

**Introduction**

The rapid entry of Ca\(^{2+}\) into excitable cells is mediated by a heterogeneous class of molecule, the Ca\(^{2+}\) channel. In the nervous system, Ca\(^{2+}\) channels play roles in mediating a wide variety of events including the patterning of neuronal firing, neurotransmitter release, and gene expression. To date, four major types of Ca\(^{2+}\) channel have been described in neurons (called T, L, N and P) [1,2]. Low-threshold Ca\(^{2+}\) channels (T-type) are transiently activated by relatively small depolarizations from hyperpolarized holding potentials and are completely inactivated at positive potentials. The other three Ca\(^{2+}\) channel types are activated at more positive potentials (high-threshold) and display diverse kinetic properties. A major distinguishing characteristic of the different high-threshold Ca\(^{2+}\) channels is their sensitivity to various pharmacological agents: L-type channels are sensitive to dihydropyridine (DHP) agonists and antagonists, N-type channels are blocked by the Conus geographus peptide toxin, \(\omega\)-conotoxin GVIA (\(\omega\)-CgTx), and P-type channels are blocked by a crude venom fraction from the funnel web spider *Agelenopsis aperta*. Much research has been directed towards understanding Ca\(^{2+}\) channel diversity and it has been proposed that the distinct Ca\(^{2+}\) channel types are selectively localized in neurons and that each type may make unique contributions to neuronal physiology (for examples, see [3,4]).

The molecular dissection of neuronal Ca\(^{2+}\) channels has been made possible by the previous biochemical and molecular characterization of the skeletal muscle L-type Ca\(^{2+}\) channel (reviewed in [5,6]). This channel is a heterooligomeric complex consisting of five subunits (\(\alpha_1, \alpha_2, \beta, \gamma \) and \(\delta\)), with the \(\alpha_2\)- and \(\delta\)-subunits being derived from the same gene and proteolytically cleaved in vivo [7,8]. In a number of test systems the \(\alpha_1\)-subunits of several cloned L-type channels have been shown to function as both the voltage sensor and Ca\(^{2+}\)-selective pore [9–12]. This brief review will focus on recent studies addressing the molecular nature of neuronal Ca\(^{2+}\) channel diversity and on the modulation of Ca\(^{2+}\) channels by voltage and ligands.

**Structural and functional diversity of cloned neuronal Ca\(^{2+}\) channels**

While neuronal Ca\(^{2+}\) channel diversity is likely to be the result of a number of factors, including modulation by accessory subunits and second-messenger mechanisms (see below), it is now evident that a significant portion of Ca\(^{2+}\) channel heterogeneity is due to the expression of unique \(\alpha_1\)-subunits. Currently, molecular cloning has identified five primary types of \(\alpha_1\)-subunit and four of these are expressed in the mammalian nervous system (classes A, B, C and D), Table 1, [13]. The deduced amino acid sequences of the Ca\(^{2+}\) channel \(\alpha_1\)-subunits show an overall conservation in structure, and are evolutionarily related to voltage-gated Na\(^{+}\) and K\(^{+}\) channels (Fig.1).

In addition to the five major types of \(\alpha_1\)-subunit (Table 1), molecular cloning and polymerase chain reaction studies have revealed a previously unanticipated degree of Ca\(^{2+}\) channel heterogeneity. Within each of the class A–D \(\alpha_1\)-subunits, multiple isoforms are expressed. Of potential functional significance is the observation that in a number of instances the isoforms found within a given class are the result of a nearly precise substitution of putative transmembrane segments [14–17]. Furthermore, the expression of some isoforms appears to be spatially regulated and may result in qualitative differences between Ca\(^{2+}\) channels in different cell types. In the case of the rat class C \(\alpha_1\)-subunit, the generation of distinct isoforms is clearly a result of alternate splicing from a single gene [14+]. Alternate splicing is also suggested, but not yet proven, to be responsible
### Table 1. Properties of cloned full-length Ca\(^{2+}\) channel \(\alpha_1\)-subunits.

<table>
<thead>
<tr>
<th>Class</th>
<th>cDNA</th>
<th>Amino acids</th>
<th>Predicted molecular mass (kD)</th>
<th>Channel properties</th>
<th>Distribution</th>
<th>Notes</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skeletal muscle (L-type)</td>
<td></td>
<td>1,873</td>
<td>212</td>
<td>High threshold, DHP-sensitive, slow activation in L cells</td>
<td>Skeletal muscle</td>
<td>Rate of activation and inactivation increased by (\beta)-subunits</td>
<td>[9,11,34*,35*]</td>
</tr>
<tr>
<td>A</td>
<td>B-1</td>
<td>2,273</td>
<td>257</td>
<td>High threshold, blocked by crude venom from Agelenopsis apera</td>
<td>Brain, heart, pituitary</td>
<td>In oocytes expression increased by skeletal muscle (\alpha_2)- and (\beta)-subunits</td>
<td>[19**,20]</td>
</tr>
<tr>
<td></td>
<td>B-2</td>
<td>2,424</td>
<td>273</td>
<td>DHP-sensitive, increased by (\beta)-subunit and (\alpha)-CgTx</td>
<td>CH4C1, PC12, C-cells</td>
<td>High levels of expression in cerebellum isoforms differ in cerebellum</td>
<td></td>
</tr>
<tr>
<td></td>
<td>dbA-1</td>
<td>2,212</td>
<td>252</td>
<td></td>
<td></td>
<td>16pS single channel conductance</td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>rbB-I</td>
<td>2,336</td>
<td>262</td>
<td>Not available</td>
<td>Brain, PC12, C-cells</td>
<td>Antibodies against rbB-I immunoprecipitate brain (\alpha)-CgTx binding sites</td>
<td>[26*]</td>
</tr>
<tr>
<td>C</td>
<td>pCARD3</td>
<td>2,171</td>
<td>243</td>
<td>High-threshold, DHP-sensitive</td>
<td>Brain, heart, lung,</td>
<td>Distinct isoforms generated by splicing</td>
<td>[10,12]</td>
</tr>
<tr>
<td>(L-type)</td>
<td>pSCaL</td>
<td>2,166</td>
<td>242</td>
<td></td>
<td>pituitary, kidney, aorta,</td>
<td>Modulated by (\beta)-, (\alpha_2)- and (\gamma)-subunits</td>
<td>[14*,17]</td>
</tr>
<tr>
<td></td>
<td>rbC-I</td>
<td>2,140</td>
<td>240</td>
<td></td>
<td>CH4C1, PC12, C-cells</td>
<td></td>
<td>[32*,36*,37*]</td>
</tr>
<tr>
<td></td>
<td>rbC-II</td>
<td>2,143</td>
<td>240</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>UlD</td>
<td>2,161</td>
<td>245</td>
<td>High-threshold, DHP-sensitive, reversible block by 10-15 mM Ca(^{2+})</td>
<td>Brain, heart, pituitary, pancreas, CH4C1, PC12, C cells</td>
<td>Expression in oocytes requires (\beta)-subunit</td>
<td>[10**,60,61]</td>
</tr>
<tr>
<td>(L-type)</td>
<td>CACN4</td>
<td>2,181</td>
<td>248</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>RbD(_1)</td>
<td>1,634</td>
<td>187</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Fig.1.** The predicted transmembrane folding model of the Ca\(^{2+}\) channel \(\alpha_1\)-subunit. The five cloned types of Ca\(^{2+}\) channel \(\alpha_1\)-subunit are between 210 kD and 270 kD in predicted molecular mass and possess four internal repeated domains (I–IV) that are modelled to contain six \(\alpha\)-helical transmembrane regions (S1–S6), including one (S4) that is positively charged and is thought to form part of the voltage sensor. By analogy to K\(^+\) channels the region separating segments S5 and S6 of each domain may contain two additional transmembrane segments (S51 and S52) that together form the pore of the channel (S6). The regions with the highest degree of amino acid identity among the five cloned types of \(\alpha_1\)-subunit are the four repeated domains and a short segment immediately flanking S6 of domain IV. The latter region, together with the loop between segments S5 and S6 in domain III, is implicated in the formation of the binding site for dihydropyridines in L-type Ca\(^{2+}\) channels (white regions) [57–59]. Compared with other cloned Ca\(^{2+}\) channel \(\alpha_1\)-subunits, the rat brain class D cDNA, RbD\(_1\) [60], encodes a 187 kD protein truncated in the carboxyl terminus (arrow). The functional significance of this truncated \(\alpha_1\)-subunit remains unclear, however, as both a second rat brain class D clone (H Kim et al.: Soc Neurosci Abstr 1991, 17:772), and the human brain [18**] and pancreas [61] class D homologues possess carboxyl segments that extend more than 500 amino acids past the end of RbD\(_1\).
Ca\(^{2+}\) channels in neurons (Table 1). Overall, the class C and D \(\alpha_1\) subunits are more closely related to each other (70–76% amino acid identity) than to the class A and B proteins (33–44%). The structural similarity between the class C and D proteins is also reflected in their functional properties. Antisense oligonucleotides against brain class C transcripts selectively block the expression of DHP-sensitive Ca\(^{2+}\) channels induced in C transcripts. Synthetic RNA derived from cardiac and lung class C \(\alpha_1\) subunits into oocytes results in the expression of high-voltage threshold Ca\(^{2+}\) channels that are sensitive to both DHP agonists and antagonists [10,12]. Although the human brain class D \(\alpha_1\) subunit alone is not functional in oocytes, co-injection of RNAs encoding the class D \(\alpha_1\) subunit and a brain \(\beta\)-subunit results in the expression of high-threshold Ca\(^{2+}\) channels that are also DHP-sensitive [16**]. The class C and D Ca\(^{2+}\) channels appear to differ in their current-voltage relations as well as pharmacologically, as the class D channels are partially and reversibly blocked by 10–15 \(\mu\)M \(\omega\)-conotoxin [18**]. The class C and D Ca\(^{2+}\) channels are co-expressed in several cell lines (Table 1) and it will be particularly interesting to determine whether this co-localization extends to the mammalian nervous system, and if these distinct L-type Ca\(^{2+}\) channels make unique contributions to neuronal physiology.

Structurally, class A \(\alpha_1\) subunits differ significantly from DHP-sensitive Ca\(^{2+}\) channels in two hydrophilic regions predicted to be cytoplasmic: the segment separating domains II and III, and the carboxy-terminal region (Fig.1) [19**]. Of particular interest is that the class A domain II–III segment is much larger than that of DHP-sensitive Ca\(^{2+}\) channels (~430 versus ~130 amino acids) and shows no detectable homology to other proteins. The analogous region of the skeletal muscle \(\alpha_1\) subunit is involved in mediating excitation-contraction coupling [21], and it will be of interest to determine the functional role of this divergent region in Ca\(^{2+}\) channels expressed in the nervous system.

A significant development in the past year has been the demonstration that the rabbit brain class A \(\alpha_1\) subunit encodes a high-threshold Ca\(^{2+}\) channel that is insensitive to both DHP antagonists and \(\omega\) Gctx, but is blocked by crude venom from the funnel web spider Agelenopsis aperta [19**]. Together with the finding that class A transcripts are highly abundant in the cerebellum [19**,20], these results suggest that class A Ca\(^{2+}\) channels correspond to the P-type Ca\(^{2+}\) channels first described by Llinas and coworkers [22]. The physiological properties of the rabbit class A Ca\(^{2+}\) channel expressed in Xenopus oocytes do not correlate exactly with those described for P-type channels in cerebellar Purkinje cells (for a discussion, see [23]). Two pieces of evidence suggest that P-type Ca\(^{2+}\) channels may be more widespread than originally thought: first, a high-threshold Ca\(^{2+}\) current that is not blocked by \(\omega\) Gctx or DHP antagonists has recently been described in a variety of central nervous system neurons [24**,25*]; and second, class A transcripts have been detected in the heart, pituitary, and several neuronal and endocrine cell lines (Table 1).

Still actively being sought are cDNAs encoding T and N-type Ca\(^{2+}\) channels. A possible candidate for N-type channels is the class B \(\alpha_1\) subunit. Analogous to class A Ca\(^{2+}\) channels, the class B \(\alpha_1\) subunit possesses a large hydrophilic segment linking domains II and III and also shares >80% amino acid identity in the four domains with class A \(\alpha_1\) subunits [26*]. Interestingly, there is little detectable identity between the class A and B \(\alpha_1\) subunits in either their domain II–III segments or in their carboxyl termini. Linking the class B protein to N-type channels are the results that antibodies directed against the class B \(\alpha_1\) subunit immunoprecipitate radiolabelled brain \(\omega\)-Gctx binding sites, and that class B transcripts are selectively localized to the nervous system [26*]. Direct evidence of the cloning of an N-type channel awaits the expression of the class B protein, however. At present, there are no leading molecular candidates for T-type Ca\(^{2+}\) channels. One possibility is that T-type channels are derived by alternate splicing from one of the classes of \(\alpha_1\) subunit already cloned. Alternatively, T-type channels may be evolutionary quite distant from the high-threshold Ca\(^{2+}\) channels, and cloning may require the use of cell lines enriched for T-type channel expression and cloning strategies using alternative probes.

### Subunit composition of neuronal Ca\(^{2+}\) channels

Neuronal N- and L-type Ca\(^{2+}\) channels are blocked with high-affinity by the Agelenopsis aperta peptide toxins \(\omega\)-Aga-III, indicating that they share some common structural features [27]. Furthermore, recent evidence suggests that neuronal N- and L-type channels are heteromeric complexes of roughly similar composition to the skeletal muscle DHP receptor. The purified brain \(\omega\)-Gctx receptor is composed of a 230 kD \(\alpha_2\delta\)-like protein that binds \(\omega\)-Gctx and four smaller proteins of between 60 kD and 140 kD [28*]. Two of the smaller proteins are likely to be \(\alpha_2\delta\)- and \(\beta\)-subunits as monoclonal antibodies against the skeletal muscle \(\alpha_2\delta\) [29,30] and \(\beta\) [31*] subunits immunoprecipitate both brain DHP and \(\omega\) Gctx binding sites. Indeed, molecular cloning results from a number of laboratories have identified \(\beta\) and \(\alpha_2\delta\)-subunit isoforms that are expressed in the brain [18**,32*,33]. The existence of multiple brain \(\beta\)-subunit isoforms is also indicated by immunoprecipitation results that identify two distinct \(\beta\)-like subunits associated with the \(\omega\)-Gctx receptor [31*].

### Modulation of \(\alpha_1\)-subunits

A number of new studies are providing evidence as to the roles of the other subunits in affecting the functional properties of the \(\alpha_1\) subunits. Perez-Reyes and co-workers [11] initially demonstrated that the skeletal muscle
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2α-subunit transfected into mouse L cells resulted in the expression of Ca²⁺ currents that were DHP-sensitive, but which showed an uncharacteristically slow activation. Two independent studies have now shown that the rate of activation and inactivation of the skeletal muscle 2α-subunit is dramatically increased by co-expression with the skeletal muscle β-subunit [34*,35*]. Co-expression of α₁- and β-subunits also increases the number of DHP binding sites in transfected L cells. Surprisingly, further combining the α₂δ and γ subunits seems to actually decrease the number of DHP binding sites found with α₁ and β together [35*]. In *Xenopus* oocytes the level of expression of brain class A and cardiac class C α₁-subunits is significantly increased by co-expression with α₂δ- and β-subunits [19**,32*,36*,37*]. In addition, the α₂δ, β- and γ-subunits affect various functional properties of the class C α₁-subunit, including changes in kinetics and the voltage-dependence of activation and inactivation [32*,36*,37*]. No modulatory effects of the β- and α₂δ-subunits on the class A channel have been reported [19**]. While the modulatory effects of the other subunits seem to depend somewhat on the type of α₁-subunit and the expression system used, it is clear that both the level of expression and the kinetic properties of Ca²⁺ channel α₁-subunits are affected by the α₂δ-, β- and γ-subunits.

**Nomenclature**

With the increasing number of full-length α₁-subunit cDNAs isolated from various laboratories, it has become increasingly difficult to keep track of the names assigned to them. The situation becomes even more complex when the large number of partial cDNAs generated by RNA polymerase chain reaction analyses are considered. Some clones are named after the tissue from which the cDNAs were first derived, some are named alphabetically, and some are named numerically. With the more recent demonstration of specific isoforms of α₂δ- and β-subunits, a further degree of complexity has been introduced into the nomenclature of Ca²⁺ channels. As future molecular cloning studies will undoubtedly define even further Ca²⁺ channel diversity, this may be an appropriate time to adopt a standardized Ca²⁺ channel nomenclature, perhaps analogous to that recently adopted for voltage-gated K⁺ channels [38].

Both voltage and ligands can alter the kinetics of Ca²⁺ channels — facilitation

A subset of high-threshold Ca²⁺ channels exhibit facilitation—depolarizing pre-pulses enhance the amount of current evoked by subsequent depolarizations [39,40]. Facilitation involves a change in kinetic behavior of Ca²⁺ channels such that the facilitated channel exhibits openings of longer duration accompanied by an increased probability of opening [41]. In contrast, in the absence of facilitation the channel is characterized by brief openings. For example, in chromaffin cells facilitation involves a change in the kinetic behavior of a 27 pS channel sensitive to DHPs [42**]. It appears that more than one class of high-threshold Ca²⁺ channel may be subject to facilitation, however, as it is also exhibited by Ca²⁺ channels in rat sympathetic neurons sensitive to α-CgTx [43].

The process underlying Ca²⁺ channel facilitation may be affected by receptor activation as well as by voltage. Neutrotransmitters, acting through GTP-binding protein (G protein)-coupled receptors, have been shown to inhibit high-threshold Ca²⁺ currents in both sympathetic and dorsal root ganglion cells [44,45]. This inhibition appears to be due to a change in the voltage-dependence of the Ca²⁺ channel [46], and the agonist-induced inhibition can be overcome by depolarizing pre-pulses [47-49]. The available data suggest that under basal conditions the channels behave as if they had been facilitated by a depolarizing pre-pulse, i.e. they exhibit frequent long-duration openings. Agonist converts the channels to the mode in which openings of short duration predominate, and this can be overcome by depolarizing pre-pulses. Exactly the opposite situation prevails for those Ca²⁺ channels that are enhanced by agonists, i.e. the basal condition appears to be one in which the channels reside in the short-opening mode, and agonist converts them to a long-opening mode [50].

Because agonist-induced changes in Ca²⁺ channel behavior are relieved by depolarizing pre-pulses in a fashion essentially identical to that seen during the process of facilitation, it seems likely that the mode of Ca²⁺ channel behavior in any given cell is under constitutive control. An important question to be addressed is whether this phenomenon is a property of the Ca²⁺ channel complex or some as yet to be identified cellular process. A G-protein-dependent blocking molecule (either the G protein itself or a soluble intracellular messenger) coupled to Ca²⁺ channels has been proposed [16,51**]. During differentiation of neuroblastoma cells there arises a tonic inhibition of an α-CgTx-sensitive Ca²⁺ channel, and the effect appears to be mediated by a G protein [52**]. Tonic modulation of Ca²⁺ channels provides a plausible explanation for both voltage- and agonist-mediated enhancement and diminution of Ca²⁺ channel activity.

From a functional point of view, facilitation may contribute to frequency-dependent Ca²⁺ entry in synaptic terminals. Ca²⁺ channels are facilitated not only by single long depolarizing pre-pulses, but also by a series of brief repetitive depolarizations. Moreover, the available data suggest that switching between two gating modes characterized by long- and short-duration openings is fundamental to modulation of Ca²⁺ channels. Dual control over this process by agonists and voltage provides a powerful and dynamic control over Ca²⁺ channel function in neurons.
An unexpected source of Ca\textsuperscript{2+}-dependent inactivation of Ca\textsuperscript{2+} channels

It has long been known that voltage-gated Ca\textsuperscript{2+} channels can be inactivated by a rise in intracellular Ca\textsuperscript{2+}. Classically, it has been thought that the source of such elevations in intracellular Ca\textsuperscript{2+} is the Ca\textsuperscript{2+} channel itself, an example of negative feedback. Using nystatin-perforated patch-clamp electrodes, which maintain the normal dynamics of intracellular Ca\textsuperscript{2+} levels, Kramer et al. [55*] have now shown that agonist-induced release of intracellular Ca\textsuperscript{2+}, via production of inositol 1,4,5-triphosphate, can also result in inhibition of voltage-gated Ca\textsuperscript{2+} channels. Because studies employing the whole cell patch clamp technique commonly buffer intracellular Ca\textsuperscript{2+}, this phenomenon had been previously overlooked.

Low-threshold Ca\textsuperscript{2+} currents and action-potential generation

The central role of low-threshold Ca\textsuperscript{2+} channels (T-type) in the bursting behavior of neurons has been appreciated for nearly a decade [54]. Now, using a new technique called action-potential clamp, McCobb and Beam [55*] have shown that in dorsal root ganglion neurons the low-threshold Ca\textsuperscript{2+} current is the major Ca\textsuperscript{2+} current responsible for Ca\textsuperscript{2+} entry during a normal brief action potential, and is relatively insensitive to changes in action potential duration. In contrast, the contribution of high-threshold currents to Ca\textsuperscript{2+} entry increases markedly with action potential duration. These studies provide a new and intriguing glimpse into the functional roles of Ca\textsuperscript{2+} channels in neurons.

Perspective

A pressing objective of future molecular studies will be to correlate the functional properties of exogenously expressed Ca\textsuperscript{2+} channel cDNAs with those of Ca\textsuperscript{2+} channels described in neurons. The rather heterogeneous properties of Ca\textsuperscript{2+} channels found in the nervous system may make this task more difficult than it initially appears. In this regard, it may ultimately be necessary to compare the biophysical and pharmacological properties of Ca\textsuperscript{2+} channels found in defined neurons and neuronal cell lines with those of cDNAs isolated from the same cells. Together with the use of specific \( \alpha_1 \) subunit antibodies to determine the cellular and subcellular localization of cloned Ca\textsuperscript{2+} channels, these studies will help address questions concerning the contributions of individual Ca\textsuperscript{2+} channel subtypes to neuronal function and the mechanisms of processes such as facilitation.

Acknowledgements

We are grateful to J Tomlinson for providing data concerning the expression of Ca\textsuperscript{2+} channel \( \alpha_1 \) subunits in various cell lines shown in Table 1 and also to S Dubel for providing Fig. 1. Supported by research grants from the Medical Research Council of Canada (TP Snutch and PB Reiner) and the Howard Hughes Medical Institute International Research Scholars Program (TP Snutch). TP Snutch is a recipient of a fellowship from the Alfred P Sloan Research Foundation.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
* of special interest
** of outstanding interest

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and are Differentially Expressed in the Mammalian CNS. Neuron 1991, 7:45-57.

This paper demonstrates that class C α2-subunits are encoded by a single gene and provides the first direct evidence that alternate splicing is responsible for generating Ca2+ channel isoforms.


This thorough study reports the primary sequences of human brain class D α2, α2-β and β-subunits. Microinjection of synthetic RNA into Xenopus oocytes shows that in the presence of a brain β-subunit the class D α2-subunit encodes an L-Type Ca2+ channel. This is described in the intriguing result that microinjection of β-subunit alone into oocytes induces the expression of DHP-insensitive Ca2+ channels that resemble the endogenous oocyte Ca2+ channel.


This article reports the primary sequence and functional expression of two class A α1-subunits from rabbit brain that differ in their carboxyl termini. The Ca2+ currents induced in Xenopus oocytes are insensitive to DHPs and α-CgTx. This shows that the endogenous oocyte Ca2+ channel.


The purified brain α-CgTx receptor is a heteroligomeric complex consisting of a 230 kD subunit that binds α-CgTx and four smaller subunits. The paper describes the primary structure of the class B α1-subunit and demonstrates that polyclonal antibodies against this protein selectively immunoprecipitate rat brain α-CgTx binding sites.


The purified brain α-CgTx receptor contains 574 kD and 78 kD polypeptides that are homologous to the skeletal muscle L-Type Ca2+ channel β-subunit.


This demonstrates that the partially purified brain α-CgTx receptor contains 574 kD and 78 kD polypeptides that are homologous to the skeletal muscle L-Type Ca2+ channel β-subunit.


This study demonstrates that the partially purified brain α-CgTx receptor contains 574 kD and 78 kD polypeptides that are homologous to the skeletal muscle L-Type Ca2+ channel β-subunit.


Co-expression of a β-subunit found in heart with the cardiac class C α1-subunit shows that the β-subunit affects the current-voltage relationship and rate of activation.


This paper shows that the co-expression of skeletal muscle α1-β-subunits affects Ca2+ channel activation and inactivation properties. Co-expression of the α1-β- and γ-subunits has minimal effects on the α1-subunit properties.


Transfection into L cells of the skeletal muscle α1 and β-subunits demonstrates that the β-subunit increases the rate of activation over that of the α1-subunit alone.


Similar to [34•], this paper shows that co-expression of skeletal muscle α1 and β-subunits affects Ca2+ channel activation and inactivation properties. Co-expression of the α1-β- and γ-subunits has minimal effects on the α1-subunit properties.


The cardiac class C α1-subunit expressed in Xenopus oocytes is modulated by skeletal muscle β- and γ-subunits. The β-subunit increases the rate of activation of the α1-subunit and also alters the current-voltage relationship. The γ-subunit further enhances the rate of activation and peak current.


Similar to [30•], this article shows that the functional properties of the skeletal muscle class C α1-subunit can be modulated by other subunits. Co-expression of the γ-subunit has a significant effect on the voltage-dependence of inactivation.
This analysis of single Ca<sup>2+</sup> channels in chromaffin cells presents the most complete and thorough analysis of facilitation to date.
This paper shows that there are two pathways leading to Ca<sup>2+</sup> channel inhibition in sympathetic neurons, and at least one of them is due to activation of a soluble second messenger. Surprisingly, this intracellular message is not carried by either Ca<sup>2+</sup>, cGMP, CAMP or protein kinase C.
Using differentiation of neuroblastoma cells as a model system, this study provides strong support for the notion that tonic modulation of Ca<sup>2+</sup> channels is mediated by a G-protein coupled process.
Perforated patch recordings, which do not perturb intracellular Ca<sup>2+</sup>, reveal that Ca<sup>2+</sup> release from internal stores is capable of inhibiting voltage-gated Ca<sup>2+</sup> channels.
Capitalizing upon the new technique of action potential clamp, this study examines the contribution of different classes of Ca<sup>2+</sup> channel to action potential generation.

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