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Nomenclature and Structure-Function Relationships of
Voltage-Gated Calcium Channels

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Abstract—The family of voltage-gated calcium channels serves as the key transducers of cell surface membrane potential changes into local intracellular calcium transients that initiate many different physiological events. There are 10 members of the voltage-gated calcium channel family that have been characterized in mammals, and they serve distinct roles in cellular signal transduction. This article presents the molecular relationships and physiological functions of these calcium channel proteins and provides comprehensive information on their molecular, genetic, physiological, and pharmacological properties.

Introduction

Voltage-gated calcium channels mediate calcium influx in response to membrane depolarization and regulate intracellular processes such as contraction, secretion, neurotransmission, and gene expression in many different cell types. Their activity is essential to couple electrical signals in the cell surface to physiological events in cells. They are members of a gene superfamily of transmembrane ion channel proteins that includes voltage-gated potassium and sodium channels (Yu and Catterall, 2004). This compendium presents an introduction to their biochemical, molecular, and genetic properties, their physiological roles, and their pharmacological significance. Table 1 and the summary tables that follow the text of this article give comprehensive information on each member of the calcium channel family.

Calcium Channel Subunits

The calcium channels that have been characterized biochemically are complex proteins composed of four or five distinct subunits that are encoded by multiple genes (Fig. 1; Catterall, 2000). The \( \alpha_1 \) subunit of 190 to 250 kDa is the largest subunit, and it incorporates the conduction pore, the voltage sensor and gating apparatus, and most of the known sites of channel regulation by second messengers, drugs, and toxins. Like the \( \alpha \) subunits of sodium channels, the \( \alpha_1 \) subunit of voltage-gated calcium channels is organized in four homologous domains (I–IV), with six transmembrane segments (S1–S6) in each. The S4 segment serves as the voltage sensor. The pore loop between transmembrane segments S5 and S6 in each domain determines ion conductance and selectivity, and changes of only three amino acids in the pore loops in domains I, III, and IV will convert a sodium channel to calcium selectivity. An intracellular \( \beta \) subunit and a transmembrane, disulfide-linked \( \alpha_2 \delta \) subunit complex are components of most types of calcium channels. A \( \gamma \) subunit has also been found in skeletal muscle calcium channels, and related subunits are expressed in heart and brain. Although these auxiliary subunits modulate the properties of the channel complex, the pharmacological and electrophysiological diversity of calcium channels arises primarily from the existence of multiple \( \alpha_1 \) subunits (Hofmann et al., 1994).

Calcium Currents

Calcium currents recorded in different cell types have diverse physiological and pharmacological properties, and an alphabetical nomenclature has evolved for the distinct classes of calcium currents (Tsien et al., 1995). L-type calcium currents typically require a strong depolarization for activation, are long-lasting, and are blocked by the organic L-type calcium channel antagonists, including dihydropyridines, phenylalkylamines, and benzothiazepines. They are the main calcium currents recorded in muscle and endocrine cells, where they initiate contraction and secretion. L-type currents activating at lower voltages also exist predominantly in neurons and cardiac pacemaker cells. N-type, P/Q-type, and R-type calcium currents...
also require strong depolarization for activation. They are relatively unaffected by L-type calcium channel antagonist drugs but are blocked by specific polypeptide toxins from snail and spider venoms. They are expressed primarily in neurons, where they initiate neurotransmission at most fast synapses and mediate calcium entry into cell bodies and dendrites. T-type calcium currents are activated by weak depolarization and are transient. They are resistant to both organic antagonists and to the snake and spider toxins used to define the N- and P/Q-type calcium currents. They are expressed in a wide variety of cell types, where they are involved in shaping the action potential and controlling patterns of repetitive firing.

### Calcium Channel Genes

Mammalian α1 subunits are encoded by at least 10 distinct genes. Historically, various names have been given to the corresponding gene products, giving rise to
distinct and sometimes confusing nomenclatures. In 1994, a unified but arbitrary nomenclature was adopted in which \( \alpha_1 \) subunits were referred to as \( \alpha_{1S} \) for the original skeletal muscle isoform and \( \alpha_{1A} \) through \( \alpha_{1E} \) for those discovered subsequently (Birnbaumer et al., 1994). In 2000, a rational nomenclature was adopted (Ertel et al., 2000) based on the well defined potassium channel nomenclature (Chandy and Gutman, 1993). Calcium channels were named using the chemical symbol of the principal permeating ion (Ca) with the principal physiological regulator (voltage) indicated as a subscript (Ca\( \text{V}_{1}\)). The numerical identifier corresponds to the Ca\( \text{V}\) channel \( \alpha_1 \) subunit gene subfamily (1 to 3 at present) and the order of discovery of the \( \alpha_1 \) subunit within that subfamily (1 through \( n \)). According to this nomenclature, the Ca\( \text{V}_1 \) subfamily (Ca\( \text{V}_{1.1} \)–Ca\( \text{V}_{1.4} \)) includes channels containing \( \alpha_{1S} \), \( \alpha_{1C} \), \( \alpha_{1D} \), and \( \alpha_{1F} \), which mediate L-type \( \text{Ca}^{2+} \) currents (Table 1). The Ca\( \text{V}_2 \) subfamily (Ca\( \text{V}_{2.1} \)–Ca\( \text{V}_{2.3} \)) includes channels containing \( \alpha_{1A} \), \( \alpha_{1B} \), and \( \alpha_{1E} \), which mediate P/Q-type, N-type, and R-type \( \text{Ca}^{2+} \) currents, respectively (Table 1). The Ca\( \text{V}_3 \) subfamily (Ca\( \text{V}_{3.1} \)–Ca\( \text{V}_{3.3} \)) includes channels containing \( \alpha_{1G} \), \( \alpha_{1H} \), and \( \alpha_{1I} \), which mediate T-type \( \text{Ca}^{2+} \) currents.

The complete amino acid sequences of these \( \alpha_1 \) subunits are more than 70% identical within a subfamily but less than 40% identical among the three subfamilies. These family relationships are illustrated for the more conserved transmembrane and pore domains in Fig. 2. The division of calcium channels into these three families is phylogenetically ancient, as representatives of each are found in the Caenorhabditis elegans genome. Consequently, the genes for the different \( \alpha_1 \) subunits have become widely dispersed in the genome, and even the most closely related members of the family are not clustered on single chromosomes in mammals.

**Calcium Channel Molecular Pharmacology**

The pharmacology of the three subfamilies of calcium channels is quite distinct. The Ca\( \text{V}_1 \) channels are the molecular targets of the organic calcium channel blockers used widely in the therapy of cardiovascular diseases. These drugs are thought to act at three separate, but allosterically coupled, receptor sites (Table 1; reviewed in Glossmann and Striessnig, 1990). Phenylalkylamines are intracellular pore blockers, which are thought to enter the pore from the cytoplasmic side of the channel and block it. Their receptor site is formed by amino acid residues in the S6 segments in domains III and IV, in close analogy to the local anesthetic receptor site on sodium channels (Hockerman et al., 1997; Hofmann et al., 1999; Striessnig, 1999). Dihydropyridines can be channel activators or inhibitors and therefore are thought to act allosterically to shift the channel toward the open or closed state rather than by occluding the pore. Their receptor site includes amino acid residues in the S6 segments of domains III and IV and the S5 segment of domain III. The dihydropyridine receptor site is closely apposed to the phenylalkylamine receptor site and shares some common amino acid residues. Diltiazem and related benzothiazepines are thought to bind to a third receptor site, but the amino acid residues that are required for their binding overlap extensively with those required for phenylalkylamine binding.

The Ca\( \text{V}_2 \) subfamily of calcium channels is relatively insensitive to dihydropyridine calcium channel blockers, but these calcium channels are specifically blocked with high affinity by peptide toxins from spiders and marine snails (Miljanich and Ramachandran, 1995). The Ca\( \text{V}_{2.1} \) channels are blocked specifically by \( \omega \)-agatoxin IVA from funnel web spider venom. The Ca\( \text{V}_{2.2} \) channels are blocked specifically by \( \omega \)-conotoxin GVia and related cone snail toxins. The Ca\( \text{V}_{2.3} \) channels are blocked specifically by the synthetic peptide toxin SNX-482 derived from tarantula venom. These peptide toxins are potent blockers of synaptic transmission because of their specific effects on the Ca\( \text{V}_2 \) family of calcium channels.

The Ca\( \text{V}_3 \) subfamily of calcium channels is insensitive to both the dihydropyridines that block Ca\( \text{V}_1 \) channels and the spider and cone snail toxins that block the Ca\( \text{V}_2 \) channels, and there are no widely useful pharmacological agents that block T-type calcium currents (Perez-Reyes, 2003). The organic calcium channel blocker mibebradil is somewhat selective for T-type versus L-type calcium currents (3- to 5-fold). The peptide kurtoxin inhibits the activation gating of Ca\( \text{V}_{3.1} \) and Ca\( \text{V}_{3.2} \) channels. Development of more specific and high-affinity blockers of the Ca\( \text{V}_3 \) family of calcium channels would be useful for therapy and a more detailed analysis of the physiological roles of these channels.

Tables 2 through 11 summarize the major molecular, physiological, and pharmacological properties for each of the 10 calcium channels that have been functionally expressed. Quantitative data are included for
voltage dependence of activation and inactivation, single-channel conductance, and binding of drugs and neurotoxins, focusing on those agents that are widely used and diagnostic of channel identity and function.

REFERENCES


TABLE 2

<table>
<thead>
<tr>
<th>Ca(_{\alpha}1.1) channels</th>
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<tr>
<td><strong>Channel name</strong></td>
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<tr>
<td><strong>Description</strong></td>
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<td><strong>Other names</strong></td>
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<tr>
<td><strong>Molecular information</strong></td>
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<tr>
<td><strong>Associated subunits</strong></td>
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<td><strong>Functional assays</strong></td>
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<td><strong>Current</strong></td>
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<td><strong>Conductance</strong></td>
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<td><strong>Ion selectivity</strong></td>
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<td><strong>Activation</strong></td>
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<td><strong>Inactivation</strong></td>
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<td><strong>Activators</strong></td>
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<td><strong>Gating modifiers</strong></td>
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<td><strong>Channel distribution</strong></td>
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<td><strong>Physiological functions</strong></td>
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<td><strong>Mutations and pathophysiologic susceptibility</strong></td>
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<tr>
<td><strong>Pharmacological significance</strong></td>
</tr>
<tr>
<td><strong>Comments</strong></td>
</tr>
</tbody>
</table>

aa, amino acids; chr., chromosome; Bay K8644, methyl 1,4-di-hydro-2,6-dimethyl-3-nitro-4-(2-trifluoromethyl phenyl)-pyridine-5-carboxylate; FPL64176, methyl 2,5-dimethyl-4-[2-(phenylmethylbenzoyl)-1H-pyrrrole-3-carboxylate].

TABLE 3
Ca_{1,2} channels

<table>
<thead>
<tr>
<th>Channel name</th>
<th>Description</th>
<th>Other names</th>
<th>Molecular information</th>
<th>Associated subunits</th>
<th>Functional assays</th>
<th>Current</th>
<th>Conductance</th>
<th>Ion selectivity</th>
<th>Activation</th>
<th>Inactivation</th>
<th>Physiological functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca_{1,2}</td>
<td>Voltage-gated calcium channel α_{1c} subunit</td>
<td>Ca_{1,2}</td>
<td>Human: 2169aa, L29529 (cardiac; PMID: 8392192), 2138aa, Z34815 (fibroblast; PMID: 1316612); 2138aa, AP46548 (jejunum; PMID: 12176756); chr. 12p13.3, CACNA1C, LOCUS ID: 775 Rat: 2169aa, M59786 (sorstic smooth muscle; PMID: 2170396); 2140/2143aa, M67516/M67515 (brain; PMID: 1648941); chr. 4q42, Cacn1, LOCUS ID: 24239 Mouse: 2139aa, L01776 (brain; PMID: 1385406); chr. 6, Cacn1c, LOCUS ID: 12288 (see ‘Comments’)</td>
<td>α_{1b}, β, γ_{1,2}</td>
<td>Patch-clamp (whole-cell, single-channel), calcium imaging, cardiac or smooth muscle contraction</td>
<td>I_{Ca,L}^{L}</td>
<td>Ba^{2+} &gt; (25pS) &gt; Sr^{2+} = Ca^{2+} (9pS)^{3}</td>
<td>Ca^{2+} &gt; Sr^{2+} &gt; Ba^{2+} &gt;&gt; Mg^{2+}, from permeability ratios</td>
<td>V_{0} = -17 mV (in 2 mM Ca^{2+}; HEK cells) ; -4 mV (in 15 mM Ba^{2+}; HEK cells) to -18.8 mV (in 5 mM Ba^{2+}; HEK cells and Xenopus oocytes)^{6,7}; r_{f} = 1 ms at +10 mV</td>
<td>V_{0} = -50 to -60 mV (in 2 mM Ca^{2+}; HEK cells), -18 to -42 mV (in 5-15 mM Ba^{2+}; HEK cells)^{6,7,8,9}; t_{inact} = 150 ms, t_{thn} = 1100 ms; 61% inactivated after 250 ms in HEK cells (at V_{max} in 15 mM Ba^{2+})^{1}; -70% inactivation after 1 s (at V_{max} in 2 mM Ca^{2+})^{1}; inactivation is accelerated with Ca^{2+} as charge carrier (calcium-dependent inactivation: 86% inactivated after 250 ms)^{10,11}</td>
<td>Required for normal embryonic development (mouse, zebrafish)^{18,19}; de novo G406R mutation in CACNA1C; OMIM no. 114205.</td>
</tr>
</tbody>
</table>

**aa:** amino acids; **chr.:** chromosome; **HEK:** human embryonic kidney.

20. CACNAIC OMIM no. 114205.
**TABLE 4**

**Ca\textsubscript{v}1.3 channels**

<table>
<thead>
<tr>
<th>Channel name</th>
<th>Ca\textsubscript{v}1.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Voltage-gated calcium channel α\textsubscript{1} subunit</td>
</tr>
<tr>
<td>Other names</td>
<td>α\textsubscript{1D}, “neuroendocrine” L-type Ca\textsuperscript{2+} channel</td>
</tr>
<tr>
<td>Molecular information</td>
<td>Human: 2161aa, M76558 (brain; PMID: 1309651); 2181aa, M83566 (pancreatic β-cells; PMID: 1309948); chr. 3p14.3, CACNA1D, LocusID: 776 Rat: 1646aa, M57682 (brain; PMID: 1648940); 2203aa, D38101 (pancreatic β-cells; PMID: 7760845); chr. 16p16, Cacna1d, LocusID: 29716 Mouse: 2144aa, A4437291 (embryonic heart; PMID: 12900400); chr. 14, Cacna1d, LocusID: 12289 (see “Comments”)</td>
</tr>
<tr>
<td>Associated subunits</td>
<td>Most likely at least α\textsubscript{2}, β, and δ subunits</td>
</tr>
<tr>
<td>Functional assays</td>
<td>Patch-clamp (whole-cell, single-channel), calcium imaging</td>
</tr>
<tr>
<td>Current</td>
<td>I\textsubscript{Ca,L}</td>
</tr>
<tr>
<td>Ion selectivity</td>
<td>Not established</td>
</tr>
<tr>
<td>Activation</td>
<td>(V_n = -15 \text{ to } -20 \text{ mV (mouse cochlear hair cells); 10 nM Ba}\textsuperscript{2+} \text{ at } -18 \text{ mV (in 15 mM Ba}\textsuperscript{2+}; \text{ HEK cells) to } -37 \text{ mV (5 mM Ba}\textsuperscript{2+}; 2 \text{ mM Ca}\textsuperscript{2+} \text{ HEK cells or Xenopus oocytes)} \textsuperscript{1A}; \tau_n &lt; 1 \text{ ms at } +10 \text{ mV} \textsuperscript{3A}</td>
</tr>
<tr>
<td>Inactivation</td>
<td>(V_h = -36 \text{ to } -43 \text{ mV} \textsuperscript{1A}; \tau_{\text{rest}} = 190 \text{ ms}, \tau_{\text{slow}} = 1700 \text{ ms (at } V_{\text{max}} \text{ in HEK cells)} \textsuperscript{1B}; \text{ calcium-induced inactivation is observed after expression in HEK cells} \textsuperscript{1C} \text{ and in cochlear outer hair cells but not in inner hair cells} \textsuperscript{1C}</td>
</tr>
<tr>
<td>Activators</td>
<td>BayK8644 \textsuperscript{1A−5}</td>
</tr>
<tr>
<td>Gating modifiers</td>
<td>Dihydropyridine antagonists (e.g., isradipine, (IC_{50} = 30 \text{ nM at } -50 \text{ mV and 300 nM at } -90 \text{ mV); nimodipine, } IC_{50} = 3 \mu M \text{ at } -80 \text{ mV} \textsuperscript{1D,B}</td>
</tr>
<tr>
<td>Blockers</td>
<td>Nonselective: Cd\textsuperscript{2+} \textsuperscript{1A−5}</td>
</tr>
<tr>
<td>Radioligands</td>
<td>(+)-\textsuperscript{3H}isradipine ((K_d &lt; 0.5 \text{ nM}) \textsuperscript{1E}; in radioreceptor assays, HEK cell-expressed Ca\textsubscript{v}1.2 and Ca\textsubscript{v}1.3 channels bind (+)-\textsuperscript{3H}isradipine with indistinguishable (K_d \textsuperscript{1E}; in functional experiments, however, Ca\textsubscript{v}1.2 channels show higher DHP sensitivity—this discrepancy is explained by the slower inactivation of Ca\textsubscript{v}1.3 decreasing the availability of inactivated channels for state-dependent DHP block</td>
</tr>
<tr>
<td>Channel distribution</td>
<td>Sensory cells (photoreceptors, cochlear hair cells), endocrine cells (including pancreatic β-cells, pituitary, adrenal chromaffin cells, pinealocytes), low density in heart (atrial muscle, sinoatrial and atrioventricular node), vascular smooth muscle; neurons; subcellular localization: on neurons preferentially located on proximal dendrites and cell bodies</td>
</tr>
<tr>
<td>Physiological functions</td>
<td>Neurotransmitter release in sensory cells, control of cardiac rhythm and atrioventricular node conductance at rest, mood behavior, hormone secretion</td>
</tr>
<tr>
<td>Mutations and pathophysiology</td>
<td>Deafness, sinoatrial and atrioventricular node dysfunction, no convincing evidence for contribution to pancreatic β-cell L-type currents and insulin secretion in mouse models</td>
</tr>
<tr>
<td>Pharmacological significance</td>
<td>Hypothetical drug targets for modulators of heart rate, antidepressant drugs and drugs for hearing disorders</td>
</tr>
<tr>
<td>Comments</td>
<td>Tissue-specific and developmental (exon 1b) splice variants exist—in addition to brain, pancreatic β-cell and cochlear variants have been cloned; it is likely that Ca\textsubscript{v}1.3 channels form most of the so-called ‘low-voltage-activated’ L-type currents found in the brain and sinoatrial node, although some splice variants of Ca\textsubscript{v}1.2 can also activate at more negative potentials</td>
</tr>
</tbody>
</table>

aa, amino acids; chr., chromosome; HEK, human embryonic kidney; DHP, dihydropyridine.


7. Takimoto K, Li D, Nerbhonne JM, and Levitan ES (1997) Distribution, splicing and glucocorticoid-induced expression of cardiac α\textsubscript{1C} and α\textsubscript{1D} voltage-gated calcium channel mRNAs. *J Mol Cell Cardiol* **29**:3035–3042.


### NOMENCLATURE AND RELATIONSHIPS OF VOLTAGE-GATED CALCIUM CHANNELS

#### CaV1.4 channels

<table>
<thead>
<tr>
<th>Channel name</th>
<th>Description</th>
<th>Molecular information</th>
<th>Associated subunits</th>
<th>Functional assays</th>
<th>Current</th>
<th>Conductance</th>
<th>Ion selectivity</th>
<th>Activation</th>
<th>Inactivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>CaV1.4</td>
<td>Voltage-gated calcium channel α1 subunit</td>
<td>Human: 1966aa, AJ224874 (PMID: 9662399); chr. Xp11.23, CACNA1F, LocusID: 778</td>
<td>Not established; preliminary functional evidence for β2 association in retinal neurons</td>
<td>Patch-clamp (whole-cell, single-channel), calcium imaging</td>
<td>I_{Ca,L}</td>
<td>Preliminary evidence for very small single channel conductance (less than half of CaV1.2); Ba^{2+} &gt; Ca^{2+}</td>
<td>Not established</td>
<td>( V_o = -2.5 ) to (-12 ) mV (2–20 mM Ca^{2+} or 15–20 mM Ba^{2+}; HEK cells); for slower components were also observed</td>
<td>( V_o = -9 ) to (-27 ) mV (10–20 mM Ba^{2+}; HEK cells); inactivation kinetics even slower than those of CaV1.3 with incomplete inactivation during 10-s depolarizations to ( V_{max} ); calcium-induced inactivation is not observed for CaV1.4 channels expressed in HEK cells but after expression in Xenopus oocytes</td>
</tr>
</tbody>
</table>

### REFERENCES

11. CACNA1F; OMIM no. 300110.
### TABLE 6

**Ca_{2.1} channels**

<table>
<thead>
<tr>
<th>Channel name</th>
<th>Molecular information</th>
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</thead>
<tbody>
<tr>
<td><strong>Ca_{2.1}</strong></td>
<td>Human: 2510aa, AF004883, 2662aa, AF004884, chr. 19p13, CACNA1A</td>
</tr>
<tr>
<td><strong>Rat</strong></td>
<td>Rat: 2212a, M64373</td>
</tr>
<tr>
<td><strong>Mouse</strong></td>
<td>Mouse: 2165aa, NM007578, NP031604</td>
</tr>
<tr>
<td><strong>Rabbit</strong></td>
<td>Rabbit: 2273aa, X57476 (see “Comments”)</td>
</tr>
</tbody>
</table>

#### Associated subunits

- **α2δ, β, possibly γ**

#### Functional assays

- Voltage-clamp, patch-clamp, calcium imaging, neurotransmitter release

#### Conductance

- **9, 14, 19p (P-type, cerebellar Purkinje neurones)**
- **16–17p** (for α_{1A}/α_{2δ}β in Xenopus oocytes)

#### Ion selectivity

- **Ba^{2+} > Ca^{2+}**

#### Activation

<table>
<thead>
<tr>
<th>Voltage (mV)</th>
<th>Tau (ms)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>V_{o}</strong></td>
<td><strong>V_{h}</strong></td>
</tr>
<tr>
<td><strong>V_{o}</strong> = -5 mV for native P-type, V_{h} = -11 mV for native Q-type (with 5 mM Ba^{2+} charge carrier)**</td>
<td><strong>V_{o}</strong> = -4.1 mV for rat α_{1A}/α_{2δ}β_{4}, V_{h} = +1.1 mV for rat α_{1A}/α_{2δ}β_{4} (with 5 mM Ba^{2+} charge carrier)**</td>
</tr>
<tr>
<td><strong>V_{o}</strong> = +9.5 mV; τ_{a} = 2.2 ms at +10 mV for human α_{1A}/α_{2δ}β_{1} in HEK293 cells (with 15 mM Ba^{2+} charge carrier)**</td>
<td><strong>V_{o}</strong> = -17.2 mV for α_{1A}/α_{2δ}β_{4}; V_{h} = -1.6 mV for α_{1A}/α_{2δ}β_{4} (with 5 mM Ba^{2+} charge carrier); V_{h} = -17 mV; τ_{a} = 690 ms at +10 mV human α_{1A}/α_{2δ}β_{1} in HEK293 cells (with 15 mM Ba^{2+} charge carrier); τ_{a} &gt; 1 s at 0 mV native P-type (with 5 mM Ba^{2+} charge carrier)**</td>
</tr>
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</table>

#### Deactivation

<table>
<thead>
<tr>
<th>Voltage (mV)</th>
<th>Tau (ms)</th>
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<tbody>
<tr>
<td><strong>V_{o}</strong></td>
<td><strong>V_{h}</strong></td>
</tr>
<tr>
<td>τ_{d} = 17 mV for native P-type, V_{d} = 5 mV for native Q-type (with 5 mM Ba^{2+} charge carrier)**</td>
<td></td>
</tr>
<tr>
<td>τ_{d} = 60 mV at 10 mV human α_{1A}/α_{2δ}β_{1} in HEK293 cells (with 15 mM Ba^{2+} charge carrier)**</td>
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</table>

#### Gating modifiers

- **None**

#### Blockers

- **ω-agatoxin IVA (P-type)**
- **ω-agatoxin IVB**
- **ω-conotoxin MVIIIC**
- **Ba^{2+} > Ca^{2+}**

#### Mutations and pathophysiology

- **Missense mutations in IIS1-IVS5 cause episodic ataxia type-2, a polyglutamine expansion in the carboxyl region causes spinocerebellar ataxia type-6, and mutation of ISIS-6 and ISVS6 causes episodic and progressive ataxia**

#### Pharmacological significance

- **Peptide toxins that selectively inhibit Ca_{2.1} channel block a significant portion of neurotransmitter in the mammalian CNS**
- **Block of Ca_{2.1} channels inhibits the late-phase formalin response and inflammatory pain but has no significant effect on mechanical allodynia or thermal hyperalgesia**
- **Nociceptive and thermal responses are differentially affected by coexpression with β_{3a}, β_{2a}, β_{3b}, or β_{4a} subunits, as well as by alternative splicing of the α_{1A} subunit, identified regions of alternative splicing include the domain I-II linker, domain III-III linker, IVS3-IVS4, and the carboxy terminus**
- **Whole-cell currents with P-type kinetics seem to be conducted by the α_{1A}β_{4} splice variant coexpressed with any of the β subunits or by the α_{1A}α_{2}β_{4} splice variant coexpressed with the β_{4a} subunit**
- **Whole-cell currents with Q-type kinetics seem to be encoded by the α_{1A}β_{4} splice variant coexpressed with any of the β_{4a}, β_{3b}, or β_{4} subunits**
- **Whole-cell currents with Q-type pharmacology seem to be conducted by α_{1A} splice variants containing Asp Pro residues in the domain IV S3-S4 linker, whereas whole-cell currents with P-type pharmacology seem to be conducted by α_{1A} splice variants missing Asp Pro residues in IV S3-S4 linker**
- **Alternative splicing also alters current density, current-voltage relations, calcium/calmodulin-dependent facilitation, sensitivity to mibefradil, and binding to intracellular synaptic proteins such as Mint1, CASK, syntaxin, and SNAP-25**

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aa, amino acids; chr., chromosome; HEK, human embryonic kidney; FHM, familial hemiplegic migraine; CNS, central nervous system.

hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the calcium channel gene CACNL1A4.

presynaptic proteins syntaxin and SNAP-25.

synthase activity in primary cultures of neurons from mouse cerebral cortex.

single human CaV2.1 channels and decrease maximal CaV2.1 current density in neurons.

1A subunit.

nociception.

269:

channel /H9251

Proc Natl Acad Sci USA

calcium channel kinetics. J Biol Chem

reflect similarities to neuronal Q- and P-type channels.

toxin, DW13.3.

neurotransmission arising from Ca2+

atrophy in Cacnl4 null mice lacking P/Q calcium channel activity.

are correlated with

inhibition of K

Pain

71:157–164.

Sluka KA (1998) Blockade of N- and P/Q-type calcium channels reduces the secondary heat hyperalgesia induced by acute inflammation. J Pharmaco Exp Ther

287:252–257.


Sah DW and Bean BP (1994) Inhibition of P-type and N-type calcium channels by dopamine receptor antagonists. Mol Pharmaco 54:85–92.


TABLE 7

<table>
<thead>
<tr>
<th>Channel name</th>
<th>Ca(_{\alpha,2.2}) channels</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Description</strong></td>
<td>Voltage-gated calcium channel (\alpha_1) subunit</td>
</tr>
<tr>
<td><strong>Other names</strong></td>
<td>N-type, (\alpha_{\text{II}}); rbB-I, rbB-II (in rat); (\text{III}^{(1,2)}); (\text{III}^{(\text{in rabbit})})³</td>
</tr>
<tr>
<td><strong>Molecular information</strong></td>
<td>Human: 2339aa, M94172, 2237aa, M94173,⁴ chr. 9q34, CACNIB</td>
</tr>
<tr>
<td><strong>Rat</strong></td>
<td>2336aa, M92905⁷</td>
</tr>
<tr>
<td><strong>Mouse</strong></td>
<td>2329aa, NM007579, NP031605</td>
</tr>
<tr>
<td><strong>Associated subunits</strong></td>
<td>(\lambda_9\delta\beta_1, \beta_3, \beta_4, \gamma) possibly</td>
</tr>
<tr>
<td><strong>Functional assays</strong></td>
<td>Voltage-clamp, patch-clamp, calcium imaging, neurotransmitter release, (\delta^{14}\text{Ca}^{2+}) uptake into synaptosomes</td>
</tr>
<tr>
<td><strong>Current</strong></td>
<td>(I_{\text{Ca,N}})</td>
</tr>
<tr>
<td><strong>Conductance</strong></td>
<td>20pS (bullfrog sympathetic neurons)⁶; 14.3pS (rabbit (\text{III}^{(\text{in rabbit})}))³</td>
</tr>
<tr>
<td><strong>Ion selectivity</strong></td>
<td>(\text{Ba}^{2+} &gt; \text{Ca}^{2+})</td>
</tr>
<tr>
<td><strong>Activation</strong></td>
<td>(V_\text{a} = +7.8 \text{mV}, \tau_\text{a} = 3 \text{ms at } +10 \text{mV (human } \alpha_{\text{II}}/\lambda_9\delta\beta_1\beta_3\text{ in HEK293 cells, 15 mM Ba}^{2+}\text{ charge carrier)}^{4,7}; V_\text{a} = +9.7 \text{mV, } \tau_\text{a} = 2.8 \text{ms at } +20 \text{mV (rat } \alpha_{\text{II}}/\beta_1\beta_3\text{ in Xenopus oocytes, 40 mM Ba}^{2+}\text{ charge carrier)}^{2})</td>
</tr>
<tr>
<td><strong>Inactivation</strong></td>
<td>(V_\text{i} = -61 \text{mV, } \tau_\text{i} = 200 \text{ms at } +10 \text{mV (human } \alpha_{\text{II}}/\lambda_9\delta\beta_1\beta_3\text{ in HEK293 cells, 15 mM Ba}^{2+}\text{ charge carrier)}^{4,7}; V_\text{i} = -67.5 \text{mV, } \tau_\text{i} = 112 \text{ms at } +20 \text{mV (rat } \alpha_{\text{II}}/\beta_1\beta_3\text{ in Xenopus oocytes, 40 mM Ba}^{2+}\text{ charge carrier)}^{2})</td>
</tr>
<tr>
<td><strong>Activators</strong></td>
<td>None</td>
</tr>
<tr>
<td><strong>Gating modifiers</strong></td>
<td>None</td>
</tr>
<tr>
<td><strong>Blockers</strong></td>
<td>(\omega)-conotoxin GVIA (1–2 \mu\text{M, irreversible block}), (\omega)-conotoxin MVIIA (SNX-111, Ziconotide/Prialt), (\omega)-conotoxin MVIIC³; other blockers include piperidines, substituted dipephylbutylpiperidines, long alky aliphatic monoamines, tetrandine, gabapentin, peptidylamines, volatile anesthetics, the peptide toxins SNX-325 and DW13.3, as well as the (\omega)-conotoxins SXV, SVB, and CVID³⁰–³⁴</td>
</tr>
<tr>
<td><strong>Radioligands</strong></td>
<td>([^{125}\text{I}]\omega)-conotoxin GVIA ((K_\text{d} = 55 \text{pM, human } \alpha_{\text{II}}/\lambda_9\delta\beta_1\beta_3\text{ in HEK293 cells})^{4})</td>
</tr>
<tr>
<td><strong>Channel distribution</strong></td>
<td>Neurons (presynaptic terminals, dendrites, cell bodies)³</td>
</tr>
<tr>
<td><strong>Physiological functions</strong></td>
<td>Neurotransmitter release in central and sympathetic neurons¹⁰; sympathetic regulation of the circulatory system¹¹,³⁵; activity and vigilance state control³⁶; sensation and transmission of pain¹²; identified regions of alternative splicing include the domain I-II linker, domain II-III linker, IIIS3-IIIS4, and the carboxyl terminus¹–³⁷–³⁹; splicing affects a number of channel properties, including current-voltage relations and kinetics, and is associated with cell-specific expression—in particular, expression of the c37a splice isoform in dorsal root ganglia correlates with a subset of nociceptive neurons⁴⁰–⁴²; alternative splicing also alters interactions with intracellular synaptic proteins such as Mint1, CASK, syntaxin, and SNAP-25³³–⁴⁵</td>
</tr>
<tr>
<td><strong>Mutations and pathophysiology</strong></td>
<td>Differing reports exist: mice lack a functional (\text{Ca}<em>{\alpha,2.2}) gene exhibit a normal life span and no detectable behavioral modifications compared with wild type but possess an increase in basal mean atrial pressure and other functional alterations to the sympathetic nervous system¹—however, in a different study, approximately 1/3 of the mice lacking a functional (\text{Ca}</em>{\alpha,2.2}) gene did not survive to weaning, but surviving animals were normal except for a decrease in anxiety-related behavior and a suppression of inflammatory and neuropathic pain responses¹²; no point mutations in the native (\text{Ca}_{\alpha,2.2}) gene have been reported to date</td>
</tr>
<tr>
<td><strong>Pharmacological significance</strong></td>
<td>In rats, intrathecal administration of (\omega)-conotoxin GVIA or (\omega)-conotoxin MVIIA shows strong effects on inflammatory pain, postsurgical pain, thermal hyperalgesia, and mechanical allodynia¹³–¹⁵; in humans, intrathecal administration of SNX-111 (Ziconotide/Prialt, synthetic (\omega)-conotoxin MVIIA) to patients unresponsive to intrathecal opiates significantly reduced pain scores and in a number of specific instances resulted in relief after many years of continuous pain¹⁶</td>
</tr>
<tr>
<td><strong>Comments</strong></td>
<td>In case studies, Ziconotide/Prialt has been examined for usefulness in the management of intractable spasticity following spinal cord injury in patients unresponsive to baclofen and morphine¹⁷; side effects of intrathecal administration of Ziconotide/Prialt include nystagmus, sedation, confusion, auditory and visual hallucinations, severe agitation, and unruly behavior¹⁸; intravenous administration of (\omega)-conotoxin to humans results in significant orthostatic hypotension¹⁹; identified regions of alternative splicing include the domain I-II linker, domain II-III linker, IIIS3-IIIS4, IVS3-IVS4, and the carboxyl terminus¹–³⁷–³⁹; splicing affects a number of channel properties, including current-voltage relations and kinetics, and is associated with cell-specific expression—in particular, expression of the c37a splice isoform in dorsal root ganglia correlates with a subset of nociceptive neurons⁴⁰–⁴²; alternative splicing also alters interactions with intracellular synaptic proteins such as Mint1, CASK, syntaxin, and SNAP-25³³–⁴⁵</td>
</tr>
</tbody>
</table>

aa, amino acid; chr., chromosome; HEK, human embryonic kidney.


**Table 8**

<table>
<thead>
<tr>
<th>Channel name</th>
<th>Ca(_{2.3}) channels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Voltage-gated calcium channel (\alpha_2) subunit</td>
</tr>
<tr>
<td>Other names</td>
<td>R-type, (\alpha_{2g}); rbE-II (in rat)(^1); BII-1, BII-2 (in rabbit)(^2)</td>
</tr>
<tr>
<td>Molecular information</td>
<td>Human: 2251aa, L29384, 2270aa, L29385,(^3) chr.1q25-q31, CACNAIE - Rat: 2222aa,(^4) GenBank accession no. L15453 - Mouse: 2272aa, Q61290</td>
</tr>
<tr>
<td>Associated subunits</td>
<td>(\alpha_2\Delta\beta), possibly (\gamma)</td>
</tr>
<tr>
<td>Functional assays</td>
<td>Voltage-clamp, patch-clamp, calcium imaging, neurotransmitter release</td>
</tr>
<tr>
<td>Current</td>
<td>(I_{Ca,R})</td>
</tr>
<tr>
<td>Conductance</td>
<td>Not established</td>
</tr>
<tr>
<td>Ion selectivity</td>
<td>Ba(^{2+})</td>
</tr>
<tr>
<td>Activation</td>
<td>(V_a = +3.5) mV, (\tau_a = 1.3) ms at 0 mV (human (\alpha_{1g}/\alpha_2\Delta\beta_{1-3}), 15 mM Ba(^{2+}) charge carrier in HEK293 cells)(^3) - (V_a = -29.1) mV, (\tau_a = 2.1) ms at -10 mV (rat (\alpha_{1g}/\alpha_2\Delta\beta_{1-4}), 4 mM Ba(^{2+}) charge carrier in Xenopus oocytes)(^1)</td>
</tr>
<tr>
<td>Inactivation</td>
<td>(V_i = -71) mV, (\tau_i = 74) ms at 0 mV (human (\alpha_{1g}/\alpha_2\Delta\beta_{1-3}), 15 mM Ba(^{2+}) charge carrier in HEK293 cells)(^3) - (V_i = -78.1) mV, (\tau_i = 100) ms at -10 mV (rat (\alpha_{1g}/\alpha_2\Delta\beta_{1-4}), 4 mM Ba(^{2+}) charge carrier in Xenopus oocytes)(^1)</td>
</tr>
<tr>
<td>Activators</td>
<td>None</td>
</tr>
<tr>
<td>Gating modifiers</td>
<td>None</td>
</tr>
<tr>
<td>Blockers</td>
<td>SNX-482, Ni(^{2+}) (IC(<em>{50}) = 27 (\mu)M), Cd(^{2+}) (IC(</em>{50}) = 0.8 (\mu)M), mibefradil (IC(_{50}) = 0.4 (\mu)M),(^{10}) volatile anesthetics(^{11})</td>
</tr>
<tr>
<td>Radioligands</td>
<td>None</td>
</tr>
<tr>
<td>Channel distribution</td>
<td>Neurons (cell bodies, dendrites, some presynaptic terminals), heart, testes, pituitary</td>
</tr>
<tr>
<td>Physiological functions</td>
<td>Neurotransmitter release, repetitive firing, long-term potentiation, post-tetanic potentiation, neurosecretion(^{12–14})</td>
</tr>
<tr>
<td>Mutations and pathophysiology</td>
<td>No point mutations in the native Ca(<em>{2.3}) gene have been reported; mice deficient for the Ca(</em>{2.3}) gene retain a substantial cerebellar R-type current,(^{5}) suggesting that R-type currents actually reflect a heterogeneous mixture of channels; homozygous Ca(<em>{2.3})-null mice survive to adulthood, reproduce, and are apparently behaviorally normal(^{1,6}), mutant mice exhibit an increased resistance to formalin-induced pain, suggesting an involvement of the Ca(</em>{2.3}) calcium channel in transmitting and/or the development of somatic inflammatory pain(^5)</td>
</tr>
<tr>
<td>Pharmacological significance</td>
<td>See “Comments”</td>
</tr>
<tr>
<td>Comments</td>
<td>Ca(<em>{2.3}) has been variously reported to encode a novel type of calcium channel with properties shared between both low- and high-threshold calcium channels(^{14}) or a type of high-threshold channel resistant to DHPs, (\omega)-agatoxin-IVA, and (\omega)-conotoxin-GVIA and called R-type (for “residual”(^7)) The tarantula toxin SNX-482 blocks exogenously expressed Ca(</em>{2.3}) currents(^{8}) but is only partially effective on native cerebellar R-type currents,(^{9}) suggesting that Ca(_{2.3}) does not always conduct a significant portion of the R-type current as originally defined(^{7}); identified regions of alternative splicing include the domain II-III linker and carboxyl terminus and have been shown to affect channel kinetics and Ca(^{2+})-dependent stimulation(^{1,3,15,16})</td>
</tr>
</tbody>
</table>

\(\alpha\), amino acids; chr., chromosome; HEK, human embryonic kidney; DHP, dihydropyridine.

**Table 9**

<table>
<thead>
<tr>
<th>Channel name</th>
<th>Ca$_{3.1}$ channels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Voltage-gated calcium channel $\alpha_2$ subunit</td>
</tr>
<tr>
<td>Other names</td>
<td>T-type, $\alpha_{3.1}$, $\alpha_{1G}$</td>
</tr>
<tr>
<td>Molecular information</td>
<td>Human: 2377aa, O43497, NM_018896, chr. 17q22, CACNA1G$^1$</td>
</tr>
<tr>
<td></td>
<td>Rat: 2504aa, O54889, AF027984</td>
</tr>
<tr>
<td></td>
<td>Mouse: 2288aa, CAI25956, NM_009783 (see “Comments”)</td>
</tr>
</tbody>
</table>

**Associated subunits**

No biochemical evidence, small changes induced by $\alpha_2\beta_2$ and $\alpha_2\delta_2$.4

**Functional assays**

Voltage-clamp, calcium imaging

**Current**

$\frac{I_{Ca,T}}{h_{1005}}$

**Conductance**

7.5$pS$

**Ion selectivity**

$Sr^{2+} >> Ba^{2+} = Ca^{2+}$

**Activation**

$V_a = 46$mV, $\tau_a = 1$ms at $-10$mV

**Inactivation**

$V_h = -73$mV, $\tau_h = 11$ms at $-10$mV

**Activators**

Not established

**Gating modifiers**

Kurtoxin, $IC_{50} = 15$mM

**Blockers**

No subtype-specific blocker; selective for Ca$_{3.3}$x relative to Ca$_{1.1}.x$ and Ca$_{2.2}.x$: mibefradil,9,10 U92032,11 penfluridol and pimozide;12 nonselective: nickel ($IC_{50} = 250$mM),13 amiloride14

**Radioligands**

None

**Channel distribution**

Brain, especially soma and dendrites of neurons in olfactory bulb, amygdala, cerebral cortex, hippocampus, thalamus, hypothalamus, cerebellum, brain stem (human RNA blots,1,5 rat in situ hybridization15 and immunocytochemistry16); ovary, placenta, heart (especially sinoatrial node; mouse in situ hybridization17)

**Physiological functions**

Thalamic oscillations18

**Mutations and pathophysiology**

Not established

**Pharmacological significance**

May mediate effect of absence antiepileptic drugs such as ethosuximide19 and other thalamocortical dysrhythmias20

**Comments**

Splice variants that differ in their voltage dependence have been cloned25

aa, amino acids; chr., chromosome; U92032, 7-[[4-bis(fluorophenyl)methyl]-1-piperazinylmethyl]-2-[(2-hydroxyethyl)amino]4-(1-methylethyl)-2,4,6-cycloheptatrien-1-one.


TABLE 10

Ca\(_{\text{3.2}}\) channels

<table>
<thead>
<tr>
<th>Channel name</th>
<th>Ca(_{\text{3.2}})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Voltage-gated calcium channel (\alpha) subunit</td>
</tr>
<tr>
<td>Other names</td>
<td>T-type, (\alpha_{\text{3.2}},\alpha_{\text{1H}})</td>
</tr>
<tr>
<td>Molecular information</td>
<td>Human: 2353aa, 095180, AF051946, chr0.16p13.3, CACNAIH</td>
</tr>
<tr>
<td>Associated subunits</td>
<td>Not established</td>
</tr>
<tr>
<td>Functional assays</td>
<td>Voltage-clamp, calcium imaging</td>
</tr>
<tr>
<td>Current</td>
<td>I(_{\text{Ca,T}})</td>
</tr>
<tr>
<td>Conductance</td>
<td>9pS</td>
</tr>
<tr>
<td>Ion selectivity</td>
<td>Ba(^{2+}) = Ca(^{2+})</td>
</tr>
<tr>
<td>Activation</td>
<td>(V_{\text{th}} = -46, \text{mV}, \tau = 2, \text{ms at} -10, \text{mV}^3)</td>
</tr>
<tr>
<td>Inactivation</td>
<td>(V_{\text{th}} = -72, \text{mV}, \tau_{\text{h}} = 16, \text{ms at} -10, \text{mV}^3)</td>
</tr>
<tr>
<td>Activators</td>
<td>None</td>
</tr>
<tr>
<td>Gating modifiers</td>
<td>Kurtxin(^4)</td>
</tr>
<tr>
<td>Blockers</td>
<td>Ca(<em>{\text{3.2}}) is more sensitive than Ca(</em>{\text{3.1}}) to block by nickel (IC(<em>{50}) = 12 (\mu)M) and possibly phenytoin(^6) and amiloride(^2); selective for Ca(</em>{\text{3.2}}) relative to Ca(<em>{\text{1.2}},\text{Ca}</em>{\text{2.2}},\text{mibefradil},\text{thalamocortical dysrhythmias}; potential drug target in hypertension and angina pectoris(^{24})</td>
</tr>
<tr>
<td>Radioligands</td>
<td>None</td>
</tr>
<tr>
<td>Channel distribution</td>
<td>Kidney (human Northern), rat smooth muscle (RT-PCR(^1)), liver (human Northern), adrenal cortex (rat, bovine; in situ hybridization and RT-PCR(^14)), brain (especially in olfactory bulb, striatum, cerebral cortex, hippocampus, reticular thalamic nucleus; rat in situ hybridization(^19)), and heart (especially sinoatrial node; mouse in situ hybridization(^19))</td>
</tr>
<tr>
<td>Physiological functions</td>
<td>Smooth muscle contraction(^17), smooth muscle proliferation,(^18) aldosterone secretion,(^19) cortisol secretion(^20)</td>
</tr>
<tr>
<td>Mutations and pathophysiology</td>
<td>Single nucleotide polymorphisms associated with childhood absence epilepsy patients in a Chinese population(^{21})</td>
</tr>
<tr>
<td>Pharmacological significance</td>
<td>May mediate effect of absence antiepileptic drugs such as ethosuximide(^{22}) and other thalamocortical dysrhythmias(^23); potential drug target in hypertension and angina pectoris(^{24})</td>
</tr>
<tr>
<td>Comments</td>
<td>Splice variation found in the linker connecting repeat 3 and 4(^25)</td>
</tr>
</tbody>
</table>

aa, amino acids; chr., chromosome; RT-PCR, reverse-transcriptase-polymerase chain reaction.

4. Avery RB and Johnston D (1997) Ca\(^{2+}\) currents induced by expression of three cloned \(\alpha_{\text{1b}}\) subunits, \(\alpha_{\text{1c}},\alpha_{\text{1H}}\) and \(\alpha_{\text{1p}}\), of low-voltage-activated T-type Ca\(^{2+}\) channels. Eur J Neurosci 11:4171–4178.
**TABLE 11**

<table>
<thead>
<tr>
<th>Channel name</th>
<th>Description</th>
<th>Other names</th>
<th>Molecular information</th>
<th>Associated subunits</th>
</tr>
</thead>
<tbody>
<tr>
<td>CaV3.3</td>
<td>Voltage-gated calcium channel subunit</td>
<td>T-type, α3.3, α11</td>
<td>Human: 2251aa, AAM67414, AF393329, chr. 22q13.1, CACNAII</td>
<td>No biochemical evidence, small changes induced by γ2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Rat: 1835aa, AF086827, AAD17796</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mouse 2753aa: XP_139476, XM_139476</td>
<td></td>
</tr>
</tbody>
</table>

**Pharmacological significance**

May mediate effect of absence antiepileptic drugs such as ethosuximide and other thalamocortical dysrythmias.

**Mutations and pathophysiology**

Not established.

**Physiological functions**

Thalamic oscillations.

**Channel distribution**

Brain, especially olfactory bulb, striatum, cerebral cortex, hippocampus, reticular nucleus, lateral habenula, cerebellum (rat in situ hybridization, human Northern).}

**Current**

I_{Ca,T}

**Ion selectivity**

Ba^{2+} = Ca^{2+}

**Activation**

- \( V_a = -44 \text{ mV}, \tau_a = 7 \text{ ms} \) at \(-10 \text{ mV}\)
- \( V_a = -72 \text{ mV}, \tau_a = 69 \text{ ms} \) at \(-10 \text{ mV}\)

**Activators**

Not established.

**Gating modifiers**

None.

**Blockers**

No subtype-specific blocker; selective for CaV3.2 relative to CaV1.x and CaV2.x: mibefradil, penfluridol, pimozide; nonselective: nickel (IC_{50} = 216 \mu M).

**Radioligands**

None.

**Channel substrate**

Brain, especially olfactory bulb, striatum, cerebral cortex, hippocampus, reticular nucleus, lateral habenula, cerebellum (rat in situ hybridization, human Northern).

**Comments**

Splice variants have been reported.


