Calcium Channel α2δ Subunits: Structure, Functions and Target Site for Drugs

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Abstract: In this review we describe the genes encoding α2δ subunits, their topology and predicted structure. We then review the electrophysiological effects of α2δ subunits. It is clear from most studies that α2δ subunits increase channel density at the plasma membrane, but there is less agreement between studies and between channel subtypes concerning the effects of α2δ subunits on voltage-dependence of activation and inactivation. Most studies agree that α2δ subunits increase the kinetics of inactivation, for a number of different calcium channel subtypes. We also discuss the link between α2δ subunits and disease, particularly in terms of Ducky, the spontaneously occurring mutant mouse strain that has mutations in α2δ-2, and exhibits cerebellar ataxia and absence epilepsy. Finally, we will examine the evidence that α2δ subunits are the site of action of the anti-epileptic, anti-nociceptive drug gabapentin.

INTRODUCTION

Voltage-gated calcium channels are essential for the function of numerous excitable cells, including contraction in muscle and transmitter release from neurons [1]. The subunit composition was defined by purification of the skeletal muscle calcium channel complex, also termed the dihydropyridine receptor (DHPR), which is highly enriched in t tubules. It was found to contain five components: α1 (170 kDa), α2 (150 kDa), β (52 kDa), δ (17-25 kDa) and γ (32 kDa) in an approximately stoichiometric ratio [2;3]. The α1 subunit was identified as the subunit that bound 1,4-DHPs, and was established as the pore-forming subunit (Fig. **1**).

TOPOLOGY OF α2δ SUBUNITS

The topology of the α2 and δ subunits, and their relationship, took some time to establish. Whilst in reducing conditions the skeletal muscle α2 subunit migrated at 150 kDa, and the δ subunit could be resolved into 3 peaks (δ1, δ 2 and δ3 of about 25, 22 and 17 kDa), in non-reducing conditions the α2 and δ subunits migrated as a single band of about 175 kDa, indicating that they are disulfide-linked. N terminal sequencing of the α2 and δ proteins, and the subsequent cloning of a single gene [4] then indicated that α2 and δ are the products of the same gene, with δ making up the C terminal end of a pro-protein that is post-translationally cleaved. Comparative studies with the native and expressed α2δ proteins confirmed this to be the case. Both N terminal sequencing and the fact that the three δ peptides are antigenically cross-reactive indicated that they are all proteolytic products of the same α2δ gene product, with the same cleavage site [5]. Both α2 and δ are also highly glycosylated, as shown by treatment with glycosidase enzymes [5;6]. The different sizes of the δ peptides are thought to represent different glycosylation states [5]. The timing of the disulfide-linking and cleavage of α2 and δ during assembly and trafficking of the channel complex is unknown.

The exact transmembrane topology was an initial matter of debate. The α2 subunit has an N terminal signal sequence, indicating that it has an extracellular N terminus. It was deemed possible, based on hydrophobicity studies, that there were three transmembrane segments [4;5]. However, in this model several of the potential N- glycosylation sites would be situated intracellularly. Furthermore, α2 can be released from membranes into the supernatant in reducing conditions with alkaline wash, indicating that it is not a transmembrane protein [5]. Under these conditions δ remains membrane-associated, indicating it is an integral membrane protein [5]. Subsequently, topology mapping using site-directed antibodies, and studies using truncated α2δ-1 constructs also found that α2 is entirely extracellular [6-9].

GENES ENCODING α2-δ SUBUNITS

Four α2δ subunit genes have now been cloned, α2δ-1 being the original skeletal muscle α2δ subunit, whose distribution is fairly ubiquitous, whilst α2δ-2 and α2δ-3 are more selectively found in neurons and a small number of other tissues [10;11]. The most recently cloned α2δ-4 is largely non-neuronal [12]. The gene structure is similar for all α2δ subunits, with α2δ-2 having 39 exons. All α2δ subunits exhibit a number of splice variants [10;12;13].

The topology of the protein was only determined in detail for α2δ-1, but appears to generalize for all four α2δ subunits. All four have predicted N terminal signal sequences, indicating that the N terminus is extracellular, although in the case of α2δ-2, the N terminal signal peptide is unusually long [14]. The α2δ-2 subunit is clearly reduced in molecular weight by disulfide bond reduction [15], and when expressed the signal sequence is cleaved and the α2 moiety is extracellular [14]. All of the α2δ subunits have a C terminal hydrophobic and potentially transmembrane region. There are up to 14 conserved cysteines throughout the α2δ-1, 2 and

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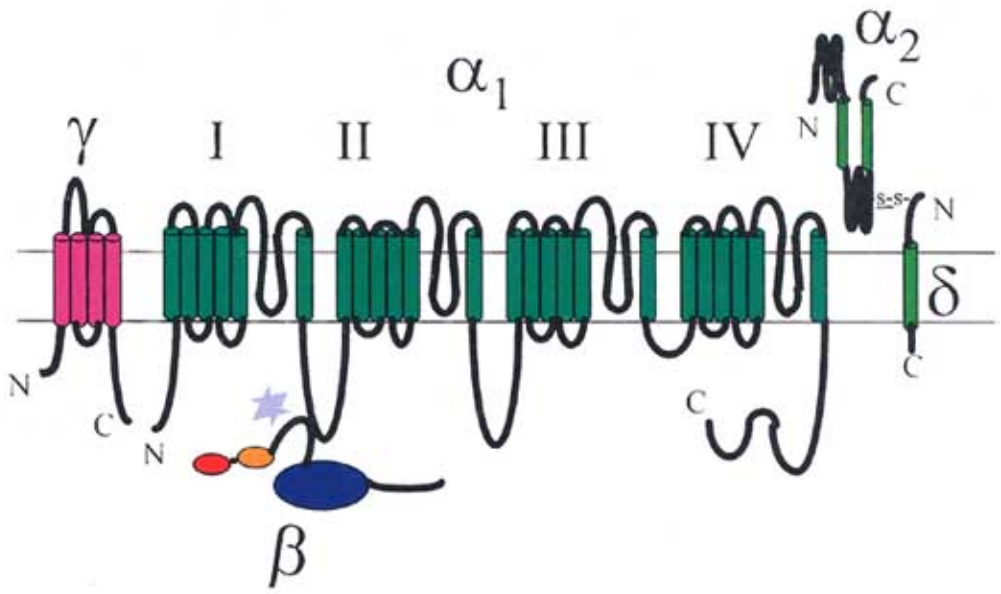

Fig. (1). Diagram of calcium channel subunits- indicating transmembrane topology.

3 sequences, six of which are within δ, providing additional evidence that α2 and δ are disulfide-bonded. However, the exact pairs of cysteines involved in this interaction are unknown.

Following the identification of α2δ subunits as stoichiometric components of skeletal muscle calcium channels, they have also been shown to be associated with native cardiac (L type) [16] and neuronal N and P/Q type channels [17;18]. Thus it would appear that high voltage-activated (HVA) calcium channels associate with α2δ subunits, although it has not been determined whether HVA α1 subunits in the plasma membrane may also exist functionally in the absence of α2δ subunits. The α2δ-1 subunit has been shown to bind to extracellular regions including Domain III on the $Ca_v1.2$ subunit [9;19].

Parallel purification experiments have not been performed on native low voltage-activated (LVA) or T-type calcium channels, hampered by the lack of selective ligands. Since the expression of cloned channels is robust in the absence of α2δ subunits, it is assumed that native T-type channels probably exist in their absence in the plasma membrane.

Although there is only limited structural information available for voltage-gated calcium channels, a number of electron microscopic single particle studies of purified skeletal muscle calcium channels have been published recently. One study shows the monomeric calcium channel complex to have a protruding ring-like handle that the authors suggest to be the α2δ-1 subunit [20]. In the other study a 3-D reconstruction of purified calcium channel complexes was performed, whose size indicated that they were dimeric, in which a pair of α2δ subunits were thought to create a hollow cap over the α1 subunits [21]. Thus both studies suggest that α2δ forms a hollow structure, although the function of this is unknown. It is possible that it produces a vestibule in which Ca^{2+} ions accumulate. However, if this were the case, one might expect a different single channel conductance in the absence of α2δ co-expression, and this has not generally been observed. However, we did notice an additional small conductance mode of several calcium channel α1 subunits expressed in the absence of accessory subunits, which may relate to a different conformation of the α1 subunit expressed alone [22]. Furthermore, others have shown that purified L type calcium channels require oligomerisation to exhibit native single channel properties in planar lipid bilayers [23].

The approximate molecular correlate of the α2δ subunit in voltage-gated Na^+ channels is the transmembrane β subunit, and $Na_V\beta1$ has been shown to have a conserved immunoglobulin (Ig) domain in its extracellular structure, which results in binding to the cell adhesion molecule tenascin-R [24]. No Ig domains exist in α2δ subunits.

One domain identified by sequence homology in the extracellular sequence of all α2δ subunits is the von Willebrand factor type A (VWFA) domain. This domain was first identified in von Willebrand Factor, where it mediates binding to collagen and factor VIII, among other proteins. VWFA-like domains are approximately 200 amino acids long, and found in certain integrin subunits, laminin, and some collagens [25]. The domain is a dinucleotide binding fold with a metal ion adhesion (MIDAS) site, mediating divalent cation-dependent interactions. Other recently identified domains in α2δ subunits are two Cache domains, the first of which immediately follows the VWFA domain [26]. Cache was identified by homology with an extracellular

domain in diverse chemotaxis receptors, including methyl-sensing receptors, where it binds small molecule ligands.

LOCALIZATION OF α2δ SUBUNITS

A number of studies have examined the tissue localization of the different α2δ subunits at both the message and the protein level. Message and protein for the α2δ-1 subunit is highly expressed in skeletal muscle but is also found fairly ubiquitously in other tissues [4;15]. Within the mouse brain α2δ-1 message is strongly expressed in cerebellum, hippocampus and cerebral cortex [10].

In contrast, the other α2δ subunits are expressed in a more limited range of tissues. Both human and mouse α2δ-2 are found in brain, from Northern blots [27;28], *in situ* hybridization and PCR based localization [11]. Within brain, α2δ-2 is found to be particularly concentrated in cerebellum (Fig. **2A**), and strongly expressed in Purkinje cells [11;14] (Fig. **2B**). It is also present at moderate levels in other brain regions including medulla, hippocampus and striatum [11]. Message for α2δ-2 was found to be strongly expressed in human lung tissue, in two studies [15;28], although not in an earlier study [10]. However, the α2δ-2 protein was barely detectable [15]. The reason for this discrepancy between high transcription level and low protein expression level is unknown, as is the cell type in which the message is found in human lung. In contrast, in the mouse α2δ-2 message was not detected in lung tissue [11].

In the mouse, message and protein for α2δ-3 is solely expressed in brain, whereas in man the expression of message is also detected in heart and skeletal muscle [15]. Within the mouse brain, α2δ-3 is strongly expressed in cerebral cortex, caudate-putamen and hippocampus. The α2δ-4 subunit shows very restricted distribution in certain endocrine tissues, and is absent from brain [12].

ELECTROPHYSIOLOGICAL EFFECTS OF α2 δ SUBUNITS

The function(s) of the α2δ subunits still remain incompletely defined as they have been reported to have a variety of effects on the properties of different calcium channels, some of which are dependent on the additional presence of a β subunit [29].

EFFECT OF α2δ ON CHANNEL DENSITY AT THE PLASMA MEMBRANE

For HVA calcium channels, β subunits are essential for trafficking voltage-gated calcium channels to the plasma membrane [30]. The effect of the α2δ subunits in the absence of β subunits is difficult to determine as several expression systems, particularly *Xenopus* oocytes, contain endogenous β subunits [31]. It must also be taken into consideration that a number of expression systems also contain some endogenous α2δ [32;33].

A number of studies have shown that α2δ subunits increase the expression of a number of different HVA α1 subunit/β subunit combinations, and all α2δ subunits appear to have similar effects. For $Ca_V1.2$, when α2δ-1 was co-

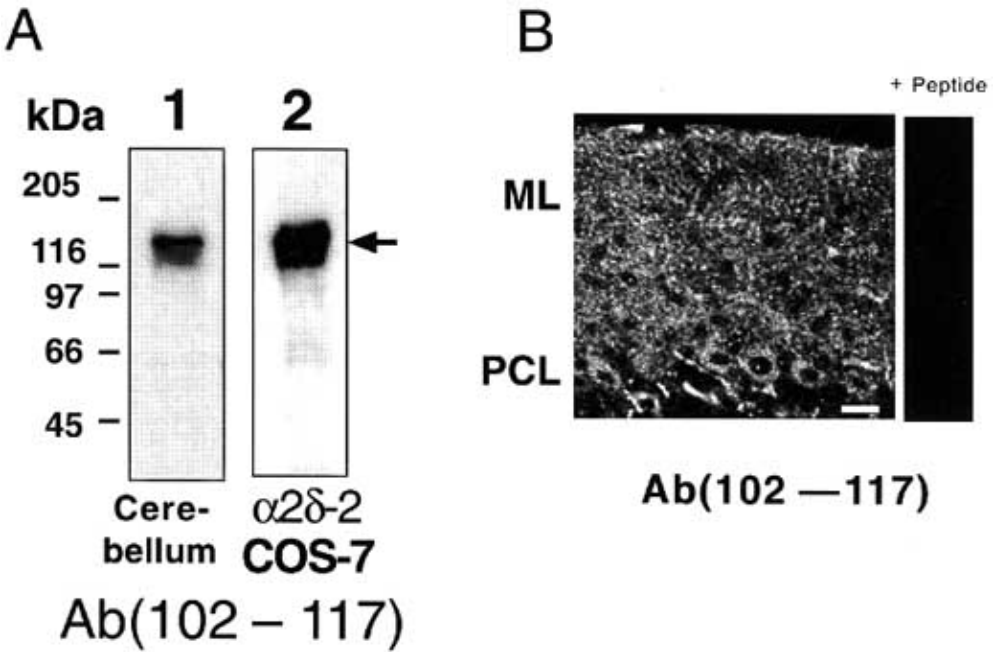

Fig. (2). The distribution of α2δ-2 in the cerebellum: (A) Identification of the α2 moiety of α2δ-2 in cerebellum, as a band of identical size to that obtained when α2δ-2 is expressed in COS-7 cells. Gels were run under reducing conditions, and the α2-2 band identified with an anti-peptide Ab raised against amino acids 102-117. **(B)** Distribution of α2δ-2 in cerebellum using immunohistochemistry with the same Ab as used in A. Data and Methods in both A and B are from Brodbeck *et al*. (2002) [14].

expressed with the α1 subunit, it increased the amount of α1 subunit protein associated with the oocyte plasma membrane [34]. It also increased the number of DHP binding sites, as well as increasing their affinity for the DHP ligand ^{3}H-PN200-110 [19]. This result indicates that as well as increasing the number of expressed channels, it also altered their conformation. The increased affinity suggests that α2δ-1 favours states of the calcium channel which show high affinity DHP binding, or that it increased the amount of the channel on the plasma membrane, where the affinity is higher, rather than internal membranes. In the same study, the peak $Ca_V1.2$ current amplitude was also increased 3-fold by co-expression of α2δ-1 [19].

For $Ca_V2.1$, the maximum conductance of the α1/β4 currents was increased about 2.8-fold by α2δ-2, and this complement of calcium channels is thought to be physiologically relevant for cerebellar Purkinje cells, in which α2δ-2 is strongly expressed [11;14] (Fig. **3A, B**). At the single channel level, α2δ-2 had no effect on the main single channel conductance of $Ca_V2.1$/β4 (Fig. **4**), or any of the other properties measured, suggesting strongly that the large increase in whole cell current is solely due to an increased number of channels at the plasma membrane [11;14]. However, we have previously shown that α1 subunits expressed in the absence of accessory subunits also show a small single channel conductance mode, which may represent a different conformation of the channel promoted under these conditions [22].

The α2δ-2 subunit has also been shown to increase $Ca_V2.2$ peak currents 9-fold and $Ca_V1.2$ currents 2-fold [35]. For the $Ca_V2.2$/β1b combination, we found both α2δ-1 and α2δ-2 subunits to increase the maximum current about 2.8-fold and the maximum conductance of the channels expressed in *Xenopus* oocytes (Fig. **5A, B**).

The situation for $Ca_V2.3$ channels is unclear. It has been reported that α2δ-1 subunits do not increase $Ca_V2.3$ current amplitude when co-expressed in *Xenopus* oocytes [36]. However, despite not increasing the ionic current, the authors did find that α2δ-1 increased the limiting gating currents (consistent with a larger number of channels in the membrane). In contrast, β subunits increased the maximum gating charge, but also increased the charge movement/ conductance ratio, consistent with both an increase in the efficiency with which movement of the voltage-sensor is translated into current activation, and an increase in the number of channels in the membrane [36].

A different result was obtained in HEK293 cells, where α2δ-1 produced a 2-fold increase in the maximum conductance for $Ca_V2.3$ expressed alone, although it gave no additional increase over and above that of β subunits [37]. In the latter study there was no change in the ratio of maximum conductance to gating charge movement, indicating that the increase was entirely due to an increase in the number of channels in the membrane [37].

From these results it is possible that $Ca_V2.3$ may be different from the other HVA channels in being less influenced by α2δ subunits, but this will require confirmation.

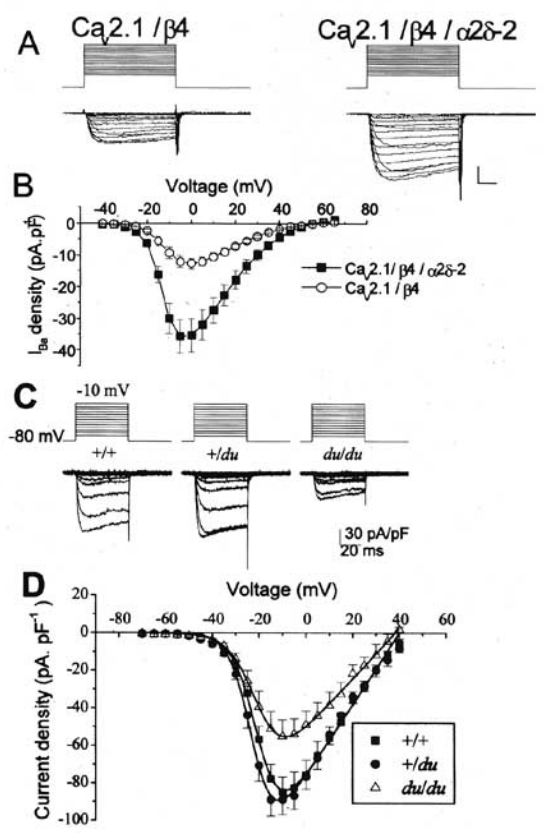

Fig. (3). Electrophysiological effects of α2δ-2 on $Ca_V2.1$: (A, B) The effect of α2δ-2 on the $Ca_V2.1$/β4 combination of calcium channel subunits expressed in COS-7 cells. **(A)** representative traces in the absence (left) and presence (right) of α2δ-2. **(B)** mean current-voltage relationships for the two conditions. **(C, D)** The effect of loss of α2δ-2 on calcium channel currents from Purkinje cells in Ducky mice. **(C)** representative traces from +/+, +/*du* and *du/du* mice. **(D)** mean current-voltage relationships for the three conditions. Data and Methods for this Figure are from [11] and [14].

The LVA calcium channels express very well in the absence of co-expressed accessory β or α2δ subunits. Nevertheless, both α2δ-1 and α2δ-2 were found to increase $Ca_V3.1$ currents almost 2-fold [33;35], and thus it is possible that T type channels may be able to associate with α2δ subunits. However, in other studies α2δ-1 and α2δ-3 produced only small or no increases in $Ca_V3.1$ current., but α2δ-2 had a larger effect on $Ca_V3.1$ current density [10;27;38].

EFFECTS OF α2δ SUBUNITS ON VOLTAGE-DEPENDENCE OF ACTIVATION AND INACTIVATION

The effects of α2δ subunits on the voltage-dependent and kinetic properties of calcium channels may also depend on the presence of a β subunit, and indeed on which β subunit is expressed. Many studies have been performed in *Xenopus*

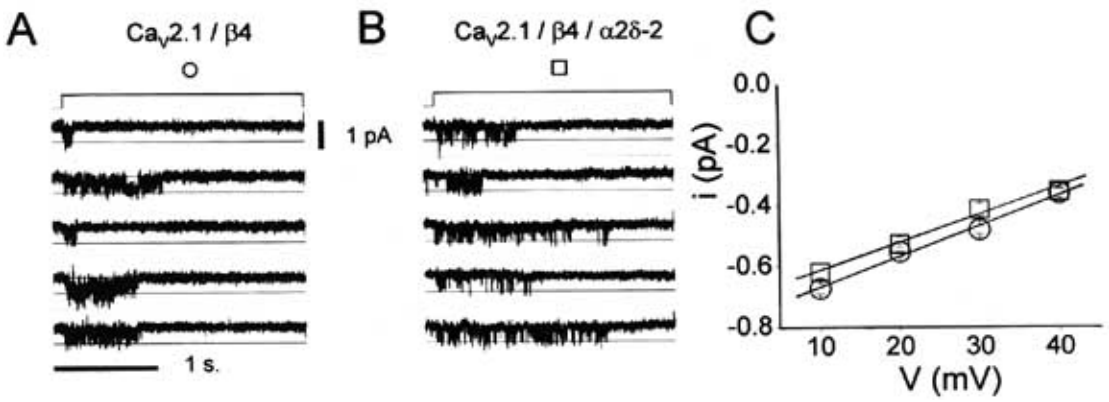

Fig. (4). Lack of effect of α2δ-2 on Ca_V2.1/β4 single channel properties: (A) Single channels recorded in cell-attached patch mode for the Ca_V2.1/β4 combination expressed in COS-7 cells. **(B)** Single channels recorded as in A, for the Ca_V2.1/β4/ α2δ-2 combination. **(C)** Single channel conductance for the two conditions Ca_V2.1/β4 (O), Ca_V2.1/β4/ α2δ-2 ( ). Data are from Brodbeck *et al.* (2002) [14].

oocytes, in which two electrode voltage clamp does not provide perfect control of the membrane voltage, especially for larger currents.

In the case of Ca_V1.2, initial studies reported that the α2δ-1 subunit had little effect on the voltage-dependence of activation [34;39-41]. This is supported by a more recent study on the voltage-dependence of charge movement [42]. In contrast, Felix *et al*. (1997) found that α2δ-1 hyperpolarized the voltage-dependence of activation of Ca_V1.2/β4 by about 10 mV. It is of interest that this was entirely reproduced by the transmembrane δ construct, although δ had no effect on current amplitude [19]. Platano *et al* (2000) using the cut-open oocyte technique, which gives a more accurate control of voltage than conventional two electrode voltage clamp of oocytes, also found that the activation of the Ca_V1.2/β3 combination was shifted to more hyperpolarized potentials by α2δ-1. However they found that α2δ-1 did not affect the voltage-dependence of charge movement, but did increase the total amount of charge moved, indicative of more channels in the membrane [43].

For Ca_V2.1, co-expressed with β4 in Cos-7 cells, α2δ-2 also had little effect on the voltage-dependence of activation [14]. This was also true for the effect of α2δ-1 and α2δ-2 on the Ca_V2.2/β1b combination (Fig. **5B**).

Contrasting results were found for Ca_V2.3, which shows a greater ability than Ca_V1.2 to express in the absence of accessory subunits [36;44]. Using the cut-open oocyte technique for Ca_V2.3, α2δ-1 was found to shift the activation to more depolarized potentials, either in the absence of β subunits or in the presence of β1b or β2a, from both current-voltage relationships and conductance-voltage relationships, determined from tail current measurements [36]. In contrast in HEK293 cells α2δ-1 had no effect on the voltage-dependence of activation gating [37].

In most cases α2δ-1 and α2δ-2 were also found to hyperpolarize the steady-state inactivation of Ca_V1.2, Ca_V2.2 and Ca_V2.3 currents to similar extents [19;27] (Fig. **5C**). However for Ca_V2.3 it was found in cut-open oocytes that, whilst β1b hyperpolarized the steady-state inactivation, α2δ-1 had no effect, either in the absence or presence of a β subunit [36].

Thus it is clear that there is no complete consensus on the effects of α2δ subunits on voltage-dependent properties of calcium channels. The reason for this may be that it is very difficult to dissect these effects from the fact that there are also more mature channels, and their associated β subunits at the plasma membrane.

EFFECT ON KINETICS OF ACTIVATION AND INACTIVATION

The α2δ-1 subunit increased the rate of inactivation for both the Ca_V1.2/β4 and Ca_V2.1/β4 combinations [19]. In another study, both α2δ-1 and α2δ-2 increased the inactivation rate of Ca_V1.2, Ca_V2.3 and Ca_V3.1 currents [27]. The α2δ-1 subunit was also found to speed up the process of inactivation of gating currents due to expression of the Ca_V1.2/β2a combination [42]. The effect on inactivation may explain the effect of α2δ-1 to increase the affinity for DHP antagonists, since such antagonists also favour the inactivated state of the channel [45]. We also found α2δ-1 and to a lesser extent α2δ-2 to speed up inactivation for the Ca_V2.2/ β1b combination (Fig. **5D**).

EFFECTS ON PREPULSE FACILITATION

Facilitation is the phenomenon whereby current is potentiated by applying a large depolarizing pulse immediately before the test pulse. It is understood that the channels are all converted by the prepulse into a state from which they will open readily with voltage. There is one report that α2δ-1 prevents prepulse facilitation for Ca_V1.2/β3, and the authors suggest that α2δ-1, by hyperpolarizing the conductance-voltage curve, performs the same task as a prepulse, maintaining the channels in this

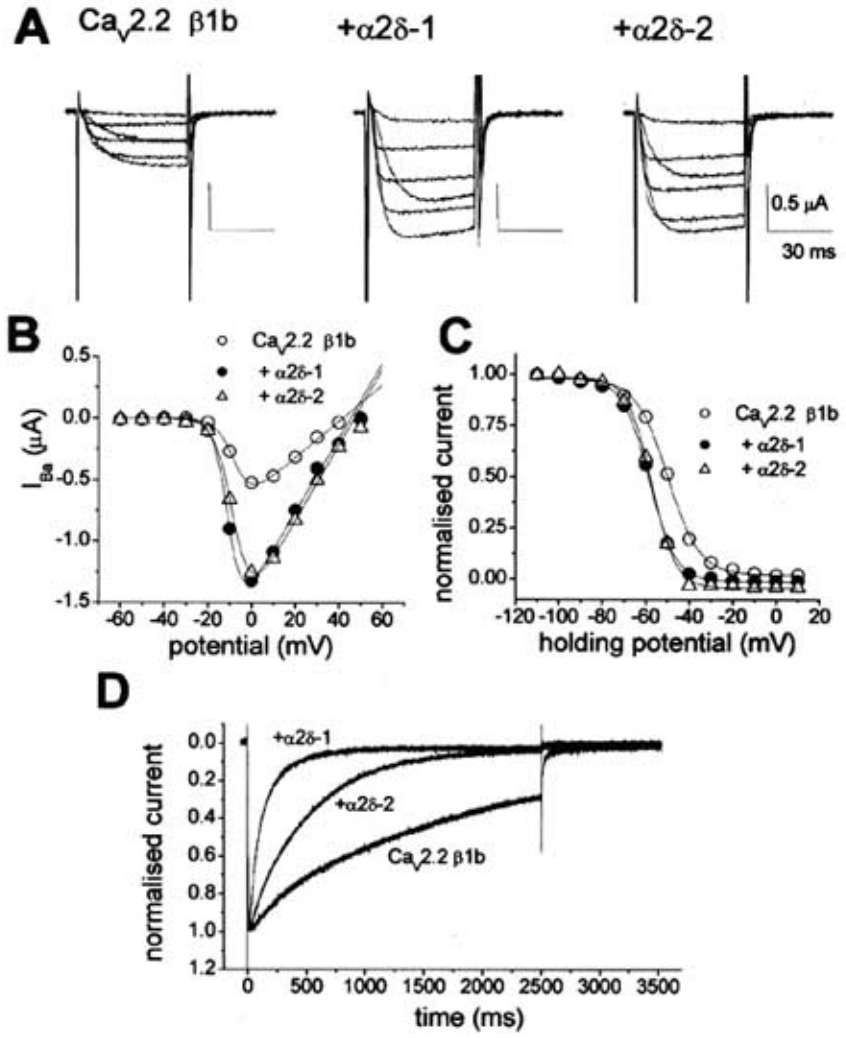

Fig. (5). Effects of α2δ-1 and α2δ-2 on Ca_V2.2/β1b current properties: (A) Examples of I_{Ba} for the Ca_V2.2/β1b combination, expressed alone (left), in the presence of α2δ-1 (centre) and in the presence of α2δ-2 (right). **(B)** Representative current-voltage relationships for the three conditions. **(C)** Representative steady-state inactivation curves for the three conditions. **(D)** Representative examples of currents activated by steps of 2.5 s. and normalised to show the relative effects of α2δ-1 and α2δ-2 on the inactivation kinetics. A-C are recorded in 10 mM Ba^{2+} as charge carrier, and D in 2 mM Ba^{2+}. All recordings were made in *Xenopus* oocytes.

state [43]. However, it must be noted that the α2δ subunits also increase the inactivation rate, and a depolarizing prepulse will induce both facilitation and inactivation, which will counteract each other.

SPECIFICITY OF INTERACTION BETWEEN α2δ AND Ca_V α1 SUBUNITS

With the cloning of three additional α2δ subunit genes, the question arises as to whether there is any specific association between particular pore-forming α1 (or Ca_V) and α2δ subunits. In heterologous expression systems this does not appear to be the case, but it is possible that *in vivo* there may be more specificity. For example in Purkinje cells α2δ-2 is the main, if not the only α2δ expressed, at least in mice [11], and Ca_V2.1 is the main α1 subunit, so that it is likely that most calcium channels in Purkinje cells consist of these two subunits, together with one of several β subunits (mainly β2 and β4) expressed in Purkinje cells.

LINK BETWEEN α2δ SUBUNITS AND DISEASE

One link between α2δ-2 and disease is that the *CACNA2D2* gene is found in the critical human tumour suppressor gene region in human chromosome 3p21.3, which shows frequent allele loss in lung, breast and other tumours. It is thus one of several candidate tumour suppressor genes in this region, although no causal link has been found [28]. Another link, which relates calcium channels and epilepsy, is

the spontaneously arising mutant mouse strain Ducky (*du).* These mice show cerebellar ataxia, absence epilepsy and demyelination of the hindbrain and spinal cord. The mutation was found to be in the α2δ-2 subunit gene, which is strongly expressed in cerebellar Purkinje cells. The mutation results in a loss of full length α2δ-2, and a second allele (du^{2J}) produces a similar phenotype [11]. We have shown that there is a reduction of calcium currents in Purkinje cells of *du/du* mice at 6 – 8 days old [11] (Fig. **3C, D**). Subsequently we have found that *du/du* Purkinje cells do not show normal maturation by 21 – 24 days, with a reduction of the Purkinje cell dendritic tree and multiple primary dendrites (Fig. **6**) [14]. It is unknown whether this is due to a reduction in calcium currents in these cells, or whether it is more directly due to a reduction in full length α2δ-2 expressed at the plasma membrane, and possibly a loss of interaction with the putative extracellular binding partner for α2δ-2, thus involving a loss of interaction with neighbouring cells or with the extracellular matrix.

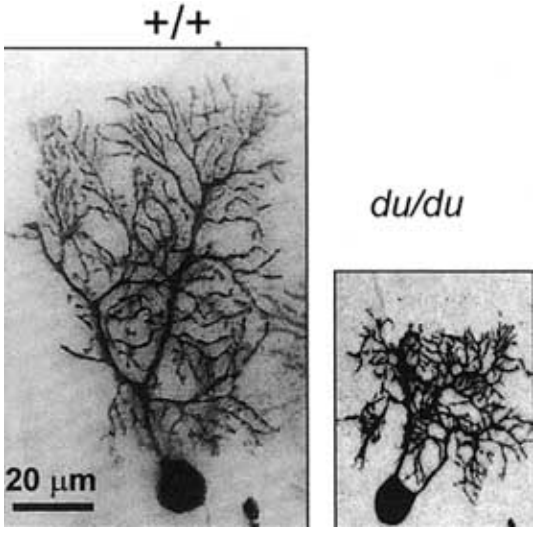

Fig. (6). Golgi-Cox staining of Purkinje cells from +/+ and *du/du* mice: Data and Methods are from Brodbeck *et al*. (2002) [14].

There is another possible corollary of the observation that α2δ-2 selectively enhances $Ca_V2.1$/β4 currents in Purkinje cells, which stems from the finding that a number of other calcium channelopathies in humans and mice are associated with mutations in $Ca_V2.1$ and β4 [46]. Several of these mutations may reduce the surface expression of the channel, for example in episodic ataxia type 2 (EA-2), where truncated non-functional channels are produced (see [46] for review). This may result in a corresponding loss of surface expression of the associated α2δ-2 in Purkinje cells and other neurons. However, so far no mutations in α2δ-2 have been associated with disease in man.

A further link between α2δ subunits and disease relates to the observation that α2δ-1 subunits are upregulated in neuropathic pain [47;48], but this will be covered in more detail elsewhere [49;50].

INTERACTION OF GABAPENTIN WITH α2δ SUBUNITS

The anti-epileptic and anti-nociceptive drug gabapentin was found to exhibit high affinity binding to sites in the brain, and when the target binding site was identified it was shown to be the α2δ-1 subunit [51]. Furthermore transient transfection of cells with α2δ-1 increased the number of gabapentin binding sites [51]. Subsequently gabapentin has been found to bind to two isoforms of α2δ subunits (the α2δ-1 and α2δ-2 isoforms, but not α2δ-3 or α2δ-4) [15;51-54]. This binding may involve the Cache and other domains [26], but it is unknown how gabapentin exerts its action.

EFFECTS OF GABAPENTIN ON CALCIUM CURRENTS

The effects of gabapentin on native calcium currents are controversial, with some, but not all authors reporting small inhibitions of calcium currents in different cell types, which are of fairly slow onset [55-58]. They are reviewed in more detail elsewhere in this issue [49, 59], but it is notable that there are very few studies reporting effects of gabapentin on cloned calcium channels.

Recently, gabapentin has been reported to have no acute effect on the amplitude of $Ca_V2.1$/ α2δ-1/β3 co-expressed in *Xenopus* oocytes, but slowed the inactivation of the currents (from a time constant of about 200 ms to 250 ms at -10mV). The inactivation kinetics in the presence of gabapentin resembled those in the absence of α2δ, and gabapentin had no effect on calcium current inactivation in the absence of α2δ [60]. We have also found no acute effect of gabapentin on the amplitude of $Ca_V2.2$/β1b currents co-expressed with either α2δ-1 or α2δ-2 (Fig. **7**). It was hypothesized that gabapentin and related drugs might interfere with α2δ binding to the α1 subunit, thus destabilizing the heteromeric complex. However, the integrity of the skeletal muscle calcium channel complex was not affected by gabapentin [60].

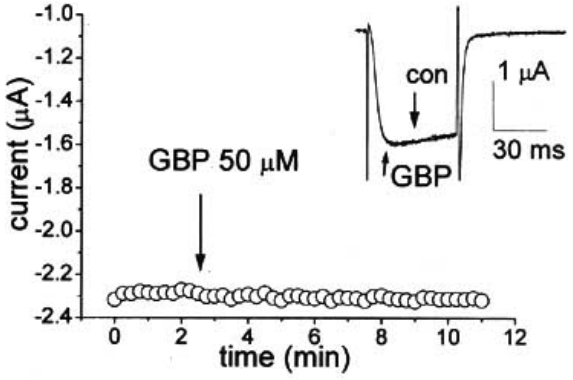

Fig. (7). Lack of acute effect of gabapentin on $Ca_V2.2$ calcium currents: Oocytes were injected intranuclearly with cDNA for $Ca_V2.2$, α2δ-1 and β1b. Currents were recorded in the presence of 2 mM Ba^{2+} as charge carrier. The methods used have been described previously [57]. No effect was observed of acute application of 50 μM gabapentin on the amplitude of the currents (n =2). A time course and representative maximum current traces are shown. No effect was observed of gabapentin when α2δ-2 was used in place of α2δ-1 (n =2, data not shown).

CONCLUSION

The α2δ subunits have marked effects on calcium channel properties and also very clear links to disease processes. It is still an open question whether the antinociceptive and antiepileptic effects of gabapentin are mediated via its identified interaction with α2δ-1 and α2δ-2 subunits.

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