells (560). The extrahepatic biliary tract is innervated by dense networks of extrinsic and intrinsic nerves that regulate both smooth muscle tone and epithelial cell function (84). Portal fibroblasts inhibit bile ductular proliferation via expression of the ectonucleotidase NTPDase2 and blockade of P2Y activation (832).

5. Reproductive organs

ATP regulates ion transport in bovine oviduct epithelial cells (400). P1 (A_{2A} subtype) and P2 (P2Y₂ subtype) receptors have been claimed to be present in oviductal ciliated cells (1178). There have been no studies about the origin of the ATP acting on these receptors. ATP stimulates Ca²⁺ release from rat epididymal cells and stimu-

lates Cl⁻ fluid secretion in both rat and mouse epididymis; both P2X and P2Y receptors are involved (1546). The epithelial cells of the endometrial gland in the uterus were shown to express P2Y₂ and P2Y₄ receptors, although the origin of the ATP and UTP activating these receptors was not discussed (1295).

6. Adipose tissue

The metabolism, proliferation, and thermogenesis of adipose tissue are controlled by the sympathetic nervous system (see Refs. 743, 1400). High-fat diets are associated with a reduction in sympathetic activity to brown adipose tissue (1482). P2Y receptor stimulation increases membrane trafficking in brown adipocytes, and it has been proposed that it is likely that the ATP involved is released as a cotransmitter with NE from the sympathetic nerves (1280, 1309). P2Y₂, P2Y₆, and P2Y₁₂ receptors have been identified as the nucleotide receptors on brown fat cells (1011). Activation of P2X receptors contributes to aromatase induction in adipose tissue stromal cells (1516). ATP, probably from sympathetic nerves, modulates via P2 receptor activation the amount and voltage dependence of voltage-gated K⁺ currents in brown adipocytes (1870) and increases membrane conductance in single rat adipocytes (363). P2 receptors provide a direct link between sympathetic nerve activity and estrogen biosynthesis contributing to the regulation of lipolysis in human white preadipocytes (1516). P2Y₂ and P2Y₁₁ receptors have been identified on white adipocytes, and it has been suggested that P2Y₁₁ receptors might be involved in inhibition of insulin-mediated leptin production and stimulation of lipolysis (1009).

ATP enhanced 3T3-L1 preadipocyte cell migration into fat cell clusters, one of the essential processes of adipose tissue development, by activating P2Y receptors, as well as enhancing the differentiation of adipocytes by adipogenic hormones (1279). Deficits in receptor regulation, transporter mobilization, and adipocyte hormone secretion are all thought to contribute to the pathology of obesity. Stimulation of lipogenesis in rat adipocytes by ATP, which regulates fat stores independently from established hormones, has been reported (1517). Some of the effects of ATP act through its breakdown product, adenosine, which has been known for a long time to be involved in the activities of adipocytes (see Ref. 578).

E. Immune Cells

Cells of the immune system were not considered for many years to be innervated, since neural boutons could not be found on their surface membranes. However, as discussed earlier, in accordance with the definition of the autonomic neuroeffector junction, close contact of nerve varicosities with effector cells in effect constitutes inner-

vation, albeit of a transient nature (see Ref. 274). Also there is increasing recognition that nerves can influence the immune system, and the field of neuroimmunology is growing (144, 515, 1540).

Cells of the immune system consist of a large family including lymphocytes, mast cells, macrophages, neutrophils, eosinophils, thymocytes, dendritic, and hematopoietic cells as well as microglia and osteoclasts. All these immune cells express multiple P1 and P2 functional receptors (see Refs. 263, 292, 453, 712). The sympathetic nervous system innervates immune organs and releases its cotransmitters NE and ATP in the vicinity of immune cells (713).

Mast cells were the first immune cell type to be shown to be innervated (see Ref. 1868). For example, antidromic stimulation of sensory nerves was shown to increase degranulation of mast cells in the skin and to be mimicked by ATP by Kiernan in 1974 (903). Electron microscopic studies showed close opposition of nerve varicosities containing small and large vesicles and mast cells in the mucosa of intestine (145, 1239) and in cerebral blood vessels (458). The activities of synovial mast cells, which contribute to inflammation in joints, were shown to be influenced by both unmyelinated afferent and sympathetic efferent nerves (1025). Sympathetic as well as trigeminal sensory nerve fibers influence rat dural mast cells and play a role in the edema pathophysiology of vascular headache (887). Functional relationships between sensory nerves and mast cells of the dura mater have been demonstrated in both normal and inflammatory conditions (459). Electrical stimulation of the vagus nerve modulates the histamine control of mast cells in the rat jejunal mucosa (662), although which cotransmitters were involved was not investigated. Extracellular ATP inhibits cytokine generation by human mast cells through G_s -coupled P2Y receptors (541), while ATP induces cytokine expression and apoptosis through P2X₇ receptors on murine mast cells (232).

There have been few investigations of the influence of nerves on non-mast cell immune cells, but the possibility that varicose nerve fibers form close relationships with some of these cell types too, cannot be discounted. For example, electron micrographs showing close association of nerves with eosinophils has been described (57). The sympathetic nervous system has been shown to modulate macrophage function (331), and alterations in T- and B-lymphocyte proliferation and differentiation have been described following chemical sympathectomy (1090). Close contacts between enteric nerves and lymphocytes in mouse intestinal mucosa and submucosa have been reported (402, 630). Interactions of neurally released ATP with microglia are discussed in section VIII D and with osteoclasts in section IX F.

F. Bone Cells, Joints, and Keratinocytes

Sympathetic and sensory nerves innervate bone, and sympathectomy modifies bone development and resorption (see Ref. 166). ATP, probably released as a cotransmitter with NE, regulates Ca^{2+} metabolism in osteoblast-like bone cells (979). Evidence has been presented to demonstrate a role for the sympathetic nervous system in controlling bone density via leptin that activates hypothalamic nerves, which in turn activate the sympathetic nerves that innervate osteoblasts (1684). P2X₂, P2X₅, P2X₇, P2Y₁, P2Y₂, P2Y₄, and P2Y₆ receptors are expressed in osteoblasts, while P2X₁, P2X₂, P2X₄, P2X₅, P2X₆, and P2X₇, P2Y₁, P2Y₂, P2Y₄, P2Y₆, and P2Y₁₁ receptors are expressed by osteoclasts and P2X₂, P2X₅, P2Y₁, and P2Y₂ by chondrocytes (746). ATP has been shown to inhibit bone formation by osteoblasts and to stimulate bone resorption by osteoclasts (185, 393). While sympathetic nerves innervating bone provide one source of nucleotides, there is also evidence for physiological release of ATP from osteoblasts and chondrocytes (229, 1441). Activation of P2Y₂ receptors elevates intracellular calcium and enhances bFGF-induced proliferation of sheep chondrocytes (866). Mitogenic effects of ATP and synergistic actions with growth factors on osteoblast proliferation have been reported (see Ref. 746). More recently, P2X₇ receptors have been implicated in the control of osteoblast apoptosis (622), and intercellular calcium signaling between human osteoblasts and osteoclasts requires activation of osteoblast P2X₇ receptors (844). Chemical sympathectomy impairs bone resorption, suggesting that depletion of sympathetic mediators may disturb osteogenic cell-mediated osteoclast differentiation (347). Deletion of the P2X₇ receptor led to significant reduction in total and cortical bone content and periosteal femur circumference, and increased trabecular bone resorption in tibias (884). Modulation of bradykinin-induced plasma extravasation in the rat knee joint by ATP as a sympathetic cotransmitter has been reported (673).

In the stratified epithelium of the skin, P2Y₁ and P2Y₂ receptors regulate proliferation in the basal layers, P2X₅ receptors mediate differentiation in the stratum granulosum, and P2X₇ receptors mediate apoptotic cell death in the stratum corneum (677, 681, 1351). P2Y₂ receptor-mediated effects of nucleotides enhance impaired wound healing in mice (200). ATP stimulates IL-6 production, probably via P2Y₂ receptors in human HaCaT keratinocytes (1938). It appears that ATP is released locally and the epithelium cell turnover cycle is under autocrine and/or paracrine control rather than neural. ATP release from human keratinocytes has been reported recently (296). However, Ca^{2+} waves on keratinocytes are transmitted to sensory neurons involving release of ATP and P2Y₂ receptor activation (947). Wound healing in skin flaps has been shown to be delayed in denervated

wounds, and possible roles for purinergic signaling and its relation to NGF in wound healing have been explored (676, 1820). An important role of the skin for terrestrial animals is protecting water-rich internal organs from environmental dryness. The stratum corneum plays a critical role as the water-impermeable barrier. Cutaneous barrier repair after barrier disruption can be regulated by cation flux through P2X₃-like ATP receptors (447).

G. Choroid Plexus

The mammalian choroid plexus is a highly vascularized villous structure, covered with a single layer of cuboidal epithelial cells. It is present in all four ventricles in the brain and plays a major role in the production and regulation of cerebral spinal fluid. The choroid plexus is supplied by a well-developed sympathetic and parasympathetic innervation and also probably by some nerve fibers originating in the brain stem reaching both the secretory epithelium and the blood vessels. Sympathetic stimulation evokes an inhibition of cerebral spinal fluid formation.

GTP γ S-evoked currents in patch-clamped epithelial cells of choroid plexus were only observed when 2 mM ATP was present in the electrode solution (960). P2X receptors (P2X₁, P2X₂, P2X₄₋₇ subunits) are expressed and have been localized in subpopulations of rat choroid plexus epithelial cells, but not on the capillary endothelium (1902). In an earlier study, P2Y₄ receptor mRNA was shown to be moderately expressed in rat choroid plexus (1842).

H. Interstitial Cells of Cajal

ICCs are a specialized cell type that control the activities of smooth muscle cells in the gut and probably other organs such as urinary bladder, ureter, blood, and lymphatic vessels. In the gut, they have been shown to be innervated by enteric nerves (122, 1835). P2X₂ and P2X₅ receptors are expressed on ICCs in guinea pig intestine (293), and more recently, P2Y₄ receptors have also been identified on ICCs in guinea pig gastrointestinal tract to modulate intracellular Ca²⁺ oscillations (1770), which would be consistent with ATP being released as a cotransmitter from enteric nerves to regulate the activities of these cells. Purinergic modulation of pacemaker [Ca²⁺]_i activity in ICCs is mediated by P2X receptors (606).

I. Sensory Epithelia

1. Eye

In addition to smooth muscle, ciliary, conjunctival, lens, corneal, and retinal pigment epithelial cells as well

as photoreceptor cells, horizontal amacrine and Müller cells are present in the eye. Are the activities of these epithelial cells influenced by ATP released from nerves? P2Y₂ receptors are expressed in all of these epithelial cell types (see Ref. 1098).

The retinal pigment epithelium forms a major component of the blood-retinal barrier, and extracellular ATP activates calcium signaling as well as ion and fluid transport in these cells via both P2X and P2Y receptors (1337, 1466, 1666). While there is no direct evidence for a neuronal source of ATP to activate these epithelial cells, this possibility cannot be discounted. Both amacrine cells and the pigment epithelial cells themselves have been shown to release ATP (1159, 1324) as well as retinal astrocytes (1235) and inner retinal amacrine-like neurons (1499).

The ciliary epithelium secretes the aqueous humor from the underlying stroma into the posterior chamber of the eye. These cells consist of both pigmented and non-pigmented layers. Both P1 and P2 receptors are expressed in ciliary epithelial cells (534, 562). P2Y₂ receptors have been identified on bovine ciliary epithelial cells (1544). There is evidence for storage and release of ATP from both layers of the ciliary epithelium, suggesting that it is likely to modulate aqueous humor flow by paracrine and/or autocrine mechanisms (1160). However, ATP is also released from antidromically stimulated sensory nerve endings into the ciliary body (1123), and both sympathetic and parasympathetic nerves have been identified in the ciliary processes, localized in the vicinity of the epithelial cells.

The stratified corneal epithelium is composed of a superficial cell layer, a wing cell layer in the mid region, and a basal cell layer located in the stroma. ATP produces an increase in [Ca²⁺]_i in cells in all layers; the responses are synchronized in the wing cell layer (913, 971). ATP also enhanced proliferation of cultured bovine corneal epithelial cells (325), and UTP and Ap₄A have been claimed to accelerate wound healing following superficial corneal injury (931, 1355). Mechanical stimulation induces release of ATP from corneal epithelial cells and a concomitant intercellular Ca²⁺ wave via P2Y receptors, suggesting a paracrine mechanism (658).

P2Y₂ receptors in both goblet and nongoblet secretory conjunctival epithelial cells mediate Cl⁻, fluid, and mucin secretion (848, 1042, 1195). It seems likely that ATP released from damaged cells is the main source for activation of the P2Y₂ receptors expressed by these cells. A review of the expression of P2Y₂ receptors in rabbit and monkey ocular epithelial tissues is available (399). Sympathetic innervation regulates basement membrane thickening and pericyte number in rat retina (1864).

2. Ear

A role for ATP as a cotransmitter generating $[Ca^{2+}]_i$ currents in cochlea inner hair cells was first proposed in 1990 (66, 1201). Later various P2X and P2Y receptor subtypes were shown to be expressed in other cell types in the cochlea, including outer hair cells, nonsensory epithelial cells (787), Henson cells, supporting cells, and Deiters' cells in the organ of Corti (332), mucociliary cells in the inner ear (360, 1931), epithelial cells of the endolymphatic sac (1888), strial marginal cells, and vestibular dark cell epithelium (1479). Physiological studies suggested that ATP acts as a neurotransmitter, but probably not as part of the efferent system as previously supposed, but rather as a cotransmitter with glutamate in auditory afferent nerves activated by glutamate released from hair cells and acting postsynaptically on the spiral ganglion neuron afferent dendrites (765, 1656). ATP has been shown to be released by gap junctional hemichannels in cochlear-supporting cells (1964).

3. Nasal mucosa

There are three types of epithelial cells in the nasal mucosa: nonkeratinized stratified squamous epithelium, respiratory epithelium, and olfactory epithelium. Primary olfactory neurons lie in the olfactory epithelium and function to detect odiferous substances, sending information to the olfactory cortex. P2X₅ and P2X₇ receptors are expressed in squamous, respiratory, and olfactory epithelial cells, while P2Y₁ receptors are present in respiratory epithelium submucosal glandular tissue, and P2Y₂ and P2Y₁₁ receptors are localized to the mucous-secreting cells within the vomeronasal organ (360, 624). P2X₂ receptors are localized on different subpopulations of primary olfactory neurons located both in the olfactory epithelium and vomeronasal organs, and on sensory fibers arising from the trigeminal ganglion (624, 1619). Sympathetic nerves supply the nasal mucosa, but are probably largely involved in vasomotor control (987). ATP released from olfactory epithelium modulates odor sensitivity and nociception (725, 1708). P2X and P2Y receptors mediate mucous secretion, ion transport, fluid transport, and ciliary beat frequency, perhaps largely by autocrine and/or paracrine mechanisms (905).

X. ONTOGENY AND PHYLOGENY OF PURINERGIC NEUROTRANSMISSION

A. Pre- and Postnatal Development and Aging

Readers are referred to a review of the earlier literature by Burnstock (264) about the involvement of purinergic signaling in both embryonic and postnatal development. There have been relatively few reports about

changes in purinergic transmission during aging, and these are mostly concerned with the brain and cardiovascular system.

Together with muscarinic cholinergic receptors, extracellular receptors to ATP were shown to be the first functionally active membrane receptors in chick embryo cells at the time of germ layer formation. In gastrulating chick embryo, ATP caused rapid accumulation of IP₃ and Ca²⁺ mobilization in a similar way and to the same extent as ACh, whereas other neuroendocrine substances such as insulin and NE had much weaker effects. This suggests that, alongside ACh, other phylogenetically old and universal regulators of cell metabolism such as ATP (and perhaps NO) might play leading roles in the functional regulation of gastrulation via the activation of specific receptors triggering Ca²⁺ mobilization.

1. Central nervous system

An immunohistochemical study revealed intense labeling of P2X₃ receptors in the embryonic and postnatal (P7 and P14), but not adult, rat brain (901). The staining was restricted to the hindbrain at E16, in particular the mesencephalic trigeminal nucleus, the superior and inferior olive, the intermediate reticular zone, the spinal trigeminal tract, and the prepositus hypoglossal nucleus. In the E19 rat embryo, P2X₇ receptor mRNA was detected by *in situ* hybridization in brain ependyma but not neurons (377). Primary cultures of human fetal astrocytes express low levels of P2X₇ receptor mRNA and protein (1215).

Utilization of GFP-tagged P2X₂ receptors on embryonic hippocampal neurons has led to the claim that ATP application can lead to changes in dendritic morphology and receptor distribution (898). P2X₂ receptors were identified on Purkinje neurons in the neonatal cerebellum and with the aid of RT-PCR technology, mRNAs for P2X₁₋₄ and P2X₆ subunits were identified in the cerebellum during the first postnatal week with coexpression of two units in Purkinje cells demonstrated with patch-clamping (620).

A combined immunohistochemical and physiological study of purinergic signaling on precursor cells, neuroglial progenitors, and differentiating neurons during neurogenesis of embryonic rat neocortex was carried out (1106). Neuroglial progenitors from the ventricular and subventricular zones prominently exhibited Ca²⁺ response to ATP. A detailed expression pattern for the P2X₃ receptor in embryonic neurogenesis has been published (353). P2X₃ receptors first appeared in the hindbrain neural tube and sensory ganglia in E11–11.5 embryos; at E14.5 they appeared in the optic tract, NTS mesencephalic trigeminal nucleus, but P2X₃ immunoreactivity was downregulated in early postnatal brain stem. The P2X₃ receptor was coexpressed with the P2X₂ receptor in neurons in NTS and sensory ganglia.

Changes in expression of P2X receptors during postnatal development of the rat cerebellum have been reported (1900). At P3, all P2X receptor subtypes were expressed (except P2X₃) in Purkinje cells and deep cerebellar nuclei, P2X₅ receptor immunoreactivity being most prominent; at P7 there was upregulation of these receptors, particularly P2X₅ and P2X₆, and microglial cells showed P2X₁ and P2X₇ receptor immunoreactivity. At P14, the dendritic trees of Purkinje cells were intensely labeled by P2X₁₋₇ (except for P2X₃). P2X₄ receptors were also expressed in microglia and P2X₅ receptor immunoreactivity in granular cells upregulated; at P21 and P66, the P2X receptors were downregulated in Purkinje cells and deep cerebellar nuclei, although P2X₅ receptor immunoreactivity in granular cells was again upregulated. P2X receptors in Purkinje cells were colocalized with calbindin, while many of the P2X receptor immunoreactive granular cells were colocalized with calretinin. Endogenous release of ATP starts to enhance the synaptic activity in rat Purkinje neurons by the end of the second postnatal week (316).

P2Y receptors (particularly the P2Y₁ subtype) were widely expressed in the embryonic rat brain as early as day 11 (355). There was a marked decrease in mRNA to P2Y₁ receptors and upregulation of mRNA for P2Y₂ receptors on freshly isolated astrocytes during development of rat hippocampus (1974). P2Y receptor proteins were strongly expressed transiently in structures that do not have correlates in the adult animal, suggesting that these receptors were likely to be involved in functions specific to embryonic development. For example, P2Y₄ receptors disappeared from the brain stem and ventricle spinal cord postnatally.

The sequential expression of P2X receptor subtypes during embryonic rat brain development was examined (354; Fig. 8). P2X₃ receptors appeared first at E11, P2X₂ and P2X₇ receptors at E14, while P2X₄, P2X₅, and P2X₆ receptors did not appear until birth and P2X₁ receptors even later. In this study, ATP was shown to inhibit motor axon outgrowth during early embryonic neurogenesis, most likely via the P2X₃ receptor, and it was speculated that P2X₇ receptors might be involved in programmed cell death during embryogenesis. At E9.5, P2X₃ immunostaining was found in the hindbrain, midbrain, diencephalon, and forebrain neuroectoderm of mouse brain and in the marginal layer of diencephalon, midbrain, and hindbrain at E10.5 (167). However, P2X₃ receptor immunoreactivity disappeared from the marginal and mantle layers of the ventral horn by E14.5, although it was retained in the dorsal horn.

A subset of spontaneous and evoked postsynaptic currents in embryonic chick hypothalamus appears to arise from the concurrent activation of both GABA and P2X receptors (836). The radial glial cell is a transient embryonic cell type known for its crucial role in neuronal

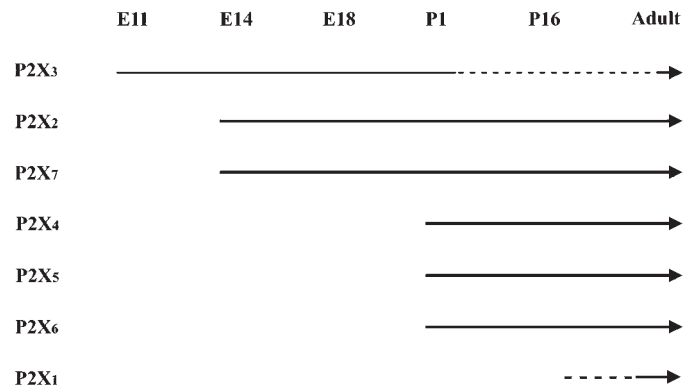


FIG. 8. Summary of the sequential expression of P2X receptor mRNA and protein during neurogenesis in the rat brain. P2X receptors are arranged from top to bottom according to the chronological order of expression during rat brain development from E11 to adult. While P2X₃ receptors appeared early, they declined in the stages that followed (represented by dotted line). P2X₂ and P2X₇ receptors were expressed from the same day (E14) onwards, while P2X₄, P2X₅, and P2X₆ receptors were expressed from P1 onwards. Initial dotted line for P2X₁ receptor represents an unknown starting point, since expression of P2X₁ receptor was not observed in any of the developmental ages examined in this study. [From Cheung et al. (354), with permission from Elsevier.]

migration and a progenitor cell for most cortical pyramidal neurons. It has been shown that calcium waves propagate through radial glial cells in the proliferative central ventricular zone, and this requires both P2Y₁ receptors and connexin hemichannels (1848). ATP has been shown to induce proliferation of human neural stem cells cultured from telencephalon tissues from a 15-wk gestational age embryo (1472).

ATP operating via distinct P2X and P2Y receptors directly contributes to modulate network-driven giant depolarizing potentials in the rat hippocampus at the early stages of postnatal development (1478). On the basis of experiments carried out on cultures of hippocampal neurons from neonatal mice, it was suggested that ATP, via both P2X and P2Y receptors, can shape hippocampal connectivity during postnatal development (728). ATP, acting via P2Y₁ receptors, increased the frequency of GABA_A-mediated spontaneous postsynaptic current in CA3 principal neurons in the early postnatal (P1-P6) rat hippocampus (1477).

Both ATP and adenosine have been shown to modulate the activity of inspiratory neurons in the brain stem of neonatal rats (see Ref. 264). Adenosine depressed both the activity of neurons in the RVLM and the respiratory motor output, with a more pronounced decrease in respiratory activity in younger animals. ATP excitation of glutamate inspiratory drive to mouse hypoglossal neurons remained constant during the first 2 wk of postnatal development. A secondary inhibitory response was due to adenosine acting on A₁ receptors after breakdown of ATP. ATP and adenosine mediate responses of sympathetic preganglionic neurons in a neonatal rat brain stem-

spinal cord preparation. P2 receptors in rat locus coeruleus neurons first appear to be functional soon after birth, thereafter increasing to reach maturity in animals older than 18 days. Wide distribution of P2Y₁ receptors in the 1-day-old chick brain has been claimed, based on *in vitro* ligand autoradiography of [³⁵S]2'-deoxy-5'-O-(1-thio)-ATP binding sites and *in situ* hybridization histochemistry. *In vitro* studies of sensorimotor cortical neurons from 14-day-old (P14) and 30-day-old (P30) rats have shown that Ca²⁺ release could be evoked by ATP in Ca²⁺-free external solution, indicating the presence of P2Y receptors. Almost all P14 neurons appeared to possess such receptors, whereas only about one-third of neurons from P30 rats responded to ATP, suggesting that substantial changes in signaling mechanisms occur in neocortical neurons in the third to fourth week of postnatal development.

α,β-MeATP is ineffective on glycinergic presynaptic nerve terminals projecting to rat substantia gelatinosa neurons at P10–12 and is strongly active at P28–30, perhaps contributing to the fine control of the pain signal in spinal cord dorsal horn neurons (823). In rat superficial dorsal horn, excitatory synapses mediated by both glutamate and ATP are functional from the first postnatal days (101). P2X₃ receptors in motoneurons of the compact division of the nucleus ambiguus are profoundly down-regulated during the first two postnatal weeks, perhaps indicating P2X₃ receptor involvement in the control of esophageal motor networks in early development (214).

There are a number of reports about changes in the distribution of the ectoenzymes involved in the breakdown of ATP and adenosine in the brain during fetal and neonatal development (264, 704). 5'-Nucleotidase shows a marked redistribution during development of the cat visual cortex and is thought to be involved in the remodeling of ocular dominance columns. A later electron microscopic study suggested that synapse-bound 5'-nucleotidase activity plays a role in synaptic malleability during development; its later association with glial cell profiles may reflect other functions for this enzyme. At 30 and 35 days of gestation of fetal guinea pigs, 5'-nucleotidase levels were low, but increased rapidly during the 40- to 60-day period; in contrast, adenosine deaminase was present at 30 days of gestation and remained at the same level until 60 days. Complex changes in the activity of adenosine deaminase in the different regions of the developing rat brain suggest that there are important roles for purines in very early stages of development from 15 to 18 days of gestation in specific regions of the brain, namely, the hypoglossal motor nucleus, cingulate, retrosplenial and visual cortex, posterior basal hypothalamus and in the facial motor nucleus. Adenosine deaminase-staining neurons were seen in the olfactory cortex of rat embryos as early as E15; this was taken to indicate precocious development of purinergic neurotransmission

within this system. Ca²⁺-ATPase in the rat spinal cord during embryonic development showed intense activity in the roof and floor plates, rather than in the basal and lateral plates at embryonic day 12, indicating a possible role for Ca²⁺-ATPase in early differentiation of neuroepithelial cells. ATP induces rises in intracellular Ca²⁺ in embryonic spinal cord astrocytes. Roles for both P1 and P2 receptors in the proliferation of human fetal cortical astrocytes have been reported. Ecto-NTPDase2 is transiently expressed at E18 in astrocytic cells in the outer molecular layer of the dentate gyrus and in cerebellar white matter (201). Functional expression of the ectonucleotidase NTPDase2 and of P2X receptors by neuronal progenitor cells in the adult murine hippocampus has been described, inferring that purinergic signaling may play a role in the control of hippocampal neurogenesis (1565). Postnatal development of ectonucleotidase activity in the cerebral cortex has been studied. The activities increased steadily from birth, reaching maximum values at 21 days of age. A marked increase in activity of 5'-nucleotidase was also seen in rat olfactory bulb during neonatal development. 5'-Nucleotidase first appeared in immature Purkinje cells at birth and increased throughout postnatal development; it was observed in migratory granular neurons during the critical period from 3 to 15 postnatal days. In contrast, peak alkaline phosphatase activity in the developing cerebellum did not appear on the granular neurons until day 7 postnatally. Ecto-ATPase, ecto-ADPase, and ecto-5'-nucleotidase activities change in relation to age (and gender) in synaptosomes of rat spinal cord (1719). NTPDase1 activity in synaptic plasma membranes isolated from rat cerebral cortex increased from birth to day 30, after which it declined and remained unchanged from adulthood (90 days) to senescence (305 days) (1229). In general, ATP and ADP hydrolyses decreases in older animals.

Early studies about the development of A₁ receptors in guinea pig and rat brain have been reviewed (264). In guinea pig forebrain it appears that A₁ receptors are present from embryonic day 19, with adult binding levels achieved ~25 days postpartum. In guinea pig cerebellum, however, A₁ receptor binding is low until just before birth, when a dramatic increase in binding is observed which then continues to increase up to adulthood. A similar development is seen in rat forebrain and cerebellum with A₁ receptor binding changing very gradually in the forebrain, whereas binding in the cerebellum increases markedly after birth. Expression of A₁ receptor mRNA in brain was first detected on gestation day 14 and was restricted to portions of neuroepithelium caudate putamen, piriform cortex, hypoglossal nucleus, and ventral horn of spinal cord; by gestational age 17, patterns of A₁ receptor expression in the brain were similar to those observed in adults. The ontogeny of adenosine uptake sites in the guinea pig brain has been described. A₁ receptor down-

regulation has been shown in fetal brain after caffeine or theophylline treatment of pregnant rats (1016). There is a downregulation and reduced responsiveness to presynaptic A₁ receptors modulating ACh release in the hippocampus during postnatal development and aging. The magnitude of this reduction varies in different regions: hippocampus and thalamus showed a gradual decline, while some cortical and septal regions showed a more abrupt decline after the age of 24 mo (1139).

Postnatal changes in expression of A_{2A} receptors have been described in various brain regions (838). The authors suggest that postnatal changes in these adenosine receptors may explain age-dependent differences in stimulatory effects of caffeine and endogenous protection against seizures throughout development. Caffeine decreases the incidence of neonatal respiratory disturbances, which may reflect the early dominance of the adenosinergic system in the brain (625). The developmental properties of adenosine A_{2A} receptors differ from those of A₁ receptors during postnatal development of rat striatum. A_{2A} receptor binding sites were low at birth (~3% of adult levels) and then increased mostly between birth and 5 days, and then again from 15 days to adulthood. In contrast, A₁ receptors are widely distributed at birth (~10% of adult levels) and then increase gradually until adulthood, with a peak during the second week of postnatal life. The ratio of adenosine A_{2A} receptors to dopamine D₂ receptors in the rat striatum increases with age, involving both presynaptic and postsynaptic mechanisms. A decrease in striatal A₂ receptor mRNA expression has been demonstrated in rat striatum between 3 and 24 mo, but it has been suggested that this may be related to neuronal loss over the same period. Adenosine receptors appeared earlier and reached higher adult levels in the brains (most notably in the cerebellum) of mice pups chronically exposed in utero to caffeine.

Several studies of purinoceptors in the embryonic development of the brain of nonmammalian vertebrates have contributed to the field (see sect. xB). For example, a novel P2Y receptor (p2y₈) has been cloned and sequenced that is expressed (as seen by Northern blots and in situ hybridization) in the neural plate of *Xenopus* embryos from stages 13–18 and again at stage 28 when secondary neurulation occurs in the tail bud (164). It differs from other members of the P2Y purinoceptor family in that it has an intracellular COOH terminus with 216 amino acid residues (compared with 16 to 67 in P2Y₁₋₇). When expressed as a recombinant receptor in *Xenopus* oocytes, it shows equipotent responses to triphosphates ATP, UTP, ITP, CTP, and GTP and smaller responses to diphosphates and tetraphosphates, but is not responsive to inorganic phosphates. Responses to activation of the p2y₈ receptor have a long duration (40–60 min). These data suggest that this novel P2Y receptor may be involved

in the early formation of the nervous system. Regulation of rhythmic movements by purinergic transmitters in frog embryos has been described (421). It was shown that ATP is released during swimming that activates P2Y receptors to reduce voltage-gated K⁺ currents and cause an increase in the excitability of the spinal motor circuits. It was also shown that adenosine, resulting from the breakdown of ATP, acts on P1 receptors to reduce the voltage-gated Ca²⁺ currents to lower excitability of the motor circuits, thereby opposing the actions of ATP. The author suggests that a gradually changing balance between ATP and adenosine underlies the rundown of the motor pattern for swimming in *Xenopus*.

Widespread programmed cell death has been demonstrated in proliferative regions of chick optic tectum during early development, particularly in the ventricular zone between stages E7.5 and E8. This is of particular interest since some P2X receptor subtypes (particularly P2X₇) can mediate apoptosis. The cloning and functional characterization of a P2X receptor subunit in embryonic chick brain has been reported, which is highly homologous to the mammalian P2X₄ receptor (human and rat) with ~75% sequence identity (1464). P2X₃ receptors are expressed in the trigeminal ganglia of zebrafish from a very early stage of development, most likely in neural crest-derived trigeminal cells rather than placode-derived cells (1259). P2X₃ receptors were also expressed in the spinal sensory Rohan-Beard cells and in the putative lateral line ganglion in the early development of zebrafish.

It is known that neonatal hypothyroidism leads to abnormal development of the CNS. Hypothyroidism changes adenine nucleotide hydrolysis by 5'-nucleotidase activities in synaptosomes from hippocampus and cerebral cortex in rats in different phases of postnatal development (223). Neonatal hypothyroidism enhances the metabolism of adenine nucleotides in astrocyte cultures from rat brain (192).

There have been some studies of changes in purinergic signaling in aging. Two populations of adenosine binding sites, probably corresponding to A₁ and A₂ receptors, were detected in both young and old rats, but both the numbers of binding sites and dissociation constants for both high- and low-affinity binding sites were greater in old rats (1791). Electrophysiological evidence has been presented that adenosinergic inhibition of synaptic potentials (EPSPs) was significantly enhanced in hippocampal slices from aged rats and contributed to an age-related decline in synaptic efficacy (119). The modulatory role of endogenous adenosine via A₁ receptors on synaptic plasticity (both LTP and LTD) is maintained in aged rats (391). Caffeine has been proposed as a drug to counteract age-related cognitive decline. For example, olfactory discrimination and short-term social memory were impaired in aging rats, but acute treatment with caffeine was claimed to reverse these age-related deficits (1378).

The extracellular levels of adenosine in the striatum are not affected by age, although there are differences in the regulatory mechanisms of adenosine release and metabolism. For example, the adenosine deaminase inhibitor erythro-2-(hydroxy-3-nonyl)adenine increased adenosine levels in the striatum of young, but not old, rats (1323). It appears that the maintenance of a constant extracellular adenosine level in the ageing brain may be an important homeostatic mechanism. It was reported that in the old striatum, the levels of A₂ receptor mRNA and A₂ receptor binding sites were reduced by 32 and 20%, respectively (1514). Both A₁ and A_{2A} receptors play a functional role in control of motor activity in rats as evidenced by stimulation of motor activity by selective antagonists; there was increased effectiveness in aged rats (1368). The A_{2A} receptor agonist 2-[4-(2-*p*-carboxyethyl)phenylamino]-5'-*N*-ethyl-carboxamidoadenosine (CGS21680) significantly increased spontaneous outflow of glutamate and aspartate in young, but not in old rats (389). In contrast, CGS21680 significantly increased spontaneous outflow of GABA in old, but not young rats, although it increased K⁺-evoked GABA release in old but not young rats (390). Modification of A₁ and A_{2A} receptor binding in aged striatum, hippocampus, and cortex of the rat has been reported (408).

Purinergic modulation of cortical ACh release is decreased in aging rats (648). A decrease in A₁ receptor gene expression has been described in mouse cerebral cortex of aged rats (346). There is reduced efficiency of A₁ receptors to modulate synaptic transmission in the hippocampus of aged rats, but this may be compensated by the enhanced inhibitory tonus by endogenous adenosine (1532). Since adenosine depresses electrical activity in hippocampus, a downregulation of adenosinergic function may be related to the enhanced excitability seen in hippocampal neurons of the CA1 subregion of aged animals and the increased levels of adenosine in the extracellular fluid (1629). There is cross-talk between A₁ and A_{2A} receptors in the hippocampus and cortex and A_{2A} receptors to control A₁ receptor function via PKC, but not protein kinase A (PKA), in young adult, but not aged rats (1071). The adenosinergic system seems to be unaffected by ageing in the cerebellum and substantia nigra.

2. Ganglia

During early embryological development, the neural ectoderm folds to form the neural tube. Cells in the overlying ectoderm (the neural crest) then migrate within ectoderm and into the mesoderm. The cells that follow this latter pathway differentiate and mature to become glial cells and neurons. Some become primary afferent neurons of the DRG, while others become the postganglionic neurons of the sympathetic and parasympathetic ganglia. A third group of cells go on to form the enteric

nervous system. One group of potential sympathetic neurons becomes surrounded by developing adrenal cortical cells and develops into adrenomedullary chromaffin cells. The sensory neurons of cranial nerves, including those of nodose, petrosal, and trigeminal ganglia, however, are derived partly or entirely from the neural placodes.

ATP-gated currents activated in cultured embryonic rat DRG neurons show heterogeneity of time courses comparable to that seen in different adult subpopulations of dissociated adult DRG neurons associated with the immunohistochemical demonstration of expression of P2X₂ and P2X₃ subunits (985). Activation of P2X receptors on cultured embryonic DRG neurons results in the release of SP (1210). Uniform immunostaining of P2X₃ receptors found in most neurons was observed in embryonic mouse trigeminal and DRG, in contrast to adult ganglia, which express P2X₃ receptors only on small-diameter neurons (167, 353, 1453). Nearly all sensory neurons in mouse DRG, trigeminal, and nodose ganglia expressed P2X₃ receptors at embryonic day 14, but after birth there was a gradual decline to ~50% of neurons showing positive staining (1453). IB₄-positive neurons in sensory ganglia did not appear until birth, the numbers increased to ~50% by postnatal day 14, when they were mostly colocalized with P2X₃ receptors. Responses to ATP have been described in ciliary neurons acutely dissociated from embryonic chick ciliary ganglia taken at day 14 (10). ATP augments peptide release from neurons in embryonic DRG through activation of P2Y receptors (773).

Sympathetic neurons of the rat SCG are more responsive to ATP and α,β -meATP at E18, birth, and during the early postnatal period, with sustained inward currents via P2X_{2/3} heteromultimer receptors, but these responses are much reduced in mature rats (494). Since this change in P2X receptor expression occurs at a time when synaptogenesis is taking place in the SCG, this might indicate a role for purinergic signaling in this process. IB₄-binding DRG neurons (that express P2X₃ receptors) switch from NGF to glial cell-derived neurotrophic factor (GDNF) dependence in early postnatal life (1165). A study of P2 receptors modulating NE release from chick sympathetic neurons cultured from 12-day-old embryos suggested that two different P2 receptor subtypes were involved: a facilitatory receptor and an inhibitory receptor (35). Cultured paravertebral sympathetic neurons taken from mice and rats in the first few days after birth appear to express different purinoceptors (1255). Neurons from both species respond to UTP via P2Y receptors to cause depolarization and NE release. However, the rat, but not the mouse, neurons possess P2X receptors, which also cause depolarization and NE release. Sympathetic neurons of the rat SCG are more responsive to ATP and α,β -meATP at birth and during the early postnatal period, due largely

to the expression of the P2X₃ subunit, but these responses are much reduced in mature rats (494).

In both young and old rats, 93% of the tyrosine hydroxylase-negative (parasympathetic) neurons in the rat pelvic ganglion expressed P2X₂ receptors (472). However, while this suggests that purinergic transmission in pelvic organs may be largely unaffected by aging, there was a reduction in the number of small intensely fluorescent cells that were highly P2X₂ receptor-positive in old age.

Adenosine inhibited neurite outgrowth of chick sympathetic neurons taken from 11-day-old chick embryos and killed by apoptosis ~80% of sympathetic nerves supported by growth factor over the next 2 days in culture (1815).

3. Retina

While there are many studies of purinergic signaling in the retina of adult mammals, there are only a few reports about embryonic retina. Spontaneous waves of excitation in the developing mammalian retina are believed to play an important role in activity-dependent visual development of retinogeniculate connectivity (1636). The earliest age at which spontaneous waves were detected in rabbit retina was E22, and the possibility of an involvement of purinergic receptor activation in these waves was investigated (1677). Suramin blocked the wave, but PPADS did not have a consistent antagonist action. Adenosine has also been implicated in chick retinal development. Adenosine induction of cAMP increased strongly from the 14th to the 17th embryonic day, P1(A₁) subtype receptors modulating D₁ dopamine receptor-mediated stimulation of adenylate cyclase activity. It was suggested that A₁ receptors may have different functions in the embryonic retina compared with mature chick retina, and the localization of A₁ receptors and uptake sites in the developing chick retina were examined (1290). A₁ receptors were localized predominantly in plexiform regions by embryonic day 12 (E12). They were absent in the retina at E8, but were detected at E12 in the ganglion cell layer, as well as cells in the nuclear cell layer and photoreceptors.

Studies of embryonic chick neural retina (see Ref. 264) have shown that the ATP-induced rise in intracellular Ca²⁺ is mediated by P_{2u} (P2Y₂ or P2Y₄) receptors and that there is a dramatic decline of the ATP-induced rise in intracellular Ca²⁺ just before synaptogenesis. Suramin and Reactive blue 2 almost completely block these responses. Injection of Reactive blue 2 into early embryonic chicks produced severe effects in embryogenesis. While both the muscarinic and purinergic Ca²⁺-mobilizations utilize IP₃-sensitive Ca²⁺ stores, different signal transduction pathways are involved. P2 purinergic receptors activated by autocrine or paracrine release of ATP have been claimed to be involved in the regulation of DNA synthesis

in the neural retina at early embryonic stages (1658). ATP increased [³H]thymidine incorporation in retinal cultures from E3, and suramin and PPADS inhibited these activities in a dose-dependent manner; the concentration of ATP increased 25-fold in the medium of E3 retinal organ cultures within 1 h of incubation and was maintained for at least 24 h. It was suggested that the change in Ca²⁺ signaling mediated by P_{2u} (i.e., P2Y₂ or P2Y₄) receptors during development may underlie the differentiation of neuroepithelial cells or undifferentiated progenitor cells into neurons. ATP acting on P2 receptors is involved in the regulation of retinal progenitor cell proliferation at early embryonic stages perhaps in collaboration with growth factors (1658). ATP, probably via P2Y₁ receptors coupled to PLC, PKC, and mitogen-activated protein kinases, stimulates proliferation of both bipolar and Müller cells in early developing chick retina at embryonic days 6–8 (1494). RT-PCR studies of P2X₇ mRNA in postnatal rats (P23–P210) showed positive identification in the retina; in the adult retina, immunolabeling for P2X₇ receptors was detected in amacrine and retinal ganglion cells (199).

4. Skeletal neuromuscular junction

A transmitter-like action of ATP on patched membranes of myoblasts and myotubes cultured from 12-day-old chicken embryos was first demonstrated by Kolb and Wakelam (950). In later papers reviewed by Burnstock (264) from the groups of Heilbronn and Thomas and Hume, ATP-induced cation influx was demonstrated in myotubes prepared from 11-day-old chick embryos and shown to be additive to cholinergic agonist action. The myotube P2 receptor triggers phosphoinositide turnover and alters Ca²⁺ influx through dihydropyridine-sensitive channels. ATP has a potent depolarizing action on myotubes derived from pectoral muscle cultured from 11-day-old chick embryos, and its physiological and pharmacological properties have been described. At embryonic day 6, ATP elicits vigorous contractions in all the muscles tested, but by embryonic day 17, none of the muscles contracts in response to ATP. However, denervation of muscles in newly hatched chicks leads to the reappearance of sensitivity to ATP, suggesting that the expression of ATP receptors is regulated by motor neurons. An immunohistochemical study of the distribution of 5'-nucleotidase during the development of chick striated muscle showed that the adult exhibits a more restricted distribution compared with the embryo. An ortholog of the mammalian P2X₁ receptor has been identified in embryonic chicken skeletal muscle, perhaps forming heteromultimers with P2X₄ and P2X₅ receptor subunits (1615). P2X₅ and P2X₆ receptors were identified in developing chick skeletal muscles (1147, 1465).

Purinergic receptors have been characterized in mouse C2C12 myotubes (732). P1 receptors activating cAMP formation were identified, and a P2 receptor was also postulated, sensitive to ATP, ADP, and ATP γ S. This receptor was also sensitive to UTP, but not to α,β -meATP, 2-MeSATP, GTP, or CTP, thus resembling the P2Y₂ (or P2Y₄) receptor. The response to ATP and UTP was biphasic, a transient hyperpolarization being followed by a slowly declining depolarization: the hyperpolarization was blocked by apamin and suramin and abolished under Ca²⁺-free conditions. Functional studies have been described, which are consistent with the presence of P2X receptors in freshly isolated skeletal muscle cells from prenatal mice (375). At postnatal day 1, a bright punctate staining pattern for P2X₇ receptors was present at mouse motor nerve terminals. At 7 days, the pattern of staining of P2X₇ receptors was characteristic of adult terminals (1176). It was concluded that P2X₇ receptors are found in both myelinating Schwann cells and motor neuron terminals, suggesting an autoregulatory role for ATP released by nerve terminals during synaptic transmission.

ATP released at the neuromuscular junction is involved in regulation of skeletal muscle development and proliferation. P2Y₁ receptors appear to modulate muscle development via dual signaling mechanisms, i.e., IP₃ receptor-modulated Ca²⁺ transients and Ca²⁺-insensitive phosphorylation of ERK1/2 (1124). Transient changes in responsiveness to ATP (1849) and in P2 receptor expression have been described in developing skeletal muscle (1147, 1468, 1469). In particular, P2X₅, P2X₆, and P2X₂ receptors were expressed in a sequential manner. P2X₅ and P2X₆ receptors appear to be associated in the development of the myotube, while P2X₂ and P2Y₁ receptors appear to be involved in the formation of the skeletal neuromuscular junction (361, 1051, 1469; M. Ryten, R. Koshi, G. Knight, M. Turmaine, D. Cockayne, A. Ford, and G. Burnstock, unpublished data).

There have been a number of studies of the actions of ATP in developing *Xenopus* neuromuscular synapses by Fu and colleagues (586, 587). Extracellular applications of ATP to developing *Xenopus* neuromuscular synapses in culture potentiate ACh responses of developing muscle cells during the early phase of synaptogenesis. The possibility that extracellular ATP, coreleased with ACh, may serve as a positive trophic factor at developing neuromuscular synapses was also raised. It was further suggested that CGRP and ATP coreleased with ACh from the nerve terminal may act together to potentiate postsynaptic ACh channel activity during the early phase of synaptogenesis. CGRP actions are mediated by cAMP-dependent PKA, while ATP exerts its effects via PKC. It was suggested that endogenously released ATP, acting in concert with various protein kinases, is involved in the maintenance and/or development of the quantum size of synaptic vesicles at embryonic neuromuscular synapses.

5. Gastrointestinal tract

In the gastrointestinal tract, NANC nerve-mediated effects were observed before birth in mouse and rabbit small intestine (633). Also, quinacrine fluorescence, which indicates the presence of high levels of vesicle-bound ATP, was observed before birth in enteric neurons of rabbit ileum and stomach, ~3 days before catecholamine fluorescence was detected in enteric nerves (403). NANC inhibitory and cholinergic excitatory innervation appear simultaneously in the rabbit at 17 days of gestation, and both were present in the mouse by the 16th day of gestation; however, the development of adrenergic innervation lagged far behind the other two components, clearly establishing that the intrinsic innervation of the gut is not adrenergic. An electrophysiological study of developmental changes in the innervation of the guinea pig taenia coli has been carried out (1943). The nonadrenergic (largely purinergic) inhibitory system appeared before and matured faster than the cholinergic excitatory system. The NANC inhibitory system was present by 8 weeks of gestation, while cholinergic excitatory transmission was not seen until birth. Responses to α,β -meATP were also recorded in the fetal taenia coli.

The perinatal development of nerves expressing P2X₃ receptors in the myenteric plexus of the rat stomach has been examined (1899). P2X₃ receptor immunoreactive nerves in the embryonic rat stomach are of both extrinsic and intrinsic origin. The extrinsic sensory nerve fibers first express P2X₃ receptors as early as E12 and extend rapidly onto the whole stomach by E14. In contrast, the intrinsic enteric neuron cell bodies showing positive for P2X immunoreactivity did not appear until birth (P1), reached peak numbers by P14, but decreased in maturing animals. Intraganglionic laminar nerve endings and intramuscular arrays were first seen postnatally at P1 and P7, respectively. P2X₃ receptor immunoreactive neurons in the gastric myenteric plexus expressed calbindin only in the early postnatal days, while 14–21% of neurons from P1 to P60 increasingly expressed calretinin. About 20% of P2X₃ positive neurons coexpressed NOS throughout perinatal development.

There have been several studies of postnatal developmental changes in purinergic signaling in the small intestine (see Refs. 264, 764). In rat duodenal segments, ATP and ADP produced contractile responses on postnatal day 1; this response increased with age, peaking on day 7, followed by a gradual decrease and was nonexistent by day 21. In contrast, the relaxant responses to ATP and ADP were apparent at day 21 and continued to increase up to day 70 (the latest age examined). Adenosine or AMP did not elicit responses before day 14, which were then small relaxations that increased with age. In a later study of rat duodenum, it was reported that, if the tissues were precontracted with carbachol, low concentrations of ATP

could be shown to produce relaxations from day 2 increasing with age, while higher concentrations of ATP (3 μ M and above) were excitatory, but only until day 15, and it was postulated that P2Y receptors mediated both relaxations and contractions. Weak responses to adenosine as early as day 2 were also reported. The response of the rat duodenum to the ganglion stimulant nicotine was contraction in neonatal rats, but changed from contraction to relaxation around the third postnatal week. The striking switch from contractile responses to purines to relaxant effects is probably associated with the major changes that take place in the gut at weaning, which occurs during the third postnatal week, when the food source and composition change from being liquid and rich in fat to being solid and rich in carbohydrate.

In a study of the ontology of P1 receptor signaling in the longitudinal muscle of the rat duodenum, it was shown that A_{2B} receptors are present at day 15, but A₁ receptors did not appear until after day 20, both receptor subtypes mediating relaxation and that A_{2B} receptors mediated contraction of the muscularis mucosa from day 10. The ontogeny of P2 receptors in the duodenum was also examined. It was concluded that P2Y receptors mediate relaxation of the longitudinal muscle at day 25, while in the muscularis mucosa, P2Y receptors mediate contraction, but that after day 20, contractions are mediated by P2X receptors, as well as P2Y receptors.

Responses to adenosine, ATP, and α,β -meATP were examined in the rat colon longitudinal muscle and muscularis mucosa during postnatal development. The longitudinal muscle relaxes via A_{2B} and P2Y receptors, while the muscularis mucosa contracts through A₁ and probably P2Y₂ or P2Y₄ receptors. The contractile responses of the muscularis mucosa to all three agonists were observed from the day after birth, but much lower than in the adult; the responses increased with time to reach a maximum at days 10–15, at which time they were greater than in the adult.

In a recent study of the postnatal development of P2 receptors in the mouse gastrointestinal tract (638), pharmacological and immunohistochemical studies were combined to show that from P3-P8, P2Y₁ receptors mediated contraction, but there was relaxation of longitudinal muscle throughout the gastrointestinal tract from day 12 onwards and was via P2Y₁ receptors located both on smooth muscle and on a subpopulation of myenteric neurons; P1, P2Y₂, and/or P2Y₄ receptors and α,β -meATP selective P2Y receptors were also present in intestinal smooth muscles. During postnatal development, the relaxant response mediated by P2Y₁ receptors gradually appeared along the length of the gastrointestinal tract, being detectable in the stomach from day 3, from day 6 in the duodenum, from day 8 in the ileum, and from day 12 in the colon. The shift from contraction to relaxation occurs 1 wk before weaning and may contribute to the changes that take place in

the gut when the food composition changes from maternal milk to solid food.

6. Cardiovascular system

The development of A₁ adenosine receptors in the heart has been studied extensively (see Ref. 264). Functional A₁ receptors are present in greater numbers in the immature perinatal heart than in the adult rat heart. There is no indication that the origin of the adenosine is neuronal. Adenosine was claimed not to be as effective as a vasodilator of internal carotid arteries in the newborn pig as it is in the adult. In fetal sheep, centrally administered adenosine influences cardiac function. Intravenous infusion of adenosine analogs into fetal lambs produced dose-dependent bradycardia and hypotension. In contrast, in the newborn, 5'-N-ethylcarboxamidoadenosine produced dose-dependent tachycardia, while R-PIA and cyclohexyladenosine produced dose-dependent bradycardia. Differential expression of A₁ and A_{2A} receptor genes in rat peripheral arterial chemoreceptors has been observed during postnatal development (623). Increased myocardial adenosine production and reduction of β -adrenergic contractile response was described in the hearts of ageing rats. Later, it was shown that there was an increase in density of A₁ receptors in rabbit heart in old age in contrast to the diminished β -adrenergic responsiveness in the senescent heart.

P2 receptors are widely expressed in human fetal heart (165). Sequence analysis demonstrated P2X₁, P2X₃, and P2X₄ receptor subtypes as well as P2Y₂, P2Y₄, and P2Y₆ receptors were present. It has been claimed that a new subunit of the P2X receptor family had been isolated from cardiomyocytes and brain from 14-day-old chick embryos; the primary sequence shares 75% identity with the rat and human P2X₄ receptor, suggesting that the cDNA isolated may be the corresponding chick isoform and the pharmacological properties of the receptor expressed in *Xenopus* oocytes were consistent with this view (1464).

Multiple P2Y receptor subtypes are expressed in rat heart, and the expression in myocytes changes from neonate to the adult. P2Y₁ receptors are expressed at higher levels compared with P2Y₂, P2Y₄, and P2Y₆ receptors in the neonatal myocyte, while P2Y₄ receptors could not be detected in the adult myocytes. Intravenous injection of ATP and α,β -meATP increased heart rate in rats aged 21, 56, and 100 days, but had a more potent effect in 21-day-old animals (48). Extracellular ATP has been shown to inhibit adrenergic agonist-induced hypertrophy of neonatal cardiac myocytes and alter differentially the changes in gene expression that accompany hypertrophy. ATP had been previously shown by this group to increase expression of the immediate-early genes *c-fos* and *jun B* in cultured neonatal cardiac myocytes, but by a different

pathway from that produced by NE. UTP, but not ATP, causes hypertrophic growth in neonatal rat cardiomyocytes, while prolonged exposure to ATP, but not UTP, has hypertrophic growth-inhibitory effects (1340).

Age-related changes in P2 receptor mRNA have been observed in rat arteries (1149). In basilar artery from 19-compared with 2-mo-old rats, P2X₁ receptor mRNA was reduced, but P2Y₁ and P2Y₂ receptor mRNA increased. In the mesenteric artery of the rat, the sympathetic and sensory nerve fiber plexuses develop over the first three postnatal weeks, but functionally mature nerve-mediated contractile responses cannot be elicited before 14 days postnatally. From day 9 onwards, EJPs, which were resistant to α -adrenergic antagonists, were recorded and are likely to be mediated by ATP (see sect. IIIA). Prior to this period, intracellular recordings from animals aged 4–9 days showed slow depolarizing potentials, which were mediated by α -adrenoceptors. Following denervation studies in the rat mesenteric vascular bed, electrical responses similar to those seen during the early stages of development were recorded, suggesting that a similar sequence of events occurs during regeneration as takes place during development. A developmental profile for P2X receptor subtype mRNA expression in rat mesenteric artery showed very strong expression for P2X₁ and P2X₄ at postnatal day 7, which was retained during development until day 360 (the oldest animals examined) (1341). P2X receptor mRNA was described in postnatal rat mesenteric arteries (739). P2X₁ and P2X₄ receptors were strongly expressed, P2X₂ and P2X₇ receptors less so, while P2X₃ and P2X₅ receptors were weakly expressed and there was no expression of P2X₆ receptors; no differences in expression were seen between 7 and 28 days postnatally.

There are conflicting reports about changes in purinergic signaling in the vascular system in old age, but this may be explained by the wide variation in expression of P2 receptor subtypes in different vessels in different species and in different pathophysiological conditions. Age-related changes have been described concerning the relative importance of NE and ATP as mediators of the contractile responses of the rat tail artery to sympathetic nerve stimulation; the ATP component is dominant in young rats, but declines with age (90). In some young rats, ATP appeared to be the sole mediator of the sympathetic contractile response in the tail artery, and in a recent study, the shift from purinergic to adrenergic signaling was confirmed and also showed that the responses to ATP and α, β -meATP, as well as the expression of P2X receptors decreased with age (1817). Contractile responses to 2-MeSADP and UTP and expression of P2Y₁ and P2Y₂ receptors, respectively, were also decreased with age. The authors speculated that the dramatic reduction in expression of P2 receptors in the rat tail artery during development and aging are related to the role of the tail

artery in temperature regulation. ATP-induced constriction of rat mesenteric arteries decreases with age (957). The rat mesenteric artery contracted to UTP, the responses at 4 and 6 wk being longer than at other ages, although P2Y₂ receptor expression did not significantly differ with age (1817). In a review about the development of autonomic control of blood vascular tone, Hill et al. (739) make the point that expression of neurotransmitter receptors on postjunctional sites may be largely independent of neural influence. ATP acts as a cotransmitter with NE in sympathetic nerves supplying blood vessels in young human skin; however, NE becomes the dominant neurotransmitter in old age (1707). Aged rat cerebral microvessels show reduced ATPase activity, perhaps contributing to the altered blood-brain barrier functions found in old rats (1171).

7. Lung

Early papers about the development of purinergic signaling in the lung have been reviewed (264). ATP and UTP evoke $[Ca^{2+}]_i$ signals in rat fetal lung epithelial cells, but only if grown into functionally polarized epithelia. In another study of epithelia explanted from fetal rat lung, receptors to adenosine, ATP, and UTP were present on apical membranes throughout the lung; basolateral receptors for these agonists in distal lung and in trachea function later in gestation. In E19 rat embryos, P2X₇ mRNA was detected by in situ hybridization in bronchial epithelium. In newborn rats, ATP increased surfactant secretion as early as day 1, but the effect of UTP did not become significant until 4 days after birth. Fetal breathing movements were interrupted by adenosine analogs, but they did not produce apnea in newborn lambs. ATP, ADP, and adenosine are claimed to be important mediators of oxygen-induced pulmonary vasodilatation in fetal lambs, probably via both A_{2A} and P2Y receptors (955). Vagal sensory nerve terminals in rat lung express P2X₃ receptors from the first moment that they make contact with NEBs a few days before birth (218). This is consistent with the important function of NEBs as oxygen sensors perinatally before the carotid body O₂-sensory system is fully developed at ~2 wk after birth. The effect of the adenosine agonist R-PIA on respiration was studied in rabbit pups (1–8 days old). It has been claimed that adenosine plays a central role in modulating ventilation in the newborn piglet and is involved in the diphasic ventilatory responses to hypoxia. Postnatally, at 3 days, adenosine released from the CNS and within the kidney is a major contributor to the secondary fall in ventilation and renal vasoconstriction, whereas at 3 wk adenosine makes little contribution to the ventilatory responses or renal vasoconstriction, although it is largely responsible for hypoxia-induced vasodilatation in skeletal muscle.

8. Urinary bladder

In fetal human bladder, expression of P2X₁ receptor transcripts was much lower than in adult bladder; P2X₄ and P2X₇ receptors were also present in the fetus (1267). With increasing gestation, the P2 receptor expression shifted from the dome to the body of the bladder. Obstruction of the fetal male sheep bladder leads to enlarged, hypocontractile, and compliant bladder; however, there was no clear evidence for changes in purinergic (or in cholinergic or nitrenergic) neurotransmitter effects (1702).

ATP and ACh are cotransmitters in parasympathetic nerves supplying the bladder (see Ref. 265). In an early study of the responses of the rabbit urinary bladder to autonomic neurotransmitters, receptors to ATP and ACh were recognized in the newborn animals, but adrenoceptors were poorly expressed until a later stage. Newborn bladders were shown later to generate much greater tension in response to ATP than adult tissue and then decline, while the response to cholinergic agonists did not decline. Responses of rat urinary bladder to adenosine (inhibitory) and ATP (excitatory) mediated by P1 and P2X receptors, respectively, were present as early as postnatal day 2, the earliest day studied. Adenosine was more potent in the neonate than in the adult, while the potency of ATP initially increased with age, but then declined, being highest between postnatal days 10 and 25. In a recent study it was shown that the main pathway for nerve activation of the urinary bladder of newborn mice is cholinergic, with a low contribution of the purinergic component, while adult bladder is equally dependent on cholinergic and purinergic components (510). The authors claimed that these differences were due to properties of ATP release, rather than to a change in receptor function.

The rate and pattern of breakdown of ATP and adenosine by ectoenzymes in the rat urinary bladder were shown to be identical in neonates and adults, indicating that the marked differences in potency to ATP and adenosine during development is likely to be due to changes in receptor number and/or agonist affinity or efficacy. The distribution of P2X receptors on smooth muscle cells during postnatal development has been studied (501). Small clusters of P2X receptors (~0.4 μm in diameter) were present at day P1, although few varicose nerve fibers were present at this time. At P4, many varicose fibers were present and small clusters of P2X receptors; some appeared to be in association with varicosities. By P21, many of the P2X receptor clusters were found adjacent to varicosities of parasympathetic nerve fibers, but others were not. Newborn rat detrusor smooth muscle showed markedly increased purinoceptor-mediated contractions, which reached adult levels 1 mo after birth (1735).

The contractile response of the rat bladder to ATP released as a cotransmitter from parasympathetic nerves increases with age (855). The contractile responses of the aged rat bladder to ATP are significantly greater than those of the young bladder, although there is no change in the responses to ACh or KCl (1480). The atropine-resistant (purinergic) component of nerve-mediated contractions of the human bladder was also increased with age, largely due to increased release of ATP (1940). The sensitivity of the bladder to α,β-meATP increased with age (1891). However, the mRNA detected for P2X₁ and P2X₃ receptors did not change with age.

9. Inner ear

During embryonic development of the rat inner ear, P2X₂ receptor mRNA expression was present in the precursors of the cells bordering the cochlear endolymphatic compartment at E12, as well as spinal and vestibular ganglia (765). Both inner and outer hair cells did not exhibit P2X₂ receptor mRNA until after P10 through P12, concomitant with the onset of hearing. These data are consistent with roles for the P2X₂ receptor both in the process of labyrinthine development and in the regulation of auditory and vestibular sensory transduction. A later paper from this group showed that P2X₁ receptors provide the signal transduction pathway for development of afferent and efferent innervation of the sensory hair cells and purinergic influence on cochlea morphogenesis (1246). P2X₃ receptor expression has been characterized in the mouse cochlea from E16 using confocal immunofluorescence (774). From E18 to P6, spiral ganglion neuron cell bodies and peripheral neurites projecting to the inner and outer hair cells were labeled for P2X₃ receptor protein, but diminished around P6, and were no longer detected at the onset of hearing (around P11). These data suggest a role for P2X₃ receptor-mediated purinergic signaling in cochlea synaptic reorganization and establishment of neurotransmission that occurs just prior to the onset of hearing function (775).

10. Vas deferens and seminal vesicles

Changes in purinergic signaling in the vas deferens might be expected to occur later than in the gut, because rats are not sexually active until ~10 wk, although the morphology of the vas deferens appears mature by day 35. ATP and NE are now well established as cotransmitters in the sympathetic nerves supplying vas deferens (see sect. IIIA). As far back as 1970, it was shown that EJPs, now known to be produced by ATP in response to nerve stimulation of the vas deferens, were not observed for mice of less than 18 days postnatal (602). Another early study of postnatal development of functional neurotransmission in the rat vas deferens showed that at 3 wk postnatal (the earliest time studied), the responses to the

field stimulation with single or trains of pulses lacked the adrenergic component, although the nonadrenergic component was present (1087). Responses to ATP first appeared at day 15 and increased with age (764).

Examination of the ontogeny of P1 receptors, which mediate inhibition of neurotransmission by sympathetic nerves in the rat vas deferens, showed that adenosine, acting via prejunctional A₁ receptors, inhibited when nerve-mediated contractions were first seen at day 15, but that its potency decreased with age. Inhibitory postjunctional A₂-like receptors were also identified in the rat vas deferens, although the selective agonists and antagonists available at that time do not make the observation decisive. It was later claimed that inhibitory postjunctional A₂-like receptors and prejunctional A₁ receptors were present from days 10 and 15, respectively. In contrast, they identified postjunctional excitatory A₁ receptors that did not appear until after day 20. In 2-wk-old guinea pigs, stimulation of the hypogastric nerve produced monophasic contractions of the vas deferens, which were only partially blocked by the combination of prazosin and α,β -meATP, suggesting the involvement of an unknown transmitter; however, in 10- to 15-wk-old animals, stimulation produced a biphasic contraction, which was almost completely inhibited by both blockers. Sympathetic nerve-evoked contractions of the circular muscle layer of the guinea pig vas deferens showed significant decrease with increasing age, apparently due to postjunctional rather than prejunctional mechanisms, responses to α,β -meATP decreasing in parallel. In old guinea pigs, the purinergic component of sympathetic cotransmission is dominant in seminal vesicles (1353).

11. Other organs

Ectoenzymes for purines have been measured in the developing rat testis; it was concluded that full metabolic involvement in terms of Mg²⁺-ATPase and 5'-nucleotidase is not achieved until 45 days postnatal. Adenosine is important in regulating the action of insulin on rat fat cell metabolism during postnatal development and aging.

There is abundant expression of P2Y₂ receptors in NE-containing adrenal chromaffin cells and very little on epinephrine-containing cells in mature rats. However, in newborn rats, P2Y₂ receptors are expressed equally on both NE and epinephrine-containing cells, and by 1 wk, the majority of P2Y receptor labeled cells contain epinephrine (16). There is a dramatic loss of P2Y₂ receptor expression on both NE- and epinephrine-containing cells in the adrenal gland of old (22 mo) rats compared with newborn animals. Thus ATP, acting via P2Y₂ receptors, may influence the phenotypic expression of chromaffin cells into NE- or epinephrine-containing cells during early development and aging.

There is differential coupling of P2Y₁ receptors to G α_{14} and G $\alpha_{q/11}$ proteins during the development of rat salivary (submandibular) gland; two bands (42 and 52 kDa) were detected in 1-wk-old rats, but only the 42-kDa band was present in the submandibular gland cells of 4- to 6-wk-old rats (81). P2X₁ and P2X₄ receptor expression increased in islet pancreas in old age, while P2Y₁ receptor expression was lost (397). ATP and ADP and, to a much lesser extent AMP and adenosine, increase insulin secretion from the isolated, perfused newborn dog pancreas. Merkel cells appear in the epidermis of the planum nasale of rat fetuses from the 16th day of intrauterine development, and nerve fibers form close association with them by day 20. This is of interest since it is known that Merkel cells contain high levels of peptide-bound ATP and are in close association with sensory fibers expressing P2X₃ receptors (see Ref. 295).

B. Purinergic Neurotransmission in Invertebrates and Lower Vertebrates

There are many reports of the extracellular actions of purine nucleosides and nucleotides in invertebrate and lower vertebrate species, which were reviewed by Burnstock in 1996 (258). However, few attempts have been made to clone the receptors involved, with the exception of the Platyhelminth parasite *Schistosoma mansoni*, where P2X₁-like cloned receptors have been reported (17), a P2X-like receptor in the nematode *Caenorhabditis elegans* involved in mechanotransduction and neurodegeneration (758), and a putative P2X receptor from genome sequencing in *Dictyostelium discoideum*, a cellular slime mold (1076). Nevertheless, the pharmacological characteristics suggest that P1-, P2Y-, and P2X-like receptors are present early in evolution.

1. Invertebrates

A) COELENTERATES. Encompassing the jellyfish, sea anemones, and corals, these mainly marine organisms are radially symmetrical with a two-layered body wall enclosing a single cavity with a single aperture, the mouth. The pedal disc of the sea anemone, *Actinia eqina*, has been shown to possess a purinoceptor that is responsive to ATP, ADP, and adenosine, all of which cause contractions. ATP causes ciliary reversal in the comb plates of ctenophores, probably by increasing intracellular Ca²⁺. While there is no direct evidence for the source of ATP being nerves in these events, both pedal discs circular muscle and comb plate cells are innervated. Hair bundle mechanoreceptors of sea anemones are similar to those of the acousticolateralis system of vertebrates. Evidence has been presented to suggest that ATP released from sensory neurons after the hair bundles it supplies lose

their structural integrity, enhances the repair process in sea anemones (1840).

B) PLATYHELMINTHS. A P2X-like receptor (SchP2X or SmP2X) has been cloned and characterized from the parasitic blood fluke *Schistosoma mansoni* and is the first clear example of a nonvertebrate ATP-gated ion channel (17, 1395). A number of functionally important amino acid residues conserved throughout the vertebrate P2X receptor subtypes are also present in SchP2X. These include 10 extracellular cysteines, aromatic and positively charged residues involved in ATP recognition, and a consensus PKC site in the NH₂-terminal tail. The amino acid sequence identity of SchP2X receptors with human P2X₁₋₇ receptors ranges from 25.8 to 36.6% homology. ATP evoked concentration-dependent currents at SchP2X channels expressed in *Xenopus* oocytes with an EC₅₀ of 22.1 μM. BzATP was a partial agonist, with a higher potency than ATP. Suramin and PPADS, but not TNP-ATP, blocked SchP2X receptor-mediated responses, while ivermectin potentiated ATP-evoked currents. The SchP2X receptor has a relatively high calcium permeability and an estimated minimum pore diameter similar to that of vertebrate P2X receptors. SmP2X mediates the uptake of the dye Yo-Pro-1 through the formation of large pores and can be blocked by submicromolar concentrations of Zn²⁺ (1395).

C) ECHINODERMS. This phylum includes the starfishes, sea urchins, brittle stars, feather stars, and sea cucumbers. The nervous system consists of a nerve ring around the oral part of the gut with projections along the radii. Many echinoderms have a deeper-lying motor nerve component. There are several reports of the effects of purine compounds in echinoderms. In a review of several marine species, Hoyle and Greenberg (767) found that adenosine, AMP, ADP, and ATP all relaxed the gastric ligament of the starfish *Asterias forbesi*, with ATP being the most potent of the purines examined.

ATP (as well as ACh and octopamine) produce tonic contractions of the spine muscle of the sea urchin, and these were proposed to be neurotransmitters released from the nerves that supply these muscles (1557). ATP and adenosine had a potentiating effect on ACh-induced luminescence in the brittle star, *Amphipholis squamata*, and it was suggested that ACh and ATP might be synergistically acting cotransmitters from the nerves that control luminescence (431).

D) ANNELIDS. This phylum comprises the segmented worms, including the polychaetes, oligochaetes, and hirudines. The worms possess both circular and longitudinal body muscles. The nervous system consists of dorsal cerebral ganglia and ventral nerve cord, with nerve cells along the length of the cord, not necessarily confined within ganglia, and with peripheral nerves from each segment. Electrophysiological investigations, using both intracellular microelectrodes and whole cell patch-clamp

recording on identified neurons in the central nervous system of the leech *Hirudo medicinalis*, revealed that ATP and ADP depolarized selected neurons (76). The most effective responses were observed in the noxious and touch cells. In most neurons the stable analog of ATP, ATPγS, induced larger depolarizations than ATP, indicating that ectonucleotidases were probably present. The authors concluded from further experiments that ATP activates nonselective cation channels in medial noxious cells of the leech with an order of potency ATP > ADP > AMP. This suggests that these cells express receptors of the P2X type, although suramin was not an effective antagonist of this receptor. In a more recent report, ATP was shown to dose-dependently depolarize or hyperpolarize leech neuropile glial cells in the CNS, probably via P2Y receptors, and some ATP-insensitive cells responded to adenosine (1191). Salivary cells of the leech *Haementeria ghilianii* exhibit a selective response to ATP, but not adenosine, modulating action potential firing, thought to be via a mammalian-like P2 receptor. A later study showed that the P2 receptor involved was suramin insensitive and that activation by ATP inhibited Ca²⁺ influx through voltage-gated Ca²⁺ channels (1892).

E) NEMATODES. The nematode parasite *Trichinella spiralis* invades the small intestine of mammals by migration of infective larvae through the mucosal epithelial cells. It has been shown that these larvae secrete a cascade of enzymes that hydrolyze ADP and UDP (663). The authors speculate that since bacterial pathogens and hematophagous insects also secrete similar enzymes and that purinergic receptors regulate different facets of immune and inflammatory responses, the parasite can modulate these to its own advantage.

F) MOLLUSCS. These animals do not show segmentation, with the body consisting of a head-foot and visceral mass extended into the folds, which often secrete a shell. The nervous system consists of ganglia connected by commissures. This group includes snails, bivalves, and octopuses. Nanomolar concentrations of extracellular ATP were shown in an early study to activate membrane Ca²⁺ channels in identified F1, F2, E1, and E2 neurons from the subesophageal ganglia of the snail, *Helix aspersa* (1930). The hearts of the snail *H. aspersa* and the slug *Arion ater* are responsive to adenine nucleotides and nucleosides. ATP and α,β-meATP enhanced the excitatory responses of F1 neurons to ACh in this species, while adenosine depressed these responses, suggesting that both P1 and P2X-like receptors are expressed. Nucleotidase activity in membrane preparations of subesophageal ganglia from *Helix* has been demonstrated (173). Exposure to heavy metals produced a significant inhibition of nucleotidase activities in the digestive gland of *H. aspersa* (438). ATP release from the molluscan CNS in response to KCl activation has been described using real-time imaging in situ in the intact nervous system (684). The freshwater

snail *Lymnaea* was used in this study because of the large size of its neurons and high sensitivity of ATP imaging in *Lymnaea* HEPES-buffered saline. Release varied between different ganglia and within ganglia. In general, nerves in the heart and gut of the pulmonate gastropod molluscs show a high affinity for quinacrine, suggesting that they contain high levels of granule-bound ATP. Uptake and metabolism of [³H]adenosine has been shown for neurons of ganglia of the sea hare *Aplysia*. A unique Ca²⁺-activated ATPase has been identified in the ganglia of the slug *Phyllocaulis soleiformis* (416). AMP was found to be the most potent chemoattractant of *Octopus vulgaris*, initiating a locomotor response. The arms are believed to carry the sensory organs, with chemoreceptors having been morphologically identified in the suckers, which would direct the arms towards the meal.

G) ARTHROPODS: CRUSTACEANS. The phylum Arthropoda includes crustaceans, centipedes, millipedes, insects, and arachnids. The CNS consists of cerebral ganglia and a ventral nerve cord made up of separate paired ganglia connected by commissures. There is a contractile heart lying in a hemocoelic pericardial cavity.

There is considerable information about the effects of ATP and adenosine in crustaceans in the early literature, particularly by Carr and colleagues, which has been reviewed (258). The olfactory organ of the spiny lobsters *Panulirus argus* and *Panulirus interruptus* have different populations of purinergic chemoreceptors that are excited by AMP, ADP, or ATP, via receptors that show similarities to P1 and P2 receptors described in vertebrates. These receptors reside on chemosensitive neurons that are contained within aesthetasc sensilla on the lateral filaments of the antennules. 5'-AMP odorant receptor sites have been localized ultrastructurally, utilizing 5'-AMP-biotin, along the entire dendritic region, including the transitional zone between inner and outer dendritic segments, the region that also contains 5'-ectonucleotidase and phosphatase. Since these receptors are more sensitive to the slowly degradable analogs of ATP, α,β -meATP and β,γ -meATP, they appear to be comparable to mammalian P2X₁ and P2X₃ receptors. Similarities between the P1 and P2 receptors of these crustacean and mammalian purinoceptor subtypes are extended further, in that the chemosensory sensilla inactivate excitatory nucleotides by a two-step process. Ectonucleotidases dephosphorylate adenine nucleotides to yield a nucleoside, which is internalized by an uptake system.

Activation of olfactory and gustatory P2 receptors in lobsters is thought to induce a feeding behavioral response. ATP is an ideal stimulus for such animals that feed on wounded or recently killed animals, since ATP occurs at high concentrations in fresh animal flesh but decays rapidly as cells die. Since predators, such as lobsters, often inhabit crevices and only emerge to feed at night, foraging is directed principally by chemical stimuli,

rather than visual or mechanical stimuli. ATP is detected in prey organisms, such as mussels and oysters, which contain high concentrations of nucleotides and are released when the animal dies. Modulatory actions of AMP and adenosine were recorded in brain cells of the spiny lobster. AMP was the most potent of the purines examined, and its effect was antagonized by theophylline. Olfactory purinoceptors have also been identified in the shrimp *Palaemonetes pugio* and blue crab *Callinectes sapidus*. In lobsters and other decapod crustaceans, the sites of olfaction and gustation are anatomically distinct, the former in the antennules, the latter on the walking legs, maxillipeds, and mouth parts. The sensilla on the walking legs of the spiny lobster, *Panulirus argus*, have also been shown to possess ATP- and AMP-sensitive cells as well as enzymes that dephosphorylate purine nucleotides.

Extracellular ATP has been shown to modulate calcium uptake and transmitter release from neuromuscular junctions in the walking leg of the crayfish, *Procambarus clarkii*, reminiscent of purinergic modulation of transmitter release at the skeletal neuromuscular junction of vertebrates. The presence of presynaptic adenosine receptors regulating transmitter release at insect motor nerve terminals has been demonstrated (1092). The inhibitory effects of ATP on the heart of the spiny spider crab *Maiia* were reported many years ago (1850). ATP potentiates the effects of electrical field stimulation of neurons in the terminal intestine of the lobster *P. argus* via a P2-like receptor (767).

H) ARTHROPODS: INSECTS. ATP released from mammalian erythrocytes stimulates the gorging responses in a variety of blood-feeding insects such as the mosquitoes, *Aedes aegypti* and *caspius*, *Culex pipiens univittatus* and *quinquefasciatus*, and *Culiseta inornata*; the blackfly, *Stimulium venustum*; the horse fly, *Tabanus nigrovittatus*; the stable fly, *Stomoxys calcitrans*; the tsetse fly, *Glossina austeni morsitans*, *tachinoides*, and *palpalis*; the bug, *Rhodnius prolixus*; and the hematophagous ticks, *Ixodes dammini* and *Boophilus microplus* (see Ref. 258 for earlier references, Ref. 1851, and particularly the work of Galun and colleagues). Electrophysiological methods have been used to demonstrate that the apical sensilla of the labrum of *Culex pipiens* express the ATP receptors involved in blood feeding. Novobiocin, which blocks ATP access to its binding site on ATPase, inhibits the gorging response. The ED₅₀ of ATP for tsetse fly, *Glossina tachinoides*, females is 13 nM, while for males it is 140 nM; this level of sensitivity for detecting ATP is the highest recorded for an insect (616). Other chemosensory P2 receptors have been identified that are involved in the recognition of a blood meal in hematophagous insects. These represent a heterogeneous group. Many blood-feeding insects recognize ATP and related compounds as phagostimulants. In mosquitoes and tsetse flies, ATP is found

to be more potent than ADP at stimulating feeding, while AMP is a very poor phagostimulant, indicating an ATP-selective P2 receptor. A similar ATP-selective receptor mediates the phagostimulatory response of *Glossina tachinoides* and *Rhodnius prolixus* larvae, suggesting that this response is not limited to the adult form. Further investigations have revealed that α,β -meATP and β,γ -meATP are less potent than ATP as phagostimulants in *Glossina palpalis palpalis* and the possibility that the receptor involved may be a P2Y receptor was raised (616). A similar order of potency was found for *Rhodnius prolixus*. A P2 receptor has also been identified that initiates feeding of the culicine mosquitoes *Culex pipiens* and *Culiseta inornata*. The potency order was found to be ADP > ATP \geq AMP > β,γ -meATP for *C. pipiens* and ADP > ATP > β,γ -meATP >> AMP for *C. inornata*. ADP was also found to be the most potent phagostimulant of the horsefly *Tabanus nigrovittatus*. ADP-selective receptors, namely, P2Y₁, P2Y₁₂, and P2Y₁₃, have been identified in mammals. In contrast, in the stable fly the ATP-mediated response is antagonised by ANAPP₃, suggesting a receptor that resembles the P2X receptor subtype.

It is fascinating that apyrase (ATP diphosphohydrolase) has been reported to have exceptionally high activity in the salivary glands or saliva of blood-sucking insects, including the bug *Rhodnius prolixus*, tsetse fly mosquito, and sandfly. In all cases, since ADP induces platelet aggregation, breakdown of ADP by apyrase leads to enhanced hemorrhage and more effective blood sucking.

Taste chemosensilla sensitive to nucleotides have been identified in some nonhamatophagous insects. ATP was first reported to be a feeding stimulant in a flea, *Xenopsylla cheopis*, and tick, *Ornithodoros tholozani* (617). In the omnivorous common blowfly *Phormia regina*, ATP does not have a direct stimulatory action, but rather modulates the responses of the labilla sensilla; it reduces the responses to NaCl and fructose, but enhances responses to sucrose and glucose. Adenosine stimulates feeding in the African army worm *Spodoptera exampta*; this larva of an owlmoth exclusively feeds on grasses. There are multiple nucleotide receptor sites in the labelar taste receptor cells of the flesh fly, *Boettcharisca peregrina*: ATP, ADP, and AMP stimulate the sugar receptor cells, while the salt receptor cells only responded to GDP and to a lesser extent IDP and UDP (605). A *Drosophila* temperature-sensitive seizure mutant in phosphoglycerate kinase disrupts ATP generation and alters synaptic function (1828).

2. Lower vertebrates

The vertebrates are characterized by the presence of a notochord at some time during their life history and a high degree of cephalization so that a proper head region is recognizable, with a brain enclosed by a cranium. The

cyclostomes comprise one class, and the Gnathostomata encompass all the more familiar vertebrates, including elasmobranchs, teleosts, amphibians, reptiles, birds, and mammals. Studies of purinergic signaling in lower vertebrates up to 1996 have been reviewed by Burnstock (258), so the emphasis in this section is largely on research carried out since that time.

A) ELASMOBRANCH FISH. There are various reports of the effect of purine compounds in elasmobranch cartilaginous fish, including reactivity in both the gastrointestinal and cardiovascular system, partly by ATP released from nerves. Studies in the 1980s by J. Z. Young (see Ref. 258) showed that spontaneous activity in various preparations of elasmobranch gut were inhibited by ATP, such as the stomach and spiral intestine of the ray *Raja clavata* and the dogfish *Scyliorhinus canicula* as well as the rectum of *Raja*. ATP was reported to cause contraction or relaxation of the rectum of the stomach of the dogfish, contraction of the stomach of the ray, and relaxation of the rectum of the skate. There have been more recent reports of novel P2Y receptors on hepatocytes of the little skate *Raja ermanacea* (477). Purinergic modulation of vagal control of the heart of *S. stellaris* has been proposed. In the coronary artery of the skate *Raja nasuta*, ADP and ATP cause vasoconstriction in low concentrations but vasodilatation at higher concentrations. In the coronary artery of the mako shark *Isurus oxyrinchus*, adenosine is a dilator, as in the dogfish, and ADP is a vasoconstrictor.

The electric organ of electric elasmobranch fish, which is phylogenetically derived from neuromuscular junctions, consists of motor nerves and electrocyte cells forming electroplaques that are derived from myoblasts. Synchronous discharge of the electrocytes by motor nerve stimulation produces a total discharge of ~40 V. It has been shown that ACh and ATP are costored (in a ratio of ~5:1) and coreleased during synaptic activity of the electric organ of the electric eel *Electrophorus* and the electric ray *Torpedo* (see sect. III E). Synaptic vesicles of *Torpedo* electromotor neurons contain ~120 mM ATP, whereas free ATP is ~5–6 mM; decrease in the ATP concentration in synaptic vesicles increases the opening probability of the nonspecific ion channel in the vesicle membrane (19). Release of ATP from synaptosomes isolated from the electric organ of *Torpedo* by either depolarization with KCl or after the action of venom extracted from the annelid *Glycera* exhibited closely similar kinetics to that of ACh release. In addition to ATP and small amounts of ADP, the diadenosine polyphosphates Ap₄A and Ap₅A are both present in synaptic vesicles of *Torpedo marmorata*, and binding of Ap₄A to P2 receptors has been demonstrated in *Torpedo* synaptosomes and presynaptic plasma membranes. Vesicles from the closely related *Narcine* electric organ contain considerable amounts of GTP (17% of ATP content). One function for the ATP is that it increases receptor sensitivity to ACh,

i.e., it acts as a postjunctional modulator. A binding site from ATP within the extracellular region of the *Torpedo* nicotinic ACh receptor β -subunit has been demonstrated. A further role is that adenosine resulting from hydrolysis of ATP by ectoenzymes acts as a prejunctional modulator of ACh release. The ability of bound ectoenzymes, obtained from *Torpedo* electric organ synaptosomes, to dephosphorylate ATP to adenosine supported this hypothesis. This was later further substantiated as a result of chemiluminescent investigations and studies showing that adenosine can inhibit ACh release. ATP hydrolysis reduced by the inhibitory effects of suramin prevented the formation of adenosine and eventually prevented synaptic depression (1113). A cDNA encoding 5'-nucleotidase was identified by screening a cDNA library from the electric lobe of the electric ray.

ATP causes increases in intracellular Ca^{2+} in the perisynaptic Schwann cells of skate electric organ by activating P2Y receptors, suggesting that Schwann cells may be targets for synaptically released ATP (see sect. VIII C).

B) TELEOST FISH. ATP and adenosine both produce relaxation of the intestine of the Atlantic cod, *Gadus morhua*, and the circular muscle of the stomach of the rainbow trout, *Salmo gairdneri*. However, ATP contracts both the longitudinal and circular muscle layers of the intestinal bulb of the carp *Cyprinus carpio*, the intestine of the angler fish *Lophius*, and the intestine of the goldfish *Carassius auratus* (see Ref. 258). Adenosine relaxed the stomach and intestine of the stickleback *Gasterosteus aculeatus*, and this response was antagonized by 8-phenyltheophylline (8-PT), indicating the presence of a P1 receptor; ATP and its analogs, 2-MeSATP and α,β -meATP, caused contractions of the stomach and intestine, indicating a P2 receptor. ATP has been found to closely mimic the NANC responses to vagal stimulation of the pyloric caeci and duodenum of *Lophius*, even at very low concentrations, producing an inhibition followed by a rebound contraction. The ileum and rectum of the flounder, *Pleuronectes*, both possess excitatory P2X receptors and inhibitory P1 receptors.

Examples of the presence of various types of purinoceptors within the cardiovascular system include a P1 receptor in the gill vasculature of the rainbow trout *Salmo gairdneri* and of the tropical cichlid *Oreochromis niloticus* that mediates vasoconstriction. A P2 receptor is also likely to be present in the gill vessels, since the contraction potency order of purine compounds in the rainbow trout was ATP = ADP > AMP = adenosine, while ATP produced vasodilatation in cichlid. ATP constricts the systemic vasculature of the rainbow trout, and adenosine contracts the coronary artery of both the rainbow and steelhead trout.

Many fish are capable of spectacular color changes due to the motile activities of chromatophores, controlled

both by nerves and by hormones. These include melanophore-stimulating hormone secreted from the intermediate lobe of the pituitary, giving rise to darkening, often antagonized by melanin-concentrating hormone which causes blanching by aggregation of pigments. A role for purines in the neural control of fish chromatophores was first suggested by Fujii and Mayashita (590), in a study of dispersion of melanophore inclusions in the guppy *Lebistes reticulatus*. This was confirmed later with cultured goldfish erythrophores. Since methylxanthines antagonize the darkening reaction, it was concluded that an adenosine receptor was involved in the responses of melanosomes in the siluroid catfish, *Parasilurus*, of both melanophores and iridophores in the blue damselfish *Chrysiptera cyanea* and of leucophores in the medaka *Oryzias latipes*. In more recent studies of denervated melanophores in the medaka melanophore, dispersion by adenosine was antagonized by 8-PT and by adenosine deaminase, and the action of adenosine was mimicked by forskolin, a potent activator of adenylate cyclase. It was concluded that the P1 receptor involved was of the A_2 subtype. There is evidence that ATP is liberated as a cotransmitter together with NE from melanosome aggregating sympathetic nerves in the tilapia fish *Sarotherodon niloticus*. It seems likely that ATP released from sympathetic nerves is broken down by ectoenzymes to adenosine, which then acts on P1 receptors both on chromatophore membranes leading to dispersion of pigment, and also on prejunctional sites leading to modulation of sympathetic transmitter release (1284). In a more recent study, Fujii and colleagues (see Ref. 258) found that the circadian motile activity of the erythrophores in the red abdominal skin of the tetra tropical fish, *Paracheirodon innesi* and *axelrodi*, are controlled partly by ATP as well as adenosine.

A_1 adenosine receptor binding sites and/or pharmacological characteristics have been identified in the brain of goldfish, the brown trout, and both shallow and deep living marine fish. A_1 receptors mediate retinotectal pre-synaptic inhibition in the goldfish (1951) and ACh release from the brain of brown trout, *Salmo trutta* (1362), and synaptic transmission in eel, *Anguilla anguilla* (1363). NTPDase has been shown to be present in synaptosomes and prepared from fish brain (1513).

A NANC inhibitory response to electrical stimulation has been observed in the urinary bladder of the cod *Gadus morhua*; ATP has an excitatory effect on about half of the bladder preparations examined and was included as a putative candidate for the NANC transmitter. There is evidence that some fish are attracted to purine compounds in a manner similar to that of carnivorous crustaceans. Chemoreceptors on the lip of the puffer fish, *Fogo pandalis*, exhibit an especially high sensitivity for ADP and are thought to direct the fish to food sources.

It has been suggested that ATP released from the nerves supplying the testis of the rainbow trout influence the induction, speeding up, and later slowing down of spermatogenesis (1068). ATP, UTP, and UDP acting via P2 receptors are factors promoting regulatory volume decrease of trout hepatocytes, while adenosine acting on P1 receptors inhibits this process (1291). Two distinct ENTPDases have been identified in the liver of goldfish (33).

There are recent reports of the cloning and characterization of P2X₃ receptors in the zebrafish (507, 972). Expression of P2X₃ receptors was described in the trigeminal ganglion and spinal Rohon-Beard cells of the embryonic zebrafish (180, 1259). P2X₃ receptors are also expressed on nerve fibers supplying the gill (842). P2X₄ and P2X₅ receptor orthologs were also cloned from zebrafish (454). ATP and ADP hydrolysis by NTPDases and ecto-5'-nucleotidase in brain membranes of zebrafish have been described (1428) as well as inhibition of nucleotide hydrolysis by carbofuran and malathion (1539). Selective labeling of central and peripheral sensory neurons in the developing zebrafish has been described recently, using P2X₃ receptor subunit transgenes (973).

C) AMPHIBIANS. Evidence was presented in the early 1970s that ATP was a transmitter in the NANC nerves supplying the toad stomach duodenum and ileum (see Ref. 258). ATP, ADP, and AMP were shown to be released upon stimulation of vagal NANC fibers, and ATP mimicked the relaxation in response to nerve stimulation. Evidence that ATP is the transmitter substance released from NANC excitatory fibers in the splanchnic nerves supplying the small intestine of the toad was also presented, where again responses to nerve stimulation were mimicked by ATP. A P2X₇-like receptor has been identified in freshly dissected smooth muscle cells from toad stomach (1753). Cultures of ciliated cells from the frog esophageal epithelium and palate have been used as a model for studying the role of ATP in control of mucociliary activity. ATP in micromolar concentrations increases the ciliary activity by three- to fourfold in frequency and four- to fivefold in the rate of transport, as well as stimulating mucin release. ATP induces hyperpolarization and motility of ciliary cells. Activation of an apical Cl⁻ conductance by ATP in *Necturus* gallbladder is mediated by cAMP and not by [Ca²⁺]_i (1774).

Early studies of the effect of ATP on the frog heart have been reviewed (258). It has been shown that frog atria receive a NANC excitatory innervation. ATP has a biphasic action, initial excitation followed by inhibition, the excitatory effects being mediated by P2 receptors, while the inhibitory effects are mediated by P1 receptors, following the degradation of ATP to adenosine. The excitatory responses to ATP partially mimics NANC stimulation of the frog and toad heart where it is believed that ATP is a cotransmitter with epinephrine, acting on P2X

receptors. ATP also has a biphasic action on the heart of the axolotl, *Ambystoma mexicanum*. Unlike fish, the amphibian ventricle is sensitive to adenosine and ATP. Currents activated by extracellular ATP were studied on single voltage-clamped bullfrog atrial cells; two ATP-activated conductances were demonstrated. In frog ventricular cells, P2 receptors stimulate increases in Ca²⁺ current by a pathway that might involve phosphoinositide turnover. It was shown that under conditions of physiological stress, such as hypoxia, ATP is released from the heart. Thus ATP is available to directly modulate activity, and indirectly after degradation to adenosine. Adenosine excites ventricular muscle of *Xenopus laevis*, but is inhibitory in the axolotl. Adenosine exerts effects on the amphibian heart in a manner similar to its effect upon the mammalian heart, having negative chronotropic and inotropic effects, mimicking the response to ACh by slowing the heart. A study of single pacemaker cells isolated from the sinus venosus of cane toads showed that ATP produced biphasic effects, with an initial increase followed by a decline in firing rate; these effects are mediated by P2Y₁ receptors (846).

A P2 receptor has been identified in the aorta of frog that mediates vasoconstriction that resembles a P2X subtype in terms of agonist potencies and is antagonized by PPADS (934). However, no evidence for a P2Y receptor mediating vasodilatation was found. A prejunctional A₁ adenosine receptor has been shown to mediate inhibition of sympathetic nerve activities in frog cutaneous arterioles.

ATP has been implicated as a synaptic transmitter in both sympathetic and sensory ganglia of amphibians. After an early paper, where high concentrations of adenine nucleosides and nucleotides were shown to have depressant and hyperpolarizing actions on both dorsal and ventral root neurons in isolated hemisectioned perfused toad spinal cords (1346), ATP was shown to depolarize bullfrog sympathetic ganglion cells (1602). ATP inhibition of M current in frog sympathetic neurons involves PLC, but not IP₃, Ca²⁺, PKC, or Ras (1637). PPADS antagonizes the P2Y receptor-mediated inhibition of M current in bullfrog sympathetic neurons (1144). ATP also depressed the maximum amplitude of action potential afterhyperpolarizations, and it was suggested that ATP released with ACh from presynaptic nerve terminals may act as a modulator of nicotinic transmission. Inhibition of ACh release from preganglionic nerves supplying neurons in the ninth lumbar sympathetic chain ganglion of the frog, *Rana pipiens*, was claimed to be largely by ATP itself rather than by adenosine after breakdown of ATP (1570). ATP was later shown to increase the sensitivity of the nicotinic ACh receptor in bullfrog ganglia cells, and it was suggested that ATP had this effect by acting on an allosteric site of the ACh receptor-ionic channel complex. The concentration dependence and kinetics of ionic currents activated

by ATP have been studied in voltage-clamped DRG cells from bullfrogs. About 40% of the neurons responded with an increase in membrane conductance but showed rapid desensitization, typical of the P2X₃ receptor described in rat dorsal root neurons (120). Akasu and colleagues showed with dissociated bullfrog DRG cells that, whereas in small C-cell ATP (1–10 μM) activated a sodium-potassium current, in large A cells (~65 μm in diameter) ATP inhibited M current. In some bullfrog primary afferent neurons, ATP reversibly augmented GABA-induced depolarizations. Inhibition of ATP-activated current by zinc in DRG neurons has been demonstrated (1032).

Low concentrations of extracellular ATP, present in the perilymphatic compartment of the semi-circular canal of the frog inner ear, appear to play a role in vestibular physiology. The ampullary epithelium appears to express P2X and P2Y-like receptors including a P2Y UTP-sensitive receptor. P2 receptor occupancy regulates like transductive processes of sound and/or motion (298, 1691).

In keeping with mammalian and fish neuromuscular junctions (see sect. III E), ATP is released together with ACh from motor nerve endings of frog, where it can then act as a postjunctional potentiator of ACh action, and following breakdown by ectoenzymes to adenosine to act prejunctionally to inhibit ACh release (1573). ATP is released synchronously together with ACh in response to an individual nerve impulse and with a brief (millisecond) latency characteristic of quantal release from synaptic vesicles. Later studies show that when ATP is released as a cotransmitter, it acts presynaptically to inhibit ACh release both directly via P2Y (probably P2Y₂) receptors as well as via P1(A₁) receptors after breakdown to adenosine (1599, 1659). Adenosine inhibits a Ca²⁺-independent step of transmitter exocytosis (776), while the presynaptic depressant action of ATP is mediated by inhibition of Ca²⁺ channels and by a mechanism acting downstream of Ca²⁺ entry (678). It has also been discovered that reactive oxygen species contribute to the presynaptic action of extracellular ATP at the frog neuromuscular junction (646).

ATP has been shown to activate membrane current in frog Schwann cells, perhaps playing a role in neuroglial interactions, since perisynaptic Schwann cells at the frog neuromuscular junction showed increases in intracellular calcium during motor nerve stimulation, an effect mimicked by local application of ATP (see sect. VIII C). Since spontaneous ACh release is known to regulate the development of contractile properties of postsynaptic muscle cell, it was suggested that ATP coreleased with ACh may serve as a positive trophic factor at developing neuromuscular synapses. Endogenously released ATP may be involved in the regulation of synaptic quantum size at developing *Xenopus* neuromuscular synapses (587). All nine members of the NTPDase ectonucleotide family have been cloned in *Xenopus* (1118).

Injections of ATP into the third ventricle of the brain of the mud puppy, *Necturus maculosus*, elicited dose-related increases in thermal tolerance. Adenosine, via A₁ receptors, inhibits α-MSH from frog pituitary melanotrophs, suggesting that A₁ receptors may play a physiological role in regulation of hormone release from the intermediate lobe of the pituitary. Regulation of rhythmic swimming movements in frog embryos by purinergic signaling in spinal cord has been described (422).

Vagal stimulation of the visceral muscle of the lung of *Bufo marinus* is purely inhibitory and the transmitter unknown, although ATP was proposed as a candidate. Extracellular ATP raises cytosolic calcium and activates basolateral chloride conductance in the proximal tubule of the kidney of the urodele amphibian, *Necturus* (184). ATP increases ciliary beat frequency in epithelial cells of frog palate esophagus (1021). Evidence has been presented for both P2X receptor regulation of Na⁺ transport (211) and P2Y receptors (probably P2Y₂) on the serosal membrane (212) of frog skin epithelium.

D) REPTILES. In early studies (see Ref. 258), an excitatory NANC innervation was identified in the ileum of the lizard *Tiliqua rugosa*, stimulation of which was mimicked by ATP. An excitatory effect of ATP was also noted in the rectum of the rainbow lizard *Agama agama*.

There have been few studies of purinoceptors in the cardiovascular system of reptiles. Webb and Fenn (1841) reported variable responses to adenosine and ATP in the heart of the turtle. The ionic basis of the hyperpolarizing action of adenylyl compounds on sinus venosus of the tortoise heart was examined. In a study of purinoceptors in the aorta of the garter snake, *Thamnophis sirtalis*, it was concluded that both P1 receptors mediating vasodilatation and P2 receptors mediating vasoconstriction were present (933). However, in contrast to mammalian aorta, both P2X and P2Y subtypes mediated vasoconstriction; there was no evidence for vasodilatation by ATP or its analogs. In contrast, the portal vein of the rainbow lizard, *Agama agama*, dilated in the presence of ATP.

Release of ATP and adenosine from the brain of the freshwater turtle (*Trachemys scripta*) during long-term anoxia has been described (1082) that might have a neuroprotective role.

Purines play a central role in envenomation by most advanced venomous snakes involving prey immobilization via paralysis and/or hypotension and prey digestion (21). Since they are endogenous regulatory compounds in all vertebrates, it is impossible for any prey organisms to develop resistance to them. Adenosine contributes to prey immobilization by activation of neuronal A₁ receptors suppressing ACh release from motor neurons and excitatory transmitters from central sites. It also exacerbates venom-induced hypotension by activating A₂ receptors. Analysis of most snake venoms shows that free purines, principally adenosine, inosine, and guanosine,

are comprised of as much as 8.7% of the solid components (22).

E) BIRDS. Adenosine has been shown to modulate calcium currents in postganglionic neurons of cultured avian ciliary ganglia. A P2X-like purinergic receptor on cholinergic presynaptic terminals in the chicken ciliary ganglion has been identified that might mediate enhanced transmitter release (1669). P1(A₂) receptor-mediated stimulation of cAMP in cultured chicken pineal cells has been reported. P1 receptors were identified on both pre- and postganglionic cholinergic nerve terminals in the chick esophagus.

ATP is a potent dilator of vessels in the duck foot, where doses of 1.9–19 nmol produce falls in perfusion pressure comparable to those produced by stimulation of dorsal metatarsal nerves. ATP has also been shown to cause selective dilatation of arteriovenous shunts in the foot of the chicken. Since the feet of birds form an area of skin devoid of insulative feathers, change in blood flow is used to regulate body heat as well as preventing freezing of the foot so that purinergic receptors may play a part in this mechanism. A recent electrophysiological study of excitatory neuromuscular transmission in the longitudinal smooth muscle of chicken anterior mesenteric artery showed that the excitation was largely purinergic, mediated via P2Y receptors (899).

There is evidence for P2 receptors in different preparations of bird gut (see Ref. 258). The esophagus of the chicken contracts to ATP via a P2 receptor, as does the rectum. α,β -MeATP also causes a contraction of the chicken rectum and is able to desensitize the excitatory response to stimulation of Remak's nerve, suggesting that P2X receptors are involved in purinergic excitatory transmission. Inhibitory NANC innervation of the gizzard has also been demonstrated (954). Ectonucleotidases have been localized in chicken gizzard and stomach (1030).

ATP triggers intracellular Ca²⁺ oscillations in chicken granulosa cells obtained from the two largest preovulatory ovarian follicles (1186). While the involvement of ATP as a purinergic cotransmitter with ACh was first described in cultured chick myotubes (see sect. III E), ATP responsiveness disappeared shortly after muscle becomes innervated (1849). The responses to ATP show rapid desensitization, which is typical of the P2X₁ and P2X₃ subclasses of the P2X ionotropic receptor family. P2Y₁ and P2Y₂ receptors expressed at chick neuromuscular junctions appear to be involved in the regulation of the ACh receptor and of AChE (1737).

3. Summary

Purinergic signaling appears to play a major role in early development (before classical adrenergic signaling) and receptors usually show more restricted localization

with maturation. Both P1 and P2 receptors are present early in development of many systems, but there are a few examples where the earliest effects of ATP are mediated via adenylate cyclase, and only later in receptor activation does the IP₃ second messenger system for P2Y receptor transduction come into operation. Fast P2X purinergic signaling may appear a little later in development compared with P1 and P2Y receptors, except perhaps in urinary bladder. This is reminiscent of what appears to occur during phylogeny, thus being consistent with the general principle that "ontogeny repeats phylogeny."

During postnatal development, responses to nucleosides and nucleotides increase and decrease with age depending on the physiological demands of a particular system involved.

Changes in purinergic transmission in aging appear to differ in different systems. There are reports of both increase and decrease of the purinergic components of cotransmission in old age.

In general, there is sufficient pharmacological evidence to support the view that two distinct receptor subclasses, one selective for adenosine and one selective for ATP, exist in invertebrates and lower vertebrates. Subclasses of P1 receptors into A₁ and A₂ subtypes have been claimed in molluscs. There are records of fast P2X receptors involving ion channels in the nervous system of molluscs, annelids, and arthropods. It is speculated that the primitive P2Y receptor acted via an adenylate cyclase transduction system in parallel with P1 receptors and only later diverged to act via IP₃ second messenger systems.

There is good evidence, including cloning, for P1, P2X, and P2Y receptors in lower vertebrates and a number of subtypes recognized as orthologs of the established mammalian receptors. There have been few molecular studies of receptors to purines and pyrimidines in invertebrates, but a P2X-like receptor has been cloned in *Schistosoma mansoni*.

XI. NEUROPATHOLOGY

There is growing interest in the pathophysiology of purinergic signaling, and therapeutic applications are being explored for a number of diseases (see Refs. 276, 278, 897).

A. Peripheral Nervous System

1. Diseases of the lower urinary tract

Although the purinergic component of parasympathetic neuromuscular transmission in the urinary bladder is between 40 and 75% in laboratory animals, in normal human bladder, atropine will block over 95% of parasympathetic nerve-mediated contraction, despite the fact that

P2X receptors are present (265). However, there are a number of examples where the purinergic component of cotransmission is increased up to 40% in pathological conditions such as interstitial cystitis (1294), outflow obstruction (1267, 1588), idiopathic detrusor instability (1268), and some types of neurogenic bladder (46). Contractile responses of bladder from streptozotocin-diabetic rats to ATP and nerve stimulation peaked at 6–9 wk, but reverted to those of control by 12–20 wk (425).

Stretch-activated ATP release from bladder epithelial cells from patients with interstitial cystitis is significantly greater than from healthy cells (1671) and also in the cat model of interstitial cystitis (147) and in cyclophosphamide-induced cystitis in rats and mice (1587). The P2X₃ receptor subunit was upregulated during stretch of cultured urothelial cells from patients with interstitial cystitis (1670); P2X₂ and P2X₃ receptor expression has been demonstrated on human bladder urothelial cells (as well as on afferent nerve terminals); the expression was greater in cells from interstitial cystitis bladder (147, 1692).

P2X₁ receptor subtype expression was also markedly increased in unstable bladders (1267). A further possible explanation for the increased potency of ATP in generating contractions in detrusor from unstable bladders may be reduced extracellular ATP hydrolysis (711). Reduction of P2X₃ and P2X₅ receptors in human detrusor from adults with urge incontinence has been claimed (1175).

Purinergic signaling also plays a role in afferent sensation from the bladder (see sect. XI A 8 A). Purinergic agonists acting on P2X₃ receptors in the bladder can sensitize bladder afferent nerves, and these effects mimic the sensitizing effect of cystitis induced by cyclophosphamide. Thus P2X₃ receptors are a potential target for pharmacological manipulation in the treatment of both pain and detrusor instability. Subsensitivity of P2X₃ and P2X_{2/3} receptors, but not vanilloid receptors, has been shown in L6-S1 DRG in the rat model of cyclophosphamide cystitis (176). Release of ATP from urothelial cells with hypotonic mechanical stimulation was increased by over 600% in inflamed bladder from cyclophosphamide-treated animals; botulinum toxin inhibited this release (1587). Botulinum neurotoxin type A is effective in the treatment of intractable detrusor overactivity; decreased levels of sensory receptors P2X₃ and/or TRPV1 may contribute to its clinical effect (55, 68).

In the absence of P2X₃ receptors in mouse knockouts, the bladder is hyperactive (372, 1797). The recently developed P2X₃ and P2X_{2/3} antagonist RO3, which is orally bioavailable and metabolically stable, is being explored as a therapeutic agent for urinary tract dysfunction (567). The P2X₃ receptor is largely expressed in the IB₄ small nociceptive capsaicin-sensitive nerves in the DRG, so it is interesting that IB₄-conjugated saporin, a cytotoxin that destroys neurons binding IB₄, when administered

intrathecally at the level of L6-S1 spinal cord, reduced bladder overactivity induced by ATP infusion (1248). The authors suggest that targeting IB₄-binding, nonpeptidergic afferent pathways sensitive to capsaicin and ATP may be an effective treatment of overactivity and/or pain responses of the bladder (see sect. XI A 8).

It has been claimed that suburothelial myofibroblast cells isolated from human and guinea pig bladder that are distinct from epithelial cells provide an intermediate regulatory step between urothelial ATP release and afferent excitation involved in the sensation of bladder fullness (1662).

The majority of lumbosacral neurons (93%) supplying the bladder were sensitive to α,β -meATP, compared with 50% of thoracolumbar neurons, suggesting that bladder pelvic and hypogastric/lumbar splanchnic afferents are functionally distinct and are likely to mediate different sensations arising from the urinary bladder (426).

Activation of P2 receptors in the brain stem (both periaqueductal gray matter and Barrington's nucleus/locus coeruleus) generates patterns of activity in the parasympathetic innervation of the bladder (1436). In patients with idiopathic detrusor instability, there is abnormal purinergic transmission to the bladder; this may account for some of the symptoms of overactive bladder (46, 1268). Voiding dysfunction involves P2X₃ receptors in conscious chronic spinal cord injured rats, which raises the possibility that P2X₃ receptor antagonists might be useful for the treatment of neurogenic bladder dysfunction. Drugs that alter ATP release or breakdown might also be therapeutic targets (349, 711). Copper inhibits purinergic transmission in the bladder, and the copper(I) chelator neocuproine enhances bladder activity by facilitating purinergic excitatory responses (656).

Incontinence can be a problem in adult women. The first symptoms of urinary incontinence can arise after the first pregnancy, and the risk of incontinence increases with multiple deliveries. However, the sensitivity of the rat detrusor muscle to ATP was not modified by multiple pregnancies, while there was increased sensitivity to adrenergic and cholinergic stimulation (670). However, earlier studies reported that the responses to adrenergic and cholinergic stimulation were reduced (1022) and that the responses to ATP increased during pregnancy in both rat and rabbit bladders (1716).

Overdistension of the bladder is caused by urinary retention, but it has also been used as a method for treating unstable bladder or interstitial cystitis (492, 843), possibly damaging sensory nerve fibers. However, micriturition problems often reoccur after overdistension treatment.

Intravesically applied ATP does not penetrate the intact bladder epithelial layer in the rat because of the permeability barrier and ecto-ATPase activity of the urothelium (1247). Therefore, increased permeabil-

ity is needed for ATP to activate subepithelial P2X receptors to sensitize C-fiber afferents and induce detrusor overactivity.

Recent reviews of management of detrusor dysfunction highlight the growing potential of therapeutic strategies related to purinergic signaling (e.g., Refs. 46, 567, 570, 980, 1181, 1286, 1396, 1459).

2. Penile erection

Normal penile erectile function is dependent on a delicate balance between contracting and relaxing factors in the corpus cavernosum smooth muscle, which are modulated by signaling from both nerves and endothelial cells. Evidence has accumulated to support a pivotal role for NANC neurotransmitters. NO plays a central role in mediating cavernosal smooth muscle relaxation, but other neurotransmitters can modulate this action and may play a role in erectile dysfunction. ATP potently relaxes cavernosal smooth muscle strips *in vitro*, an action pharmacologically consistent with P2Y receptors. Indeed, P2Y receptors are present in both cavernosal smooth muscle cells and endothelial cells, and ATP is released from a subpopulation of the cavernosal nerves. It appears that smooth muscle relaxation is caused both by ATP acting directly on the cavernosal smooth muscle cells and indirectly, mediated by NO released from the endothelial cells. ATP-mediated cavernosal relaxation is impaired in diabetes mellitus (independent of NO), implying that purinergic signaling may be involved in the pathophysiology of erectile dysfunction (694). Knockout mice lacking P2X₁ receptors appear normal, but fail to breed, and this is associated with loss of the purinergic component of sympathetic cotransmission in the vas deferens; these findings raise the possibility of developing nonhormonal ways of regulating male fertility (493).

3. Heart failure

Quantitative densitometry of Western blots have revealed changes in expression of the 50- and 70-kDa components of the P2X₁ receptor in the atria from patients in the terminal stages of dilated cardiomyopathy (135). Excessive purine degradation in the heart has been described in patients with congestive heart failure, which might be the result of changes in the supply of ATP caused by a shift of cellular metabolism from aerobic glycolysis to anaerobic glycolysis during submaximal exercise (745). Increase in cardiac P2X₁ and P2Y₂ receptor mRNA levels in congestive heart failure has been reported (762). More recently, the full repertoire of P2 receptors in left myocardia from control subjects and patients with chronic heart failure (CHF) undergoing heart transplantation has been analyzed (88). All known P2X and P2Y receptors were found to be expressed; of these, only P2X₆ was upregulated in CHF. It was suggested that the inter-

action between TNF- α and the upregulated P2X₆ receptor may represent a novel pathogenic mechanism in CHF.

Enhanced sympathetic nerve activity causes cardiac dysfunction, arrhythmias, and sudden cardiac death in myocardial ischemia. ATP is coreleased with NE and enhances NE release from sympathetic nerve terminals. A role for the ectonucleotidase E-NTPDase1 at sympathetic nerve terminals may offer a novel therapeutic approach to hyperadrenergic states such as myocardial ischemia (1543). Intravenous adenosine protects the myocardium from ischemic damage, primarily by activation of a neurogenic pathway (1099). ATP released as a cotransmitter from sympathetic nerves produces a positive inotropic effect, probably largely via P2Y₁₁ receptors; in cardiomyocytes from desmin-deficient mice with cardiomyopathy, there was a downregulation of P2Y₁₁ receptor function (87). Of interest for the development of CHF, besides adenine nucleotides, uracil nucleotides have been also reported to act as positive inotropic agents in rat and mouse cardiomyocytes (1861). Venous plasma levels of UTP as well as ATP are increased by over 50% in patients with myocardial infarction. Thus both adenine and uracil nucleotides could be important inotropic factors involved in the development of cardiac disease.

4. Hypertension

ATP plays a significant cotransmitter role in sympathetic nerves supplying hypertensive blood vessels. Increase in sympathetic nerve activity in hypertension is well established, and there is an associated hyperplasia and hypertrophy of arterial walls. There is evidence that ATP plays a significantly greater role as a sympathetic cotransmitter in spontaneously hypertensive rats (209, 237, 1785). ATP is a rapidly acting hypotensive agent that compares favorably with sodium nitroprusside (902). Defective prejunctional P1 receptor-mediated modulation has been claimed to contribute to enhanced sympathetic neurotransmission in hypertension (793, 861). Impaired α -adrenergic autoreceptor modulation of purinergic transmission in mesenteric arteries of DOCA-salt hypertensive rats has also been shown (446). Constrictor responses of the isolated kidney to renal nerve stimulation were increased in spontaneously hypertensive rats compared with controls and appeared to be entirely due to ATP released from sympathetic nerves (1461). In the kidney of a transgenic, hypertensive model, the glomeruli show an abundance of P2X₇ receptor immunostaining, and a similar expression of P2X₇ receptors has been found in the glomeruli of diabetic rats with kidney damage (1808).

ATP-MgCl₂ is a safe, effective, and preferential pulmonary vasodilator in children with pulmonary hypertension secondary to congenital heart defects; it has also been used for treating pulmonary hypertension after cardiac surgery (213).

In spontaneously hypertensive rats, with increased sympathetic nerve activity, there is hyperactive bladder voiding that appears to be associated with higher secretion of NGF by bladder smooth muscle and hyperinnervation (368).

Central adenosine (A_{2A}) receptor-mediated signaling plays a key role in clonidine-evoked hypotension in conscious, aortic barodenervated rats (1216).

5. Diabetes

Changes in sympathetic cotransmitter control of the mesenteric arterial bed have been described in streptozotocin-diabetic rats (1390). A feature of diabetic retinopathy is the apoptotic death of microvascular pericytes and endothelial cells; there appears to be an enhancement of $P2X_7$ receptor-induced pore formation and apoptosis in early diabetes on the retinal microvasculature (1660) and support the suggestion that retinal circulation disorder accelerated by activation of $P2X_7$ receptors may be involved in the early changes of diabetic retinopathy (1661). In streptozotocin-diabetic animals, $P2X_7$ receptor expression, located in glucagon-containing α -cells in pancreatic islets, increases and migrates centrally to take the place of the insulin-containing β -cells, although the functional significance of this is not known (398). The potential role of purinergic compounds as novel treatments for diabetes has yet to be explored. Stimulation of insulin secretion and improvement of glucose tolerance in rats and dogs by the $P2Y$ receptor agonist adenosine-5'-*O*-(2-thiodiphosphate) has been claimed (740). Glomerular expression of $P2X_7$ receptors is significantly upregulated in diabetic rats (1808). An enhancement of purinergic neurotransmission and a reduction of cholinergic neurotransmission occur in the bladder detrusor of the diabetic rabbit (1193).

Electrical recording from gastric smooth muscle from streptozotocin-induced diabetic rats during transmural nerve stimulation showed IJPs of reduced amplitude and no EJPs (1914). The IJPs in response to ATP were similar in the circular muscle of the cecum of streptozotocin-diabetic (8 wk) and untreated control rats, although the rate of hyperpolarization of single IJPs was slower in the diabetic tissues (768). While ATP-induced relaxations of longitudinal strips from the gastric fundus were not significantly different in control and diabetic rats, the stimulation-induced release of ATP increased threefold in diabetic compared with control gastric fundus. Desensitization of receptors to ATP with α, β -meATP reduced the relaxant responses to both ATP and electrical field stimulation, suggesting a role for ATP in NANC neurotransmission in rat gastric fundus, and this reduction was greater in diabetic tissues (125). In view of these data it was suggested that the purinergic component of the vagal NANC responses of the stomach may be increased in diabetes, a finding reminiscent of an increased

purinergic component in parasympathetic control of bladder in interstitial cystitis and in sympathetic nerves supplying blood vessels in spontaneously hypertensive rats. While maximum relaxant responses and sensitivity of the colon to ATP were unchanged in 8-wk streptozotocin-diabetic rats, the responses to adenosine were reduced (693). There is downregulation of A_1 receptors and upregulation of A_{2A} receptors in the hippocampus of streptozotocin-induced diabetic rats (484).

6. Gut and liver disorders

Purinergic signaling plays a major role in different activities of the gut (see sect. IV D). ATP is a cotransmitter in NANC nerves mediating the inhibitory phase in peristalsis; it participates in synaptic transmission in the myenteric and submucosal ganglia; it is involved in vascular control of the gastrointestinal tract and in control of mucosal secretion.

A limited number of studies have been conducted to date on changes in purinergic signaling in the diseased gut. ATP and adenosine have been implicated in the development of gastric ulcers, Hirschsprung's and Chaga's diseases, ischemia, and colonic tumors (266). Extracellular nucleotides and their receptors have been implicated in the pathogenesis of inflammatory bowel disease (IBD) (1603). T lymphocytes are thought to play a primary role in the induction of epithelial cell damage in IBD, and the $P2Y_6$ receptor was found by this group to be highly expressed on the T cells infiltrating IBD, but absent in T cells of unaffected bowel. This suggests that $P2Y_6$ receptor and its selective agonist, UDP, may play a role in the pathogenesis of IBD. Later papers have shown that $P2Y_6$ receptors are involved in monocytic release of IL-8 and stimulation of NaCl secretion (961). During inflammation of the gastrointestinal tract, glial cells proliferate and produce cytokines; thus $P2X_7$ receptors may play a role in the response of enteric glia to inflammation (1773). Functional expression of the $P2X_7$ receptor in colonic macrophages and T lymphocytes in the mucosa of IBD suggests they may play a role in the immunopathology of the disease (1034).

Bile induces ATP depletion and contributes to the early mucosal permeability alteration and barrier lesions that occur during experimental esophageal reflux (1679). $P2Y$ receptors on smooth muscle and ATP production in myenteric neurons increase in postoperative ileus, probably contributing to delayed colonic transit (1824). Recent reviews have highlighted the potential of purinergic drugs for the treatment of functional bowel disorders (614, 757, 920). Intestinal epithelial cells from patients with cystic fibrosis fail to consistently conduct Cl^- in response to ATP and UTP that elevate intracellular Ca^{2+} , and this may be of value in the design of treatments to ameliorate gastrointestinal symptoms of cystic fibrosis (1590).

Intrinsic sensory neurons in the submucous plexus of the gut, as well as extrinsic sensory nerves, show positive immunoreactivity for P2X₃ receptors (1899). It has been proposed by Burnstock (267) that during moderate distension, low-threshold intrinsic enteric sensory fibers may be activated via P2X₃ receptors by ATP released from mucosal epithelial cells, leading to reflexes concerned with propulsion of material down the gut. Studies showing that peristalsis is impaired in the small intestine of mice lacking the P2X₃ receptor subunit support this view (139). In contrast, during substantial (colic) distension associated with pain, higher threshold extrinsic sensory fibers may be activated by ATP released from the mucosal epithelia; these fibers pass messages through the DRG to pain centers in the CNS (1894, 1895). P2X₃ purinergic signaling enhancement in an animal model of colonic inflammation has been described, due, at least in part, to the appearance of P2X₃ receptor expression in a greater number of CGRP-labeled small nociceptive neurons in the DRG (1894). P2X₃ receptor expression is increased in the enteric plexuses in human IBD, suggesting a potential role in dysmotility and pain (1935), and the possibility that P2X receptors are potential targets for the drug treatment of irritable bowel syndrome (IBS) has been raised (614). It has also been suggested that agonists acting on P2X receptors on intrinsic enteric neurons may enhance gastrointestinal propulsion and secretion and that these drugs might be useful for treating constipation-predominant IBS, while P2X antagonists might be useful for treating diarrhea-predominant IBS. The peripheral sensitization of P2X₃ receptors on vagal and spinal afferents in the stomach may contribute to dyspeptic symptoms and the development of visceral hyperalgesia (426). During chronic interstitial inflammation induced by infection of mice with the parasite *Schistosoma mansoni* for 16 wk, purinergic modulation of cholinergic nerve activity was impaired (434).

In aganglionic intestine in Hirschsprung's disease, there was only weak P2X₃ receptor immunostaining in the myenteric and submucous plexuses compared with normal intestine (531). This finding is consistent with experimental studies that reported that no IJPs could be evoked in smooth muscle by intramural nerve stimulation of the rectosigmoidal part of the large intestine of Hirschsprung's patients, and ATP caused contraction of the muscle (1945).

In Chaga's disease, enhancement of P2X₇ receptor-associated cell permeabilization during the acute phase of the disease was reported (396), although purinergic signaling through other P2X receptor subtypes and P2Y receptors also seems to be impaired, perhaps because the parasite protozoan that causes the disease contains high levels of ATPases.

Gastric ulcers evoke hyperexcitability and enhance P2X receptor function in rat gastric sensory neurons,

thereby potentially contributing to the development of dyspeptic symptoms (426). Enhanced activity in purinergic pathways occurs in postoperative ileus, but is reversed by orphanin FQ (1824).

In the liver, purinergic receptors have been identified in the plasma membrane of the two principal epithelial cell types that form the bile secreting unit, namely, hepatocytes, which constitute the liver parenchymal cells and cholangiocytes, which line the lumen of intrahepatic bile ducts (543, 1218). Activation of the receptors has been linked to several fundamental responses important to cellular metabolism, ion channel activation, cell volume regulation, and bile formation. It is suggested that pharmacological modulation of ATP release and purinergic signaling might provide novel strategies for the management of cholestasis and other disorders characterized by impaired bile flow. Purinergic receptors are present on both quiescent and activated hepatic stellate cells; quiescent cells express P2Y₂ and P2Y₄ receptors activated by UTP and ATP, whereas activated cells express P2Y₆ receptors activated by UDP and ATP (478). It was speculated by these authors that the P2Y receptors on satellite cells might be an attractive target to prevent or treat liver fibrosis, via regulation of procollagen-1 transcription. ATP has been shown recently to rapidly activate multiple components of the *c-jun* NH₂-terminal kinase (JNK) cascade, a central player in hepatocyte proliferation and liver regeneration (1701). This study identifies extracellular ATP as a hepatic mitogen with implications about the regulation of liver growth and repair. Sympathetic nerves utilizing NE and ATP as cotransmitters alleviate immune-mediated experimental hepatitis in the mouse; it is speculated that nerve-immune cell interactions may offer novel therapeutic strategies in immune and inflammatory liver diseases (1234). Phenylketonuria is a deficiency of phenylalanine hydroxylase activity in the liver, which causes increased brain levels of phenylalanine and its metabolites, leading to permanent brain damage in the early period of postnatal brain development. Phenylalanine has been shown to inhibit ATP diphosphohydrolase, resulting in increases in ATP levels, perhaps the neurotoxic mechanism underlying brain damage in this disease (136).

The effect of ATP on salivary glands has been recognized since 1982. Both P2X and P2Y subtypes are expressed, and opportunities for utilization of these receptors as pharmaceutical targets for diseases involving salivary gland dysfunction appear promising (see Refs. 59, 1741).

7. Diseases of kidney and ureter

The distribution and roles of different P2X and P2Y receptor subtypes in the kidney have been discussed in section IXD2. The distribution of NTPDases 1 and 2 parallels the localization of P2 receptors in the kidney and is

likely to influence physiological as well as pathophysiological events in the kidney (921). It has been suggested that release of ATP from both neuronal and nonneuronal sources contributes to the progression of renal disease by having mitogenic effects on mesangial cells and by amplifying PDGF-induced cell hyperplasia (1805). ATP and adenosine have been used to protect kidneys from renal ischemic-reperfusion injury and are being explored for the treatment of chronic renal failure and transplantation-induced erythrocytosis (816). ATP exerts a dual effect on mesangial extracellular matrix (ECM) production, stimulatory probably via P2X₇ receptors and inhibitory via a P2Y receptor (1601). In the presence of elevated ATP levels in inflammatory or ischemic conditions, ECM proteins accumulate due to functional predominance of P2X receptors. This mechanism might participate in the pathogenesis of mesangial expression that occurs in diabetes. The P2 receptor antagonist PPADS inhibits mesangial cell proliferation in experimental mesangial proliferative glomerulonephritis (1448).

In polycystic kidney disease, tubules are altered, leading to dilated tubules or cysts encapsulated by a single monolayer of renal epithelium. It has been postulated that autocrine purinergic signaling enhances cyst expansion and accelerates disease progression (1527), but ATP released from nerves might also be involved. An increase in expression of P2Y₂, P2Y₆, and P2X₇ receptors has been reported in cystic tissue from the Han:SPRD cy⁺ rat model of autosomal dominant polycystic kidney disease (1738, 1739). P2 receptor antagonists and inhibitors of ATP release are being explored as therapeutic agents to treat this disease. ATP may inhibit pathological renal cyst growth through P2X₇ receptor signaling (742). There is increased glomerular expression of P2X₇ receptors in two rat models of glomerular injury due to diabetes and hypertension (1808). A recent study of human and experimental glomerulonephritis also shows increase in P2X₇ receptor expression (1740).

Administration of ATP complexed with MgCl₂ has been used for many years to improve postischemic and drug-induced glomerular and tubular function (1667). There is convincing evidence that there is increased sympathetic activity in renal disease, especially ischemia (840). Since ATP is established as a cotransmitter with NE in sympathetic nerves, this may be a source of enhanced ATP in these conditions. The role of P2X₃ receptors in mechanosensory transduction in relation to renal colic is discussed in section XI A 8 B.

8. Purinergic mechanosensory transduction and nociception

This section focuses largely on the mechanisms underlying the initiation of nociception in the periphery, while section XI B 9 concerns the nerve pathways in the

spinal cord and brain, involved in neuropathic pain. There is some overlap coverage of inflammatory pain between the two sections.

There were early hints that ATP might be involved in pain including the demonstration of pain produced by injection of ATP into human skin blisters (152, 376, 885), ATP involvement in migraine (247), and ATP participation in pain pathways in the spinal cord (see sect. XI B 9). A significant advance was made when the P2X₃ ionotropic ion channel purinergic receptor was cloned in 1995 and shown to be localized predominantly on small nociceptive sensory neurons in DRG together with P2X_{2/3} heteromultimer receptors (335, 1027). Later, Burnstock (256) put forward a unifying purinergic hypothesis for the initiation of pain, suggesting that ATP released as a cotransmitter with NE and NPY from sympathetic nerve terminal varicosities might be involved in sympathetic pain (causalgia and reflex sympathetic dystrophy); that ATP released from vascular endothelial cells of microvessels during reactive hyperemia is associated with pain in migraine, angina, and ischemia; and that ATP released from tumor cells (which contain very high levels), damaged during abrasive activity, reaches P2X₃ receptors on nociceptive sensory nerves. This has been followed by an increasing number of papers expanding on this concept (see Ref. 276). Immunohistochemical studies showed that the nociceptive fibers expressing P2X₃ receptors arose largely from the population of small neurons that labeled with the lectin IB₄ (188, 1809). The central projections of these neurons were shown to be in inner lamina II of the dorsal horn and peripheral projections demonstrated to skin, tooth pulp, tongue, and subepithelial regions of visceral organs. A schematic illustrating the initiation of nociception on primary afferent fibers in the periphery and purinergic relay pathways in the spinal cord was presented by Burnstock and Wood (295) (Fig. 9).

The decreased sensitivity to noxious stimuli associated with the loss of IB₄-binding neurons expressing P2X₃ receptors indicates that these sensory neurons are essential for the signaling of acute pain (1810). The loss of IB₄-binding neurons also led to compensatory changes relating to recovery of sensitivity to acute pain. There is strong enhancement of nociception produced via P2X₃ and P2X_{2/3} receptors in rat hindpaw by NE and serotonin (1816). Prostaglandin E₂, an inflammatory mediator, potentiates P2X₃ receptor-mediated responses in DRG neurons.

The search is on for selective P2X₃ and P2X_{2/3} receptor antagonists that are orally bioavailable and do not degrade *in vivo* for the treatment of pain (see Refs. 276, 634). Table 5 summarizes the drugs widely available. Suramin, PPADS, and Reactive blue 2 have been used as nonselective antagonists at P2X₃ and P2X_{2/3} receptors on nociceptive sensory nerve endings. PPADS has the advantage that it associates and dissociates ~100 to 10,000

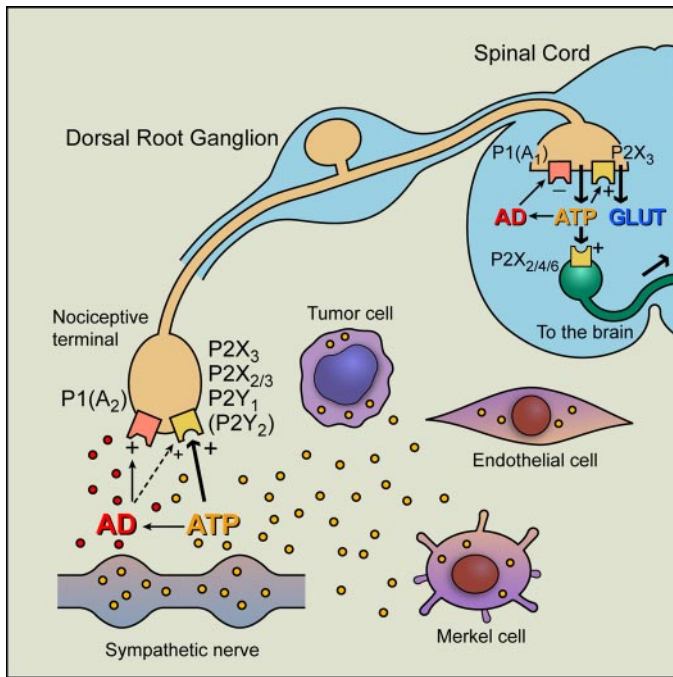


FIG. 9. Hypothetical schematic of the roles of purine nucleotides and nucleosides in pain pathways. At sensory nerve terminals in the periphery, P2X₃ and P2X_{2/3} receptors have been identified as the principal P2X purinoceptors present, although recent studies have also shown expression of P2Y₁ and possibly P2Y₂ receptors on a subpopulation of P2X₃ receptor-immunopositive fibers. Other known P2X purinoceptor subtypes (1–7) are also expressed at low levels in dorsal root ganglia. Although less potent than ATP, adenosine (AD) also appears to act on sensory terminals, probably directly via P1(A₂) purinoceptors; however, it also acts synergistically (broken black line) to potentiate P2X_{2/3} receptor activation, which also may be true for 5-hydroxytryptamine, capsaicin, and protons. At synapses in sensory pathways in the CNS, ATP appears to act postsynaptically via P2X₂, P2X₄, and/or P2X₆ purinoceptor subtypes, perhaps as heteromultimers, and after breakdown to adenosine, it acts as a prejunctional inhibitor of transmission via P1(A₂) purinoceptors. P2X₃ receptors on the central projections of primary afferent neurons in lamina II of the dorsal horn mediate facilitation of glutamate and probably also ATP release. Sources of ATP acting on P2X₃ and P2X_{2/3} receptors on sensory terminals include sympathetic nerves as well as endothelial, Merkel, and tumor cells. Yellow dots, molecules of ATP; red dots, molecules of adenosine. [Modified from Burnstock and Wood (295), with permission from Elsevier.]

times more slowly than other known antagonists (1620). The trinitrophenyl-substituted nucleotide TNP-ATP is a very potent antagonist at both P2X₃ and P2X_{2/3} receptors. A-317491 (synthesized by Abbott Laboratories) and compound RO3 (synthesized by Roche Palo Alto) are both effective P2X₃ and P2X_{2/3} antagonists, the latter being orally bioavailable and stable in vivo. Antagonism of P2X₁ and P2X₃ receptors by phenol red has been reported, and tetramethylpyrazine, a traditional Chinese medicine, used as an analgesic for dysmenorrhea, was claimed to block P2X₃ receptor signaling (1043).

Antisense oligonucleotides have been used to down-regulate the P2X₃ receptor, and in models of neuropathic (partial sciatic nerve ligation) and inflammatory [complete Freund's adjuvant (CFA)] pain, inhibition of the

development of mechanical hyperalgesia as well as significant reversal of established hyperalgesia, were observed within 2 days of treatment (98, 759, 1646). P2X₃ antisense oligonucleotides or antagonists appear to be less effective for treating discogenic (lumbar intervertebral disc) than cutaneous tissue pain (53). Combined antisense and RNA interference-mediated treatment for specific inhibition of the recombinant rat P2X₃ receptor appears to be promising for pain therapy (730). P2X₃ double-stranded short interfering RNA (siRNA) relieves chronic neuropathic pain and opens up new avenues for therapeutic pain strategies in humans (467).

While P2X₃ and P2X_{2/3} receptors, expressed in sensory neurons, were the predominant P2 receptor subtypes first recognized to be involved in the initiation of nociception (see Refs. 262, 295), it has become apparent more recently that P2Y receptors are also present (1202, 1212, 1451) and that these are involved in modulation of pain transmission (631). P2Y receptors appear to potentiate pain induced by chemical or physical stimuli via capsaicin-sensitive TRPV1 channels, and it has been proposed that the functional interaction between P2Y₂ receptors and TRPV1 channels in nociceptors could underlie ATP-induced inflammatory pain (990). P2Y₁ receptor-mediated responses also enhance the sensitivity of VR1-mediated responses to capsaicin, protons, and temperature in a PKC-dependent manner (1715). ATP-induced hyperalgesia was abolished in mice lacking VR1 receptors.

Reviews of the roles played by both adenosine (1508) and ATP (295, 267, 276, 278, 826) in peripheral nociception have been published.

A hypothesis was proposed that purinergic mechanosensory transduction occurred in visceral tubes and sacs, including ureter, bladder, and gut, where ATP released from epithelial cells during distension acted on P2X₃ homomeric and P2X_{2/3} heteromeric receptors on subepithelial sensory nerves initiating impulses in sensory pathways to pain centers in the CNS (261) (Fig. 10A).

TABLE 5. P2X₃ and P2X_{2/3} receptor antagonists

Antagonist	P2X ₃	P2X _{2/3}	Reference Nos.
Suramin and analogs NF449 and NF110	✓	✓	717
PPADS and derivatives MRS2159 and MRS2257	✓✓	✓	996
Reactive blue 2 and derivatives	✓	✓	650
TNP-ATP	✓✓✓	✓✓✓	1790
A-317491 (selective)	✓✓✓	✓✓✓	827
Phenol red	✓✓	—	915
Tetramethylpyrazine	✓✓	?	1043
RO ₃ (orally bioavailable, stable)	✓✓	✓✓	634
Ip ₅ I	✓✓	—	495
βγ-Carboxymethylene ATP	?	✓✓	1621
βγ-Chlorophosphomethylene ATP	?	✓✓	1621

✓, Yes; -, no; ?, unknown.

Evidence supporting this hypothesis in various organs is reviewed below.

A) URINARY BLADDER. Early evidence for ATP release from rabbit urinary bladder epithelial cells by hydrostatic pressure changes was presented by Ferguson et al. (544), who speculated about this being the basis of a sensory mechanism. Prolonged exposure to a desensitizing concentration of α,β -meATP significantly reduced the activity of mechanosensitive pelvic nerve afferents in an in vitro model of rat urinary bladder (1214). Later, it was shown that mice lacking the $P2X_3$ receptor exhibited reduced inflammatory pain and marked urinary bladder hyporeflexia with reduced voiding frequency and increased voiding volume, suggesting that $P2X_3$ receptors are involved in mechanosensory transduction underlying both inflammatory pain and physiological voiding reflexes (372). A later study from this group, using $P2X_2$ knockout mice and $P2X_2/P2X_3$ double knockout mice, revealed a role for the

$P2X_2$ subtype too in mediating the sensory effect of ATP (371). In a systematic study of purinergic mechanosensory transduction in the mouse urinary bladder, ATP was shown to be released from urothelial cells during distension, and discharge initiated in pelvic sensory nerves was mimicked by ATP and α,β -meATP and attenuated by $P2X_3$ antagonists as well as in $P2X_3$ knockout mice; $P2X_3$ receptors were localized on suburothelial sensory nerve fibers (1797). Single unit analysis of sensory fibers in the mouse urinary bladder revealed both low- and high-threshold fibers sensitive to ATP contributing to physiological (nonnociceptive) and nociceptive mechanosensory transduction, respectively (1445). Several functionally distinct populations of bladder sensory nerves have been recognized recently, not all of which respond to ATP (1944). Purinergic agonists increase the excitability of afferent fibers to distension (1445). It appears that the bladder sensory DRG neurons, projecting via pelvic

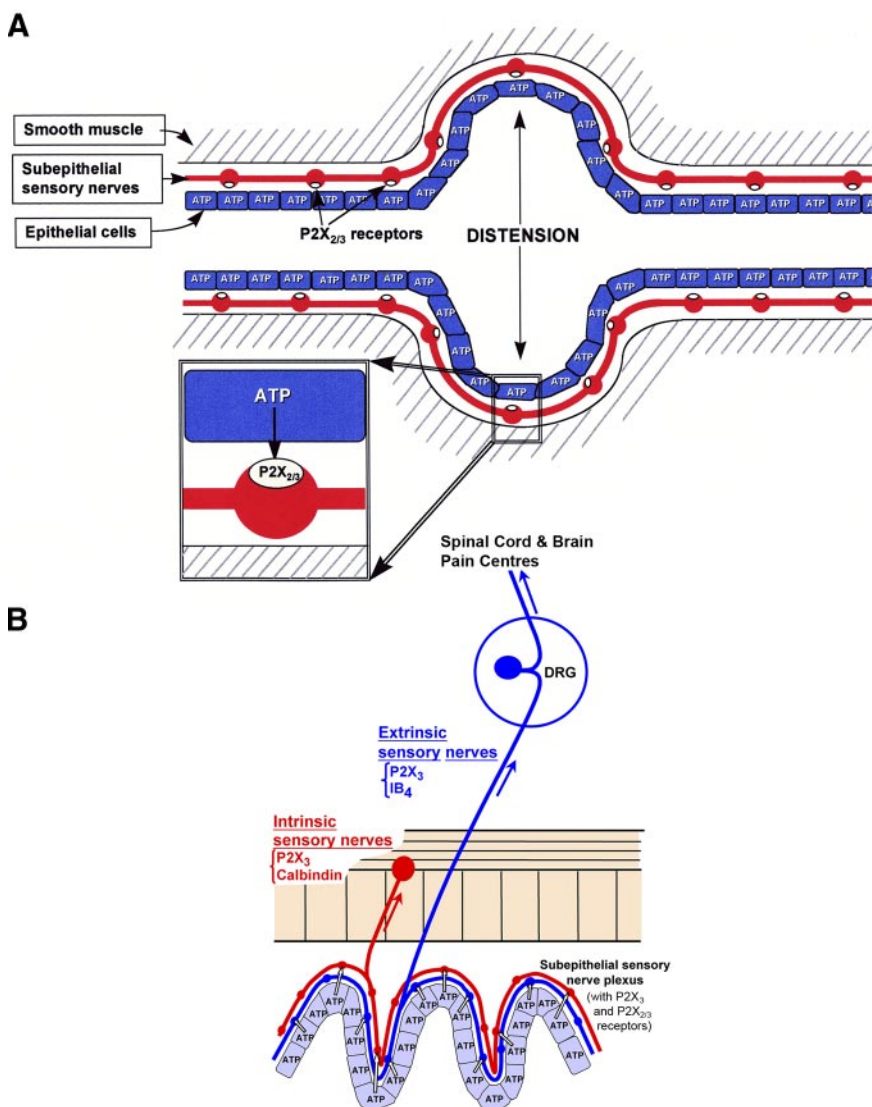


FIG. 10. Purinergic mechanosensory transduction. A: schematic representation of hypothesis for purinergic mechanosensory transduction in tubes (e.g., ureter, vagina, salivary and bile ducts, gut) and sacs (e.g., urinary and gall bladders, lung). It is proposed that distension leads to release of ATP from epithelium lining the tube or sac, which then acts on $P2X_3$ and/or $P2X_{2/3}$ receptors on subepithelial sensory nerves to convey sensory/nociceptive information to the CNS. [From Burnstock (261), with permission from Blackwell.] B: schematic of a novel hypothesis about purinergic mechanosensory transduction in the gut. It is proposed that ATP released from mucosal epithelial cells during moderate distension acts preferentially on $P2X_3$ and/or $P2X_{2/3}$ receptors on low-threshold subepithelial intrinsic sensory nerve fibers (labeled with calbindin) to modulate peristaltic reflexes. ATP released during extreme (colic) distension also acts on $P2X_3$ and/or $P2X_{2/3}$ receptors on high-threshold extrinsic sensory nerve fibers [labeled with isolectin B4 (IB₄)] that send messages via the dorsal root ganglia (DRG) to pain centers in the CNS. [From Burnstock (268), with permission from John Wiley and Sons, Inc.]

nerves, express predominantly P2X_{2/3} heteromultimer receptors (1967). Botulinum toxin A, which has antinociceptive effects in treating interstitial cystitis, inhibits distension-mediated urothelial release of ATP in conditions of bladder inflammation (1587).

ATP given intravesically stimulates the micturition reflex in awake freely moving rats, probably by stimulating suburothelial C-fibers, although it was suggested that other mediators might also be involved (1298). Studies of resiniferatoxin desensitization of capsaicin-sensitive afferents on detrusor overactivity induced by intravesicle ATP in conscious rats supported the view that increased extracellular ATP has a role in mechanosensory transduction and that ATP-induced facilitation of the micturition reflex is mediated, at least partly, by nerves other than capsaicin-sensitive afferents (190). ATP has also been shown to induce a dose-dependent hypereflexia in conscious and anesthetized mice, largely via capsaicin-sensitive C-fibers; these effects were dose-dependently inhibited by PPADS and TNP-ATP (772). P2X₁ and P2X₃ receptors play a fundamental role in the micturition reflex in female urethane-anesthetized rats; P2X₃ receptor blockade by phenol red raised the pressure and volume thresholds for the reflex, while P2X₁ receptor blockade diminished motor activity associated with voiding (914).

The roles of ATP released from urothelial cells and suburothelial myofibroblasts on various bladder functions have been considered at length in several reviews (54, 1005, 1663, 1893), and evidence presented that urothelial-released ATP may alter afferent nerve excitability (146, 432). The kinetics of ATP release from bladder urothelium have been described recently (1029).

B) URETER. The uroteric colic induced by the passage of a kidney stone causes severe pain. Distension of the ureter resulted in substantial ATP release from the urothelium in a pressure-dependent manner (932). Cell damage was shown not to occur during distension with scanning electron microscopy, and after removal of the urothelium, there was no ATP release during distension. Evidence was presented that the release of ATP from urothelial cells was vesicular. Immunostaining of P2X₃ receptors in sensory nerves in the subepithelial region was reported (1010). Multifiber recordings of ureter afferent were made using a guinea pig preparation perfused *in vitro* (1442). Distension of the ureter resulted in a rapid, followed by maintained, increase in afferent nerve discharge. The rapid increase was mimicked by intraluminal application of ATP or α,β -meATP, and TNP-ATP attenuated these nerve responses to distension; the maintained increase was partly due to adenosine.

C) GUT. A hypothesis was proposed suggesting that purinergic mechanosensory transduction in the gut initiated both physiological reflex modulation of peristalsis via intrinsic sensory fibers and nociception via extrinsic sensory fibers (266, 267; Fig. 10B). Evidence in support of

this hypothesis was obtained from a rat pelvic sensory nerve-colorectal preparation (1895). Distension of the colorectum led to pressure-dependent increase in release of ATP from mucosal epithelial cells and also evoked pelvic nerve excitation. This excitation was mimicked by application of ATP and α,β -meATP and attenuated by the selective P2X₃ and P2X_{2/3} antagonist TNP-ATP and by PPADS. The sensory discharge was potentiated by ARL-67156, an ATPase inhibitor. Single fiber analysis showed that high-threshold fibers were particularly affected by α,β -meATP. ATP release and P2X₃ and P2X_{2/3} receptor-mediated nociceptive sensory nerve responses were enhanced in a model of IBD (1894). Lumbar splanchnic (LSN) and sacral pelvic (PN) nerves convey different mechanosensory information from the colon to the spinal cord. Forty percent of LSN afferents responded to α,β -meATP compared with only 7% of PN afferents (206).

The excitability of visceral afferent nerves is enhanced following injury or ischemia and during inflammation, for example, in IBS (see sect. XI A6). Under these conditions, substances are released from various sources that often act synergistically to cause sensitization of afferent nerves to mechanical or chemical stimuli. Receptors to these substances (including ATP) represent potential targets for drug treatment aimed at attenuating the inappropriate visceral sensation and subsequent reflex activities that underlie abnormal bowel function and visceral pain (see Refs. 757, 920). α,β -MeATP was shown to stimulate mechanosensitive mucosal and tension receptors in mouse stomach and esophagus leading to activity in vagal afferent nerves (1292). The sensitizing effects of P2X₃ receptor agonists on mechanosensory function are induced in esophagitis (1293).

D) UTERUS. It has been hypothesized that tissue stress or damage in the uterine cervix during late pregnancy and parturition leads to ATP release and sensory signaling via P2X receptors (1306). In support of this proposal, these authors have shown P2X₃ receptor immunoreactivity in axons in the cervix, in small and medium-sized neurons in L6/S1 DRG, and in lamina II of the L6/S1 spinal cord segments and increases in P2X₃ receptor expression between pregnancy day 10 and parturition (day 22/23) in the rat cervix, although not in DRG or spinal cord.

E) TOOTH PULP. P2X₃ and P2X_{2/3} receptors on sensory afferents in tooth pulp appear to mediate nociception (26, 383, 833, 1413), perhaps from ATP released by mechanical distension or inflammation of odontoblasts. Mustard oil application to the tooth pulp in anesthetized rats produced long-lasting central sensitization, reflected by increases in neuronal mechanoreceptive field size; TNP-ATP reversibly attenuated the mustard oil sensitization for more than 15 min (769).

F) TONGUE. P2X₃ receptors are abundantly present on sensory nerve terminals in the tongue (153), and ATP and α,β -meATP have been shown to excite trigeminal lingual

nerve terminals in an in vitro preparation of intra-arterially perfused rat mimicking nociceptive responses to noxious mechanical stimulation and high temperature (1443). A purinergic mechanosensory transduction mechanism for the initiation of pain was considered. Taste sensations appear to be mediated both by P2Y₁ receptor-activated impulses in sensory fibers in the chorda tympani (877) and by P2X₂ and P2X₃ and, perhaps, P2X_{2/3} receptors (558).

G) OLFACTORY EPITHELIUM. The olfactory epithelium and vomeronasal organs contain olfactory receptor neurons that express P2X₂, P2X₃, and P2X_{2/3} receptors (624, 1619). It is suggested that the neighboring epithelial supporting cells or the olfactory neurons themselves may release ATP in response to noxious stimuli, acting on P2X receptors as an endogenous modulator of odor sensitivity (725, 1619). Enhanced sensitivity to odors was observed in the presence of P2 receptor antagonists, suggesting that low-level endogenous ATP normally reduces odor responsiveness. It was suggested that the predominantly suppressive effect of ATP on odor sensitivity could play a role in reduced odor sensitivity that occurs during acute exposure to noxious fumes and may be a novel neuroprotective mechanism (725).

H) SKIN, MUSCLE, AND JOINTS. ATP and α,β -meATP activate nociceptive sensory nerve terminals in the skin, which increase in magnitude in inflammatory conditions due to increase in number and responsiveness of P2X₃ and P2X_{2/3} receptors (702). Skin cell damage caused action potential firing and inward currents in nociceptive fibers, which was eliminated by enzymatic degradation of ATP or blockade of P2X receptors, indicating release of cytosolic ATP (382). ATP appears to be involved in fast nociceptive signals, while persistent pain after tissue damage involves other algogenic compounds, notably, bradykinin, prostaglandin, and serotonin. However, persistent pain during inflammation may also involve sensitization and/or spread of P2X receptors. Nocifensive behaviors induced by administration of ATP and BzATP to the hindpaw appear to recruit an additional set of fibers that are not activated by α,β -meATP and which trigger the spinal release of SP and are capsaicin selective (1876). Locally released ATP can sensitize large mechanosensitive afferent endings via P2 receptors, leading to increased nociceptive responses to pressure or touch; it was suggested that such a mechanism, together with central changes in the dorsal horn, may contribute to touch-evoked pain (1962; see sect. XI B9). In a study of the behavioral effects of intraplantar injections of ATP in freely moving rats, evidence was presented that ATP was more effective in exciting nociceptors in inflamed versus normal skin (702). This was reported to be due to upregulation of P2X₂ and P2X₃ receptors on DRG neurons (1908). Enhanced expression of GDNF in the skin can change the mechanical sensitivity of IB₄-positive nocicep-

tive afferents (which express P2X₃ and P2X_{2/3} receptors) (27).

With the use of a mouse skin-sensory nerve preparation, evidence was presented that P2Y₂ receptors in the terminals of capsaicin-sensitive cutaneous sensory neurons mediate nociceptive transmission and further that P2Y signaling may contribute to mechanotransduction in low-threshold A β fibers (1650). Treatment with oxidized ATP, a selective inhibitor of P2X₇ receptors, reduced the hyperalgesia produced by Freund's complete adjuvant and carrageenan-induced inflammation in rats (597). Data have been presented to support a pathogenic role for keratinocyte-derived ATP in irritant dermatitis (1161).

Pain related to the musculoskeletal system (myofascial pain) is very common, and ATP has been claimed to excite or sensitize myofascial nociceptors (148). Prolonged muscle pain and tenderness were produced in human muscle by infusion of a combination of ATP, serotonin, histamine, and prostaglandin E₂ (1185). Strenuous exercise of muscle as well as inflammation and ischemia are associated with tissue acidosis. Intramuscular injections of acidic phosphate buffer at pH 6 or ATP excited a subpopulation of unmyelinated (group IV) muscle afferent fibers (749), perhaps implicating P2X₂ or P2X_{2/3} receptors that are sensitive to acidic pH (1057). ATP induces sustained facilitation of cranial nociception through P2X receptors on neck muscle nociceptors in mice (1094).

ATP has been shown to be a stimulant of articular nociceptors in the knee joint via P2X₃ receptors (469, 1537) and also to some extent in lumbar intervertebral disc, but not as prominently as in the skin (53). P2Y₂ receptor mRNA is expressed in both cultured normal and osteoarthritic chondrocytes taken from human knee joints, and ATP is shown to be released by mechanical stimulation (1153). When monoarthritis was induced by injection of CFA into the unilateral temporomandibular joint of the rat, the pain produced was associated with an increase in P2X₃ receptor-positive small neurons in the trigeminal ganglion (1558). Activation of P2X receptors in rat temporomandibular joint induces nociception, and that blockage by PPADS decreases carrageenan-induced inflammatory hyperalgesia (1277). Oxidized ATP inhibits inflammatory pain in arthritic rats by inhibition of the P2X₇ receptor for ATP localized in nerve terminals (445). Evidence is accumulating to suggest that blockers of P2X₇ receptors may have a future as anti-inflammatory drugs (see Ref. 546) (see sect. XI A11).

I) CANCER. Purinergic mechanisms are beginning to be explored in relation to cancer pain (256, 304, 641, 1101). It was suggested that the unusually high levels of ATP contained in tumor cells (1091) may be released by mechanical rupture to activate P2X₃ receptors on nearby nociceptive sensory nerve fibers (256). There is increased expression of P2X₃ receptors on CGRP immunoreactive

epidermal sensory nerve fibers in a bone cancer pain model (641) and in other cancers that involve mechanically sensitive tumors (1101). For example, in bone tumors, destruction reduces the mechanical strength of the bone, and antagonists that block the mechanically gated channels and/or ATP receptors in the richly innervated periosteum might reduce movement-associated pain. The hyperalgesia associated with tumors appears to be linked to increase in expression of P2X₃ receptors in nociceptive sensory neurons expressing CGRP by analogy with that described for increased P2X₃ receptor expression in a model of inflammatory colitis (1894). Increased expression of P2X₃ receptors was also reported associated with thermal and mechanical hyperalgesia in a rat model of squamous cell carcinoma of the lower gingival (1199).

9. Respiratory diseases

It is suggested that ATP could play a role in asthma and chronic obstructive pulmonary disease (COPD) through its actions on multiple cell types relevant to these disorders, including mast cells, eosinophils, dendritic cells, and neurons (see Ref. 1328). ATP and UTP stimulate P2Y₂ receptor-mediated surfactant secretion and transepithelial chloride secretion in type II alveolar cells; there are abnormalities in this mechanism in cystic fibrosis (224, 1933). Nucleotides increase mucus secretion from goblet cells and increase the ciliary beat frequency of airway epithelial cells (888). P2X₄ receptors have been identified on lung epithelial cells and appear to be involved in regulation of ciliary beat, manipulation of which may also be of therapeutic benefit for cystic fibrosis (1987). Vagal afferent purinergic signaling may be involved in the hyperactivity associated with asthma and COPD (12).

The need to support the failing lung (acute respiratory distress syndrome) with mechanical ventilation is potentially life-saving, but unfortunately, alveolar overdistension and pulmonary shear stress may cause lung injury (ventilator-induced lung injury, VILI), increasing bronchoalveolar lavage leading to lung edema. It has been suggested that VILI may involve stretch-associated release of ATP from neuroepithelial cell bodies and activation of sensory nerves and reflex responses (215, 217, 218, 1425) and may therefore be a therapeutic target for this condition.

Aerosolized ATP is a more potent bronchoconstrictor and has greater effects on dyspnea and other symptoms than AMP in asthmatic patients and could be useful as a bronchoprovocator in the clinical setting (115).

Alveolar macrophages express functional P2X₇ receptors, which, upon stimulation, activate proinflammatory IL-1 to IL-6 cytokine cascade and the formation of multinucleate giant cells, a feature of granulomatous re-

actions (1014). Furthermore, Th1 and Th2 cytokines reciprocally regulate P2X₇ receptor function, suggesting a role for P2X₇ receptors in pulmonary diseases, particularly lung hypersensitivity associated with chronic inflammatory responses.

Purinergic receptors (probably P2Y₁ and P2Y₂ subtypes) exert a protective role against infection of the lungs by *Pseudomonas aeruginosa* by decreasing protein leak and enhancing the proinflammatory cytokine response; double P2Y₁ and P2Y₂ receptor knockout mice succumbed to the infection (626).

Elevated levels of adenosine have been found in bronchoalveolar lavage, blood, and exhaled breath condensate of patients with asthma and COPD, conditions characterized by chronic airway inflammation; furthermore, inhaled adenosine induces bronchoconstriction in asthmatics, but not in healthy subjects (315, 752, 1630). Adenosine bronchoconstriction in animal models of asthma suggests that this is mediated by inflammatory mediators released from mast cells, but other immune cells are also likely to be involved; pharmacological manipulation of A_{2B} receptors may represent a novel therapeutic approach for inflammatory airway diseases (315, 1474).

10. Musculoskeletal disorders and arthritis

Several reports implicate purinergic signaling in bone development and remodeling (see sect. 1xF).

Involvement of ATP in ultrasound-induced fracture repair has been claimed (720). The bisphosphonate clodronate, which is used in the treatment of Paget's disease and tumor-induced osteolysis, may act by inhibiting ATP-utilizing enzymes (401) or perhaps through osteoclast P2 receptors. Very low (nM) concentrations of ADP, acting through P2Y₁ receptors, turn on osteoclast activity (746). Deletion of the P2X₇ receptor revealed its regulatory roles in bone formation and resorption (884). It reduces bone resorption by decreasing osteoclast survival (958), and P2X₇ receptors are expressed in a subpopulation of osteoblasts (622). The multiple purinoceptors on bone and cartilage represent potential targets for the development of novel therapeutics to inhibit bone resorption in diseases such as rheumatoid arthritis, osteoporosis, tumor-induced osteolysis, and periodontitis (463).

Lymphoblastoid cells isolated from Duchenne muscular dystrophy patients are highly sensitive to stimulation by extracellular ATP (545). Recent studies provide the first evidence for a role for purinergic signaling in muscle regeneration using the mdx mouse model of muscular dystrophy and raises the possibility of new therapeutic strategies for the treatment of muscle disease (1471, 1934). The responses to ATP of myotubes prepared from E18 mouse embryos from normal and mutant *mdg/mdg* mice with muscular dysgenesis were studied by Tas-

sin et al. (1688). Using fura 2 as a probe, they showed that many of the *mdg/mdg* myotube preparations showed little or no increase in cytoplasmic Ca^{2+} levels.

It was recognized early that the nervous system may contribute to the pathophysiology of rheumatoid arthritis (1026, 1122). A role for purinergic signaling in rheumatic diseases has been considered (78, 672). Quinacrine (Atabrine), a drug that binds strongly to ATP, has been used for the treatment of rheumatoid arthritis patients for many years (1818). One of its mechanisms of action is to decrease levels of prostaglandin E_2 and cyclooxygenase-2 (COX-2), which are known to be produced following occupation of P2Y receptors by ATP (195, 1232). The articular fluid removed from arthritic joints contains high levels of ATP (1467). Purinergic regulation of bradykinin-induced plasma extravasation and adjuvant-induced arthritis has been reported (672). ATP and UTP activate calcium-mobilizing P2Y₂ or P2Y₄ receptors and act synergistically with IL-1 to stimulate prostaglandin E_2 release from human rheumatoid synovial cells (1072). Spinal P1 receptor activation has been claimed to inhibit inflammation and joint destruction in rat adjuvant-induced arthritis, supporting the view that therapeutic strategies, which target the CNS, might be useful in arthritis (187, 1612).

B. Central Nervous System

In the brain, P2 purinergic signaling is involved in the regulation of a variety of physiological and pathophysiological processes, including development and nervous tissue remodeling following trauma, stroke, ischemia, or neurodegenerative disorders (272, 574, 1225). Agonists and antagonists of adenosine and inhibitors of adenosine kinase are also being explored as therapeutic neuroprotective agents and neuropsychiatric disorders (581, 817, 951, 963, 1423, 1647).

1. Trauma

Cellular damage can release large amounts of ATP into the extracellular environment because the internal concentration can reach 3–5 mM (1977). Such ATP release might be important in triggering cellular responses to trauma (see Ref. 577). Astrocytes can sense the severity of damage in the CNS via ATP release from damaged cells and can modulate the TNF- α -mediated inflammatory response, depending on the extracellular ATP concentration and corresponding type of astrocyte P2 receptor activated (see sect. VIII, with which there is some overlap). Thus micromolar ATP activation of P2Y receptors may act to boost a moderate inflammatory response, whereas millimolar ATP activation of P2X receptors may prevent the perpetuation of a comparatively large inflammatory response perhaps by induction of apoptosis. PKB/Akt is a key signaling molecule that regulates cell survival,

growth, and metabolism and inhibits apoptosis. Traumatic brain injury activates Akt. When cortical astrocytes were subjected to mechanical strain, ATP is released, leading to Akt activation; PPADS attenuated the Akt activation (1224). Furthermore, mechanical strains, similar to those that occur in humans upon traumatic brain injury, cause release of ATP from astrocytes and activation of purinergic receptors coupled to protein kinase cascades that regulate expression of genes involved in long-term, trophic actions (1223). For example, trauma-induced activation of purinergic signaling in astrocytes via P2Y₄ receptors stimulates the synthesis and release of thrombospondin-1, an extracellular matrix molecule that induces synapse formation during development and may play a role in CNS repair and remodeling after injury (1722). Subsequently, this group has shown that the activity of GSK-3, which is known to be involved in cell proliferation and survival, is regulated by ATP in astrocytes and may be involved in the response of the brain to injury on release of ATP (1221).

Astrocyte gap junctions are involved in the neuroprotective process, in particular, to protect neurons from oxidative stress and glutamate toxicity. ATP released from astrocytes has been demonstrated in vivo to be essential in mediating the injury-induced defensive responses of microglial processes (427). In this study, time-lapse two-photon imaging of GFP-labeled microglia demonstrated that, in intact mouse cortex, the fine termini of microglial processes are highly dynamic. Upon traumatic brain injury, microglial processes rapidly and autonomously converge on the site of injury without cell body movement. This rapid chemotactic response can be mimicked by local injection of ATP and can be inhibited by the ATP-hydrolyzing enzyme apyrase or by blockers of P2Y receptors and connexin channels, which are highly expressed in astrocytes. Thus extracellular ATP regulates microglial branch dynamics in the intact brain, and its release from the damaged tissue and surrounding astrocytes mediates a rapid microglial response towards injury, establishing a potential barrier between the healthy and injured tissue (535). Microglial cells play important roles in orchestrating inflammatory brain responses to trauma and hypoxia. They express multiple P2 receptors and are activated by purines and pyrimidines to release inflammatory cytokines such as IL-1 β and IL-6 and TNF- α . Activated microglia can also act as scavenger cells that induce apoptosis in damaged neurons by releasing toxic factors, including NO (800, 1500).

Trophic factors ensure neuronal viability and regeneration. Neuronal injury releases FGF, EGF, and PDGF as well as NGF from both neurons and glial cells (4). In combination with these growth factors, ATP can stimulate astrocyte proliferation, contributing to the process of reactive astrogliosis, and to hypertrophic/hyperplastic responses (811, 1223; see also sect. VIII). P2 receptors stim-

ulate the signal transducer and activator of transcription 3 (STAT3), suggesting that P2 receptor/STAT3 signaling may play an important role in astrocyte proliferation and reactive astrogliosis (1836). P2Y receptors mediate reactive astrogliosis via induction of COX-2, and P2Y receptor antagonists might counteract excessive COX-2 activation in both acute and chronic neurological disease (195). P2 receptors also mediate regulation of COX-2 in microglia (359).

Cerebellar lesions result in upregulation of P2X and P2X₂ receptors in precerebellar nuclei (563), and stab wound injury in the nucleus accumbens leads to increases in expression of several subtypes of P2X and P2Y receptors (577). There is a significant increase in ecto-NTPDase and ecto-5'-nucleotidase activities following cortical stab injury in rats, whereas in other brain areas only an increase in 5'-nucleotidase activity was seen (1230). A_{2A} receptor agonists reduce long-term neurologic injury after blunt spinal trauma (1403). A novel mechanism for inhibition of apoptosis in neuroprotection implicates parallel, interacting systems involving extracellular ATP acting via P2Y₂ receptors and neurotrophin acting via TrkA (65). It has been claimed that P2Y₂ receptors activate neuroprotective mechanisms in astrocytes (362).

Different lines of evidence indicate that ATP and NO play key roles in mediating neuronal responses after cell damage. After cerebellar lesion, nitrergic and purinergic systems are activated with similar time courses in precerebellar stations, and a high percentage of colocalization of P2X₁ and P2X₂ receptors with nNOS was observed in olivary and pontine neurons (1792). ATP decreases LPS-stimulated inducible NOS and COX-2 expression and reduces NO release in microglia by a mechanism involving p38 mitogen-activated protein kinase; furthermore, the inhibitory effects of ATP on NO production correlate with activation of the transcription factor CREB (205).

ATP, released during trauma, acts via P2 receptors to inhibit the release of the cytotoxic excitatory transmitter glutamate and stimulates release of the inhibitory transmitter GABA from hippocampal nerves, thus serving a protective role (799). The number of P2Y₁ receptor-positive neurons and glial cells in the rat nucleus accumbens significantly increased after injury, and there was coexpression of P2Y₁ receptors and vesicular glutamate transporters immunopositive cells (572). The authors concluded that the enhanced sensitivity of neurons to purinergic signaling in trauma may be related directly or indirectly to changes in glutamatergic transmission. Antagonism of P2 receptors with PPADS confers neuroprotection against glutamate NMDA receptor-mediated toxicity (1047).

Spinal cord injuries are a health problem. ATP-MgCl₂ has been shown to decrease lipid peroxidation in spinal cord injury and protect the spinal cord from secondary injury after trauma; it was concluded that ATP-MgCl₂

should be explored for the treatment of spinal cord injuries in conjunction with other treatment modulators (305). Topical application of ATP after spinal cord injury significantly improved locomotor function (1553). A role for P2X₇ receptors in mediating spinal cord injury has been proposed, suggesting that specific P2 receptors may play differential roles in regulating the viability of spinal cord neurons (1829). Furthermore, they showed that the peritraumatic zone was characterized by sustained, high ATP release. Systemic administration to rats of both oxidized ATP and PPADS significantly improved functional recovery and diminished cell death in the peritraumatic zone. Since P2X₇ receptors have been claimed to be highly expressed in spinal cord neurons, it was concluded that spinal cord injury is associated with prolonged activation of this purinoceptor subtype, which results in excitotoxicity-based neuronal degeneration. More importantly, this study confirms the role of ATP as an early danger signal in neurodegenerative damage.

Some of the responses to ATP released during brain injury are neuroprotective, but in some cases ATP contributes to the pathophysiology initiated after trauma (554, 1142, 1225). After brain trauma, resting microglia, characterized by a complex network of processes, migrate to the site of damage and become transformed into the activated amoeboid form; ATP has been shown to replicate this transformation (1904).

2. Neurodegenerative diseases

P2Y receptor antagonists have been proposed as potential neuroprotective agents in the cortex, hippocampus, and cerebellum by modulation of kainate- and AMPA-induced currents, excessive activation of glutamate receptor systems being implicated in neuronal cell death associated with stroke and neurodegenerative diseases such as Alzheimer's, Parkinson's, Huntington's, and amyotrophic lateral sclerosis (1984). The P1 receptor antagonist caffeine (in coffee and tea) appears to have beneficial actions in both Alzheimer's and Parkinson's diseases (see Ref. 1423). Guanine nucleotides inhibit NMDA- and kainate-induced neurotoxicity in cultured rat hippocampal and neocortical neurons and may be candidates for antagonizing glutamate receptor-mediated neurotoxicity (1180). P2 receptors have been claimed to mediate neuroprotective effects in the cerebellum, and the possible therapeutic use of P2 receptor agonists as neuroprotective agents has been raised (1799). It has been suggested that adenine is involved in the control of Purkinje cell survival (1837). Cross-talk between neurons and mast cells has been implicated in neurodegenerative diseases with an inflammatory and/or autoimmune component, such as Alzheimer's disease and multiple sclerosis (MS) (1385).

Whereas microglia may play an important role against infection in the CNS, overstimulation of this immune reaction may accelerate the neuronal damage caused by ischemia, trauma, or neurodegenerative diseases such as Alzheimer's and Parkinson's disease, human immunodeficiency virus encephalopathy, MS, and amyotrophic lateral sclerosis, which exhibit microglial proliferation and activation (1269). These authors showed that ATP inhibits cytokine release from LPS-activated microglia via P2Y receptors and suggested that P2Y agonists may be a potential treatment for toxic immunoreactions. P2X₄ receptors, induced in spinal microglia, gate tactile allodynia after nerve injury (1731) (see sect. XI B9).

A) ALZHEIMER'S DISEASE. ATP release during neuronal excitation or injury can enhance the inflammatory effects of cytokines and prostaglandin E₂ in astrocytes and may contribute to the chronic inflammation seen in Alzheimer's disease (1910). Purine derivatives are in clinical trials as memory-enhancing agents in Alzheimer's disease; two of these, propentofylline and AIT-082, appear to act as trophic effectors, increasing the production of neurotrophic factors in brain and spinal cord (1398). It has been reported that aluminium can produce Alzheimer-like symptoms, and a mechanism has been proposed whereby the aluminium binds to ATP to act on P2 receptors leading to formation of amyloid fibrils (529).

P2X₇ receptors mediate superoxide production in primary microglia and are upregulated in a transgenic model of Alzheimer's disease, particularly around β -amyloid plaques (1314). Stimulation of microglial P2X₇ receptors also leads to enhancement of INF- γ -induced type II NOS activity (629). P2X₇ receptors may therefore provide a therapeutic target for inflammatory responses seen in neurodegenerative disorders.

In contrast to normal human brain, P2Y₁ receptors were localized to a number of characteristic Alzheimer's disease structures, such as neurofibrillary tangles, neuritic plaques, and neuropil threads (1173). P2Y₂ nucleotide receptors mediate enhanced α -secretase-dependent amyloid precursor protein processing (309). Abnormalities in calcium-mediated signal transduction triggered by ATP in microglia from Alzheimer's disease patients have been reported (1136).

Hippocampal presynaptic A₁ receptors are decreased in Alzheimer's disease, including axon terminals of extrinsic pathways and intrinsic pyramidal neurons that release glutamate (857). A₁ receptors accumulate in neurodegenerative structures in Alzheimer's disease and mediate both amyloid precursor protein processing and Tau phosphorylation and translocation (47).

B) PARKINSON'S DISEASE. The neurodegenerative process underlying Parkinson's disease causes progressive loss of dopaminergic neurons of the substantia nigra pars compacta projecting to the striatum. The use of A_{2A} receptor antagonists for the treatment of Parkinson's disease has

been recognized for some time and is gaining popularity (see Refs. 338, 715, 1096, 1352, 1427, 1577, 1912) involving adenosine-dopamine interactions in the basal ganglia (548, 797). The adenosine is probably derived from ATP released as a cotransmitter following its breakdown by ectonucleotides (874). The dopamine precursor L-3,4-dihydroxyphenylalanine (L-DOPA) is still the most commonly prescribed treatment for Parkinson's disease. However, long-term treatment with L-DOPA often produces uncontrollable movements known as dyskinesia; A_{2A} receptor antagonists have antidyskinetic actions (149). Increased expression of A_{2A} receptors in the brain of Parkinson's disease patients with dyskinesia has been reported (306). Dual blockade of A_{2A} and metabotropic glutamate mGlu5 receptors acutely and synergistically stimulates motor activity in Parkinsonian mice and may have therapeutic potential (852).

Interaction of A₁ receptors with mGlu5 has also been described (813). Paeoniflorin, the major active component of the Chinese herb *Paeoniae alba* Radix, has a neuroprotective effect in the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine mouse model of Parkinson's disease and has been shown to attenuate neuroinflammation and dopaminergic neurodegeneration by activation of A₁ receptors (1055).

Release of ATP from disrupted cells may cause cell death in neighboring cells expressing P2X₇ receptors, leading to a necrotic volume increase, which has been proposed as a cellular mechanism in the pathogenesis of Parkinson's disease (849).

C) HUNTINGTON'S DISEASE. A₂ receptors have been shown to be localized on striatal output neurons, which are dramatically decreased in Huntington's disease (1111). A_{2A} receptor blockade prevents EEG and motor abnormalities in a rat model of Huntington's disease (1366). There is a decrease of striatal A₁ and A_{2A} receptors in hyperkinetic neurodegenerative movement disorder characteristic of Huntington's disease (651, 1253).

D) MS. P2 receptors on oligodendrocytic progenitor cells mediate an increase in [Ca²⁺]_i and may mediate the formation of myelin, raising the possibility that activation of P2 receptors may offer new approaches to the treatment of demyelinating diseases in the CNS, such as MS (18, 1641; see sect. VIII C).

Neuronal pathology is an early feature of MS and its animal model, experimental autoimmune encephalomyelitis (EAE). Lesional accumulation of P2X receptors on macrophages in rat CNS during EAE has been described (691). Mice deficient in P2X₇ receptors are more susceptible to EAE than wild-type mice and show enhanced inflammation in the CNS, reflected by a loss of apoptotic activity in lymphocytes (340). The cytokine IFN- γ disrupts the functionality of P2X₇ receptors, a key step controlling endocannabinoid production by microglia; thus induction of EAE in P2X₇ receptor knockout mice results in lower

endocannabinoid levels and more pronounced cell damage than in wild-type mice (1879). The authors suggest that the high levels of brain IFN- γ associated with EAE disrupt endocannabinoid-mediated neuroprotection. The temporal pattern of plasma membrane calcium ATPase2 expression in spinal cord correlates with the course of clinical symptoms in two rodent models of autoimmune encephalomyelitis (1242). IFN- β has shown beneficial effects in relapsing-remitting MS, perhaps by having a protective effect against apoptotic death of astrocytes; apyrase and 5'-nucleotidase increased in synaptosomes from the cerebral cortex of rats experimentally demyelinated with ethidium bromide and treated with IFN- β (1618).

In MS lesions, P2X₇ receptors were demonstrated on reactive astrocytes in autopsy brain tissues, and P2X₇ receptor stimulation increased the production of IL-1 β -induced NOS activity in cultured astrocytes (1215).

3. Cerebral ischemia

Ischemia can produce and exacerbate many serious insults to the CNS, including stroke and paralysis. Adenosine is usually considered to play an important protective role against ischemic damage in the brain, although the underlying mechanism is still debated (61, 580, 1325, 1383, 1713, 1942). However, ATP, rather than adenosine, has been shown to accelerate recovery from hypoxic/hypoglycemic perturbation of guinea pig hippocampal neurotransmission via a P2 receptor (20), and suramin reduces infarct volume in a model of focal brain ischemia (900). The use of ATP-MgCl₂ early in reperfusion is claimed to substantially improve brain protein synthesis after global ischemia (1316). There is upregulation of ectonucleotidase after transient forebrain ischemia (203) as well as an increase in release of purines into cerebral cortical perfusates (1349). Upregulation of P2X₂ and P2X₄ receptors in organotypic cultures of hippocampus, cortex, and striatum is associated with ischemic cell death and was prevented by P2 receptor antagonists (321). A recent study describes the neuroprotective effect of the P2 receptor antagonist PPADS on focal cerebral ischemic-induced injury in rats (997), and cotreatment by the P2X antagonists PPADS and suramin and vigabatrin, an inhibitor of GABA breakdown, protect against ischemic neuronal cell death in the gerbil hippocampus (906). It has been claimed that ischemic brain injury is regulated by extracellular ATP-mediated IL-10 expression in microglia (703).

There is a postischemic, time-dependent upregulation of P2X₇ receptors on both neurons and glial cells in rat cerebral cortex, suggesting a role for these receptors in the pathophysiology of cerebral ischemia *in vivo* (573, 1141), although earlier studies showed that deletion of P2X₇ receptors (knockout mice) and/or treatment with

the P2X₇ antagonist KN62 had little effect on ischemic cell death (1007). Supersensitivity of P2X₇ receptors in cerebrocortical cell cultures after *in vitro* ischemia has been reported (1873). Microglial P2X₄ and P2X₇ receptors appear to be involved in cortical damage produced by oxygen/glucose deprivation (320). Activation of P2X receptors contributes to the ischemia-induced facilitation of glutamate release (1961). Ap₄A protects against ischemic injury in rat brain and has been suggested as a potentially useful molecule in the therapy of stroke (1831). P2X receptors (as well as NMDA receptors) contribute to cell death in CA1 hippocampal neurons subjected to oxygen and glucose deprivation, and inhibition of P2X receptor activation has a neuroprotective effect similar to that produced by inhibition of NMDA receptors (1462).

Perinatal brain injury in survivors of premature birth show paraventricular white matter injury, the leading cause of chronic neurological morbidity. While adenosine plays an important neuroprotective role in the mature brain, A₁ receptor activation does not confer neuroprotection during early development and has a deleterious effect on cerebral maturation (11). Adenosine antagonists reduce hypoxic-ischemic injury in neonatal mice (see Ref. 75). Aging reduces the cardioprotective effect of adenosine to ischemia (542, 1865).

4. Migraine

Classical migraine is associated with two distinct cerebrovascular phases: an initial vasoconstriction (not associated with pain) followed by vasodilatation (reactive hyperemia) associated with pain. The "purinergic" hypothesis for migraine was originally put forward in 1981 as a basis for the reactive hyperemia and pain during the headache phase (247). It was suggested that ATP and its breakdown products AMP and adenosine were strong contenders for mediating the vasodilatation following the initial vasospasm and subsequent hypoxia. ATP was also implicated in the pathogenesis of pain during migraine via stimulation of primary afferent nerve terminals located in the cerebral microvasculature. Later studies have shown that ATP-induced cerebral vasodilatation is endothelium dependent via activation of P2X and P2Y receptors on the endothelial cell surface and subsequent release of endothelium-derived relaxing factor and that the endothelial cells are the main local source of ATP involved, although ADP and ATP released from aggregating platelets may also contribute to this vasodilatation. These findings have extended the purinergic hypothesis for migraine in two ways. First, they have clarified the mechanism of purinergic vasodilatation during the headache phase of migraine. Second, they suggest that a purinergic mechanism may also be involved in the initial local vasospasm, via P2X receptors on smooth muscle cells occupied by ATP released either as a cotransmitter with NE from perivascu-

lar sympathetic nerves or from damaged endothelial cells (251). The hypothesis gained further support by the identification of P2X₃ receptors on primary afferent nerve terminals supplying cerebral vessels arising from trigeminal, nodose, and spinal ganglia (267, 335). Thus P2X₃ receptor antagonists may be candidates for antimigraine drug development (1813). CGRP is expressed in human trigeminal neurons and is released during migraine attacks; a recent study shows that the algogenic action of CGRP is linked to sensitization of trigeminal P2X₃ nociceptive receptors, suggesting that trigeminal P2X₃ receptors may be a potential target for the early phase of migraine attack (530). There is also evidence that migraine is a chronic sympathetic nervous system disorder, with which there is an increase in release of sympathetic cotransmitters, including ATP (1336), which may contribute to the initial vasospasm. ATP may contribute to pain in migraine by sensitizing nociceptors against acidosis via P2Y₂ receptor-supported release of endogenous prostaglandin (1981). It has been suggested that there is an interaction of P2Y receptors on trigeminal sensory terminals with P2X₃ receptors after sensitization of trigeminal neurons with algogenic stimuli (e.g., NGF, BDNF, or bradykinin) and that this may help identify new targets for the development of novel antimigraine drugs (599).

5. Neuropsychiatric disorders

Early hints that purines may play a role in neuropsychiatric disorders were discussed in section III C, and there was some consideration of purinergic influences on mood in section VI H5. More recently, it has been claimed that purinergic signaling dysfunction (perhaps largely reduced adenosinergic activity) is involved in mania and aggressive behavior (1088). A_{2A} receptors have been implicated in panic disorder (995). Endogenous ATP has been claimed to be involved in the regulation of anxiety via stimulation of P2Y₁ receptors in the dorsomedial hypothalamus in rats (926). Chronically administered guanosine has anticonvulsant, amnesic, and anxiolytic effects of mice, perhaps associated with modulation of glutamatergic excitation (1788). 5'-Nucleotidase activity is increased in synaptosomes from hippocampus and cerebral cortex of hypothyroid rats and may be related to the cognitive disorders found in hypothyroidism (222).

The P2X₇ receptor gene is located within a region in chromosome 12q24.31 that has been identified as a susceptibility locus for affective disorders by linkage and association studies (1074). In patients suffering from recurrent major depressive disorder (MDD), a nonsynonymous coding single-nucleotide polymorphism within the P2X₇ and adjacent receptor genes (rs 2230912), previously found to be associated with bipolar disorder (100), was found to be significantly associated with MDD. This polymorphism results in an amino acid exchange in the

COOH-terminal domain of the P2X₇ receptor, suggesting that the observed P2X₇ receptor polymorphism might play a critical role in the development of depression.

The involvement of ATP receptors in schizophrenia has been discussed in relation to reports that antipsychotic drugs such as haloperidol, chlorpromazine, and fluspirilene inhibit ATP-evoked responses mediated by P2X receptors (804). It was suggested that ATP may have a facilitating role for dopaminergic neurons and that various antipsychotic drugs express their therapeutic effects by suppression of dopaminergic hyperactivity through the inhibition of P2X receptor-mediated effects. Adenosine has been considered as a contributing element in the pathophysiology of schizophrenia (see Ref. 1001). Adenosine-dopamine interactions in the ventral striatum have been implicated in schizophrenia (547, 853, 1728). A_{2A} and D₂ receptor hetero-oligomerization has been postulated (1728). A hypothesis in which dysfunction of purinergic signaling (for example, decreased ATPase activity in erythrocytes, leading to increased levels of ATP and decreased adenosine) may lead to schizophrenia has been put forward (1002). Upregulation of striatal A_{2A} receptors has been observed in schizophrenia (441). The possible therapeutic use of A_{2A} receptor agonists combined with D₂ antagonists has been raised (797). Glial P1 receptors have been implicated in mood disorders (1765).

6. Epileptic seizures

Microinjection of ATP analogs into the prepiriform cortex induces generalized motor seizures (935). Epileptiform activity in the CA3 region of rat hippocampal slices was modulated by adenine nucleotides, probably acting via an excitatory P2X receptor (1447). P2X₂, P2X₄, and P2X₆ receptors are expressed in the prepiriform cortex, suggesting that P2X receptor antagonists may have potential as neuroleptic agents. The hippocampus of chronic epileptic rats shows abnormal responses to ATP associated with increased expression of P2X₇ receptors. It has been shown that P2X₇ receptors are upregulated (perhaps in microglia) and may participate in the pathophysiology of temporal lobe epilepsy (1784). In a recent study of kainate-provoked seizures, enhanced immunoreactivity of the P2X₇ receptor was observed on microglia as they changed from the resting to the activated state (1397). The amount of extracellular ATP detected in hippocampal slices following electrical stimulation of Schiffer collaterals was significantly greater in D2 mice that have an inherited susceptibility to audiogenic seizures, in contrast to B6 mice that are resistant to these seizures (1860). It was suggested that the increased levels of extracellular ATP in D2 mice are associated with reduced brain Ca²⁺-ATPase activity. Uridine is released during epileptic activity and may act as an inhibitory neuromodulator (1585). Increased hydrolysis of ATP occurs in rat hippocampal

slices after seizures induced by quinolinic acid (1241). There is a decrease of presynaptic P2X receptors in the hippocampus of rats that have suffered a convulsive period, which may be associated with the development of seizures and/or of neurodegeneration during epilepsy (1283).

P1 receptors have also been implicated in epileptic seizures (73, 473, 500, 777, 1950). Decreased extracellular adenosine levels and altered A₁ and P2 receptor activation caused by hypercapnia in hippocampal slices provide a plausible mechanism for hyperventilation-induced epileptic seizures in vulnerable humans (490). Adenosine, acting via A₁ receptors, reduces seizures in an experimental model of temporal lobe epilepsy induced by pilocarpine in rats (1783). A lower density of P1(A₁) receptors in the nucleus reticularis thalami in rats with genetic absence epilepsy has been reported (512). Several antiepileptic agents reduce the ability of astrocytes to transmit calcium waves, raising the possibility that purinergic receptor antagonists blocking intercellular calcium waves in astrocytes could offer new treatments for epileptic disorders. Adenosine controls hyperexcitability and epileptogenesis (1097), and release of glutamate from astrocytes has been implicated in epileptogenesis (1709).

7. Cancer and encephalitis

Neuroblastoma, the most common extracranial tumor of childhood, expresses the P2X₇ receptor, which appears to mediate proliferation, rather than apoptosis, partially due to SP release (1389). Experimental infusion of ATP into nucleus accumbens or cerebral hemisphere of rats suggests that purines might be a signal for induction of malignant brain tumors.

Acanthamoeba is a protozoan parasite that can cause fatal granulomatous amoebic encephalitis. It has been shown recently to hydrolyze ATP, and it was suggested that this ecto-ATPase activity may play a role in the pathogenesis of this disease (1582).

8. Abnormalities in central control of peripheral function

Purinergic signaling appears to play a significant role in the regulation of body temperature during fever by central hypothalamic and brain stem nuclei (666). Mice lacking the P2X₃ receptor subunit exhibit enhanced avoidance of both hot and cold thermal extremes (1556).

P2X and GABA_A receptors play an important role in CO₂ chemoreception and are involved in mediation of the ventilatory response to hypercapnia (664). Different NTS purinoceptor subtypes may contribute to patterned autonomic responses observed in specific physiological or pathological situations (1530). Evaluation of the roles of purinergic signaling in processing of the sympathoexcitatory component of the chemoreflex at the NTS level may

illuminate the mechanisms underlying the sympathetic overactivity observed in pathophysiological conditions such as hypertension, obstructive sleep apnea, and heart failure (437).

9. Central purinergic pathways and neuropathic pain

Changes in central purinergic pathways that occur in neuropathic pain have attracted considerable attention in recent years and have been well reviewed (357, 801, 1131, 1162, 1209, 1508, 1730, 1748).

There is purinoceptor involvement in nociceptive pathways in the spinal cord (see Refs. 262, 701). For example, intrathecally administered P2 receptor antagonists, suramin and PPADS, produced antinociceptive effects in rats (480). ATP-activated P2X receptors in lamina II of the rat spinal cord play a role in transmitting or modulating nociceptive information (102). Presynaptic P2X₂ receptors modulate excitatory synaptic transmission between primary afferent fibers and spinal cord dorsal horn neurons of the lumbar spinal cord of rats (1039). The vanilloid receptor, VR1, is colocalized with the P2X₃ receptor and with binding sites for the lectin IB₄ within a large proportion of DRG neurons and their terminals in the dorsal horn of the spinal cord (690). Single deep dorsal horn neurons in lamina V often receive convergent excitatory inputs from both capsaicin-sensitive and α , β -meATP-sensitive pathways (1207). α , β -MeATP-induced thermal hyperalgesia may be mediated by spinal P2X₃ receptors, perhaps by evoking glutamate release (1733). Spinal endogenous ATP may play a role in capsaicin-induced neurogenic pain via P2X₃ or P2X_{2/3} receptors and Formalin-induced inflammatory pain via different P2X and/or P2Y receptors (1732). It has also been suggested that spinal P2X receptors play a role in the modulation of spinal nociceptive transmission following development of inflammation (1634). Of the six lamina regions in the dorsal horn of the spinal cord, inner lamina II (188) and lamina I (341) are the major sensory regions involved in nociceptive transmission, as well as lamina V (1561). Central terminals of nociceptive afferents coexpress ionotropic glutamate (kainate) and P2X₃ receptors (1075).

There are three potential sources of ATP release during sensory transmission in the spinal cord. ATP may be released from the central terminals of primary afferent neurons. ATP may be also released from astrocytes and/or postsynaptic dorsal horn neurons. In the DRG, the presence of P2X₃ mRNA-labeled neurons increased 3 days after peripheral injury (1734). P2X₃ receptors on DRG neurons increase their activity after inflammation and contribute to the hypersensitivity to mechanical stimulation in the inflammatory state (418). After induction of painful peripheral neuropathy by sciatic nerve entrapment, evidence has been presented for increased release of ATP from DRG neurons on the side of the injury;

however, sensitization of P2X₃ receptors rather than a change in ATP release appears to be responsible for the neuropathic pain behavior (342).

For neuropathic pain, the tactile allodynia that follows peripheral nerve injury is reduced by A-134974, a novel adenosine kinase inhibitor acting at spinal sites (1973). PPADS, TNP-ATP, and apyrase attenuate central sensitization in nociceptive neurons in medullary dorsal horn, which suggests that release of ATP in the dorsal horn plays a key role in the central sensitization induced by injury or inflammation of peripheral tissues (356). Upregulated homomeric P2X₃ and heteromeric P2X_{2/3} receptors augmented thermal hyperalgesia and mechanical allodynia, respectively, at the spinal level in the acute stage of chronic constriction injury; at the chronic stage (>40 days), thermal hyperalgesia disappeared, but mechanical allodynia persisted (1750). A-317491, a potent and selective antagonist of P2X₃ and P2X_{2/3} receptors, reduces chronic inflammatory and neuropathic pain in the rat, but not acute, inflammatory, or visceral pain (1132). When A-317491 and also Compound A (US patent no. 2005/0209260A1) were administered spinally to animals after chronic nerve constriction injury, there was a reduction in sensory fiber responses unmasking a central role for these P2X receptors, suggesting a potential role of their antagonists in the modulation of neuropathic pain (1547). Endogenous ATP acting on P2X receptors appears to be necessary for the induction of the postoperative pain characterized by mechanical allodynia (1731). ATP causes the activation of p38 or ERK/2 mitogen-activated protein kinases in microglia, resulting in the release of TNF (1673), as well as IL-6 (801). Intraspinal administration of p38 inhibitor suppressed allodynia, which suggests that neuropathic pain hypersensitivity depends on the activation of the p38 signaling pattern in microglia in the dorsal horn following peripheral nerve injury (801). Suramin inhibits spinal cord microglia activation and long-term hyperalgesia induced by inflammation produced by Formalin injection (692).

Endogenous opioid mechanisms partially mediate spinal P2X₃/P2X_{2/3} receptor-related antinociception in rat models of inflammatory and chemogenic pain, but not neuropathic pain (1130). Runxl, a Runt domain transcription factor, regulates the expression of P2X and opioid receptors, on a subpopulation of nociceptive sensory fibers, and mice lacking Runxl exhibit specific defects in thermal and neuropathic pain (336).

Analgesic effects with intrathecal administration of P2Y receptor agonists UTP and UDP in normal and neuropathic pain rat model have been reported, suggesting that P2Y₂ (and/or P2Y₄) and P2Y₆ receptors produce inhibitory effects in spinal pain transmission (1273). It has been suggested that, while P2X₃ receptor activation leads to increased firing of DRG neurons and subsequently to increased release of sensory transmitter from their cen-

tral processes (1208), P2Y₁ receptor activation may decrease the release of sensory transmitter onto spinal cord neurons and may thereby partly counterbalance the algogenic effect of ATP (177, 631). P2Y₁ receptor expression is upregulated in rat DRG neurons following transection of sciatic nerves and has been implicated in the mechanisms underlying neuropathic pain (1906). The RVM serves as a critical link in bulbospinal nociceptive modulation. Within the RVM, "on-cells" discharge and "off-cells" pause immediately prior to a nociceptive reflex. Data have been presented to suggest that on-cells preferentially express P2X receptors and off-cells P2Y receptors (1538). Satellite glial cells in mouse trigeminal ganglia have been shown to express P2Y, probably P2Y₄, receptors, and it was speculated that they may be activated by ATP released during nerve injury (1845).

With the use of in situ hybridization, P2X₇ mRNA was demonstrated on presynaptic terminals to numerous neurons in the spinal cord and medulla oblongata (450). Disruption of the P2X₇ receptor gene abolishes chronic inflammatory and neuropathic pain (350), as does a recently developed selective P2X₇ receptor antagonist, compound 15d (1233). P2X₇ receptor activation of cultured astrocytes from rat brain increases the release of cysteinyl leukotrienes, which are potent lipid mediators of inflammation, further supporting a role for extracellular ATP as an integral component of the inflammatory brain pain response (85). P2X₄ and P2X₇ knockout mice share a common pain phenotype, but apparently via different mechanisms (351). The roles of microglia in neuropathic and inflammatory pain, as well as in neuronal cell death and regeneration, have attracted strong interest in the past few years (see Refs. 535, 1373, 1723). ATP selectively suppresses the synthesis of the inflammatory protein MRF-1 through Ca²⁺ influx via P2X₇ receptors in microglia (883). ATP, ADP, and BzATP, acting through P2X₇ receptors, induce release of the principal proinflammatory cytokine IL-1β from microglial cells (1500). Activation of P2X₇ receptors enhances IFN-γ-induced NOS activity in microglial cells and may contribute to inflammatory responses (629). ATP, via P2X₇ receptors, increases production of 2-arachidonoylglycerol, which is also involved in inflammation by microglial cells (1880). P2X₇ receptors have been shown to be essential for the development of CFA-mediated hypersensitivity, and the inflammatory response is attenuated in P2X₇ receptor-null mice through modulation of IL-1β and other cytokines (350). Astrocyte-derived ATP has been identified as the endogenous factor responsible for microvesicle shedding via P2X₇ receptor activation in microglia and IL-1β release from these cells (143).

There is growing evidence that immune cells contribute to pathological pain states (1839; see also sect. VIII). After spinal cord injury, an increased number of lumbar microglia expressing the P2X₄ receptor in the spinal cord

of rats with allodynia and hyperalgesia have been reported (801, 1523, 1731). Pharmacological blockade of P2X₄ receptors reversed tactile allodynia caused by peripheral nerve injury without affecting acute pain behaviors in naive animals (1731). Intrathecal delivery of the P2 receptor antagonist suramin blocked microglia activation and long-term hyperalgesia induced by Formalin injection (1890). Intraspinal administration of P2X₄ antisense oligodeoxynucleotide decreased the induction from P2X₄ receptors and suppressed tactile allodynia after nerve injury. On this basis, it has been claimed that blocking of P2X₄ receptors on microglia might be a new therapeutic strategy for pain induced by nerve injury (1730). A recent study suggests that spinal fibronectin is elevated after peripheral nerve injury and may be involved in the up-regulation of P2X₄ receptors in microglia, associated with neuropathic pain (1217). Inflammatory mediators, such as TNF- α , IL-1 β , and prostaglandin E₂, released from immune cells can contribute to persistent pain states in both inflammatory and neuropathic pain caused by damage to peripheral nerves or to the CNS (1104).

It has been suggested that heat shock proteins (HSPs) may be involved in inflammation-related nociception, and it has been shown that inhibitors of HSP90 increase the magnitude of currents mediated by P2X and VR1 receptors that are known to be involved in inflammation-related nociception (1129). ATP potentiates the expression of HSP60 in astrocytes (337).

Platelet-activating factor (PAF) is a potent inducer of tactile allodynia and thermal hyperalgesia at the level of the spinal cord; it is suggested that PAF-evoked tactile allodynia is mediated by ATP and after a NMDA and NO cascade through capsaicin-sensitive fibers (1184). Hypothyroidism changed ATP and ADP hydrolysis in the rat spinal cord, and this was related to nociceptive responses (222).

Intracerebroventricular administration of α,β -meATP has an antinociceptive effect; evidence has been presented to suggest the involvement of supraspinal β -adrenergic and μ -opioid receptors in this effect (593). Intracerebroventricular coadministration of antagonists to both purinergic and glutamatergic receptors resulted in a deeper level of the analgesic and anesthetic actions of the individual agents (1115). Studies suggest that ascending noradrenergic nerves arising from the locus coeruleus are involved in the supraspinal antinociception by α,β -meATP through P2X receptors in the locus coeruleus (594). Nociceptive stimulation activates locus coeruleus neurons projecting to the somatosensory thalamus in the rat (1798).

Adenosine A₁ receptor agonists are effective antinociceptive agents in neuropathic pain as well as in inflammatory pain, acting at the spinal cord level (457, 1508), probably as prejunctional inhibitors of transmitter release in the pain pathways.

Recent experiments have demonstrated a role of the mitochondrial electron transport chain, which drives ATP synthesis, in neuropathic and some forms of inflammatory pain (845).

10. Alcohol and drug addiction

Addiction is a chronic relapsing neurological disorder, and adenosine A_{2A} receptors have been implicated in the underlying mechanism (498, 797). For example, specific involvement of A_{2A} receptors in the addictive-related properties of cannabinoids has been reported (1607). The lack of A_{2A} receptors in knockout mice diminishes the addictive-reinforcing efficacy of cocaine (1608). A number of studies have suggested that opioids can interact with adenosine systems (see Ref. 500). Morphine has been shown to release purines in brain and spinal cord (303, 1345), and opioid analgesia can be at least partially antagonized by P1 receptor antagonists (see Ref. 1509). In animals withdrawn from chronic treatment with either morphine or cocaine, there are persistent increases in extracellular adenosine in the ventral tegmental region, a brain region intimately involved in the rewarding effects of these drugs (172). Heroin administration appears to enhance the catabolism of adenosine in the brain by increasing adenosine deaminase (1922). It has been suggested that A_{2A} receptor antagonists may be effective therapeutic agents for the management of abstinent heroin addicts (1924). P2Y₁ receptors were upregulated in both astrocytes and neurons in the striatum and nucleus accumbens of rats treated for 5 days with amphetamine (575).

Although ethanol is probably the oldest and most widely used psychoactive drug, the cellular mechanisms by which it affects the nervous system have been poorly understood, although some insights in relation to purinergic P2 receptor signaling have emerged in recent years (see Refs. 428, 1093, 1847). Chronic ethanol exposure inhibits calcium influx through voltage-independent cationic channels associated with purinergic receptors on PC12 cells (908). Ethanol inhibits P2X receptor-mediated responses of DRG neurons by an allosteric mechanism (1033). Ethanol differentially affects ATP-gated P2X₃ and P2X₄ receptor subtypes expressed in *Xenopus* oocytes (428). The mechanism by which ethanol inhibits responses mediated by rat P2X₄ receptors is altered by mutation of histidine-241 (1907). A₁ receptor activation mediates ethanol-induced inhibition of stimulated glutamate release in the hippocampus of the near-term fetal guinea pig (1417).

11. Diseases of special senses

A) EYE. Purinergic signaling is widespread in the eye (1354), and novel therapeutic strategies are being developed for glaucoma, dry eye, and retinal detachment

(1357). P2Y receptors on human corneal epithelial cells appear to play a critical role in the injury-repair process (931).

ATP, acting via both P2X and P2Y receptors, modulates retinal neurotransmission, affecting retinal blood flow and intraocular pressure. The ATP analog β, γ -meATP is more effective in reducing intraocular pressure (40%) than muscarinic agonists such as pilocarpine (25%) and β -adrenoceptor blockers (30%), raising the potential for the use of purinergic agents in glaucoma (1357). Dinucleoside polyphosphates acting via P2Y₁ receptors on trabecular network cells increase aqueous humor outflow and may be another target for antiglaucomatous drugs (1358, 1614). Suramin, a P2 receptor antagonist, has been shown to inhibit the fibrotic wound healing reactions that sometimes follow trabeculectomies for surgically treating eyes with glaucoma (1150).

The formation of P2X₇ receptor pores and apoptosis is enhanced in retinal microvessels early in the course of experimental diabetes, suggesting that purinergic vaso-toxicity may play a role in microvascular cell death, a feature of diabetic retinopathy (1660). A recent article has raised the possibility that alterations in sympathetic nerves may underlie some of the complications observed in diabetic retinopathy (1864) and may therefore involve ATP as a cotransmitter released from sympathetic nerves.

A_{2A} receptor immunoreactivity was shown to be associated with developing dog retinal vessels and added support for the view that A_{2A} receptors are involved in the vasoproliferative stage of canine oxygen-induced retinopathy. P2X₇ receptor mRNA and protein in the mouse retina changes during retinal degeneration in the mouse model (BALBCrds) of the hereditary disease retinitis pigmentosa (576).

Upregulation of P2X₇ and P2Y₂ (and/or P2Y₄) receptor-mediated responses has been demonstrated in Müller glial cells during proliferative vitreoretinopathy (208, 571). Upregulation of P2Y receptors in retinal glial Müller cells from rats infected with Borna disease virus has also been described (1304). During the differentiation of immature radial glia into mature Müller cells, there is a decrease in responses to ATP (1746).

P2Y₂ receptor activation increases salt, water, and mucus excretion and thus represents a potential treatment for dry eye conditions (1195, 1933). In the pigmented layer of the retina, P2Y₂ receptor activation promotes fluid absorption and may be involved in retinal detachment. INS37217, a long-lasting synthetic P2Y₂ receptor agonist, stimulates the retinal pigment epithelium by activating P2Y₂ receptors at the apical membrane, and in vivo treatment enhances the rate of subretinal fluid reabsorption in experimentally induced retinal detachments and may be useful for treating a variety of retinal diseases that result in fluid accumulation in the subretinal space (1098). Reactive responses of Müller cells occur within

24 h of retinal detachment. Suramin inhibits some of these responses and may provide a therapeutic candidate to limit the detrimental effects of immune cell activation and Müller cell gliosis during retinal detachment (1754).

ATP and UTP restore the rates of both net Cl⁻ and fluid secretion in adenovirus type 5-infected conjunctival tissues and are considered as potential therapeutic modulators for the treatment of various transport defects encountered in ocular tissues in diseased and/or inflamed states (978). UTP and Ap₄A accelerate wound healing in the rabbit cornea, by regulating the rate of epithelial cell migration (1355).

The UPL rat is a dominant hereditary cataract model derived from Sprague-Dawley rats and has been used to show that Ca²⁺-ATPase expression increases, whereas ATP control decreases in lenses during the development of the cataract and opacification; disulfiram and aminoguanidine, which inhibit inducible NO and scavenge reactive oxygen species, attenuate the decrease in ATP, resulting in a delay in cataract development (1197).

B) EAR. In the auditory system, ATP, acting via P2Y receptors, depresses sound-evoked gross compound action potentials in the auditory nerve, and the distortion produces otoacoustic emission, the latter being a measure of the active process of the outer hair cells (765, 1656; see sect. *vF6* and *ixI2*). P2X splice variants are found on the endolymphatic surface of the cochlear endothelium, an area associated with sound transduction. Both P2X and P2Y receptors have been identified in the vestibular system (1897). ATP may regulate fluid homeostasis, cochlear blood flow, hearing sensitivity, and development and thus may be useful in the treatment of Ménière's disease, tinnitus, and sensorineural deafness.

Sustained loud noise alters the response of outer hair cells in the inner ear to ATP (333) and produces an upregulation of P2X₂ receptors, particularly at the site of outer hair cell sound transduction. P2X₂ expression is also increased in spiral ganglion neurons, indicating that extracellular ATP acts as a modulator of auditory neurotransmission that is adaptive and dependent on the noise level (1822). Excessive noise can irreversibly damage hair cell stereocilia leading to deafness. Data have been presented showing that release of ATP from damaged hair cells is required for Ca²⁺ wave propagation through the support cells of the organ of Corti, involving P2Y receptors, and this may constitute the fundamental mechanism to signal the occurrence of hair cell damage (609, 1194). ATP is claimed to mitigate the effects of noise trauma (820, 1657), although the mechanisms involved are not clear.

C) NASAL ORGANS. Purinergic receptors have been described in the nasal mucosa, including the expression of P2X₃ receptors on olfactory neurons (624; see sect. *vF7*). Enhanced sensitivity to odors in the presence of P2 receptor antagonists suggests that low-level endogenous

ATP normally reduces odor responsiveness (725). It appears that the induction of HSPs by noxious odor damage can be prevented by the *in vivo* administration of P2 receptor antagonists (726). The predominantly suppressive effect of ATP in odor responses could play a role in the reduced odor sensitivity that occurs during acute exposure to noxious fumes and may be a novel neuroprotective mechanism.

XII. CONCLUDING COMMENTS AND FUTURE DIRECTIONS

This review has covered a wide spectrum of information about the roles of purinergic signaling in the physiology and pathophysiology of neurotransmission and neuromodulation, including autonomic and somatic neuromuscular transmission, synaptic transmission in peripheral ganglia and in the CNS, cotransmission, and mechanosensory transduction. The development and comparative physiology of neurotransmission have also been included, as well as plasticity of purinergic neurosignaling in developmental and pathological situations.

Coordinating the wide variety of cells in the nervous system requires some means of intercellular communication that can integrate vascular, glial, immune, and neural elements into a dynamic but highly regulated system. Perhaps more than any other molecule, extracellular ATP meets this requirement. All of these cell types can release ATP for intercellular communication, and all are equipped with a rich diversity of membrane receptors for extracellular ATP and its metabolites, as well as the extracellular enzymes regulating ATP hydrolysis. The second messenger systems and protein kinase cascades activated by these receptors mediate a diverse range of nervous system processes, from the millisecond duration of synaptic transmission to time scales of development and regeneration (see Fig. 11).

The last 10 years have been a period of rapid progress in identifying the numerous types of purinergic receptors and in understanding their relationships, pharmacology, and intracellular signaling. This progress has facilitated new appreciation of the wide spectrum of neural activities involving purinergic signaling, including the roles of ATP and adenosine in neuron-glia interactions, bringing new and unexpected insights into how glia respond to neural impulse activity and participate in nervous system function (see Ref. 552). Another important area of growing interest, referred to in several sections, is the involvement and interactions of purinergic signaling pathways in immunity and inflammation. The role of endogenous ATP and adenosine during the course of inflammatory and immune responses *in vivo* is extremely complex. However, it appears that purinergic signaling contributes to

the fine-tuning of inflammatory and immune responses in such a way that the danger to the host is eliminated efficiently with minimal damage to healthy tissues (183).

ATP signaling should be considered together with adenosine signaling. The often antagonistic and sometimes synergistic actions of ATP and adenosine provide a mechanism for sophisticated cellular interactions.

The expression and distribution of specific purinergic receptors in neurons and nonneuronal cells must be analyzed at a much finer level (see Ref. 1800). This analysis is difficult because of the large number of receptor types and complex interactions between multiple types of purinergic receptors coexpressed in many cells, often expressed in different regions of the cells and because the receptors can mediate both short- and long-term events. This difficulty is augmented by the overlapping specificity of many agonists and antagonists currently available and because heteromultimers can form between P1, P2X, and P2Y receptors as well as with receptors to other messenger systems.

The chemistry of ATP in the extracellular environment is dynamic and complex, and more must be learned about the extracellular biochemistry and enzymes that regulate the synthesis and degradation of ATP outside the cell. The activity of ectonucleotidases in subcellular domains and how these enzymes change during development, disease, and physiological state are not known in sufficient detail. The development of selective inhibitors for the different subtypes of ectonucleotidases would be a valuable step forward.

Nucleosides and nucleotides are part of a primitive signaling system with potent actions in both invertebrates and lower vertebrates, but it is highly desirable to learn more about the molecular biology of the receptors involved. An ATP receptor cloned in the platyhelminth *Schistosoma mansoni* shows surprisingly close similarity to mammalian P2X receptors (17). Equally important is to follow-up the few early studies of the roles of purinergic signaling in both embryonic and postnatal development and regeneration. Studies of purinergic signaling in stem cells are beginning; the preliminary reports are encouraging and hopefully will develop into a major new area of purinergic research (see, for example, Refs. 1154, 1158, 1472, 1565, 1980).

While it is now clear that many different cell types release ATP physiologically in response to mechanical distortion, hypoxia, and various agents, we still await a clear understanding of the mechanisms that underlie ATP transport. Hopefully, when this becomes clearer, agents will be developed that will be able to enhance or inhibit ATP release, another useful way forward as a therapeutic strategy.

While there is now much known about the roles of purines and pyrimidines as neurotransmitters and in neu-

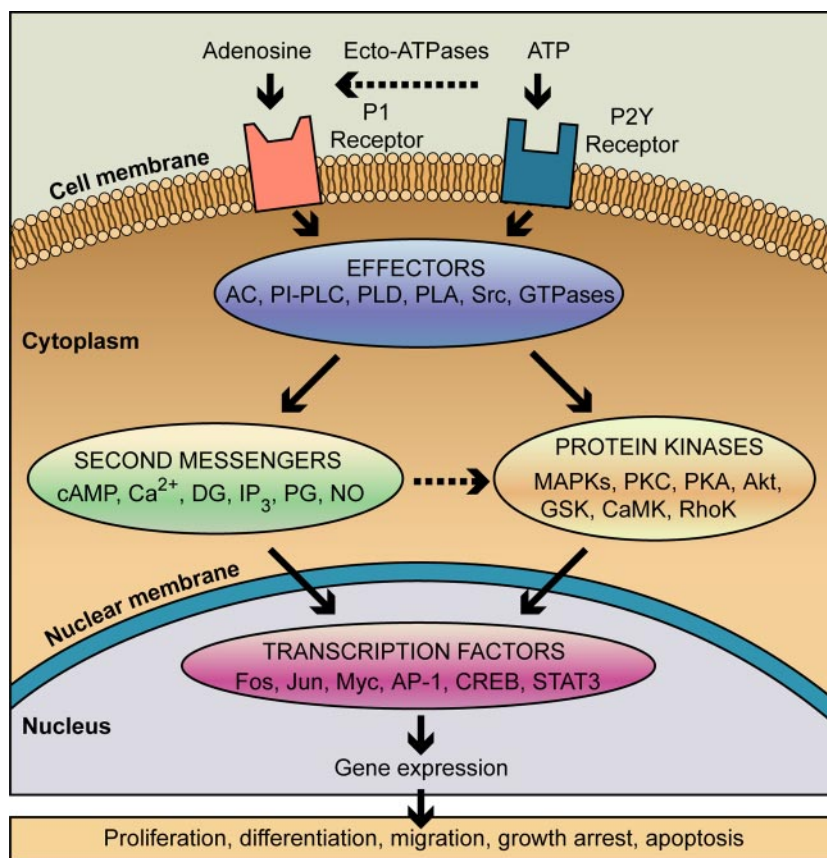


FIG. 11. Schematic overview of purinergic signaling mechanisms that regulate long-term, trophic effects. Extracellular nucleotides and nucleosides bind to purinergic receptors coupled to signal-transducing effector molecules. Activation of the effectors leads to generation of second messengers and/or stimulation of protein kinases that regulate expression of genes needed for long-term, trophic actions. In some cases, P2X receptors such as P2X₇ are also coupled to protein kinase cascades and can mediate proliferation and apoptosis. Cell-specific and/or receptor subtype-specific differences are likely to account for variations in signaling pathways and functional outcomes. It should be noted that the list of elements is not meant to be all-inclusive. Other protein kinases, e.g., MEK and PI3K, are upstream of the listed kinases involved in purinergic signaling, while others are downstream, e.g., p70S6K. In addition, dashed arrows indicate that not all listed elements are activated by the upstream component, e.g., not all P1 receptors are coupled to all listed effectors. AC, adenylyl cyclase; AP-1, activator protein-1; CaMK, calcium/calmodulin protein kinase; CREB, cAMP response element binding protein; DG, diacylglycerol; GSK, glycogen synthase kinase; IP₃, inositol trisphosphate; MAPKs, mitogen-activated protein kinases [including extracellular signal-regulated protein kinase (ERK), p38 MAPK, and stress-activated protein kinase (SAPK)/c-Jun NH₂-terminal kinase (JNK)]; MEK, MAPK/ERK kinase; NO, nitric oxide; PG, prostaglandin; PI3K, phosphoinositide 3-kinase; PI-PLC, phosphatidylinositol-specific phospholipase C; PKA, protein kinase A; PKC, protein kinase C; PLD, phospholipase D; PLA, phospholipase A; STAT3, signal transducer and activator of transcription-3. (Figure kindly prepared by Jo Neary, Research Service, Miami Department of Veteran's Affairs Medical Center, Miami, FL.)

ronal activity in different regions of the brain, there are still relatively few studies of the physiological significance of these pathways in behavioral terms in both healthy and pathological conditions (see sects. viH8 and xiB).

There are an increasing number of explorations of the therapeutic potential of purinergic signaling in various diseases of the nervous system, and hopefully this will expand even further. Advances still depend on the serious endeavors of medicinal chemists to produce receptor subtype-selective, small, orally bioavailable agonists and antagonists that survive degradation in vivo. However, other approaches are promising, including the development of agents that control the expression of receptors that inhibit ATP breakdown

by selective inhibition of the known ectonucleotidases and agents that can be used to regulate ATP transport.

Knockout mice are available for a number of P1, P2X, and P2Y receptor subtypes, but there are gaps that need to be filled, and transgenic models that overexpress receptors, as well as antisense oligonucleotides, are also needed. The siRNA technique is only just beginning to be explored for purinergic signaling.

To conclude, while studies of purinergic neurosignaling are moving forward rapidly and we are clearly on the steep slope of the growth curve, the field is still in its infancy and much new knowledge will hopefully emerge in the coming years.

ACKNOWLEDGMENTS

I thank Joe Neary, Gerta Vrbová, Maria Abbraccio, and Scott Wildman for constructive criticism and Gill Knight for brilliant editorial assistance.

I especially wish to recognize the strong support of my wife Nomi and her excellent advice during our 50 years of marriage.

Address for reprint requests and other correspondence: G. Burnstock, Autonomic Neuroscience Centre, Royal Free and University College Medical School, Rowland Hill St., London NW3 2PF, UK (e-mail: g.burnstock@ucl.ac.uk).

REFERENCES

- Abbraccio MP. ATP in brain function. In: *Purinergic Approaches in Experimental Therapeutics*, edited by Jacobson KA and Jarvis MF. New York: Wiley-Liss, 1997, p. 383–404.
- Abbraccio MP, Boeynaems JM, Barnard EA, Boyer JL, Kennedy C, Miras-Portugal MT, King BF, Gachet C, Jacobson KA, Weisman GA, Burnstock G. Characterization of the UDP-glucose receptor (re-named here the P2Y₁₄ receptor) adds diversity to the P2Y receptor family. *Trends Pharmacol Sci* 24: 52–55, 2003.
- Abbraccio MP, Burnstock G. Purinoceptors: are there families of P_{2X} and P_{2Y} purinoceptors? *Pharmacol Ther* 64: 445–475, 1994.
- Abbraccio MP, Burnstock G. Purinergic signalling: pathophysiological roles. *Jpn J Pharmacol* 78: 113–145, 1998.
- Abbraccio MP, Burnstock G, Boeynaems JM, Barnard EA, Boyer JL, Kennedy C, Knight GE, Fumagalli M, Gachet C, Jacobson KA, Weisman GA. International Union of Pharmacology. Update and subclassification of the P2Y G protein-coupled nucleotide receptors: from molecular mechanisms and pathophysiology to therapy. *Pharmacol Rev* 58: 281–341, 2006.
- Abdulla YH, Hamadah K. 3',5' Cyclic adenosine monophosphate in depression and mania. *Lancet* 1: 378–381, 1970.
- Abdulla YH, McFarlane E. Control of prostaglandin biosynthesis in rat brain homogenates by adenine nucleotides. *Biochem Pharmacol* 21: 2841–2847, 1972.
- Abdullah LH, Bundy JT, Ehre C, Davis CW. Mucin secretion and PKC isoforms in SPOC1 goblet cells: differential activation by purinergic agonist and PMA. *Am J Physiol Lung Cell Mol Physiol* 285: L149–L160, 2003.
- Abe M, Endoh T, Suzuki T. Extracellular ATP-induced calcium channel inhibition mediated by P1/P2Y purinoceptors in hamster submandibular ganglion neurons. *Br J Pharmacol* 138: 1535–1543, 2003.
- Abe Y, Sorimachi M, Itoyama Y, Furukawa K, Akaike N. ATP responses in the embryo chick ciliary ganglion cells. *Neuroscience* 64: 547–551, 1995.
- Aden U, Leverin AL, Hagberg H, Fredholm BB. Adenosine A₁ receptor agonism in the immature rat brain and heart. *Eur J Pharmacol* 426: 185–192, 2001.
- Adriaensens D, Timmermans JP. Purinergic signalling in the lung: important in asthma and COPD? *Curr Opin Pharmacol* 4: 207–214, 2004.
- Adrian K, Bernhard MK, Breitingner HG, Ogilvie A. Expression of purinergic receptors (ionotropic P2X_{1–7} and metabotropic P2Y_{1–11}) during myeloid differentiation of HL60 cells. *Biochim Biophys Acta* 1492: 127–138, 2000.
- Afework M, Burnstock G. Distribution of P2X receptors in the rat adrenal gland. *Cell Tissue Res* 298: 449–456, 1999.
- Afework M, Burnstock G. Localization of P2X receptors in the guinea pig adrenal gland. *Cells Tissues Org* 167: 297–302, 2000.
- Afework M, Burnstock G. Changes in P2Y₂ receptor localization on adrenaline- and noradrenaline containing chromaffin cells in the rat adrenal gland during development and ageing. *Int J Dev Neurosci* 23: 567–573, 2005.
- Agboh KC, Webb TE, Evans RJ, Ennion SJ. Functional characterization of a P2X receptor from *Schistosoma mansoni*. *J Biol Chem* 279: 41650–41657, 2004.
- Agresti C, Meomartini ME, Amadio S, Ambrosini E, Volonté C, Aloisi F, Visentin S. ATP regulates oligodendrocyte progenitor migration, proliferation, differentiation: involvement of metabotropic P2 receptors. *Brain Res* 48: 157–165, 2005.
- Ahdut-Hacohen R, Meiri H, Rahamimoff R. ATP dependence of the non-specific ion channel in *Torpedo* synaptic vesicles. *Neuroreport* 17: 653–656, 2006.
- Aihara H, Fujiwara S, Mizuta I, Tada H, Kanno T, Tozaki H, Nagai K, Yajima Y, Inoue K, Kondoh T, Motooka Y, Nishizaki T. Adenosine triphosphate accelerates recovery from hypoxic/hypoglycemic perturbation of guinea pig hippocampal neurotransmission via a P₂ receptor. *Brain Res* 952: 31–37, 2002.
- Aird SD. Ophidian envenomation strategies and the role of purines. *Toxicon* 40: 335–393, 2002.
- Aird SD. Taxonomic distribution and quantitative analysis of free purine and pyrimidine nucleosides in snake venoms. *Comp Biochem Physiol B Biochem Mol Biol* 140: 109–126, 2005.
- Akasu T, Hirai K, Koketsu K. Increase of acetylcholine-receptor sensitivity by adenosine triphosphate: a novel action of ATP on ACh-sensitivity. *Br J Pharmacol* 74: 505–507, 1981.
- Akasu T, Hirai K, Koketsu K. Modulatory actions of ATP on membrane potentials of bullfrog sympathetic ganglion cells. *Brain Res* 258: 313–317, 1983.
- Akasu T, Shinnick-Gallagher P, Gallagher JP. Adenosine mediates a slow hyperpolarizing synaptic potential in autonomic neurones. *Nature* 311: 62–65, 1984.
- Alavi AM, DUBYAK GR, Burnstock G. Immunohistochemical evidence for ATP receptors in human dental pulp. *J Dental Res* 80: 476–483, 2001.
- Albers KM, Woodbury CJ, Ritter AM, Davis BM, Koerber HR. Glial cell-line-derived neurotrophic factor expression in skin alters the mechanical sensitivity of cutaneous nociceptors. *J Neurosci* 26: 2981–2990, 2006.
- Albert JL, Boyle JP, Roberts JA, Challiss RA, Gubby SE, Boarder MR. Regulation of brain capillary endothelial cells by P2Y receptors coupled to Ca²⁺, phospholipase C and mitogen-activated protein kinase. *Br J Pharmacol* 122: 935–941, 1997.
- Alcayaga J, Cerpa V, Retamal M, Arroyo J, Iturriaga R, Zapata P. Adenosine triphosphate-induced peripheral nerve discharges generated from the cat petrosal ganglion in vitro. *Neurosci Lett* 282: 185–188, 2000.
- Alcayaga J, Retamal M, Cerpa V, Arroyo J, Zapata P. Dopamine inhibits ATP-induced responses in the cat petrosal ganglion in vitro. *Brain Res* 966: 283–287, 2003.
- Alcayaga J, Soto CR, Vargas RV, Ortiz FC, Arroyo J, Iturriaga R. Carotid body transmitters actions on rabbit petrosal ganglion in vitro. *Adv Exp Med Biol* 580: 331–337, 2006.
- Allen TGJ, Burnstock G. The actions of adenosine 5'-triphosphate on guinea pig intracardiac neurones in culture. *Br J Pharmacol* 100: 269–276, 1990.
- Allewa KE, Espelt MV, Krumschnabel G, Schwarzbaum PJ. Identification of two distinct E-NTPDases in liver of goldfish (*Carassius auratus* L.). *Comp Biochem Physiol B Biochem Mol Biol* 131: 725–731, 2002.
- Allgaier C, Reinhardt R, Schadlich H, Rubini P, Bauer S, Reichenbach A, Illes P. Somatic and axonal effects of ATP via P2X₂ but not P2X₇ receptors in rat thoracolumbar sympathetic neurones. *J Neurochem* 90: 359–367, 2004.
- Allgaier C, Wellmann H, Schobert A, von Kügelgen I. Cultured chick sympathetic neurons: modulation of electrically evoked noradrenaline release by P2-purinoceptors. *Naunyn-Schmiedeberg's Arch Pharmacol* 352: 17–24, 1995.
- Alloisio S, Aiello R, Ferroni S, Nobile M. Potentiation of native and recombinant P2X₇-mediated calcium signaling by arachidonic acid in cultured cortical astrocytes and human embryonic kidney 293 cells. *Mol Pharmacol* 69: 1975–1983, 2006.
- Almeida T, Rodrigues RJ, de MA, Ribeiro JA, Cunha RA. Purinergic P2 receptors trigger adenosine release leading to adenosine A_{2A} receptor activation and facilitation of long-term potentiation in rat hippocampal slices. *Neuroscience* 122: 111–121, 2003.
- Alves LA, Coutinho-Silva R, Savino W. Extracellular ATP: a further modulator in neuroendocrine control of the thymus. *Neuroimmunomodulation* 6: 81–89, 1999.

39. **Amadio S, D'Ambrosi N, Cavaliere F, Murra B, Sancesario G, Bernardi G, Burnstock G, Volonté C.** P2 receptor modulation and cytotoxic function in cultured CNS neurons. *Neuropharmacology* 42: 489–501, 2002.
40. **Amadio S, D'Ambrosi N, Trincavelli ML, Tuscano D, Sancesario G, Bernadi G, Martini C, Volonté C.** Differences in the neurotoxicity profile induced by ATP and ATP γ S in cultured cerebellar granule neurons. *Neurochem Int* 47: 334–342, 2005.
41. **Amadio S, Tramini G, Martorana A, Viscomi MT, Sancesario G, Bernardi G, Volonté C.** Oligodendrocytes express P2Y $_{12}$ metabotropic receptor in adult rat brain. *Neuroscience* 141: 1171–1180, 2006.
42. **Ambache N.** The use and limitations of atropine for pharmacological studies on autonomic effectors. *Pharmacol Rev* 7: 467–494, 1955.
43. **Ambache N, Zar MA.** Non-cholinergic transmission by post-ganglionic motor neurones in the mammalian bladder. *J Physiol* 210: 761–783, 1970.
44. **Ambalavanar R, Moritani M, Dessem D.** Trigeminal P2X $_3$ receptor expression differs from dorsal root ganglion and is modulated by deep tissue inflammation. *Pain* 117: 280–291, 2005.
45. **Anderson CM, Nedergaard M.** Emerging challenges of assigning P2X $_7$ receptor function and immunoreactivity in neurons. *Trends Neurosci* 29: 257–262, 2006.
46. **Andersson KE, Hedlund P.** Pharmacologic perspective on the physiology of the lower urinary tract. *Urology* 60: 13–20, 2002.
47. **Angulo E, Casadó V, Mallol J, Canela EI, Viñals F, Ferrer I, Lluís C, Franco R.** A $_1$ adenosine receptors accumulate in neurodegenerative structures in Alzheimer disease and mediate both amyloid precursor protein processing and tau phosphorylation and translocation. *Brain Pathol* 13: 440–451, 2003.
48. **Anikina TA, Sitdikov FG, Khamzina EY, Bilalova GA.** Role of purinoceptors in cardiac function in rats during ontogeny. *Bull Exp Biol Med* 140: 483–485, 2005.
49. **Antle MC, Steen NM, Mistlberger RE.** Adenosine and caffeine modulate circadian rhythms in the Syrian hamster. *Neuroreport* 12: 2901–2905, 2001.
50. **Antonou K, Papadopoulou-Daifoti Z, Hyphantis T, Papatheanasiou G, Bekris E, Marselos M, Panlilio L, Muller CE, Goldberg SR, Ferre S.** A detailed behavioral analysis of the acute motor effects of caffeine in the rat: involvement of adenosine A $_1$ and A $_{2A}$ receptors. *Psychopharmacology* 183: 154–162, 2005.
51. **Antunes VR, Bonagamba LG, Machado BH.** Hemodynamic and respiratory responses to microinjection of ATP into the intermediate and caudal NTS of awake rats. *Brain Res* 1032: 85–93, 2005.
52. **Antunes VR, Braga VA, Machado BH.** Autonomic and respiratory responses to microinjection of ATP into the intermediate or caudal nucleus tractus solitarius in the working heart-brainstem preparation of the rat. *Clin Exp Pharmacol Physiol* 32: 467–472, 2005.
53. **Aoki Y, Ohtori S, Takahashi K, Ino H, Ozawa T, Douya H, Chiba T, Moriya H.** P2X $_3$ -immunoreactive primary sensory neurons innervating lumbar intervertebral disc in rats. *Brain Res* 989: 214–220, 2003.
54. **Apodaca G.** The uroepithelium: not just a passive barrier. *Traffic* 5: 117–128, 2004.
55. **Apostolidis A, Popat R, Yiangou Y, Cockayne D, Ford AP, Davis JB, Dasgupta P, Fowler CJ, Anand P.** Decreased sensory receptors P2X $_3$ and TRPV1 in suburothelial nerve fibers following intradetrusor injections of botulinum toxin for human detrusor overactivity. *J Urol* 174: 977–982, 2005.
56. **Arcuino G, Lin JH, Takano T, Liu C, Jiang L, Gao Q, Kang J, Nedergaard M.** Intercellular calcium signaling mediated by point-source burst release of ATP. *Proc Natl Acad Sci USA* 99: 9840–9845, 2002.
57. **Arizono N, Matsuda S, Hattori T, Kojima Y, Maeda T, Galli SJ.** Anatomical variation in mast cell nerve associations in the rat small intestine, heart, lung, skin. Similarities of distances between neural processes and mast cells, eosinophils, or plasma cells in the jejunal lamina propria. *Lab Invest* 62: 626–634, 1990.
58. **Armstrong JN, Brust TB, Lewis RG, MacVicar BA.** Activation of presynaptic P2X $_7$ -like receptors depresses mossy fiber-CA3 synaptic transmission through p38 mitogen-activated protein kinase. *J Neurosci* 22: 5938–5945, 2002.
59. **Arreola J, Melvin JE.** A novel chloride conductance activated by extracellular ATP in mouse parotid acinar cells. *J Physiol* 547: 197–208, 2003.
60. **Arrigoni E, Chamberlin NL, Saper CB, McCarley RW.** The effects of adenosine on the membrane properties of basal forebrain cholinergic neurons. *Sleep* 26: 45–50, 2003.
61. **Arrigoni E, Crocker AJ, Saper CB, Greene RW, Scammell TE.** Deletion of presynaptic adenosine A $_1$ receptors impairs the recovery of synaptic transmission after hypoxia. *Neuroscience* 132: 575–580, 2005.
62. **Arrigoni E, Rainnie DG, McCarley RW, Greene RW.** Adenosine-mediated presynaptic modulation of glutamatergic transmission in the laterodorsal tegmentum. *J Neurosci* 21: 1076–1085, 2001.
63. **Arthur DB, Akassoglou K, Insel PA.** P2Y $_2$ receptor activates nerve growth factor/TrkA signaling to enhance neuronal differentiation. *Proc Natl Acad Sci USA* 102: 19138–19143, 2005.
64. **Arthur DB, Akassoglou K, Insel PA.** ATP γ S enhances NGF-promoted neurite formation in PC12 and dorsal root ganglion cells: a role for P2 receptors in neural development (Abstract). *FASEB J* 19: A1541, 2005.
65. **Arthur DB, Georgi S, Akassoglou K, Insel PA.** Inhibition of apoptosis by P2Y $_2$ receptor activation: novel pathways for neuronal survival. *J Neurosci* 26: 3798–3804, 2006.
66. **Ashmore JF, Ohmori H.** Control of intracellular calcium by ATP in isolated outer hair cells of the guinea-pig cochlea. *J Physiol* 428: 109–131, 1990.
67. **Ashour F, Deuchars J.** Electron microscopic localisation of P2X $_4$ receptor subunit immunoreactivity to pre- and post-synaptic neuronal elements and glial processes in the dorsal vagal complex of the rat. *Brain Res* 1026: 44–55, 2004.
68. **Atiemo H, Wynes J, Chuo J, Nipkow L, Sklar GN, Chai TC.** Effect of botulinum toxin on detrusor overactivity induced by intravesical adenosine triphosphate and capsaicin in a rat model. *Urology* 65: 622–626, 2005.
69. **Atkinson L, Batten TF, Deuchars J.** P2X $_2$ receptor immunoreactivity in the dorsal vagal complex and area postrema of the rat. *Neuroscience* 99: 683–696, 2000.
70. **Atkinson L, Batten TFC, Deuchars J.** The P2X $_2$ receptor is localised presynaptically in vagal afferent fibers in the nucleus tractus solitarius of the rat. *J Physiol* 523: 259P, 2000.
71. **Atkinson L, Deuchars J.** P2X $_{1,2,4}$ and $_7$ receptors in rat vagal afferent neurones (Abstract). *J Physiol* 536: 153P, 2001.
72. **Atkinson L, Shigetomi E, Kato F, Deuchars J.** Differential increases in P2X receptor levels in rat vagal efferent neurones following a vagal nerve section. *Brain Res* 977: 112–118, 2003.
73. **Avsar E, Empson RM.** Adenosine acting via A1 receptors, controls the transition to status epilepticus-like behaviour in an in vitro model of epilepsy. *Neuropharmacology* 47: 427–437, 2004.
74. **Babskii EB, Malkiman II.** Effect of adenosine-triphosphoric acid on the chronaxy of the motor zone of the cerebral cortex. *C R Acad Sci USSR* 74: 1135–1137, 1950.
75. **Back SA.** Perinatal white matter injury: the changing spectrum of pathology and emerging insights into pathogenetic mechanisms. *Ment Retard Dev Disabil Res* 12: 129–140, 2006.
76. **Backus KH, Braum S, Lohner F, Deitmer JW.** Neuronal responses to purinoceptor agonists in the leech central nervous system. *J Neurobiol* 25: 1283–1292, 1994.
77. **Bagley EE, Vaughan CW, Christie MJ.** Inhibition by adenosine receptor agonists of synaptic transmission in rat periaqueductal grey neurons. *J Physiol* 516: 219–225, 1999.
78. **Baharav E, Dubrosin A, Fishman P, Bar-Yehuda S, Halpren M, Weinberger A.** Suppression of experimental zymosan-induced arthritis by intraperitoneal administration of adenosine. *Drug Dev Res* 57: 182–186, 2002.
79. **Bailey MA, Turner C, Hus-Citharel A, Marchetti J, Imbert-Teboul M, Milner P, Burnstock G, Unwin R.** P2Y receptors present in the native and isolated rat glomerulus. *Nephron Physiol* 96: P79–P90, 2004.

80. **Baker MD.** Protein kinase C mediates up-regulation of tetrodotoxin-resistant, persistent Na⁺ current in rat and mouse sensory neurons. *J Physiol* 567: 851–867, 2005.
81. **Baker OJ, Camden JM, Ratchford AM, Seye CI, Erb L, Weisman GA.** Differential coupling of the P2Y₁ receptor to G_{α14} and G_{αq11} proteins during the development of the rat salivary gland. *Arch Oral Biol* 51: 359–370, 2006.
82. **Balachandran C, Bennett MR.** ATP-activated cationic and anionic conductances in cultured rat hippocampal neurons. *Neurosci Lett* 204: 73–76, 1996.
83. **Balcar VJ, Li Y, Killinger S, Bennett MR.** Autoradiography of P_{2x} ATP receptors in the rat brain. *Br J Pharmacol* 115: 302–306, 1995.
84. **Balemba OB, Salter MJ, Mawe GM.** Innervation of the extrahepatic biliary tract. *Anat Rec A Discov Mol Cell Evol Biol* 280: 836–847, 2004.
85. **Ballerini P, Ciccarelli R, Caciagli F, Rathbone MP, Werstiuk ES, Traversa U, Buccella S, Giuliani P, Jang S, Nargi E, Visini D, Santavenere C, Di IP.** P2X₇ receptor activation in rat brain cultured astrocytes increases the biosynthetic release of cysteinyl leukotrienes. *Int J Immunopathol Pharmacol* 18: 417–430, 2005.
86. **Ballerini P, Di Iorio P, Caciagli F, Rathbone MP, Jiang S, Nargi E, Buccella S, Giuliani P, D'Alimonte I, Fischione G, Masciulli A, Romano S, Ciccarelli R.** P2Y₂ receptor up-regulation induced by guanosine or UTP in rat brain cultured astrocytes. *Int J Immunopathol Pharmacol* 19: 293–308, 2006.
87. **Balogh J, Wihlborg AK, Isackson H, Joshi BV, Jacobson KA, Arner A, Erlinge D.** Phospholipase C and cAMP-dependent positive inotropic effects of ATP in mouse cardiomyocytes via P2Y₁₁-like receptors. *J Mol Cell Cardiol* 39: 223–230, 2005.
88. **Banfi C, Ferrario S, De Vincenti O, Ceruti S, Fumagalli M, Mazzola A, D'Ambrosi N, Volontè C, Fratto P, Vitali E, Burnstock G, Beltrami E, Parolari A, Polvani G, Biglioli P, Tremoli E, Abbraccio MP.** P2 receptors in human heart: up-regulation of P2X₆ in patients undergoing heart transplantation, interaction with TNF α and potential role in myocardial cell death. *J Mol Cell Cardiol* 39: 929–939, 2005.
89. **Banks F, Knight G, Calvert RC, Thompson CS, Mikhailidis DP, Morgan R, Burnstock G.** The purinergic component of human vas deferens contraction. *Fertil Steril* 85: 932–939, 2006.
90. **Bao JX, Eriksson IE, Stjärne L.** Age-related variations in the relative importance of noradrenaline and ATP as mediators of the contractile response of rat tail artery to sympathetic nerve stimulation. *Acta Physiol Scand* 136: 287–288, 1989.
91. **Barajas-López C, Espinosa-Luna R, Christofi FL.** Changes in intracellular Ca²⁺ by activation of P2 receptors in submucosal neurons in short-term cultures. *Eur J Pharmacol* 409: 243–257, 2000.
92. **Barajas-López C, Espinosa-Luna R, Gerzanich V.** ATP closes a potassium and opens a cationic conductance through different receptors in neurons of guinea pig submucous plexus. *J Pharmacol Exp Ther* 268: 1397–1402, 1994.
93. **Barajas-López C, Espinosa-Luna R, Zhu Y.** Functional interactions between nicotinic and P2X channels in short-term cultures of guinea-pig submucosal neurons. *J Physiol* 513: 671–683, 1998.
94. **Barajas-López C, Montano LM, Espinosa-Luna R.** Inhibitory interactions between 5-HT₃ and P2X channels in submucosal neurons. *Am J Physiol Gastrointest Liver Physiol* 283: G1238–G1248, 2002.
95. **Barajas-López C, Peres AL, Espinosa-Luna R.** Cellular mechanisms underlying adenosine actions on cholinergic transmission in enteric neurons. *Am J Physiol Cell Physiol* 271: C264–C275, 1996.
96. **Barberis C, Guibert B, Daudet F, Charriere B, Leviel V.** In vivo release of adenosine from cat basal ganglia-studies with a push pull cannula. *Neurochem Int* 6: 545–551, 1984.
97. **Barberis C, McIlwain H.** 5'-Adenine mononucleotides in synaptosomal preparations from guinea pig neocortex: their change on incubation, superfusion and stimulation. *J Neurochem* 26: 1015–1021, 1976.
98. **Barclay J, Patel S, Dorn G, Wotherspoon G, Moffatt S, Eunsion L, Abdel'al S, Natt F, Hall J, Winter J, Bevan S, Wishart W, Fox A, Ganju P.** Functional downregulation of P2X₃ receptor subunit in rat sensory neurons reveals a significant role in chronic neuropathic and inflammatory pain. *J Neurosci* 22: 8139–8147, 2002.
99. **Barden JA, Bennett MR.** Distribution of P2X purinoceptor clusters on individual rat dorsal root ganglion cells. *Neurosci Lett* 287: 183–186, 2000.
100. **Barden N, Harvey M, Gagné B, Shink E, Tremblay M, Raymond C, Labbé M, Villeneuve A, Rochette D, Bordeleau L, Stadler H, Holsboer F, Müller-Myhsok B.** Analysis of single nucleotide polymorphisms in genes in the chromosome 12Q2431 region points to P2RX7 as a susceptibility gene to bipolar affective disorder. *Am J Med Genet B Neuropsychiatr Genet* 141: 374–382, 2006.
101. **Bardoni R.** Excitatory synaptic transmission in neonatal dorsal horn: NMDA and ATP receptors. *News Physiol Sci* 16: 95–100, 2001.
102. **Bardoni R, Goldstein PA, Lee CJ, Gu JG, MacDermott AB.** ATP P_{2x} receptors mediate fast synaptic transmission in the dorsal horn of the rat spinal cord. *J Neurosci* 17: 5297–5304, 1997.
103. **Barnard EA, Burnstock G, Webb TE.** G protein-coupled receptors for ATP and other nucleotides: a new receptor family. *Trends Pharmacol Sci* 15: 67–70, 1994.
104. **Barnea A, Cho G, Katz BM.** A putative role for extracellular ATP: facilitation of ⁶⁷Cu uptake and of copper stimulation of the release of luteinizing hormone-releasing hormone from median eminence explants. *Brain Res* 541: 93–97, 1991.
105. **Barraco RA, Coffin VL, Altman HJ, Phillis JW.** Central effects of adenosine analogs on locomotor activity in mice and antagonism of caffeine. *Brain Res* 272: 392–395, 1983.
106. **Barraco R, Ergene E, El-Ridi M.** Purinergic receptors in the nucleus tractus solitarius mediate distinct cardiorespiratory response patterns. *Drug Dev Res* 28: 309–314, 1993.
107. **Barraco RA, Martens KA, Parizon M, Normile HJ.** Adenosine A_{2a} receptors in the nucleus accumbens mediate locomotor depression. *Brain Res Bull* 31: 397–404, 1993.
108. **Barraco RA, O'Leary DS, Ergene E, Scislo TJ.** Activation of purinergic receptor subtypes in the nucleus tractus solitarius elicits specific regional vascular response patterns. *J Auton Nerv Syst* 59: 113–124, 1996.
109. **Barrera NP, Ormond SJ, Henderson RM, Murrell-Lagnado RD, Edwardson JM.** Atomic force microscopy imaging demonstrates that P2X₂ receptors are trimers but that P2X₆ receptor subunits do not oligomerize. *J Biol Chem* 280: 10759–10765, 2005.
110. **Barry MA.** Ecto-calcium-dependent ATPase activity of mammalian taste bud cells. *J Histochem Cytochem* 40: 1919–1928, 1992.
111. **Bartel DL, Sullivan SL, Lavoie EG, Sévigny J, Finger TE.** Nucleoside triphosphate diphosphohydrolase-2 is the ecto-ATPase of type I cells in taste buds. *J Comp Neurol* 497: 1–12, 2006.
112. **Bartfai T, Iverfeldt K, Fisone G.** Regulation of the release of coexisting neurotransmitters. *Annu Rev Pharmacol Toxicol* 28: 285–310, 1988.
113. **Baryshnikov SG, Rogachevskaja OA, Kolesnikov SS.** Calcium signaling mediated by P2Y receptors in mouse taste cells. *J Neurophysiol* 90: 3283–3294, 2003.
114. **Basheer R, Strecker RE, Thakkar MM, McCarley RW.** Adenosine and sleep-wake regulation. *Prog Neurobiol* 73: 379–396, 2004.
115. **Basoglu OK, Pelleg A, Essilfie-Quaye S, Brindicci C, Barnes PJ, Kharitonov SA.** Effects of aerosolized adenosine 5'-triphosphate vs adenosine 5'-monophosphate on dyspnea and airway caliber in healthy nonsmokers and patients with asthma. *Chest* 128: 1905–1909, 2005.
116. **Batra AK, Hanno PM, Ruggieri MR.** Detubularization-induced contractile response change of the ileum following ileocystoplasty. *J Urol* 148: 195–199, 1992.
117. **Battastini AM, da Rocha JB, Barcellos CK, Dias RD, Sarkis JJ.** Characterization of an ATP diphosphohydrolase (EC 3.6.1.5) in synaptosomes from cerebral cortex of adult rats. *Neurochem Res* 16: 1303–1310, 1991.
118. **Bauer A, Holschbach MH, Meyer PT, Boy C, Herzog H, Olsson RA, Coenen HH, Zilles K.** In vivo imaging of adenosine A₁

- receptors in the human brain with [¹⁸F]CPFPX and positron emission tomography. *Neuroimage* 19: 1760–1769, 2003.
119. **Bauman LA, Mahle CD, Boissard CG, Gribkoff VK.** Age-dependence of effects of A₁ adenosine receptor antagonism in rat hippocampal slices. *J Neurophysiol* 68: 629–638, 1992.
 120. **Bean BP.** ATP-activated channels in rat and bullfrog sensory neurons: concentration dependence and kinetics. *J Neurosci* 10: 1–10, 1990.
 121. **Beaudoin AR, Sévigny J, Picher M.** ATP-diphosphohydrolases, apyrases, nucleotide phosphohydrolases: biochemical properties and functions. *Biomembranes* 5: 369–401, 1996.
 122. **Beckett EA, Takeda Y, Yanase H, Sanders KM, Ward SM.** Synaptic specializations exist between enteric motor nerves and interstitial cells of Cajal in the murine stomach. *J Comp Neurol* 493: 193–206, 2005.
 123. **Beierlein M, Regehr WG.** Brief bursts of parallel fiber activity trigger calcium signals in Bergmann glia. *J Neurosci* 26: 6958–6967, 2006.
 124. **Belai A, Burnstock G.** Evidence for coexistence of ATP and nitric oxide in non-adrenergic, non-cholinergic (NANC) inhibitory neurones in the rat ileum, colon and anococcygeus muscle. *Cell Tissue Res* 278: 197–200, 1994.
 125. **Belai A, Lefebvre RA, Burnstock G.** Motor activity and neurotransmitter release in the gastric fundus of streptozotocin-diabetic rats. *Eur J Pharmacol* 194: 225–234, 1991.
 126. **Belcher SM, Zsarnovszky A, Crawford PA, Hemani H, Spurling L, Kirley TL.** Immunolocalization of ecto-nucleoside triphosphate diphosphohydrolase 3 in rat brain: implications for modulation of multiple homeostatic systems including feeding and sleep-wake behaviors. *Neuroscience* 137: 1331–1346, 2006.
 127. **Bell PD, Lapointe JY, Sabirov R, Hayashi S, Peti-Peterdi J, Manabe K, Kovacs G, Okada Y.** Macula densa cell signaling involves ATP release through a maxi anion channel. *Proc Natl Acad Sci USA* 100: 4322–4327, 2003.
 128. **Bellingham MC, Berger AJ.** Adenosine suppresses excitatory glutamatergic inputs to rat hypoglossal motoneurons in vitro. *Neurosci Lett* 177: 143–146, 1994.
 129. **Bender E, Buist A, Jurzak M, Langlois X, Baggerman G, Verhasselt P, Ercken M, Guo HQ, Wintmolders C, Van den Wyngaert I, Van Oers I, Schoofs L, Luyten W.** Characterization of an orphan G protein-coupled receptor localized in the dorsal root ganglia reveals adenine as a signaling molecule. *Proc Natl Acad Sci USA* 99: 8573–8578, 2002.
 130. **Benkó R, Undi S, Wolf M, Barthó L.** Effects of acute administration of and tachyphylaxis to α,β -methylene ATP in the guinea-pig small intestine. *Basic Clin Pharmacol Toxicol* 97: 369–373, 2005.
 131. **Bennett GC, Boarder MR.** The effect of nucleotides and adenosine on stimulus-evoked glutamate release from rat brain cortical slices. *Br J Pharmacol* 131: 617–623, 2000.
 132. **Benrezzak O, Grondin G, Proulx J, Rousseau E, D'Orléans-Juste P, Beaudoin AR.** Characterization and immunohistochemical localization of nucleoside triphosphate diphosphohydrolase (NTPDase) in pig adrenal glands (presence of a non-sedimentable isoform). *Biochim Biophys Acta* 1524: 94–101, 2000.
 133. **Berman PH, Balis ME, Dancis J.** A method for the prenatal diagnosis of the Lesch-Nyhan syndrome using fresh amniotic cells. *Trans Am Neurol Assoc* 94: 222–224, 1969.
 134. **Bern MJ, Sturbaum CW, Karayalcin SS, Berschneider HM, Wachsmann JT, Powell DW.** Immune system control of rat and rabbit colonic electrolyte transport. Role of prostaglandins and enteric nervous system. *J Clin Invest* 83: 1810–1820, 1989.
 135. **Berry D, Yao M, Barden JA, Balcar VJ, Hansen MA, Bennett MR, Keogh A, dos Remedios CG.** Alterations in the expression of P2X₁ receptors in failing and nondiseased human atria. *Electrophoresis* 19: 856–859, 1998.
 136. **Berti SL, Bonan CD, da Silva FL, Battastini AM, Sarkis JJ, Wannmacher CM.** Phenylalanine and phenylpyruvate inhibit ATP diphosphohydrolase from rat brain cortex. *Int J Dev Neurosci* 19: 649–653, 2001.
 137. **Bertrand G, Chapal J, Loubatières-Mariani MM, Roye M.** Evidence for two different P2-purinoreceptors on beta cell and pancreatic vascular bed. *Br J Pharmacol* 91: 783–787, 1987.
 138. **Bertrand PP, Bornstein JC.** ATP as a putative sensory mediator: activation of intrinsic sensory neurons of the myenteric plexus via P2X receptors. *J Neurosci* 22: 4767–4775, 2002.
 139. **Bian X, Ren J, DeVries M, Schnegelsberg B, Cockayne DA, Ford AP, Galligan JJ.** Peristalsis is impaired in the small intestine of mice lacking the P2X₃ subunit. *J Physiol* 551: 309–322, 2003.
 140. **Bian XC, Bertrand PP, Bornstein JC.** Descending inhibitory reflexes involve P2X receptor-mediated transmission from interneurons to motor neurons in guinea-pig ileum. *J Physiol* 528: 560, 2000.
 141. **Bianco F, Ceruti S, Colombo A, Fumagalli M, Ferrari D, Pizzirani C, Matteoli M, Di VF, Abbracchio MP, Verderio C.** A role for P2X₇ in microglial proliferation. *J Neurochem* 99: 745–758, 2006.
 142. **Bianco F, Fumagalli M, Pravettoni E, D'Ambrosi N, Volonte C, Matteoli M, Abbracchio MP, Verderio C.** Pathophysiological roles of extracellular nucleotides in glial cells: differential expression of purinergic receptors in resting and activated microglia. *Brain Res* 48: 144–156, 2005.
 143. **Bianco F, Pravettoni E, Colombo A, Schenk U, Möller T, Matteoli M, Verderio C.** Astrocyte-derived ATP induces vesicle shedding and IL-1 β release from microglia. *J Immunol* 174: 7268–7277, 2005.
 144. **Bienenstock J, Goetzl EJ, Blennerhassett MG.** Autonomic neuroimmunology. In: *The Autonomic Nervous System*, edited by G. Burnstock. London: Taylor & Francis, 2003, vol. 15.
 145. **Bienenstock J, MacQueen G, Sestini P, Marshall JS, Stead RH, Perdue MH.** Mast cell/nerve interactions in vitro and in vivo. *Am Rev Respir Dis* 143: S55–S58, 1991.
 146. **Birder LA.** More than just a barrier: urothelium as a drug target for urinary bladder pain. *Am J Physiol Renal Physiol* 289: F489–F495, 2005.
 147. **Birder LA, Ruan HZ, Chopra B, Xiang Z, Barrick S, Buffington CA, Roppolo JR, Ford AP, de Groat WC, Burnstock G.** Alterations in P2X and P2Y purinergic receptor expression in urinary bladder from normal cats and cats with interstitial cystitis. *Am J Physiol Renal Physiol* 287: F1084–F1091, 2004.
 148. **Bland-Ward PA, Humphrey PPA.** Acute nociception mediated by hindpaw P2X receptor activation in the rat. *Br J Pharmacol* 122: 365–371, 1997.
 149. **Blandini F.** Adenosine receptors and L-DOPA-induced dyskinesia in Parkinson's disease: potential targets for a new therapeutic approach. *Exp Neurol* 184: 556–560, 2003.
 150. **Blaschko H, Born GV, D'Iorio A, Eade NR.** Observations on the distribution of catecholamines and adenosinetriphosphate in the bovine adrenal medulla. *J Physiol* 133: 548–557, 1956.
 151. **Blaug S, Rymer J, Jalickee S, Miller SS.** P2 purinoceptors regulate calcium-activated chloride and fluid transport in 31EG4 mammary epithelia. *Am J Physiol Cell Physiol* 284: C897–C909, 2003.
 152. **Bleehen T, Keele CA.** Observations on the algogenic actions of adenosine compounds on human blister base preparation. *Pain* 3: 367–377, 1977.
 153. **Bo X, Alavi A, Xiang Z, Oglesby I, Ford A, Burnstock G.** Localization of ATP-gated P2X₂ and P2X₃ receptor immunoreactive nerves in rat taste buds. *Neuroreport* 10: 1107–1111, 1999.
 154. **Bo X, Burnstock G.** Distribution of [³H] α,β -methylene ATP binding sites in rat brain and spinal cord. *Neuroreport* 5: 1601–1604, 1994.
 155. **Bo X, Zhang Y, Nassar M, Burnstock G, Schoepfer R.** A P2X purinoceptor cDNA conferring a novel pharmacological profile. *FEBS Lett* 375: 129–133, 1995.
 156. **Bobanovic LK, Royle SJ, Murrell-Lagnado RD.** P2X receptor trafficking in neurons is subunit specific. *J Neurosci* 22: 4814–4824, 2002.
 157. **Bobbin RP.** ATP-induced movement of the stalks of isolated cochlear Deiters' cells. *Neuroreport* 12: 2923–2926, 2001.
 158. **Bock P.** Adenine nucleotides in the carotid body. *Cell Tissue Res* 206: 279–290, 1980.
 159. **Bodin P, Burnstock G.** Increased release of ATP from endothelial cells during acute inflammation. *Inflamm Res* 47: 351–354, 1998.

160. **Bodin P, Burnstock G.** Purinergic signalling: ATP release. *Neurochem Res* 26: 959–969, 2001.
161. **Boehm S.** ATP stimulates sympathetic transmitter release via presynaptic P2X purinoceptors. *J Neurosci* 19: 737–746, 1999.
162. **Boehm S.** P2Ys go neuronal: modulation of Ca²⁺ and K⁺ channels by recombinant receptors. *Br J Pharmacol* 138: 1–3, 2003.
163. **Boeynaems JM, Communi D, Gonzalez NS, Robaye B.** Overview of the P2 receptors. *Semin Thromb Hemost* 31: 139–149, 2005.
164. **Bogdanov Y, Dale L, King B, Whittock N, Burnstock G.** Early expression of a novel nucleotide receptor in the neural plate of *Xenopus* embryos. *J Biol Chem* 272: 12583–12590, 1997.
165. **Bogdanov Y, Rubino A, Burnstock G.** Characterisation of subtypes of the P2X and P2Y families of receptors in the foetal human heart. *Life Sci* 62: 697–703, 1998.
166. **Boggio V, Ladizesky MG, Cutrera RA, Cardinali DP.** Autonomic neural signals in bone: physiological implications for mandible and dental growth. *Life Sci* 75: 383–395, 2004.
167. **Boldogkői Z, Schütz B, Sallach J, Zimmer A.** P2X₃ receptor expression at early stage of mouse embryogenesis. *Mech Dev* 118: 255–260, 2002.
168. **Bolego C, Centemeri C, Abbraccio MP, Ceruti S, Cattabeni F, Jacobson KA, Puglisi L, Rovati GE, Burnstock G, Nicosia S.** Two distinct P2Y receptors are involved in purine- and pyrimidine-evoked Ca²⁺ elevation in mammalian brain astrocyte cultures. *Drug Dev Res* 52: 122–132, 2001.
169. **Bonan CD, Roesler R, Pereira GS, Battastini AM, Izquierdo I, Sarkis JJ.** Learning-specific decrease in synaptosomal ATP diphosphohydrolase activity from hippocampus and entorhinal cortex of adult rats. *Brain Res* 854: 253–256, 2000.
170. **Bonan CD, Roesler R, Quevedo J, Battastini AM, Izquierdo I, Sarkis JJ.** Effects of suramin on hippocampal apyrase activity and inhibitory avoidance learning of rats. *Pharmacol Biochem Behav* 63: 153–158, 1999.
171. **Bonan CD, Schetinger MR, Battastini AM, Sarkis JJ.** Ectonucleotidases and synaptic plasticity: implications in physiological and pathological conditions. *Drug Dev Res* 52: 57–65, 2001.
172. **Bonci A, Williams JT.** A common mechanism mediates long-term changes in synaptic transmission after chronic cocaine and morphine. *Neuron* 16: 631–639, 1996.
173. **Borges E, Cognato GP, Vuaden FC, Bogo MR, Fauth MG, Bonan CD, Dias RD.** Nucleotidase activities in membrane preparations of nervous ganglia and digestive gland of the snail *Helix aspersa*. *Comp Biochem Physiol B Biochem Mol Biol* 137: 297–307, 2004.
174. **Borison HL, Hawken MJ, Hubbard JI, Sirett NE.** Unit activity from cat area postrema influenced by drugs. *Brain Res* 92: 153–156, 1975.
175. **Bornstein JC, Costa M, Grider JR.** Enteric motor and interneuronal circuits controlling motility. *Neurogastroenterol Motil* 16 Suppl 1: 34–38, 2004.
176. **Borvendeg SJ, Al Khrasani M, Rubini P, Fischer W, Allgaier C, Wirkner K, Himmel HM, Gillen C, Illes P.** Subsensitivity of P2X but not vanilloid 1 receptors in dorsal root ganglia of rats caused by cyclophosphamide cystitis. *Eur J Pharmacol* 474: 71–75, 2003.
177. **Borvendeg SJ, Gerevich Z, Gillen C, Illes P.** P2Y receptor-mediated inhibition of voltage-dependent Ca²⁺ channels in rat dorsal root ganglion neurons. *Synapse* 47: 159–161, 2003.
178. **Boucsein C, Zacharias R, Farber K, Pavlovic S, Hanisch UK, Kettenmann H.** Purinergic receptors on microglial cells: functional expression in acute brain slices and modulation of microglial activation in vitro. *Eur J Neurosci* 17: 2267–2276, 2003.
179. **Boudreault F, Grygorczyk R.** Cell swelling-induced ATP release is tightly dependent on intracellular calcium elevations. *J Physiol* 561: 499–513, 2004.
180. **Boué-Grabot E, Akimenko MA, Séguéla P.** Unique functional properties of a sensory neuronal P2X ATP-gated channel from zebrafish. *J Neurochem* 75: 1600–1607, 2000.
181. **Boué-Grabot E, Barajas-Lopez C, Chakfe Y, Blais D, Belanger D, Emerit MB, Seguela P.** Intracellular cross talk and physical interaction between two classes of neurotransmitter-gated channels. *J Neurosci* 23: 1246–1253, 2003.
182. **Boué-Grabot E, Toulmé E, Émerit MB, Garret M.** Subunit-specific coupling between gamma-aminobutyric acid type A and P2X₂ receptor channels. *J Biol Chem* 279: 52517–52525, 2004.
183. **Bours MJ, Swennen EL, Di VF, Cronstein BN, Dagnelie PC.** Adenosine 5'-triphosphate and adenosine as endogenous signaling molecules in immunity and inflammation. *Pharmacol Ther* 112: 358–404, 2006.
184. **Bouyer P, Paulais M, Coughon M, Hulin P, Anagnostopoulos T, Planelles G.** Extracellular ATP raises cytosolic calcium and activates basolateral chloride conductance in *Necturus* proximal tubule. *J Physiol* 510: 535–548, 1998.
185. **Bowler WB, Dixon CJ, Halleux C, Maier R, Bilbe G, Fraser WD, Gallagher JA, Hipskind RA.** Signaling in human osteoblasts by extracellular nucleotides. Their weak induction of the *c-fos* proto-oncogene via Ca²⁺ mobilization is strongly potentiated by a parathyroid hormone/cAMP-dependent protein kinase pathway independently of mitogen-activated protein kinase. *J Biol Chem* 274: 14315–14324, 1999.
186. **Bowser DN, Khakh BS.** ATP excites interneurons and astrocytes to increase synaptic inhibition in neuronal networks. *J Neurosci* 24: 8606–8620, 2004.
187. **Boyle DL, Moore J, Yang L, Sorkin LS, Firestein GS.** Spinal adenosine receptor activation inhibits inflammation and joint destruction in rat adjuvant-induced arthritis. *Arthritis Rheum* 46: 3076–3082, 2002.
188. **Bradbury EJ, Burnstock G, McMahon SB.** The expression of P2X₃ purinoceptors in sensory neurons: effects of axotomy and glial-derived neurotrophic factor. *Mol Cell Neurosci* 12: 256–268, 1998.
189. **Bradley E, Law A, Bell D, Johnson CD.** Effects of varying impulse number on cotransmitter contributions to sympathetic vasoconstriction in rat tail artery. *Am J Physiol Heart Circ Physiol* 284: H2007–H2014, 2003.
190. **Brady CM, Apostolidis A, Yiangou Y, Baecker PA, Ford AP, Freeman A, Jacques TS, Fowler CJ, Anand P.** P2X₃-immunoreactive nerve fibers in neurogenic detrusor overactivity and the effect of intravesical resiniferatoxin. *Eur Urol* 46: 247–253, 2004.
191. **Braet K, Paemeleire K, D'Herde K, Sanderson MJ, Leybaert L.** Astrocyte-endothelial cell calcium signals conveyed by two signalling pathways. *Eur J Neurosci* 13: 79–91, 2001.
192. **Braganhof E, Bruno AN, Bavaresco L, Barreto-Chaves ML, Sarkis JJ, Battastini AM.** Neonatal hypothyroidism affects the adenine nucleotides metabolism in astrocyte cultures from rat brain. *Neurochem Res* 31: 449–454, 2006.
193. **Braiman A, Silbergberg SD, Priel Z.** Purinergic stimulation of ciliary activity. *Drug Dev Res* 50: 550–554, 2000.
194. **Brake AJ, Wagenbach MJ, Julius D.** New structural motif for ligand-gated ion channels defined by an ionotropic ATP receptor. *Nature* 371: 519–523, 1994.
195. **Brambilla R, Burnstock G, Bonazzi A, Ceruti S, Cattabeni F, Abbraccio MP.** Cyclo-oxygenase-2 mediates P2Y receptor-induced reactive astrogliosis. *Br J Pharmacol* 126: 563–567, 1999.
196. **Brambilla R, Cottini L, Fumagalli M, Ceruti S, Abbraccio MP.** Blockade of A_{2A} adenosine receptors prevents basic fibroblast growth factor-induced reactive astrogliosis in rat striatal primary astrocytes. *Glia* 43: 190–194, 2003.
197. **Brand A, Vissienon Z, Eschke D, Nieber K.** Adenosine A₁ and A₃ receptors mediate inhibition of synaptic transmission in rat cortical neurons. *Neuropharmacology* 40: 85–95, 2001.
198. **Brändle U, Guenther E, Irrle C, Wheeler-Schilling TH.** Gene expression of the P2X receptors in the rat retina. *Brain Res* 59: 269–272, 1998.
199. **Brändle U, Kohler K, Wheeler-Schilling TH.** Expression of the P2X₇-receptor subunit in neurons of the rat retina. *Brain Res* 62: 106–109, 1998.
200. **Braun M, Lelieur K, Kietzmann M.** Purinergic substances promote murine keratinocyte proliferation and enhance impaired wound healing in mice. *Wound Repair Regen* 14: 152–161, 2006.
201. **Braun N, Sevigny J, Mishra SK, Robson SC, Barth SW, Gerstberger R, Hammer K, Zimmermann H.** Expression of the ecto-ATPase NTPDase2 in the germinal zones of the developing and adult rat brain. *Eur J Neurosci* 17: 1355–1364, 2003.

202. **Braun N, Sevigny J, Robson SC, Hammer K, Hanani M, Zimmermann H.** Association of the ecto-ATPase NTPDase2 with glial cells of the peripheral nervous system. *Glia* 45: 124–132, 2004.
203. **Braun N, Zhu Y, Krieglstein J, Culmsee C, Zimmermann H.** Upregulation of the enzyme chain hydrolyzing extracellular ATP after transient forebrain ischemia in the rat. *J Neurosci* 18: 4891–4900, 1998.
204. **Braunstein GM, Schwiebert EM.** Epithelial purinergic receptors and signaling in health and disease. *Curr Top Membr* 54: 205–241, 2003.
205. **Brautigam VM, Frasier C, Nikodemova M, Watters JJ.** Purinergic receptor modulation of BV-2 microglial cell activity: potential involvement of p38 MAP kinase and CREB. *J Neuroimmunol* 166: 113–125, 2005.
206. **Brierley SM, Carter R, Jones W, III, Xu L, Robinson DR, Hicks GA, Gebhart GF, Blackshaw LA.** Differential chemosensory function and receptor expression of splanchnic and pelvic colonic afferents in mice. *J Physiol* 567: 267–281, 2005.
207. **Briggs CA, Cooper JR.** A synaptosomal preparation from the guinea pig ileum myenteric plexus. *J Neurochem* 36: 1097–1108, 1981.
208. **Bringmann A, Pannicke T, Moll V, Milenkovic I, Faude F, Enzmann V, Wolf S, Reichenbach A.** Upregulation of P2X₇ receptor currents in Müller glial cells during proliferative vitreoretinopathy. *Invest Ophthalmol Vis Sci* 42: 860–867, 2001.
209. **Brock JA, Van Helden DF.** Enhanced excitatory junction potentials in mesenteric arteries from spontaneously hypertensive rats. *Pflügers Arch* 430: 901–908, 1995.
210. **Brockhaus J, Dressel D, Herold S, Deitmer JW.** Purinergic modulation of synaptic input to Purkinje neurons in rat cerebellar brain slices. *Eur J Neurosci* 19: 2221–2230, 2004.
211. **Brodin B, Nielsen R.** Electrophysiological evidence for an ATP-gated ion channel in the principal cells of the frog skin epithelium. *Pflügers Arch* 439: 227–233, 2000.
212. **Brodin B, Nielsen R.** Evidence for P₂Y-type ATP receptors on the serosal membrane of frog skin epithelium. *Pflügers Arch* 439: 234–239, 2000.
213. **Brook MM, Fineman JR, Bolinger AM, Wong AF, Heymann MA, Soifer SJ.** Use of ATP-MgCl₂ in the evaluation and treatment of children with pulmonary hypertension secondary to congenital heart defects. *Circulation* 90: 1287–1293, 1994.
214. **Brosenitsch TA, Adachi T, Lipski J, Housley GD, Funk GD.** Developmental downregulation of P2X₃ receptors in motoneurons of the compact formation of the nucleus ambiguus. *Eur J Neurosci* 22: 809–824, 2005.
215. **Brouns I, Adriaensen D, Burnstock G, Timmermans JP.** Intraepithelial vagal sensory nerve terminals in rat pulmonary neuroepithelial bodies express P2X₃ receptors. *Am J Respir Cell Mol Biol* 23: 52–61, 2000.
216. **Brouns I, De Proost I, Pintelon I, Timmermans JP, Adriaensen D.** Sensory receptors in the airways: neurochemical coding of smooth muscle-associated airway receptors and pulmonary neuroepithelial body innervation. *Auton Neurosci* 126–127: 307–319, 2006.
217. **Brouns I, Van Genechten J, Burnstock G, Timmermans JP, Adriaensen D.** Ontogenesis of P2X₃ receptor-expressing nerve fibres in the rat lung, with special reference to neuroepithelial bodies. *Biomed Res* 14: 80–86, 2003.
218. **Brouns I, Van Genechten J, Hayashi H, Gajda M, Gomi T, Burnstock G, Timmermans JP, Adriaensen D.** Dual sensory innervation of pulmonary neuroepithelial bodies. *Am J Respir Cell Mol Biol* 28: 275–285, 2003.
219. **Brown BL, Salway JG, Albano JD, Hullin RP, Ekins RP.** Urinary excretion of cyclic AMP and manic-depressive psychosis. *Br J Psychiatry* 120: 405–408, 1972.
220. **Brown P, Dale N.** Modulation of K⁺ currents in *Xenopus* spinal neurons by p2y receptors: a role for ATP and ADP in motor pattern generation. *J Physiol* 540: 843–850, 2002.
221. **Brown SG, King BF, Kim YC, Jang SY, Burnstock G, Jacobson KA.** Activity of novel adenine nucleotide derivatives as agonists and antagonists at recombinant rat P2X receptors. *Drug Dev Res* 49: 253–259, 2000.
222. **Bruno AN, Pochmann D, Ricachenevsky FK, Fontella FU, Bonan CD, Dalmaz C, Barreto-Chaves ML, Sarkis JJ.** Nociceptive response and adenine nucleotide hydrolysis in synaptosomes isolated from spinal cord of hypothyroid rats. *Neurochem Res* 30: 1155–1161, 2005.
223. **Bruno AN, Ricachenevsky FK, Pochmann D, Bonan CD, Battastini AM, Barreto-Chaves ML, Sarkis JJ.** Hypothyroidism changes adenine nucleotide hydrolysis in synaptosomes from hippocampus and cerebral cortex of rats in different phases of development. *Int J Dev Neurosci* 23: 37–44, 2005.
224. **Bucheimer RE, Linden J.** Purinergic regulation of epithelial transport. *J Physiol* 555: 311–321, 2004.
225. **Buchthal F, Engbaek L, Sten-Knudsen O, Thomassen E.** Application of adenosinetriphosphate and related compounds to the spinal cord of the cat. *J Physiol* 106: 3P–4P, 1947.
226. **Buchthal F, Folkow B.** Close arterial injection of adenosine triphosphate and inorganic triphosphate into frog muscle. *Acta Physiol Scand* 8: 312–316, 1944.
227. **Buchthal F, Folkow B.** Interaction between acetylcholine and adenosine triphosphate in normal, curarised and denervated muscle. *Acta Physiol Scand* 15: 150–160, 1948.
228. **Buchthal F, Kahlson G.** The motor effect of adenosine triphosphate and allied phosphorus compounds on smooth mammalian muscle. *Acta Physiol Scand* 8: 325–334, 1944.
229. **Buckley KA, Golding SL, Rice JM, Dillon JP, Gallagher JA.** Release and interconversion of P2 receptor agonists by human osteoblast-like cells. *FASEB J* 17: 1401–1410, 2003.
230. **Buell G, Collo G, Rassendren F.** P2X receptors: an emerging channel family. *Eur J Neurosci* 8: 2221–2228, 1996.
231. **Buijs RM, Wortel J, Van Heerikhuizen JJ, Feenstra MG, Ter Horst GJ, Romijn HJ, Kalsbeek A.** Anatomical and functional demonstration of a multisynaptic suprachiasmatic nucleus adrenal (cortex) pathway. *Eur J Neurosci* 11: 1535–1544, 1999.
232. **Bulanova E, Budagian V, Orinska Z, Hein M, Petersen F, Thon L, Adam D, Bulfone-Paus S.** Extracellular ATP induces cytokine expression and apoptosis through P2X₇ receptor in murine mast cells. *J Immunol* 174: 3880–3890, 2005.
233. **Bülbring E, Tomita T.** Properties of the inhibitory potential of smooth muscle as observed in the response to field stimulation of the guinea-pig taenia coli. *J Physiol* 189: 299–315, 1967.
234. **Buljubasich R, Ventura S.** Adenosine 5'-triphosphate and noradrenaline are excitatory cotransmitters to the fibromuscular stroma of the guinea pig prostate gland. *Eur J Pharmacol* 499: 335–344, 2004.
235. **Buller KM, Khanna S, Sibbald JR, Day TA.** Central noradrenergic neurons signal via ATP to elicit vasopressin responses to haemorrhage. *Neuroscience* 73: 637–642, 1996.
236. **Bulloch JM, McGrath JC.** Selective blockade by nifedipine of “purinergic” rather than adrenergic nerve-mediated vasopressor responses in the pithed rat. *Br J Pharmacol* 95: 695–700, 1988.
237. **Bulloch JM, McGrath JC.** Evidence for increased purinergic contribution in hypertensive blood vessels exhibiting co-transmission. *Br J Pharmacol* 107: 145P, 1992.
238. **Burgard EC, Niforatos W, van Biesen T, Lynch KJ, Touma E, Metzger RE, Kowaluk EA, Jarvis MF.** P2X receptor-mediated ionic currents in dorsal root ganglion neurons. *J Neurophysiol* 82: 1590–1598, 1999.
239. **Burnstock G.** Evolution of the autonomic innervation of visceral and cardiovascular systems in vertebrates. *Pharmacol Rev* 21: 247–324, 1969.
240. **Burnstock G.** Neural nomenclature. *Nature* 229: 282–283, 1971.
241. **Burnstock G.** Purinergic nerves. *Pharmacol Rev* 24: 509–581, 1972.
242. **Burnstock G.** Purinergic transmission. In: *Handbook of Psychopharmacology*, edited by Iversen LI, Iversen SD, and Snyder SH. New York: Plenum, 1975, vol. 5, p. 131–194.
243. **Burnstock G.** Do some nerve cells release more than one transmitter? *Neuroscience* 1: 239–248, 1976.
244. **Burnstock G.** Purinergic receptors. *J Theor Biol* 62: 491–503, 1976.
245. **Burnstock G.** Purine nucleotides and nucleosides as neurotransmitters or neuromodulators in the central nervous system. In: *Neuroregulators and Psychiatric Disorders*, edited by Usdin E,

- Hamburg DA, and Barchas JD. New York: Oxford Univ. Press, 1977, p. 470–477.
246. **Burnstock G.** A basis for distinguishing two types of purinergic receptor. In: *Cell Membrane Receptors for Drugs and Hormones: A Multidisciplinary Approach*, edited by Straub RW and Bolis L. New York: Raven, 1978, p. 107–118.
 247. **Burnstock G.** Pathophysiology of migraine: a new hypothesis. *Lancet* i: 1397–1399, 1981.
 248. **Burnstock G.** The non-adrenergic non-cholinergic nervous system. *Arch Int Pharmacodyn Ther* 280: 1–15, 1986.
 249. **Burnstock G.** The changing face of autonomic neurotransmission. *Acta Physiol Scand* 126: 67–91, 1986.
 250. **Burnstock G.** Sympathetic purinergic transmission in small blood vessels. *Trends Pharmacol Sci* 9: 116–117, 1988.
 251. **Burnstock G.** The role of adenosine triphosphate in migraine. *Biomed Pharmacother* 43: 727–736, 1989.
 252. **Burnstock G.** Co-transmission. The fifth Heymans memorial lecture-Ghent. *Arch Int Pharmacodyn Ther* 304: 7–33, 1990.
 253. **Burnstock G.** Noradrenaline and ATP as cotransmitters in sympathetic nerves. *Neurochem Int* 17: 357–368, 1990.
 254. **Burnstock G.** Plasticity in expression of cotransmitters and autonomic nerves in aging and disease. In: *Plasticity and Regeneration of the Nervous System*, edited by Timiras PS and Privat A. New York: Plenum, 1991, p. 291–301.
 255. **Burnstock G.** Introduction: changing face of autonomic and sensory nerves in the circulation. In: *Vascular Innervation and Receptor Mechanisms: New Perspectives*, edited by Edvinsson L and Uddman R. Orlando, FL: Academic, 1993, p. 1–22.
 256. **Burnstock G.** A unifying purinergic hypothesis for the initiation of pain. *Lancet* 347: 1604–1605, 1996.
 257. **Burnstock G** (Editor). Purinergic neurotransmission. *Semin Neurosci* 8: 171–257, 1996.
 258. **Burnstock G.** Purinoceptors: ontogeny and phylogeny. *Drug Dev Res* 39: 204–242, 1996.
 259. **Burnstock G.** Cotransmission with particular emphasis on the involvement of ATP. In: *Molecular Mechanisms of Neuronal Communication. A Tribute to Nils-Ake Hillarp*, edited by Fuxe K, Hökfelt T, Olson L, Ottoson D, Dahlström A, and Björklund A. Oxford, UK: Pergamon Press, 1996, p. 67–87.
 260. **Burnstock G.** The past, present and future of purine nucleotides as signalling molecules. *Neuropharmacology* 36: 1127–1139, 1997.
 261. **Burnstock G.** Release of vasoactive substances from endothelial cells by shear stress and purinergic mechanosensory transduction. *J Anat* 194: 335–342, 1999.
 262. **Burnstock G.** P2X receptors in sensory neurones. *Br J Anaesth* 84: 476–488, 2000.
 263. **Burnstock G.** Overview of P2 receptors: possible functions in immune cells. *Drug Dev Res* 53: 53–59, 2001.
 264. **Burnstock G.** Purinergic signalling in development. In: *Handbook of Experimental Pharmacology. I. Purinergic and Pyrimidinergic Signalling I: Molecular, Nervous and Urinogenitry System Function*, edited by Abbracchio MP and Williams M. Berlin: Springer-Verlag, 2001, vol. 151, p. 89–127.
 265. **Burnstock G.** Purinergic signalling in lower urinary tract. In: *Handbook of Experimental Pharmacology. I. Purinergic and Pyrimidinergic Signalling I: Molecular, Nervous and Urinogenitry System Function*, edited by Abbracchio MP and Williams M. Berlin: Springer-Verlag, 2001, vol. 151, p. 423–515.
 266. **Burnstock G.** Purinergic signalling in gut. In: *Handbook of Experimental Pharmacology. II. Purinergic and Pyrimidinergic Signalling II: Cardiovascular, Respiratory, Immune, Metabolic and Gastrointestinal Tract Function*, edited by Abbracchio MP and Williams M. Berlin: Springer-Verlag, 2001, vol. 151, p. 141–238.
 267. **Burnstock G.** Purine-mediated signalling in pain and visceral perception. *Trends Pharmacol Sci* 22: 182–188, 2001.
 268. **Burnstock G.** Expanding field of purinergic signaling. *Drug Dev Res* 52: 1–10, 2001.
 269. **Burnstock G.** Purinergic signalling and vascular cell proliferation and death. *Arterioscler Thromb Vasc Biol* 22: 364–373, 2002.
 270. **Burnstock G.** Structural and chemical organisation of the autonomic neuroeffector system. In: *Handbook of the Autonomic Nervous System in Health and Disease*, edited by Bolis CL, Licinio J, and Govoni S. New York: Dekker, 2002, p. 1–54.
 271. **Burnstock G.** Introduction: ATP and its metabolites as potent extracellular agonists. In: *Current Topics in Membranes. Purinergic Receptors and Signalling*, edited by Schwiebert EM. San Diego, CA: Academic, 2003, vol. 54, p. 1–27.
 272. **Burnstock G.** Purinergic receptors in the nervous system. In: *Current Topics in Membranes. Purinergic Receptors and Signalling*, edited by Schwiebert EM. San Diego: Academic Press, 2003, vol. 54, p. 307–368.
 273. **Burnstock G.** Cotransmission. *Curr Opin Pharmacol* 4: 47–52, 2004.
 274. **Burnstock G.** The autonomic neuroeffector junction. In: *Primer on the Autonomic Nervous System* (2nd ed.), edited by Robertson D, Low P, Burnstock G, and Biaggioni I. Amsterdam: Elsevier, 2004, p. 29–33.
 275. **Burnstock G.** Introduction: P2 receptors. *Curr Top Med Chem* 4: 793–803, 2004.
 276. **Burnstock G.** Purinergic P2 receptors as targets for novel analgesics. *Pharmacol Ther* 110: 433–454, 2006.
 277. **Burnstock G.** Historical Review: ATP as a neurotransmitter. *Trends Pharmacol Sci* 27: 166–176, 2006.
 278. **Burnstock G.** Pathophysiology and therapeutic potential of purinergic signalling. *Pharmacol Rev* 58: 58–86, 2006.
 279. **Burnstock G.** Structural and chemical organisation of the autonomic nervous system with special reference to non-adrenergic, non-cholinergic transmission. In: *Autonomic Failure. A Textbook of Clinical Disorders of the Autonomic Nervous System*, edited by Mathias CJ and Bannister R. Oxford, UK: Oxford Univ. Press, 2006.
 280. **Burnstock G.** Neurotransmission, neuromodulation: cotransmission. In: *New Encyclopedia of Neuroscience* (4th ed.), edited by Squires LR. Oxford, UK: Elsevier Science, 2007.
 281. **Burnstock G, Allen TGJ, Hassall CJS, Pittam BS.** Properties of intramural neurones cultured from the heart and bladder. In: *Histochemistry and Cell Biology of Autonomic Neurons and Paraganglia*, edited by Heym C. Heidelberg, Germany: Springer-Verlag, 1987, p. 323–328. (Exp. Brain Res. Ser. 16)
 282. **Burnstock G, Campbell G, Bennett M, Holman ME.** Inhibition of the smooth muscle of the taenia coli. *Nature* 200: 581–582, 1963.
 283. **Burnstock G, Campbell G, Bennett M, Holman ME.** Innervation of the guinea-pig taenia coli: are there intrinsic inhibitory nerves which are distinct from sympathetic nerves? *Int J Neuropharmacol* 3: 163–166, 1964.
 284. **Burnstock G, Campbell G, Rand MJ.** The inhibitory innervation of the taenia of the guinea-pig caecum. *J Physiol* 182: 504–526, 1966.
 285. **Burnstock G, Campbell G, Satchell D, Smythe A.** Evidence that adenosine triphosphate or a related nucleotide is the transmitter substance released by non-adrenergic inhibitory nerves in the gut. *Br J Pharmacol* 40: 668–688, 1970.
 286. **Burnstock G, Cocks T, Crowe R, Kasakov L.** Purinergic innervation of the guinea-pig urinary bladder. *Br J Pharmacol* 63: 125–138, 1978.
 287. **Burnstock G, Costa M.** *Adrenergic Neurones: Their Organisation, Function and Development in the Peripheral Nervous System*. London: Chapman and Hall, 1975.
 288. **Burnstock G, Hökfelt T, Gershon MD, Iverson LL, Kosterlitz HW, Szurszewski JH.** Non-adrenergic, non-cholinergic autonomic neurotransmission mechanisms. In: *Neuroscience Research Program Bulletin 17, No. 3*, Cambridge, MA: MIT Press, 1979, p. 379–519.
 289. **Burnstock G, Holman ME.** Autonomic nerve-smooth muscle transmission. *Nature* 187: 951–952, 1960.
 290. **Burnstock G, Holman ME.** The transmission of excitation from autonomic nerve to smooth muscle. *J Physiol* 155: 115–133, 1961.
 291. **Burnstock G, Kennedy C.** Is there a basis for distinguishing two types of P₂-purinoceptor? *Gen Pharmacol* 16: 433–440, 1985.
 292. **Burnstock G, Knight GE.** Cellular distribution and functions of P2 receptor subtypes in different systems. *Int Rev Cytol* 240: 31–304, 2004.
 293. **Burnstock G, Lavin S.** Interstitial cells of Cajal and purinergic signalling. *Auton Neurosci* 97: 68–72, 2002.

294. **Burnstock G, Wong H.** Comparison of the effects of ultraviolet light and purinergic nerve stimulation on the guinea-pig taenia coli. *Br J Pharmacol* 62: 293–302, 1978.
295. **Burnstock G, Wood JN.** Purinergic receptors: their role in nociception and primary afferent neurotransmission. *Curr Opin Neurobiol* 6: 526–532, 1996.
296. **Burrell HE, Wlodarski B, Foster BJ, Buckley KA, Sharpe GR, Quayle JM, Simpson AW, Gallagher JA.** Human keratinocytes release ATP and utilize three mechanisms for nucleotide interconversion at the cell surface. *J Biol Chem* 280: 29667–29676, 2005.
297. **Burrows GH, Barnea A.** Comparison of the effects of ATP, Mg²⁺, MgATP on the release of luteinizing hormone-releasing hormone from isolated hypothalamic granules. *J Neurochem* 38: 569–573, 1982.
298. **Butlen D, Bernard C, Ferrary E.** Pharmacological characterization of ATP receptors in ampulla from frog semicircular canal. *Am J Physiol Regul Integr Comp Physiol* 275: R253–R261, 1998.
299. **Butt AM, Hamilton N, Hubbard P, Pugh M, Ibrahim M.** Synaptosomes: the fifth element. *J Anat* 207: 695–706, 2005.
300. **Buttigieg J, Nurse CA.** Detection of hypoxia-evoked ATP release from chemoreceptor cells of the rat carotid body. *Biochem Biophys Res Commun* 322: 82–87, 2004.
301. **Buxton DB, Robertson SM, Olson MS.** Stimulation of glycolysis by adenine nucleotides in the perfused rat liver. *Biochem J* 237: 773–780, 1986.
302. **Bystrova MF, Yatzenko YE, Fedorov IV, Rogachevskaja OA, Kolesnikov SS.** P2Y isoforms operative in mouse taste cells. *Cell Tissue Res* 323: 377–382, 2006.
303. **Cahill CM, White TD, Sawynok J.** Synergy between μ/δ -opioid receptors mediates adenosine release from spinal cord synaptosomes. *Eur J Pharmacol* 298: 45–49, 1996.
304. **Cain DM, Wacnik PW, Eikmeier L, Beitz A, Wilcox GL, Simone DA.** Functional interactions between tumor and peripheral nerve in a model of cancer pain in the mouse. *Pain Med* 2: 15–23, 2001.
305. **Cakir E, Baykal S, Karahan SC, Kuzeyli K, Uydu H.** Acute phase effects of ATP-MgCl₂ on experimental spinal cord injury. *Neurosurg Rev* 26: 67–70, 2003.
306. **Calon F, Dridi M, Hornykiewicz O, Bédard PJ, Rajput AH, Di Paolo T.** Increased adenosine A_{2A} receptors in the brain of Parkinson's disease patients with dyskinesias. *Brain* 127: 1075–1084, 2004.
307. **Calvert JA, Atterbury-Thomas AE, Leon C, Forsythe ID, Gachet C, Evans RJ.** Evidence for P2Y₁, P2Y₂, P2Y₆ and atypical UTP-sensitive receptors coupled to rises in intracellular calcium in mouse cultured superior cervical ganglion neurons and glia. *Br J Pharmacol* 143: 525–532, 2004.
308. **Calvert JA, Evans RJ.** Heterogeneity of P2X receptors in sympathetic neurons: contribution of neuronal P2X₁ receptors revealed using knockout mice. *Mol Pharmacol* 65: 139–148, 2004.
309. **Camden JM, Schrader AM, Camden RE, Gonzalez FA, Erb L, Seye CI, Weisman GA.** P2Y₂ nucleotide receptors enhance α -secretase-dependent amyloid precursor protein processing. *J Biol Chem* 280: 18696–18702, 2005.
310. **Capiod T.** ATP-activated cation currents in single guinea-pig hepatocytes. *J Physiol* 507: 795–805, 1998.
311. **Carew MA, Wu ML, Law GJ, Tseng YZ, Mason WT.** Extracellular ATP activates calcium entry and mobilization via P2U-purinoreceptors in rat lactotrophs. *Cell Calcium* 16: 227–235, 1994.
312. **Carley DW, Radulovacki M.** Adenosine effects in sleep apnea. In: *Purinergic Approaches in Experimental Therapeutics*, edited by Jacobson KA and Jarvis MF. New York: Wiley-Liss, 1997, p. 515–526.
313. **Carlsson A, Hillarp NA, Hökfelt B.** The concomitant release of adenosine triphosphate and catecholamines from the adrenal medulla. *J Biol Chem* 227: 243–252, 1957.
314. **Carrasquero LM, Delicado EG, Jiménez AI, Pérez-Sen R, Miras-Portugal MT.** Cerebellar astrocytes co-express several ADP receptors. Presence of functional P2Y₁₃-like receptors. *Purinergic Signalling* 1: 153–159, 2005.
315. **Caruso M, Holgate ST, Polosa R.** Adenosine signalling in airways. *Curr Opin Pharmacol* 6: 251–256, 2006.
316. **Casel D, Brockhaus J, Deitmer JW.** Enhancement of spontaneous synaptic activity in rat Purkinje neurones by ATP during development. *J Physiol* 568: 111–122, 2005.
317. **Castelucci P, Robbins HL, Furness JB.** P2X₂ purine receptor immunoreactivity of intraganglionic laminar endings in the mouse gastrointestinal tract. *Cell Tissue Res* 312: 167–174, 2003.
318. **Castelucci P, Robbins HL, Poole DP, Furness JB.** The distribution of purine P2X₂ receptors in the guinea-pig enteric nervous system. *Histochem Cell Biol* 117: 415–422, 2002.
319. **Cavaliere F, Amadio S, Angelini DF, Sancesario G, Bernardi G, Volonté C.** Role of the metabotropic P2Y₄ receptor during hypoglycemia: cross talk with the ionotropic NMDAR1 receptor. *Exp Cell Res* 300: 149–158, 2004.
320. **Cavaliere F, Dinkel K, Reymann K.** Microglia response and P2 receptor participation in oxygen/glucose deprivation-induced cortical damage. *Neuroscience* 136: 615–623, 2005.
321. **Cavaliere F, Florenzano F, Amadio S, Fusco FR, Viscomi MT, D'Ambrosi N, Vacca F, Sancesario G, Bernardi G, Molinari M, Volonté C.** Up-regulation of P2X₂, P2X₄ receptor and ischemic cell death: prevention by P2 antagonists. *Neuroscience* 120: 85–98, 2003.
322. **Cavaliere F, Sancesario G, Bernardi G, Volonté C.** Extracellular ATP and nerve growth factor intensify hypoglycemia-induced cell death in primary neurons: role of P2 and NGFRp75 receptors. *J Neurochem* 83: 1129–1138, 2002.
323. **Cechin SR, Schetinger MR, Zanatta N, Madruga CC, Pacholski IL, Flores DC, Bonacorso HG, Martins MA, Morsch VM.** Inhibitory effect of novel pyrimidines on ATP and ADP hydrolysis in synaptosomes from rat cerebral cortex. *Chem Res Toxicol* 16: 1433–1439, 2003.
324. **Ceruti C, Fumagalli M, Verderio C, Abbracchio MP.** Nucleotides as neurotransmitters of pain in migraine: a role for P2Y receptors in primary cultures from mouse trigeminal ganglia. *Proc Am Soc Neurosci Atlanta GA October 14–18, 2006.*
325. **Cha SH, Hahn TW, Sekine T, Lee KH, Endou H.** Purinoceptor-mediated calcium mobilization and cellular proliferation in cultured bovine corneal endothelial cells. *Jpn J Pharmacol* 82: 181–187, 2000.
326. **Chaban VV, Mayer EA, Ennes HS, Micevych PE.** Estradiol inhibits ATP-induced intracellular calcium concentration increase in dorsal root ganglia neurons. *Neuroscience* 118: 941–948, 2003.
327. **Cham JL, Owens NC, Barden JA, Lawrence AJ, Badoer E.** P2X purinoceptor subtypes on paraventricular nucleus neurones projecting to the rostral ventrolateral medulla in the rat. *Exp Physiol* 91: 403–411, 2006.
328. **Chan CM, Unwin RJ, Burnstock G.** Potential for functional roles of extracellular ATP in the kidney and urinary tract. *Exp Nephrol* 6: 200–207, 1998.
329. **Chan-Palay V, Palay SL.** *Co-existence of Neuroactive Substances in Neurones.* New York: Wiley, 1984.
330. **Chari RS, Schutz SM, Haebig JE, Shimokura GH, Cotton PB, Fitz JG, Meyers WC.** Adenosine nucleotides in bile. *Am J Physiol Gastrointest Liver Physiol* 270: G246–G252, 1996.
331. **Chelmicka-Schorr E, Kwasniewski MN, Czlonkowska A.** Sympathetic nervous system modulates macrophage function. *Int J Immunopharmacol* 14: 841–846, 1992.
332. **Chen C, Bobbin RP.** P2X receptors in cochlear Deiters' cells. *Br J Pharmacol* 124: 337–344, 1998.
333. **Chen C, Nenov A, Bobbin RP.** Noise exposure alters the response of outer hair cells to ATP. *Hear Res* 88: 215–221, 1995.
334. **Chen C, Parker MS, Barnes AP, Deininger P, Bobbin RP.** Functional expression of three P2X₂ receptor splice variants from guinea pig cochlea. *J Neurophysiol* 83: 1502–1509, 2000.
335. **Chen CC, Akopian AN, Sivilotti L, Colquhoun D, Burnstock G, Wood JN.** A P2X purinoceptor expressed by a subset of sensory neurons. *Nature* 377: 428–431, 1995.
336. **Chen CL, Broom DC, Liu Y, de Nooij JC, Li Z, Cen C, Samad OA, Jessell TM, Woolf CJ, Ma Q.** Runx1 determines nociceptive sensory neuron phenotype and is required for thermal and neuropathic pain. *Neuron* 49: 365–377, 2006.
337. **Chen HB, Chan YT, Hung AC, Tsai YC, Sun SH.** Elucidation of ATP-stimulated stress protein expression of RBA-2 type-2 astrocytes: ATP potentiates HSP60 and Cu/Zn SOD expression and

- stimulates pI shift of peroxiredoxin II. *J Cell Biochem* 97: 314–326, 2006.
338. **Chen JF**. The adenosine A_{2A} receptor as an attractive target for Parkinson's disease treatment. *Drug News Perspect* 16: 597–604, 2003.
339. **Chen JF, Beilstein M, Xu YH, Turner TJ, Moratalla R, Standaert DG, Aloyo VJ, Fink JS, Schwarzschild MA**. Selective attenuation of psychostimulant-induced behavioral responses in mice lacking A_{2A} adenosine receptors. *Neuroscience* 97: 195–204, 2000.
340. **Chen L, Brosnan CF**. Exacerbation of experimental autoimmune encephalomyelitis in P2X₇R^{-/-} mice: evidence for loss of apoptotic activity in lymphocytes. *J Immunol* 176: 3115–3126, 2006.
341. **Chen M, Gu JG**. A P2X receptor-mediated nociceptive afferent pathway to lamina I of the spinal cord. *Mol Pain* 1: 4, 2005.
342. **Chen Y, Li GW, Wang C, Gu Y, Huang LY**. Mechanisms underlying enhanced P2X receptor-mediated responses in the neuropathic pain state. *Pain* 119: 38–48, 2005.
343. **Chen Y, Zhang YH, Bie BH, Zhao ZQ**. Sympathectomy induces novel purinergic sensitivity in sciatic afferents. *Acta Pharmacol Sin* 21: 1002–1004, 2000.
344. **Chen ZP, Kratzmeier M, Levy A, McArdle CA, Poch A, Day A, Mukhopadhyay AK, Lightman SL**. Evidence for a role of pituitary ATP receptors in the regulation of pituitary function. *Proc Natl Acad Sci USA* 92: 5219–5223, 1995.
345. **Chen ZP, Levy A, Lightman SL**. Activation of specific ATP receptors induces a rapid increase in intracellular calcium ions in rat hypothalamic neurons. *Brain Res* 641: 249–256, 1994.
346. **Cheng JT, Liu IM, Juang SW, Jou SB**. Decrease of adenosine A-1 receptor gene expression in cerebral cortex of aged rats. *Neurosci Lett* 283: 227–229, 2000.
347. **Cherruau M, Facchinetti P, Baroukh B, Saffar JL**. Chemical sympathectomy impairs bone resorption in rats: a role for the sympathetic system on bone metabolism. *Bone* 25: 545–551, 1999.
348. **Chesher GB, James B**. The “nicotinic” and “muscarinic” receptors of the urinary bladder of the guinea-pig. *J Pharm Pharmacol* 18: 417–423, 1966.
349. **Chess-Williams R**. Potential therapeutic targets for the treatment of detrusor overactivity. *Expert Opin Ther Targets* 8: 95–106, 2004.
350. **Chessell IP, Hatcher JP, Bountra C, Michel AD, Hughes JP, Green P, Egerton J, Murfin M, Richardson J, Peck WL, Grahames CB, Casula MA, Yiangou Y, Birch R, Anand P, Buell GN**. Disruption of the P2X₇ purinoceptor gene abolishes chronic inflammatory and neuropathic pain. *Pain* 114: 386–396, 2005.
351. **Chessell IP, Hatcher JP, Hughes JP, Ulmann L, Green P, Mander PK, Reeve AJ, Rassendren F**. The role of P2X₇ and P2X₄ in pain processing: common or divergent pathways? *Purinergic Signalling* 2: 46–47, 2006.
352. **Chessell IP, Michel AD, Humphrey PP**. Functional evidence for multiple purinoceptor subtypes in the rat medial vestibular nucleus. *Neuroscience* 77: 783–791, 1997.
353. **Cheung KK, Burnstock G**. Localisation of P2X₃ and co-expression with P2X₂ receptors during rat embryonic neurogenesis. *J Comp Neurol* 443: 368–382, 2002.
354. **Cheung KK, Chan WY, Burnstock G**. Expression of P2X receptors during rat brain development and their inhibitory role on motor axon outgrowth in neural tube explant cultures. *Neuroscience* 133: 937–945, 2005.
355. **Cheung KK, Ryten M, Burnstock G**. Abundant and dynamic expression of G protein-coupled P2Y receptors in mammalian development. *Dev Dyn* 228: 254–266, 2003.
356. **Chiang CY, Zhang S, Xie YF, Hu JW, Dostrovsky JO, Salter MW, Sessle BJ**. Endogenous ATP involvement in mustard-oil-induced central sensitization in trigeminal subnucleus caudalis (medullary dorsal horn). *J Neurophysiol* 94: 1751–1760, 2005.
357. **Chizh BA, Illes P**. P2X receptors and nociception. *Pharmacol Rev* 53: 553–568, 2000.
358. **Choca JI, Proudfit HK, Green RD**. Identification of A₁ and A₂ adenosine receptors in the rat spinal cord. *J Pharmacol Exp Ther* 242: 905–910, 1987.
359. **Choi HB, Hong SH, Ryu JK, Kim SU, McLarnon JG**. Differential activation of subtype purinergic receptors modulates Ca²⁺ mobilization and COX-2 in human microglia. *Glia* 43: 95–103, 2003.
360. **Choi JY, Shin JH, Kim JL, Jung SH, Son EJ, Song MH, Kim SH, Yoon JH**. P2Y₂ agonist induces mucin secretion via Ca²⁺- and inositol 1,4,5-triphosphate-dependent pathway in human middle ear epithelial cells. *Hear Res* 209: 24–31, 2005.
361. **Choi RC, Siow NL, Cheng AW, Ling KK, Tung EK, Simon J, Barnard EA, Tsim KW**. ATP acts via P2Y₁ receptors to stimulate acetylcholinesterase and acetylcholine receptor expression: transcription and transcription control. *J Neurosci* 23: 4445–4456, 2003.
362. **Chorna NE, Santiago-Perez LI, Erb L, Seye CI, Neary JT, Sun GY, Weisman GA, Gonzalez FA**. P2Y₂ receptors activate neuroprotective mechanisms in astrocytic cells. *J Neurochem* 91: 119–132, 2004.
363. **Chowdhury HH, Grilc S, Zorec R**. Correlated ATP-induced changes in membrane area and membrane conductance in single rat adipocytes. *Ann NY Acad Sci* 1048: 281–286, 2005.
364. **Chowdhury M, Fillenz M**. Presynaptic adenosine A2 and N-methyl-D-aspartate receptors regulate dopamine synthesis in rat striatal synaptosomes. *J Neurochem* 56: 1783–1788, 1991.
365. **Christofi FL, Wunderlich J, Yu JG, Wang YZ, Xue J, Guzman J, Javed N, Cooke H**. Mechanically evoked reflex electrogenic chloride secretion in rat distal colon is triggered by endogenous nucleotides acting at P2Y₁, P2Y₂, P2Y₄ receptors. *J Comp Neurol* 469: 16–36, 2004.
366. **Christofi FL, Zhang H, Yu JG, Guzman J, Xue J, Kim M, Wang YZ, Cooke HJ**. Differential gene expression of adenosine A1, A2a, A2b, A3 receptors in the human enteric nervous system. *J Comp Neurol* 439: 46–64, 2001.
367. **Clanachan AS, Johns A, Paton DM**. Presynaptic inhibitory actions of adenine nucleotides and adenosine on neurotransmission in the rat vas deferens. *Neuroscience* 2: 597–602, 1977.
368. **Clemow DB, Steers WD, McCarty R, Tuttle JB**. Altered regulation of bladder nerve growth factor and neurally mediated hyperactive voiding. *Am J Physiol Regul Integr Comp Physiol* 275: R1279–R1286, 1998.
369. **Cloues R, Jones S, Brown DA**. Zn²⁺ potentiates ATP-activated currents in rat sympathetic neurons. *Pflügers Arch* 424: 152–158, 1993.
370. **Cobb BR, Clancy JP**. Molecular and cell biology of adenosine receptors. *Curr Top Membr* 54: 151–181, 2003.
371. **Cockayne DA, Dunn PM, Zhong Y, Hamilton SG, Cain GR, Knight G, Ruan HZ, Ping Y, Nunn P, Bei M, McMahon SB, Burnstock G, Ford APDW**. P2X₂ knockout mice and P2X₂/P2X₃ double knockout mice reveal a role for the P2X₂ receptor subunit in mediating multiple sensory effects of ATP. *J Physiol* 567: 621–639, 2005.
372. **Cockayne DA, Hamilton SG, Zhu QM, Dunn PM, Zhong Y, Novakovic S, Malmberg AB, Cain G, Berson A, Kassotakis L, Hedley L, Lachnit WG, Burnstock G, McMahon SB, Ford APDW**. Urinary bladder hyporeflexia and reduced pain-related behaviour in P2X₃-deficient mice. *Nature* 407: 1011–1015, 2000.
373. **Coco S, Calegari F, Pravettoni E, Pozzi D, Taverna E, Rosa P, Matteoli M, Verderio C**. Storage and release of ATP from astrocytes in culture. *J Biol Chem* 278: 1354–1362, 2003.
374. **Coelho JE, Rebola N, Fragata I, Ribeiro JA, de Mendonça A, Cunha RA**. Hypoxia-induced desensitization and internalization of adenosine A₁ receptors in the rat hippocampus. *Neuroscience* 138: 1195–1203, 2006.
375. **Collet C, Strube C, Csernoch L, Mallouk N, Ojeda C, Allard B, Jacquemond V**. Effects of extracellular ATP on freshly isolated mouse skeletal muscle cells during pre-natal and post-natal development. *Pflügers Arch* 443: 771–778, 2002.
376. **Collier HO, James GWL, Schneider C**. Antagonism by aspirin and fenamates of bronchoconstriction and nociception induced by adenosine-5'-triphosphate. *Nature* 212: 411–412, 1966.
377. **Collo G, Neidhart S, Kawashima E, Kosco-Vilbois M, North RA, Buell G**. Tissue distribution of the P2X₇ receptor. *Neuropharmacology* 36: 1277–1283, 1997.
378. **Collo G, North RA, Kawashima E, Merlo-Pich E, Neidhart S, Surprenant A, Buell G**. Cloning of P2X₅ and P2X₆ receptors and

- the distribution and properties of an extended family of ATP-gated ion channels. *J Neurosci* 16: 2495–2507, 1996.
379. **Colomar A, Amédee T.** ATP stimulation of P2X₇ receptors activates three different ionic conductances on cultured mouse Schwann cells. *Eur J Neurosci* 14: 927–936, 2001.
 380. **Colomar A, Robitaille R.** Glial modulation of synaptic transmission at the neuromuscular junction. *Glia* 47: 284–289, 2004.
 381. **Conde SV, Obeso A, Vicario I, Rigual R, Rocher A, Gonzalez C.** Caffeine inhibition of rat carotid body chemoreceptors is mediated by A_{2A} and A_{2B} adenosine receptors. *J Neurochem* 98: 616–628, 2006.
 382. **Cook SP, McCleskey EW.** Cell damage excites nociceptors through release of cytosolic ATP. *Pain* 95: 41–47, 2002.
 383. **Cook SP, Vulchanova L, Hargreaves KM, Elde R, McCleskey EW.** Distinct ATP receptors on pain-sensing and stretch-sensing neurons. *Nature* 387: 505–508, 1997.
 384. **Cooke HJ, Wunderlich J, Christofi FL.** “The force be with you”: ATP in gut mechanosensory transduction. *News Physiol Sci* 18: 43–49, 2003.
 385. **Cornforde EM, Oldendorf WH.** Independent blood-brain barrier transport systems for nucleic acid precursors. *Biochim Biophys Acta* 394: 211, 1975.
 386. **Corodimas KP, Tomita H.** Adenosine A1 receptor activation selectively impairs the acquisition of contextual fear conditioning in rats. *Behav Neurosci* 115: 1283–1290, 2001.
 387. **Correia-de-Sá P, Adães S, Timóteo MA, Vieira C, Magalhães-Cardoso T, Nascimento C, Duarte-Araújo M.** Fine-tuning modulation of myenteric motoneurons by endogenous adenosine: on the role of secreted adenosine deaminase. *Auton Neurosci* 126–127: 211–224, 2006.
 388. **Correia-de-Sá P, Timóteo MA, Ribeiro JA.** Presynaptic A₁ inhibitory/A_{2A} facilitatory adenosine receptor activation balance depends on motor nerve stimulation paradigm at the rat hemidiaphragm. *J Neurophysiol* 76: 3910–3919, 1996.
 389. **Corsi C, Melani A, Bianchi L, Pepeu G, Pedata F.** Striatal A_{2A} adenosine receptors differentially regulate spontaneous and K⁺-evoked glutamate release in vivo in young and aged rats. *Neuroreport* 10: 687–691, 1999.
 390. **Corsi C, Melani A, Bianchi L, Pepeu G, Pedata F.** Effect of adenosine A_{2A} receptor stimulation on GABA release from the striatum of young and aged rats in vivo. *Neuroreport* 10: 3933–3937, 1999.
 391. **Costenla AR, de Mendonça A, Ribeiro JA.** Adenosine modulates synaptic plasticity in hippocampal slices from aged rats. *Brain Res* 851: 228–234, 1999.
 392. **Costenla AR, Lopes LV, de MA, Ribeiro JA.** A functional role for adenosine A₃ receptors: modulation of synaptic plasticity in the rat hippocampus. *Neurosci Lett* 302: 53–57, 2001.
 393. **Costessi A, Pines A, D’Andrea P, Romanello M, Damante G, Cesaratto L, Quadrioglio F, Moro L, Tell G.** Extracellular nucleotides activate Runx2 in the osteoblast-like HOBIT cell line: a possible molecular link between mechanical stress and osteoblasts’ response. *Bone* 36: 418–432, 2005.
 394. **Cotrina ML, Lin JH, Alves-Rodrigues A, Liu S, Li J, Azmi-Ghadimi H, Kang J, Naus CC, Nedergaard M.** Connexins regulate calcium signaling by controlling ATP release. *Proc Natl Acad Sci USA* 95: 15735–15740, 1998.
 395. **Cotrina ML, Lin JH, Lopez-Garcia JC, Naus CC, Nedergaard M.** ATP-mediated glia signaling. *J Neurosci* 20: 2835–2844, 2000.
 396. **Coutinho CMLM, Pons AH, Araujo-Jorge TC, Persechini PM, Coutinho-Silva R.** Enhancement of P2Z-associated cell permeabilization during acute phase of Chagas’ disease. *Drug Dev Res* 43: 38, 1998.
 397. **Coutinho-Silva R, Parsons M, Robson T, Burnstock G.** Changes in expression of P2 receptors in rat and mouse pancreas during development and aging. *Cell Tissue Res* 306: 373–383, 2001.
 398. **Coutinho-Silva R, Parsons M, Robson T, Lincoln J, Burnstock G.** P2X and P2Y purinoceptor expression in pancreas from streptozotocin-diabetic rats. *Mol Cell Endocrinol* 204: 141–154, 2003.
 399. **Cowlen MS, Zhang VZ, Warnock L, Moyer CF, Peterson WM, Yerxa BR.** Localization of ocular P2Y₂ receptor gene expression by in situ hybridization. *Exp Eye Res* 77: 77–84, 2003.
 400. **Cox CI, Leese HJ.** Effect of purinergic stimulation on intracellular calcium concentration and transepithelial potential difference in cultured bovine oviduct cells. *Biol Reprod* 52: 1244–1249, 1995.
 401. **Coxon FP, Thompson K, Rogers MJ.** Recent advances in understanding the mechanism of action of bisphosphonates. *Curr Opin Pharmacol* 6: 307–312, 2006.
 402. **Crivellato E, Soldano F, Travan L, Fusaroli P, Mallardi F.** Apposition of enteric nerve fibers to plasma cells and immunoblasts in the mouse small bowel. *Neurosci Lett* 241: 123–126, 1998.
 403. **Crowe R, Burnstock G.** Perinatal development of quinacrine-positive neurons in the rabbit gastrointestinal tract. *J Auton Nerv Syst* 4: 217–230, 1981.
 404. **Crowe R, Burnstock G, Light JK.** Intramural ganglia in the human urethra. *J Urol* 140: 183–187, 1988.
 405. **Crowe R, Haven AJ, Burnstock G.** Intramural neurons of the guinea-pig urinary bladder: histochemical localization of putative neurotransmitters in cultures and newborn animals. *J Auton Nerv Syst* 15: 319–339, 1986.
 406. **Crowe R, Whitear M.** Quinacrine fluorescence of Merkel cells in *Xenopus laevis*. *Cell Tissue Res* 190: 273–283, 1978.
 407. **Cuello AC.** Co-transmission. In: *Proc Symp 50th Anniversary Meet Br Pharmacol Soc, Oxford*. London: Macmillan, 1982, p. 1–264.
 408. **Cunha RA, Constantino MC, Sebastiao AM, Ribeiro JA.** Modification of A₁ and A_{2A} adenosine receptor binding in aged striatum, hippocampus and cortex of the rat. *Neuroreport* 6: 1583–1588, 1995.
 409. **Cunha RA, Ribeiro JA.** ATP as a presynaptic modulator. *Life Sci* 68: 119–137, 2000.
 410. **Cunha RA, Vizi ES, Ribeiro JA, Sebastiao AM.** Preferential release of ATP and its extracellular catabolism as a source of adenosine upon high- but not low-frequency stimulation of rat hippocampal slices. *J Neurochem* 67: 2180–2187, 1996.
 411. **Currie KP, Fox AP.** ATP serves as a negative feedback inhibitor of voltage-gated Ca²⁺ channel currents in cultured bovine adrenal chromaffin cells. *Neuron* 16: 1027–1036, 1996.
 412. **Czesnik D, Kuduz J, Schild D, Manzini I.** ATP activates both receptor and sustentacular supporting cells in the olfactory epithelium of *Xenopus laevis* tadpoles. *Eur J Neurosci* 23: 119–128, 2006.
 413. **D’Albora H, Lombide P, Ojeda SR.** Intrinsic neurons in the rat ovary: an immunohistochemical study. *Cell Tissue Res* 300: 47–56, 2000.
 414. **D’Alcantara P, Ledent C, Swillens S, Schiffmann SN.** Inactivation of adenosine A_{2A} receptor impairs long term potentiation in the accumbens nucleus without altering basal synaptic transmission. *Neuroscience* 107: 455–464, 2001.
 415. **D’Ambrosi N, Murra B, Cavaliere F, Amadio S, Bernardi G, Burnstock G, Volonté C.** Interaction between ATP and nerve growth factor signalling in the survival and neuritic outgrowth from PC12 cells. *Neuroscience* 108: 527–534, 2001.
 416. **Da Silva RS, de Paula CG, Bogo MR, da Graca FM, Fin CA, Thome JW, Bonan CD, Dutra DR.** Unique Ca²⁺-activated ATPase in the nervous ganglia of *Phyllocaulis soleiformis* (Mollusca). *Comp Biochem Physiol B Biochem Mol Biol* 131: 55–61, 2002.
 417. **Dahl G, Locovei S.** Pannexin: to gap or not to gap, is that a question? *IUBMB Life* 58: 409–419, 2006.
 418. **Dai Y, Fukuoka T, Wang H, Yamanaka H, Obata K, Tokunaga A, Noguchi K.** Contribution of sensitized P2X receptors in inflamed tissue to the mechanical hypersensitivity revealed by phosphorylated ERK in DRG neurons. *Pain* 108: 258–266, 2004.
 419. **Dale H.** Pharmacology and nerve endings. *Proc R Soc Med* 28: 319–332, 1935.
 420. **Dale HH, Gaddum JH.** Reactions of denervated voluntary muscle, their bearing on the mode of action of parasympathetic and related nerves. *J Physiol* 70: 109–144, 1930.
 421. **Dale N.** Resetting intrinsic purinergic modulation of neural activity: an associative mechanism? *J Neurosci* 22: 10461–10469, 2002.
 422. **Dale N, Gilday D.** Regulation of rhythmic movements by purinergic neurotransmitters in frog embryos. *Nature* 383: 259–263, 1996.

423. **Daly JW.** Adenosine receptors. *Adv Cyclic Nucleotide Protein Phosphorylation Res* 19: 29–46, 1985.
424. **Damann N, Rothermel M, Klupp BG, Mettenleiter TC, Hatt H, Wetzel CH.** Chemosensory properties of murine nasal and cutaneous trigeminal neurons identified by viral tracing. *BMC Neurosci* 7: 46, 2006.
425. **Daneshgari F, Liu G, Imrey PB.** Time dependent changes in diabetic cystopathy in rats include compensated and decompensated bladder function. *J Urol* 176: 380–386, 2006.
426. **Dang K, Bielfeldt K, Lamb K, Gebhart GF.** Gastric ulcers evoke hyperexcitability and enhance P2X receptor function in rat gastric sensory neurons. *J Neurophysiol* 93: 3112–3119, 2005.
427. **Davalos D, Grutzendler J, Yang G, Kim JV, Zuo Y, Jung S, Littman DR, Dustin ML, Gan WB.** ATP mediates rapid microglial response to local brain injury in vivo. *Nat Neurosci* 8: 752–758, 2005.
428. **Davies DL, Kochegarov AA, Kuo ST, Kulkarni AA, Woodward JJ, King BF, Alkana RL.** Ethanol differentially affects ATP-gated P2X₃ and P2X₄ receptor subtypes expressed in *Xenopus* oocytes. *Neuropharmacology* 49: 243–253, 2005.
429. **Dawid-Milner MS, Silva-Carvalho L, Goldsmith GR, Spyer KM.** A potential role of central A₁ adenosine receptors in the responses to hypothalamic stimulation in the anaesthetized cat. *J Auton Nerv Syst* 49: 15–19, 1994.
430. **Day TA, Sibbald JR, Khanna S.** ATP mediates an excitatory noradrenergic neuron input to supraoptic vasopressin cells. *Brain Res* 607: 341–344, 1993.
431. **De Bremaeker N, Baguet F, Mallefet J.** Effects of catecholamines and purines on luminescence in the brittlestar *Amphipholis squamata* (Echinodermata). *J Exp Biol* 203: 2015–2023, 2000.
432. **De Groat WC.** Integrative control of the lower urinary tract: preclinical perspective. *Br J Pharmacol* 147: S25–S40, 2006.
433. **De Lorenzo S, Veggetti M, Muchnik S, Losavio A.** Presynaptic inhibition of spontaneous acetylcholine release mediated by P2Y receptors at the mouse neuromuscular junction. *Neuroscience* 142: 71–85, 2006.
434. **De Man JG, Seerden TC, De Winter BY, Van Marck EA, Herman AG, Pelckmans PA.** Alteration of the purinergic modulation of enteric neurotransmission in the mouse ileum during chronic intestinal inflammation. *Br J Pharmacol* 139: 172–184, 2003.
435. **De Mendonça A, Costenla AR, Ribeiro JA.** Persistence of the neuromodulatory effects of adenosine on synaptic transmission after long-term potentiation and long-term depression. *Brain Res* 932: 56–60, 2002.
436. **De Mey J, Burnstock G, Vanhoutte PM.** Modulation of the evoked release of noradrenaline in canine saphenous vein via presynaptic receptors for adenosine but not ATP. *Eur J Pharmacol* 55: 401–405, 1979.
437. **De Paula PM, Antunes VR, Bonagamba LG, Machado BH.** Cardiovascular responses to microinjection of ATP into the nucleus tractus solitarius of awake rats. *Am J Physiol Regul Integr Comp Physiol* 287: R1164–R1171, 2004.
438. **De Souza Dahm KC, Rückert C, Tonial EM, Bonan CD.** In vitro exposure of heavy metals on nucleotidase and cholinesterase activities from the digestive gland of *Helix aspersa*. *Comp Biochem Physiol C Toxicol Pharmacol* 143: 316–320, 2006.
439. **De Vuyst E, Decrock E, Cabooter L, Dubyak GR, Naus CC, Evans WH, Leybaert L.** Intracellular calcium changes trigger connexin 32 hemichannel opening. *EMBO J* 25: 34–44, 2006.
440. **De Young MB, Scarpa A.** Extracellular ATP induces Ca²⁺ transients in cardiac myocytes which are potentiated by norepinephrine. *FEBS Lett* 223: 53–58, 1987.
441. **Deckert J, Brenner M, Durany N, Zöchling R, Paulus W, Ransmayr G, Tatschner T, Danielczyk W, Jellinger K, Riederer P.** Up-regulation of striatal adenosine A_{2A} receptors in schizophrenia. *Neuroreport* 14: 313–316, 2003.
442. **Deitmer JW, Brockhaus J, Casel D.** Modulation of synaptic activity in Purkinje neurons by ATP. *Cerebellum* 5: 49–54, 2006.
443. **Delicado EG, Jiménez AI, Carrasquero LM, Castro E, Miras-Portugal MT.** Cross-talk among epidermal growth factor, Ap_{5A}, nucleotide receptors causing enhanced ATP Ca²⁺ signaling involves extracellular kinase activation in cerebellar astrocytes. *J Neurosci Res* 81: 789–796, 2005.
444. **Delicado EG, Miras-Portugal MT, Carrasquero LM, León D, Pérez-Sen R, Gualix J.** Dinucleoside polyphosphates and their interaction with other nucleotide signaling pathways. *Pflügers Arch* 452: 563–572, 2006.
445. **Dell'Antonio G, Quattrini A, Cin ED, Fulgenzi A, Ferrero ME.** Relief of inflammatory pain in rats by local use of the selective P2X₇ ATP receptor inhibitor, oxidized ATP. *Arthritis Rheum* 46: 3378–3385, 2002.
446. **Demel SL, Galligan JJ.** Impaired α -adrenergic autoreceptor modulation of purinergic transmission in mesenteric arteries of DOCA-salt rats (Abstract). *FASEB J* 20: A242–A243, 2006.
447. **Denda M, Inoue K, Fuziwara S, Denda S.** P2X purinergic receptor antagonist accelerates skin barrier repair and prevents epidermal hyperplasia induced by skin barrier disruption. *J Invest Dermatol* 119: 1034–1040, 2002.
448. **Deng G, Matute C, Kumar CK, Fogarty DJ, Miledi R.** Cloning and expression of a P_{2y} purinoceptor from the adult bovine corpus callosum. *Neurobiol Dis* 5: 259–270, 1998.
449. **Deng Z, Fyffe RE.** Expression of P2X₇ receptor immunoreactivity in distinct subsets of synaptic terminals in the ventral horn of rat lumbar spinal cord. *Brain Res* 1020: 53–61, 2004.
450. **Deuchars SA, Atkinson L, Brooke RE, Musa H, Milligan CJ, Batten TF, Buckley NJ, Parson SH, Deuchars J.** Neuronal P2X₇ receptors are targeted to presynaptic terminals in the central and peripheral nervous systems. *J Neurosci* 21: 7143–7152, 2001.
451. **Deuticke HJ.** über den einfluss von adenosin und adenosinphosphoräuren auf den isolierten meerschweinchenuterus. *Pflügers Arch* 230: 555, 1932.
452. **Di Virgilio F.** Purinergic signalling between axons and microglia. In: *Novartis Foundation Symposium 276 Purinergic Signalling in Neuron-Glial Interactions*. Chichester, UK: Wiley, 2006, p. 253–262.
453. **Di Virgilio F, Chiozzi P, Ferrari D, Falzoni S, Sanz JM, Morelli A, Torboli M, Bolognesi G, Baricordi OR.** Nucleotide receptors: an emerging family of regulatory molecules in blood cells. *Blood* 97: 587–600, 2001.
454. **Díaz-Hernandez M, Cox JA, Migita K, Haines W, Egan TM, Voigt MM.** Cloning and characterization of two novel zebrafish P2X receptor subunits. *Biochem Biophys Res Commun* 295: 849–853, 2002.
455. **Díaz-Hernández M, Pintor J, Castro E, Miras-Portugal MT.** Co-localisation of functional nicotinic and ionotropic nucleotide receptors in isolated cholinergic synaptic terminals. *Neuropharmacology* 42: 20–33, 2002.
456. **DiBona GF.** Neural control of renal function: cardiovascular implications. *Hypertension* 13: 539–548, 1989.
457. **Dickenson AH, Suzuki R, Reeve AJ.** Adenosine as a potential analgesic target in inflammatory and neuropathic pains. *CNS Drugs* 13: 77–85, 2000.
458. **Dimitriadou V, Aubineau P, Taxi J, Seylaz J.** Ultrastructural evidence for a functional unit between nerve fibers and type II cerebral mast cells in the cerebral vascular wall. *Neuroscience* 22: 621–630, 1987.
459. **Dimitriadou V, Rouleau A, Trung T, Newlands GJ, Miller HR, Luffau G, Schwartz JC, Garbarg M.** Functional relationships between sensory nerve fibers and mast cells of dura mater in normal and inflammatory conditions. *Neuroscience* 77: 829–839, 1997.
460. **Diógenes MJ, Fernandes CC, Sebastião AM, Ribeiro JA.** Activation of adenosine A_{2A} receptor facilitates brain-derived neurotrophic factor modulation of synaptic transmission in hippocampal slices. *J Neurosci* 24: 2905–2913, 2004.
461. **Diverse-Pierluissi M, Dunlap K, Westhead EW.** Multiple actions of extracellular ATP on calcium currents in cultured bovine chromaffin cells. *Proc Natl Acad Sci USA* 88: 1261–1265, 1991.
462. **Dixon CJ, White PJ, Hall JF, Kingston S, Boarder MR.** Regulation of human hepatocytes by P2Y receptors: control of glycogen phosphorylase, Ca²⁺, mitogen-activated protein kinases. *J Pharmacol Exp Ther* 313: 1305–1313, 2005.

463. **Dixon SJ, Sims SM.** P2 purinergic receptors on osteoblasts and osteoclasts: potential targets for drug development. *Drug Dev Res* 49: 187–200, 2000.
464. **Dolphin AC, Prestwich SA.** Pertussis toxin reverses adenosine inhibition of neuronal glutamate release. *Nature* 316: 148–150, 1985.
465. **Domercq M, Brambilla L, Pilati E, Marchaland J, Volterra A, Bezzi P.** P2Y₁ receptor-evoked glutamate exocytosis from astrocytes: control by tumor necrosis factor- α and prostaglandins. *J Biol Chem* 281: 30684–30696, 2006.
466. **Donaldson SH, Lazarowski ER, Picher M, Knowles MR, Stutts MJ, Boucher RC.** Basal nucleotide levels, release, metabolism in normal and cystic fibrosis airways. *Mol Med* 6: 969–982, 2000.
467. **Dorn G, Patel S, Wotherspoon G, Hemmings-Mieszczak M, Barclay J, Natt FJ, Martin P, Bevan S, Fox A, Ganju P, Wishart W, Hall J.** siRNA relieves chronic neuropathic pain. *Nucleic Acids Res* 32: e49, 2004.
468. **Douglas WW, Poisner AM.** Evidence that the secreting adrenal chromaffin cell releases catecholamines directly from ATP-rich granules. *J Physiol* 183: 236–248, 1966.
469. **Dowd E, McQueen DS, Chessell IP, Humphrey PPA.** P2X receptor-mediated excitation of nociceptive afferents in the normal and arthritic rat knee joint. *Br J Pharmacol* 125: 341–346, 1998.
470. **Dowdall MJ, Boyne AF, Whittaker VP.** Adenosine triphosphate. A constituent of cholinergic synaptic vesicles. *Biochem J* 140: 1–12, 1974.
471. **Dowe GH, Kilbinger H, Whittaker VP.** Isolation of cholinergic synaptic vesicles from the myenteric plexus of guinea-pig small intestine. *J Neurochem* 35: 993–1003, 1980.
472. **Dowling P, Ransom R, Santer N.** Age-associated changes in distribution of the P2X₂ receptor in the major pelvic ganglion of the male rat. *Neuroscience Lett* 404: 320–323, 2006.
473. **Dragunow M.** Purinergic mechanisms in epilepsy. *Prog Neurobiol* 31: 85–108, 1988.
474. **Draid M, Shiina T, El-Mahmoudy A, Boudaka A, Shimizu Y, Takewaki T.** Neurally released ATP mediates endothelium-dependent hyperpolarization in the circular smooth muscle cells of chicken anterior mesenteric artery. *Br J Pharmacol* 146: 983–989, 2005.
475. **Drakulich DA, Spellmon C, Hexum TD.** Effect of the ecto-ATPase inhibitor, ARL 67156, on the bovine chromaffin cell response to ATP. *Eur J Pharmacol* 485: 137–140, 2004.
476. **Drakulich DA, Walls AM, Toews ML, Hexum TD.** Neuropeptide Y receptor-mediated sensitization of ATP-stimulated inositol phosphate formation. *J Pharmacol Exp Ther* 307: 559–565, 2003.
477. **Dranoff JA, O'Neill AF, Franco AM, Cai SY, Connolly GC, Ballatori N, Boyer JL, Nathanson MH.** A primitive ATP receptor from the little skate *Raja erinacea*. *J Biol Chem* 275: 30701–30706, 2000.
478. **Dranoff JA, Ogawa M, Kruglov EA, Gaca MD, Seigny J, Robson SC, Wells RG.** Expression of P2Y nucleotide receptors and ectonucleotidases in quiescent and activated rat hepatic stellate cells. *Am J Physiol Gastrointest Liver Physiol* 287: G417–G424, 2004.
479. **Driessen B, Bültmann R, Jurna I, Baldauf J.** Depression of C fiber-evoked activity by intrathecally administered reactive red 2 in rat thalamic neurons. *Brain Res* 796: 284–290, 1998.
480. **Driessen B, Reimann W, Selve N, Friderichs E, Bültmann R.** Antinociceptive effect of intrathecally administered P2-purinoceptor antagonists in rats. *Brain Res* 666: 182–188, 1994.
481. **Drury AN, Szent-Györgyi A.** The physiological activity of adenine compounds with special reference to their action upon the mammalian heart. *J Physiol* 68: 213–237, 1929.
482. **Duan S, Anderson CM, Keung EC, Chen Y, Chen Y, Swanson RA.** P2X₇ receptor-mediated release of excitatory amino acids from astrocytes. *J Neurosci* 23: 1320–1328, 2003.
483. **Duan S, Neary JT.** P2X₇ receptors: properties and relevance to CNS function. *Glia* 54: 738–746, 2006.
484. **Duarte JM, Oliveira CR, Ambrósio AF, Cunha RA.** Modification of adenosine A₁ and A_{2A} receptor density in the hippocampus of streptozotocin-induced diabetic rats. *Neurochem Int* 48: 144–150, 2006.
485. **Duarte-Araújo M, Nascimento C, Alexandrina TM, Magalhães-Cardoso T, Correia-de-Sá P.** Dual effects of adenosine on acetylcholine release from myenteric motoneurons are mediated by junctional facilitatory A_{2A} and extrajunctional inhibitory A₁ receptors. *Br J Pharmacol* 141: 925–934, 2004.
486. **Dubyak GR.** Signal transduction by P₂-purinergic receptors for extracellular ATP. *Am J Respir Cell Mol Biol* 4: 295–300, 1991.
487. **Dubyak GR.** ATP release mechanisms. In: *Edited Monograph: Nucleotides and Regulation of Bone Cell Function*, edited by Burnstock G and Arnett TR. Boca Raton, FL: Taylor & Francis, 2006, p. 99–158.
488. **Dubyak GR, El Moatassim C.** Signal transduction via P2-purinergic receptors for extracellular ATP and other nucleotides. *Am J Physiol Cell Physiol* 265: C577–C606, 1993.
489. **Dugué GP, Dumoulin A, Triller A, Dieudonné S.** Target-dependent use of co-released inhibitory transmitters at central synapses. *J Neurosci* 25: 6490–6498, 2005.
490. **Dulla CG, Dobilis P, Pearson T, Frenguelli BG, Staley KJ, Masino SA.** Adenosine and ATP link P_{CO2} to cortical excitability via pH. *Neuron* 48: 1011–1023, 2005.
491. **Dulon D, Jagger DJ, Lin X, Davis RL.** Neuromodulation in the spiral ganglion: shaping signals from the organ of corti to the CNS. *J Membr Biol* 209: 167–175, 2006.
492. **Dunn M, Smith JC, Ardran GM.** Prolonged bladder distension as a treatment of urgency and urge incontinence of urine. *Br J Urol* 46: 645–652, 1974.
493. **Dunn PM.** Fertility: purinergic receptors and the male contraceptive pill. *Curr Biol* 10: R305–R307, 2000.
494. **Dunn PM, Gever J, Ruan HZ, Burnstock G.** Developmental changes in heteromeric P2X_{2/3} receptor expression in rat sympathetic ganglion neurons. *Dev Dyn* 234: 505–511, 2005.
495. **Dunn PM, Liu M, Zhong Y, King BF, Burnstock G.** Diinosine pentaphosphate: an antagonist which discriminates between recombinant P2X₃ and P2X_{2/3} receptors and between two P2X receptors in rat sensory neurones. *Br J Pharmacol* 130: 1378–1384, 2000.
496. **Dunn PM, Zhong Y, Burnstock G.** P2X receptors in peripheral neurones. *Prog Neurobiol* 65: 107–134, 2001.
497. **Dunwiddie TV.** The physiological role of adenosine in the central nervous system. *Int Rev Neurobiol* 27: 63–139, 1985.
498. **Dunwiddie TV.** Adenosine and ethanol: is there a caffeine connection in the actions of ethanol? In: *The "Drunken" Synapse: Studies of Alcohol-Related Disorders*, edited by Liu Y and Hunt WA. New York: Kluwer/Plenum, 1999, p. 119–133.
499. **Dunwiddie TV, Diao L, Proctor WR.** Adenine nucleotides undergo rapid, quantitative conversion to adenosine in the extracellular space in rat hippocampus. *J Neurosci* 17: 7673–7682, 1997.
500. **Dunwiddie TV, Masino SA.** The role and regulation of adenosine in the central nervous system. *Annu Rev Neurosci* 24: 31–55, 2001.
501. **Dutton JL, Hansen MA, Balcar VJ, Barden JA, Bennett MR.** Development of P2X receptor clusters on smooth muscle cells in relation to nerve varicosities in the rat urinary bladder. *J Neurocytol* 28: 4–16, 1999.
502. **Eccles JC.** The clinical significance of research work on the chemical transmitter substances of the nervous system. *Med J Aust* 44: 745–753, 1957.
503. **Eccles JC.** *The Physiology of Synapses*. Berlin: Springer-Verlag, 1964.
504. **Edwards AV, Jones CT.** Autonomic control of adrenal function. *J Anat* 183: 291–307, 1993.
505. **Edwards FA, Gibb AJ.** ATP—a fast neurotransmitter. *FEBS Lett* 325: 86–89, 1993.
506. **Edwards FA, Gibb AJ, Colquhoun D.** ATP receptor-mediated synaptic currents in the central nervous system. *Nature* 359: 144–147, 1992.
507. **Egan TM, Cox JA, Voigt MM.** Molecular cloning and functional characterization of the zebrafish ATP-gated ionotropic receptor P2X₃ subunit. *FEBS Lett* 475: 287–290, 2000.
508. **Egan TM, Samways DS, Li Z.** Biophysics of P2X receptors. *Pflügers Arch* 452: 501–512, 2006.

509. **Eika B, Salling LN, Christensen LL, Andersen A, Laurberg S, Danielsen CC.** Long-term observation of the detrusor smooth muscle in rats. Its relationship to ovariectomy and estrogen treatment. *Urol Res* 18: 439–442, 1990.
510. **Ekman M, Andersson KE, Arner A.** Developmental regulation of nerve and receptor mediated contractions of mammalian urinary bladder smooth muscle. *Eur J Pharmacol* 532: 99–106, 2006.
511. **Ekokoski E, Webb TE, Simon J, Tornquist K.** Mechanisms of P2 receptor-evoked DNA synthesis in thyroid FRTL-5 cells. *J Cell Physiol* 187: 166–175, 2001.
512. **Ekonomou A, Angelatou F, Vergnes M, Kostopoulos G.** Lower density of A1 adenosine receptors in nucleus reticularis thalami in rats with genetic absence epilepsy. *Neuroreport* 9: 2135–2140, 1998.
513. **Ekström J, Asztely A, Tobin G.** Parasympathetic non-adrenergic, non-cholinergic mechanisms in salivary glands and their role in reflex secretion. *Eur J Morphol* 36 Suppl: 208–212, 1998.
514. **Ekström J, Henningsson AC, Henningsson S, Malmberg L.** Hyperplasia and hypertrophy in the denervated and distended rat urinary bladder. *Acta Physiol Scand* 122: 45–48, 1984.
515. **Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES.** The sympathetic nerve—an integrative interface between two supersystems: the brain and the immune system. *Pharmacol Rev* 52: 595–638, 2000.
516. **Ellis JL, Burnstock G.** Neuropeptide Y neuromodulation of sympathetic co-transmission in the guinea-pig vas deferens. *Br J Pharmacol* 100: 457–462, 1990.
517. **Ellis JL, Burnstock G.** Modulation by prostaglandin E₂ of ATP and noradrenaline co-transmission in the guinea-pig vas deferens. *J Auton Pharmacol* 10: 363–372, 1990.
518. **Emmelin N, Feldberg W.** Systemic effects of adenosine triphosphate. *Br J Pharmacol Chemother* 3: 273–284, 1948.
519. **Endoh T.** Modulation of voltage-dependent calcium channels by neurotransmitters and neuropeptides in parasympathetic submandibular ganglion neurons. *Arch Oral Biol* 49: 539–557, 2004.
520. **Ennion SJ, Powell AD, Seward EP.** Identification of the P2Y₁₂ receptor in nucleotide inhibition of exocytosis from bovine chromaffin cells. *Mol Pharmacol* 66: 601–611, 2004.
521. **Erb L, Liao Z, Seye CI, Weisman GA.** P2 receptors: intracellular signaling. *Pflügers Arch* 452: 552–562, 2006.
522. **Eriksson J, Bongehiell U, Kidd E, Matthews B, Fried K.** Distribution of P2X₃ receptors in the rat trigeminal ganglion after inferior alveolar nerve injury. *Neurosci Lett* 254: 37–40, 1998.
523. **Ergene E, Dunbar JC, O'Leary DS, Barraco RA.** Activation of P₂-purinoceptors in the nucleus tractus solitarius mediate depressor responses. *Neurosci Lett* 174: 188–192, 1994.
524. **Erlinge D.** Extracellular ATP: a growth factor for vascular smooth muscle cells. *Gen Pharmacol* 31: 1–8, 1998.
525. **Eroglu L, Tuna R, Caglayan B.** Effects of nifedipine and Bay K 8644 on the R-PLA and caffeine-induced changes in the locomotor activity of rats. *Pharmacol Res* 33: 141–144, 1996.
526. **Evans RJ, Derkach V, Surprenant A.** ATP mediates fast synaptic transmission in mammalian neurons. *Nature* 357: 503–505, 1992.
527. **Evans RJ, Surprenant A.** Vasoconstriction of guinea-pig submucosal arterioles following sympathetic nerve stimulation is mediated by the release of ATP. *Br J Pharmacol* 106: 242–249, 1992.
528. **Ewald DA.** Potentiation of postjunctional cholinergic sensitivity of rat diaphragm muscle by high-energy-phosphate adenine nucleotides. *J Membr Biol* 29: 47–65, 1976.
529. **Exley C, Korchazhkina OV.** Promotion of formation of amyloid fibrils by aluminium adenosine triphosphate (AlATP). *J Inorg Biochem* 84: 215–224, 2001.
530. **Fabbretti E, D'Arco M, Fabbro A, Simonetti M, Nistri A, Giniatullin R.** Delayed upregulation of ATP P2X₃ receptors of trigeminal sensory neurons by calcitonin gene-related peptide. *J Neurosci* 26: 6163–6171, 2006.
531. **Facer P, Knowles CH, Tam PK, Ford AP, Dyer N, Baecker PA, Anand P.** Novel capsaicin (VR1) and purinergic (P2X₃) receptors in Hirschsprung's intestine. *J Pediatr Surg* 36: 1679–1684, 2001.
532. **Fam SR, Gallagher CJ, Salter MW.** P2Y₁ purinoceptor-mediated Ca²⁺ signaling and Ca²⁺ wave propagation in dorsal spinal cord astrocytes. *J Neurosci* 20: 2800–2808, 2000.
533. **Fang X, Hu HZ, Gao N, Liu S, Wang GD, Wang XY, Xia Y, Wood JD.** Neurogenic secretion mediated by the purinergic P2Y₁ receptor in guinea-pig small intestine. *Eur J Pharmacol* 536: 113–122, 2006.
534. **Farahbakhsh NA, Cilluffo MC.** P2 purinergic receptor-coupled signaling in the rabbit ciliary body epithelium. *Invest Ophthalmol Vis Sci* 43: 2317–2325, 2002.
535. **Färber K, Kettenmann H.** Purinergic signaling and microglia. *Pflügers Arch* 452: 615–621, 2006.
536. **Fedan JS, Hogaboom GK, O'Donnell JP, Colby J, Westfall DP.** Contributions by purines to the neurogenic response of the vas deferens of the guinea-pig. *Eur J Pharmacol* 69: 41–53, 1981.
537. **Feldberg W, Hebb C.** The stimulating action of phosphate compounds on the perfused superior cervical ganglion of the cat. *J Physiol* 107: 210–221, 1948.
538. **Feldberg W, Sherwood PD.** Injections of drugs into the lateral ventricle of the cat. *J Physiol* 123: 148–167, 1954.
539. **Fellin T, Carmignoto G.** Neurone-to-astrocyte signalling in the brain represents a distinct multifunctional unit. *J Physiol* 559: 3–15, 2004.
540. **Fellin T, Sul JS, D'Ascenzo M, Takano H, Pascual O, Haydon PG.** Bidirectional astrocyte-neuron communication: the many roles of glutamate and ATP. In: *Novartis Foundation Symposium 276 Purinergic Signalling in Neuron-Glial Interactions*, Chichester, UK: Wiley, 2006, p. 208–221.
541. **Feng C, Mery AG, Beller EM, Favot C, Boyce JA.** Adenine nucleotides inhibit cytokine generation by human mast cells through a G_s-coupled receptor. *J Immunol* 173: 7539–7547, 2004.
542. **Fenton RA, Dickson EW, Meyer TE, Dobson JG Jr.** Aging reduces the cardioprotective effect of ischemic preconditioning in the rat heart. *J Mol Cell Cardiol* 32: 1371–1375, 2000.
543. **Feranchak AP, Fitz JG.** Purinergic receptors and hepatobiliary function. *Curr Top Membr* 54: 395–414, 2003.
544. **Ferguson DR, Kennedy I, Burton TJ.** ATP is released from rabbit urinary bladder epithelial cells by hydrostatic pressure changes—a possible sensory mechanism? *J Physiol* 505: 503–511, 1997.
545. **Ferrari D, Munerati M, Melchiorri L, Hanau S, Di Virgilio F, Baricordi OR.** Responses to extracellular ATP of lymphoblastoid cell lines from Duchenne muscular dystrophy patients. *Am J Physiol Cell Physiol* 267: C886–C892, 1994.
546. **Ferrari D, Pizzirani C, Adinolfi E, Lemoli RM, Curti A, Idzko M, Panther E, Di Virgilio F.** The P2X₇ receptor: a key player in IL-1 processing and release. *J Immunol* 176: 3877–3883, 2006.
547. **Ferré S, Ciruela F, Canals M, Marcellino D, Burgueno J, Casadó V, Hillion J, Torvinen M, Fanelli F, Benedetti PP, Goldberg SR, Bouvier M, Fuxe K, Agnati LF, Lluís C, Franco R, Woods A.** Adenosine A_{2A}-dopamine D₂ receptor-receptor heteromers. Targets for neuro-psychiatric disorders. *Parkinsonism Relat Disord* 10: 265–271, 2004.
548. **Ferré S, Fredholm BB, Morelli M, Popoli P, Fuxe K.** Adenosine-dopamine receptor-receptor interactions as an integrative mechanism in the basal ganglia. *Trends Neurosci* 20: 482–487, 1997.
549. **Ferreira ZS, Markus RP.** Characterisation of P2Y₁-like receptor in cultured rat pineal glands. *Eur J Pharmacol* 415: 151–156, 2001.
550. **Fiacco TA, McCarthy KD.** Intracellular astrocyte calcium waves in situ increase the frequency of spontaneous AMPA receptor currents in CA1 pyramidal neurons. *J Neurosci* 24: 722–732, 2004.
551. **Fieber LA, Adams DJ.** Adenosine triphosphate-evoked currents in cultured neurones dissociated from rat parasympathetic cardiac ganglia. *J Physiol* 434: 239–256, 1991.
552. **Fields D, Burnstock G.** Purinergic signaling in neuron-glia interactions. *Nature Neurosci* Rev 7: 423–436, 2006.
553. **Fields RD.** Myelination: an overlooked mechanism of synaptic plasticity? *Neuroscientist* 11: 528–531, 2005.
554. **Fields RD, Stevens-Graham B.** New insights into neuron-glia communication. *Science* 298: 556–562, 2002.
555. **Filippov AK, Choi RC, Simon J, Barnard EA, Brown DA.** Activation of P2Y₁ nucleotide receptors induces inhibition of the M-type K⁺ current in rat hippocampal pyramidal neurons. *J Neurosci* 26: 9340–9348, 2006.

556. **Filippov AK, Simon J, Barnard EA, Brown DA.** Coupling of the nucleotide P2Y₄ receptor to neuronal ion channels. *Br J Pharmacol* 138: 400–406, 2003.
557. **Filippov AK, Webb TE, Barnard EA, Brown DA.** P2Y₂ nucleotide receptors expressed heterologously in sympathetic neurons inhibit both N-type Ca²⁺ and M-type K⁺ currents. *J Neurosci* 18: 5170–5179, 1998.
558. **Finger TE, Danilova V, Barrows J, Bartel DL, Vigers AJ, Stone L, Hellekant G, Kinnamon SC.** ATP signaling is crucial for communication from taste buds to gustatory nerves. *Science* 310: 1495–1499, 2005.
559. **Fischer KG, Saueressig U, Jacobshagen C, Wichelmann A, Pavenstädt H.** Extracellular nucleotides regulate cellular functions of podocytes in culture. *Am J Physiol Renal Physiol* 281: F1075–F1081, 2001.
560. **Fitz JG, Basavappa S, McGill J, Melhus O, Cohn JA.** Regulation of membrane chloride currents in rat bile duct epithelial cells. *J Clin Invest* 91: 319–328, 1993.
561. **Flavahan NA, Vanhoutte P.** Sympathetic purinergic vasoconstriction and thermosensitivity in a canine cutaneous vein. *J Pharmacol Exp Ther* 239: 784–789, 1986.
562. **Fleischhauer JC, Mitchell CH, Peterson-Yantorno K, Coca-Prados M, Civan MM.** PGE₂, Ca²⁺, cAMP mediate ATP activation of Cl⁻ channels in pigmented ciliary epithelial cells. *Am J Physiol Cell Physiol* 281: C1614–C1623, 2001.
563. **Florenzano F, Viscomi MT, Cavaliere F, Volonté C, Molinari M.** Cerebellar lesion up-regulates P2X₁ and P2X₂ purinergic receptors in precerebellar nuclei. *Neuroscience* 115: 425–434, 2002.
564. **Florenzano F, Viscomi MT, Mercaldo V, Longone P, Bernardi G, Bagni C, Molinari M, Carrive P.** P2X₂R purinergic receptor subunit mRNA and protein are expressed by all hypothalamic hypocretin/orexin neurons. *J Comp Neurol* 498: 58–67, 2006.
565. **Fong AY, Krstew EV, Barden J, Lawrence AJ.** Immunoreactive localisation of P2Y₁ receptors within the rat and human nodose ganglia and rat brainstem: comparison with [α -³³P]deoxyadenosine 5'-triphosphate autoradiography. *Neuroscience* 113: 809–823, 2002.
566. **Fontanez DE, Porter JT.** Adenosine A₁ receptors decrease thalamic excitation of inhibitory and excitatory neurons in the barrel cortex. *Neuroscience* 137: 1177–1184, 2006.
567. **Ford AP, Gever JR, Nunn PA, Zhong Y, Cefalu JS, Dillon MP, Cockayne DA.** Purinoceptors as therapeutic targets for lower urinary tract dysfunction. *Br J Pharmacol* 147 Suppl 2: S132–S143, 2006.
568. **Foresta C, Rossato M, Nogara A, Gottardello F, Bordon P, Di Virgilio F.** Role of P2-purinergic receptors in rat Leydig cell steroidogenesis. *Biochem J* 320: 499–504, 1996.
569. **Forrester T, Lind AR.** Identification of adenosine triphosphate in human plasma and the concentration in the venous effluent of forearm muscles before, during and after sustained contractions. *J Physiol* 204: 347–364, 1969.
570. **Fowler CJ.** Integrated control of lower urinary tract: clinical perspective. *Br J Pharmacol* 147: S14–S24, 2006.
571. **Francke M, Weick M, Pannicke T, Uckermann O, Grosche J, Goczalik I, Milenkovic I, Uhlmann S, Faude F, Wiedemann P, Reichenbach A, Bringmann A.** Upregulation of extracellular ATP-induced Muller cell responses in a dispass model of proliferative vitreoretinopathy. *Invest Ophthalmol Vis Sci* 43: 870–881, 2002.
572. **Franke H, Grummich B, Härtig W, Grosche J, Regenthal R, Edwards RH, Illes P, Krügel U.** Changes in purinergic signaling after cerebral injury—involvement of glutamatergic mechanisms? *Int J Dev Neurosci* 24: 123–132, 2006.
573. **Franke H, Günther A, Grosche J, Schmidt R, Rossner S, Reinhardt R, Faber-Zuschratter H, Schneider D, Illes P.** P2X₇ receptor expression after ischemia in the cerebral cortex of rats. *J Neuropathol Exp Neurol* 63: 686–699, 2004.
574. **Franke H, Illes P.** Involvement of P2 receptors in the growth and survival of neurons in the CNS. *Pharmacol Ther* 109: 297–324, 2006.
575. **Franke H, Kittner H, Grosche J, Illes P.** Enhanced P2Y₁ receptor expression in the brain after sensitisation with D-amphetamine. *Psychopharmacology* 167: 187–194, 2003.
576. **Franke H, Klimke K, Brinckmann U, Grosche J, Francke M, Sperlagh B, Reichenbach A, Liebert UG, Illes P.** P2X₇ receptor-mRNA and -protein in the mouse retina; changes during retinal degeneration in BALB/c mice. *Neurochem Int* 47: 235–242, 2005.
577. **Franke H, Krügel U, Illes P.** P2 receptors and neuronal injury. *Pflügers Arch* 452: 622–644, 2006.
578. **Fredholm BB.** Adenosine and lipolysis. *Int J Obes* 5: 643–649, 1981.
579. **Fredholm BB.** Purinoceptors in the nervous system. *Pharmacol Toxicol* 76: 228–239, 1995.
580. **Fredholm BB.** Adenosine and neuroprotection. In: *Neuroprotective Agents and Cerebral Ischaemia*, edited by Green AR and Cross AJ. San Diego, CA: Academic, 1997, p. 259–280.
581. **Fredholm BB, Chen JF, Masino SA, Vaugeois JM.** Actions of adenosine at its receptors in the CNS: insights from knockouts and drugs. *Annu Rev Pharmacol Toxicol* 45: 385–412, 2005.
582. **Fredholm BB, IJerman AP, Jacobson KA, Klotz KN, Linden J.** International Union of Pharmacology. XXV. Nomenclature and classification of adenosine receptors. *Pharmacol Rev* 53: 527–552, 2001.
583. **Frenguelli BG, Llaudet E, Dale N.** High-resolution real-time recording with microelectrode biosensors reveals novel aspects of adenosine release during hypoxia in rat hippocampal slices. *J Neurochem* 86: 1506–1515, 2003.
584. **Fries JE, Goczalik IM, Wheeler-Schilling TH, Kohler K, Guenther E, Wolf S, Wiedemann P, Bringmann A, Reichenbach A, Francke M, Pannicke T.** Identification of P2Y receptor subtypes in human Muller glial cells by physiology, single cell RT-PCR, immunohistochemistry. *Invest Ophthalmol Vis Sci* 46: 3000–3007, 2005.
585. **Frohlich R, Boehm S, Illes P.** Pharmacological characterization of P₂ purinoceptor types in rat locus coeruleus neurons. *Eur J Pharmacol* 315: 255–261, 1996.
586. **Fu WM.** Regulatory role of ATP at developing neuromuscular junctions. *Prog Neurobiol* 47: 31–44, 1995.
587. **Fu WM, Chen YH, Lee KF, Liou JC.** Regulation of quantal transmitter secretion by ATP and protein kinases at developing neuromuscular synapses. *Eur J Neurosci* 9: 676–685, 1997.
588. **Fu XW, Nurse CA, Cutz E.** Expression of functional purinergic receptors in pulmonary neuroepithelial bodies and their role in hypoxia chemotransmission. *Biol Chem* 385: 275–284, 2004.
589. **Fuder H, Muth U.** ATP and endogenous agonists inhibit evoked [³H]-noradrenaline release in rat iris via A₁ and P_{2y}-like purinoceptors. *Naunyn-Schmiedeberg Arch Pharmacol* 348: 352–357, 1993.
590. **Fujii K, Miyashita Y.** *Pigment Cell*. Basel: Karger, 1976.
591. **Fujii S, Kuroda Y, Ito K, Kato H.** Long-term potentiation induction: a synaptic catch mechanism released by extracellular phosphorylation. *Neuroscience* 96: 259–266, 2000.
592. **Fujii S, Sasaki H, Mikoshiba K, Kuroda Y, Yamazaki Y, Mostafa TA, Kato H.** A chemical LTP induced by co-activation of metabotropic and N-methyl-D-aspartate glutamate receptors in hippocampal CA1 neurons. *Brain Res* 999: 20–28, 2004.
593. **Fukui M, Nakagawa T, Minami M, Satoh M.** Involvement of β 2-adrenergic and μ -opioid receptors in antinociception produced by intracerebroventricular administration of α, β -methylene-ATP. *Jpn J Pharmacol* 86: 423–428, 2001.
594. **Fukui M, Takishita A, Zhang N, Nakagawa T, Minami M, Satoh M.** Involvement of locus coeruleus noradrenergic neurons in supraspinal antinociception by α, β -methylene-ATP in rats. *J Pharmacol Sci* 94: 153–160, 2004.
595. **Fukushi Y.** Heterologous desensitization of muscarinic receptors by P_{2z} purinoceptors in rat parotid acinar cells. *Eur J Pharmacol* 364: 55–64, 1999.
596. **Fuldner HH, Stadler H.** ³¹P-NMR analysis of synaptic vesicles. Status of ATP and internal pH. *Eur J Biochem* 121: 519–524, 1982.
597. **Fulgenzi A, Dell'Antonio G, Foglieni C, Dal CE, Ticozzi P, Franzone JS, Ferrero ME.** Inhibition of chemokine expression in rat inflamed paws by systemic use of the antihyperalgesic oxidized ATP. *BMC Immunol* 6: 18, 2005.
598. **Fumagalli M, Brambilla R, D'Ambrosi N, Volonte C, Matteoli M, Verderio C, Abbraccio MP.** Nucleotide-mediated calcium

- signaling in rat cortical astrocytes: role of P2X and P2Y receptors. *Glia* 43: 218–303, 2003.
599. **Fumagalli M, Ceruti S, Verderio C, Abbracchio MP.** ATP as a neurotransmitter of pain in migraine: a functional role for P2Y receptors in primary cultures from mouse trigeminal sensory ganglia. *Purinergic Signalling* 2: 120–121, 2006.
 600. **Funk GD, Kanjhan R, Walsh C, Lipski J, Comer AM, Parkis MA, Housley GD.** P2 receptor excitation of rodent hypoglossal motoneuron activity in vitro and in vivo: a molecular physiological analysis. *J Neurosci* 17: 6325–6337, 1997.
 601. **Furness JB.** *The Enteric Nervous System*. Massachusetts: Blackwell, 2006.
 602. **Furness JB, Campbell GR, Gillard SM, Malmfors T, Cobb JL, Burnstock G.** Cellular studies of sympathetic denervation produced by 6-hydroxydopamine in the vas deferens. *J Pharmacol Exp Ther* 174: 111–122, 1970.
 603. **Furness JB, Kunze WA, Bertrand PP, Clerc N, Bornstein JC.** Intrinsic primary afferent neurons of the intestine. *Prog Neurobiol* 54: 1–18, 1998.
 604. **Furness JB, Morris JL, Gibbins IL, Costa M.** Chemical coding of neurons and plurichemical transmission. *Annu Rev Pharmacol Toxicol* 29: 289–306, 1989.
 605. **Furuyama A, Koganezawa M, Shimada I.** Multiple receptor sites for nucleotide reception in the labellar taste receptor cells of the fleshfly *Boettcherisca peregrina*. *J Insect Physiol* 45: 249–255, 1999.
 606. **Furuzono S, Nakayama S, Imaizumi Y.** Purinergic modulation of pacemaker Ca^{2+} activity in interstitial cells of Cajal. *Neuropharmacology* 48: 264–273, 2005.
 607. **Fuxe K, Ferre S, Zoli M, Agnati LF.** Integrated events in central dopamine transmission as analyzed at multiple levels. Evidence for intramembrane adenosine A2A/dopamine D2 and adenosine A1/dopamine D1 receptor interactions in the basal ganglia. *Brain Res* 26: 258–273, 1998.
 608. **Fyffe REW, Perl ER.** Is ATP a central synaptic mediator for certain primary afferent fibres from mammalian skin? *Proc Natl Acad Sci USA* 81: 6890–6893, 1984.
 609. **Gale JE, Piazza V, Ciubotaru CD, Mammano F.** A mechanism for sensing noise damage in the inner ear. *Curr Biol* 14: 526–529, 2004.
 610. **Galindo A, Krnjevic K, Schwartz S.** Micro-iontophoretic studies on neurones in the cuneate nucleus. *J Physiol* 192: 359–377, 1967.
 611. **Galkin AV, Giniatullin RA, Mukhtarov MR, Svandova I, Grishin SN, Vyskocil F.** ATP but not adenosine inhibits non-quantal acetylcholine release at the mouse neuromuscular junction. *Eur J Neurosci* 13: 2047–2053, 2001.
 612. **Gallacher DV.** Are there purinergic receptors on parotid acinar cells? *Nature* 296: 83–86, 1982.
 613. **Galligan JJ.** Pharmacology of synaptic transmission in the enteric nervous system. *Curr Opin Pharmacol* 2: 623–629, 2002.
 614. **Galligan JJ.** Enteric P2X receptors as potential targets for drug treatment of the irritable bowel syndrome. *Br J Pharmacol* 141: 1294–1302, 2004.
 615. **Galligan JJ, North RA.** Pharmacology and function of nicotinic acetylcholine and P2X receptors in the enteric nervous system. *Neurogastroenterol Motil* 16 Suppl 1: 64–70, 2004.
 616. **Galun R, Kabayo JP.** Gorging response of *Glossinia palpalis palpalis* to ATP analogues. *Physiol Entomol* 13: 419–423, 1988.
 617. **Galun R, Kindler S.** Chemical basis of feeding in the tick *Ornithodoros tholozani*. *J Insect Physiol* 14: 1409–1421, 1968.
 618. **Gao N, Hu HZ, Zhu MX, Fang X, Liu S, Gao C, Wood JD.** The P2Y₁ purinergic receptor expressed by enteric neurones in guinea-pig intestine. *Neurogastroenterol Motil* 18: 316–323, 2006.
 619. **Gao Z, Kehoe V, Sinoway LI, Li J.** Spinal P2X receptor modulates reflex pressor response to activation of muscle afferents. *Am J Physiol Heart Circ Physiol* 288: H2238–H2243, 2005.
 620. **García-Leccea M, Sen RP, Soto F, Miras-Portugal MT, Castro E.** P2 receptors in cerebellar neurons: molecular diversity of ionotropic ATP receptors in Purkinje cells. *Drug Dev Res* 52: 104–113, 2001.
 621. **Garcia-Marcos M, Pochet S, Marino A, Dehaye JP.** P2X₇ and phospholipid signalling: the search of the “missing link” in epithelial cells. *Cell Signal* 18: 2098–2104, 2006.
 622. **Gartland A, Hipskind RA, Gallagher JA, Bowler WB.** Expression of a P2X₇ receptor by a subpopulation of human osteoblasts. *J Bone Miner Res* 16: 846–856, 2001.
 623. **Gauda EB, Northington FJ, Linden J, Rosin DL.** Differential expression of A_{2a}, A₁-adenosine and D₂-dopamine receptor genes in rat peripheral arterial chemoreceptors during postnatal development. *Brain Res* 872: 1–10, 2000.
 624. **Gayle S, Burnstock G.** Immunolocalisation of P2X and P2Y nucleotide receptors in the rat nasal mucosa. *Cell Tissue Res* 319: 27–36, 2005.
 625. **Gaytan SP, Saadani-Makki F, Bodineau L, Frugière A, Larnicol N, Pásaro R.** Effect of postnatal exposure to caffeine on the pattern of adenosine A₁ receptor distribution in respiration-related nuclei of the rat brainstem. *Auton Neurosci* 126–127: 339–346, 2006.
 626. **Geary C, Akinbi H, Korfhagen T, Fabre JE, Boucher R, Rice W.** Increased susceptibility of purinergic receptor-deficient mice to lung infection with *Pseudomonas aeruginosa*. *Am J Physiol Lung Cell Mol Physiol* 289: L890–L895, 2005.
 627. **Geffen LB, Livett BG.** Synaptic vesicles in sympathetic neurons. *Physiol Rev* 51: 98–157, 1971.
 628. **Geiger JD, LaBella FS, Nagy JI.** Characterization and localization of adenosine receptors in rat spinal cord. *J Neurosci* 4: 2303–2310, 1984.
 629. **Gendron FP, Chalimoniuk M, Strosznajder J, Shen S, Gonzalez FA, Weisman GA, Sun GY.** P2X₇ nucleotide receptor activation enhances IFN γ -induced type II nitric oxide synthase activity in BV-2 microglial cells. *J Neurochem* 87: 344–352, 2003.
 630. **Genton L, Kudsk KA.** Interactions between the enteric nervous system and the immune system: role of neuropeptides and nutrition. *Am J Surg* 186: 253–258, 2003.
 631. **Gerevich Z, Borvendeg SJ, Schroder W, Franke H, Wirkner K, Norenberg W, Furst S, Gillen C, Illes P.** Inhibition of N-type voltage-activated calcium channels in rat dorsal root ganglion neurons by P2Y receptors is a possible mechanism of ADP-induced analgesia. *J Neurosci* 24: 797–807, 2004.
 632. **Gerevich Z, Müller C, Illes P.** Metabotropic P2Y₁ receptors inhibit P2X₃ receptor-channels in rat dorsal root ganglion neurons. *Eur J Pharmacol* 521: 34–38, 2005.
 633. **Gershon MD, Thompson EB.** The maturation of neuromuscular function in a multiply innervated structure: development of the longitudinal smooth muscle of the foetal mammalian gut and its cholinergic excitatory, adrenergic inhibitory, non-adrenergic inhibitory innervation. *J Physiol* 234: 257–277, 1973.
 634. **Gever J, Cockayne DA, Dillon MP, Burnstock G, Ford APDW.** Pharmacology of P2X channels. *Pflügers Arch* 452: 513–537, 2006.
 635. **Ghanem E, Robaye B, Leal T, Leipziger J, Van DW, Beauwens R, Boeynaems JM.** The role of epithelial P2Y₂ and P2Y₄ receptors in the regulation of intestinal chloride secretion. *Br J Pharmacol* 146: 364–369, 2005.
 636. **Ghildyal P, Manchanda R.** Neurotransmission by ATP: new insights, novel mechanisms. *Indian J Biochem Biophys* 39: 137–147, 2002.
 637. **Giaroni C, Knight GE, Ruan HZ, Glass R, Bardini M, Lecchini S, Frigo G, Burnstock G.** P2 receptors in the murine gastrointestinal tract. *Neuropharmacology* 43: 1313–1323, 2002.
 638. **Giaroni C, Knight GE, Zanetti E, Chiarelli RA, Lecchini S, Frigo G, Burnstock G.** Postnatal development of P2 receptors in the murine gastrointestinal tract. *Neuropharmacology* 50: 690–704, 2006.
 639. **Gibb AJ, Halliday FC.** Fast purinergic transmission in the central nervous system. *Semin Neurosci* 8: 225–232, 1996.
 640. **Gil-Rodrigo CE, Gomez R, Gandarias JM, Galdiz B, Carou M, Bergaretxe I, Vallejo A, Ainz LF.** Effect of adenosine 5'-triphosphate on secretagogue-stimulated (¹⁴C)-aminopyrine accumulation by rabbit isolated gastric glands. *Gen Physiol Biophys* 12: 27–36, 1993.
 641. **Gilchrist LS, Cain DM, Harding-Rose C, Kov AN, Wendelschafer-Crabb G, Kennedy WR, Simone DA.** Re-organiza-

- tion of P2X₃ receptor localization on epidermal nerve fibers in a murine model of cancer pain. *Brain Res* 1044: 197–205, 2005.
642. **Gillespie JH**. The biological significance of the linkages in adenosine triphosphoric acid. *J Physiol* 80: 345–359, 1934.
643. **Gillespie JS**. Non-adrenergic, non-cholinergic inhibitory control of gastrointestinal motility. In: *Motility of the Digestive Tract*, edited by Wienbeck M. New York: Raven, 1982, p. 51–66.
644. **Giménez-Llort L, Masino SA, Diao L, Fernández-Teruel A, Tobeña A, Halldner L, Fredholm BB**. Mice lacking the adenosine A₁ receptor have normal spatial learning and plasticity in the CA1 region of the hippocampus, but they habituate more slowly. *Synapse* 57: 8–16, 2005.
645. **Ginés S, Hillion J, Torvinen M, Le Crom S, Casadó V, Canela EI, Rondin S, Lew JY, Watson S, Zoli M, Agnati LF, Verniera P, Lluís C, Ferré S, Fuxe K, Franco R**. Dopamine D1 and adenosine A1 receptors form functionally interacting heteromeric complexes. *Proc Natl Acad Sci USA* 97: 8606–8611, 2000.
646. **Giniatullin AR, Grishin SN, Sharifullina ER, Petrov AM, Zefirov AL, Giniatullin RA**. Reactive oxygen species contribute to the presynaptic action of extracellular ATP at the frog neuromuscular junction. *J Physiol* 565: 229–242, 2005.
647. **Ginsborg BL, Hirst GDS**. The effect of adenosine on the release of the transmitter from the phrenic nerve of the rat. *J Physiol* 224: 629–645, 1972.
648. **Giovannelli L, Giovannini MG, Pedata F, Pepeu G**. Purinergic modulation of cortical acetylcholine release is decreased in aging rats. *Exp Gerontol* 23: 175–181, 1988.
649. **Giraldez L, Diaz-Hernandez M, Gomez-Villafuertes R, Pintor J, Castro E, Miras-Portugal MT**. Adenosine triphosphate and diadenosine pentaphosphate induce [Ca²⁺]_i increase in rat basal ganglia aminergic terminals. *J Neurosci Res* 64: 174–182, 2001.
650. **Glänzel M, Bültmann R, Starke K, Frahm AW**. Structure-activity relationships of novel P2-receptor antagonists structurally related to Reactive Blue 2. *Eur J Med Chem* 40: 1262–1276, 2005.
651. **Glass M, Dragunow M, Faull RL**. The pattern of neurodegeneration in Huntington's disease: a comparative study of cannabinoid, dopamine, adenosine and GABA_A receptor alterations in the human basal ganglia in Huntington's disease. *Neuroscience* 97: 505–519, 2000.
652. **Glass R, Bardini M, Robson T, Burnstock G**. Expression of nucleotide P2X receptor subtypes during spermatogenesis in the adult rat testis. *Cells Tissues Org* 169: 377–387, 2001.
653. **Glass R, Burnstock G**. Immunohistochemical identification of cells expressing ATP-gated cation channels (P2X receptors) in the adult rat thyroid. *J Anat* 198: 569–579, 2001.
654. **Glushakov AV, Glushakova HY, Skok VI**. Two types of P_{2X}-purinoceptors in neurons of the guinea pig ileum submucous plexus. *Neurophysiology* 30: 242–245, 1998.
655. **Glushakov AV, Melishchuk AI, Skok VI**. ATP-induced currents in submucous plexus neurons of the guinea-pig small intestine. *Neurophysiology* 28: 77–85, 1996.
656. **Göcmen C, Giesselman B, de Groot WC**. Effect of neocuproine, a copper(i) chelator, on rat bladder function. *J Pharmacol Exp Ther* 312: 1138–1143, 2005.
657. **Goding JW, Grobden B, Slegers H**. Physiological and pathophysiological functions of the ecto-nucleotide pyrophosphatase/phosphodiesterase family. *Biochim Biophys Acta* 1638: 1–19, 2003.
658. **Gomes P, Srinivas SP, Vereecke J, Himpens B**. ATP-dependent paracrine intercellular communication in cultured bovine corneal endothelial cells. *Invest Ophthalmol Vis Sci* 46: 104–113, 2005.
659. **Gómez-Villafuertes R, Pintor J, Gualix J, Miras-Portugal MT**. GABA_B receptor-mediated presynaptic potentiation of ATP ionotropic receptors in rat midbrain synaptosomes. *Neuropharmacology* 44: 311–323, 2003.
660. **Gordon GR, Baimoukhametova DV, Hewitt SA, Rajapaksha WR, Fisher TE, Bains JS**. Norepinephrine triggers release of glial ATP to increase postsynaptic efficacy. *Nat Neurosci* 8: 1078–1086, 2005.
661. **Gordon JL**. Extracellular ATP: effects, sources and fate. *Biochem J* 233: 309–319, 1986.
662. **Gottwald TP, Hewlett BR, Lhotak S, Stead RH**. Electrical stimulation of the vagus nerve modulates the histamine content of mast cells in the rat jejunal mucosa. *Neuroreport* 7: 313–317, 1995.
663. **Gounaris K, Selkirk ME**. Parasite nucleotide-metabolizing enzymes and host purinergic signalling. *Trends Parasitol* 21: 17–21, 2005.
664. **Gourine AV**. On the peripheral and central chemoreception and control of breathing: an emerging role of ATP. *J Physiol* 568: 715–724, 2005.
665. **Gourine AV, Atkinson L, Deuchars J, Spyer KM**. Purinergic signalling in the medullary mechanisms of respiratory control in the rat: respiratory neurones express the P2X₂ receptor subunit. *J Physiol* 552: 197–211, 2003.
666. **Gourine AV, Dale N, Gourine VN, Spyer KM**. Fever in systemic inflammation: roles of purines. *Front Biosci* 9: 1011–1022, 2004.
667. **Gourine AV, Laudet E, Dale N, Spyer KM**. Release of ATP in the ventral medulla during hypoxia in rats: role in hypoxic ventilatory response. *J Neurosci* 25: 1211–1218, 2005.
668. **Gourine AV, Laudet E, Dale N, Spyer KM**. ATP is a mediator of chemosensory transduction in the central nervous system. *Nature* 436: 108–111, 2005.
669. **Gourine AV, Melenchuk EV, Poputnikov DM, Gourine VN, Spyer KM**. Involvement of purinergic signalling in central mechanisms of body temperature regulation in rats. *Br J Pharmacol* 135: 2047–2055, 2002.
670. **Grandadam F, Lluet P, Palea S, Martin DJ**. Pharmacological and urodynamic changes in rat urinary bladder function after multiple pregnancies. *BJU Int* 84: 861–866, 1999.
671. **Grapengiesser E, Salehi A, Qader SS, Hellman B**. Glucose induces glucagon release pulses antisynchronous with insulin and sensitive to purinoceptor inhibition. *Endocrinology* 147: 3472–3477, 2006.
672. **Green PG, Basbaum AI, Helms C, Levine JD**. Purinergic regulation of bradykinin-induced plasma extravasation and adjuvant-induced arthritis in the rat. *Proc Natl Acad Sci USA* 88: 4162–4165, 1991.
673. **Green PG, Luo J, Heller P, Levine JD**. Modulation of bradykinin-induced plasma extravasation in the rat knee joint by sympathetic co-transmitters. *Neuroscience* 52: 451–458, 1993.
674. **Green ST**. Intrathyroidal autonomic nerves can directly influence hormone release from rat thyroid follicles: a study in vitro employing electrical field stimulation and intracellular microelectrodes. *Clin Sci* 72: 233–238, 1987.
675. **Greenwood D, Yao WP, Housley GD**. Expression of the P2X₂ receptor subunit of the ATP-gated ion channel in the retina. *Neuroreport* 8: 1083–1088, 1997.
676. **Greig AVH, James SE, McGrouther DA, Terenghi G, Burnstock G**. Purinergic receptor expression in the regenerating epidermis in a rat model of normal and delayed wound healing. *Exp Dermatol* 12: 860–871, 2003.
677. **Greig AVH, Linge C, Cambrey A, Burnstock G**. Purinergic receptors are part of a signalling system for keratinocyte proliferation, differentiation and apoptosis in human fetal epidermis. *J Invest Dermatol* 121: 1145–1149, 2003.
678. **Grishin S, Shakirzyanova A, Giniatullin A, Afzalov R, Giniatullin R**. Mechanisms of ATP action on motor nerve terminals at the frog neuromuscular junction. *Eur J Neurosci* 21: 1271–1279, 2005.
679. **Groenewegen HJ, Uylings HB**. The prefrontal cortex and the integration of sensory, limbic and autonomic information. *Prog Brain Res* 126: 3–28, 2000.
680. **Gromada J, Jorgensen TD, Dissing S**. Role of protein kinase C in the regulation of inositol phosphate production and Ca²⁺ mobilization evoked by ATP and acetylcholine in rat lacrimal acini. *Pflügers Arch* 429: 578–586, 1995.
681. **Gröschel-Stewart U, Bardini M, Robson T, Burnstock G**. Localisation of P2X₅ and P2X₇ receptors by immunohistochemistry in rat stratified squamous epithelia. *Cell Tissue Res* 296: 599–605, 1999.
682. **Gröschel-Stewart U, Bardini M, Robson T, Burnstock G**. P2X receptors in the rat duodenal villus. *Cell Tissue Res* 297: 111–117, 1999.

683. **Grubb BD, Evans RJ.** Characterization of cultured dorsal root ganglion neuron P2X receptors. *Eur J Neurosci* 11: 149–154, 1999.
684. **Gruehagen JA, Lovell P, Moroz LL, Yeung ES.** Monitoring real-time release of ATP from the molluscan central nervous system. *J Neurosci Methods* 139: 145–152, 2004.
685. **Grunditz T, Hakanson R, Sundler F, Uddman R.** Neuronal pathways to the rat thyroid revealed by retrograde tracing and immunocytochemistry. *Neuroscience* 24: 321–335, 1988.
686. **Gu JG, Heft MW.** P2X receptor-mediated purinergic sensory pathways to the spinal cord dorsal horn. *Purinergic Signalling* 1: 11–16, 2004.
687. **Gu JG, MacDermott AB.** Activation of ATP P2X receptors elicits glutamate release from sensory neuron synapses. *Nature* 389: 749–753, 1997.
688. **Gu YZ, Yin GF, Guan BC, Li ZW.** Characteristics of P2X purinoceptors in the membrane of rat trigeminal ganglion neurons. *Sheng Li Xue Bao* 58: 164–170, 2006.
689. **Gualix J, Gómez-Villafuertes R, Díaz-Hernández M, Miras-Portugal MT.** Presence of functional ATP and dinucleotide receptors in glutamatergic synaptic terminals from rat midbrain. *J Neurochem* 87: 160–171, 2003.
690. **Guo A, Vulchanova L, Wang J, Li X, Elde R.** Immunocytochemical localization of the vanilloid receptor 1 (VR1): relationship to neuropeptides, the P2X₃ purinoceptor and IB4 binding sites. *Eur J Neurosci* 11: 946–958, 1999.
691. **Guo LH, Schluesener HJ.** Lesional accumulation of P2X₄ receptor⁺ macrophages in rat CNS during experimental autoimmune encephalomyelitis. *Neuroscience* 134: 199–205, 2005.
692. **Guo LH, Trautmann K, Schluesener HJ.** Expression of P2X₄ receptor by lesional activated microglia during formalin-induced inflammatory pain. *J Neuroimmunol* 163: 120–127, 2005.
693. **Gür S, Karahan ST.** Effects of adenosine 5'-triphosphate, adenosine and acetylcholine in urinary bladder and colon muscles from streptozotocin diabetic rats. *Arzneimittelforschung* 47: 1226–1229, 1997.
694. **Gür S, Öztürk B.** Altered relaxant responses to adenosine and adenosine 5'-triphosphate in the corpus cavernosum from men and rats with diabetes. *Pharmacology* 60: 105–112, 2000.
695. **Gustafsson LE, Wiklund NP.** Adenosine-modulation of cholinergic and non-adrenergic non-cholinergic neurotransmission in the rabbit iris sphincter. *Br J Pharmacol* 88: 197–204, 1986.
696. **Guthrie PB, Knappenberger J, Segal M, Bennett MV, Charles AC, Kater SB.** ATP released from astrocytes mediates glial calcium waves. *J Neurosci* 19: 520–528, 1999.
697. **Guzman SJ, Gerevich Z, Hengstler JG, Illes P, Kleemann W.** P2Y₁ receptors inhibit both strength and plasticity of glutamatergic synaptic neurotransmission in the rat prefrontal cortex. *Synapse* 57: 235–238, 2005.
698. **Haas B, Schipke CG, Peters O, Söhl G, Willecke K, Kettenmann H.** Activity-dependent ATP-waves in the mouse neocortex are independent from astrocytic calcium waves. *Cereb Cortex* 16: 237–246, 2006.
699. **Haines WR, Torres GE, Voigt MM, Egan TM.** Properties of the novel ATP-gated ionotropic receptor composed of the P2X₁ and P2X₂ isoforms. *Mol Pharmacol* 56: 720–727, 1999.
700. **Halliday FC, Gibb AJ.** Single-channel properties of P2X ATP receptors in rat cerebellar slices (Abstract). *J Physiol* 504: 51P, 1997.
701. **Hamilton SG, McMahon SB.** ATP as a peripheral mediator of pain. *J Auton Nerv Syst* 81: 187–194, 2000.
702. **Hamilton SG, McMahon SB, Lewin GR.** Selective activation of nociceptors by P2X receptor agonists in normal and inflamed rat skin. *J Physiol* 534: 437–445, 2001.
703. **Han WJ, Kim SY, Lee YB.** Neuroprotective effect of extracellular ATP induced interleukin-10 expression in an in vitro model of brain ischemia. *2004 Abstract Viewer/Itinerary Planner; Program no 100 1 Society for Neuroscience, Washington, DC 2004.*
704. **Hanahisa Y, Yamaguchi M.** Increase of Ca²⁺-ATPase activity in the brain microsomes of rats with increasing ages: involvement of protein kinase C. *Brain Res Bull* 46: 329–332, 1998.
705. **Hanani M.** Satellite glial cells in sensory ganglia: from form to function. *Brain Res* 48: 457–476, 2005.
706. **Hanna RL, Kaufman MP.** Role played by purinergic receptors on muscle afferents in evoking the exercise pressor reflex. *J Appl Physiol* 94: 1437–1445, 2003.
707. **Hansen MA, Dutton JL, Balcar VJ, Barden JA, Bennett MR.** P_{2X} (purinergic) receptor distributions in rat blood vessels. *J Auton Nerv Syst* 75: 147–155, 1999.
708. **Hansen O.** Blood nucleoside and nucleotide studies in mental disease. *Br J Psychiatry* 121: 341–350, 1972.
709. **Hansen O, Dimitrakoudi M.** The relation of blood adenosine triphosphate to changes of mood in affective disorders. *Br J Psychiatry* 125: 268–274, 1974.
710. **Harms L, Finta EP, Tschöpl M, Illes P.** Depolarization of rat locus coeruleus neurons by adenosine 5'-triphosphate. *Neuroscience* 48: 941–952, 1992.
711. **Harvey RA, Skennerton DE, Newgreen D, Fry CH.** The contractile potency of adenosine triphosphate and ecto-adenosine triphosphatase activity in guinea pig detrusor and detrusor from patients with a stable, unstable or obstructed bladder. *J Urol* 168: 1235–1239, 2002.
712. **Haskó G, Pacher P, Vizi ES, Illes P.** Adenosine receptor signaling in the brain immune system. *Trends Pharmacol Sci* 26: 511–516, 2005.
713. **Haskó G, Szabó C.** Regulation of cytokine and chemokine production by transmitters and co-transmitters of the autonomic nervous system. *Biochem Pharmacol* 56: 1079–1087, 1998.
714. **Haulica I, Ababei L, Branisteanu D, Topoliceanu F, Busuioac A.** Preliminary data on the possible hypnogenic role of adenosine. *Rev Roum Physiol* 10: 275–279, 1973.
715. **Hauser RA, Schwarzschild MA.** Adenosine A_{2A} receptor antagonists for Parkinson's disease: rationale, therapeutic potential and clinical experience. *Drugs Aging* 22: 471–482, 2005.
716. **Häussinger D, Stehle T, Gerok W.** Actions of extracellular UTP and ATP in perfused rat liver. A comparative study. *Eur J Biochem* 167: 65–71, 1987.
717. **Hausmann R, Rettinger J, Gerevich Z, Meis S, Kassack MU, Illes P, Lambrecht G, Schmalzing G.** The suramin analog 4,4',4''',4''''-(carbonylbis(imino-5,1,3-benzenetriylbis(carbonylimino)))tetra-kis-benzenesulfonic acid (NF110) potently blocks P2X₃ receptors: subtype selectivity is determined by location of sulfonic acid groups. *Mol Pharmacol* 69: 2058–2067, 2006.
718. **Hayashi T, Kawakami M, Sasaki S, Katsumata T, Mori H, Yoshida H, Nakahari T.** ATP regulation of ciliary beat frequency in rat tracheal and distal airway epithelium. *Exp Physiol* 90: 535–544, 2005.
719. **Haydon PG.** GLIA: listening and talking to the synapse. *Nat Rev Neurosci* 2: 185–193, 2001.
720. **Hayton MJ, Dillon JP, Glynn D, Curran JM, Gallagher JA, Buckley KA.** Involvement of adenosine 5'-triphosphate in ultrasound-induced fracture repair. *Ultrasound Med Biol* 31: 1131–1138, 2005.
721. **He L, Chen J, Dinger B, Stensaas L, Fidone S.** Effect of chronic hypoxia on purinergic synaptic transmission in rat carotid body. *J Appl Physiol* 100: 157–162, 2006.
722. **He ML, Gonzalez-Iglesias AE, Stojilkovic SS.** Role of nucleotide P2 receptors in calcium signaling and prolactin release in pituitary lactotrophs. *J Biol Chem* 278: 46270–46277, 2003.
723. **He ML, Gonzalez-Iglesias AE, Tomic M, Stojilkovic SS.** Release and extracellular metabolism of ATP by ecto-nucleotidase eNTPDase 1–3 in hypothalamic and pituitary cells. *Purinergic Signalling* 1: 135–144, 2005.
724. **Hedqvist P, Fredholm BB.** Effects of adenosine on adrenergic neurotransmission: prejunctional inhibition and postjunctional enhancement. *Naunyn-Schmiedeberg Arch Pharmacol* 293: 217–223, 1976.
725. **Hegg CC, Greenwood D, Huang W, Han P, Lucero MT.** Activation of purinergic receptor subtypes modulates odor sensitivity. *J Neurosci* 23: 8291–8301, 2003.
726. **Hegg CC, Lucero MT.** Purinergic receptor antagonists inhibit odorant-induced heat shock protein 25 induction in mouse olfactory epithelium. *Glia* 53: 182–190, 2006.
727. **Heilbronn E, Eriksson H.** Second messengers mobilized by ATP and ACh in the myotube/muscle fiber. In: *Neuromuscular Junc-*

- tion, edited by Sellin LC, Libelius R, and Thesleff S. Amsterdam: Elsevier, 1989, p. 395–404.
728. **Heine C, Heimrich B, Vogt J, Wegner A, Illes P, Franke H.** P₂ receptor-stimulation influences axonal outgrowth in the developing hippocampus in vitro. *Neuroscience* 138: 303–311, 2006.
 729. **Heinemann A, Shahbazian A, Barthó L, Holzer P.** Different receptors mediating the inhibitory action of exogenous ATP and endogenously released purines on guinea-pig intestinal peristalsis. *Br J Pharmacol* 128: 313–320, 1999.
 730. **Hemmings-Mieszczak M, Dorn G, Natt FJ, Hall J, Wishart WL.** Independent combinatorial effect of antisense oligonucleotides and RNAi-mediated specific inhibition of the recombinant rat P₂X₃ receptor. *Nucleic Acids Res* 31: 2117–2126, 2003.
 731. **Henderson VE, Roepke MH.** The role of acetylcholine in bladder contractile mechanisms and in parasympathetic ganglia. *J Pharmacol Exp Ther* 51: 97–111, 1934.
 732. **Henning RH.** Purinoceptors in neuromuscular transmission. *Pharmacol Ther* 74: 115–128, 1997.
 733. **Hentschel S, Lewerenz A, Nieber K.** Activation of A₃ receptors by endogenous adenosine inhibits synaptic transmission during hypoxia in rat cortical neurons. *Restor Neurol Neurosci* 21: 55–63, 2003.
 734. **Henz SL, Ribeiro CG, Rosa A, Chiarelli RA, Casali EA, Sarkis JJ.** Kinetic characterization of ATP diphosphohydrolase and 5'-nucleotidase activities in cells cultured from submandibular salivary glands of rats. *Cell Biol Int* 30: 214–220, 2006.
 735. **Herlenius E, Lagercrantz H.** Adenosinergic modulation of respiratory neurones in the neonatal rat brainstem in vitro. *J Physiol* 518: 159–172, 1999.
 736. **Hervás C, Perez-Sen R, Miras-Portugal MT.** Coexpression of functional P₂X and P₂Y nucleotide receptors in single cerebellar granule cells. *J Neurosci Res* 73: 384–399, 2003.
 737. **Hervás C, Pérez-Sen R, Miras-Portugal MT.** Presence of diverse functional P₂X receptors in rat cerebellar synaptic terminals. *Biochem Pharmacol* 70: 770–785, 2005.
 738. **Hide I, Tanaka M, Inoue A, Nakajima K, Kohsaka S, Inoue K, Nakata Y.** Extracellular ATP triggers tumor necrosis factor- α release from rat microglia. *J Neurochem* 75: 965–972, 2000.
 739. **Hill CE, Phillips JK, Sandow SL.** Development of peripheral autonomic synapses: neurotransmitter receptors, neuroeffector associations and neural influences. *Clin Exp Pharmacol Physiol* 26: 581–590, 1999.
 740. **Hillaire-Buys D, Bertrand G, Chapal J, Puech R, Ribes G, Loubatieres-Mariani MM.** Stimulation of insulin secretion and improvement of glucose tolerance in rat and dog by the P₂Y-purinoceptor agonist, adenosine-5'-O-(2-thiodiphosphate). *Br J Pharmacol* 109: 183–187, 1993.
 741. **Hillarp NA, Nilson B, Hogberg B.** Adenosine triphosphate in the adrenal medulla of the cow. *Nature* 176: 1032–1033, 1955.
 742. **Hillman KA, Woolf AS, Johnson TM, Wade A, Unwin RJ, Winyard PJ.** The P₂X₇ ATP receptor modulates renal cyst development in vitro. *Biochem Biophys Res Commun* 322: 434–439, 2004.
 743. **Himms-Hagen J, Cui J, Lynn Sigurdson S.** Sympathetic and sensory nerves in control of growth of brown adipose tissue: effects of denervation and of capsaicin. *Neurochem Int* 17: 271–279, 1990.
 744. **Hiruma H, Bourque CW.** P₂ purinoceptor-mediated depolarization of rat supraoptic neurosecretory cells in vitro. *J Physiol* 489: 805–811, 1995.
 745. **Hisatome I, Ishiko R, Miyakoda H, Saito M, Kitamura H, Kinugawa T, Kobayashi M, Kotake H, Mashiba H, Sato R.** Excess purine degradation caused by an imbalance in the supply of adenosine triphosphate in patients with congestive heart failure. *Br Heart J* 64: 359–361, 1990.
 746. **Hoebertz A, Arnett TR, Burnstock G.** Regulation of bone resorption and formation by purines and pyrimidines. *Trends Pharmacol Sci* 24: 290–297, 2003.
 747. **Hoesch RE, Yienger K, Weinreich D, Kao JP.** Coexistence of functional IP₃ and ryanodine receptors in vagal sensory neurons and their activation by ATP. *J Neurophysiol* 88: 1212–1219, 2002.
 748. **Hogan YH, Hawkins R, Alkadhi KA.** Adenosine A₁ receptor activation inhibits LTP in sympathetic ganglia. *Brain Res* 807: 19–28, 1998.
 749. **Hoheisel U, Reinohl J, Unger T, Mense S.** Acidic pH and capsaicin activate mechanosensitive group IV muscle receptors in the rat. *Pain* 110: 149–157, 2004.
 750. **Hökfelt T, Fuxe K, Pernow B.** *Coexistence of Neuronal Messengers: A New Principle in Chemical Transmission. Progress in Brain Research.* Amsterdam: Elsevier, 1986, vol. 68, p. 1–411.
 751. **Holck MI, Marks BH.** Purine nucleoside and nucleotide interactions on normal and subsensitive alpha adrenoreceptor responsiveness in guinea-pig vas deferens. *J Pharmacol Exp Ther* 205: 104–117, 1978.
 752. **Holgate ST.** The identification of the adenosine A₂B receptor as a novel therapeutic target in asthma. *Br J Pharmacol* 145: 1009–1015, 2005.
 753. **Hollins B, Ikeda SR.** Heterologous expression of a P₂X-purinoceptor in rat chromaffin cells detects vesicular ATP release. *J Neurophysiol* 78: 3069–3076, 1997.
 754. **Hollopeter G, Jantzen HM, Vincent D, Li G, England L, Ramakrishnan V, Yang RB, Nurden P, Nurden A, Julius D, Conley PB.** Identification of the platelet ADP receptor targeted by antithrombotic drugs. *Nature* 409: 202–207, 2001.
 755. **Holton FA, Holton P.** The capillary dilator substances in dry powders of spinal roots: a possible role of adenosine triphosphate in chemical transmission from nerve endings. *J Physiol* 126: 124–140, 1954.
 756. **Holton P.** The liberation of adenosine triphosphate on antidromic stimulation of sensory nerves. *J Physiol* 145: 494–504, 1959.
 757. **Holzer P.** Gastrointestinal pain in functional bowel disorders: sensory neurons as novel drug targets. *Expert Opin Ther Targets* 8: 107–123, 2004.
 758. **Hong K, Driscoll M.** A transmembrane domain of the putative channel subunit MEC-4 influences mechanotransduction and neurodegeneration in *C. elegans*. *Nature* 367: 470–473, 1994.
 759. **Honore P, Mikusa J, Bianchi B, McDonald H, Cartmell J, Faltynek C, Jarvis MF.** TNP-ATP, a potent P₂X₃ receptor antagonist, blocks acetic acid-induced abdominal constriction in mice: comparison with reference analgesics. *Pain* 96: 99–105, 2002.
 760. **Höpker VH, Saffrey MJ, Burnstock G.** Neurite outgrowth of striatal neurons in vitro: involvement of purines in the growth promoting effect of myenteric plexus explants. *Int J Dev Neurosci* 14: 439–451, 1996.
 761. **Horiuchi J, Potts PD, Tagawa T, Dampney RAL.** Effects of activation and blockade of P₂X receptors in the ventrolateral medulla on arterial pressure and sympathetic activity. *J Auton Nerv Syst* 76: 118–126, 1999.
 762. **Hou M, Malmisjo M, Moller S, Pantev E, Bergdahl A, Zhao XH, Sun XY, Hedner T, Edvinsson L, Erlinge D.** Increase in cardiac P₂X₁- and P₂Y₂-receptor mRNA levels in congestive heart failure. *Life Sci* 65: 1195–1206, 1999.
 763. **Hou M, Möller S, Edvinsson L, Erlinge D.** Cytokines induce upregulation of vascular P₂Y₂ receptors and increased mitogenic responses to UTP and ATP. *Arterioscler Thromb Vasc Biol* 20: 2064–2069, 2000.
 764. **Hourani SM.** Postnatal development of purinoceptors in rat visceral smooth muscle preparations. *Gen Pharmacol* 32: 3–7, 1999.
 765. **Housley GD, Marcotti W, Navaratnam D, Yamoah EN.** Hair cells: beyond the transducer. *J Membr Biol* 209: 89–118, 2006.
 766. **Hoyle CHV.** Purinergic cotransmission: parasympathetic and enteric nerves. *Semin Neurosci* 8: 207–215, 1996.
 767. **Hoyle CHV, Greenberg MJ.** Actions of adenylyl compounds in invertebrates from several phyla: evidence for internal purinoceptors. *Comp Biochem Physiol* 90: 113–122, 1988.
 768. **Hoyle CHV, Reilly WM, Lincoln J, Burnstock G.** Adrenergic, but not cholinergic or purinergic, responses are potentiated in the cecum of diabetic rats. *Gastroenterology* 94: 1357–1367, 1988.
 769. **Hu B, Chiang CY, Hu JW, Dostrovsky JO, Sessle BJ.** P₂X receptors in trigeminal subnucleus caudalis modulate central sensitization in trigeminal subnucleus oralis. *J Neurophysiol* 88: 1614–1624, 2002.

770. **Hu HZ, Gao N, Lin Z, Gao C, Liu S, Ren J, Xia Y, Wood JD.** P2X₇ receptors in the enteric nervous system of guinea-pig small intestine. *J Comp Neurol* 440: 299–310, 2001.
771. **Hu HZ, Gao N, Zhu MX, Liu S, Ren J, Gao C, Xia Y, Wood JD.** Slow excitatory synaptic transmission mediated by P2Y₁ receptors in the guinea-pig enteric nervous system. *J Physiol* 550: 493–504, 2003.
772. **Hu ST, Gever J, Nunn PA, Ford AP, Zhu QM.** Cystometric studies with ATP, PPADS and TNP-ATP in conscious and anaesthetised C57BL/6 mice. *J Urol* 171: 461–462, 2004.
773. **Huang H, Wu X, Nicol GD, Meller S, Vasko MR.** ATP augments peptide release from rat sensory neurons in culture through activation of P2Y receptors. *J Pharmacol Exp Ther* 306: 1137–1144, 2003.
774. **Huang LC, Greenwood D, Thorne PR, Housley GD.** Developmental regulation of neuron-specific P2X₃ receptor expression in the rat cochlea. *J Comp Neurol* 484: 133–143, 2005.
775. **Huang LC, Ryan AF, Cockayne DA, Housley GD.** Developmentally regulated expression of the P2X₃ receptor in the mouse cochlea. *Histochem Cell Biol* 125: 681–692, 2006.
776. **Huang SM, Kitamura A, Akita T, Narita K, Kuba K.** Adenosine depresses a Ca²⁺-independent step in transmitter exocytosis at frog motor nerve terminals. *Eur J Neurosci* 15: 1291–1298, 2002.
777. **Huber A, Padrun V, Déglon N, Aebischer P, Möhler H, Boison D.** Grafts of adenosine-releasing cells suppress seizures in kindling epilepsy. *Proc Natl Acad Sci USA* 98: 7611–7616, 2001.
778. **Hubscher CH, Petruska JC, Rau KK, Johnson RD.** Co-expression of P2X receptor subunits on rat nodose neurons that bind the isolectin GS-IB₄. *Neuroreport* 12: 2995–2997, 2001.
779. **Hugel S, Schlichter R.** Presynaptic P2X receptors facilitate inhibitory GABAergic transmission between cultured rat spinal cord dorsal horn neurons. *J Neurosci* 20: 2121–2130, 2000.
780. **Hughes J, Vane JR.** An analysis of the responses of the isolated portal vein of the rabbit to electrical stimulation and to drugs. *Br J Pharmacol Chemother* 30: 46–466, 1967.
781. **Hukovic S, Rand MJ, Vanov S.** Observations on an isolated, innervated preparation of rat urinary bladder. *Br J Pharmacol Chemother* 24: 178–188, 1965.
782. **Hwang IK, Lee HY, Yoo KY, Seong NS, Chung HG, Kim JH, Lee HJ, Lee WH, Kang TC, Won MH.** Chronological alterations of P2X₃ receptor expression in the trigeminal ganglion after ischaemic insult in the Mongolian gerbil. *Anat Histol Embryol* 33: 220–224, 2004.
783. **Iacobas DA, Suadicani SO, Spray DC, Scemes E.** A stochastic two-dimensional model of intercellular Ca²⁺ wave spread in glia. *Biophys J* 90: 24–41, 2006.
784. **Ichikawa H, De Repentigny Y, Kothary R, Sugimoto T.** The survival of vagal and glossopharyngeal sensory neurons is dependent upon dystonin. *Neuroscience* 137: 531–536, 2006.
785. **Ichikawa H, Fukunaga T, Jin HW, Fujita M, Takano-Yamamoto T, Sugimoto T.** VRL-1- and P2X₃ receptor-immunoreactive innervation of the rat temporomandibular joint. *Brain Res* 1008: 131–136, 2004.
786. **Igawa Y, Mattiasson A, Andersson KE.** Functional importance of cholinergic and purinergic neurotransmission for micturition contraction in the normal, unanaesthetized rat. *Br J Pharmacol* 109: 473–479, 1993.
787. **Ikeda K, Suzuki M, Furukawa M, Takasaka T.** Calcium mobilization and entry induced by extracellular ATP in the non-sensory epithelial cell of the cochlear lateral wall. *Cell Calcium* 18: 89–99, 1995.
788. **Ikeuchi Y, Nishizaki T.** ATP-evoked potassium currents in rat striatal neurons are mediated by a P2 purinergic receptor. *Neurosci Lett* 190: 89–92, 1995.
789. **Ikeuchi Y, Nishizaki T.** P₂ purinoceptor-operated potassium channel in rat cerebellar neurons. *Biochem Biophys Res Commun* 218: 67–71, 1996.
790. **Ikeuchi Y, Nishizaki T, Mori M, Okada Y.** Adenosine activates the K⁺ channel and enhances cytosolic Ca²⁺ release via a P2Y purinoceptor in hippocampal neurons. *Eur J Pharmacol* 304: 191–199, 1996.
791. **Ikeuchi Y, Nishizaki T, Okada Y.** A P₂ purinoceptor activated by ADP in rat medullar neurons. *Neurosci Lett* 198: 71–74, 1995.
792. **Illes P, Ribeiro JA.** Molecular physiology of P2 receptors in the central nervous system. *Eur J Pharmacol* 483: 5–17, 2004.
793. **Illes P, Rickmann H, Brod I, Bucher B, Stoclet JC.** Subsensitization of presynaptic adenosine A₁-receptors in caudal arteries of spontaneously hypertensive rats. *Eur J Pharmacol* 174: 237–251, 1989.
794. **Illes P, Sevcik J, Finta EP, Frohlich R, Nieber K, Norenberg W.** Modulation of locus coeruleus neurons by extra- and intracellular adenosine 5'-triphosphate. *Brain Res Bull* 35: 513–519, 1994.
795. **Illes P, Wirkner K, Nörenberg W, Masino SA, Dunwiddie TV.** Interaction between the transmitters ATP and glutamate in the central nervous system. *Drug Dev Res* 52: 76–82, 2001.
796. **Illes P, Zimmermann H.** Nucleotides and their receptors in the nervous system. *Prog Brain Res* 120: 1–432, 1999.
797. **Impagnatiello F, Bastia E, Ongini E, Monopoli A.** Adenosine receptors in neurological disorders. *Emerging Therapeutic Targets* 4: 635–664, 2001.
798. **Innocenti B, Parpura V, Haydon PG.** Imaging extracellular waves of glutamate during calcium signaling in cultured astrocytes. *J Neurosci* 20: 1800–1808, 2000.
799. **Inoue K.** ATP receptors for the protection of hippocampal functions. *Jpn J Pharmacol* 78: 405–410, 1998.
800. **Inoue K.** Microglial activation by purines and pyrimidines. *Glia* 40: 156–163, 2002.
801. **Inoue K.** The function of microglia through purinergic receptors: neuropathic pain and cytokine release. *Pharmacol Ther* 109: 210–226, 2006.
802. **Inoue T, Kannan MS.** Nonadrenergic and noncholinergic excitatory neurotransmission in rat intrapulmonary artery. *Am J Physiol Heart Circ Physiol* 254: H1142–H1148, 1988.
803. **Inoue K, Koizumi S, Nakazawa K.** Glutamate-evoked release of adenosine 5'-triphosphate causing an increase in intracellular calcium in hippocampal neurons. *Neuroreport* 6: 437–440, 1995.
804. **Inoue K, Koizumi S, Ueno S.** Implication of ATP receptors in brain functions. *Prog Neurobiol* 50: 483–492, 1996.
805. **Inoue K, Koizumi S, Ueno S, Kita A, Tsuda M.** The functions of ATP receptors in the synaptic transmission in the hippocampus. *Prog Brain Res* 120: 193–206, 1999.
806. **Inoue K, Nakajima K, Morimoto T, Kikuchi Y, Koizumi S, Illes P, Kohsaka S.** ATP stimulation of Ca²⁺-dependent plasminogen release from cultured microglia. *Br J Pharmacol* 123: 1304–1310, 1998.
807. **Inoue K, Nakazawa K, Watano T, Ohara-Imaizumi M, Fujimori K, Takanaka A.** Dopamine receptor agonists and antagonists enhance ATP-activated currents. *Eur J Pharmacol* 215: 321–324, 1992.
808. **Ireland MF, Noakes PG, Bellingham MC.** P2X₇-like receptor subunits enhance excitatory synaptic transmission at central synapses by presynaptic mechanisms. *Neuroscience* 128: 269–280, 2004.
809. **Irnich D, Burgstahler R, Bostock H, Grafe P.** ATP affects both axons and Schwann cells of unmyelinated C fibres. *Pain* 92: 343–350, 2001.
810. **Irnich D, Tracey DJ, Polten J, Burgstahler R, Grafe P.** ATP stimulates peripheral axons in human, rat and mouse—differential involvement of A_{2B} adenosine and P2X purinergic receptors. *Neuroscience* 110: 123–129, 2002.
811. **Ishibashi T, Dakin KA, Stevens B, Lee PR, Kozlov SV, Stewart CL, Fields RD.** Astrocytes promote myelination in response to electrical impulses. *Neuron* 49: 823–832, 2006.
812. **Ishii K, Kaneda M, Li H, Rockland KS, Hashikawa T.** Neuron-specific distribution of P2X₇ purinergic receptors in the monkey retina. *J Comp Neurol* 459: 267–277, 2003.
813. **Ismayilova N, Crossman A, Verkhatsky A, Brotchie J.** Effects of adenosine A₁, dopamine D1 and metabotropic glutamate 5 receptors-modulating agents on locomotion of the reserpinised rats. *Eur J Pharmacol* 497: 187–195, 2004.
814. **Ito K, Dulon D.** Nonselective cation conductance activated by muscarinic and purinergic receptors in rat spiral ganglion neurons. *Am J Physiol Cell Physiol* 282: C1121–C1135, 2002.
815. **Jabs R, Guenther E, Marquardt K, Wheeler-Schilling TH.** Evidence for P2X₃, P2X₄, P2X₅ but not for P2X₇ containing puri-

- nergic receptors in Müller cells of the rat retina. *Brain Res* 76: 205–210, 2000.
816. **Jackson EK.** P1 and P2 receptors in the renal system. In: *Purinergic and Pyrimidinergic Signalling II: Cardiovascular, Respiratory, Immune, Metabolic and Gastrointestinal Tract Function*, edited by Abbracchio MP and Williams M. Berlin: Springer, 2001, p. 33–71.
817. **Jacobson KA, Gao ZG.** Adenosine receptors as therapeutic targets. *Nat Rev Drug Discov* 5: 247–264, 2006.
818. **Jacques-Silva MC, Rodnight R, Lenz G, Liao Z, Kong Q, Tran M, Kang Y, Gonzalez FA, Weisman GA, Neary JT.** P2X₇ receptors stimulate AKT phosphorylation in astrocytes. *Br J Pharmacol* 141: 1106–1117, 2004.
819. **Jahr CE, Jessell TM.** ATP excites a subpopulation of rat dorsal horn neurones. *Nature* 304: 730–733, 1983.
820. **Jakobi H, Spinar H, Kuhl KD, Lotz P, Haberland EJ.** Clinical and experimental use of ATP in internal ear diseases. *Acta Otolaryngol* 83: 195–199, 1977.
821. **James G, Butt AM.** P2Y and P2X purinoceptor mediated Ca²⁺ signalling in glial cell pathology in the central nervous system. *Eur J Pharmacol* 447: 247–260, 2002.
822. **James S, Richardson PJ.** Production of adenosine from extracellular ATP at the striatal cholinergic synapse. *J Neurochem* 60: 219–227, 1993.
823. **Jang IS, Rhee JS, Kubota H, Akaike N, Akaike N.** Developmental changes in P2X purinoceptors on glycinergic presynaptic nerve terminals projecting to rat substantia gelatinosa neurones. *J Physiol* 536: 505–519, 2001.
824. **Jänig W.** Spinal cord reflex organization of sympathetic systems. *Prog Brain Res* 107: 43–77, 1996.
825. **Jankowski J, Jankowski V, Seibt B, Henning L, Zidek W, Schlüter H.** Identification of dinucleoside polyphosphates in adrenal glands. *Biochem Biophys Res Commun* 304: 365–370, 2003.
826. **Jarvis MF.** Contributions of P2X₃ homomeric and heteromeric channels to acute and chronic pain. *Expert Opin Ther Targets* 7: 513–522, 2003.
827. **Jarvis MF, Burgard EC, McGaraughty S, Honore P, Lynch K, Brennan TJ, Subieta A, van Biesen T, Cartmell J, Bianchi B, Niforatos W, Kage K, Yu H, Mikusa J, Wismer CT, Zhu CZ, Chu K, Lee CH, Stewart AO, Polakowski J, Cox BF, Kowaluk E, Williams M, Sullivan J, Faltynek C.** A-317491, a novel potent and selective non-nucleotide antagonist of P2X₃ and P2X_{2/3} receptors, reduces chronic inflammatory and neuropathic pain in the rat. *Proc Natl Acad Sci USA* 99: 17179–17184, 2002.
828. **Jarvisch A, Landgrens S, Neill E, Zotterman Y.** Impulse activity in the carotid sinus nerve following intra-carotid injection of potassium chloride, veratrine, sodium citrate, adenosine-triphosphate and α -dinitrophenol. *Acta Physiol Scand* 25: 195–211, 1952.
829. **Jeftinija SD, Jeftinija KV.** ATP stimulates release of excitatory amino acids from cultured Schwann cells. *Neuroscience* 82: 927–934, 1998.
830. **Jenner FA, Vlissides DN, Kenyon P, Chard N, Grant L.** Mood and whole blood adenosine triphosphate. *Br J Psychiatry* 127: 478–481, 1975.
831. **Jennings EA, Christie MJ, Sessle BJ.** ATP potentiates neurotransmission in the rat trigeminal subnucleus caudalis. *Neuroreport* 17: 1507–1510, 2006.
832. **Jhandier MN, Kruglov EA, Lavoie EG, Sevigny J, Dranoff JA.** Portal fibroblasts regulate the proliferation of bile duct epithelia via expression of NTPDase2. *J Biol Chem* 280: 22986–22992, 2005.
833. **Jiang J, Gu J.** Expression of adenosine triphosphate P2X₃ receptors in rat molar pulp and trigeminal ganglia. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 94: 622–626, 2002.
834. **Jin YH, Bailey TW, Li BY, Schild JH, Andresen MC.** Purinergic and vanilloid receptor activation releases glutamate from separate cranial afferent terminals in nucleus tractus solitarius. *J Neurosci* 24: 4709–4717, 2004.
835. **Jo YH, Role LW.** Coordinate release of ATP and GABA at in vitro synapses of lateral hypothalamic neurons. *J Neurosci* 22: 4794–4804, 2002.
836. **Jo YH, Role LW.** Cholinergic modulation of purinergic and GABAergic co-transmission at in vitro hypothalamic synapses. *J Neurophysiol* 88: 2501–2508, 2002.
837. **Jo YH, Schlichter R.** Synaptic corelease of ATP and GABA in cultured spinal neurons. *Nat Neurosci* 2: 241–245, 1999.
838. **Johansson B, Georgiev V, Fredholm BB.** Distribution and postnatal ontogeny of adenosine A_{2A} receptors in rat brain: comparison with dopamine receptors. *Neuroscience* 80: 1187–1207, 1997.
839. **Johansson B, Halldner L, Dunwiddie TV, Masino SA, Poelchen W, Giménez-Llort L, Escorihuela RM, Fernández-Teruel A, Wiesenfeld-Hallin Z, Xu XJ, Hårdemark A, Betsholtz C, Herlenius E, Fredholm BB.** Hyperalgesia, anxiety, decreased hypoxic neuroprotection in mice lacking the adenosine A₁ receptor. *Proc Natl Acad Sci USA* 98: 9407–9412, 2001.
840. **Joles JA, Koomans HA.** Causes and consequences of increased sympathetic activity in renal disease. *Hypertension* 43: 699–706, 2004.
841. **Jones SL, Blikslager AT.** Role of the enteric nervous system in the pathophysiology of secretory diarrhea. *J Vet Intern Med* 16: 222–228, 2002.
842. **Jonz MG, Nurse CA.** Neuroepithelial cells and associated innervation of the zebrafish gill: a confocal immunofluorescence study. *J Comp Neurol* 461: 1–17, 2003.
843. **Jørgensen L, Mortensen SO, Colstrup H, Andersen JT.** Bladder distension in the management of detrusor instability. *Scand J Urol Nephrol* 19: 101–104, 1985.
844. **Jørgensen NR, Henriksen Z, Sorensen OH, Eriksen EF, Civitelli R, Steinberg TH.** Intercellular calcium signaling occurs between human osteoblasts and osteoclasts and requires activation of osteoclast P2X₇ receptors. *J Biol Chem* 277: 7574–7580, 2002.
845. **Joseph EK, Levine JD.** Mitochondrial electron transport in models of neuropathic and inflammatory pain. *Pain* 121: 105–114, 2006.
846. **Ju YK, Huang W, Jiang L, Barden JA, Allen DG.** ATP modulates intracellular Ca²⁺ and firing rate through a P2Y₁ purinoceptor in cane toad pacemaker cells. *J Physiol* 552: 777–787, 2003.
847. **Judelson DA, Armstrong LE, Sokmen B, Roti MW, Casa DJ, Kellogg MD.** Effect of chronic caffeine intake on choice reaction time, mood, visual vigilance. *Physiol Behav* 85: 629–634, 2005.
848. **Jumblatt JE, Jumblatt MM.** Regulation of ocular mucin secretion by P2Y₂ nucleotide receptors in rabbit and human conjunctiva. *Exp Eye Res* 67: 341–346, 1998.
849. **Jun D, Kim K.** ATP-mediated necrotic volume increase (NVI) in substantia nigra pars compacta dopaminergic neuron. *2004 Abstract Viewer/Itinerary Planner; Program no 222 18 Society for Neuroscience, Washington, DC 2004.*
850. **Jung SR, Kim MH, Hille B, Nguyen TD, Koh DS.** Regulation of exocytosis by purinergic receptors in pancreatic duct epithelial cells. *Am J Physiol Cell Physiol* 286: C573–C579, 2004.
851. **Jurányi Z, Orso E, Janossy A, Szalay KS, Sperlagh B, Windisch K, Vinson GP, Vizi ES.** ATP and [³H]noradrenaline release and the presence of ecto-Ca²⁺-ATPases in the capsule-glomerulosa fraction of the rat adrenal gland. *J Endocrinol* 153: 105–114, 1997.
852. **Kachroo A, Orlando LR, Grandy DK, Chen JF, Young AB, Schwarzschild MA.** Interactions between metabotropic glutamate 5 and adenosine A_{2A} receptors in normal and parkinsonian mice. *J Neurosci* 25: 10414–10419, 2005.
853. **Kafka SH, Corbett R.** Selective adenosine A_{2A} receptor/dopamine D₂ receptor interactions in animal models of schizophrenia. *Eur J Pharmacol* 295: 147–154, 1996.
854. **Kage K, Niforatos W, Zhu CZ, Lynch KJ, Honore P, Jarvis MF.** Alteration of dorsal root ganglion P2X₃ receptor expression and function following spinal nerve ligation in the rat. *Exp Brain Res* 147: 511–519, 2002.
855. **Kageyama S, Fujita K, Suzuki K, Shinbo H, Masuda N, Uchida W.** Effect of age on the responses of rat bladder detrusor strips to adenosine triphosphate. *BJU Int* 85: 899–904, 2000.
856. **Kakuyama M, Vallance P, Ahluwalia A.** Endothelium-dependent sensory NANC vasodilation: involvement of ATP, CGRP and a possible NO store. *Br J Pharmacol* 123: 310–316, 1998.
857. **Kalaria RN, Sromek S, Wilcox BJ, Unnerstall JR.** Hippocampal adenosine A₁ receptors are decreased in Alzheimer's disease. *Neurosci Lett* 118: 257–260, 1990.

858. **Kamei J, Takahashi Y.** Involvement of ionotropic purinergic receptors in the histamine-induced enhancement of the cough reflex sensitivity in guinea pigs. *Eur J Pharmacol* 547: 160–164, 2006.
859. **Kamei J, Takahashi Y, Yoshikawa Y, Saitoh A.** Involvement of P2X receptor subtypes in ATP-induced enhancement of the cough reflex sensitivity. *Eur J Pharmacol* 528: 158–161, 2005.
860. **Kamiji T, Morita K, Katayama Y.** ATP regulates synaptic transmission by pre- and postsynaptic mechanisms in guinea-pig myenteric neurons. *Neuroscience* 59: 165–174, 1994.
861. **Kamikawa Y, Cline WH, Su C.** Diminished purinergic modulation of the vascular adrenergic neurotransmission in spontaneously hypertensive rats. *Eur J Pharmacol* 66: 347–353, 1980.
862. **Kaneda M, Ishii K, Morishima Y, Akagi T, Yamazaki Y, Nakanishi S, Hashikawa T.** OFF-cholinergic-pathway-selective localization of P2X₂ purinoceptors in the mouse retina. *J Comp Neurol* 476: 103–111, 2004.
863. **Kang J, Jiang L, Goldman SA, Nedergaard M.** Astrocyte-mediated potentiation of inhibitory synaptic transmission. *Nat Neurosci* 1: 683–692, 1998.
864. **Kanjhan R, Housley GD, Burton LD, Christie DL, Kippenberger A, Thorne PR, Luo L, Ryan AF.** Distribution of the P2X₂ receptor subunit of the ATP-gated ion channels in the rat central nervous system. *J Comp Neurol* 407: 11–32, 1999.
865. **Kanjhan R, Housley GD, Thorne PR, Christie DL, Palmer DJ, Luo L, Ryan AF.** Localization of ATP-gated ion channels in cerebellum using P2X₂R subunit-specific antisera. *Neuroreport* 7: 2665–2669, 1996.
866. **Kaplan AD, Kilkenny DM, Hill DJ, Dixon SJ.** Extracellular nucleotides act through P2U purinoceptors to elevate [Ca²⁺]_i and enhance basic fibroblast growth factor-induced proliferation in sheep chondrocytes. *Endocrinology* 137: 4757–4766, 1996.
867. **Kapoor JR, Sladek CD.** Purinergic and adrenergic agonists synergize in stimulating vasopressin and oxytocin release. *J Neurosci* 20: 8868–8875, 2000.
868. **Kapoor JR, Sladek CD.** Substance P and NPY differentially potentiate ATP and adrenergic stimulated vasopressin and oxytocin release. *Am J Physiol Regul Integr Comp Physiol* 280: R69–R78, 2001.
869. **Karanjia R, García-Hernández LM, Miranda-Morales M, Soman N, Espinosa-Luna R, Montañó LM, Barajas-Lopez C.** Cross-inhibitory interactions between GABA_A and P2X channels in myenteric neurones. *Eur J Neurosci* 23: 3259–3268, 2006.
870. **Kardos J, Kovács I, Szárics E, Kovács R, Skuban N, Nyitrai G, Dobolyi A, Juhász G.** Uridine activates fast transmembrane Ca²⁺ ion fluxes in rat brain homogenates. *Neuroreport* 10: 1577–1582, 1999.
871. **Kasai Y, Ito S, Kitamura N, Ohta T, Nakazato Y.** On-line measurement of adenosine triphosphate and catecholamine released from adrenal chromaffin cells. *Comp Biochem Physiol A Mol Integr Physiol* 122: 363–368, 1999.
872. **Kasakov L, Burnstock G.** The use of the slowly degradable analog, α,β -methylene ATP, to produce desensitisation of the P₂-purinoceptor: effect on non-adrenergic, non-cholinergic responses of the guinea-pig urinary bladder. *Eur J Pharmacol* 86: 291–294, 1983.
873. **Kasakov L, Ellis J, Kirkpatrick K, Milner P, Burnstock G.** Direct evidence for concomitant release of noradrenaline, adenosine 5'-triphosphate and neuropeptide Y from sympathetic nerve supplying the guinea-pig vas deferens. *J Auton Nerv Syst* 22: 75–82, 1988.
874. **Kase H.** New aspects of physiological and pathophysiological functions of adenosine A_{2A} receptor in basal ganglia. *Biosci Biotechnol Biochem* 65: 1447–1457, 2001.
875. **Kaster MP, Rosa AO, Rosso MM, Goulart EC, Santos AR, Rodrigues AL.** Adenosine administration produces an antidepressant-like effect in mice: evidence for the involvement of A₁ and A_{2A} receptors. *Neurosci Lett* 355: 21–24, 2004.
876. **Kastritsis CH, McCarthy KD.** Oligodendroglial lineage cells express neurotrophin receptors. *Glia* 8: 106–113, 1993.
877. **Kataoka S, Toyono T, Seta Y, Ogura T, Toyoshima K.** Expression of P2Y₁ receptors in rat taste buds. *Histochem Cell Biol* 121: 419–426, 2004.
878. **Katayama Y, Morita K.** Adenosine 5'-triphosphate modulates membrane potassium conductance in guinea-pig myenteric neurones. *J Physiol* 408: 373–390, 1989.
879. **Kato F, Kawamura M, Shigetomi E, Tanaka J, Inoue K.** ATP- and adenosine-mediated signaling in the central nervous system: synaptic purinoceptors: the stage for ATP to play its “dual-role.” *J Pharmacol Sci* 94: 107–111, 2004.
880. **Kato F, Shigetomi E.** Distinct modulation of evoked and spontaneous EPSCs by purinoceptors in the nucleus tractus solitarii of the rat. *J Physiol* 530: 469–486, 2001.
881. **Katsuragi T, Su C.** Purine release from vascular adrenergic nerves by high potassium and a calcium ionophore A-23187. *J Pharmacol Exp Ther* 215: 685–690, 1980.
882. **Kawamura M, Matsui T, Niitsu A, Kondo T, Ohno Y, Nakanishi N.** Extracellular ATP stimulates steroidogenesis in bovine adrenocortical fasciculata cells via P2 purinoceptors. *Jpn J Pharmacol* 56: 543–545, 1991.
883. **Kaya N, Tanaka S, Koike T.** ATP selectively suppresses the synthesis of the inflammatory protein microglial response factor (MRF)-1 through Ca²⁺ influx via P2X₇ receptors in cultured microglia. *Brain Res* 952: 86–97, 2002.
884. **Ke HZ, Qi H, Weidema AF, Zhang Q, Panupinthu N, Crawford DT, Grasser WA, Paralkar VM, Li M, Audoly LP, Gabel CA, Jee WS, Dixon SJ, Sims SM, Thompson DD.** Deletion of the P2X₇ nucleotide receptor reveals its regulatory roles in bone formation and resorption. *Mol Endocrinol* 17: 1356–1367, 2003.
885. **Keele CA, Armstrong D.** *Substances Producing Pain and Itch.* London: Arnold, 1964.
886. **Keeton TK, Campbell WB.** The pharmacologic alteration of renin release. *Pharmacol Rev* 32: 81–227, 1980.
887. **Keller JT, Dimlich RV, Zuccarello M, Lanker L, Strauss TA, Fritts MJ.** Influence of the sympathetic nervous system as well as trigeminal sensory fibres on rat dural mast cells. *Cephalalgia* 11: 215–221, 1991.
888. **Kemp PA, Sugar RA, Jackson AD.** Nucleotide-mediated mucin secretion from differentiated human bronchial epithelial cells. *Am J Respir Cell Mol Biol* 31: 446–455, 2004.
889. **Kennedy C, Saville VL, Burnstock G.** The contributions of noradrenaline and ATP to the responses of the rabbit central ear artery to sympathetic nerve stimulation depend on the parameters of stimulation. *Eur J Pharmacol* 122: 291–300, 1986.
890. **Khakh BS.** Molecular physiology of P2X receptors and ATP signalling at synapses. *Nat Rev Neurosci* 2: 165–174, 2001.
891. **Khakh BS, Burnstock G, Kennedy C, King BF, North RA, Séguéla P, Voigt M, Humphrey PPA.** International Union of Pharmacology. XXIV. Current status of the nomenclature and properties of P2X receptors and their subunits. *Pharmacol Rev* 53: 107–118, 2001.
892. **Khakh BS, Fisher JA, Nashmi R, Bowser DN, Lester HA.** An angstrom scale interaction between plasma membrane ATP-gated P2X₂ and $\alpha_4\beta_2$ nicotinic channels measured with fluorescence resonance energy transfer and total internal reflection fluorescence microscopy. *J Neurosci* 25: 6911–6920, 2005.
893. **Khakh BS, Gittermann D, Cockayne DA, Jones A.** ATP modulation of excitatory synapses onto interneurons. *J Neurosci* 23: 7426–7437, 2003.
894. **Khakh BS, Henderson G.** ATP receptor-mediated enhancement of fast excitatory neurotransmitter release in the brain. *Mol Pharmacol* 54: 372–378, 1998.
895. **Khakh BS, Humphrey PP, Henderson G.** ATP-gated cation channels (P2X purinoceptors) in trigeminal mesencephalic nucleus neurons of the rat. *J Physiol* 498: 709–715, 1997.
896. **Khakh BS, Humphrey PPA, Surprenant A.** Electrophysiological properties of P2X₂-purinoceptors in rat superior cervical, nodose and guinea-pig coeliac neurones. *J Physiol* 484: 385–395, 1995.
897. **Khakh BS, North RA.** P2X receptors as cell-surface ATP sensors in health and disease. *Nature* 442: 527–532, 2006.
898. **Khakh BS, Smith WB, Chiu CS, Ju D, Davidson N, Lester HA.** Activation-dependent changes in receptor distribution and dendritic morphology in hippocampal neurons expressing P2X₂-green fluorescent protein receptors. *Proc Natl Acad Sci USA* 98: 5288–5293, 2001.

899. **Khalifa M, El-Mahmoudy A, Shiina T, Shimizu Y, Nikami H, El-Sayed M, Kobayashi H, Takewaki T.** An electrophysiological study of excitatory purinergic neuromuscular transmission in longitudinal smooth muscle of chicken anterior mesenteric artery. *Br J Pharmacol* 144: 830–839, 2005.
900. **Kharlamov A, Jones SC, Kim DK.** Suramin reduces infarct volume in a model of focal brain ischemia in rats. *Exp Brain Res* 147: 353–359, 2002.
901. **Kidd EJ, Miller KJ, Sansum AJ, Humphrey PPA.** Evidence for P2X₃ receptors in the developing rat brain. *Neuroscience* 87: 533–539, 1998.
902. **Kien ND, White DA, Reitan JA, Eisele JH Jr.** Cardiovascular function during controlled hypotension induced by adenosine triphosphate or sodium nitroprusside in the anesthetized dog. *Anesth Analg* 66: 103–110, 1987.
903. **Kiernan JA.** Action of adenosine triphosphate on mast cells in normal and denervated skin. *Arch Dermatol Forsch* 251: 83–86, 1974.
904. **Kim C, Chung JM, Chung K.** Changes in the gene expression of six subtypes of P2X receptors in rat dorsal root ganglion after spinal nerve ligation. *Neurosci Lett* 337: 81–84, 2003.
905. **Kim CH, Kim SS, Choi JY, Shin JH, Kim JY, Namkung W, Lee JG, Lee MG, Yoon JH.** Membrane-specific expression of functional purinergic receptors in normal human nasal epithelial cells. *Am J Physiol Lung Cell Mol Physiol* 287: L835–L842, 2004.
906. **Kim DS, Kwak SE, Kim JE, Ho Won M, Kang TC.** The co-treatments of vigabatrin and P2X receptor antagonists protect ischemic neuronal cell death in the gerbil hippocampus. *Brain Res* 1120: 151–160, 2006.
907. **Kim JH, Nam JH, Kim MH, Koh DS, Choi SJ, Kim SJ, Lee JE, Min KM, Uhm DY, Kim SJ.** Purinergic receptors coupled to intracellular Ca²⁺ signals and exocytosis in rat prostate neuroendocrine cells. *J Biol Chem* 279: 27345–27356, 2004.
908. **Kim WK, Hawthorn M, Rabin RA.** Differential effects of chronic ethanol exposure on ATP- and bradykinin-induced increases in intracellular calcium levels in PC-12 cells. *Mol Pharmacol* 44: 405–411, 1993.
909. **Kim YV, Bobkov YV, Kolesnikov SS.** Adenosine triphosphate mobilizes cytosolic calcium and modulates ionic currents in mouse taste receptor cells. *Neurosci Lett* 290: 165–168, 2000.
910. **Kimball BC, Mulholland MW.** Enteric glia exhibit P_{2U} receptors that increase cytosolic calcium by a phospholipase C-dependent mechanism. *J Neurochem* 66: 604–612, 1996.
911. **Kimball BC, Yule DI, Mulholland MW.** Extracellular ATP mediates Ca²⁺ signaling in cultured myenteric neurons via a PLC-dependent mechanism. *Am J Physiol Gastrointest Liver Physiol* 270: G587–G593, 1996.
912. **Kimelberg HK.** Increased release of excitatory amino acids by the actions of ATP and peroxynitrite on volume-regulated anion channels (VRACs) in astrocytes. *Neurochem Int* 45: 511–519, 2004.
913. **Kimura K, Nishimura T, Satoh Y.** Effects of ATP and its analogues on [Ca²⁺]_i dynamics in the rabbit corneal epithelium. *Arch Histol Cytol* 62: 129–138, 1999.
914. **King BF, Knowles I, Burnstock G, Ramage A.** Investigation of the effects of P2 purinoceptor ligands on the micturition reflex in female urethane-anesthetized rats. *Br J Pharmacol* 142: 519–530, 2004.
915. **King BF, Liu M, Townsend-Nicholson A, Pfister J, Padilla F, Ford APDW, Gever J, Oglesby IB, Schorge S, Burnstock G.** Antagonism of ATP responses at P2X receptor subtypes by the pH indicator dye, Phenol red. *Br J Pharmacol* 145: 313–322, 2005.
916. **King BF, Townsend-Nicholson A, Wildman SS, Thomas T, Spyer KM, Burnstock G.** Coexpression of rat P2X₂ and P2X₆ subunits in *Xenopus* oocytes. *J Neurosci* 20: 4871–4877, 2000.
917. **Kinoshita N, Takahashi T, Tada S, Shinozuka K, Mizuno N, Takahashi K.** Activation of P2Y receptor enhances high-molecular compound absorption from rat ileum. *J Pharm Pharmacol* 58: 195–200, 2006.
918. **Kirischuk S, Matiash V, Kulik A, Voitenko N, Kostyuk P, Verkhratsky A.** Activation of P₂-purino-, α₁-adreno and H₁-histamine receptors triggers cytoplasmic calcium signalling in cerebellar Purkinje neurons. *Neuroscience* 73: 643–647, 1996.
919. **Kirkpatrick K, Burnstock G.** Sympathetic nerve-mediated release of ATP from the guinea-pig vas deferens is unaffected by reserpine. *Eur J Pharmacol* 138: 207–214, 1987.
920. **Kirkup AJ, Brunnsden AM, Grundy D.** Receptors and transmission in the brain-gut axis: potential for novel therapies. I. Receptors on visceral afferents. *Am J Physiol Gastrointest Liver Physiol* 280: G787–G794, 2001.
921. **Kishore BK, Isaac J, Fausther M, Tripp SR, Shi H, Gill PS, Braun N, Zimmermann H, Sevigny J, Robson SC.** Expression of NTPDase1 and NTPDase2 in murine kidney: relevance to regulation of P2 receptor signaling. *Am J Physiol Renal Physiol* 288: F1032–F1043, 2005.
922. **Kitahara S, Yamashita M, Ikemoto Y.** Effects of pentobarbital on purinergic P2X receptors of rat dorsal root ganglion neurons. *Can J Physiol Pharmacol* 81: 1085–1091, 2003.
923. **Kitchen AM, Collins HL, DiCarlo SE, Scislo TJ, O'Leary DS.** Mechanisms mediating NTS P2X receptor-evoked hypotension: cardiac output vs. total peripheral resistance. *Am J Physiol Heart Circ Physiol* 281: H2198–H2203, 2001.
924. **Kitchen AM, O'Leary DS, Scislo TJ.** Sympathetic and parasympathetic component of bradycardia triggered by stimulation of NTS P2X receptors. *Am J Physiol Heart Circ Physiol* 290: H807–H812, 2006.
925. **Kitchen AM, Scislo TJ, O'Leary DS.** NTS A_{2a} purinoceptor activation elicits hindlimb vasodilation primarily via a β-adrenergic mechanism. *Am J Physiol Heart Circ Physiol* 278: H1775–H1782, 2000.
926. **Kittner H, Franke H, Fischer W, Schultheis N, Krügel U, Illes P.** Stimulation of P2Y₁ receptors causes anxiolytic-like effects in the rat elevated plus-maze: implications for the involvement of P2Y₁ receptor-mediated nitric oxide production. *Neuropsychopharmacology* 28: 435–444, 2003.
927. **Kittner H, Franke H, Harsch JI, El-Ashmawy IM, Seidel B, Krügel U, Illes P.** Enhanced food intake after stimulation of hypothalamic P2Y₁ receptors in rats: modulation of feeding behaviour by extracellular nucleotides. *Eur J Neurosci* 24: 2049–2056, 2006.
928. **Kittner H, Krügel U, Hoffmann E, Illes P.** Effects of intracerebellar injection of 2-methylthio ATP: a combined open field and electroencephalographic study in rats. *Psychopharmacology* 150: 123–131, 2000.
929. **Kittner H, Krügel U, Hoffmann E, Illes P.** Modulation of feeding behaviour by blocking purinergic receptors in the rat nucleus accumbens: a combined microdialysis, electroencephalographic and behavioural study. *Eur J Neurosci* 19: 396–404, 2004.
930. **Kittner H, Krügel U, Illes P.** The purinergic P2 receptor antagonist pyridoxalphosphate-6-azophenyl-2'-4'-disulphonic acid prevents both the acute locomotor effects of amphetamine and the behavioural sensitization caused by repeated amphetamine injections in rats. *Neuroscience* 102: 241–243, 2001.
931. **Klepeis VE, Weinger I, Kaczmarek E, Trinkaus-Randall V.** P2Y receptors play a critical role in epithelial cell communication and migration. *J Cell Biochem* 93: 1115–1133, 2004.
932. **Knight GE, Bodin P, de Groat WC, Burnstock G.** ATP is released from guinea pig ureter epithelium on distension. *Am J Physiol Renal Physiol* 282: F281–F288, 2002.
933. **Knight GE, Burnstock G.** Responses of the aorta of the garter snake (*Thamnophis sirtalis parietalis*) to purines. *Br J Pharmacol* 114: 41–48, 1995.
934. **Knight GE, Burnstock G.** The effects of purine compounds on the isolated aorta of the frog *Rana temporaria*. *Br J Pharmacol* 117: 873–878, 1996.
935. **Knutsen LJS, Murray TF.** Adenosine and ATP in epilepsy. In: *Purinergic Approaches in Experimental Therapeutics*, edited by Jacobson KA and Jarvis MF. New York: Wiley-Liss, 1997, p. 423–447.
936. **Ko WH, Au CL, Yip CY.** Multiple purinergic receptors lead to intracellular calcium increases in cultured rat Sertoli cells. *Life Sci* 72: 1519–1535, 2003.
937. **Ko WH, O'Dowd JJM, Pediani JD, Bovell DL, Elder HY, Jenkinson DM, Wilson SM.** Extracellular ATP can activate autonomic signal transduction pathways in cultured equine sweat gland epithelial cells. *J Exp Biol* 190: 239–252, 1994.

938. **Kobayashi S, Conforti L, Millhorn DE.** Gene expression and function of adenosine A_{2A} receptor in the rat carotid body. *Am J Physiol Lung Cell Mol Physiol* 279: L273–L282, 2000.
939. **Kobayashi K, Fukuoka T, Iyamanaka H, Dai Y, Obata K, Tokunaga A, Noguchi K.** Neurons and glial cells differentially express P2Y receptor mRNAs in the rat dorsal root ganglion and spinal cord. *J Comp Neurol* 498: 443–454, 2006.
940. **Koch H, von Kügelgen I, Starke K.** P2-receptor-mediated inhibition of noradrenaline release in the rat hippocampus. *Naunyn-Schmiedeberg's Arch Pharmacol* 355: 707–715, 1997.
941. **Kochukov MY, Ritchie AK.** A P2X₇ receptor stimulates plasma membrane trafficking in the FRTL rat thyrocyte cell line. *Am J Physiol Cell Physiol* 287: C992–C1002, 2004.
942. **Kocsis JD, Eng DL, Bhisitkul RB.** Adenosine selectively blocks parallel-fiber-mediated synaptic potentials in rat cerebellar cortex. *Proc Natl Acad Sci USA* 81: 6531–6534, 1984.
943. **Koehler RC, Gebremedhin D, Harder DR.** Role of astrocytes in cerebrovascular regulation. *J Appl Physiol* 100: 307–317, 2006.
944. **Koganezawa T, Ishikawa T, Fujita Y, Yamashita T, Tajima T, Honda M, Nakayama K.** Local regulation of skin blood flow during cooling involving presynaptic P2 purinoceptors in rats. *Br J Pharmacol* 148: 579–586, 2006.
945. **Kogure K, Alonso OF.** A pictorial representation of endogenous brain ATP by a bioluminescent method. *Brain Res* 154: 273–284, 1978.
946. **Koizumi S, Fujishita K, Inoue K.** Dynamic astrocyte-to-neuron communication mediated by astrocytic ATP in hippocampal cultures. *International Proceedings of VII European Meeting on Glial Cell Function in Health and Disease Amsterdam 2005*, p. 13–18.
947. **Koizumi S, Fujishita K, Inoue K, Shigemoto-Mogami Y, Tsuda M, Inoue K.** Ca²⁺ waves in keratinocytes are transmitted to sensory neurons: the involvement of extracellular ATP and P2Y₂ receptor activation. *Biochem J* 380: 329–338, 2004.
948. **Koizumi S, Fujishita K, Tsuda M, Inoue K.** Neuron-to-astrocyte communication by endogenous ATP in mixed culture of rat hippocampal neurones and astrocytes. *Drug Dev Res* 59: 88–94, 2003.
949. **Koizumi S, Inoue K.** Inhibition by ATP of calcium oscillations in rat cultured hippocampal neurones. *Br J Pharmacol* 122: 51–58, 1997.
950. **Kolb HA, Wakelam MJO.** Transmitter-like action of ATP on patched membranes of cultured myoblasts and myotubes. *Nature* 303: 621–623, 1983.
951. **Köles L, Furst S, Illes P.** P2X and P2Y receptors as possible targets of therapeutic manipulations in CNS illnesses. *Drug News Perspect* 18: 85–101, 2005.
952. **Kollarik M, Dinh QT, Fischer A, Undem BJ.** Capsaicin-sensitive and -insensitive vagal bronchopulmonary C-fibres in the mouse. *J Physiol* 551: 869–879, 2003.
953. **Komlosi P, Fintha A, Bell PD.** Renal cell-to-cell communication via extracellular ATP. *Physiology* 20: 86–90, 2005.
954. **Komori S, Unno T, Ohashi H.** Pharmacological properties of non-adrenergic, non-cholinergic inhibitory transmission in chicken gizzard. *Br J Pharmacol* 121: 572–578, 1997.
955. **Konduri GG, Forman K, Mital S.** Characterization of purine receptors in fetal lamb pulmonary circulation. *Pediatr Res* 47: 114–120, 2000.
956. **Kong Q, Wang M, Liao Z, Camden J, Yu S, Simonyi A, Sun G, Gonzalez F, Erb L, Seye C, Weisman G.** P2X₇ nucleotide receptors mediate caspase-8/9/3-dependent apoptosis in rat primary cortical neurons. *Purinergic Signalling* 1: 337–347, 2005.
957. **Konishi C, Naito Y, Ohara N.** Age-related changes in adenosine 5'-triphosphate-induced constriction of isolated, perfused mesenteric arteries of rats. *Life Sci* 64: 1265–1273, 1999.
958. **Korocok J, Raimundo LN, Ke HZ, Sims SM, Dixon SJ.** Extracellular nucleotides act through P2X₇ receptors to activate NF-κB in osteoclasts. *J Bone Miner Res* 19: 642–651, 2004.
959. **Kostopoulos GK, Limacher JJ, Phillis JW.** Action of various adenine derivatives on cerebellar Purkinje cells. *Brain Res* 88: 162–165, 1975.
960. **Kotera T, Brown PD.** Activation of chloride currents in choroid plexus by GTP-γ-S and cyclic-AMP. *Jpn J Physiol* 44 Suppl 2: S161–S165, 1994.
961. **Kottgen M, Löffler T, Jacobi C, Nitschke R, Pavenstadt H, Schreiber R, Frische S, Nielsen S, Leipziger J.** P2Y₆ receptor mediates colonic NaCl secretion via differential activation of cAMP-mediated transport. *J Clin Invest* 111: 371–379, 2003.
962. **Kovács I, Lasztocki B, Szarics E, Heja L, Sagi G, Kardos J.** Characterisation of an uridine-specific binding site in rat cerebrocortical homogenates. *Neurochem Int* 43: 101–112, 2003.
963. **Kowaluk EA, Jarvis MF.** Therapeutic potential of adenosine kinase inhibitors. *Expert Opin Invest Drugs* 9: 551–564, 2000.
964. **Kriegler S, Chiu SY.** Calcium signaling of glial cells along mammalian axons. *J Neurosci* 13: 4229–4245, 1993.
965. **Krishnamurthy VS, Kadowitz PJ.** Influence of adenosine triphosphate on the isolated perfused mesenteric artery of the rabbit. *Can J Physiol Pharmacol* 61: 1409–1417, 1983.
966. **Krishtal OA, Marchenko SM, Pidoplichko VI.** Receptor for ATP in the membrane of mammalian sensory neurones. *Neurosci Lett* 35: 41–45, 1983.
967. **Krügel U, Kittner H, Franke H, Illes P.** Stimulation of P2 receptors in the ventral tegmental area enhances dopaminergic mechanisms in vivo. *Neuropharmacology* 40: 1084–1093, 2001.
968. **Krügel U, Kittner H, Franke H, Illes P.** Purinergic modulation of neuronal activity in the mesolimbic dopaminergic system in vivo. *Synapse* 47: 134–142, 2003.
969. **Krügel U, Schraft T, Kittner H, Kiess W, Illes P.** Basal and feeding-evoked dopamine release in the rat nucleus accumbens is depressed by leptin. *Eur J Pharmacol* 482: 185–187, 2003.
970. **Krügel U, Spies O, Regenthal R, Illes P, Kittner H.** P2 receptors are involved in the mediation of motivation-related behavior. *Purinergic Signalling* 1: 21–29, 2004.
971. **Kubo-Watanabe S, Satoh Y, Saino T.** Adenosine-5'-triphosphate-induced intracellular calcium changes through gap-junctional communication in the corneal epithelium. *Jpn J Ophthalmol* 46: 479–487, 2002.
972. **Kucenas S, Li Z, Cox JA, Egan TM, Voigt MM.** Molecular characterization of the zebrafish P2X receptor subunit gene family. *Neuroscience* 121: 935–945, 2003.
973. **Kucenas S, Soto F, Cox JA, Voigt MM.** Selective labeling of central and peripheral sensory neurons in the developing zebrafish using P2X₃ receptor subunit transgenes. *Neuroscience* 138: 641–652, 2006.
974. **Kukley M, Schwan M, Fredholm BB, Dietrich D.** The role of extracellular adenosine in regulating mossy fiber synaptic plasticity. *J Neurosci* 25: 2832–2837, 2005.
975. **Kukley M, Stausberg P, Adelman G, Chessell IP, Dietrich D.** Ecto-nucleotidases and nucleoside transporters mediate activation of adenosine receptors on hippocampal mossy fibers by P2X₇ receptor agonist 2'-3'-O-(4-benzoylbenzoyl)-ATP. *J Neurosci* 24: 7128–7139, 2004.
976. **Kukulski F, Lévesque SA, Lavoie ÉG, Lecka J, Bigonnesse F, Knowles AF, Robson SC, Kirley TL, Sévigny J.** Comparative hydrolysis of P2 receptor agonists by NTPDases 1, 2, 3 and 8. *Purinergic Signalling* 1: 193–204, 2005.
977. **Kukulski F, Sévigny J, Komoszynski M.** Comparative hydrolysis of extracellular adenine nucleotides and adenosine in synaptic membranes from porcine brain cortex, hippocampus, cerebellum and medulla oblongata. *Brain Res* 1030: 49–56, 2004.
978. **Kulkarni AA, Trousdale MD, Stevenson D, Gukasyan HJ, Shiue MH, Kim KJ, Read RW, Lee VH.** Nucleotide-induced restoration of conjunctival chloride and fluid secretion in adenovirus type 5-infected pigmented rabbit eyes. *J Pharmacol Exp Ther* 305: 1206–1211, 2003.
979. **Kumagai H, Sakamoto H, Guggino S, Filburn CR, Sacktor B.** Neurotransmitter regulation of cytosolic calcium in osteoblast-like bone cells. *Calcif Tissue Int* 45: 251–254, 1989.
980. **Kumar V, Templeman L, Chapple CR, Chess-Williams R.** Recent developments in the management of detrusor overactivity. *Curr Opin Urol* 13: 285–291, 2003.
981. **Kuperman AS, Okamoto M, Beyer AM, Volpert WA.** Procaine action: antagonism by adenosine triphosphate and other nucleotides. *Science* 144: 1222–1223, 1964.

982. **Kupfermann I.** Functional studies of cotransmission. *Physiol Rev* 71: 683–732, 1991.
983. **Kuroda Y, McIlwain H.** Subcellular localization of [¹⁴C]adenine derivatives newly-formed in cerebral tissues and the effects of electrical excitation. *J Neurochem* 21: 889–900, 1973.
984. **Kuzmin A, Johansson B, Gimenez L, Ogren SO, Fredholm BB.** Combination of adenosine A₁ and A_{2A} receptor blocking agents induces caffeine-like locomotor stimulation in mice. *Eur Neuropsychopharmacol* 16: 129–136, 2006.
985. **Labrakakis C, Gerstner E, MacDermott AB.** Adenosine triphosphate-evoked currents in cultured dorsal root ganglion neurons obtained from rat embryos: desensitization kinetics and modulation of glutamate release. *Neuroscience* 101: 1117–1126, 2000.
986. **Labrakakis C, Tong CK, Weissman T, Torsney C, MacDermott AB.** Localization and function of ATP and GABA_A receptors expressed by nociceptors and other postnatal sensory neurons in rat. *J Physiol* 549: 131–142, 2003.
987. **Lacroix JS, Ulman LG, Potter EK.** The role of ATP in non-adrenergic sympathetic vascular control of the nasal mucosa in anaesthetized cats and dogs. *J Physiol* 476: 429–435, 1994.
988. **Lagercrantz H, Stjärne L.** Evidence that most noradrenaline is stored without ATP in sympathetic large dense core nerve vesicles. *Nature* 249: 843–845, 1974.
989. **Laitinen JT, Uri A, Raidaru G, Miettinen R.** [³⁵S]GTPγS autoradiography reveals a wide distribution of G_vo-linked ADP receptors in the nervous system: close similarities with the platelet P2Y(ADP) receptor. *J Neurochem* 77: 505–518, 2001.
990. **Lakshmi S, Joshi PG.** Co-activation of P2Y₂ receptor and TRPV channel by ATP: implications for ATP induced pain. *Cell Mol Neurobiol* 25: 819–832, 2005.
991. **Lakshmi S, Joshi PG.** Activation of Src/kinase/phospholipase c/mitogen-activated protein kinase and induction of neurite expression by ATP, independent of nerve growth factor. *Neuroscience* 141: 179–189, 2006.
992. **Lalo UV, Pankratov YV, Arndts D, Krishtal OA.** Ω-Conotoxin GVIA potently inhibits the currents mediated by P2X receptors in rat DRG neurons. *Brain Res Bull* 54: 507–512, 2001.
993. **Lalo U, Pankratov Y, Krishtal O, North RA.** Methyllycaconitine, α-bungarotoxin and (+)-tubocurarine block fast ATP-gated currents in rat dorsal root ganglion cells. *Br J Pharmacol* 142: 1227–1232, 2004.
994. **Lalo U, Voitenko N, Kostyuk P.** Iono- and metabotropically induced purinergic calcium signalling in rat neocortical neurons. *Brain Res* 799: 285–291, 1998.
995. **Lam P, Hong CJ, Tsai SJ.** Association study of A2a adenosine receptor genetic polymorphism in panic disorder. *Neurosci Lett* 378: 98–101, 2005.
996. **Lambrecht G, Braun K, Damer M, Ganso M, Hildebrandt C, Ullmann H, Kassack MU, Nickel P.** Structure-activity relationships of suramin and pyridoxal-5'-phosphate derivatives as P2 receptor antagonists. *Curr Pharm Des* 8: 2371–2399, 2002.
997. **Lämmer A, Günther A, Beck A, Krügel U, Kittner H, Schneider D, Illes P, Franke H.** Neuroprotective effects of the P2 receptor antagonist PPADS on focal cerebral ischaemia-induced injury in rats. *Eur J Neurosci* 23: 2824–2828, 2006.
998. **Langer SZ, Pinto JEB.** Possible involvement of a transmitter different from norepinephrine in residual responses to nerve stimulation of cat nictitating membrane after pretreatment with reserpine. *J Pharmacol Exp Ther* 166: 697–713, 1976.
999. **Langley JN.** On inhibitory fibres in the vagus to the end of the oesophagus and stomach. *J Physiol* 23: 407–414, 1898.
1000. **Langley JN, Anderson HK.** The innervation of the pelvic and adjoining viscera. IV. The internal generative organs. *J Physiol* 19: 122–130, 1895.
1001. **Lara DR, Dall'Igna OP, Ghisolfi ES, Brunstein MG.** Involvement of adenosine in the neurobiology of schizophrenia and its therapeutic implications. *Prog Neuropsychopharmacol Biol Psychiatry* 30: 617–629, 2006.
1002. **Lara DR, Souza DO.** Schizophrenia: a purinergic hypothesis. *Med Hypotheses* 54: 157–166, 2000.
1003. **Laube B.** Potentiation of inhibitory glycinergic neurotransmission by Zn²⁺: a synergistic interplay between presynaptic P2X₂ and postsynaptic glycine receptors. *Eur J Neurosci* 16: 1025–1036, 2002.
1004. **Lazarowski ER, Boucher RC, Harden TK.** Mechanisms of release of nucleotides and integration of their action as P2X- and P2Y-receptor activating molecules. *Mol Pharmacol* 64: 785–795, 2003.
1005. **Lazzeri M.** The physiological function of the urothelium: more than a simple barrier. *Urol Int* 76: 289–295, 2006.
1006. **Lê KT, Babinski K, Séguéla P.** Central P2X₄ and P2X₆ channel subunits coassemble into a novel heteromeric ATP receptor. *J Neurosci* 18: 7152–7159, 1998.
1007. **Le Feuvre RA, Brough D, Touzani O, Rothwell NJ.** Role of P2X₇ receptors in ischemic and excitotoxic brain injury in vivo. *J Cereb Blood Flow Metab* 23: 381–384, 2003.
1008. **Lee FS, Chao MV.** Activation of Trk neurotrophin receptors in the absence of neurotrophins. *Proc Natl Acad Sci USA* 98: 3555–3560, 2001.
1009. **Lee H, Jun DJ, Suh BC, Choi BH, Lee JH, Do MS, Suh BS, Ha H, Kim KT.** Dual roles of P2 purinergic receptors in insulin-stimulated leptin production and lipolysis in differentiated rat white adipocytes. *J Biol Chem* 280: 28556–28563, 2005.
1010. **Lee HY, Bardini M, Burnstock G.** Distribution of P2X receptors in the urinary bladder and the ureter of the rat. *J Urol* 163: 2002–2007, 2000.
1011. **Lee SC, Vielhauer NS, Leaver EV, Pappone PA.** Differential regulation of Ca²⁺ signaling and membrane trafficking by multiple P2 receptors in brown adipocytes. *J Membr Biol* 207: 131–142, 2005.
1012. **Lee YJ, Han HJ.** Role of ATP in DNA synthesis of renal proximal tubule cells: involvement of calcium, MAPKs, CDKs. *Am J Physiol Renal Physiol* 291: F98–F106, 2006.
1013. **Leipzig J.** Control of epithelial transport via luminal P2 receptors. *Am J Physiol Renal Physiol* 284: F419–F432, 2003.
1014. **Lemaire I, Leduc N.** Purinergic P2X₇ receptor function in lung alveolar macrophages: pharmacologic characterisation and bidirectional regulation by Th1 and Th2 cytokines. *Drug Dev Res* 59: 118–127, 2004.
1015. **Léon C, Freund M, Latchoumanin O, Farret A, Petit P, Cazenave JP, Gachet C.** The P2Y₁ receptor is involved in the maintenance of glucose homeostasis and in insulin secretion in mice. *Purinergic Signalling* 1: 145–151, 2005.
1016. **León D, Albasanz JL, Ruiz MA, Fernandez M, Martin M.** Adenosine A1 receptor down-regulation in mothers and fetal brain after caffeine and theophylline treatments to pregnant rats. *J Neurochem* 82: 625–634, 2002.
1017. **León D, Hervás C, Miras-Portugal MT.** P2Y₁ and P2X₇ receptors induce calcium/calmodulin-dependent protein kinase II phosphorylation in cerebellar granule neurons. *Eur J Neurosci* 23: 2999–3013, 2006.
1018. **LePard KJ, Galligan JJ.** Analysis of fast synaptic pathways in myenteric plexus of guinea pig ileum. *Am J Physiol Gastrointest Liver Physiol* 276: G529–G538, 1999.
1019. **LePard KJ, Ren J, Galligan JJ.** Presynaptic modulation of cholinergic and non-cholinergic fast synaptic transmission in the myenteric plexus of guinea pig ileum. *Neurogastroenterol Motil* 16: 355–364, 2004.
1020. **Lesch M, Nyhan WL.** A familial disorder of uric acid metabolism and central nervous system function. *Am J Med* 36: 561–570, 1964.
1021. **Levin R, Braiman A, Priel Z.** Protein kinase C induced calcium influx and sustained enhancement of ciliary beating by extracellular ATP. *Cell Calcium* 21: 103–113, 1997.
1022. **Levin RM, Tong YC, Wein AJ.** Effect of pregnancy on the autonomic response of the rabbit urinary bladder. *Neurobiol Urodyn* 10: 313, 1991.
1023. **Levine AS, Grace M, Krahn DD, Billington CJ.** The adenosine agonist N⁶-R-phenylisopropyladenosine (R-PIA) stimulates feeding in rats. *Brain Res* 477: 280–285, 1989.
1024. **Levine AS, Morley JE.** Purinergic regulation of food intake. *Science* 217: 77–79, 1982.
1025. **Levine JD, Coderre TJ, Covinsky K, Basbaum AI.** Neural influences on synovial mast cell density in rat. *J Neurosci Res* 26: 301–307, 1990.

1026. **Levine JD, Collier DH, Basbaum AI, Moskowitz MA, Helms CA.** Hypothesis: the nervous system may contribute to the pathophysiology of rheumatoid arthritis. *J Rheumatol* 12: 406–411, 1985.
1027. **Lewis C, Neidhart S, Holy C, North RA, Buell G, Surprenant A.** Coexpression of P2X₂ and P2X₃ receptor subunits can account for ATP-gated currents in sensory neurons. *Nature* 377: 432–435, 1995.
1028. **Lewis J.** *The Blood Vessels of the Human Skin and Their Responses.* London: Shaw & Sons, 1927.
1029. **Lewis SA, Lewis JR.** Kinetics of urothelial ATP release. *Am J Physiol Renal Physiol* 291: F332–F340, 2006.
1030. **Lewis-Carl S, Kirley TL.** Immunolocalization of the ecto-ATPase and ecto-apyrase in chicken gizzard and stomach. Purification and N-terminal sequence of the stomach ecto-apyrase. *J Biol Chem* 272: 23645–23652, 1997.
1031. **Li C, Peoples RW, Lanthorn TH, Li ZW, Weight FF.** Distinct ATP-activated currents in different types of neurons dissociated from rat dorsal root ganglion. *Neurosci Lett* 263: 57–60, 1999.
1032. **Li C, Peoples RW, Weight FF.** Enhancement of ATP-activated current by protons in dorsal root ganglion neurons. *Pflügers Arch* 433: 446–454, 1997.
1033. **Li C, Peoples RW, Weight FF.** Ethanol-induced inhibition of a neuronal P2X purinoceptor by an allosteric mechanism. *Br J Pharmacol* 123: 1–3, 1998.
1034. **Li CK, Bowers K, Pathmakanthan S, Gray T, Lawson M, Fagura M, Hawkey CJ.** Expression and functions of purinergic receptor P2X₇ in colonic macrophages and T lymphocytes from normal and inflammatory bowel disease mucosa. *Gastroenterology* 120: 2654, 2001.
1035. **Li GH, Lee EM, Blair D, Holding C, Poronnik P, Cook DC, Barden JA, Bennett MR.** The disposition of P2X receptor clusters on individual neurons in sympathetic ganglia and their redistribution on agonist activation. *J Biol Chem* 275: 29107–29112, 2000.
1036. **Li H, Wu L, Li YQ.** Adenosine suppresses GABA_A receptor-mediated responses in rat sacral dorsal commissural neurons. *Auton Neurosci* 111: 71–79, 2004.
1037. **Li J, Perl ER.** ATP modulation of synaptic transmission in the spinal substantia gelatinosa. *J Neurosci* 15: 3357–3365, 1995.
1038. **Li J, Sinoway LI.** ATP stimulates chemically sensitive and sensitizes mechanically sensitive afferents. *Am J Physiol Heart Circ Physiol* 283: H2636–H2643, 2002.
1039. **Li P, Calejesan AA, Zhou M.** ATP P_{2X} receptors and sensory synaptic transmission between primary afferent fibers and spinal dorsal horn neurons in rats. *J Neurophysiol* 80: 3356–3360, 1998.
1040. **Li X, Eisenach JC.** Adenosine reduces glutamate release in rat spinal synaptosomes. *Anesthesiology* 103: 1060–1065, 2005.
1041. **Li X, Ikezu T, Hexum TD.** $\beta\gamma$ Subunits mediate the NPY enhancement of ATP-stimulated inositol phosphate formation. *Peptides* 25: 267–274, 2004.
1042. **Li Y, Kuang K, Yerxa B, Wen Q, Rosskothan H, Fischbarg J.** Rabbit conjunctival epithelium transports fluid, P2Y₂ receptor agonists stimulate Cl⁻ and fluid secretion. *Am J Physiol Cell Physiol* 281: C595–C602, 2001.
1043. **Liang SD, Gao Y, Xu CS, Xu BH, Mu SN.** Effect of tetramethylpyrazine on acute nociception mediated by signaling of P2X receptor activation in rat. *Brain Res* 995: 247–252, 2004.
1044. **Light AR, Wu Y, Hughen RW, Guthrie PB.** Purinergic receptors activating rapid intracellular Ca²⁺ increases in microglia. *Neuron Glia Biol* 2: 125–138, 2006.
1045. **Lim W, Isaac JT.** ATP hydrolysis is required for the rapid regulation of AMPA receptors during basal synaptic transmission and long-term synaptic plasticity. *Neuropharmacology* 48: 949–955, 2005.
1046. **Lim W, Kim SJ, Yan HD, Kim J.** Ca²⁺-channel-dependent and -independent inhibition of exocytosis by extracellular ATP in voltage-clamped rat adrenal chromaffin cells. *Pflügers Arch* 435: 34–42, 1997.
1047. **Lin Y, Desbois A, Jiang S, Hou ST.** P2 receptor antagonist PPADS confers neuroprotection against glutamate/NMDA toxicity. *Neurosci Lett* 377: 97–100, 2005.
1048. **Lin YQ, Bennett MR.** Varicosity-Schwann cell interactions mediated by ATP in the mouse vas deferens. *J Neurophysiol* 93: 2787–2796, 2005.
1049. **Lin YQ, Bennett MR.** Schwann cells in rat vascular autonomic nerves activated via purinergic receptors. *Neuroreport* 17: 531–535, 2006.
1050. **Lindsay SL, Elder HT, Tavadia S, Bovell DL.** Immunolocalisation of the P2Y₁, P2Y₂ and P2Y₄ receptor subtypes in human eccrine sweat glands (Abstract). *J Physiol* 543: 92P, 2002.
1051. **Ling KK, Siow NL, Choi RC, Tsim KW.** ATP potentiates the formation of AChR aggregate in the co-culture of NG108–15 cells with C2C12 myotubes. *FEBS Lett* 579: 2469–2474, 2005.
1052. **Liu DM, Adams DJ.** Ionic selectivity of native ATP-activated (P2X) receptor channels in dissociated neurones from rat parasympathetic ganglia. *J Physiol* 534: 423–435, 2001.
1053. **Liu DM, Katnik C, Stafford M, Adams DJ.** P2Y purinoceptor activation mobilizes intracellular Ca²⁺ and induces a membrane current in rat intracardiac neurones. *J Physiol* 526: 287–298, 2000.
1054. **Liu GJ, Werry EL, Bennett MR.** Secretion of ATP from Schwann cells in response to uridine triphosphate. *Eur J Neurosci* 21: 151–160, 2005.
1055. **Liu HQ, Zhang WY, Luo XT, Ye Y, Zhu XZ.** Paeoniflorin attenuates neuroinflammation and dopaminergic neurodegeneration in the MPTP model of Parkinson's disease by activation of adenosine A₁ receptor. *Br J Pharmacol* 148: 314–325, 2006.
1056. **Liu M, Dunn PM, King BF, Burnstock G.** Rat chromaffin cells lack P2X receptors while those of the guinea-pig express a receptor with novel pharmacology. *Br J Pharmacol* 128: 61–68, 1999.
1057. **Liu M, King BF, Dunn PM, Rong W, Townsend-Nicholson A, Burnstock G.** Coexpression of P2X₃ and P2X₂ receptor subunits in varying amounts generates heterogeneous populations of P2X receptors that evoke a spectrum of agonist responses comparable to that seen in sensory neurons. *J Pharmacol Exp Ther* 296: 1043–1050, 2001.
1058. **Liu QS, Xu Q, Arcuino G, Kang J, Nedergaard M.** Astrocyte-mediated activation of neuronal kainate receptors. *Proc Natl Acad Sci USA* 101: 3172–3177, 2004.
1059. **Liu QS, Xu Q, Kang J, Nedergaard M.** Astrocyte activation of presynaptic metabotropic glutamate receptors modulates hippocampal inhibitory synaptic transmission. *Neuron Glia Biol* 1: 307–316, 2004.
1060. **Liu SF, Crawley DE, Evans TW, Barnes PJ.** Endothelium-dependent nonadrenergic, noncholinergic neural relaxation in guinea pig pulmonary artery. *J Pharmacol Exp Ther* 260: 541–548, 1992.
1061. **Llaudet E, Hatz S, Droniou M, Dale N.** Microelectrode biosensor for real-time measurement of ATP in biological tissue. *Anal Chem* 77: 3267–3273, 2005.
1062. **Llewellyn-Smith IJ, Burnstock G.** Ultrastructural localization of P2X₃ receptors in rat sensory neurons. *Neuroreport* 9: 2245–2250, 1998.
1063. **Lo WC, Jan CR, Wu SN, Tseng CJ.** Cardiovascular effects of nitric oxide and adenosine in the nucleus tractus solitarii of rats. *Hypertension* 32: 1034–1038, 1998.
1064. **Loesch A, Burnstock G.** Electron-immunocytochemical localization of P2X₁ receptors in the rat cerebellum. *Cell Tissue Res* 294: 253–260, 1998.
1065. **Loesch A, Burnstock G.** Ultrastructural localisation of ATP-gated P2X₂ receptor immunoreactivity in vascular endothelial cells in rat brain. *Endothelium* 7: 93–98, 2000.
1066. **Loesch A, Burnstock G.** Immunoreactivity to P2X₆ receptors in the rat hypothalamo-neurohypophysial system: an ultrastructural study with ExtrAvidin and colloidal gold-silver immunolabelling. *Neuroscience* 106: 621–631, 2001.
1067. **Loesch A, Miah S, Burnstock G.** Ultrastructural localisation of ATP-gated P2X₂ receptor immunoreactivity in the rat hypothalamo-neurohypophysial system. *J Neurocytol* 28: 495–504, 1999.
1068. **Loir M.** Spermatogonia of rainbow trout. III. In vitro study of the proliferative response to extracellular ATP and adenosine. *Mol Reprod Dev* 53: 443–450, 1999.
1069. **Londos C, Cooper DM, Wolff J.** Subclasses of external adenosine receptors. *Proc Natl Acad Sci USA* 77: 2551–2554, 1980.

1070. **Lopes LV, Cunha RA, Kull B, Fredholm BB, Ribeiro JA.** Adenosine A_{2A} receptor facilitation of hippocampal synaptic transmission is dependent on tonic A₁ receptor inhibition. *Neuroscience* 112: 319–329, 2002.
1071. **Lopes LV, Cunha RA, Ribeiro JA.** Cross talk between A₁ and A_{2A} adenosine receptors in the hippocampus and cortex of young adult and old rats. *J Neurophysiol* 82: 3196–3203, 1999.
1072. **Loredo GA, Benton HP.** ATP and UTP activate calcium-mobilizing P2U-like receptors and act synergistically with interleukin-1 to stimulate prostaglandin E₂ release from human rheumatoid synovial cells. *Arthritis Rheum* 41: 246–255, 1998.
1073. **Lu Z, Smith DO.** Adenosine 5'-triphosphate increases acetylcholine channel opening frequency in rat skeletal muscle. *J Physiol* 436: 45–56, 1991.
1074. **Lucae S, Salyakina D, Barden N, Harvey M, Gagné B, Labbé M, Binder EB, Uhr M, Paez-Pereda M, Sillaber I, Ising M, Brückl T, Lieb R, Holsboer F, Muller-Myhsok B.** P2RX7, a gene coding for a purinergic ligand-gated ion channel, is associated with major depressive disorder. *Hum Mol Genet* 15: 2438–2445, 2006.
1075. **Lucifora S, Willcockson HH, Lu CR, Darstein M, Phend KD, Valtchanoff JG, Rustioni A.** Presynaptic low- and high-affinity kainate receptors in nociceptive spinal afferents. *Pain* 120: 97–105, 2006.
1076. **Ludlow M, Ennion S.** A putative *Dictyostelium discoideum* P2X receptor. *Purinergic Signalling* 2: 81–82, 2006.
1077. **Lundberg JM.** Pharmacology of cotransmission in the autonomic nervous system: integrative aspects on amines, neuropeptides, adenosine triphosphate, amino acids and nitric oxide. *Pharmacol Rev* 48: 113–178, 1996.
1078. **Lundy PM, Hamilton MG, Mi L, Gong W, Vair C, Sawyer TW, Frew R.** Stimulation of Ca²⁺ influx through ATP receptors on rat brain synaptosomes: identification of functional P2X₇ receptor subtypes. *Br J Pharmacol* 135: 1616–1626, 2002.
1079. **Luo X, Zheng W, Yan M, Lee MG, Muallem S.** Multiple functional P2X and P2Y receptors in the luminal and basolateral membranes of pancreatic duct cells. *Am J Physiol Cell Physiol* 277: C205–C215, 1999.
1080. **Lustig KD, Shiau AK, Brake AJ, Julius D.** Expression cloning of an ATP receptor from mouse neuroblastoma cells. *Proc Natl Acad Sci USA* 90: 5113–5117, 1993.
1081. **Luthardt J, Borvendeg SJ, Sperlagh B, Poelchen W, Wirkner K, Illes P.** P2Y₁ receptor activation inhibits NMDA receptor-channels in layer V pyramidal neurons of the rat prefrontal and parietal cortex. *Neurochem Int* 42: 161–172, 2003.
1082. **Lutz PL, Kabler S.** Release of adenosine and ATP in the brain of the freshwater turtle (*Trachemys scripta*) during long-term anoxia. *Brain Res* 769: 281–286, 1997.
1083. **Lyons SA, Morell P, McCarthy KD.** Schwann cell ATP-mediated calcium increases in vitro and in situ are dependent on contact with neurons. *Glia* 13: 27–38, 1995.
1084. **Ma B, Rong W, Dunn PM, Burnstock G.** 17β-Estradiol attenuates α,β-meATP-induced currents in rat dorsal root ganglion neurons. *Life Sci* 76: 2547–2558, 2005.
1085. **Ma B, Ruan HZ, Burnstock G, Dunn PM.** Differential expression of P2X receptors on neurons from different parasympathetic ganglia. *Neuropharmacology* 48: 766–777, 2005.
1086. **Ma W, Korngreen A, Weil S, Cohen EB, Priel A, Kuzin L, Silberberg SD.** Pore properties and pharmacological features of the P2X receptor channel in airway ciliated cells. *J Physiol* 571: 503–517, 2006.
1087. **MacDonald A, McGrath JC.** Post-natal development of functional neurotransmission in rat vas deferens. *Br J Pharmacol* 82: 25–34, 1984.
1088. **Machado-Vieira R, Lara DR, Souza DO, Kapczynski F.** Purinergic dysfunction in mania: an integrative model. *Med Hypotheses* 58: 297–304, 2002.
1089. **Mackiewicz M, Nikonova EV, Zimmermann JE, Romer MA, Cater J, Galante RJ, Pack AI.** Age-related changes in adenosine metabolic enzymes in sleep/wake regulatory areas of the brain. *Neurobiol Aging* 27: 351–360, 2006.
1090. **Madden KS, Moynihan JA, Brenner GJ, Felten SY, Felten DL.** Sympathetic nervous system modulation of the immune system. III. Alterations in T and B cell proliferation and differentiation in vitro following chemical sympathectomy. *J Neuroimmunol* 49: 77–87, 1994.
1091. **Maehara Y, Kusumoto H, Anai H, Kusumoto T, Sugimachi K.** Human tumor tissues have higher ATP contents than normal tissues. *Clin Chim Acta* 169: 341–343, 1987.
1092. **Magazanik LG, Fedorova IM.** Modulatory role of adenosine receptors in insect motor nerve terminals. *Neurochem Res* 28: 617–624, 2003.
1093. **Mailliard WS, Diamond I.** Recent advances in the neurobiology of alcoholism: the role of adenosine. *Pharmacol Ther* 101: 39–46, 2004.
1094. **Makowska A, Panfil C, Ellrich J.** ATP induces sustained facilitation of craniofacial nociception through P2X receptors on neck muscle nociceptors in mice. *Cephalalgia* 26: 697–706, 2006.
1095. **Malinowski MN, Cannady SB, Schmit KV, Barr PM, Schrock JW, Wilson DF.** Adenosine depresses transmitter release but is not the basis for “tetanic fade” at the neuromuscular junction of the rat. *Neurosci Lett* 230: 81–84, 1997.
1096. **Mally J, Stone TW.** Potential of adenosine A_{2A} receptor antagonists in the treatment of movement disorders. *CNS Drugs* 10: 311–320, 1998.
1097. **Malva JO, Silva AP, Cunha RA.** Presynaptic modulation controlling neuronal excitability and epileptogenesis: role of kainate, adenosine and neuropeptide Y receptors. *Neurochem Res* 28: 1501–1515, 2003.
1098. **Maminishkis A, Jalickee S, Blaug SA, Rymer J, Yerxa BR, Peterson WM, Miller SS.** The P2Y₂ receptor agonist INS37217 stimulates RPE fluid transport in vitro and retinal reattachment in rat. *Invest Ophthalmol Vis Sci* 43: 3555–3566, 2002.
1099. **Manintveld OC, te Lintel Hekkert M, Keijzer E, Verdouw PD, Duncker DJ.** Intravenous adenosine protects the myocardium primarily by activation of a neurogenic pathway. *Br J Pharmacol* 145: 703–711, 2005.
1100. **Manita S, Kawamura Y, Sato K, Inoue M, Kudo Y, Miyakawa H.** Adenosine A₁-receptor-mediated tonic inhibition of glutamate release at rat hippocampal CA3-CA1 synapses is primarily due to inhibition of N-type Ca²⁺ channels. *Eur J Pharmacol* 499: 265–274, 2004.
1101. **Mantyh PW, Clohisy DR, Koltzenburg M, Hunt SP.** Molecular mechanisms of cancer pain. *Nat Rev Cancer* 2: 201–209, 2002.
1102. **Marangos PJ, Boulenger JP.** Basic and clinical aspects of adenosinergic neuromodulation. *Neurosci Biobehav Rev* 9: 421–430, 1985.
1103. **Marcaida G, Minana MD, Grisolia S, Felipe V.** Lack of correlation between glutamate-induced depletion of ATP and neuronal death in primary cultures of cerebellum. *Brain Res* 695: 146–150, 1995.
1104. **Marchand F, Perretti M, McMahon SB.** Role of the immune system in chronic pain. *Nat Rev Neurosci* 6: 521–532, 2005.
1105. **Marchi M, Raiteri L, Risso F, Vallarino A, Bonfanti A, Monopoli A, Ongini E, Raiteri M.** Effects of adenosine A₁ and A_{2A} receptor activation on the evoked release of glutamate from rat cerebrocortical synaptosomes. *Br J Pharmacol* 136: 434–440, 2002.
1106. **Maric D, Maric I, Chang YH, Barker JL.** Stereotypical physiological properties emerge during early neuronal and glial lineage development in the embryonic rat neocortex. *Cereb Cortex* 10: 729–747, 2000.
1107. **Marley E, Nistico G.** Effects of catecholamines and adenosine derivatives given into the brain of fowls. *Br J Pharmacol* 46: 619–636, 1972.
1108. **Marsal J, Solsona C, Rabasseda X, Blasi J, Casanova A.** Depolarization-induced release of ATP from cholinergic synaptosomes is not blocked by botulinum toxin type A. *Neurochem Int* 10: 295–302, 1987.
1109. **Martin ED, Buno W.** Stabilizing effects of extracellular ATP on synaptic efficacy and plasticity in hippocampal pyramidal neurons. *Eur J Neurosci* 21: 936–944, 2005.
1110. **Martin SC.** ATP activates a Ca²⁺-dependent Cl⁻ current in the rat thyroid cell line, FRTL-5. *J Membr Biol* 125: 243–253, 1992.

1111. **Martinez-Mir MI, Probst A, Palacios JM.** Adenosine A₂ receptors: selective localization in the human basal ganglia and alterations with disease. *Neuroscience* 42: 697–706, 1991.
1112. **Martinson J, Muren A.** Excitatory and inhibitory effects of vagus stimulation on gastric motility in the cat. *Acta Physiol Scand* 57: 309–316, 1963.
1113. **Martí E, Cantí C, Gómez DA, I, Miralles F, Solsona C.** Action of suramin upon ecto-ATPase activity and synaptic depression of *Torpedo* electric organ. *Br J Pharmacol* 118: 1232–1236, 1996.
1114. **Marty V, Medina C, Combe C, Parnet P, Amedee T.** ATP binding cassette transporter ABC1 is required for the release of interleukin-1 β by P2X₇-stimulated and lipopolysaccharide-primed mouse Schwann cells. *Glia* 49: 511–519, 2005.
1115. **Masaki E, Kawamura M, Kato F.** Reduction by sevoflurane of adenosine 5'-triphosphate-activated inward current of locus coeruleus neurons in pontine slices of rats. *Brain Res* 921: 226–232, 2001.
1116. **Masino SA, Diao L, Illes P, Zahniser NR, Larson GA, Johanson B, Fredholm BB, Dunwiddie TV.** Modulation of hippocampal glutamatergic transmission by ATP is dependent on adenosine A₁ receptors. *J Pharmacol Exp Ther* 303: 356–363, 2002.
1117. **Masino SA, Dunwiddie TV.** Role of purines and pyrimidines in the central nervous system. In: *Handbook of Experimental Pharmacology. Purinergic and Pyrimidinergic Signalling. I. Molecular, Nervous and Urinogenital System Function*, edited by Abbracchio MP and Williams M. Berlin: Springer-Verlag, 2001, p. 251–288.
1118. **Massé K, Eason R, Bhamra S, Dale N, Jones EA.** Comparative genomic and expression analysis of the conserved NTPDase gene family in *Xenopus*. *Genomics* 87: 366–381, 2006.
1119. **Matos JE, Robaye B, Boeynaems JM, Beauwens R, Leipziger J.** K⁺ secretion activated by luminal P2Y₂ and P2Y₄ receptors in mouse colon. *J Physiol* 564: 269–279, 2005.
1120. **Matsuka Y, Neubert JK, Maidment NT, Spigelman I.** Concurrent release of ATP and substance P within guinea pig trigeminal ganglia in vivo. *Brain Res* 915: 248–255, 2001.
1121. **Matsuoka I, Ohkubo S.** ATP- and adenosine-mediated signaling in the central nervous system: adenosine receptor activation by ATP through rapid and localized generation of adenosine by ectonucleotidases. *J Pharmacol Sci* 94: 95–99, 2004.
1122. **Matucci Cerinic M, McCarthy G, Lombardi A, Pignone A, Partsch G.** Neurogenic influences in arthritis: potential modification by capsaicin. *J Rheumatol* 22: 1447–1449, 1995.
1123. **Maul E, Sears M.** ATP is released into the rabbit eye by antidromic stimulation of the trigeminal nerve. *Invest Ophthalmol Vis Sci* 18: 256–262, 1979.
1124. **May C, Weigl L, Karel A, Hohenegger M.** Extracellular ATP activates ERK1/ERK2 via a metabotropic P2Y₁ receptor in a Ca²⁺ independent manner in differentiated human skeletal muscle cells. *Biochem Pharmacol* 71: 1497–1509, 2006.
1125. **Mayer C, Quasthoff S, Grafe P.** Differences in the sensitivity to purinergic stimulation of myelinating and non-myelinating Schwann cells in peripheral human and rat nerve. *Glia* 23: 374–382, 1998.
1126. **Mayer C, Wachtler J, Kamleiter M, Grafe P.** Intracellular calcium transients mediated by P2 receptors in the paranodal Schwann cell region of myelinated rat spinal root axons. *Neurosci Lett* 224: 49–52, 1997.
1127. **Mayfield RD, Suzuki F, Zahniser NR.** Adenosine A_{2a} receptor modulation of electrically evoked endogenous GABA release from slices of rat globus pallidus. *J Neurochem* 60: 2334–2337, 1993.
1128. **McClure JM, O'Leary DS, Scislo TJ.** Stimulation of NTS A1 adenosine receptors evokes counteracting effects on hindlimb vasculature. *Am J Physiol Heart Circ Physiol* 289: H2536–H2542, 2005.
1129. **McDowell TS, Yukhananov RY.** HSP90 inhibitors alter capsaicin- and ATP-induced currents in rat dorsal root ganglion neurons. *Neuroreport* 13: 437–441, 2002.
1130. **McGaraughty S, Honore P, Wismer CT, Mikusa J, Zhu CZ, McDonald HA, Bianchi B, Faltynek CR, Jarvis MF.** Endogenous opioid mechanisms partially mediate P2X₃/P2X_{2/3}-related antinociception in rat models of inflammatory and chemogenic pain but not neuropathic pain. *Br J Pharmacol* 146: 180–188, 2005.
1131. **McGaraughty S, Jarvis MF.** Purinergic control of neuropathic pain. *Drug Dev Res* 67: 376–388, 2006.
1132. **McGaraughty S, Wismer CT, Zhu CZ, Mikusa J, Honore P, Chu KL, Lee CH, Faltynek CR, Jarvis MF.** Effects of A-317491, a novel and selective P2X₃/P2X_{2/3} receptor antagonist, on neuropathic, inflammatory and chemogenic nociception following intrathecal and intraplantar administration. *Br J Pharmacol* 140: 1381–1388, 2003.
1133. **McKee SC, Thompson CS, Sabourin LA, Hakim AM.** Regulation of expression of early growth response transcription factors in rat primary cortical neurons by extracellular ATP. *Brain Res* 1088: 1–11, 2006.
1134. **McLachlan EM, Luff SE.** Sympathetic innervation of renal and extra-renal arterial vessels. *Kidney Int Suppl* 37: S56–S60, 1992.
1135. **McLarnon JG.** Purinergic mediated changes in Ca²⁺ mobilization and functional responses in microglia: effects of low levels of ATP. *J Neurosci Res* 81: 349–356, 2005.
1136. **McLarnon JG, Choi HB, Lue LF, Walker DG, Kim SU.** Perturbations in calcium-mediated signal transduction in microglia from Alzheimer's disease patients. *J Neurosci Res* 81: 426–435, 2005.
1137. **McQueen DS, Ribeiro JA.** Effect of adenosine on carotid chemoreceptor activity in the cat. *Br J Pharmacol* 74: 129–136, 1981.
1138. **McSwiney BA, Robson JH.** The response of smooth muscle to stimulation of the vagus nerve. *J Physiol* 68: 124–131, 1929.
1139. **Meerlo P, Roman V, Farkas E, Keijser JN, Nyakas C, Luiten PG.** Ageing-related decline in adenosine A₁ receptor binding in the rat brain: an autoradiographic study. *J Neurosci Res* 78: 742–748, 2004.
1140. **Melander A, Sundler F, Westgren U.** Sympathetic innervation of the thyroid: variation with species and with age. *Endocrinology* 96: 102–106, 1975.
1141. **Melani A, Amadio S, Gianfriddo M, Vannucchi MG, Volonté C, Bernardi G, Pedata F, Sancesario G.** P2X₇ receptor modulation on microglial cells and reduction of brain infarct caused by middle cerebral artery occlusion in rat. *J Cereb Blood Flow Metab* 26: 974–982, 2006.
1142. **Meme W, Ezan P, Venance L, Glowinski J, Giaume C.** ATP-induced inhibition of gap junctional communication is enhanced by interleukin-1 β treatment in cultured astrocytes. *Neuroscience* 126: 95–104, 2004.
1143. **Mendoza-Fernandez V, Andrew D, Barajas-López C.** ATP inhibits glutamate synaptic release by acting at P2Y receptors in pyramidal neurons of hippocampal slices. *J Pharmacol Exp Ther* 293: 172–179, 2000.
1144. **Meng H, Sakakibara M, Nakazawa H, Tokimasa T.** Pyridoxal-phosphate-6-azophenyl-2',4'-disulfonic acid can antagonize the purinoceptor-mediated inhibition of M-current in bullfrog sympathetic neurons. *Neurosci Lett* 337: 93–96, 2003.
1145. **Merlo D, Volonté C.** Binding and functions of extracellular ATP in cultured cerebellar granule neurons. *Biochem Biophys Res Commun* 225: 907–914, 1996.
1146. **Metaea MR, Newman EA.** Glial cells dilate and constrict blood vessels: a mechanism of neurovascular coupling. *J Neurosci* 26: 2862–2870, 2006.
1147. **Meyer MP, Gröschel-Stewart U, Robson T, Burnstock G.** Expression of two ATP-gated ion channels, P2X₅ and P2X₆, in developing chick skeletal muscle. *Dev Dyn* 216: 442–449, 1999.
1148. **Mi Z, Jackson EK.** Effects of α - and β -adrenoceptor blockade on purine secretion by sympathetic nerve stimulation in the rat kidney. *J Pharmacol Exp Ther* 288: 295–301, 1999.
1149. **Miao LY, Tang JP, Esposito DP, Zhang JH.** Age-related changes in P2 receptor mRNA of rat cerebral arteries. *Exp Gerontol* 37: 67–79, 2001.
1150. **Mietz H, Chevez-Barrios P, Feldman RM, Lieberman MW.** Suramin inhibits wound healing following filtering procedures for glaucoma. *Br J Ophthalmol* 82: 816–820, 1998.
1151. **Miles GB, Parkis MA, Lipski J, Funk GD.** Modulation of phrenic motoneuron excitability by ATP: consequences for respiratory-related output in vitro. *J Appl Physiol* 92: 1899–1910, 2002.
1152. **Miller RE.** Pancreatic neuroendocrinology: peripheral neural mechanisms in the regulation of the Islets of Langerhans. *Endocr Rev* 2: 471–494, 1981.

1153. **Millward-Sadler SJ, Wright MO, Flatman PW, Salter DM.** ATP in the mechanotransduction pathway of normal human chondrocytes. *Biorheology* 41: 567–575, 2004.
1154. **Milosevic J, Brandt A, Roemuss U, Arnold A, Wegner F, Schwarz SC, Storch A, Zimmermann H, Schwarz J.** Uracil nucleotides stimulate human neural precursor cell proliferation and dopaminergic differentiation: involvement of MEK/ERK signalling. *J Neurochem* 99: 913–923, 2006.
1155. **Mio K, Kubo Y, Ogura T, Yamamoto T, Sato C.** Visualization of the trimeric P2X₂ receptor with a crown-capped extracellular domain. *Biochem Biophys Res Commun* 337: 998–1005, 2005.
1156. **Miras-Portugal MT, Diaz-Hernández M, Giráldez L, Hervás C, Gómez-Villafuertes R, Sen RP, Gualix J, Pintor J.** P2X₇ receptors in rat brain: presence in synaptic terminals and granule cells. *Neurochem Res* 28: 1597–1605, 2003.
1157. **Mironov SL.** Metabotropic ATP receptor in hippocampal and thalamic neurones: pharmacology and modulation of Ca²⁺ mobilizing mechanisms. *Neuropharmacology* 33: 1–13, 1994.
1158. **Mishra SK, Braun N, Shukla V, Füllgrabe M, Schomerus C, Korf HW, Gachet C, Ikehara Y, Sévigny J, Robson SC, Zimmermann H.** Extracellular nucleotide signaling in adult neural stem cells: synergism with growth factor-mediated cellular proliferation. *Development* 133: 675–684, 2006.
1159. **Mitchell CH.** Release of ATP by a human retinal pigment epithelial cell line: potential for autocrine stimulation through subretinal space. *J Physiol* 534: 193–202, 2001.
1160. **Mitchell CH, Carré DA, McGlenn AM, Stone RA, Civan MM.** A release mechanism for stored ATP in ocular ciliary epithelial cells. *Proc Natl Acad Sci USA* 95: 7174–7178, 1998.
1161. **Mizumoto N, Mummert ME, Shalhevet D, Takashima A.** Keratinocyte ATP release assay for testing skin-irritating potentials of structurally diverse chemicals. *J Invest Dermatol* 121: 1066–1072, 2003.
1162. **Moalem G, Tracey DJ.** Immune and inflammatory mechanisms in neuropathic pain. *Brain Res* 51: 240–264, 2006.
1163. **Mokashi A, Li J, Roy A, Baby SM, Lahiri S.** ATP causes glomus cell [Ca²⁺]_i increase without corresponding increases in CSN activity. *Respir Physiol Neurobiol* 138: 1–18, 2003.
1164. **Molliver DC, Cook SP, Carlsten JA, Wright DE, McCleskey EW.** ATP and UTP excite sensory neurons and induce CREB phosphorylation through the metabotropic receptor, P2Y₂. *Eur J Neurosci* 16: 1850–1860, 2002.
1165. **Molliver DC, Wright DE, Leitner ML, Parsadanian AS, Doster K, Wen D, Yan Q, Snider WD.** IB4-binding DRG neurons switch from NGF to GDNF dependence in early postnatal life. *Neuron* 19: 849–861, 1997.
1166. **Mongin AA, Kimelberg HK.** ATP regulates anion channel-mediated organic osmolyte release from cultured rat astrocytes via multiple Ca²⁺-sensitive mechanisms. *Am J Physiol Cell Physiol* 288: C204–C213, 2005.
1167. **Monro RL, Bertrand PP, Bornstein JC.** ATP and 5-HT are the principal neurotransmitters in the descending excitatory reflex pathway of the guinea-pig ileum. *Neurogastroenterol Motil* 14: 255–264, 2002.
1168. **Monro RL, Bertrand PP, Bornstein JC.** ATP participates in three excitatory postsynaptic potentials in the submucous plexus of the guinea pig ileum. *J Physiol* 556: 571–584, 2004.
1169. **Montana V, Malarkey EB, Verderio C, Matteoli M, Parpura V.** Vesicular transmitter release from astrocytes. *Glia* 54: 700–715, 2006.
1170. **Moody CJ, Burnstock G.** Evidence for the presence of P₁-purinoceptors on cholinergic nerve terminals in the guinea-pig ileum. *Eur J Pharmacol* 77: 1–9, 1982.
1171. **Mooradian AD, Grabau G, Bastani B.** Adenosine triphosphatases of rat cerebral microvessels. Effect of age and diabetes mellitus. *Life Sci* 55: 1261–1265, 1994.
1172. **Moore D, Chambers J, Waldvogel H, Faull R, Emson P.** Regional and cellular distribution of the P2Y₁ purinergic receptor in the human brain: striking neuronal localisation. *J Comp Neurol* 421: 374–384, 2000.
1173. **Moore D, Iritani S, Chambers J, Emson P.** Immunohistochemical localization of the P2Y₁ purinergic receptor in Alzheimer's disease. *Neuroreport* 11: 3799–3803, 2000.
1174. **Moore KA, Nicoll RA, Schmitz D.** Adenosine gates synaptic plasticity at hippocampal mossy fiber synapses. *Proc Natl Acad Sci USA* 100: 14397–14402, 2003.
1175. **Moore KH, Ray FR, Barden JA.** Loss of purinergic P2X₃ and P2X₅ receptor innervation in human detrusor from adults with urge incontinence. *J Neurosci* 21: 1–6, 2001.
1176. **Moores TS, Hasdemir B, Vega-Riveroll L, Deuchars J, Parson SH.** Properties of presynaptic P2X₇-like receptors at the neuromuscular junction. *Brain Res* 1034: 40–50, 2005.
1177. **Morairty S, Rainnie D, McCarley R, Greene R.** Disinhibition of ventrolateral preoptic area sleep-active neurons by adenosine: a new mechanism for sleep promotion. *Neuroscience* 123: 451–457, 2004.
1178. **Morales B, Barrera N, Uribe P, Mora C, Villalon M.** Functional cross talk after activation of P2 and P1 receptors in oviductal ciliated cells. *Am J Physiol Cell Physiol* 279: C658–C669, 2000.
1179. **Morán-Jiménez M, Matute C.** Immunohistochemical localization of the P2Y₁ purinergic receptor in neurons and glial cells of the central nervous system. *Brain Res* 78: 50–58, 2000.
1180. **Morciano M, Ortinau S, Zimmermann H.** Guanine nucleotides inhibit NMDA and kainate-induced neurotoxicity in cultured rat hippocampal and neocortical neurons. *Neurochem Int* 45: 95–101, 2004.
1181. **Moreland RB, Brioni JD, Sullivan JP.** Emerging pharmacologic approaches for the treatment of lower urinary tract disorders. *J Pharmacol Exp Ther* 308: 797–804, 2004.
1182. **Mori M, Heuss C, Gahwiler BH, Gerber U.** Fast synaptic transmission mediated by P2X receptors in CA3 pyramidal cells of rat hippocampal slice cultures. *J Physiol* 535: 115–123, 2001.
1183. **Mori M, Tsushima H, Matsuda T.** Antidiuretic effects of ATP induced by microinjection into the hypothalamic supraoptic nucleus in water-loaded and ethanol-anesthetized rats. *Jpn J Pharmacol* 66: 445–450, 1994.
1184. **Morita K, Morioka N, Abdin J, Kitayama S, Nakata Y, Dohi T.** Development of tactile allodynia and thermal hyperalgesia by intrathecally administered platelet-activating factor in mice. *Pain* 111: 351–359, 2004.
1185. **Mørk H, Ashina M, Bendtsen L, Olesen J, Jensen R.** Experimental muscle pain and tenderness following infusion of endogenous substances in humans. *Eur J Pain* 7: 145–153, 2003.
1186. **Morley P, Chakravarthy BR, Mealing GA, Tsang BK, Whitfield JF.** Role of protein kinase C in the regulation of ATP-triggered intracellular Ca²⁺ oscillations in chicken granulosa cells. *Eur J Endocrinol* 134: 743–750, 1996.
1187. **Mosqueda-Garcia R, Tseng CJ, Appalsamy M, Beck C, Robertson D.** Cardiovascular excitatory effects of adenosine in the nucleus of the solitary tract. *Hypertension* 18: 494–502, 1991.
1188. **Motin L, Bennett MR.** Effect of P₂-purinoceptor antagonists on glutamatergic transmission in the rat hippocampus. *Br J Pharmacol* 115: 1276–1280, 1995.
1189. **Moyes DG.** Malignant hyperpyrexia caused by trimeprazine. Case report. *Br J Anaesth* 45: 1163–1164, 1973.
1190. **Mulkey DK, Mistry AM, Guyenet PG, Bayliss DA.** Purinergic P2 receptors modulate excitability but do not mediate pH sensitivity of RTN respiratory chemoreceptors. *J Neurosci* 26: 7230–7233, 2006.
1191. **Müller M, Henrich A, Klockenhoff J, Dierkes PW, Schlue WR.** Effects of ATP and derivatives on neuropile glial cells of the leech central nervous system. *Glia* 29: 191–201, 2000.
1192. **Mulligan SJ, MacVicar BA.** Calcium transients in astrocyte endfeet cause cerebrovascular constrictions. *Nature* 431: 195–199, 2004.
1193. **Mumtaz FH, Lau DH, Siddiqui EJ, Morgan RJ, Thompson CS, Mikhailidis DP.** Changes in cholinergic and purinergic neurotransmission in the diabetic rabbit bladder. *In Vivo* 20: 1–4, 2006.
1194. **Muñoz DJ, Kendrick IS, Rassam M, Thorne PR.** Vesicular storage of adenosine triphosphate in the guinea-pig cochlear lateral wall and concentrations of ATP in the endolymph during sound exposure and hypoxia. *Acta Otolaryngol* 121: 10–15, 2001.
1195. **Murakami T, Fujihara T, Nakamura M, Nakata K.** P2Y₂ receptor stimulation increases tear fluid secretion in rabbits. *Curr Eye Res* 21: 782–787, 2000.

1196. **Murillo-Rodriguez E, Blanco-Centurion C, Gerashchenko D, Salin-Pascual RJ, Shiromani PJ.** The diurnal rhythm of adenosine levels in the basal forebrain of young and old rats. *Neuroscience* 123: 361–370, 2004.
1197. **Nabekura T, Tomohiro M, Ito Y, Kitagawa S.** Changes in plasma membrane Ca^{2+} -ATPase expression and ATP content in lenses of hereditary cataract UPL rats. *Toxicology* 197: 177–183, 2004.
1198. **Nabekura J, Ueno S, Ogawa T, Akaike N.** Colocalization of ATP and nicotinic ACh receptors in the identified vagal preganglionic neurone of rat. *J Physiol* 489: 519–527, 1995.
1199. **Nagamine K, Ozaki N, Shinoda M, Asai H, Kuba K, Tohnai I, Ueda M, Sugiura Y.** Thermal and mechanical hyperalgesia induced by experimental squamous cell carcinoma of the lower gingival in rats. *Abstract Viewer/Itinerary Planner*. Washington, DC: Society for Neuroscience, 2004. (Program No.298.9 2004)
1200. **Nagel J, Schladebach H, Koch M, Schwienbacher I, Müller CE, Hauber W.** Effects of an adenosine A_{2A} receptor blockade in the nucleus accumbens on locomotion, feeding, prepulse inhibition in rats. *Synapse* 49: 279–286, 2003.
1201. **Nakagawa T, Akaike N, Kimitsuki T, Komune S, Arima T.** ATP-induced current in isolated outer hair cells of guinea-pig cochlea. *J Neurophysiol* 63: 1068–1074, 1990.
1202. **Nakamura F, Strittmatter SM.** P2Y_1 purinergic receptors in sensory neurons: contribution to touch-induced impulse generation. *Proc Natl Acad Sci USA* 93: 10465–10470, 1996.
1203. **Nakamura M, Mie M, Funabashi H, Yamamoto K, Ando J, Kobatake E.** Cell-surface-localized ATP detection with immobilized firefly luciferase. *Anal Biochem* 352: 61–67, 2006.
1204. **Nakanishi H, Takeda H.** The possible role of adenosine triphosphate in chemical transmission between the hypogastric nerve terminal and seminal vesicle in the guinea-pig. *Jpn J Pharmacol* 23: 479–490, 1973.
1205. **Nakano H, Furuya K, Yamagishi S.** Synergistic effects of ATP on oxytocin-induced intracellular Ca^{2+} response in mouse mammary myoepithelial cells. *Pflügers Arch* 442: 57–63, 2001.
1206. **Nakata H, Yoshioka K, Kamiya T.** Purinergic-receptor oligomerization: implications for neural functions in the central nervous system. *Neurotox Res* 6: 291–297, 2004.
1207. **Nakatsuka T, Furue H, Yoshimura M, Gu JG.** Activation of central terminal vanilloid receptor-1 receptors and alpha beta-methylene-ATP-sensitive P2X receptors reveals a converged synaptic activity onto the deep dorsal horn neurons of the spinal cord. *J Neurosci* 22: 1228–1237, 2002.
1208. **Nakatsuka T, Gu JG.** ATP P2X receptor-mediated enhancement of glutamate release and evoked EPSCs in dorsal horn neurons of the rat spinal cord. *J Neurosci* 21: 6522–6531, 2001.
1209. **Nakatsuka T, Gu JG.** P2X purinoceptors and sensory transmission. *Pflügers Arch* 452: 598–607, 2006.
1210. **Nakatsuka T, Mena N, Ling J, Gu JG.** Depletion of substance P from rat primary sensory neurons by ATP, an implication of P2X receptor-mediated release of substance P. *Neuroscience* 107: 293–300, 2001.
1211. **Nakatsuka T, Tsuzuki K, Ling JX, Sonobe H, Gu JG.** Distinct roles of P2X receptors in modulating glutamate release at different primary sensory synapses in rat spinal cord. *J Neurophysiol* 89: 3243–3252, 2003.
1212. **Nakayama S, Yamashita T, Konishi M, Kazama H, Kokubun S.** P2Y -mediated Ca^{2+} response is spatiotemporally graded and synchronized in sensory neurons: a two-photon photolysis study. *FASEB J* 18: 1562–1564, 2004.
1213. **Nakazawa K, Inoue K, Inoue K.** ATP reduces voltage-activated K^+ current in cultured rat hippocampal neurons. *Pflügers Arch* 429: 143–145, 1994.
1214. **Namasivayam S, Eardley I, Morrison JFB.** Purinergic sensory neurotransmission in the urinary bladder: an in vitro study in the rat. *BJU Int* 84: 854–860, 1999.
1215. **Narcisse L, Scemes E, Zhao Y, Lee SC, Brosnan CF.** The cytokine IL- β transiently enhances P2X_7 receptor expression and function in human astrocytes. *Glia* 49: 245–258, 2005.
1216. **Nassar N, Abdel-Rahman AA.** Central adenosine signaling plays a key role in centrally mediated hypotension in conscious aortic barodenervated rats. *J Pharmacol Exp Ther* 318: 255–261, 2006.
1217. **Nasu-Tada K, Koizumi S, Tsuda M, Kunifusa E, Inoue K.** Possible involvement of increase in spinal fibronectin following peripheral nerve injury in upregulation of microglial P2X_4 , a key molecule for mechanical allodynia. *Glia* 53: 769–775, 2006.
1218. **Nathanson MH, Burgstahler AD, Masyuk A, LaRusso NF.** Stimulation of ATP secretion in the liver by therapeutic bile acids. *Biochem J* 358: 1–5, 2001.
1219. **Neal M, Cunningham J.** Modulation by endogenous ATP of the light-evoked release of ACh from retinal cholinergic neurones. *Br J Pharmacol* 113: 1085–1087, 1994.
1220. **Neal MJ, Cunningham JR, Dent Z.** Modulation of extracellular GABA levels in the retina by activation of glial P2X -purinoceptors. *Br J Pharmacol* 124: 317–322, 1998.
1221. **Neary JT, Kang Y.** P2 purinergic receptors signal to glycogen synthase kinase- β in astrocytes. *J Neurosci Res* 84: 515–524, 2006.
1222. **Neary JT, Kang Y, Shi YF.** Cell cycle regulation of astrocytes by extracellular nucleotides and fibroblast growth factor-2. *Purinergic Signalling* 1: 329–336, 2005.
1223. **Neary JT, Kang Y, Shi YF, Tran MD, Wanner IB.** P2 receptor signalling, proliferation of astrocytes, expression of molecules involved in cell-cell interactions. *Novartis Found Symp* 276: 131–143, 2006.
1224. **Neary JT, Kang Y, Tran M, Feld J.** Traumatic injury activates protein kinase B/Akt in cultured astrocytes: role of extracellular ATP and P2 purinergic receptors. *J Neurotrauma* 22: 491–500, 2005.
1225. **Neary JT, Kang Y, Willoughby KA, Ellis EF.** Activation of extracellular signal-regulated kinase by stretch-induced injury in astrocytes involves extracellular ATP and P2 purinergic receptors. *J Neurosci* 23: 2348–2356, 2003.
1226. **Neary JT, Rathbone MP, Cattabeni F, Abbracchio MP, Burnstock G.** Trophic actions of extracellular nucleotides and nucleosides on glial and neuronal cells. *Trends Neurosci* 19: 13–18, 1996.
1227. **Neary JT, van Breemen C, Forster E, Norenberg LOB, Norenberg MD.** ATP stimulates calcium influx in primary astrocyte cultures. *Biochem Biophys Res Commun* 157: 1410–1416, 1988.
1228. **Neary JT, Whittmore SR, Zhu Q, Norenberg MD.** Synergistic activation of DNA synthesis in astrocytes by fibroblast growth factors and extracellular ATP. *J Neurochem* 63: 490–494, 1994.
1229. **Nedeljkovic N, Banjac A, Horvat A, Stojiljkovic M, Nikezic G.** Developmental profile of NTPDase activity in synaptic plasma membranes isolated from rat cerebral cortex. *Int J Dev Neurosci* 23: 45–51, 2005.
1230. **Nedeljkovic N, Bjelobaba I, Subasic S, Lavrnja I, Pekovic S, Stojkov D, Vjestica A, Rakic L, Stojiljkovic M.** Up-regulation of ectonucleotidase activity after cortical stab injury in rats. *Cell Biol Int* 30: 541–546, 2006.
1231. **Nedergaard M.** Direct signaling from astrocytes to neurons in cultures of mammalian brain cells. *Science* 263: 1768–1771, 1994.
1232. **Needleman P, Minkes MS, Douglas JR.** Stimulation of prostaglandin biosynthesis by adenine nucleotides. Profile of prostaglandin release by perfused organs. *Circ Res* 34: 455–460, 1974.
1233. **Nelson DW, Gregg RJ, Kort ME, Perez-Medrano A, Voight EA, Wang Y, Grayson P, Namovic MT, Donnelly-Roberts DL, Niforatos W, Honore G, Jarvis MF, Faltynek CR, Carroll WA.** Structure-activity relationship studies on a series of novel, substituted 1-benzyl-5-phenyltetrazole P2X_7 antagonists. *J Med Chem* 49: 3659–3666, 2006.
1234. **Neuhuber WL, Tieggs G.** Innervation of immune cells: evidence for neuroimmunomodulation in the liver. *Anat Rec A Discov Mol Cell Evol Biol* 280: 884–892, 2004.
1235. **Newman EA.** Propagation of intercellular calcium waves in retinal astrocytes and Müller cells. *J Neurosci* 21: 2215–2223, 2001.
1236. **Newman EA.** Glial modulation of synaptic transmission in the retina. *Glia* 47: 268–274, 2004.
1237. **Newman EA.** A purinergic dialogue between glia and neurons in the retina. In: *Novartis Foundation Symposium 276 Purinergic Signalling in Neuron-Glia Interactions*. Chichester, UK: Wiley, 2006, p. 193–207.
1238. **Newman EA, Zahs KR.** Calcium waves in retinal glial cells. *Science* 275: 844–847, 1997.

1239. **Newsom B, Dahlstrom A, Enerback L, Ahlman H.** Suggestive evidence for a direct innervation of mucosal mast cells. *Neuroscience* 10: 565–570, 1983.
1240. **Nicke A, Baumert HG, Rettinger J, Eichele A, Lambrecht G, Mutschler E, Schmalzing G.** P2X₁ and P2X₃ receptors form stable trimers: a novel structural motif of ligand-gated ion channels. *EMBO J* 17: 3016–3028, 1998.
1241. **Nicolaidis R, Bruno AN, Sarkis JJ, Souza DO.** Increase of adenosine nucleotide hydrolysis in rat hippocampal slices after seizures induced by quinolinic acid. *Neurochem Res* 30: 385–390, 2005.
1242. **Nicot A, Kurnellas M, Elkabes S.** Temporal pattern of plasma membrane calcium ATPase 2 expression in the spinal cord correlates with the course of clinical symptoms in two rodent models of autoimmune encephalomyelitis. *Eur J Neurosci* 21: 2660–2670, 2005.
1243. **Nieber K, Poelchen W, Illes P.** Role of ATP in fast excitatory synaptic potentials in locus coeruleus neurones of the rat. *Br J Pharmacol* 122: 423–430, 1997.
1244. **Nikbakht MR, Stone TW.** Suramin-sensitive suppression of paired-pulse inhibition by adenosine nucleotides in rat hippocampal slices. *Neurosci Lett* 278: 45–48, 2000.
1245. **Niklasson F, Ågren H, Hällgren R.** Purine and monoamine metabolites in cerebrospinal fluid: parallel purinergic and monoaminergic activation in depressive illness? *J Neurol Neurosurg Psychiatry* 46: 255–260, 1983.
1246. **Nikolic P, Housley GD, Luo L, Ryan AF, Thorne PR.** Transient expression of P2X₁ receptor subunits of ATP-gated ion channels in the developing rat cochlea. *Brain Res* 126: 173–182, 2001.
1247. **Nishiguchi J, Hayashi Y, Chancellor MB, de MF, de Groat WC, Kumon H, Yoshimura N.** Detrusor overactivity induced by intravesical application of adenosine 5'-triphosphate under different delivery conditions in rats. *Urology* 66: 1332–1337, 2005.
1248. **Nishiguchi J, Sasaki K, Seki S, Chancellor MB, Erickson KA, de Groat WC, Kumon H, Yoshimura N.** Effects of isolectin B4-conjugated saporin, a targeting cytotoxin, on bladder overactivity induced by bladder irritation. *Eur J Neurosci* 20: 474–482, 2004.
1249. **Nishimura T, Tokimasa T.** Purinergic cation channels in neurons of rabbit vesical parasympathetic ganglia. *Neurosci Lett* 212: 215–217, 1996.
1250. **Nishizaki T.** ATP- and adenosine-mediated signaling in the central nervous system: adenosine stimulates glutamate release from astrocytes via A_{2a} adenosine receptors. *J Pharmacol Sci* 94: 100–102, 2004.
1251. **Nishizaki T, Mori M.** Diverse signal transduction pathways mediated by endogenous P₂ receptors in cultured rat cerebral cortical neurons. *J Neurophysiol* 79: 2513–2521, 1998.
1252. **Noble MD, Liddle RA.** Neurohormonal control of exocrine pancreatic secretion. *Curr Opin Gastroenterol* 21: 531–537, 2005.
1253. **Nobrega JN, Barlow KL, Raymond R, Richter A.** Decreased adenosine receptor binding in dystonic brains of the *dt^{sz}* mutant. *Neuroscience* 134: 33–38, 2005.
1254. **Noguchi J, Yamashita H.** Adenosine inhibits voltage-dependent Ca²⁺ currents in rat dissociated supraoptic neurones via A₁ receptors. *J Physiol* 526: 313–326, 2000.
1255. **Nörenberg W, Gobel I, Meyer A, Cox SL, Starke K, Trendelenburg AU.** Stimulation of mouse cultured sympathetic neurons by uracil but not adenine nucleotides. *Neuroscience* 103: 227–236, 2001.
1256. **Nörenberg W, von Kügelgen I, Meyer A, Illes P, Starke K.** M-type K⁺ currents in rat cultured thoracolumbar sympathetic neurones and their role in uracil nucleotide-evoked noradrenaline release. *Br J Pharmacol* 129: 709–723, 2000.
1257. **North RA.** Molecular physiology of P2X receptors. *Physiol Rev* 82: 1013–1067, 2002.
1258. **North RA, Verkhratsky A.** Purinergic transmission in the central nervous system. *Pflügers Arch* 452: 479–485, 2006.
1259. **Norton WHJ, Rohr KB, Burnstock G.** Embryonic expression of a P2X₃ receptor encoding gene in zebrafish. *Mech Dev* 99: 149–152, 2000.
1260. **Novak I.** ATP as a signaling molecule: the exocrine focus. *News Physiol Sci* 18: 12–17, 2003.
1261. **Novakovic SD, Kassotakis LC, Oglesby IB, Smith JAM, Eglen RM, Ford APDW, Hunter JC.** Immunocytochemical localization of P2X₃ purinoceptors in sensory neurons in naive rats and following neuropathic injury. *Pain* 80: 273–282, 1999.
1262. **Núñez L, Villalobos C, Frawley LS.** Extracellular ATP as an autocrine/paracrine regulator of prolactin release. *Am J Physiol Endocrinol Metab* 272: E1117–E1123, 1997.
1263. **Nurgali K, Furness JB, Stebbing MJ.** Analysis of purinergic and cholinergic fast synaptic transmission to identified myenteric neurons. *Neuroscience* 116: 335–347, 2003.
1264. **Nurse CA.** Neurotransmission and neuromodulation in the chemosensory carotid body. *Auton Neurosci* 120: 1–9, 2005.
1265. **O'Connor SE, Dainty IA, Leff P.** Further subclassification of ATP receptors based on agonist studies. *Trends Pharmacol Sci* 12: 137–141, 1991.
1266. **O'Neill M, Brown VJ.** The effect of the adenosine A_{2A} antagonist KW-6002 on motor and motivational processes in the rat. *Psychopharmacology* 184: 46–55, 2006.
1267. **O'Reilly BA, Kosaka AH, Chang TK, Ford AP, Popert R, Rymer JM, McMahon SB.** A quantitative analysis of purinoceptor expression in human fetal and adult bladders. *J Urol* 165: 1730–1734, 2001.
1268. **O'Reilly BA, Kosaka AH, Knight GE, Chang TK, Ford APDW, Rymer JM, Popert R, Burnstock G, McMahon SB.** P2X receptors and their role in female idiopathic detrusor instability. *J Urol* 167: 157–164, 2002.
1269. **Ogata T, Chuai M, Morino T, Yamamoto H, Nakamura Y, Schubert P.** Adenosine triphosphate inhibits cytokine release from lipopolysaccharide-activated microglia via P2y receptors. *Brain Res* 981: 174–183, 2003.
1270. **Ohta T, Kai T, Ito S.** Evidence for paracrine modulation of voltage-dependent calcium channels by amperometric analysis in cultured porcine adrenal chromaffin cells. *Brain Res* 1030: 183–192, 2004.
1271. **Ohta T, Kubota A, Murakami M, Otsuguro K, Ito S.** P2X₂ receptors are essential for [Ca²⁺]_i increases in response to ATP in cultured rat myenteric neurons. *Am J Physiol Gastrointest Liver Physiol* 289: G935–G948, 2005.
1272. **Okada M, Kawata Y, Murakami T, Wada K, Mizuno K, Kaneko S.** Interaction between purinoceptor subtypes on hippocampal serotonergic transmission using in vivo microdialysis. *Neuropharmacology* 38: 707–715, 1999.
1273. **Okada M, Nakagawa T, Minami M, Satoh M.** Analgesic effects of intrathecal administration of P2Y nucleotide receptor agonists UTP and UDP in normal and neuropathic pain model rats. *J Pharmacol Exp Ther* 303: 66–73, 2002.
1274. **Okada Y, Kuroda Y.** Inhibitory action of adenosine and adenine nucleotides on the postsynaptic potential of olfactory cortex slices of the guinea pig. *Proc Jpn Acad* 51: 491–494, 1975.
1275. **Olah ME, Stiles GL.** The role of receptor structure in determining adenosine receptor activity. *Pharmacol Ther* 85: 55–75, 2000.
1276. **Oliveira L, Timóteo MA, Correia-de-Sá P.** Tetanic depression is overcome by tonic adenosine A_{2A} receptor facilitation of L-type Ca²⁺ influx into rat motor nerve terminals. *J Physiol* 560: 157–168, 2004.
1277. **Oliveira MC, Parada CA, Veiga MC, Rodrigues LR, Barros SP, Tambeli CH.** Evidence for the involvement of endogenous ATP and P2X receptors in TMJ pain. *Eur J Pain* 9: 87–93, 2005.
1278. **Olsson RA, Pearson JD.** Cardiovascular purinoceptors. *Physiol Rev* 70: 761–845, 1990.
1279. **Omatsu-Kanbe M, Inoue K, Fujii Y, Yamamoto T, Isono T, Fujita N, Matsuura H.** Effect of ATP on preadipocyte migration and adipocyte differentiation by activating P2Y receptors in 3T3-L1 cells. *Biochem J* 393: 171–180, 2006.
1280. **Omatsu-Kanbe M, Isono T, Matsuura H.** Multiple P2 receptors contribute to a transient increase in intracellular Ca²⁺ concentration in ATP-stimulated rat brown adipocytes. *Exp Physiol* 87: 643–652, 2002.
1281. **Oomori Y, Okuno S, Fujisawa H, Iuchi H, Ishikawa K, Satoh Y, Ono K.** Ganglion cells immunoreactive for catecholamine-synthesizing enzymes, neuropeptide Y and vasoactive intestinal polypeptide in the rat adrenal gland. *Cell Tissue Res* 275: 201–213, 1994.

1282. **Osborne NN.** *Dale's Principle and Communication Between Neurons.* Oxford, UK: Pergamon Press, 1983.
1283. **Oses JP.** Modification by kainate-induced convulsions of the density of presynaptic P2X receptors in the rat hippocampus. *Purinergic Signalling* 2: 252–253, 2006.
1284. **Oshima Y, Furuuchi T, Fujii R.** Cyclic nucleotide action is mediated through adenosine receptors in damselfish motile iridophores. *Comp Biochem Physiol* 85: 89–93, 1989.
1285. **Otsuguro K, Asano T, Ohta T, Ito S, Nakazato Y.** ATP-evoked membrane current in guinea pig adrenal chromaffin cells. *Neurosci Lett* 187: 145–148, 1995.
1286. **Ouslander JG.** Management of overactive bladder. *N Engl J Med* 350: 786–799, 2004.
1287. **Owyang C, Logsdon CD.** New insights into neurohormonal regulation of pancreatic secretion. *Gastroenterology* 127: 957–969, 2004.
1288. **Paddle BM, Burnstock G.** Release of ATP from perfused heart during coronary vasodilatation. *Blood Vessels* 11: 110–119, 1974.
1289. **Paemeleire K, Leybaert L.** ATP-dependent astrocyte-endothelial calcium signaling following mechanical damage to a single astrocyte in astrocyte-endothelial co-cultures. *J Neurotrauma* 17: 345–358, 2000.
1290. **Paes de Carvalho R, Braas KM, Alder R, Snyder SH.** Developmental regulation of adenosine A₁ receptors, uptake sites and endogenous adenosine in the chick retina. *Brain Res* 70: 87–95, 1992.
1291. **Pafundo DE, Mut P, Pérez RM, González-Lebrero RM, Fachino V, Krumshabel G, Schwarzbaum PJ.** Effects of extracellular nucleotides and their hydrolysis products on regulatory volume decrease of trout hepatocytes. *Am J Physiol Regul Integr Comp Physiol* 287: R833–R843, 2004.
1292. **Page AJ, Martin CM, Blackshaw LA.** Vagal mechanoreceptors and chemoreceptors in mouse stomach and esophagus. *J Neurophysiol* 87: 2095–2103, 2002.
1293. **Page AJ, O'Donnell TA, Blackshaw LA.** P2X purinoceptor-induced sensitization of ferret vagal mechanoreceptors in oesophageal inflammation. *J Physiol* 523: 403–411, 2000.
1294. **Palea S, Artibani W, Ostardo E, Trist DG, Pietra C.** Evidence for purinergic neurotransmission in human urinary bladder affected by interstitial cystitis. *J Urol* 150: 2007–2012, 1993.
1295. **Palmer ML, Lee SY, Carlson D, Fahrenkrug S, O'Grady SM.** Stable knockdown of CFTR establishes a role for the channel in P2Y receptor-stimulated anion secretion. *J Cell Physiol* 206: 759–770, 2006.
1296. **Panatier A, Poulain DA, Oliet SH.** Regulation of transmitter release by high-affinity group III mGluRs in the supraoptic nucleus of the rat hypothalamus. *Neuropharmacology* 47: 333–341, 2004.
1297. **Panchenko VA, Pintor J, Tsyndrenko AY, Miras-Portugal MT, Krishtal OA.** Diadenosine polyphosphates selectively potentiate N-type Ca²⁺ channels in rat central neurons. *Neuroscience* 70: 353–360, 1996.
1298. **Pandita RK, Andersson KE.** Intravesical adenosine triphosphate stimulates the micturition reflex in awake, freely moving rats. *J Urol* 168: 1230–1234, 2002.
1299. **Pankratov Y, Lalo U, Castro E, Miras-Portugal MT, Krishtal O.** ATP receptor-mediated component of the excitatory synaptic transmission in the hippocampus. *Prog Brain Res* 120: 237–249, 1999.
1300. **Pankratov YV, Lalo UV, Krishtal OA.** Role for P2X receptors in long-term potentiation. *J Neurosci* 22: 8363–8369, 2002.
1301. **Pankratov Y, Lalo U, Krishtal O, Verkhratsky A.** Ionotropic P2X purinoceptors mediate synaptic transmission in rat pyramidal neurones of layer II/III of somato-sensory cortex. *J Physiol* 542: 529–536, 2002.
1302. **Pankratov Y, Lalo U, Verkhratsky A, North RA.** Vesicular release of ATP at central synapses. *Pflügers Arch* 452: 589–597, 2006.
1303. **Pannicke T, Fischer W, Biedermann B, Schädlich H, Grosche J, Faude F, Wiedemann P, Allgaier C, Illes P, Burnstock G, Reichenbach A.** P2X₇ receptors in Müller glial cells from the human retina. *J Neurosci* 20: 5965–5972, 2000.
1304. **Pannicke T, Weick M, Uckermann O, Wheeler-Schilling T, Fries JE, Reichel MB, Mohr C, Stahl T, Fluess M, Kacza J, Seeger J, Richt JA, Reichenbach A.** Electrophysiological alterations and upregulation of ATP receptors in retinal glial Müller cells from rats infected with the Borna disease virus. *Glia* 35: 213–223, 2001.
1305. **Pape HC.** Adenosine promotes burst activity in guinea-pig geniculocortical neurones through two different ionic mechanisms. *J Physiol* 447: 729–753, 1992.
1306. **Papka RE, Hafemeister J, Storey-Workley M.** P2X receptors in the rat uterine cervix, lumbosacral dorsal root ganglia, spinal cord during pregnancy. *Cell Tissue Res* 321: 35–44, 2005.
1307. **Papp L, Balazsa T, Kofalvi A, Erdelyi F, Szabo G, Vizi ES, Sperlagh B.** P2X receptor activation elicits transporter-mediated noradrenaline release from rat hippocampal slices. *J Pharmacol Exp Ther* 310: 973–980, 2004.
1308. **Papp L, Vizi ES, Sperlagh B.** Lack of ATP-evoked GABA and glutamate release in the hippocampus of P2X₇ receptor^{-/-} mice. *Neuroreport* 15: 2387–2391, 2004.
1309. **Pappone PA, Lee SC.** Purinergic receptor stimulation increases membrane trafficking in brown adipocytes. *J Gen Physiol* 108: 393–404, 1996.
1310. **Paradiso AM, Ribeiro CM, Boucher RC.** Polarized signaling via purinoceptors in normal and cystic fibrosis airway epithelia. *J Gen Physiol* 117: 53–67, 2001.
1311. **Park KS, Jeong SW, Cha SK, Lee BS, Kong ID, Ikeda SR, Lee JW.** Modulation of N-type Ca²⁺ currents by A₁-adenosine receptor activation in male rat pelvic ganglion neurons. *J Pharmacol Exp Ther* 299: 501–508, 2001.
1312. **Park MK, Garrad RC, Weisman GA, Turner JT.** Changes in P2Y₁ nucleotide receptor activity during the development of rat salivary glands. *Am J Physiol Cell Physiol* 272: C1388–C1393, 1997.
1313. **Park SY, Kim HI, Shin YK, Lee CS, Park M, Song JH.** Modulation of sodium currents in rat sensory neurons by nucleotides. *Brain Res* 1006: 168–176, 2004.
1314. **Parvathenani LK, Tertysnikova S, Greco CR, Roberts SB, Robertson B, Posmantur R.** P2X₇ mediates superoxide production in primary microglia and is up-regulated in a transgenic mouse model of Alzheimer's disease. *J Biol Chem* 278: 13309–13317, 2003.
1315. **Pascual O, Casper KB, Kubera C, Zhang J, Revilla-Sanchez R, Sul JY, Takano H, Moss SJ, McCarthy K, Haydon PG.** Astrocytic purinergic signaling coordinates synaptic networks. *Science* 310: 113–116, 2005.
1316. **Paskitti M, Reid KH.** Use of an adenosine triphosphate-based “cocktail” early in reperfusion substantially improves brain protein synthesis after global ischemia in rats. *Neurosci Lett* 331: 147–150, 2002.
1317. **Patacchini R, De Giorgio R, Barthó L, Barbara G, Corinaldesi R, Maggi CA.** Evidence that tachykinins are the main NANC excitatory neurotransmitters in the guinea-pig common bile duct. *Br J Pharmacol* 124: 1703–1711, 1998.
1318. **Patel MK, Khakh BS, Henderson G.** Properties of native P2X receptors in rat trigeminal mesencephalic nucleus neurones: lack of correlation with known, heterologously expressed P2X receptors. *Neuropharmacology* 40: 96–105, 2001.
1319. **Paton DM.** Structure-activity relations for presynaptic inhibition of noradrenergic and cholinergic transmission by adenosine: evidence for action on A1 receptors. *J Auton Pharmacol* 1: 287–290, 1981.
1320. **Paton JF, De Paula PM, Spyer KM, Machado BH, Boscan P.** Sensory afferent selective role of P2 receptors in the nucleus tractus solitarius for mediating the cardiac component of the peripheral chemoreceptor reflex in rats. *J Physiol* 543: 995–1005, 2002.
1321. **Paton WD, Vane JR.** Analysis of the responses of the isolated stomach to electrical stimulation and to drugs. *J Physiol* 165: 10–46, 1963.
1322. **Patti L, Raiteri L, Grilli M, Parodi M, Raiteri M, Marchi M.** P2X₇ receptors exert a permissive role on the activation of release-enhancing presynaptic α7 nicotinic receptors co-existing on rat neocortex glutamatergic terminals. *Neuropharmacology* 50: 705–713, 2006.

1323. **Pazzagli M, Corsi C, Fratti S, Pedata F, Pepeu G.** Regulation of extracellular adenosine levels in the striatum of aging rats. *Brain Res* 684: 103–106, 1995.
1324. **Pearson RA, Dale N, Llaudet E, Mobbs P.** ATP released via gap junction hemichannels from the pigment epithelium regulates neural retinal progenitor proliferation. *Neuron* 46: 731–744, 2005.
1325. **Pearson T, Damian K, Lynas RE, Frenguelli BG.** Sustained elevation of extracellular adenosine and activation of A₁ receptors underlie the post-ischaemic inhibition of neuronal function in rat hippocampus in vitro. *J Neurochem* 97: 1357–1368, 2006.
1326. **Pelleg A, Hurt CM.** Evidence for ATP-triggered vagal reflex in the canine heart in vivo. *Ann NY Acad Sci* 603: 441–442, 1990.
1327. **Pelleg A, Hurt CM.** Mechanism of action of ATP on canine pulmonary vagal C fibre nerve terminals. *J Physiol* 490: 265–275, 1996.
1328. **Pelleg A, Schulman ES.** Adenosine 5'-triphosphate axis in obstructive airway diseases. *Am J Ther* 9: 454–464, 2002.
1329. **Pellegatti P, Falzoni S, Pinton P, Rizzuto R, Di Virgilio F.** A novel recombinant plasma membrane-targeted luciferase reveals a new pathway for ATP secretion. *Mol Biol Cell* 16: 3659–3665, 2005.
1330. **Peng SC, Ho CM, Ho ST, Tsai SK, Su CK.** The role of intraspinal adenosine A1 receptors in sympathetic regulation. *Eur J Pharmacol* 492: 49–55, 2004.
1331. **Percy WH, Fromm TH, Wangsness CE.** Muscularis mucosae contraction evokes colonic secretion via prostaglandin synthesis and nerve stimulation. *Am J Physiol Gastrointest Liver Physiol* 284: G213–G220, 2003.
1332. **Pereira GS, Mello e Souza T, Battastini AM, Izquierdo I, Sarkis JJ, Bonan CD.** Effects of inhibitory avoidance training and/or isolated foot-shock on ectonucleotidase activities in synaptosomes of the anterior and posterior cingulate cortex and the medial precentral area of adult rats. *Behav Brain Res* 128: 121–127, 2002.
1333. **Pereira GS, Rossato JI, Sarkis JJ, Cammarota M, Bonan CD, Izquierdo I.** Activation of adenosine receptors in the posterior cingulate cortex impairs memory retrieval in the rat. *Neurobiol Learn Mem* 83: 217–223, 2005.
1334. **Perez MT, Bruun A.** Colocalization of [³H]-adenosine accumulation and GABA immunoreactivity in the chicken and rabbit retinas. *Histochemistry* 87: 413–417, 1987.
1335. **Perez MT, Ehinger BE, Lindstrom K, Fredholm BB.** Release of endogenous and radioactive purines from the rabbit retina. *Brain Res* 398: 106–112, 1986.
1336. **Peroutka SJ.** Migraine: a chronic sympathetic nervous system disorder. *Headache* 44: 53–64, 2004.
1337. **Peterson WM, Meggyesy C, Yu K, Miller SS.** Extracellular ATP activates calcium signaling, ion, fluid transport in retinal pigment epithelium. *J Neurosci* 17: 2324–2337, 1997.
1338. **Petruska JC, Cooper BY, Gu JG, Rau KK, Johnson RD.** Distribution of P2X₁, P2X₂, P2X₃ receptor subunits in rat primary afferents: relation to population markers and specific cell types. *J Chem Neuroanat* 20: 141–162, 2000.
1339. **Pfeilschifter J.** Comparison of extracellular ATP and UTP signalling in rat renal mesangial cells. *Biochem J* 272: 469–472, 1990.
1340. **Pham TM, Morris JB, Arthur JF, Post GR, Brown JH, Woodcock EA.** UTP but not ATP causes hypertrophic growth in neonatal rat cardiomyocytes. *J Mol Cell Cardiol* 35: 287–292, 2003.
1341. **Phillips JK, Hill CE.** Neuroreceptor mRNA expression in the rat mesenteric artery develops independently of innervation. *Int J Dev Neurosci* 17: 377–386, 1999.
1342. **Phillis JW.** Potentiation of the action of adenosine on cerebral cortical neurones by the tricyclic antidepressants. *Br J Pharmacol* 83: 567–575, 1984.
1343. **Phillis JW, Barraco RA, DeLong RE, Washington DO.** Behavioral characteristics of centrally administered adenosine analogs. *Pharmacol Biochem Behav* 24: 263–270, 1986.
1344. **Phillis JW, Edstrom JP, Kostopoulos GK, Kirkpatrick JR.** Effects of adenosine and adenine nucleotides on synaptic transmission in the cerebral cortex. *Can J Physiol Pharmacol* 57: 1289–1312, 1979.
1345. **Phillis JW, Jiang ZG, Chelack BJ, Wu PH.** The effect of morphine on purine and acetylcholine release from rat cerebral cortex: evidence for a purinergic component in morphine's action. *Pharmacol Biochem Behav* 13: 421–427, 1980.
1346. **Phillis JW, Kirkpatrick JR.** The actions of adenosine and various nucleosides and nucleotides on the isolated toad spinal cord. *Gen Pharmacol* 9: 239–247, 1978.
1347. **Phillis JW, Kostopoulos GK, Limacher JJ.** Depression of corticospinal cells by various purines and pyrimidines. *Can J Physiol Pharmacol* 52: 1226–1229, 1974.
1348. **Phillis JW, Scislo TJ, O'Leary D.** Purines and the nucleus of the solitary tract: effects on cardiovascular and respiratory function. *Proc Aust Physiol Pharmacol Soc* 28: 14–21, 1997.
1349. **Phillis JW, Walter GA, Simpson RE.** Release of purines and neurotransmitter amino acids into cerebral cortical perfusates during and following transient ischaemic. *Int J Purine Pysimidine Res* 2: 41–46, 1991.
1350. **Phillis JW, Wu PH.** The role of adenosine and its nucleotides in central synaptic transmission. *Prog Neurobiol* 16: 187–239, 1981.
1351. **Pillai S, Bikle DD.** Adenosine triphosphate stimulates phosphoinositide metabolism, mobilizes intracellular calcium, inhibits terminal differentiation of human epidermal keratinocytes. *J Clin Invest* 90: 42–51, 1992.
1352. **Pinna A, Wardas J, Simola N, Morelli M.** New therapies for the treatment of Parkinson's disease: adenosine A_{2A} receptor antagonists. *Life Sci* 77: 3259–3267, 2005.
1353. **Pinna C, Rubino A, Burnstock G.** Age-related changes in purinergic and adrenergic components of sympathetic neurotransmission in guinea-pig seminal vesicles. *Br J Pharmacol* 122: 1411–1416, 1997.
1354. **Pintor J.** Purinergic signalling in the eye. In: *Nervous Control of the Eye*, edited by Burnstock G and Sillito AM. Amsterdam: Harwood Academic, 2000, p. 171–210.
1355. **Pintor J, Bautista A, Carracedo G, Peral A.** UTP and diadenosine tetraphosphate accelerate wound healing in the rabbit cornea. *Ophthalmic Physiol Opt* 24: 186–193, 2004.
1356. **Pintor J, Diaz-Hernández M, Gualix J, Gómez-Villafuertes R, Hernando F, Miras-Portugal MT.** Diadenosine polyphosphate receptors from rat and guinea-pig brain to human nervous system. *Pharmacol Ther* 87: 103–115, 2000.
1357. **Pintor J, Peral A, Pelaez T, Carracedo G, Bautista A, Hoyle CH.** Nucleotides and dinucleotides in ocular physiology: new possibilities of nucleotides as therapeutic agents in the eye. *Drug Dev Res* 59: 136–145, 2003.
1358. **Pintor J, Peral A, Pelaez T, Martin S, Hoyle CH.** Presence of diadenosine polyphosphates in the aqueous humor: their effect on intraocular pressure. *J Pharmacol Exp Ther* 304: 342–348, 2003.
1359. **Poelchen W, Sieler D, Inoue K, Illes P.** Effect of extracellular adenosine 5'-triphosphate on principal neurons of the rat ventral tegmental area. *Brain Res* 800: 170–173, 1998.
1360. **Poelchen W, Sieler D, Wirkner K, Illes P.** Co-transmitter function of ATP in central catecholaminergic neurons of the rat. *Neuroscience* 102: 593–602, 2001.
1361. **Poletto Chaves LA, Pontelli EP, Varanda WA.** P2X receptors in mouse Leydig cells. *Am J Physiol Cell Physiol* 290: C1009–C1017, 2006.
1362. **Poli A, Di Iorio P, Beraudi A, Notari S, Zaccanti F, Villani L, Traversa U.** The calcium-dependent [³H]acetylcholine release from synaptosomes of brown trout (*Salmo trutta*) optic tectum is inhibited by adenosine A₁ receptors: effects of enucleation on A₁ receptor density and cholinergic markers. *Brain Res* 892: 78–85, 2001.
1363. **Poli A, Pavan B, Lucchi R, Borasio PG, Fabbri E, Rossi R.** Biochemical and pharmacological characterization of adenosine A1 receptors in eel (*Anguilla anguilla*) brain. *Fish Physiol Biochem* 16: 19–27, 1997.
1364. **Poole DP, Castelucci P, Robbins HL, Chiocchetti R, Furness JB.** The distribution of P2X₃ purine receptor subunits in the guinea pig enteric nervous system. *Auton Neurosci* 101: 39–47, 2002.
1365. **Pooler AM, Guez DH, Benedictus R, Wurtman RJ.** Uridine enhances neurite outgrowth in nerve growth factor-differentiated PC12. *Neuroscience* 134: 207–214, 2005.
1366. **Popoli P, Pezzola A, Reggio R, Malchiodi AF, Falchi M.** Adenosine A_{2A} receptor blockade prevents EEG and motor abnormal-

- ities in a rat model of Huntington's disease. *Drug Dev Res* 50: 69, 2000.
1367. **Popoli P, Pèzzola A, Scotti de Carolis A.** Modulation of striatal adenosine A₁ and A₂ receptors induces rotational behaviour in response to dopaminergic stimulation in intact rats. *Eur J Pharmacol* 257: 21–25, 1994.
1368. **Popoli P, Reggio R, Pezzola A, Fuxe K, Ferre S.** Adenosine A₁ and A_{2A} receptor antagonists stimulate motor activity: evidence for an increased effectiveness in aged rats. *Neurosci Lett* 251: 201–204, 1998.
1369. **Porkka-Heiskanen T, Strecker RE, Thakkar M, Bjørkum AA, Greene RW, McCarley RW.** Adenosine: a mediator of the sleep-inducing effects of prolonged wakefulness. *Science* 276: 1265–1268, 1997.
1370. **Porter JT, McCarthy KD.** Hippocampal astrocytes in situ respond to glutamate released from synaptic terminals. *J Neurosci* 16: 5073–5081, 1996.
1371. **Potter DD, Furshpan EJ, Landis SC.** Multiple-transmitter status and "Dale's Principle." *Neurosci Comment* 1: 1–9, 1981.
1372. **Potter P, White TD.** Release of adenosine 5'-triphosphate from synaptosomes from different regions of rat brain. *Neuroscience* 5: 1351–1356, 1980.
1373. **Potucek YD, Crain JM, Watters JJ.** Purinergic receptors modulate MAP kinases and transcription factors that control microglial inflammatory gene expression. *Neurochem Int* 49: 204–214, 2006.
1374. **Poulsen AN, Klausen TL, Pedersen PS, Willumsen NJ, Frederiksen O.** Regulation of ion transport via apical purinergic receptors in intact rabbit airway epithelium. *Pflügers Arch* 450: 227–235, 2005.
1375. **Powell AD, Teschemacher AG, Seward EP.** P2Y purinoceptors inhibit exocytosis in adrenal chromaffin cells via modulation of voltage-operated calcium channels. *J Neurosci* 20: 606–616, 2000.
1376. **Prabhakar NR.** O₂ sensing at the mammalian carotid body: why multiple O₂ sensors and multiple transmitters? *Exp Physiol* 91: 17–23, 2006.
1377. **Prasad M, Fearon IM, Zhang M, Laing M, Vollmer C, Nurse CA.** Expression of P2X₂ and P2X₃ receptor subunits in rat carotid body afferent neurones: role in chemosensory signalling. *J Physiol* 537: 667–677, 2001.
1378. **Prediger RD, Batista LC, Takahashi RN.** Caffeine reverses age-related deficits in olfactory discrimination and social recognition memory in rats. Involvement of adenosine A₁ and A_{2A} receptors. *Neurobiol Aging* 26: 957–964, 2005.
1379. **Price GD, Robertson SJ, Edwards FA.** Long-term potentiation of glutamatergic synaptic transmission induced by activation of presynaptic P2Y receptors in the rat medial habenula nucleus. *Eur J Neurosci* 17: 844–850, 2003.
1380. **Prince FP.** Ultrastructural evidence of indirect and direct autonomic innervation of human Leydig cells: comparison of neonatal, childhood and pubertal ages. *Cell Tissue Res* 269: 383–390, 1992.
1381. **Prinster SC, Hague C, Hall RA.** Heterodimerization of G protein-coupled receptors: specificity and functional significance. *Pharmacol Rev* 57: 289–298, 2005.
1382. **Prothero LS, Mathie A, Richards CD.** Purinergic and muscarinic receptor activation activates a common calcium entry pathway in rat neocortical neurons and glial cells. *Neuropharmacology* 39: 1768–1778, 2000.
1383. **Pugliese AM, Coppi E, Spalluto G, Corradetti R, Pedata F.** A₃ adenosine receptor antagonists delay irreversible synaptic failure caused by oxygen and glucose deprivation in the rat CA1 hippocampus in vitro. *Br J Pharmacol* 147: 524–532, 2006.
1384. **Pull I, McIlwain H.** Adenine derivatives as neurohumoral agents in the brain. The quantities liberated on excitation of superfused cerebral tissues. *Biochem J* 130: 975–981, 1972.
1385. **Purcell WM, Atterwill CK.** Mast cells in neuroimmune function: neurotoxicological and neuropharmacological perspectives. *Neurochem Res* 20: 521–532, 1995.
1386. **Puthussery T, Fletcher EL.** P2X₂ receptors on ganglion and amacrine cells in cone pathways of the rat retina. *J Comp Neurol* 496: 595–609, 2006.
1387. **Puthussery T, Yee P, Vingrys AJ, Fletcher EL.** Evidence for the involvement of purinergic P2X₇ receptors in outer retinal processing. *Eur J Neurosci* 24: 7–19, 2006.
1388. **Radford KM, Virginio C, Surprenant A, North RA, Kawashima E.** Baculovirus expression provides direct evidence for heteromeric assembly of P2X₂ and P2X₃ receptors. *J Neurosci* 17: 6529–6533, 1997.
1389. **Raffaghello L, Chiozzi P, Falzoni S, Di Virgilio F, Pistoia V.** The P2X₇ receptor sustains the growth of human neuroblastoma cells through a substance P-dependent mechanism. *Cancer Res* 66: 907–914, 2006.
1390. **Ralevic V, Belai A, Burnstock G.** Effects of streptozotocin-diabetes on sympathetic nerve, endothelial and smooth muscle function in the rat mesenteric arterial bed. *Eur J Pharmacol* 286: 193–199, 1995.
1391. **Ralevic V, Burnstock G.** Postjunctional synergism of noradrenaline and adenosine 5'-triphosphate in the mesenteric arterial bed of the rat. *Eur J Pharmacol* 175: 291–299, 1990.
1392. **Ralevic V, Burnstock G.** Receptors for purines and pyrimidines. *Pharmacol Rev* 50: 413–492, 1998.
1393. **Ralevic V, Thomas T, Burnstock G, Spyer KM.** Characterization of P2 receptors modulating neural activity in rat rostral ventrolateral medulla. *Neuroscience* 94: 867–878, 1999.
1394. **Ramme D, Regenold JT, Starke K, Busse R, Illes P.** Identification of the neuroeffector transmitter in jejunal branches of the rabbit mesenteric artery. *Naunyn-Schmiedeberg's Arch Pharmacol* 336: 267–273, 1987.
1395. **Raouf R, Blais D, Séguéla P.** High zinc sensitivity and pore formation in an invertebrate P2X receptor. *Biochim Biophys Acta* 1669: 135–141, 2005.
1396. **Rapp DE, Lyon MB, Bales GT, Cook SP.** A role for the P2X receptor in urinary tract physiology and in the pathophysiology of urinary dysfunction. *Eur Urol* 48: 303–308, 2005.
1397. **Rappold PM, Lynd-Balta E, Joseph SA.** P2X₇ receptor immunoreactive profile confined to resting and activated microglia in the epileptic brain. *Brain Res* 1089: 171–178, 2006.
1398. **Rathbone MP, Middlemiss PJ, Gysbers JW, Andrew C, Herman MA, Reed JK, Ciccarelli R, Di Iorio P, Caciagli F.** Trophic effects of purines in neurons and glial cells. *Prog Neurobiol* 59: 663–690, 1999.
1399. **Raybould HE, Cooke HJ, Christofi FL.** Sensory mechanisms: transmitters, modulators and reflexes. *Neurogastroenterol Motil* 16 Suppl 1: 60–63, 2004.
1400. **Rayner DV.** The sympathetic nervous system in white adipose tissue regulation. *Proc Nutr Soc* 60: 357–364, 2001.
1401. **Rebola N, Porciuncula LO, Lopes LV, Oliveira CR, Soares-da-Silva P, Cunha RA.** Long-term effect of convulsive behavior on the density of adenosine A1 and A2A receptors in the rat cerebral cortex. *Epilepsia* 46 Suppl 5: 159–165, 2005.
1402. **Rebola N, Rodrigues RJ, Lopes LV, Richardson PJ, Oliveira CR, Cunha RA.** Adenosine A₁ and A_{2A} receptors are co-expressed in pyramidal neurons and co-localized in glutamatergic nerve terminals of the rat hippocampus. *Neuroscience* 133: 79–83, 2005.
1403. **Reece TB, Davis JD, Okonkwo DO, Maxey TS, Ellman PI, Li X, Linden J, Tribble CG, Kron IL, Kern JA.** Adenosine A_{2A} analogue reduces long-term neurologic injury after blunt spinal trauma. *J Surg Res* 121: 130–134, 2004.
1404. **Reekie FM, Burnstock G.** Some effects of purines on neurones of guinea-pig superior cervical ganglia. *Gen Pharmacol* 25: 143–148, 1994.
1405. **Rees DA, Scanlon MF, Ham J.** Novel insights into how purines regulate pituitary cell function. *Clin Sci* 104: 467–481, 2003.
1406. **Reese JH, Cooper JR.** Modulation of the release of acetylcholine from ileal synaptosomes by adenosine and adenosine 5'-triphosphate. *J Pharmacol Exp Ther* 223: 612–616, 1982.
1407. **Reichsman F, Santos S, Westhead EW.** Two distinct ATP receptors activate calcium entry and internal calcium release in bovine chromaffin cells. *J Neurochem* 65: 2080–2086, 1995.
1408. **Reinohl J, Hoheisel U, Unger T, Mense S.** Adenosine triphosphate as a stimulant for nociceptive and non-nociceptive muscle group IV receptors in the rat. *Neurosci Lett* 338: 25–28, 2003.

1409. **Reist NE, Smith SJ.** Neurally evoked calcium transients in terminal Schwann cells at the neuromuscular junction. *Proc Natl Acad Sci USA* 89: 7625–7629, 1992.
1410. **Rekling JC, Funk GD, Bayliss DA, Dong XW, Feldman JL.** Synaptic control of motoneuronal excitability. *Physiol Rev* 80: 767–852, 2000.
1411. **Ren J, Bian X, DeVries M, Schnegelsberg B, Cockayne DA, Ford AP, Galligan JJ.** P2X₂ subunits contribute to fast synaptic excitation in myenteric neurons of the mouse small intestine. *J Physiol* 552: 809–821, 2003.
1412. **Ren J, Galligan JJ.** Dynamics of fast synaptic excitation during trains of stimulation in myenteric neurons of guinea-pig ileum. *Auton Neurosci* 117: 67–78, 2005.
1413. **Renton T, Yiangou Y, Baecker PA, Ford AP, Anand P.** Capsaicin receptor VR1 and ATP purinoceptor P2X₃ in painful and nonpainful human tooth pulp. *J Orofac Pain* 17: 245–250, 2003.
1414. **Resta V, Novelli E, Di Virgilio F, Galli-Resta L.** Neuronal death induced by endogenous extracellular ATP in retinal cholinergic neuron density control. *Development* 132: 2873–2882, 2005.
1415. **Retey JV, Adam M, Honegger E, Khatami R, Luhmann UF, Jung HH, Berger W, Landolt HP.** A functional genetic variation of adenosine deaminase affects the duration and intensity of deep sleep in humans. *Proc Natl Acad Sci USA* 102: 15676–15681, 2005.
1416. **Rex CS, Kramár EA, Colgin LL, Lin B, Gall CM, Lynch G.** Long-term potentiation is impaired in middle-aged rats: regional specificity and reversal by adenosine receptor antagonists. *J Neurosci* 25: 5956–5966, 2005.
1417. **Reynolds JD, Brien JF.** The role of adenosine A1 receptor activation in ethanol-induced inhibition of stimulated glutamate release in the hippocampus of the fetal and adult guinea pig. *Alcohol* 12: 151–157, 1995.
1418. **Rhee JS, Wang ZM, Nabekura J, Inoue K, Akaike N.** ATP facilitates spontaneous glycinergic IPSC frequency at dissociated rat dorsal horn interneuron synapses. *J Physiol* 524: 471–483, 2000.
1419. **Ribeiro JA.** Potentiation of postjunctional cholinergic sensitivity of rat diaphragm muscle by high-energy-phosphate adenine nucleotides. *J Membr Biol* 33: 401–402, 1977.
1420. **Ribeiro JA.** Purinergic modulation of transmitter release. *J Theor Biol* 80: 259–270, 1979.
1421. **Ribeiro JA, Cunha RA, Lopes LV, Coelho JE, Costenla AR, Correia-de-Sá P, Cunha RA, de Mendonça A, Sebastião AM.** Adenosine receptor interactions in the hippocampus. *Drug Dev Res* 52: 337–345, 2005.
1422. **Ribeiro JA, Sebastião AM.** On the role, inactivation and origin of endogenous adenosine at the frog neuromuscular junction. *J Physiol* 384: 571–585, 1987.
1423. **Ribeiro JA, Sebastião AM, de Mendonça A.** Adenosine receptors in the nervous system: pathophysiological implications. *Prog Neurobiol* 68: 377–392, 2003.
1424. **Ribeiro JA, Walker J.** The effects of adenosine triphosphate and adenosine diphosphate on transmission at the rat and frog neuromuscular junctions. *Br J Pharmacol* 54: 213–218, 1975.
1425. **Rich PB, Douillet CD, Mahler SA, Husain SA, Boucher RC.** Adenosine triphosphate is released during injurious mechanical ventilation and contributes to lung edema. *J Trauma* 55: 290–297, 2003.
1426. **Richardson PJ, Brown SJ.** ATP release from affinity-purified rat cholinergic nerve terminals. *J Neurochem* 48: 622–630, 1987.
1427. **Richardson PJ, Kase H, Jenner PG.** Adenosine A_{2A} receptor antagonists as new agents for the treatment of Parkinson's disease. *Trends Pharmacol Sci* 18: 338–344, 1997.
1428. **Rico EP, Senger MR, Fauth MG, Dias RD, Bogo MR, Bonan CD.** ATP and ADP hydrolysis in brain membranes of zebrafish (*Danio rerio*). *Life Sci* 73: 2071–2082, 2003.
1429. **Roberts JA, Vial C, Digby HR, Agboh KC, Wen H, Tterbury-Thomas A, Evans RJ.** Molecular properties of P2X receptors. *Pflügers Arch* 452: 486–500, 2006.
1430. **Robertson SJ, Burnashev N, Edwards FA.** Ca²⁺ permeability and kinetics of glutamate receptors in rat medial habenula neurones: implications for purinergic transmission in this nucleus. *J Physiol* 518: 539–549, 1999.
1431. **Robertson SJ, Ennion SJ, Evans RJ, Edwards FA.** Synaptic P2X receptors. *Curr Opin Neurobiol* 11: 378–386, 2001.
1432. **Robertson SJ, Rae MG, Rowan EG, Kennedy C.** Characterization of a P2X-purinoceptor in cultured neurones of the rat dorsal root ganglia. *Br J Pharmacol* 118: 951–956, 1996.
1433. **Robinson DR, McNaughton PA, Evans ML, Hicks GA.** Characterization of the primary spinal afferent innervation of the mouse colon using retrograde labelling. *Neurogastroenterol Motil* 16: 113–124, 2004.
1434. **Robinson PM, Perry RA, Hardy KJ, Coghlan JP, Scoggins BA.** The innervation of the adrenal cortex in the sheep, *Ovis ovis*. *J Anat* 124: 117–129, 1977.
1435. **Robitaille R.** Modulation of synaptic efficacy and synaptic depression by glial cells at the frog neuromuscular junction. *Neuron* 21: 847–855, 1998.
1436. **Rocha I, Burnstock G, Spyer KM.** Effect on urinary bladder function and arterial blood pressure of the activation of putative purine receptors in brainstem areas. *Auton Neurosci* 88: 6–15, 2001.
1437. **Rochon D, Rouse I, Robitaille R.** Synapse-glia interactions at the mammalian neuromuscular junction. *J Neurosci* 21: 3819–3829, 2001.
1438. **Rodrigue-Candela JL, Martin-Hernandez D, Castilla-Cortazar T.** Stimulation of insulin secretion in vitro by adenosine triphosphate. *Nature* 197: 1304, 1963.
1439. **Rodrigues RJ, Almeida T, Richardson PJ, Oliveira CR, Cunha RA.** Dual presynaptic control by ATP of glutamate release via facilitatory P2X₁, P2X_{2/3}, P2X₃ and inhibitory P2Y₁, P2Y₂, and/or P2Y₄ receptors in the rat hippocampus. *J Neurosci* 25: 6286–6295, 2005.
1440. **Roman RM, Fitz JG.** Emerging roles of purinergic signaling in gastrointestinal epithelial secretion and hepatobiliary function. *Gastroenterology* 116: 964–979, 1999.
1441. **Romanello M, Codognotto A, Bicego M, Pines A, Tell G, D'Andrea P.** Autocrine/paracrine stimulation of purinergic receptors in osteoblasts: contribution of vesicular ATP release. *Biochem Biophys Res Commun* 331: 1429–1438, 2005.
1442. **Rong W, Burnstock G.** Activation of ureter nociceptors by exogenous and endogenous ATP in guinea pig. *Neuropharmacology* 47: 1093–1101, 2004.
1443. **Rong W, Burnstock G, Spyer KM.** P2X purinoceptor-mediated excitation of trigeminal lingual nerve terminals in an in vitro intra-arterially perfused rat tongue preparation. *J Physiol* 524: 891–902, 2000.
1444. **Rong W, Gourine A, Cockayne DA, Xiang Z, Ford APDW, Spyer KM, Burnstock G.** Pivotal role of nucleotide P2X₂ receptor subunit mediating ventilatory responses to hypoxia: knockout mouse studies. *J Neurosci* 23: 11315–11321, 2003.
1445. **Rong W, Spyer M, Burnstock G.** Activation and sensitisation of low and high threshold afferent fibres mediated by P2X receptors in the mouse urinary bladder. *J Physiol* 541: 591–600, 2002.
1446. **Rooney SA.** Regulation of surfactant secretion. *Comp Biochem Physiol A Mol Integr Physiol* 129: 233–243, 2001.
1447. **Ross FM, Brodie MJ, Stone TW.** Modulation by adenine nucleotides of epileptiform activity in the CA3 region of rat hippocampal slices. *Br J Pharmacol* 123: 71–80, 1998.
1448. **Rost S, Daniel C, Schulze-Lohoff E, Baumert HG, Lambrecht G, Hugo C.** P2 receptor antagonist PPADS inhibits mesangial cell proliferation in experimental mesangial proliferative glomerulonephritis. *Kidney Int* 62: 1659–1671, 2002.
1449. **Ruan HZ, Birder LA, de Groat WC, Tai C, Roppolo J, Buffington A, Burnstock G.** Localization of P2X and P2Y receptors in dorsal root ganglia of the cat. *J Histochem Cytochem* 53: 1273–1282, 2005.
1450. **Ruan HZ, Birder LA, Xiang Z, Chopra B, Buffington A, Tai C, Roppolo JR, de Groat WC, Burnstock G.** Expression of P2X and P2Y receptors in the intramural parasympathetic ganglia of the cat urinary bladder. *Am J Physiol Renal Physiol* 290: F1143–F1152, 2006.
1451. **Ruan HZ, Burnstock G.** Localisation of P2Y₁ and P2Y₄ receptors in dorsal root, nodose and trigeminal ganglia of the rat. *Histochem Cell Biol* 120: 415–426, 2003.

1452. **Ruan HZ, Burnstock G.** The distribution of P2X₅ purinergic receptors in the enteric nervous system. *Cell Tissue Res* 319: 191–200, 2005.
1453. **Ruan HZ, Moules E, Burnstock G.** Changes in P2X purinoceptors in sensory ganglia of the mouse during embryonic and postnatal development. *Histochem Cell Biol* 122: 539–551, 2004.
1454. **Ruan T, Lin YS, Lin KS, Kou YR.** Sensory transduction of pulmonary reactive oxygen species by capsaicin-sensitive vagal lung afferent fibres in rats. *J Physiol* 565: 563–578, 2005.
1455. **Ruan T, Lin YS, Lin KS, Kou YR.** Mediator mechanisms involved in TRPV1 and P2X receptor-mediated, ROS-evoked bradypneic reflex in anesthetized rats. *J Appl Physiol* 101: 644–654, 2006.
1456. **Rubino A, Burnstock G.** Capsaicin-sensitive sensory-motor neurotransmission in the peripheral control of cardiovascular function. *Cardiovasc Res* 31: 467–479, 1996.
1457. **Rubio ME, Soto F.** Distinct localization of P2X receptors at excitatory postsynaptic specializations. *J Neurosci* 21: 641–653, 2001.
1458. **Rucker B, Pereira GS, Furstenuau CR, Izquierdo I, Bonan CD, Sarkis JJ.** Inhibitory avoidance task reveals differences in ectonucleotidase activities between male and female rats. *Neurochem Res* 29: 2231–2237, 2004.
1459. **Ruggieri MR Sr.** Mechanisms of disease: role of purinergic signaling in the pathophysiology of bladder dysfunction. *Nat Clin Pract Urol* 3: 206–215, 2006.
1460. **Rühl A.** Glial cells in the gut. *Neurogastroenterol Motil* 17: 777–790, 2005.
1461. **Rump LC, Wilde K, Schollmeyer P.** Prostaglandin E₂ inhibits noradrenaline release and purinergic pressor responses to renal nerve stimulation at 1 Hz in isolated kidneys of young spontaneously hypertensive rats. *J Hypertens* 8: 897–908, 1990.
1462. **Rundén-Pran E, Tansø R, Haug FM, Ottersen OP, Ring A.** Neuroprotective effects of inhibiting N-methyl-D-aspartate receptors, P2X receptors and the mitogen-activated protein kinase cascade: a quantitative analysis in organotypical hippocampal slice cultures subjected to oxygen and glucose deprivation. *Neuroscience* 136: 795–810, 2005.
1463. **Runold M, Cherniack NS, Prabhakar NR.** Effect of adenosine on chemosensory activity of the cat aortic body. *Respir Physiol* 80: 299–306, 1990.
1464. **Ruppelt A, Liang BT, Soto F.** Cloning, functional characterization and developmental expression of a P2X receptor from chick embryo. *Prog Brain Res* 120: 81–90, 1999.
1465. **Ruppelt A, Ma W, Borchardt K, Silberberg SD, Soto F.** Genomic structure, developmental distribution and functional properties of the chicken P2X₅ receptor. *J Neurochem* 77: 1256–1265, 2001.
1466. **Ryan JS, Baldrige WH, Kelly ME.** Purinergic regulation of cation conductances and intracellular Ca²⁺ in cultured rat retinal pigment epithelial cells. *J Physiol* 520: 745–759, 1999.
1467. **Ryan LM, Rachow JW, McCarty DJ.** Synovial fluid ATP: a potential substrate for the production of inorganic pyrophosphate. *J Rheumatol* 18: 716–720, 1991.
1468. **Ryten M, Dunn PM, Neary JT, Burnstock G.** ATP regulates the differentiation of mammalian skeletal muscle by activation of a P2X₅ receptor on satellite cells. *J Cell Biol* 158: 345–355, 2002.
1469. **Ryten M, Hoebertz A, Burnstock G.** Sequential expression of three receptor subtypes for extracellular ATP in developing rat skeletal muscle. *Dev Dyn* 221: 331–341, 2001.
1471. **Ryten M, Yang SY, Dunn PM, Goldspink G, Burnstock G.** Purinoceptor expression in regenerating skeletal muscle in the mdx mouse model of muscular dystrophy and in satellite cell cultures. *FASEB J* 18: 1404–1406, 2004.
1472. **Ryu JK, Choi HB, Hatori K, Heisel RL, Pelech SL, McLarnon JG, Kim SU.** Adenosine triphosphate induces proliferation of human neural stem cells: role of calcium and p70 ribosomal protein S6 kinase. *J Neurosci Res* 72: 352–362, 2003.
1473. **Ryu JK, Kim J, Choi SH, Oh YJ, Lee YB, Kim SU, Jin BK.** ATP-induced in vivo neurotoxicity in the rat striatum via P2 receptors. *Neuroreport* 13: 1611–1615, 2002.
1474. **Ryzhov S, Goldstein AE, Matafonov A, Zeng D, Biaggioni I, Feoktistov I.** Adenosine-activated mast cells induce IgE synthesis by B lymphocytes: an A2B-mediated process involving Th2 cytokines IL-4 and IL-13 with implications for asthma. *J Immunol* 172: 7726–7733, 2004.
1475. **Sabirov R, Okada Y.** ATP release via anion channels. *Purinergic Signalling* 1: 311–328, 2005.
1476. **Saffrey MJ, Hassall CJS, Allen TGJ, Burnstock G.** Ganglia within the gut, heart, urinary bladder and airways: studies in tissue culture. *Int Rev Cytol* 136: 93–144, 1992.
1477. **Safulina VF, Afzalov R, Khiroug L, Cherubini E, Giniatullin R.** Reactive oxygen species mediate the potentiating effects of ATP on GABAergic synaptic transmission in the immature hippocampus. *J Biol Chem* 281: 23464–23470, 2006.
1478. **Safulina VF, Kasyanov AM, Sokolova E, Cherubini E, Giniatullin R.** ATP contributes to the generation of network-driven giant depolarizing potentials in the neonatal rat hippocampus. *J Physiol* 565: 981–992, 2005.
1479. **Sage CL, Marcus DC.** Immunolocalization of P2Y₄ and P2Y₂ purinergic receptors in strial marginal cells and vestibular dark cells. *J Membr Biol* 185: 103–115, 2002.
1480. **Saito M, Gotoh M, Kato K, Kondo A.** Influence of aging on the rat urinary bladder function. *Urol Int* 47: 39–42, 1991.
1481. **Saitow F, Murakoshi T, Suzuki H, Konishi S.** Metabotropic P2Y purinoceptor-mediated presynaptic and postsynaptic enhancement of cerebellar GABAergic transmission. *J Neurosci* 25: 2108–2116, 2005.
1482. **Sakaguchi T, Arase K, Fisler JS, Bray GA.** Effect of a high-fat diet on firing rate of sympathetic nerves innervating brown adipose tissue in anesthetized rats. *Physiol Behav* 45: 1177–1182, 1989.
1483. **Sakama R, Hiruma H, Kawakami T.** Effects of extracellular ATP on axonal transport in cultured mouse dorsal root ganglion neurons. *Neuroscience* 121: 531–535, 2003.
1484. **Salgado AH, Gomez MV, Romano-Silva MA, Prado MA.** Effect of vesamicol on the release of ATP from cortical synaptosomes. *Neurosci Lett* 204: 37–40, 1996.
1485. **Salgado AI, Cunha RA, Ribeiro JA.** Facilitation by P₂ receptor activation of acetylcholine release from rat motor nerve terminals: interaction with presynaptic nicotinic receptors. *Brain Res* 877: 245–250, 2000.
1486. **Salt TE, Hill RG.** Excitation of single sensory neurones in the rat caudal trigeminal nucleus by iontophoretically applied adenosine 5'-triphosphate. *Neurosci Lett* 35: 53–57, 1983.
1487. **Salter KD, Fitz JG, Roman RM.** Domain-specific purinergic signaling in polarized rat cholangiocytes. *Am J Physiol Gastrointest Liver Physiol* 278: G492–G500, 2000.
1488. **Salter MW, De Koninck Y.** An ambiguous fast synapse: a new twist in the tale of two transmitters. *Nat Neurosci* 2: 199–200, 1999.
1489. **Salter MW, De Koninck Y, Henry JL.** Physiological roles for adenosine and ATP in synaptic transmission in the spinal dorsal horn. *Prog Neurobiol* 41: 125–156, 1993.
1490. **Salter MW, Henry JL.** Effects of adenosine 5'-monophosphate and adenosine 5'-triphosphate on functionally identified units in the cat spinal dorsal horn. Evidence for a differential effect of adenosine 5'-triphosphate on nociceptive vs non-nociceptive units. *Neuroscience* 15: 815–825, 1985.
1491. **Salter MW, Hicks JL.** ATP-evoked increases in intracellular calcium in neurons and glia from the dorsal spinal cord. *J Neurosci* 14: 1563–1575, 1994.
1492. **Salter MW, Hicks JL.** ATP causes release of intracellular Ca²⁺ via the phospholipase Cβ/IP₃ pathway in astrocytes from the dorsal spinal cord. *J Neurosci* 15: 2961–2971, 1995.
1493. **Sanada M, Yasuda H, Omatsu-Kanbe M, Sango K, Isono T, Matsuura H, Kikkawa R.** Increase in intracellular Ca²⁺ and calcitonin gene-related peptide release through metabotropic P2Y receptors in rat dorsal root ganglion neurons. *Neuroscience* 111: 413–422, 2002.
1494. **Sanches G, de Alencar LS, Ventura AL.** ATP induces proliferation of retinal cells in culture via activation of PKC and extracellular signal-regulated kinase cascade. *Int J Dev Neurosci* 20: 21–27, 2002.
1495. **Sánchez-Nogueiro J, Marin-Garcia P, Miras-Portugal MT.** Characterization of a functional P2X₇-like receptor in cerebellar

- granule neurons from P2X₇ knockout mice. *FEBS Lett* 579: 3783–3788, 2005.
1496. **Sann H, Jancsó G, Ambrus A, Pierau FK.** Capsaicin treatment induces selective sensory degeneration and increased sympathetic innervation in the rat ureter. *Neuroscience* 67: 953–966, 1995.
 1497. **Sansum AJ, Chessell IP, Hicks GA, Trezise DJ, Humphrey PPA.** Evidence that P2X purinoceptors mediate the excitatory effects of α βmethylene-ADP in rat locus coeruleus neurones. *Neuropharmacology* 37: 875–885, 1998.
 1498. **Santos DA, Salgado AI, Cunha RA.** ATP is released from nerve terminals and from activated muscle fibres on stimulation of the rat phrenic nerve. *Neurosci Lett* 338: 225–228, 2003.
 1499. **Santos PF, Caramelo OL, Carvalho AP, Duarte CB.** Characterization of ATP release from cultures enriched in cholinergic amacrine-like neurons. *J Neurobiol* 41: 340–348, 1999.
 1500. **Sanz JM, Di Virgilio F.** Kinetics and mechanism of ATP-dependent IL-1 β release from microglial cells. *J Immunol* 164: 4893–4898, 2000.
 1501. **Sasaki T, Gallacher DV.** Extracellular ATP activates receptor-operated cation channels in mouse lacrimal acinar cells to promote calcium influx in the absence of phosphoinositide metabolism. *FEBS Lett* 264: 130–134, 1990.
 1502. **Sasaki T, Gallacher DV.** The ATP-induced inward current in mouse lacrimal acinar cells is potentiated by isoprenaline and GTP. *J Physiol* 447: 103–118, 1992.
 1503. **Satoh S, Matsumura H, Kanbayashi T, Yoshida Y, Urakami T, Nakajima T, Kimura N, Nishino S, Yoneda H.** Expression pattern of FOS in orexin neurons during sleep induced by an adenosine A_{2A} receptor agonist. *Behav Brain Res* 170: 277–286, 2006.
 1504. **Sattin A, Rall TW.** The effect of adenosine and adenine nucleotides on the cyclic adenosine 3',5'-phosphate content of guinea-pig cerebral cortex slices. *Mol Pharmacol* 6: 13–23, 1970.
 1505. **Savegnago L, Nogueira CW, Fachineto R, Rocha JBT.** Characterization of ATP and ADP hydrolysis activity in rat gastric mucosa. *Cell Biol Int* 29: 559–566, 2005.
 1506. **Sawynok J, Downie JW, Reid AR, Cahill CM, White TD.** ATP release from dorsal spinal cord synaptosomes: characterization and neuronal origin. *Brain Res* 610: 32–38, 1993.
 1507. **Sawynok J, Jhamandas KH.** Inhibition of acetylcholine release from cholinergic nerves by adenosine, adenine nucleotides and morphine: antagonism by theophylline. *J Pharmacol Exp Ther* 197: 379–390, 1976.
 1508. **Sawynok J, Liu XJ.** Adenosine in the spinal cord and periphery: release and regulation of pain. *Prog Neurobiol* 69: 313–340, 2003.
 1509. **Sawynok J, Sweeney MI, White TD.** Adenosine release may mediate spinal analgesia by morphine. *Trends Pharmacol Sci* 10: 186–189, 1989.
 1510. **Scammell TE, Gerashchenko DY, Mochizuki T, McCarthy MT, Estabrooke IV, Sears CA, Saper CB, Urade Y, Hayaishi O.** An adenosine A_{2A} agonist increases sleep and induces Fos in ventrolateral preoptic neurons. *Neuroscience* 107: 653–663, 2001.
 1511. **Schäfer R, Reiser G.** ATP α S is a ligand for P2Y receptors in synaptosomal membranes: solubilization of [³⁵S]ATP α S binding proteins associated with G proteins. *Neurochem Int* 34: 303–317, 1999.
 1512. **Scheibler P, Pesic M, Franke H, Reinhardt R, Wirkner K, Illes P, Norenberg W.** P2X₂ and P2Y₁ immunofluorescence in rat neostriatal medium-spiny projection neurones and cholinergic interneurones is not linked to respective purinergic receptor function. *Br J Pharmacol* 143: 119–131, 2004.
 1513. **Schetinger MR, Vieira VL, Morsch VM, Balz D.** ATP and ADP hydrolysis in fish, chicken and rat synaptosomes. *Comp Biochem Physiol B Biochem Mol Biol* 128: 731–741, 2001.
 1514. **Schiffmann SN, Vanderhaeghen JJ.** Age-related loss of mRNA encoding adenosine A₂ receptor in the rat striatum. *Neurosci Lett* 158: 121–124, 1993.
 1515. **Schipke CG, Boucsein C, Ohlemeyer C, Kirchhoff F, Kettenmann H.** Astrocyte Ca²⁺ waves trigger responses in microglial cells in brain slices. *FASEB J* 16: 255–257, 2002.
 1516. **Schmidt M, Löffler G.** Induction of aromatase activity in human adipose tissue stromal cells by extracellular nucleotides—evidence for P2-purinoceptors in adipose tissue. *Eur J Biochem* 252: 147–154, 1998.
 1517. **Schödel J, Weise I, Klinger R, Schmidt M.** Stimulation of lipogenesis in rat adipocytes by ATP, a ligand for P2-receptors. *Biochem Biophys Res Commun* 321: 767–773, 2004.
 1518. **Scholfield CN.** Depression of evoked potentials in brain slices by adenosine compounds. *Br J Pharmacol* 63: 239–244, 1978.
 1519. **Schrader J, Wahl M, Kuschinsky W, Kreutzberg GW.** Increase of adenosine content in cerebral cortex of the cat during bicuculline-induced seizure. *Pflügers Arch* 387: 245–251, 1980.
 1520. **Schreiber R, Kunzelmann K.** Purinergic P2Y₆ receptors induce Ca²⁺ and CFTR dependent Cl⁻ secretion in mouse trachea. *Cell Physiol Biochem* 16: 99–108, 2005.
 1521. **Schubert P, Kreutzberg GW.** Axonal transport of adenosine and uridine derivatives and transfer to postsynaptic neurons. *Brain Res* 76: 526–530, 1974.
 1522. **Schümann HJ.** Effects of insulin and reserpine on the adrenalin and ATP content of the chromatic granules of the adrenal medulla. *Naunyn-Schmiedeberg Arch Exp Pathol Pharmacol* 233: 237–249, 1958.
 1523. **Schwab JM, Guo L, Schluesener HJ.** Spinal cord injury induces early and persistent lesional P2X₄ receptor expression. *J Neuroimmunol* 163: 185–189, 2005.
 1524. **Schwartz AD, Whitacre CL, Lin Y, Wilson DF.** Adenosine inhibits N-type calcium channels at the rat neuromuscular junction. *Clin Exp Pharmacol Physiol* 30: 174–177, 2003.
 1525. **Schwartz DD, Malik KU.** Renal periaarterial nerve stimulation-induced vasoconstriction at low frequencies is primarily due to release of a purinergic transmitter in the rat. *J Pharmacol Exp Ther* 250: 764–771, 1989.
 1526. **Schweitzer E.** Coordinated release of ATP and ACh from cholinergic synaptosomes and its inhibition by calmodulin antagonists. *J Neurosci* 7: 2948–2956, 1987.
 1527. **Schwiebert EM, Wallace DP, Braunstein GM, King SR, Peti-Peterdi J, Hanaoka K, Guggino WB, Guay-Woodford LM, Bell PD, Sullivan LP, Grantham JJ, Taylor AL.** Autocrine extracellular purinergic signaling in epithelial cells derived from polycystic kidneys. *Am J Physiol Renal Physiol* 282: F763–F775, 2002.
 1528. **Schwiebert EM, Zsembery A.** Extracellular ATP as a signaling molecule for epithelial cells. *Biochim Biophys Acta* 1615: 7–32, 2003.
 1529. **Schwiebert EM, Zsembery A, Geibel JP.** Cellular mechanisms and physiology of nucleotide and nucleoside release from cells: current knowledge, novel assays to detect purinergic agonists, future directions. *Curr Top Membr* 54: 31–58, 2003.
 1530. **Scislo TJ, Kitchen AM, Augustyniak RA, O'Leary DS.** Differential patterns of sympathetic responses to selective stimulation of nucleus tractus solitarius purinergic receptor subtypes. *Clin Exp Pharmacol Physiol* 28: 120–124, 2001.
 1531. **Scratcherd T, Grundy D.** The physiology of intestinal motility and secretion. *Br J Anaesth* 56: 3–18, 1984.
 1532. **Sebastiao AM, Cunha RA, de MA, Ribeiro JA.** Modification of adenosine modulation of synaptic transmission in the hippocampus of aged rats. *Br J Pharmacol* 131: 1629–1634, 2000.
 1533. **Sebastiao AM, Ribeiro JA.** Adenosine A₂ receptor-mediated excitatory actions on the nervous system. *Prog Neurobiol* 48: 167–189, 1996.
 1534. **Seegmiller JE, Rosenbloom FM, Kelley WN.** Enzyme defect associated with a sex-linked human neurological disorder and excessive purine synthesis. *Science* 155: 1682–1684, 1967.
 1535. **Seidel B, Bigl M, Franke H, Kittner H, Kiess W, Illes P, Krügel U.** Expression of purinergic receptors in the hypothalamus of the rat is modified by reduced food availability. *Brain Res* 1089: 143–152, 2006.
 1536. **Seifert R, Schultz G.** Involvement of pyrimidinoceptors in the regulation of cell functions by uridine and by uracil nucleotides. *Trends Pharmacol Sci* 10: 365–369, 1989.
 1537. **Seino D, Tokunaga A, Tachibana T, Yoshiya S, Dai Y, Obata K, Yamanaka H, Kobayashi K, Noguchi K.** The role of ERK signaling and the P2X receptor on mechanical pain evoked by movement of inflamed knee joint. *Pain* 123: 193–203, 2006.
 1538. **Selden NR, Siler LN, Close LN, Heinricher MM.** Purinergic control of medullary pain-modulating neurons. In: *Abstract*

- Viewer/Itinerary Planner*. Washington, DC: Society for Neuroscience, 2004. (Program No 296 2)
1539. **Senger MR, Rico EP, de Bem AM, Rosemberg DB, Dias RD, Bogo MR, Bonan CD.** Carbofuran and malathion inhibit nucleotide hydrolysis in zebrafish (*Danio rerio*) brain membranes. *Toxicology* 212: 107–115, 2005.
 1540. **Serafeim A, Gordon J.** The immune system gets nervous. *Curr Opin Pharmacol* 1: 398–403, 2001.
 1541. **Sergeeva OA, Klyuch BP, Fleischer W, Eriksson KS, Korotkova TM, Siebler M, Haas HL.** P2Y receptor-mediated excitation in the posterior hypothalamus. *Eur J Neurosci* 24: 1413–1426, 2006.
 1542. **Serrano A, Haddjeri N, Lacaille JC, Robitaille R.** GABAergic network activation of glial cells underlies hippocampal heterosynaptic depression. *J Neurosci* 26: 5370–5382, 2006.
 1543. **Sesti C, Broekman MJ, Drosopoulos JH, Islam N, Marcus AJ, Levi R.** Ectonucleotidase in cardiac sympathetic nerve endings modulates ATP-mediated feedback of norepinephrine release. *J Pharmacol Exp Ther* 300: 605–611, 2002.
 1544. **Shahidullah M, Wilson WS.** Mobilisation of intracellular calcium by P2Y₂ receptors in cultured, non-transformed bovine ciliary epithelial cells. *Curr Eye Res* 16: 1006–1016, 1997.
 1545. **Shahraki A, Stone TW.** Interactions between adenosine and metabotropic glutamate receptors in the rat hippocampal slice. *Br J Pharmacol* 138: 1059–1068, 2003.
 1546. **Shariatmadari R, Sipila P, Vierula M, Tornquist K, Huhtaniemi I, Poutanen M.** Adenosine triphosphate induces Ca²⁺ signal in epithelial cells of the mouse caput epididymis through activation of P2X and P2Y purinergic receptors. *Biol Reprod* 68: 1185–1192, 2003.
 1547. **Sharp CJ, Reeve AJ, Collins SD, Martindale JC, Summerfield SG, Sargent BS, Bate ST, Chessell IP.** Investigation into the role of P2X₃/P2X_{2/3} receptors in neuropathic pain following chronic constriction injury in the rat: an electrophysiological study. *Br J Pharmacol* 148: 845–852, 2006.
 1548. **Shefner SA, Chiu TH.** Adenosine inhibits locus coeruleus neurons: an intracellular study in a rat brain slice preparation. *Brain Res* 366: 364–368, 1986.
 1549. **Shen J, Harada N, Nakazawa H, Kaneko T, Izumikawa M, Yamashita T.** Role of nitric oxide on ATP-induced Ca²⁺ signaling in outer hair cells of the guinea pig cochlea. *Brain Res* 1081: 101–112, 2006.
 1550. **Shen KZ, Johnson SW.** Presynaptic inhibition of synaptic transmission by adenosine in rat subthalamic nucleus in vitro. *Neuroscience* 116: 99–106, 2003.
 1551. **Shen KZ, North RA.** Excitation of rat locus coeruleus neurons by adenosine 5'-triphosphate: ionic mechanism and receptor characterization. *J Neurosci* 13: 894–899, 1993.
 1552. **Shibuya I, Tanaka K, Hattori Y, Uezono Y, Harayama N, Noguchi J, Ueta Y, Izumi F, Yamashita H.** Evidence that multiple P2X purinocceptors are functionally expressed in rat supraoptic neurones. *J Physiol* 514: 351–367, 1999.
 1553. **Shields CB, Zhang YP, Chen S, Han Y, Shields LBE, Burke DA, Haskins R.** Treatment of spinal cord injury via topical perfusion with an ATP solution. In: *Abstract Viewer/Itinerary Planner*. Washington, DC: Society for Neuroscience, 2004. (Program no 418 8)
 1554. **Shigemoto-Mogami Y, Koizumi S, Tsuda M, Ohsawa K, Kohsaka S, Inoue K.** Mechanisms underlying extracellular ATP-evoked interleukin-6 release in mouse microglial cell line, MG-5. *J Neurochem* 78: 1339–1349, 2001.
 1555. **Shigetomi E, Kato F.** Action potential-independent release of glutamate by Ca²⁺ entry through presynaptic P2X receptors elicits postsynaptic firing in the brainstem autonomic network. *J Neurosci* 24: 3125–3135, 2004.
 1556. **Shimizu I, Iida T, Guan Y, Zhao C, Raja SN, Jarvis MF, Cockayne DA, Caterina MJ.** Enhanced thermal avoidance in mice lacking the ATP receptor P2X₃. *Pain* 116: 96–108, 2005.
 1557. **Shingyoji C, Yamaguchi M.** Effects of acetylcholine, octopamine, ATP, dopamine, electrical stimulation on the spine muscle of the sea urchin, *Anthocardia crassispina*. *Comp Biochem Physiol C Comp Pharmacol Toxicol* 111: 23–32, 1995.
 1558. **Shinoda M, Ozaki N, Asai H, Nagamine K, Sugiura Y.** Changes in P2X₃ receptor expression in the trigeminal ganglion following monoarthritis of the temporomandibular joint in rats. *Pain* 116: 42–51, 2005.
 1559. **Shinohara T, Harada M, Ogi K, Maruyama M, Fujii R, Tanaka H, Fukusumi S, Komatsu H, Hosoya M, Noguchi Y, Watanabe T, Moriya T, Itoh Y, Hinuma S.** Identification of a G protein-coupled receptor specifically responsive to β-alanine. *J Biol Chem* 279: 23559–23564, 2004.
 1560. **Shinozuka K, Bjur RA, Westfall DP.** Effects of α,β-methylene ATP on the prejunctional purinoceptors of the sympathetic nerves of the rat caudal artery. *J Pharmacol Exp Ther* 254: 900–904, 1990.
 1561. **Shiokawa H, Nakatsuka T, Furue H, Tsuda M, Katafuchi T, Inoue K, Yoshimura M.** Direct excitation of deep dorsal horn neurones in the rat spinal cord by the activation of postsynaptic P2X receptors. *J Physiol* 573: 753–763, 2006.
 1562. **Shirley DG, Bailey MA, Unwin RJ.** In vivo stimulation of apical P2 receptors in collecting ducts: evidence for inhibition of sodium reabsorption. *Am J Physiol Renal Physiol* 288: F1243–F1248, 2005.
 1563. **Shneour EA, Hansen IM.** Inhibition by nucleotides of mouse brain UDP galactose 4-epimerase in vitro. *J Neurochem* 18: 1345–1349, 1971.
 1564. **Short JL, Ledent C, Borrelli E, Drago J, Lawrence AJ.** Genetic interdependence of adenosine and dopamine receptors: evidence from receptor knockout mice. *Neuroscience* 139: 661–670, 2006.
 1565. **Shukla V, Zimmermann H, Wang L, Kettenmann H, Raab S, Hammer K, Sevigny J, Robson SC, Braun N.** Functional expression of the ecto-ATPase NTPDase2 and of nucleotide receptors by neuronal progenitor cells in the adult murine hippocampus. *J Neurosci Res* 80: 600–610, 2005.
 1566. **Siggins GR, Gruol DL, Padjen AL, Formans DS.** Purine and pyrimidine mononucleotides depolarise neurones of explanted amphibian sympathetic ganglia. *Nature* 270: 263–265, 1977.
 1567. **Sigworth LA, Rea MA.** Adenosine A1 receptors regulate the response of the mouse circadian clock to light. *Brain Res* 960: 246–251, 2003.
 1568. **Silinsky EM.** On the mechanism by which adenosine receptor activation inhibits the release of acetylcholine from motor nerve endings. *J Physiol* 346: 243–256, 1984.
 1569. **Silinsky EM, Gerzanich V.** On the excitatory effects of ATP and its role as a neurotransmitter in coeliac neurons of the guinea-pig. *J Physiol* 464: 197–212, 1993.
 1570. **Silinsky EM, Ginsborg BL.** Inhibition of acetylcholine release from preganglionic frog nerves by ATP but not adenosine. *Nature* 305: 327–328, 1983.
 1571. **Silinsky EM, Hirsh JK, Searl TJ, Redman RS, Watanabe M.** Quantal ATP release from motor nerve endings and its role in neurally mediated depression. *Prog Brain Res* 120: 145–158, 1999.
 1572. **Silinsky EM, Hubbard JL.** Release of ATP from rat motor nerve terminals. *Nature* 243: 404–405, 1973.
 1573. **Silinsky EM, Redman RS.** Synchronous release of ATP and neurotransmitter within milliseconds of a motor nerve impulse in the frog. *J Physiol* 492: 815–822, 1996.
 1574. **Silveira PP, Cognato G, Crema LM, Pederiva FQ, Bonan CD, Sarkis JJ, Lucion AB, Dalmaz C.** Neonatal handling, sweet food ingestion and ectonucleotidase activities in nucleus accumbens at different ages. *Neurochem Res* 31: 693–698, 2006.
 1575. **Sim JA, Chaumont S, Jo J, Ulmann L, Young MT, Cho K, Buell G, North RA, Rassendren F.** Altered hippocampal synaptic potentiation in P2X₄ knock-out mice. *J Neurosci* 26: 9006–9009, 2006.
 1576. **Simard M, Arcuino G, Takano T, Liu QS, Nedergaard M.** Signaling at the gliovascular interface. *J Neurosci* 23: 9254–9262, 2003.
 1577. **Simola N, Fenu S, Baraldi PG, Tabrizi MA, Morelli M.** Blockade of adenosine A2A receptors antagonizes parkinsonian tremor in the rat tacrine model by an action on specific striatal regions. *Exp Neurol* 189: 182–188, 2004.
 1578. **Simon J, Kidd EJ, Smith FM, Chessell IP, Murrell-Lagnado R, Humphrey PPA, Barnard EA.** Localization and functional

- expression of splice variants of the P2X₂ receptor. *Mol Pharmacol* 52: 237–248, 1997.
1579. **Simonsen U, Garcia-Sacristan A, Prieto D.** Involvement of ATP in the non-adrenergic non-cholinergic inhibitory neurotransmission of lamb isolated coronary small arteries. *Br J Pharmacol* 120: 411–420, 1997.
1580. **Singaravelu K, Deitmer JW.** Calcium mobilization by nicotinic acid adenine dinucleotide phosphate (NAADP) in rat astrocytes. *Cell Calcium* 39: 143–153, 2006.
1581. **Siow NL, Xie HQ, Choi RC, Tsim KW.** ATP induces the post-synaptic gene expression in neuron-neuron synapses: transcriptional regulation of AChE catalytic subunit. *Chem Biol Interact* 157–158: 423–426, 2005.
1582. **Sissons J, Alsam S, Jayasekera S, Khan NA.** Ecto-ATPases of clinical and non-clinical isolates of *Acanthamoeba*. *Microb Pathog* 37: 231–239, 2004.
1583. **Skaper SD, Facci L, Culbert AA, Evans NA, Chessell I, Davis JB, Richardson JC.** P2X₇ receptors on microglial cells mediate injury to cortical neurons in vitro. *Glia* 54: 234–242, 2006.
1584. **Skladchikova G, Ronn LC, Berezin V, Bock E.** Extracellular adenosine triphosphate affects neural cell adhesion molecule (NCAM)-mediated cell adhesion and neurite outgrowth. *J Neurosci Res* 57: 207–218, 1999.
1585. **Slézia A, Kékesi AK, Szikra T, Papp AM, Nagy K, Szente M, Maglóczky Z, Freund TF, Juhász G.** Uridine release during aminopyridine-induced epilepsy. *Neurobiol Dis* 16: 490–499, 2004.
1586. **Smith AB, Hansen MA, Liu DM, Adams DJ.** Pre- and postsynaptic actions of ATP on neurotransmission in rat submandibular ganglia. *Neuroscience* 107: 283–291, 2001.
1587. **Smith CP, Vemulakonda VM, Kiss S, Boone TB, Somogyi GT.** Enhanced ATP release from rat bladder urothelium during chronic bladder inflammation: effect of botulinum toxin A. *Neurochem Int* 47: 291–297, 2005.
1588. **Smith DJ, Chapple CR.** In vitro response of human bladder smooth muscle in unstable obstructed male bladders: a study of pathophysiological causes. *Neurourol Urodyn* 13: 414–415, 1994.
1589. **Smith NCE, Burnstock G.** Mechanism underlying postjunctional synergism between responses of the vas deferens to noradrenaline and ATP. *Eur J Pharmacol* 498: 241–248, 2004.
1590. **Smitham JE, Barrett KE.** Differential effects of apical and basolateral uridine triphosphate on intestinal epithelial chloride secretion. *Am J Physiol Cell Physiol* 280: C1431–C1439, 2001.
1591. **Smyth L, Bobalova J, Ward SM, Keef KD, Mutafova-Yambolieva VN.** Cotransmission from sympathetic vasoconstrictor neurons: differences in guinea-pig mesenteric artery and vein. *Auton Neurosci* 86: 18–29, 2000.
1592. **Smyth LM, Breen LT, Mutafova-Yambolieva VN.** Nicotinamide adenine dinucleotide is released from sympathetic nerve terminals via a botulinum neurotoxin A-mediated mechanism in canine mesenteric artery. *Am J Physiol Heart Circ Physiol* 290: H1818–H1825, 2006.
1593. **Sneddon P, Burnstock G.** Inhibition of excitatory junction potentials in guinea-pig vas deferens by α,β -methylene-ATP: further evidence for ATP and noradrenaline as cotransmitters. *Eur J Pharmacol* 100: 85–90, 1984.
1594. **Sneddon P, Burnstock G.** ATP as a co-transmitter in rat tail artery. *Eur J Pharmacol* 106: 149–152, 1984.
1595. **Sneddon P, Westfall DP.** Pharmacological evidence that adenosine triphosphate and noradrenaline are co-transmitters in the guinea-pig vas deferens. *J Physiol* 347: 561–580, 1984.
1596. **Sneddon P, Westfall DP, Fedan JS.** Cotransmitters in the motor nerves of the guinea pig vas deferens: electrophysiological evidence. *Science* 218: 693–695, 1982.
1597. **Snyder SH.** Adenosine as a neuromodulator. *Annu Rev Neurosci* 8: 103–124, 1985.
1598. **Snyder SH, Katims JJ, Annau Z, Bruns RF, Daly JW.** Adenosine receptors and behavioral actions of methylxanthines. *Proc Natl Acad Sci USA* 78: 3260–3264, 1981.
1599. **Sokolova E, Grishin S, Shakirzyanova A, Talantova M, Giniatullin R.** Distinct receptors and different transduction mechanisms for ATP and adenosine at the frog motor nerve endings. *Eur J Neurosci* 18: 1254–1264, 2003.
1600. **Sokolova E, Nistri A, Giniatullin R.** The ATP-mediated fast current of rat dorsal root ganglion neurons is a novel effector for GABA_B receptor activation. *Neurosci Lett* 338: 181–184, 2003.
1601. **Solini A, Iacobini C, Ricci C, Chiozzi P, Amadio L, Pricci F, Di MU, Di VF, Pugliese G.** Purinergic modulation of mesangial extracellular matrix production: role in diabetic and other glomerular diseases. *Kidney Int* 67: 875–885, 2005.
1602. **Somei K, Sasaki K, Nara K, Ooe M, Yokota M, Miura H, Somei H.** Intracellular mechanism of ATP-induced depolarizing response in the bullfrog sympathetic ganglion cells. *Methods Find Exp Clin Pharmacol* 18: 443–448, 1996.
1603. **Somers GR, Hammet FM, Trute L, Southey MC, Venter DJ.** Expression of the P2Y₆ purinergic receptor in human T cells infiltrating inflammatory bowel disease. *Lab Invest* 78: 1375–1383, 1998.
1604. **Song Z, Sladek CD.** Does conversion of ATP to adenosine terminate ATP-stimulated vasopressin release from hypothalamo-neurohypophyseal explants? *Brain Res* 1047: 105–111, 2005.
1605. **Song Z, Sladek CD.** Site of ATP and phenylephrine synergistic stimulation of vasopressin release from the hypothalamo-neurohypophyseal system. *J Neuroendocrinol* 18: 266–272, 2006.
1606. **Sørensen CE, Novak I.** Visualization of ATP release in pancreatic acini in response to cholinergic stimulus. Use of fluorescent probes and confocal microscopy. *J Biol Chem* 276: 32925–32932, 2001.
1607. **Soria G, Castane A, Berrendero F, Ledent C, Parmentier M, Maldonado R, Valverde O.** Adenosine A_{2A} receptors are involved in physical dependence and place conditioning induced by THC. *Eur J Neurosci* 20: 2203–2213, 2004.
1608. **Soria G, Castane A, Ledent C, Parmentier M, Maldonado R, Valverde O.** The lack of A_{2A} adenosine receptors diminishes the reinforcing efficacy of cocaine. *Neuropsychopharmacology* 31: 978–987, 2006.
1609. **Sorimachi M, Ishibashi H, Moritoyo T, Akaike N.** Excitatory effect of ATP on acutely dissociated ventromedial hypothalamic neurons of the rat. *Neuroscience* 105: 393–401, 2001.
1610. **Sorimachi M, Moritoyo T, Yamagami K.** Activation of ATP receptor increases the cytosolic Ca²⁺ concentration in nucleus accumbens neurons of rat brain. *Brain Res* 882: 217–220, 2000.
1611. **Sorimachi M, Yamagami K, Wakomori M.** Activation of ATP receptor increases the cytosolic Ca²⁺ concentration in ventral tegmental area neurons of rat brain. *Brain Res* 935: 129–133, 2002.
1612. **Sorkin LS, Maruyama K, Boyle DL, Yang L, Marsala M, Firestein GS.** Spinal adenosine agonist reduces c-fos and astrocyte activation in dorsal horn of rats with adjuvant-induced arthritis. *Neurosci Lett* 340: 119–122, 2003.
1613. **Soto CR, Arroyo J, Alcayaga J.** Effects of bicarbonate buffer on acetylcholine-, adenosine 5'-triphosphate-, cyanide-induced responses in the cat petrosal ganglion in vitro. *Biol Res* 35: 359–364, 2002.
1614. **Soto D, Pintor J, Peral A, Gual A, Gasull X.** Effects of dinucleoside polyphosphates on trabecular meshwork cells and aqueous humor outflow facility. *J Pharmacol Exp Ther* 314: 1042–1051, 2005.
1615. **Soto F, Krause U, Borchardt K, Ruppelt A.** Cloning, tissue distribution and functional characterization of the chicken P2X₁ receptor. *FEBS Lett* 533: 54–58, 2003.
1616. **Soto F, Rubio ME.** Cloned P2X receptor sub-units in cerebellum and hippocampus. *Drug Dev Res* 52: 139, 2001.
1617. **Souslova V, Cesare P, Ding Y, Akopian AN, Stanfa L, Suzuki R, Saper K, Dickenson A, Boyce S, Hill R, Nebenius-Oosthuizen D, Smith AJH, Kidd E, Wood JN.** Warm-coding deficits and aberrant inflammatory pain in mice lacking P2X₃ receptors. *Nature* 407: 1015–1017, 2000.
1618. **Spanevello RM, Mazzanti CM, Kaizer R, Zanin R, Cargnelutti D, Hannel L, Correa M, Mazzanti A, Festugatto R, Graca D, Schetinger MR, Morsch VM.** Apyrase and 5'-nucleotidase activities in synaptosomes from the cerebral cortex of rats experimentally demyelinated with ethidium bromide and treated with interferon- β . *Neurochem Res* 31: 455–462, 2006.
1619. **Spehr J, Spehr M, Hatt H, Wetzel CH.** Subunit-specific P2X-receptor expression defines chemosensory properties of trigeminal neurons. *Eur J Neurosci* 19: 2497–2510, 2004.

1620. **Spelta V, Jiang LH, Surprenant A, North RA.** Kinetics of antagonist actions at rat P2X_{2/3} heteromeric receptors. *Br J Pharmacol* 135: 1524–1530, 2002.
1621. **Spelta V, Mekhalifa A, Rejman D, Thompson M, Blackburn GM, North RA.** ATP analogues with modified phosphate chains and their selectivity for rat P2X₂ and P2X_{2/3} receptors. *Br J Pharmacol* 140: 1027–1034, 2003.
1622. **Spencer NJ, Walsh M, Smith TK.** Purinergic and cholinergic neuro-neuronal transmission underlying reflexes activated by mucosal stimulation in the isolated guinea-pig ileum. *J Physiol* 522: 321–331, 2000.
1623. **Spergel D, Lahiri S.** Differential modulation by extracellular ATP of carotid chemosensory responses. *J Appl Physiol* 74: 3052–3056, 1993.
1624. **Sperlágh B, Kittel A, Lajtha A, Vizi ES.** ATP acts as fast neurotransmitter in rat habenula: neurochemical and enzymochemical evidence. *Neuroscience* 66: 915–920, 1995.
1625. **Sperlágh B, Mergl Z, Jurányi Z, Vizi ES, Makara GB.** Local regulation of vasopressin and oxytocin secretion by extracellular ATP in the isolated posterior lobe of the rat hypophysis. *J Endocrinol* 160: 343–350, 1999.
1626. **Sperlágh B, Sershen H, Lajtha A, Vizi ES.** Co-release of endogenous ATP and [³H]noradrenaline from rat hypothalamic slices: origin and modulation by α₂-adrenoceptors. *Neuroscience* 82: 511–520, 1998.
1627. **Sperlágh B, Vizi ES.** Neuronal synthesis, storage and release of ATP. *Semin Neurosci* 8: 175–186, 1996.
1628. **Sperlágh B, Vizi ES, Wirkner K, Illes P.** P2X₇ receptors in the nervous system. *Prog Neurobiol* 78: 327–346, 2006.
1629. **Sperlágh B, Zsilla G, Baranyi M, Kekes-Szabo A, Vizi ES.** Age-dependent changes of presynaptic neuromodulation via A₁-adenosine receptors in rat hippocampal slices. *Int J Dev Neurosci* 15: 739–747, 1997.
1630. **Spicuzza L, Di MG, Polosa R.** Adenosine in the airways: implications and applications. *Eur J Pharmacol* 533: 77–88, 2006.
1631. **Spray DC, Ye ZC, Ransom BR.** Functional connexin “hemichannels”: a critical appraisal. *Glia* 54: 758–773, 2006.
1632. **Squires PE, Lee PSN, Ho Yuen B, Leung PCK, Buchan AMJ.** Mechanisms involved in ATP-evoked Ca²⁺ oscillations in isolated human granulosa-luteal cells. *Cell Calcium* 21: 365–374, 1997.
1633. **Stagner JI, Samols E.** Role of intrapancreatic ganglia in regulation of periodic insular secretions. *Am J Physiol Endocrinol Metab* 248: E522–E530, 1985.
1634. **Stanfa LC, Kontinen VK, Dickenson AH.** Effects of spinally administered P2X receptor agonists and antagonists on the responses of dorsal horn neurones recorded in normal, carrageenan-inflamed and neuropathic rats. *Br J Pharmacol* 129: 351–359, 2000.
1635. **Starke K, von Kügelgen I, Driessen B, Bultmann R.** ATP release and its prejunctional modulation. *Ciba Found Symp* 198: 239–249, 1996.
1636. **Stellwagen D, Shatz CJ.** An instructive role for retinal waves in the development of retinogeniculate connectivity. *Neuron* 33: 357–367, 2002.
1637. **Stemkowski PL, Tse FW, Peuckmann V, Ford CP, Colmers WF, Smith PA.** ATP-inhibition of M current in frog sympathetic neurons involves phospholipase C but not Ins P₃, Ca²⁺, PKC, or Ras. *J Neurophysiol* 88: 277–288, 2002.
1638. **Stenberg D, Litonius E, Halldner L, Johansson B, Fredholm BB, Porkka-Heiskanen T.** Sleep and its homeostatic regulation in mice lacking the adenosine A₁ receptor. *J Sleep Res* 12: 283–290, 2003.
1639. **Stevens B.** Cross-talk between growth factor and purinergic signalling regulates Schwann cell proliferation. In: *Novartis Foundation Symposium 276 Purinergic Signalling in Neuron-Glial Interactions*. Chichester, UK: Wiley, 2006, p. 162–180.
1640. **Stevens B, Ishibashi T, Chen JF, Fields RD.** Adenosine: an activity-dependent axonal signal regulating MAP kinase and proliferation in developing Schwann cells. *Neuron Glia Biol* 1: 23–34, 2004.
1641. **Stevens B, Porta S, Haak LL, Gallo V, Fields RD.** Adenosine: a neuron-glial transmitter promoting myelination in the CNS in response to action potentials. *Neuron* 36: 855–868, 2002.
1642. **Stjärne L, Lishajko F.** Comparison of spontaneous loss of catecholamines and ATP in vitro from isolated bovine adrenomedullary, vesicular gland, vas deferens and splenic nerve granules. *J Neurochem* 13: 1213–1216, 1966.
1643. **Stjärne L, Stjärne E.** Geometry, kinetics and plasticity of release and clearance of ATP and noradrenaline as sympathetic cotransmitters: roles for the neurogenic contraction. *Prog Neurobiol* 47: 45–94, 1995.
1644. **Stojilkovic S, Koshimizu T.** Signaling by extracellular nucleotides in anterior pituitary cells. *Trends Endocrinol Metab* 12: 218–225, 2001.
1645. **Stojilkovic S, Tomic M, He ML, Yan Z, Koshimizu TA, Zemkova H.** Molecular dissection of purinergic P2X receptor channels. *Ann NY Acad Sci* 1048: 116–130, 2005.
1646. **Stone LS, Vulchanova L.** The pain of antisense: in vivo application of antisense oligonucleotides for functional genomics in pain and analgesia. *Adv Drug Deliv Rev* 55: 1081–1112, 2003.
1647. **Stone TW.** Adenosine, neurodegeneration and neuroprotection. *Neurol Res* 27: 161–168, 2005.
1648. **Stone TW, Taylor DA.** Antagonism by clonidine of neuronal depressant responses to adenosine, adenosine-5'-monophosphate and adenosine triphosphate. *Br J Pharmacol* 64: 369–374, 1978.
1649. **Stout CE, Costantin JL, Naus CC, Charles AC.** Intercellular calcium signaling in astrocytes via ATP release through connexin hemichannels. *J Biol Chem* 277: 10482–10488, 2002.
1650. **Stucky CL, Medler KA, Molliver DC.** The P2Y agonist UTP activates cutaneous afferent fibers. *Pain* 109: 36–44, 2004.
1651. **Su C.** Purinergic inhibition of adrenergic transmission in rabbit blood vessels. *J Pharmacol Exp Ther* 204: 351–361, 1978.
1652. **Su C, Bevan JA, Burnstock G.** [³H]adenosine triphosphate: release during stimulation of enteric nerves. *Science* 173: 337–339, 1971.
1653. **Suadicani SO, Brosnan CF, Scemes E.** P2X₇ receptors mediate ATP release and amplification of astrocytic intercellular Ca²⁺ signaling. *J Neurosci* 26: 1378–1385, 2006.
1654. **Suadicani SO, De Pina-Benabou MH, Urban-Maldonado M, Spray DC, Scemes E.** Acute downregulation of Cx43 alters P2Y receptor expression levels in mouse spinal cord astrocytes. *Glia* 42: 160–171, 2003.
1655. **Suadicani SO, Flores CE, Urban-Maldonado M, Beelitz M, Scemes E.** Gap junction channels coordinate the propagation of intercellular Ca²⁺ signals generated by P2Y receptor activation. *Glia* 48: 217–229, 2004.
1656. **Sueta T, Paki B, Everrett AW, Robertson D.** Purinergic receptors in auditory neurotransmission. *Hear Res* 183: 97–108, 2003.
1657. **Sugahara K, Shimogori H, Okuda T, Takemoto T, Hashimoto M, Yamashita H.** Cochlear administration of adenosine triphosphate facilitates recovery from acoustic trauma (temporary threshold shift). *ORL J Otorhinolaryngol Relat Spec* 66: 80–84, 2004.
1658. **Sugioka M, Zhou WL, Hofmann HD, Yamashita M.** Involvement of P2 purinoceptors in the regulation of DNA synthesis in the neural retina of chick embryo. *Int J Dev Neurosci* 17: 135–144, 1999.
1659. **Sugiura Y, Ko CP.** PTX-sensitive and -insensitive synaptic modulation at the frog neuromuscular junction. *Neuroreport* 11: 3017–3021, 2000.
1660. **Sugiyama T, Kobayashi M, Kawamura H, Li Q, Puro DG, Kobayashi M.** Enhancement of P2X₇-induced pore formation and apoptosis: an early effect of diabetes on the retinal microvasculature. *Invest Ophthalmol Vis Sci* 45: 1026–1032, 2004.
1661. **Sugiyama T, Oku H, Komori A, Ikeda T.** Effect of P2X₇ receptor activation on the retinal blood velocity of diabetic rabbits. *Arch Ophthalmol* 124: 1143–1149, 2006.
1662. **Sui GP, Wu C, Fry CH.** Electrical characteristics of suburothelial cells isolated from the human bladder. *J Urol* 171: 938–943, 2004.
1663. **Sui GP, Wu C, Fry CH.** Characterization of the purinergic receptor subtype on guinea-pig suburothelial myofibroblasts. *BJU Int* 97: 1327–1331, 2006.
1664. **Sul JY, Orosz G, Givens RS, Haydon PG.** Astrocytic connectivity in the hippocampus. *Neuron Glia Biol* 1: 3–11, 2004.

1665. **Sulakhe PV, Phillis JW.** The release of ^3H -adenosine and its derivatives from cat sensorimotor cortex. *Life Sci* 17: 551–555, 1975.
1666. **Sullivan DM, Erb L, Anglade E, Weisman GA, Turner JT, Csaky KG.** Identification and characterization of P2Y₂ nucleotide receptors in human retinal pigment epithelial cells. *J Neurosci Res* 49: 43–52, 1997.
1667. **Sumpio BE, Chaudry IH, Clemens MG, Baue AE.** Accelerated functional recovery of isolated rat kidney with ATP-MgCl₂ after warm ischemia. *Am J Physiol Regul Integr Comp Physiol* 247: R1047–R1053, 1984.
1668. **Sun MK, Wahlestedt C, Reis DJ.** Action of externally applied ATP on rat reticulospinal vasomotor neurons. *Eur J Pharmacol* 224: 93–96, 1992.
1669. **Sun XP, Stanley EF.** An ATP-activated, ligand-gated ion channel on a cholinergic presynaptic nerve terminal. *Proc Natl Acad Sci USA* 93: 1859–1863, 1996.
1670. **Sun Y, Chai TC.** Up-regulation of P2X₃ receptor during stretch of bladder urothelial cells from patients with interstitial cystitis. *J Urol* 171: 448–452, 2004.
1671. **Sun Y, Keay S, Deyne P, Chai T.** Stretch-activated release of adenosine triphosphate by bladder uroepithelia is augmented in interstitial cystitis. *Urology* 57: 131, 2001.
1672. **Suran AA.** 5'-Nucleotidase and an acid phosphatase of spinal cord. Comparative histochemistry and specificity of the enzymes in mouse and cat spinal cords. Cytologic localization in mouse substantia gelatinosa. *J Histochem Cytochem* 22: 802–811, 1974.
1673. **Suzuki T, Hide I, Ido K, Kohsaka S, Inoue K, Nakata Y.** Production and release of neuroprotective tumor necrosis factor by P2X₂ receptor-activated microglia. *J Neurosci* 24: 1–7, 2004.
1674. **Suzuki T, Hide I, Matsubara A, Hama C, Harada K, Miyano K, Andra M, Matsubayashi H, Sakai N, Kohsaka S, Inoue K, Nakata Y.** Microglial $\alpha 7$ nicotinic acetylcholine receptors drive a phospholipase C/IP₃ pathway and modulate the cell activation toward a neuroprotective role. *J Neurosci Res* 83: 1461–1470, 2006.
1675. **Svenningsson P, Le Moine C, Fisone G, Fredholm BB.** Distribution, biochemistry and function of striatal adenosine A_{2A} receptors. *Prog Neurobiol* 59: 355–396, 1999.
1676. **Sweeney MI, White TD, Sawynok J.** Morphine, capsaicin and K⁺ release purines from capsaicin-sensitive primary afferent nerve terminals in the spinal cord. *J Pharmacol Exp Ther* 248: 447–454, 1989.
1677. **Syed MM, Lee S, Zheng J, Zhou ZJ.** Stage-dependent dynamics and modulation of spontaneous waves in the developing rabbit retina. *J Physiol* 560: 533–549, 2004.
1678. **Szalay KS, Orso E, Juranyi Z, Vinson GP, Vizi ES.** Local non-synaptic modulation of aldosterone production by catecholamines and ATP in rat: implications for a direct neuronal fine tuning. *Horm Metab Res* 30: 323–328, 1998.
1679. **Szentpali K, Kaszaki J, Tiszlavicz L, Lazar G, Balogh A, Boros M.** Bile-induced adenosine triphosphate depletion and mucosal damage during reflux esophagitis. *Scand J Gastroenterol* 36: 459–466, 2001.
1680. **Tahani HM.** The purinergic nerve hypothesis and insulin secretion. *Z Ernahrungswiss* 18: 128–138, 1979.
1681. **Tai CJ, Chang SJ, Leung PC, Tzeng CR.** Adenosine 5'-triphosphate activates nuclear translocation of mitogen-activated protein kinases leading to the induction of early growth response 1 and raf expression in human granulosa-luteal cells. *J Clin Endocrinol Metab* 89: 5189–5195, 2004.
1682. **Tai CJ, Kang SK, Choi KC, Tzeng CR, Leung PC.** Antigonadotropic action of adenosine triphosphate in human granulosa-luteal cells: involvement of protein kinase C α . *J Clin Endocrinol Metab* 86: 3237–3242, 2001.
1683. **Takahashi T, Kusunoki M, Ishikawa Y, Kantoh M, Yamamura T, Utsunomiya J.** Adenosine 5'-triphosphate release evoked by electrical nerve stimulation from the guinea-pig gallbladder. *Eur J Pharmacol* 134: 77–82, 1987.
1684. **Takeda S, Eleftheriou F, Levasseur R, Liu X, Zhao L, Parker KL, Armstrong D, Ducy P, Karsenty G.** Leptin regulates bone formation via the sympathetic nervous system. *Cell* 111: 305–317, 2002.
1685. **Takemura H, Horio Y.** Spatial microenvironment defines Ca²⁺ entry and Ca²⁺ release in salivary gland cells. *Biochem Biophys Res Commun* 336: 223–231, 2005.
1686. **Tare M, Parkington HC, Tonta MA, Coleman HA.** Pregnancy-induced decrease in evoked excitatory junction potentials in guinea pig uterine artery. *J Vasc Res* 35: 63–71, 1998.
1687. **Taschenberger H, Jüttner R, Grantyn R.** Ca²⁺-permeable P2X receptor channels in cultured rat retinal ganglion cells. *J Neurosci* 19: 3353–3366, 1999.
1688. **Tassin AM, Haggblad J, Heilbronn E.** Receptor-triggered polyphosphoinositide turnover produces less cytosolic free calcium in cultured dysgenic myotubes than in normal myotubes. *Muscle Nerve* 13: 142–145, 1990.
1689. **Taylor DA, Stone TW.** The action of adenosine on noradrenergic neuronal inhibition induced by stimulation of locus coeruleus. *Brain Res* 183: 367–376, 1980.
1690. **Tebano MT, Martire A, Rebola N, Pepponi R, Domenici MR, Grò MC, Schwarzschild MA, Chen JF, Cunha RA, Popoli P.** Adenosine A_{2A} receptors and metabotropic glutamate 5 receptors are co-localized and functionally interact in the hippocampus: a possible key mechanism in the modulation of N-methyl-D-aspartate effects. *J Neurochem* 95: 1188–1200, 2005.
1691. **Teixeira M, Ferrary E, Butlen D.** UTP binding and phosphoinositidase C activation in ampulla from frog semicircular canal. *Am J Physiol Regul Integr Comp Physiol* 279: R803–R812, 2000.
1692. **Tempest HV, Dixon AK, Turner WH, Elneil S, Sellers LA, Ferguson DR.** P2X and P2X receptor expression in human bladder urothelium and changes in interstitial cystitis. *BJU Int* 93: 1344–1348, 2004.
1693. **Tenneti L, Gibbons SJ, Talamo BR.** Expression and trans-synaptic regulation of P_{2x4} and P_{2z} receptors for extracellular ATP in parotid acinar cells. Effects of parasympathetic denervation. *J Biol Chem* 273: 26799–26808, 1998.
1694. **Terasawa E, Keen KL, Grendell RL, Golos TG.** Possible role of 5'-adenosine triphosphate in synchronization of Ca²⁺ oscillations in primate luteinizing hormone-releasing hormone neurons. *Mol Endocrinol* 19: 2736–2747, 2005.
1695. **Tew EMM, Anderson PN, Saffrey MJ, Burnstock G.** Transplantation of the postnatal rat myenteric plexus into the adult rat corpus striatum: an electron microscopic study. *Exp Neurol* 129: 120–129, 1994.
1696. **Tew EMM, Saffrey MJ, Anderson PN, Burnstock G.** NADPH-diaphorase containing enteric neurones survive for a year in the adult rat striatum. *Neuroreport* 7: 958–960, 1996.
1697. **Thakker MM, Winston S, McCarley RW.** A1 receptor and adenosinergic homeostatic regulation of sleep-wakefulness: effects of antisense to the A1 receptor in the cholinergic basal forebrain. *J Neurosci* 23: 4278–4287, 2003.
1698. **Thapaliya S, Matsuyama H, Takewaki T.** ATP released from perivascular nerves hyperpolarizes smooth muscle cells by releasing an endothelium-derived factor in hamster mesenteric arteries. *J Physiol* 521: 191–199, 1999.
1699. **Theobald RJ Jr, de Groat WC.** The effects of ATP and related adenine derivatives on the superior cervical ganglion (SCG) of the rat. *Federation Proc* 36: 290, 1977.
1700. **Theobald RJ Jr, de Groat WC.** The effects of purine nucleotides on transmission in vesical parasympathetic ganglia of the cat. *J Auton Pharmacol* 9: 167–182, 1989.
1701. **Thevananther S, Sun H, Li D, Arjunan V, Awad SS, Wyllie S, Zimmerman TL, Goss JA, Karpen SJ.** Extracellular ATP activates c-jun N-terminal kinase signaling and cell cycle progression in hepatocytes. *Hepatology* 39: 393–402, 2004.
1702. **Thiruchelvan N, Wu C, David A, Woolf AS, Cuckow PM, Fry CH.** Neurotransmission and viscoelasticity in the ovine fetal bladder after in utero bladder outflow obstruction. *Am J Physiol Regul Integr Comp Physiol* 284: R1296–R1305, 2003.
1703. **Thomas S, Virginio C, North RA, Surprenant A.** The antagonist trinitrophenyl-ATP reveals co-existence of distinct P2X receptor channels in rat nodose neurones. *J Physiol* 509: 411–417, 1998.
1704. **Thomas T, Spyer KM.** A novel influence of adenosine on ongoing activity in rat rostral ventrolateral medulla. *Neuroscience* 88: 1213–1223, 1999.

1705. **Thomas T, Spyer KM.** ATP as a mediator of mammalian central CO₂ chemoreception. *J Physiol* 523: 441–447, 2000.
1706. **Thomas T, St Lambert JH, Dashwood MR, Spyer KM.** Localization and action of adenosine A_{2a} receptors in regions of the brainstem important in cardiovascular control. *Neuroscience* 95: 513–518, 2000.
1707. **Thompson CS, Kenney WL.** Altered neurotransmitter control of reflex vasoconstriction in aged human skin. *J Physiol* 558: 697–704, 2004.
1708. **Thürauf N, Hummel T, Kettenmann B, Kobal G.** Nociceptive and reflexive responses recorded from the human nasal mucosa. *Brain Res* 629: 293–299, 1993.
1709. **Tian GF, Azmi H, Takano T, Xu Q, Peng W, Lin J, Oberheim N, Lou N, Wang X, Zielke HR, Kang J, Nedergaard M.** An astrocytic basis of epilepsy. *Nat Med* 11: 973–981, 2005.
1710. **Todd KJ, Robitaille R.** Purinergic modulation of synaptic signalling at the neuromuscular junction. *Pflügers Arch* 452: 608–614, 2006.
1711. **Todorov LD, Mihaylova Todorova S, Westfall TD, Sneddon P, Kennedy C, Bjur RA, Westfall DP.** Neuronal release of soluble nucleotidases and their role in neurotransmitter inactivation. *Nature* 387: 76–79, 1997.
1712. **Tolkovsky AM, Suidan HS.** Adenosine 5'-triphosphate synthesis and metabolism localized in neurites of cultured sympathetic neurons. *Neuroscience* 23: 1133–1142, 1987.
1713. **Tomaselli B, Podhraski V, Heftberger V, Bock G, Baier-Bitterlich G.** Purine nucleoside-mediated protection of chemical hypoxia-induced neuronal injuries involves p42/44 MAPK activation. *Neurochem Int* 46: 513–521, 2005.
1714. **Tomic M, Jobin RM, Vergara LA, Tojilkovic S.** Expression of purinergic receptor channels and their role in calcium signaling and hormone release in pituitary gonadotrophs. Integration of P₂ channels in plasma membrane- and endoplasmic reticulum-derived calcium oscillations. *J Biol Chem* 271: 21200–21208, 1996.
1715. **Tominaga M, Wada M, Masu M.** Potentiation of capsaicin receptor activity by metabotropic ATP receptors as a possible mechanism for ATP-evoked pain and hyperalgesia. *Proc Natl Acad Sci USA* 98: 6951–6956, 2001.
1716. **Tong YC, Hung YC, Lin JSN, Hsu CT, Cheng JT.** Effects of pregnancy and progesterone on autonomic function in the rat urinary bladder. *Pharmacology* 50: 192–200, 1995.
1717. **Torres GE, Egan TM, Voigt MM.** Hetero-oligomeric assembly of P_{2X} receptor subunits. Specificities exist with regard to possible partners. *J Biol Chem* 274: 6653–6659, 1999.
1718. **Torres GE, Haines WR, Egan TM, Voigt MM.** Co-expression of P_{2X₁} and P_{2X₅} receptor subunits reveals a novel ATP-gated ion channel. *Mol Pharmacol* 54: 989–993, 1998.
1719. **Torres IL, Battastini AM, Buffon A, Furstenau CR, Siqueira I, Sarkis JJ, Dalmaz C, Ferreira MB.** Ecto-nucleotidase activities in spinal cord of rats changes as function of age. *Int J Dev Neurosci* 21: 425–429, 2003.
1720. **Torres M, Pintor J, Miras-Portugal MT.** Presence of ectonucleotidases in cultured chromaffin cells: hydrolysis of extracellular adenine nucleotides. *Arch Biochem Biophys* 279: 37–44, 1990.
1721. **Townsend-Nicholson A, King BF, Wildman SS, Burnstock G.** Molecular cloning, functional characterization and possible cooperativity between the murine P_{2X₄} and P_{2X_{4a}} receptors. *Brain Res* 64: 246–254, 1999.
1722. **Tran MD, Neary JT.** Purinergic signaling induces thrombospondin-1 expression in astrocytes. *Proc Natl Acad Sci USA* 103: 9321–9326, 2006.
1723. **Trang T, Beggs S, Salter MW.** Purinoceptors in microglia and neuropathic pain. *Pflügers Arch* 452: 645–652, 2006.
1724. **Trendelenburg AU, Bultmann R.** P₂ receptor-mediated inhibition of dopamine release in rat neostriatum. *Neuroscience* 96: 249–252, 2000.
1725. **Treziise DJ, Kennedy I, Humphrey PP.** Characterization of purinoceptors mediating depolarization of rat isolated vagus nerve. *Br J Pharmacol* 110: 1055–1060, 1993.
1726. **Troadec JD, Thirion S.** Multifaceted purinergic regulation of stimulus-secretion coupling in the neurohypophysis. *Neuroendocrinol Lett* 23: 273–280, 2002.
1727. **Troadec JD, Thirion S, Nicaise G, Lemos JR, Dayanithi G.** ATP-evoked increases in [Ca²⁺]_i and peptide release from rat isolated neurohypophysial terminals via a P_{2X₂} purinoceptor. *J Physiol* 511: 89–103, 1998.
1728. **Tsai SJ.** Adenosine A_{2a} receptor/dopamine D₂ receptor hetero-oligomerization: a hypothesis that may explain behavioral sensitization to psychostimulants and schizophrenia. *Med Hypotheses* 64: 197–200, 2005.
1729. **Tseng CJ, Biaggioni I, Appalsamy M, Robertson D.** Purinergic receptors in the brainstem mediate hypotension and bradycardia. *Hypertension* 11: 191–197, 1988.
1730. **Tsuda M, Inoue K, Salter MW.** Neuropathic pain and spinal microglia: a big problem from molecules in “small” glia. *Trends Neurosci* 28: 101–107, 2005.
1731. **Tsuda M, Shigemoto-Mogami Y, Koizumi S, Mizokoshi A, Kohsaka S, Salter MW, Inoue K.** P_{2X₄} receptors induced in spinal microglia gate tactile allodynia after nerve injury. *Nature* 424: 778–783, 2003.
1732. **Tsuda M, Ueno S, Inoue K.** Evidence for the involvement of spinal endogenous ATP and P_{2X} receptors in nociceptive responses caused by formalin and capsaicin in mice. *Br J Pharmacol* 128: 1497–1504, 1999.
1733. **Tsuda M, Ueno S, Inoue K.** In vivo pathway of thermal hyperalgesia by intrathecal administration of α,β -methylene ATP in mouse spinal cord: involvement of the glutamate-NMDA receptor system. *Br J Pharmacol* 127: 449–456, 1999.
1734. **Tsuzuki K, Kondo E, Fukuoka T, Yi D, Tsujino H, Sakagami M, Noguchi K.** Differential regulation of P_{2X₃} mRNA expression by peripheral nerve injury in intact and injured neurons in the rat sensory ganglia. *Pain* 91: 351–360, 2001.
1735. **Tugay M, Yildiz F, Utkan T, Gacar N, Ulak G, Erden F.** Age-related smooth muscle reactivity changes in the rat bladder: an in vitro study. *Pharmacol Res* 48: 329–334, 2003.
1736. **Tung A, Herrera S, Szafran MJ, Kasza K, Mendelson WB.** Effect of sleep deprivation on righting reflex in the rat is partially reversed by administration of adenosine A₁ and A₂ receptor antagonists. *Anesthesiology* 102: 1158–1164, 2005.
1737. **Tung EK, Choi RC, Siow NL, Jiang JX, Ling KK, Simon J, Barnard EA, Tsim KW.** P_{2Y₂} receptor activation regulates the expression of acetylcholinesterase and acetylcholine receptor genes at vertebrate neuromuscular junctions. *Mol Pharmacol* 66: 794–806, 2004.
1738. **Turner C, Ramesh B, Srari SKS, Burnstock G, Unwin R.** Altered P₂ receptor expression in the Han:SPRD cy⁺ rat, a model of autosomal dominant polycystic kidney disease. *Cells Tissues Org* 178: 168–179, 2004.
1739. **Turner CM, King BF, Srari KS, Unwin RJ.** Antagonism of endogenous putative P_{2Y} receptors reduces the growth of MDCK-derived cysts cultured in vitro. *Am J Physiol Renal Physiol* 292: F15–F25, 2007.
1740. **Turner CM, Tam F, Lai PC, Tarzi RM, Burnstock G, Pusey CD, Cook HT, Unwin RJ.** Increased expression of the proapoptotic ATP-sensitive P_{2X₇} receptor in experimental and human glomerulonephritis. *Nephrol Dialysis Transplant* 22: 386–395, 2007.
1741. **Turner JT, Landon LA, Gibbons SJ, Talamo BR.** Salivary gland P₂ nucleotide receptors. *Crit Rev Oral Biol Med* 10: 210–224, 1999.
1742. **Turner JT, Weisman GA, Camden JM.** Upregulation of P_{2Y₂} nucleotide receptors in rat salivary gland cells during short-term culture. *Am J Physiol Cell Physiol* 273: C1100–C1107, 1997.
1743. **Tuyau M, Hansen MA, Coleman MJ, Dampney RA, Balcar VJ, Bennett MR.** Autoradiography of [³H] α,β -methylene-ATP binding sites in medulla oblongata and spinal cord of the rat. *Neurochem Int* 30: 159–169, 1997.
1744. **Twente JW, Twente J, Giorgio NA.** Arousing effects of adenosine and adenine nucleotides in hibernating *Citellus lateralis*. *Comp Gen Pharmacol* 1: 485–491, 1970.
1745. **Uchiyama M, Nakajima Y, Sakuma Y, Kato M.** Purinergic regulation of intracellular Ca²⁺ concentration of rat pituitary folliculo-stellate cells in primary culture. *J Neuroendocrinol* 13: 378–385, 2001.

1746. Uckermann O, Grosche J, Reichenbach A, Bringmann A. ATP-evoked calcium responses of radial glial (Müller) cells in the postnatal rabbit retina. *J Neurosci Res* 70: 209–218, 2002.
1747. Uckermann O, Uhlmann S, Wurm A, Reichenbach A, Wiedemann P, Bringmann A. ADP β S evokes microglia activation in the rabbit retina in vivo. *Purinergic Signalling* 1: 383–387, 2005.
1748. Ueda H, Rashid MH. Molecular mechanism of neuropathic pain. *Drug News Perspect* 16: 605–613, 2003.
1749. Ueno S, Harata N, Inoue K, Akaike N. ATP-gated current in dissociated rat nucleus solitarii neurons. *J Neurophysiol* 68: 778–785, 1992.
1750. Ueno S, Moriyama T, Honda K, Kamiya H, Sakurada T, Katsuragi T. Involvement of P2X₂ and P2X₃ receptors in neuropathic pain in a mouse model of chronic constriction injury. *Drug Dev Res* 59: 104–111, 2003.
1751. Ueno S, Yamada H, Moriyama T, Honda K, Takano Y, Kamiya HO, Katsuragi T. Measurement of dorsal root ganglion P2X mRNA by SYBR Green fluorescence. *Brain Res* 10: 95–101, 2002.
1752. Ueno T, Ueno S, Kakazu Y, Akaike N, Nabekura J. Bidirectional modulation of P2X receptor-mediated response by divalent cations in rat dorsal motor nucleus of the vagus neurons. *J Neurochem* 78: 1009–1018, 2001.
1753. Ugur M, Drummond RM, Zou H, Sheng P, Singer JJ, Walsh JV Jr. An ATP-gated cation channel with some P2Z-like characteristics in gastric smooth muscle cells of toad. *J Physiol* 498: 427–442, 1997.
1754. Uhlmann S, Bringmann A, Uckermann O, Pannicke T, Weick M, Ulbricht E, Goczalik I, Reichenbach A, Wiedemann P, Francke M. Early glial cell reactivity in experimental retinal detachment: effect of suramin. *Invest Ophthalmol Vis Sci* 44: 4114–4122, 2003.
1755. Ulate G, Scott SR, Gilabert JA, Artalejo AR. Purinergic modulation of Ca²⁺ channels and exocytosis in bovine chromaffin cells. *Drug Dev Res* 52: 89–94, 2001.
1756. Ulrich D, Huguenard JR. Purinergic inhibition of GABA and glutamate release in the thalamus: implications for thalamic network activity. *Neuron* 15: 909–918, 1995.
1757. Udem BJ, Chuaychoo B, Lee MG, Weinreich D, Myers AC, Kollarik M. Subtypes of vagal afferent C-fibres in guinea-pig lungs. *J Physiol* 556: 905–917, 2004.
1758. Unsicker K. On the innervation of the rat and pig adrenal cortex. *Z Zellforsch Mikrosk Anat* 116: 151–156, 1971.
1759. Unwin RJ, Bailey MA, Burnstock G. Purinergic signaling along the renal tubule: the current state of play. *News Physiol Sci* 18: 237–241, 2003.
1760. Usachev YM, DeMarco SJ, Campbell C, Strehler EE, Thayer SA. Bradykinin and ATP accelerate Ca²⁺ efflux from rat sensory neurons via protein kinase C and the plasma membrane Ca²⁺ pump isoform 4. *Neuron* 3: 113–122, 2002.
1761. Ushijima I, Mizuki Y, Hara T, Kaneyuki H, Mashimoto S, Kajimura N, Yamada M. Effects of dilazep (Comelian) on the central purinergic system: inhibitory effects on clonidine-induced aggressive behavior. *Eur J Pharmacol* 161: 245–248, 1989.
1762. Vainio M, Saijonmaa O, Fyhrquist F, Tornquist K. Purinergic agonists stimulate the secretion of endothelin-1 in rat thyroid FRTL-5 cells. *J Cell Physiol* 169: 538–543, 1996.
1763. Valera S, Hussy N, Evans RJ, Adani N, North RA, Surprenant A, Buell G. A new class of ligand-gated ion channel defined by P_{2X} receptor for extra-cellular ATP. *Nature* 371: 516–519, 1994.
1764. Vallejo AI, Bo X, Burnstock G. P2Y-purinocceptors in gastric gland plasma membranes. *Eur J Pharmacol* 312: 209–214, 1996.
1765. Van Calker D, Biber K. The role of glial adenosine receptors in neural resilience and the neurobiology of mood disorders. *Neurochem Res* 30: 1205–1217, 2005.
1766. Van Calker D, Müller M, Hamprecht B. Adenosine regulates via two different types of receptors, the accumulation of cyclic AMP in cultured brain cells. *J Neurochem* 33: 999–1005, 1979.
1767. Van den Pol AN, Finkbeiner SM, Cornell-Bell AH. Calcium excitability and oscillations in suprachiasmatic nucleus neurons and glia in vitro. *J Neurosci* 12: 2648–2664, 1992.
1768. Van der Weyden L, Adams DJ, Morris BJ. Capacity for purinergic control of renin promoter via P2Y₁₁ receptor and cAMP pathways. *Hypertension* 36: 1093–1098, 2000.
1769. Van Nassauw L, Brouns I, Adriaensen D, Burnstock G, Timmermans JP. Neurochemical identification of enteric neurons expressing P2X₃ receptors in the guinea-pig ileum. *Histochem Cell Biol* 118: 193–203, 2002.
1770. Van Nassauw L, Costagliola A, Van Op den bosch J, Cecio A, Vanderwinden J-M, Burnstock G, Timmermans J-P. Region-specific distribution of the P2Y₄ receptor in enteric glial cells and interstitial cells of Cajal within the guinea-pig gastrointestinal tract. *Auton Neurosci Basic Clin* 126–127: 306, 2006.
1771. Van Nassauw L, Van Crombruggen K, De Jonge F, Burnstock G, Lefebvre RA, Timmermans JP. Distribution of P2Y receptor subtypes in the rat distal colon. *Neurogastroenterol Motil* 17: 1, 2005.
1772. Vandamme W, Braet K, Cabooter L, Leybaert L. Tumour necrosis factor α inhibits purinergic calcium signalling in blood-brain barrier endothelial cells. *J Neurochem* 88: 411–421, 2004.
1773. Vanderwinden JM, Timmermans JP, Schiffmann SN. Glial cells, but not interstitial cells, express P2X₇, an ionotropic purinergic receptor, in rat gastrointestinal musculature. *Cell Tissue Res* 312: 149–154, 2003.
1774. Vank C, Frömter E, Kottra G. Activation of an apical Cl⁻ conductance by extracellular ATP in *Necturus* gallbladder is mediated by cAMP and not by [Ca²⁺]_i. *Pflügers Arch* 438: 486–496, 1999.
1775. Varas R, Alcayaga J, Iturriaga R. ACh and ATP mediate excitatory transmission in cat carotid identified chemoreceptor units in vitro. *Brain Res* 988: 154–163, 2003.
1776. Vázquez-Cuevas FG, Juárez B, Garay E, Arellano RO. ATP-induced apoptotic cell death in porcine ovarian theca cells through P2X₇ receptor activation. *Mol Reprod Dev* 73: 745–755, 2006.
1777. Ventura S, Dewalagama RK, Lau LC. Adenosine 5'-triphosphate (ATP) is an excitatory cotransmitter with noradrenaline to the smooth muscle of the rat prostate gland. *Br J Pharmacol* 138: 1277–1284, 2003.
1778. Ventura S, Pennefather JN. Sympathetic co-transmission to the cauda epididymis of the rat: characterization of postjunctional adrenoceptors and purinoceptors. *Br J Pharmacol* 102: 540–544, 1991.
1779. Verderio C, Matteoli M. ATP mediates calcium signaling between astrocytes and microglial cells: modulation by IFN- γ . *J Immunol* 166: 6383–6391, 2001.
1780. Verhaeghe RH, Vanhoutte PM, Shepherd JT. Inhibition of sympathetic neurotransmission in canine blood vessels by adenosine and adenine nucleotides. *Circ Res* 40: 208–215, 1977.
1781. Vetrugno R, Liguori R, Cortelli P, Montagna P. Sympathetic skin response: basic mechanisms and clinical applications. *Clin Auton Res* 13: 256–270, 2003.
1782. Vial C, Evans RJ. Disruption of lipid rafts inhibits P2X₁ receptor-mediated currents and arterial vasoconstriction. *J Biol Chem* 280: 30705–30711, 2005.
1783. Vianna EP, Ferreira AT, Doná F, Cavalheiro EA, da Silva Fernandes MJ. Modulation of seizures and synaptic plasticity by adenosinergic receptors in an experimental model of temporal lobe epilepsy induced by pilocarpine in rats. *Epilepsia* 46: 166–173, 2005.
1784. Vianna EP, Ferreira AT, Naffah-Mazzacoratti MG, Sanabria ER, Funke M, Cavalheiro EA, Fernandes MJ. Evidence that ATP participates in the pathophysiology of pilocarpine-induced temporal lobe epilepsy: fluorimetric, immunohistochemical, Western blot studies. *Epilepsia* 43: 227–229, 2002.
1785. Vidal M, Hicks PE, Langer SZ. Differential effects of α , β -methylene ATP on responses to nerve stimulation in SHR and WKY tail arteries. *Naunyn-Schmiedeberg's Arch Pharmacol* 332: 384–390, 1986.
1786. Vigne P, Breittmayer JP, Frelin C. Diadenosine polyphosphates as antagonists of the endogenous P2Y₁ receptor in rat brain capillary endothelial cells of the B7 and B10 clones. *Br J Pharmacol* 129: 1506–1512, 2000.
1787. Villalobos C, Alonso-Torre SR, Nunez L, Garcia-Sancho J. Functional ATP receptors in rat anterior pituitary cells. *Am J Physiol Cell Physiol* 273: C1963–C1971, 1997.

1788. **Vinade ER, Schmidt AP, Frizzo ME, Izquierdo I, Elisabetsky E, Souza DO.** Chronically administered guanosine is anticonvulsant, amnesic and anxiolytic in mice. *Brain Res* 977: 97–102, 2003.
1789. **Vincent P.** Cationic channels sensitive to extracellular ATP in rat lacrimal cells. *J Physiol* 449: 313–331, 1992.
1790. **Virginio C, Robertson G, Surprenant A, North RA.** Trinitrophenyl-substituted nucleotides are potent antagonists selective for P2X₁, P2X₃, heteromeric P2X_{2/3} receptors. *Mol Pharmacol* 53: 969–973, 1998.
1791. **Virus RM, Baglajewski T, Radulovacki M.** [³H]N⁶-(L-Phenylisopropyl)adenosine binding in brains from young and old rats. *Neurobiol Aging* 5: 61–62, 1984.
1792. **Viscomi MT, Florenzano F, Conversi D, Bernardi G, Molinari M.** Axotomy dependent purinergic and nitrergic co-expression. *Neuroscience* 123: 393–404, 2004.
1793. **Visentin S, Belenchi DC, De Nuccio C.** P2Y receptors in microglia: an intracellular Ca²⁺ study. *Proceedings of the VII European Meeting on Glial Cell Function in Health and Disease 2005 Amsterdam, The Netherlands*, p. 133–137.
1794. **Vitolo OV, Ciotti MT, Galli C, Borsello T, Calissano P.** Adenosine and ADP prevent apoptosis in cultured rat cerebellar granule cells. *Brain Res* 809: 297–301, 1998.
1795. **Vizi ES, Knoll J.** The inhibitory effect of adenosine and related nucleotides on the release of acetylcholine. *Neuroscience* 1: 391–398, 1976.
1796. **Vizi ES, Liang SD, Sperlág B, Kittel A, Juranyi Z.** Studies on the release and extracellular metabolism of endogenous ATP in rat superior cervical ganglion: support for neurotransmitter role of ATP. *Neuroscience* 79: 893–903, 1997.
1797. **Vlaskovska M, Kasakov L, Rong W, Bodin P, Bardini M, Cockayne DA, Ford APDW, Burnstock G.** P2X₃ knockout mice reveal a major sensory role for urothelially released ATP. *J Neurosci* 21: 5670–5677, 2001.
1798. **Voisin DL, Guy N, Chalus M, Dalle R.** Nociceptive stimulation activates locus coeruleus neurones projecting to the somatosensory thalamus in the rat. *J Physiol* 566: 929–937, 2005.
1799. **Volonté C, Amadio S, Cavaliere F, D'Ambrosi N, Vacca F, Bernardi G.** Extracellular ATP and neurodegeneration. *Curr Drug Targets CNS Neurol Disord* 2: 403–412, 2003.
1800. **Volonté C, Amadio S, D'Ambrosi N, Colpi M, Burnstock G.** P2 receptor web: complexity and fine-tuning. *Pharmacol Ther* 112: 264–280, 2006.
1801. **Von Kügelgen I, Nörenberg W, Meyer A, Illes P, Starke K.** Role of action potentials and calcium influx in ATP- and UDP-induced noradrenaline release from rat cultured sympathetic neurones. *Naunyn-Schmiedeberg's Arch Pharmacol* 359: 360–369, 1999.
1802. **Von Kügelgen I, Spath L, Starke K.** Evidence for P2-purinoceptor-mediated inhibition of noradrenaline release in rat brain cortex. *Br J Pharmacol* 113: 815–822, 1994.
1803. **Von Kügelgen I, Starke K.** Noradrenaline-ATP co-transmission in the sympathetic nervous system. *Trends Pharmacol Sci* 12: 319–324, 1991.
1804. **Von Patay B, Kurz B, Mentlein R.** Effect of transmitters and co-transmitters of the sympathetic nervous system on interleukin-6 synthesis in thymic epithelial cells. *Neuroimmunomodulation* 6: 45–50, 1999.
1805. **Vonend O, Grote T, Oberhauser V, von Kügelgen I, Rump LC.** P2Y-receptors stimulating the proliferation of human mesangial cells through the MAPK^{42/44} pathway. *Br J Pharmacol* 139: 1119–1126, 2003.
1806. **Vonend O, Oberhauser V, von Kügelgen I, Apel TW, Amann K, Ritz E, Rump LC.** ATP release in human kidney cortex and its mitogenic effects in visceral glomerular epithelial cells. *Kidney Int* 61: 1617–1626, 2002.
1807. **Vonend O, Stegbauer J, Sojka J, Habel S, Quack I, Robaye B, Boeynaems JM, Rump LC.** Noradrenaline and extracellular nucleotide cotransmission involves activation of vasoconstrictive P2X_{1,3}- and P2Y₆-like receptors in mouse perfused kidney. *Br J Pharmacol* 145: 66–74, 2005.
1808. **Vonend O, Turner C, Chan CM, Loesch A, Dell'Anna GC, Srai SK, Burnstock G, Unwin R.** Glomerular expression of the ATP-sensitive P2X₇ receptor in diabetic and hypertensive rat models. *Kidney Int* 66: 157–166, 2004.
1809. **Vulchanova L, Arvidsson U, Riedl M, Wang J, Buell G, Surprenant A, North RA, Elde R.** Differential distribution of two ATP-gated channels (P2X receptors) determined by immunocytochemistry. *Proc Natl Acad Sci USA* 93: 8063–8067, 1996.
1810. **Vulchanova L, Olson TH, Stone LS, Riedl MS, Elde R, Honda CN.** Cytotoxic targeting of isolectin IB4-binding sensory neurons. *Neuroscience* 108: 143–155, 2001.
1811. **Vulchanova L, Riedl M, Shuster SJ, Buell G, Surprenant A, North RA, Elde R.** Immunocytochemical study of the P2X₂ and P2X₃ receptor subunits in rat and monkey sensory neurons and their central terminals. *Neuropharmacology* 36: 1229–1242, 1997.
1812. **Vulchanova L, Riedl MS, Shuster SJ, Stone LS, Hargreaves KM, Buell G, Surprenant A, North RA, Elde R.** P2X₃ is expressed by DRG neurons that terminate in inner lamina II. *Eur J Neurosci* 10: 3470–3478, 1998.
1813. **Waeber C, Moskowitz MA.** Therapeutic implications of central and peripheral neurologic mechanisms in migraine. *Neurology* 61: S9–20, 2003.
1814. **Wagner JA, Katz RJ.** Purinergic control of anxiety: direct behavioral evidence in the rat. *Neurosci Lett* 43: 333–337, 1983.
1815. **Wakade TD, Palmer KC, McCauley R, Przywara DA, Wakade AR.** Adenosine-induced apoptosis in chick embryonic sympathetic neurons: a new physiological role for adenosine. *J Physiol* 488: 123–138, 1995.
1816. **Waldron JB, Sawynok J.** Peripheral P2X receptors and nociception: interactions with biogenic amine systems. *Pain* 110: 79–89, 2004.
1817. **Wallace A, Knight GE, Cowen T, Burnstock G.** Changes in function and expression of P2X and P2Y receptors in the rat tail and mesenteric arteries during maturation and aging. *Neuropharmacology* 50: 191–208, 2006.
1818. **Wallace DJ.** The use of quinacrine (Atabrine) in rheumatic diseases: a reexamination. *Semin Arthritis Rheum* 18: 282–296, 1989.
1819. **Wang CM, Chang YY, Kuo JS, Sun SH.** Activation of P2X₇ receptors induced [³H]GABA release from the RBA-2 type-2 astrocyte cell line through a Cl⁻/HCO₃⁻-dependent mechanism. *Glia* 37: 8–18, 2002.
1820. **Wang D, Huang NN, Heppel LA.** Extracellular ATP shows synergistic enhancement of DNA synthesis when combined with agents that are active in wound healing or as neurotransmitters. *Biochem Biophys Res Commun* 166: 251–258, 1990.
1821. **Wang G, Dayanithi G, Custer EE, Lemos JR.** Adenosine inhibition via A₁ receptor of N-type Ca²⁺ current and peptide release from isolated neurohypophysial terminals of the rat. *J Physiol* 540: 791–802, 2002.
1822. **Wang JC, Raybould NP, Luo L, Ryan AF, Cannell MB, Thorne PR, Housley GD.** Noise induces up-regulation of P2X₂ receptor subunit of ATP-gated ion channels in the rat cochlea. *Neuroreport* 14: 817–823, 2003.
1823. **Wang JH, Ma YY, van den Buuse M.** Improved spatial recognition memory in mice lacking adenosine A_{2A} receptors. *Exp Neurol* 199: 438–445, 2006.
1824. **Wang L, Yao H, Yang YE, Song I, Owyang C.** Enhanced purinergic pathway occurs in postoperative ileus: reversal by orphanin FQ. *Gastroenterology* 126: 75, 2004.
1825. **Wang LC, Xiong W, Zheng J, Zhou Y, Zheng H, Zhang C, Zheng LH, Zhu XL, Xiong ZQ, Wang LY, Cheng HP, Zhou Z.** The timing of endocytosis after activation of a G-protein-coupled receptor in a sensory neuron. *Biophys J* 90: 3590–3598, 2006.
1826. **Wang M, Kong Q, Gonzalez FA, Sun G, Erb L, Seye C, Weisman GA.** P2Y₂ nucleotide receptor interaction with α_v integrin mediates astrocyte migration. *J Neurochem* 95: 630–640, 2005.
1827. **Wang MJ, Xiong SH, Li ZW.** Neurokinin B potentiates ATP-activated currents in rat DRG neurons. *Brain Res* 923: 157–162, 2001.
1828. **Wang P, Saraswati S, Guan Z, Watkins CJ, Wurtman RJ, Littleton JT.** A *Drosophila* temperature-sensitive seizure mutant in phosphoglycerate kinase disrupts ATP generation and alters synaptic function. *J Neurosci* 24: 4518–4529, 2004.

1829. **Wang X, Arcuino G, Takano T, Lin J, Peng WG, Wan P, Li P, Xu Q, Liu QS, Goldman SA, Nedergaard M.** P2X₇ receptor inhibition improves recovery after spinal cord injury. *Nat Med* 10: 821–827, 2004.
1830. **Wang XF, Chan HC.** Adenosine triphosphate induces inhibition of Na⁺ absorption in mouse endometrial epithelium: a Ca²⁺-dependent mechanism. *Biol Reprod* 63: 1918–1924, 2000.
1831. **Wang Y, Chang CF, Morales M, Chiang YH, Harvey BK, Su TP, Tsao LI, Chen S, Thiemermann C.** Diadenosine tetraphosphate protects against injuries induced by ischemia and 6-hydroxydopamine in rat brain. *J Neurosci* 23: 7958–7965, 2003.
1832. **Wang Y, Mackes J, Chan S, Haughey NJ, Guo Z, Ouyang X, Furukawa K, Ingram DK, Mattson MP.** Impaired long-term depression in P2X₃ deficient mice is not associated with a spatial learning deficit. *J Neurochem* 2006.
1833. **Wang Z, Haydon PG, Yeung ES.** Direct observation of calcium-independent intercellular ATP signaling in astrocytes. *Anal Chem* 72: 2001–2007, 2000.
1834. **Ward RP, Dorsa DM.** Molecular and behavioral effects mediated by G_s-coupled adenosine A_{2a}, but not serotonin 5-HT₄ or 5-HT₆ receptors following antipsychotic administration. *Neuroscience* 89: 927–938, 1999.
1835. **Ward SM, McLaren GJ, Sanders KM.** Interstitial cells of Cajal in the deep muscular plexus mediate enteric motor neurotransmission in the mouse small intestine. *J Physiol* 573: 147–159, 2006.
1836. **Washburn KB, Neary JT.** P₂ purinergic receptors signal to STAT3 in astrocytes: Difference in STAT3 responses to P₂Y and P₂X receptor activation. *Neuroscience* 142: 411–423, 2006.
1837. **Watanabe S, Yoshimi Y, Ikekita M.** Neuroprotective effect of adenine on Purkinje cell survival in rat cerebellar primary cultures. *J Neurosci Res* 74: 754–759, 2003.
1838. **Watano T, Calvert JA, Vial C, Forsythe ID, Evans RJ.** P₂X receptor subtype-specific modulation of excitatory and inhibitory synaptic inputs in the rat brainstem. *J Physiol* 558: 745–757, 2004.
1839. **Watkins LR, Maier SF.** Beyond neurons: evidence that immune and glial cells contribute to pathological pain states. *Physiol Rev* 82: 981–1011, 2002.
1840. **Watson GM, Venable S, Hudson RR, Repass JJ.** ATP enhances repair of hair bundles in sea anemones. *Hear Res* 136: 1–12, 1999.
1841. **Webb AM, Fenn WO.** The action on cardiac musculature and the vagomimetic behaviour of adenosine. *J Pharmacol Exp Ther* 47: 365–375, 1933.
1842. **Webb TE, Henderson DJ, Roberts JA, Barnard EA.** Molecular cloning and characterization of the rat P₂Y₄ receptor. *J Neurochem* 71: 1348–1357, 1998.
1843. **Webb TE, Simon J, Krishek BJ, Bateson AN, Smart TG, King BF, Burnstock G, Barnard EA.** Cloning and functional expression of a brain G-protein-coupled ATP receptor. *FEBS Lett* 324: 219–225, 1993.
1844. **Wegner CD.** P₂ receptors in the respiratory system. In: *Purinergic and Pyrimidinergic Signalling II*, edited by Abbracchio MP and Williams M. Berlin: Springer, 2001, p. 281–300.
1845. **Weick M, Cherkas PS, Hartig W, Pannicke T, Uckermann O, Bringmann A, Tal M, Reichenbach A, Hanani M.** P₂ receptors in satellite glial cells in trigeminal ganglia of mice. *Neuroscience* 120: 969–977, 2003.
1846. **Weick M, Wiedemann P, Reichenbach A, Bringmann A.** Resensitization of P₂Y receptors by growth factor-mediated activation of the phosphatidylinositol-3 kinase in retinal glial cells. *Invest Ophthalmol Vis Sci* 46: 1525–1532, 2005.
1847. **Weight FF, Li C, Peoples RW.** Alcohol action on membrane ion channels gated by extracellular ATP (P₂X receptors). *Neurochem Int* 35: 143–152, 1999.
1848. **Weissman TA, Riquelme PA, Ivic L, Flint AC, Kriegstein AR.** Calcium waves propagate through radial glial cells and modulate proliferation in the developing neocortex. *Neuron* 43: 647–661, 2004.
1849. **Wells DG, Zawisa MJ, Hume RI.** Changes in responsiveness to extracellular ATP in chick skeletal muscle during development and upon denervation. *Dev Biol* 172: 585–590, 1995.
1850. **Welsh JH.** Chemical mediation in crustaceans. The occurrence of acetylcholine in nervous tissues and its action on the decapod heart. *J Exp Biol* 16: 198–219, 1939.
1851. **Werner-Reiss U, Galun R, Crnjar R, Liscia A.** Factors modulating the blood feeding behavior and the electrophysiological responses of labral apical chemoreceptors to adenine nucleotides in the mosquito *Aedes aegypti* (Culicidae). *J Insect Physiol* 45: 801–808, 1999.
1852. **Werry EL, Liu GJ, Bennett MR.** Glutamate-stimulated ATP release from spinal cord astrocytes is potentiated by substance P. *J Neurochem* 99: 924–936, 2006.
1853. **Westfall DP, Stitzel RE, Rowe JN.** The postjunctional effects and neural release of purine compounds in the guinea-pig vas deferens. *Eur J Pharmacol* 50: 27–38, 1978.
1854. **Wheeler-Schilling TH, Marquardt K, Kohler K, Guenther E, Jabs R.** Identification of purinergic receptors in retinal ganglion cells. *Brain Res* 92: 177–180, 2001.
1855. **White TD.** Direct detection of depolarisation-induced release of ATP from a synaptosomal preparation. *Nature* 267: 67–68, 1977.
1856. **White TD, Downie JW, Leslie RA.** Characteristics of K⁺- and veratridine-induced release of ATP from synaptosomes prepared from dorsal and ventral spinal cord. *Brain Res* 334: 372–374, 1985.
1857. **White TD, Leslie RA.** Depolarization-induced release of adenosine 5'-triphosphate from isolated varicosities derived from the myenteric plexus of the guinea-pig small intestine. *J Neurosci* 2: 206–215, 1982.
1858. **Wieraszko A.** Extracellular ATP as a neurotransmitter: its role in synaptic plasticity in the hippocampus. *Acta Neurobiol Exp* 56: 637–648, 1996.
1859. **Wieraszko A, Ehrlich YH.** On the role of extracellular ATP in the induction of long-term potentiation in the hippocampus. *J Neurochem* 63: 1731–1738, 1994.
1860. **Wieraszko A, Seyfried TN.** Increased amount of extracellular ATP in stimulated hippocampal slices of seizure prone mice. *Neurosci Lett* 106: 287–293, 1989.
1861. **Wihlborg AK, Balogh J, Wang L, Borna C, Dou Y, Joshi BV, Lazarowski E, Jacobson KA, Arner A, Erlinge D.** Positive inotropic effects by uridine triphosphate (UTP) and uridine diphosphate (UDP) via P₂Y₂ and P₂Y₆ receptors on cardiomyocytes and release of UTP in man during myocardial infarction. *Circ Res* 98: 970–976, 2006.
1862. **Wildman SS, King BF, Burnstock G.** Modulation of ATP-responses at recombinant rP₂X₄ receptors by extracellular pH and zinc. *Br J Pharmacol* 126: 762–768, 1999.
1863. **Wiley JS, Ferando S, Skarratt K, Saunders B, Sluyter R, Gu B, Fuller S, Shemon A, Dao-Ung P, Georgiou J, Britton W.** Polymorphisms in the P₂X₇ receptor and their clinical associations. *Purinergic Signalling* 2: 29–30, 2006.
1864. **Wiley LA, Rupp GR, Steinle JJ.** Sympathetic innervation regulates basement membrane thickening and pericyte number in rat retina. *Invest Ophthalmol Vis Sci* 46: 744–748, 2005.
1865. **Willems L, Ashton KJ, Headrick JP.** Adenosine-mediated cardioprotection in the aging myocardium. *Cardiovasc Res* 66: 245–255, 2005.
1866. **Williams M.** Mammalian central adenosine receptors. In: *Handbook of Neurochemistry*, edited by Lajtha A. New York: Plenum, 1984, p. 1–25.
1867. **Williams M.** Purinergic receptors and central nervous system function. In: *Psychopharmacology: The Third Generation of Progress*, edited by Meltzer HY. New York: Raven, 1987, p. 289–301.
1868. **Williams RM, Bienenstock J, Stead RH.** Mast cells: the neuro-immune connection. *Chem Immunol* 61: 208–235, 1995.
1869. **Wilson SM, Law VW, Pediani JD, Allen EA, Wilson G, Khan ZE, Ko WH.** Nucleotide-evoked calcium signals and anion secretion in equine cultured epithelia that express apical P₂Y₂ receptors and pyrimidine nucleotide receptors. *Br J Pharmacol* 124: 832–838, 1998.
1870. **Wilson SM, Pappone PA.** P₂ receptor modulation of voltage-gated potassium currents in Brown adipocytes. *J Gen Physiol* 113: 125–138, 1999.
1871. **Wink MR, Braganhol E, Tamajusuku AS, Lenz G, Zerbini LF, Libermann TA, Sévigny J, Battastini AM, Robson SC.** Nucleoside triphosphate diphosphohydrolase-2 (NTPDase2/CD39L1) is the dominant ectonucleotidase expressed by rat astrocytes. *Neuroscience* 138: 421–432, 2006.

1872. **Wirkner K, Gerevich Z, Krause T, Gunther A, Koles L, Schneider D, Norenberg W, Illes P.** Adenosine A_{2A} receptor-induced inhibition of NMDA and GABA_A receptor-mediated synaptic currents in a subpopulation of rat striatal neurons. *Neuropharmacology* 46: 994–1007, 2004.
1873. **Wirkner K, Köfalvi A, Fischer W, Günther A, Franke H, Gröger-Arndt H, Nörenberg W, Madarász E, Vizi ES, Schneider D, Sperlág B, Illes P.** Supersensitivity of P2X₇ receptors in cerebrocortical cell cultures after in vitro ischemia. *J Neurochem* 95: 1421–1437, 2005.
1874. **Wirkner K, Koles L, Furst S, Illes P.** Modulation of voltage- and ligand-gated ion channels by neuronal P2Y receptors. *Drug Dev Res* 59: 49–55, 2003.
1875. **Wise SP, Jones EG.** Transneuronal or retrograde transport of [³H]adenosine in the rat somatic sensory system. *Brain Res* 107: 127–131, 1976.
1876. **Wismer CT, Faltynek CR, Jarvis MF, McGaraughty S.** Distinct neurochemical mechanisms are activated following administration of different P2X receptor agonists into the hindpaw of a rat. *Brain Res* 965: 187–193, 2003.
1877. **Witt PA, Kramer TH, Burks TF.** Norepinephrine and ATP are synergistic in the mouse vas deferens preparation. *Eur J Pharmacol* 204: 149–155, 1991.
1878. **Wittendorp MC, Boddeke HW, Biber K.** Adenosine A₃ receptor-induced CCL2 synthesis in cultured mouse astrocytes. *Glia* 46: 410–418, 2004.
1879. **Witting A, Chen L, Cudaback E, Straiker A, Walter L, Rickman B, Moller T, Brosnan C, Stella N.** Experimental autoimmune encephalomyelitis disrupts endocannabinoid-mediated neuroprotection. *Proc Natl Acad Sci USA* 103: 6362–6367, 2006.
1880. **Witting A, Walter L, Wacker J, Moller T, Stella N.** P2X₇ receptors control 2-arachidonoylglycerol production by microglial cells. *Proc Natl Acad Sci USA* 101: 3214–3219, 2004.
1881. **Wojcik WJ, Neff NH.** Adenosine A1 receptors are associated with cerebellar granule cells. *J Neurochem* 41: 759–763, 1983.
1882. **Wollmann G, Acuna-Goycolea C, van den Pol AN.** Direct excitation of hypocretin/orexin cells by extracellular ATP at P2X receptors. *J Neurophysiol* 94: 2195–2206, 2005.
1883. **Wong AY, Billups B, Johnston J, Evans RJ, Forsythe ID.** Endogenous activation of adenosine A1 receptors, but not P2X receptors, during high-frequency synaptic transmission at the calyx of Held. *J Neurophysiol* 95: 3336–3342, 2006.
1884. **Wong AY, Burnstock G, Gibb AJ.** Single channel properties of P2X ATP receptors in outside-out patches from rat hippocampal granule cells. *J Physiol* 527: 529–547, 2000.
1885. **Wood JD.** The enteric purinergic P2Y₁ receptor. *Curr Opin Pharmacol* 6: 564–570, 2006.
1886. **Wood JD, Kirchgessner A.** Slow excitatory metabotropic signal transmission in the enteric nervous system. *Neurogastroenterol Motil* 16: 71–80, 2004.
1887. **Worthington RA, Arumugam TV, Hansen MA, Balcar VJ, Barden JA.** Identification and localisation of ATP P_{2X} receptors in rat midbrain. *Electrophoresis* 20: 2077–2080, 1999.
1888. **Wu D, Mori N.** Extracellular ATP-induced inward current in isolated epithelial cells of the endolymphatic sac. *Biochim Biophys Acta* 1419: 33–42, 1999.
1889. **Wu PH, Phillis JW.** Distribution and release of adenosine triphosphate in rat brain. *Neurochem Res* 3: 563–571, 1978.
1890. **Wu Y, Willcockson HH, Maixner W, Light AR.** Suramin inhibits spinal cord microglia activation and long-term hyperalgesia induced by formalin injection. *J Pain* 5: 48–55, 2004.
1891. **Wuest M, Morgenstern K, Graf EM, Braeter M, Hakenberg OW, Wirth MP, Ravens U.** Cholinergic and purinergic responses in isolated human detrusor in relation to age. *J Urol* 173: 2182–2189, 2005.
1892. **Wuttke W, Munsch T, Deitmer J.** Inhibition of voltage-dependent Ca²⁺ influx by extracellular ATP in salivary cells of the leech *Haementeria ghilianii*. *J Exp Biol* 199: 1335–1341, 1996.
1893. **Wyndaele JJ, De Wachter S.** The basics behind bladder pain: a review of data on lower urinary tract sensations. *Int J Urol* 10 Suppl: S49–S55, 2003.
1894. **Wynn G, Bei M, Ruan HZ, Burnstock G.** Purinergic component of mechanosensory transduction is increased in a rat model of colitis. *Am J Physiol Gastrointest Liver Physiol* 287: G647–G657, 2004.
1895. **Wynn G, Rong W, Xiang Z, Burnstock G.** Purinergic mechanisms contribute to mechanosensory transduction in the rat colon. *Gastroenterology* 125: 1398–1409, 2003.
1896. **Xiang Z, Bo X, Burnstock G.** Localization of ATP-gated P2X receptor immunoreactivity in rat sensory and sympathetic ganglia. *Neurosci Lett* 256: 105–108, 1998.
1897. **Xiang Z, Bo X, Burnstock G.** P2X receptor immunoreactivity in the rat cochlea, vestibular ganglion and cochlear nucleus. *Hear Res* 128: 190–196, 1999.
1898. **Xiang Z, Burnstock G.** P2X₂ and P2X₃ purinoceptors in the rat enteric nervous system. *Histochem Cell Biol* 121: 169–179, 2004.
1899. **Xiang Z, Burnstock G.** Development of nerves expressing P2X₃ receptors in the myenteric plexus of rat stomach. *Histochem Cell Biol* 122: 111–119, 2004.
1900. **Xiang Z, Burnstock G.** Changes in expression of P2X purinoceptors in rat cerebellum during postnatal development. *Dev Brain Res* 156: 147–157, 2005.
1901. **Xiang Z, Burnstock G.** Distribution of P2Y₂ receptors in the guinea pig enteric nervous system and its coexistence with P2X₂ and P2X₃ receptors, neuropeptide Y, nitric oxide synthase and calretinin. *Histochem Cell Biol* 124: 379–390, 2005.
1902. **Xiang Z, Burnstock G.** Expression of P2X receptors on rat choroid plexus. *Neuroreport* 16: 903–907, 2005.
1903. **Xiang Z, Burnstock G.** Distribution of P2Y₆ and P2Y₁₂ receptors: their colocalisation with calbindin, calretinin and nitric oxide synthase in the guinea pig enteric nervous system. *Histochem Cell Biol* 125: 336, 2006.
1904. **Xiang Z, Chen M, Ping J, Dunn PM, Lv J, Jiao B, Burnstock G.** Microglial morphology and its transformation after challenge by extracellular ATP in vitro. *J Neurosci Res* 83: 91–101, 2006.
1905. **Xiang Z, He C, Burnstock G.** P2X₅ receptors are expressed on neurons containing arginine vasopressin and neuronal nitric oxide synthase in the rat hypothalamus. *Brain Res* 1099: 63, 2006.
1906. **Xiao HS, Huang QH, Zhang FX, Bao L, Lu YJ, Guo C, Yang L, Huang WJ, Fu G, Xu SH, Cheng XP, Yan Q, Zhu ZD, Zhang X, Chen Z, Han ZG, Zhang X.** Identification of gene expression profile of dorsal root ganglion in the rat peripheral axotomy model of neuropathic pain. *Proc Natl Acad Sci USA* 99: 8360–8365, 2002.
1907. **Xiong K, Hu XQ, Stewart RR, Weight FF, Li C.** The mechanism by which ethanol inhibits rat P2X₄ receptors is altered by mutation of histidine 241. *Br J Pharmacol* 145: 576–586, 2005.
1908. **Xu GY, Huang LY.** Peripheral inflammation sensitizes P2X receptor-mediated responses in rat dorsal root ganglion neurons. *J Neurosci* 22: 93–102, 2002.
1909. **Xu GY, Huang LY.** Ca²⁺/calmodulin-dependent protein kinase II potentiates ATP responses by promoting trafficking of P2X receptors. *Proc Natl Acad Sci USA* 101: 11868–11873, 2004.
1910. **Xu J, Chalimoniuk M, Shu Y, Simonyi A, Sun AY, Gonzalez FA, Weisman GA, Wood WG, Sun GY.** Prostaglandin E₂ production in astrocytes: regulation by cytokines, extracellular ATP, oxidative agents. *Prostaglandins Leukotrienes Essent Fatty Acids* 69: 437–448, 2003.
1911. **Xu J, Kussmaul W, Kurnik PB, Al-Ahdav M, Pelleg A.** Electrophysiological-anatomic correlates of ATP-triggered vagal reflex in the dog. V. Role of purinergic receptors. *Am J Physiol Regul Integr Comp Physiol* 288: R651–R655, 2005.
1912. **Xu K, Bastia E, Schwarzschild M.** Therapeutic potential of adenosine A_{2A} receptor antagonists in Parkinson's disease. *Pharmacol Ther* 105: 267–310, 2005.
1913. **Xu L, Enyeart JJ.** Adenosine inhibits a non-inactivating K⁺ current in bovine adrenal cortical cells by activation of multiple P1 receptors. *J Physiol* 521: 81–97, 1999.
1914. **Xue L, Suzuki H.** Electrical responses of gastric smooth muscles in streptozotocin-induced diabetic rats. *Am J Physiol Gastrointest Liver Physiol* 272: G77–G83, 1997.
1915. **Yabuuchi K, Kuroiwa M, Shuto T, Sotogaku N, Snyder GL, Higashi H, Tanaka M, Greengard P, Nishi A.** Role of adenosine A₁ receptors in the modulation of dopamine D₁ and adenosine A_{2a} receptor signaling in the neostriatum. *Neuroscience* 141: 19–25, 2006.

1916. Yamamoto K, Sokabe T, Matsumoto T, Yoshimura K, Shibata M, Ohura N, Fukuda T, Sato T, Sekine K, Kato S, Isshiki M, Fujita T, Kobayashi M, Kawamura K, Masuda H, Kamiya A, Ando J. Impaired flow-dependent control of vascular tone and remodeling in P2X₄-deficient mice. *Nat Med* 12: 133–137, 2006.
1917. Yamamoto T, Iwai M, Kimura S, Shimazu T. The mechanism of action of hepatic sympathetic nerves on ketone-body output from perfused rat liver. The effect of the interaction of noradrenaline with ATP on the release of β -hydroxybutyrate. *Eur J Biochem* 234: 466–471, 1995.
1918. Yamauchi T, Iwai M, Kobayashi N, Shimazu T. Noradrenaline and ATP decrease the secretion of triglyceride and apoprotein B from perfused rat liver. *Pflügers Arch* 435: 368–374, 1998.
1919. Yamazaki Y, Fujii S, Nakamura T, Miyakawa H, Kudo Y, Kato H, Ito K. Changes in [Ca²⁺]_i during adenosine triphosphate-induced synaptic plasticity in hippocampal CA1 neurons of the guinea pig. *Neurosci Lett* 324: 65–68, 2002.
1920. Yamazaki Y, Kaneko K, Fujii S, Kato H, Ito K. Long-term potentiation and long-term depression induced by local application of ATP to hippocampal CA1 neurons of the guinea pig. *Hippocampus* 13: 81–92, 2003.
1921. Yang Q, Wu ZZ, Li X, Li ZW, Wei JB, Hu QS. Modulation by oxytocin of ATP-activated currents in rat dorsal root ganglion neurons. *Neuropharmacology* 43: 910–916, 2002.
1922. Yang YD, Zhang JZ, Sun C, Yu HM, Li Q, Hong M. Heroin affects purine nucleotides catabolism in rats in vivo. *Life Sci* 78: 1413–1418, 2006.
1923. Yao J, Suwa M, Li B, Kawamura K, Morioka T, Oite T. ATP-dependent mechanism for coordination of intercellular Ca²⁺ signaling and renin secretion in rat juxtaglomerular cells. *Circ Res* 93: 338–345, 2003.
1924. Yao L, McFarland K, Fan P, Jiang Z, Ueda T, Diamond I. Adenosine A_{2a} blockade prevents synergy between μ -opioid and cannabinoid CB1 receptors and eliminates heroin-seeking behavior in addicted rats. *Proc Natl Acad Sci USA* 103: 7877–7882, 2006.
1925. Yao ST, Barden JA, Lawrence AJ. On the immunohistochemical distribution of ionotropic P2X receptors in the nucleus tractus solitarius of the rat. *Neuroscience* 108: 673–685, 2001.
1926. Yao ST, Fong AY, Lawrence AJ. Purinergic transmission and central autonomic regulation. *Curr Top Pharmacol* 8: 167–184, 2004.
1927. Yao ST, Gourine AV, Spyer KM, Barden JA, Lawrence AJ. Localisation of P2X₂ receptor subunit immunoreactivity on nitric oxide synthase expressing neurones in the brain stem and hypothalamus of the rat: a fluorescence immunohistochemical study. *Neuroscience* 121: 411–419, 2003.
1928. Yao ST, Lawrence AJ. Purinergic modulation of cardiovascular function in the rat locus coeruleus. *Br J Pharmacol* 145: 342–352, 2005.
1929. Yarbrough GG, McGuffin-Clineschmidt JC. In vivo behavioral assessment of central nervous system purinergic receptors. *Eur J Pharmacol* 76: 137–144, 1981.
1930. Yatani A, Tsuda Y, Akaike N, Brown AM. Nanomolar concentrations of extracellular ATP activate membrane Ca channels in snail neurones. *Nature* 296: 169–171, 1982.
1931. Yen PT, Herman P, Van den AT, Tan CT, Bordure P, Marianowski R, Friedlander G, Tran Ba HP. Extracellular ATP modulates ion transport via P_{2Y} purinoceptors in a middle-ear epithelial cell line ORL. *J Otorhinolaryngol Relat Spec* 59: 170–175, 1997.
1932. Yeoh M, McLachlan EM, Brock JA. Chronic decentralization potentiates neurovascular transmission in the isolated rat tail artery, mimicking the effects of spinal transection. *J Physiol* 561: 583–596, 2004.
1933. Yerxa BR. Therapeutic use of nucleotides in respiratory and ophthalmic diseases. *Drug Dev Res* 52: 196–201, 2001.
1934. Yeung D, Zablocki K, Lien CF, Jiang T, Arkle S, Brutkowski W, Brown J, Lochmuller H, Simon J, Barnard EA, Górecki DC. Increased susceptibility to ATP via alteration of P2X receptor function in dystrophic mdx mouse muscle cells. *FASEB J* 20: 610–620, 2006.
1935. Yiangou Y, Facer P, Baecker PA, Ford AP, Knowles CH, Chan CL, Williams NS, Anand P. ATP-gated ion channel P2X₃ is increased in human inflammatory bowel disease. *Neurogastroenterol Motil* 13: 365–369, 2001.
1936. Yokomizo T, Izumi T, Chang K, Takuwa Y, Shimizu T. A G-protein-coupled receptor for leukotriene B₄ that mediates chemotaxis. *Nature* 387: 620–624, 1997.
1937. Yoon KW, Rothman SM. Adenosine inhibits excitatory but not inhibitory synaptic transmission in the hippocampus. *J Neurosci* 11: 1375–1380, 1991.
1938. Yoshida H, Kobayashi D, Ohkubo S, Nakahata N. ATP stimulates interleukin-6 production via P2Y receptors in human HaCaT keratinocytes. *Eur J Pharmacol* 540: 1–9, 2006.
1939. Yoshida K, Nakagawa T, Kaneko S, Akaike A, Satoh M. Adenosine 5'-triphosphate inhibits slow depolarization induced by repetitive dorsal root stimulation via P2Y purinoceptors in substantia gelatinosa neurons of the adult rat spinal cord slices with the dorsal root attached. *Neurosci Lett* 320: 121–124, 2002.
1940. Yoshida M, Miyamae K, Iwashita H, Otani M, Inadome A. Management of detrusor dysfunction in the elderly: changes in acetylcholine and adenosine triphosphate release during aging. *Urology* 63: 17–23, 2004.
1941. Yoshioka K, Nakata H. ATP- and adenosine-mediated signaling in the central nervous system: purinergic receptor complex: generating adenine nucleotide-sensitive adenosine receptors. *J Pharmacol Sci* 94: 88–94, 2004.
1942. Yu L, Huang Z, Mariani J, Wang Y, Moskowitz M, Chen JF. Selective inactivation or reconstitution of adenosine A_{2A} receptors in bone marrow cells reveals their significant contribution to the development of ischemic brain injury. *Nat Med* 10: 1081–1087, 2004.
1943. Zagorodnyuk V, Hoyle CHV, Burnstock G. An electrophysiological study of developmental changes in the innervation of the guinea-pig taenia coli. *Pflügers Arch* 423: 427–433, 1993.
1944. Zagorodnyuk VP, Costa M, Brookes SJ. Major classes of sensory neurons to the urinary bladder. *Auton Neurosci* 126–127: 390–397, 2006.
1945. Zagorodnyuk VP, Vladimirova IA, Vovk EV, Shuba MF. Studies of the inhibitory non-adrenergic neuromuscular transmission in the smooth muscle of the normal human intestine and from a case of Hirschsprung's disease. *J Auton Nerv Syst* 26: 51–60, 1989.
1946. Zaidi SI, Jafri A, Martin RJ, Haxhiu MA. Adenosine A_{2A} receptors are expressed by GABAergic neurons of medulla oblongata in developing rat. *Brain Res* 1071: 42–53, 2006.
1947. Zalk R, Shoshan-Barmatz V. Characterization of DIDS-sensitive ATP accumulation in brain synaptic vesicles. *FEBS Lett* 580: 5894–5898, 2006.
1948. Zarei MM, Toro B, McCleskey EW. Purinergic synapses formed between rat sensory neurons in primary culture. *Neuroscience* 126: 195–201, 2004.
1949. Zemkova H, Balik A, Jiang Y, Kretschmannova K, Stojilkovic SS. Roles of purinergic P2X receptors as pacemaking channels and modulators of calcium-mobilizing pathway in pituitary gonadotrophs. *Mol Endocrinol* 20: 1423–1436, 2006.
1950. Zeraati M, Mirnajafi-Zadeh J, Fathollahi Y, Namvar S, Rezvani ME. Adenosine A₁ and A_{2A} receptors of hippocampal CA1 region have opposite effects on piriform cortex kindled seizures in rats. *Seizure* 15: 41–48, 2006.
1951. Zhang C, Schmidt JT. Adenosine A1 receptors mediate retinotectal presynaptic inhibition: uncoupling by C-kinase and role in LTP during regeneration. *J Neurophysiol* 79: 501–510, 1998.
1952. Zhang J, Kornecki E, Jackman J, Ehrlich YH. ATP secretion and extracellular protein phosphorylation by CNS neurons in primary culture. *Brain Res Bull* 21: 459–464, 1988.
1953. Zhang JM, Wang HK, Ye CQ, Ge W, Chen Y, Jiang ZL, Wu CP, Poo MM, Duan S. ATP released by astrocytes mediates glutamatergic activity-dependent heterosynaptic suppression. *Neuron* 40: 971–982, 2003.
1954. Zhang M, Nurse CA. CO₂/pH chemosensory signaling in co-cultures of rat carotid body receptors and petrosal neurons: role of ATP and ACh. *J Neurophysiol* 92: 3433–3445, 2004.
1955. Zhang M, Zhong H, Vollmer C, Nurse CA. Co-release of ATP and ACh mediates hypoxic signalling at rat carotid body chemoreceptors. *J Physiol* 525: 143–158, 2000.

1956. **Zhang P, Zheng J, Bradley ME, Hexum TD.** ATP stimulated cyclic AMP formation in bovine chromaffin cells is enhanced by neuropeptide Y. *Peptides* 22: 439–444, 2001.
1957. **Zhang W, Segura BJ, Lin TR, Hu Y, Mulholland MW.** Intercellular calcium waves in cultured enteric glia from neonatal guinea pig. *Glia* 42: 252–262, 2003.
1958. **Zhang X, Zhang M, Laties AM, Mitchell CH.** Stimulation of P2X₇ receptors elevates Ca²⁺ and kills retinal ganglion cells. *Invest Ophthalmol Vis Sci* 46: 2183–2191, 2005.
1959. **Zhang X, Zhang M, Laties AM, Mitchell CH.** Balance of purines may determine life or death of retinal ganglion cells as A₃ adenosine receptors prevent loss following P2X₇ receptor stimulation. *J Neurochem* 98: 566–575, 2006.
1960. **Zhang XF, Han P, Faltynek CR, Jarvis MF, Shieh CC.** Functional expression of P2X₇ receptors in non-neuronal cells of rat dorsal root ganglia. *Brain Res* 1052: 63–70, 2005.
1961. **Zhang Y, Deng P, Li Y, Xu ZC.** Enhancement of excitatory synaptic transmission in spiny neurons after transient forebrain ischemia. *J Neurophysiol* 95: 1537–1544, 2006.
1962. **Zhang YH, Chen Y, Zhao ZQ.** Alteration of spontaneous firing rate of primary myelinated afferents by ATP in adjuvant-induced inflamed rats. *Brain Res Bull* 54: 141–144, 2001.
1963. **Zhang YX, Yamashita H, Ohshita T, Sawamoto N, Nakamura S.** ATP increases extracellular dopamine level through stimulation of P2Y purinoceptors in the rat striatum. *Brain Res* 691: 205–212, 1995.
1964. **Zhao HB, Yu N, Fleming CR.** Gap junctional hemichannel-mediated ATP release and hearing controls in the inner ear. *Proc Natl Acad Sci USA* 102: 18724–18729, 2005.
1965. **Zhao LF, Iwasaki Y, Oki Y, Tsugita M, Taguchi T, Nishiyama M, Takao T, Kambayashi M, Hashimoto K.** Purinergic receptor ligands stimulate pro-opiomelanocortin gene expression in AtT-20 pituitary corticotroph cells. *J Neuroendocrinol* 18: 273–278, 2006.
1966. **Zhao M, Milner P.** Changes of P2X-purinoceptors in rat vas deferens and spleen caused by long term guanethidine treatment. *Biomed Res* 13: 1, 2002.
1967. **Zhong Y, Banning AS, Cockayne DA, Ford APDW, Burnstock G, McMahon SB.** Bladder and cutaneous sensory neurons of the rat express different functional P2X receptors. *Neuroscience* 120: 667–675, 2003.
1968. **Zhong Y, Dunn PM, Burnstock G.** Guinea-pig sympathetic neurons express varying proportions of two distinct P2X receptors. *J Physiol* 523: 391–402, 2000.
1969. **Zhong Y, Dunn PM, Burnstock G.** Pharmacological comparison of P2X receptors on rat coeliac, mouse coeliac and mouse pelvic ganglion neurons. *Neuropharmacology* 39: 172–180, 2000.
1970. **Zhong Y, Dunn PM, Burnstock G.** Multiple P2X receptors on guinea pig pelvic ganglion neurons exhibit novel pharmacological properties. *Br J Pharmacol* 132: 221–233, 2001.
1971. **Zhong Y, Dunn PM, Xiang Z, Bo X, Burnstock G.** Pharmacological and molecular characterisation of P2X purinoceptors in rat pelvic ganglion neurons. *Br J Pharmacol* 125: 771–781, 1998.
1972. **Zhou X, Galligan JJ.** Non-additive interaction between nicotinic cholinergic and P2X purine receptors in guinea-pig enteric neurons in culture. *J Physiol* 513: 685–697, 1998.
1973. **Zhu CZ, Mikusa J, Chu KL, Cowart M, Kowaluk EA, Jarvis MF, McGaraughty S.** A-134974: a novel adenosine kinase inhibitor, relieves tactile allodynia via spinal sites of action in peripheral nerve injured rats. *Brain Res* 905: 104–110, 2001.
1974. **Zhu Y, Kimelberg HK.** Developmental expression of metabotropic P2Y₁ and P2Y₂ receptors in freshly isolated astrocytes from rat hippocampus. *J Neurochem* 77: 530–541, 2001.
1975. **Ziganshin AU, Ralevic V, Burnstock G.** Contractility of urinary bladder and vas deferens after sensory denervation by capsaicin treatment of newborn rats. *Br J Pharmacol* 114: 166–170, 1995.
1976. **Zimmermann H.** Co-existence of adenosine 5'-triphosphate and acetylcholine in the electromotor synapse. In: *Co-transmission*, edited by Cuello AC. London: MacMillan, 1982, p. 243–259.
1977. **Zimmermann H.** Signalling via ATP in the nervous system. *Trends Neurosci* 17: 420–426, 1994.
1978. **Zimmermann H.** Ectonucleotidases: some recent developments and a note on nomenclature. *Drug Dev Res* 52: 44–56, 2001.
1979. **Zimmermann H.** Ectonucleotidases in the nervous system. In: *Novartis Foundation Symposium 276 Purinergic Signalling in Neuron-Glial Interactions*, Chichester, UK: Wiley, 2006, p. 113–128.
1980. **Zimmermann H.** Nucleotide signaling in nervous system development. *Pflügers Arch* 452: 573–588, 2006.
1981. **Zimmermann K, Reeh PW, Averbach B.** ATP can enhance the proton-induced CGRP release through P2Y receptors and secondary PGE₂ release in isolated rat dura mater. *Pain* 97: 259–265, 2002.
1982. **Zinchuk VS, Okada T, Kobayashi T, Seguchi H.** Ecto-ATPase activity in cerebellum: implication to the function of synaptic transmission. *Brain Res* 815: 111–115, 1999.
1983. **Zizzo MG, Mulè F, Serio R.** Inhibitory responses to exogenous adenosine in murine proximal and distal colon. *Br J Pharmacol* 148: 956–963, 2006.
1984. **Zona C, Marchetti C, Volontè C, Mercuri NB, Bernardi G.** Effect of P2 purinoceptor antagonists on kainate-induced currents in rat cultured neurons. *Brain Res* 882: 26–35, 2000.
1985. **Zonta M, Angulo MC, Gobbo S, Rosengarten B, Hossmann KA, Pozzan T, Carmignoto G.** Neuron-to-astrocyte signaling is central to the dynamic control of brain microcirculation. *Nat Neurosci* 6: 43–50, 2003.
1986. **Zou CJ, Onaka TO, Yagi K.** Effects of suramin on neuroendocrine and behavioural responses to conditioned fear stimuli. *Neuroreport* 9: 997–999, 1998.
1987. **Zsembery A, Boyce AT, Liang L, Peti-Peterdi J, Bell PD, Schwiebert EM.** Sustained calcium entry through P2X nucleotide receptor channels in human airway epithelial cells. *J Biol Chem* 278: 13398–13408, 2003.