International Union of Pharmacology. XLVIII. Nomenclature and Structure-Function Relationships of Voltage-Gated Calcium Channels

WILLIAM A. CATTERALL, EDWARD PEREZ-REYES, TERRANCE P. SNUTCH, AND JOERG STRIESSNIG

Department of Pharmacology, University of Washington, Seattle, Washington (W.A.C.); Department of Pharmacology, University of Virginia, Charlottesville, Virginia (E.P.-R.); Biotechnology Laboratory, University of British Columbia, Vancouver, British Columbia, Canada (T.P.S.); and Abteilung Pharmakologie und Toxikologie, Institut für Pharmazie, Universität Innsbruck, Innsbruck, Austria (J.S.)

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, 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 α1 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 α subunits of sodium channels, the α1 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 β subunit and a transmembrane, disulfide-linked αδ subunit complex are components of most types of calcium channels. A γ 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 α1 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 dipyridamides, 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

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**TABLE 1**

<table>
<thead>
<tr>
<th>Channel</th>
<th>Current</th>
<th>Localization</th>
<th>Specific Antagonists</th>
<th>Cellular Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>CaV1.1</td>
<td>L</td>
<td>Skeletal muscle; transverse tubules</td>
<td>Dihydropyridines; phenylalkylamines; benzo(thiazepines</td>
<td>Excitation-contraction coupling</td>
</tr>
<tr>
<td>CaV1.2</td>
<td>L</td>
<td>Cardiac myocytes; smooth muscle myocytes; endocrine cells; neuronal cell bodies; proximal dendrites</td>
<td>Dihydropyridines; phenylalkylamines; benzo(thiazepines</td>
<td>Excitation-contraction coupling; hormone release; regulation of transcription; synaptic integration</td>
</tr>
<tr>
<td>CaV1.3</td>
<td>L</td>
<td>Endocrine cells; neuronal cell bodies and dendrites; cardiac atrial myocytes and pacemaker cells; cochlear hair cells</td>
<td>Dihydropyridines; phenylalkylamines; benzo(thiazepines</td>
<td>Hormone release; regulation of transcription; synaptic regulation; cardiac pacemaking; hearing; neurotransmitter release from sensory cells</td>
</tr>
<tr>
<td>CaV1.4</td>
<td>L</td>
<td>Retinal rod and bipolar cells; spinal cord; adrenal gland; mast cells</td>
<td>Dihydropyridines; phenylalkylamines; benzo(thiazepines</td>
<td>Neurotransmitter release from photoreceptors</td>
</tr>
<tr>
<td>CaV2.1</td>
<td>P/Q</td>
<td>Nerve terminals and dendrites; neuroendocrine cells</td>
<td>α-conotoxin GVI</td>
<td>Neurotransmitter release; dendritic Ca²⁺ transients; hormone release</td>
</tr>
<tr>
<td>CaV2.2</td>
<td>N</td>
<td>Nerve terminals and dendrites; neuroendocrine cells</td>
<td>α-conotoxin GVI</td>
<td>Neurotransmitter release; dendritic Ca²⁺ transients; hormone release</td>
</tr>
<tr>
<td>CaV2.3</td>
<td>R</td>
<td>Neuronal cell bodies and dendrites</td>
<td>SNX-482</td>
<td>Repetitive firing; dendritic calcium transients</td>
</tr>
<tr>
<td>CaV3.1</td>
<td>T</td>
<td>Neuronal cell bodies and dendrites; cardiac and smooth muscle myocytes</td>
<td>None</td>
<td>Pacemaking; repetitive firing</td>
</tr>
<tr>
<td>CaV3.2</td>
<td>T</td>
<td>Neuronal cell bodies and dendrites; cardiac and smooth muscle myocytes</td>
<td>None</td>
<td>Pacemaking; repetitive firing</td>
</tr>
<tr>
<td>Cav3.3</td>
<td>T</td>
<td>Neuronal cell bodies and dendrites</td>
<td>None</td>
<td>Pacemaking; repetitive firing</td>
</tr>
</tbody>
</table>

**FIG. 1.** Subunit structure of CaV1 channels. The subunit composition and structure of calcium channels purified from skeletal muscle are illustrated. The model is updated from the original description of the subunit structure of skeletal muscle calcium channels. This model fits available biochemical and molecular biological results for other CaV1 channels and for CaV2 channels. Predicted α helices are depicted as cylinders. The lengths of lines correspond approximately to the lengths of the polypeptide segments represented.
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$\alpha$V). The numerical identifier corresponds to the Ca$\alpha$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$\alpha$V1 subfamily (Ca$\alpha$V1.1–Ca$\alpha$V1.4) includes channels containing $\alpha_{1S}$, $\alpha_{1C}$, $\alpha_{1D}$, and $\alpha_{1F}$, which mediate L-type Ca$^{2+}$ currents (Table 1). The Ca$\alpha$V2 subfamily (Ca$\alpha$V2.1–Ca$\alpha$V2.3) includes channels containing $\alpha_{1A}$, $\alpha_{1B}$, and $\alpha_{1E}$, which mediate P/Q-type, N-type, and R-type Ca$^{2+}$ currents, respectively (Table 1). The Ca$\alpha$V3 subfamily (Ca$\alpha$V3.1–Ca$\alpha$V3.3) includes channels containing $\alpha_{1G}$, $\alpha_{1H}$, and $\alpha_{1I}$, which mediate T-type 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$\alpha$V1 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$\alpha$V2 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$\alpha$V2.1 channels are blocked specifically by $\omega$-agatoxin IVA from funnel web spider venom. The Ca$\alpha$V2.2 channels are blocked specifically by $\omega$-conotoxin GIVA and related cone snail toxins. The Ca$\alpha$V2.3 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$\alpha$V2 family of calcium channels.

The Ca$\alpha$V3 subfamily of calcium channels is insensitive to both the dihydropyridines that block Ca$\alpha$V1 channels and the spider and cone snail toxins that block the Ca$\alpha$V2 channels, and there are no widely useful pharmacological agents that block T-type calcium currents (Perez-Reyes, 2003). The organic calcium channel blocker mibefradil is somewhat selective for T-type versus L-type calcium currents (3- to 5-fold). The peptide kurtoxin inhibits the activation gating of Ca$\alpha$V3.1 and Ca$\alpha$V3.2 channels. Development of more specific and high-affinity blockers of the Ca$\alpha$V3 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


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

#### TABLE 3

<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 Conductance</th>
<th>Ion selectivity</th>
<th>Activation</th>
<th>Inactivation</th>
<th>Gating modifiers</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CaV1.2</td>
<td>Voltage-gated cardiac channel α1 subunit</td>
<td>α1C, cardiac or smooth muscle L-type Ca	extsuperscript{2+} channel, cardiac or smooth muscle dihydropyridine receptor</td>
<td>Human: 2169aa, L29529 (cardiac; PMID: 8392192), 2138aa, Z34815 (fibroblast; PMID: 1316612); 2138aa, AP465484 (jejenum; PMID: 12176756); chr. 12p13.3, CACNA1C, LOCUS ID: 775; Rat: 2169aa, M59786 (sartorius smooth muscle; PMID: 2170396); 2140/2143aa, M67516/M67515 (brain; PMID: 1648941); chr. 4q42, Cacna1c, LOCUS ID: 24239</td>
<td>αδ, β, γ	extsuperscript{1,2}</td>
<td>Patch-clamp (whole-cell, single-channel), calcium imaging, cardiac or smooth muscle contraction</td>
<td>I_{Ca}^{L}</td>
<td>Ba	extsuperscript{2+}</td>
<td>V_{1/2} = -17 mV (in 2 mM Ca	extsuperscript{2+}; HEK cells); -4 mV (in 15 mM Ba	extsuperscript{2+}; HEK cells); -8 mV (in 5 mM Ba	extsuperscript{2+}; HEK cells and Xenopus oocytes); 1 ± 0 mV</td>
<td>V_{1/2} = -50 to -60 mV (in 2 mM Ca	extsuperscript{2+}; HEK cells), 18 to 42 mV (in 5-15 mM Ba	extsuperscript{2+}; HEK cells), -70% inactivation after 1 s (at V_{max} in 15 mM Ba	extsuperscript{2+}); -70% inactivation after 1 s (at V_{max} in 2 mM Ca	extsuperscript{2+})</td>
<td>Dihydropyridine antagonists, e.g., isradipine, IC_{50} = 50 nM in 10 mM Ba	extsuperscript{2+} and other phenylalkylamines; diltiazem (IC_{50} = 33 μM in 10 mM Ba	extsuperscript{2+} and 60 mV and 0.05Hz), diltiazem (IC_{50} = 50 nM)</td>
<td></td>
</tr>
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</table>

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

TABLE 4
Ca<sub>V</sub>1.3 channels

<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>Ca&lt;sub&gt;V&lt;/sub&gt;1.3</td>
<td>Voltage-gated calcium channel α&lt;sub&gt;1&lt;/sub&gt; subunit</td>
<td>α&lt;sub&gt;1D&lt;/sub&gt;, “neuroendocrine” L-type Ca&lt;sup&gt;2+&lt;/sup&gt; channel</td>
<td>Human: 2161aa, M76558 (brain; PMID: 1309651); 2181aa, M83566 (pancreatic β-cells; PMID: 1309948); Rat: 1646aa, M57682 (brain; PMID: 1648940); 2203aa, D38101 (pancreatic β-cells; PMID: 7760845); Mouse: 2144aa, A437291 (embryonic heart; PMID: 12900400); 14, Cacna1d, LocusID: 29716</td>
<td>Most likely at least α&lt;sub&gt;2&lt;/sub&gt;, β, and δ subunits</td>
</tr>
</tbody>
</table>

**Functional assays**
- Patch-clamp (whole-cell, single-channel), calcium imaging
- Calcium imaging

**Conductance**
Not established

**Activation**
V<sub>m</sub> = −15 to −20 mV (mouse cochlear hair cells; 10 mM Ba<sup>2+</sup>)<sup>1–2</sup>; −18 mV (in 15 mM Ba<sup>2+</sup>; HEK cells) to −37 mV (5 mM Ba<sup>2+</sup>; 2 mM Ca<sup>2+</sup> HEK cells or Xenopus oocytes)<sup>3,4</sup>; τ<sub>a</sub> < 1 ms at +10 mV<sup>3</sup>

**Inactivation**
V<sub>ih</sub> = −36 to −43 mV<sup>3,5</sup>; τ<sub>rest</sub> = 190 ms; τ<sub>slow</sub> = 1700 ms (at V<sub>max</sub> in HEK cells)<sup>3</sup>; calcium-induced inactivation is observed after expression in HEK cells<sup>3</sup> and in cochlear outer hair cells but not in inner hair cells<sup>2</sup>

**Activators**
BayK8644<sup>1–5</sup>

**Gating modifiers**
Dihydropyridine antagonists (e.g., isradipine, IC<sub>50</sub> = 30 nM at −50 mV and 300 nM at −90 mV; nimodipine, IC<sub>50</sub> = 3 μM at −80 mV)<sup>3,4</sup>

**Blockers**
Nonselective: CD<sup>2+</sup><sup>1–5</sup>

**Radioligands**
(+)-[<sup>3</sup>H]isradipine (K<sub>a</sub> < 0.5 nM)<sup>2</sup>; in radioreceptor assays, HEK cell-expressed Ca<sub>V</sub>1.2 and Ca<sub>V</sub>1.3 channels bind (+)-[<sup>3</sup>H]isradipine with indistinguishable K<sub>a</sub>; in functional experiments, however, Ca<sub>V</sub>1.2 channels show higher DHP sensitivity—this discrepancy is explained by the slower inactivation of Ca<sub>V</sub>1.3 decreasing the availability of inactivated channels for state-dependent DHP block

**Channel distribution**
Sensory cells (photoreceptors, cochlear hair cells<sup>1,2</sup>), endocrine cells (including pancreatic β-cells, pituitary, adrenal chromaffin cells, pinealocytes,<sup>7,8</sup> low density in heart (atrial muscle, sinoatrial and atrioventricular node)<sup>1,7,10</sup> and vascular smooth muscle<sup>9</sup>; neurons<sup>6</sup>; subcellular localization: on neurons preferentially located on proximal dendrites and cell bodies<sup>9</sup>

**Physiological functions**
Neurotransmitter release in sensory cells, control of cardiac rhythm and atrioventricular node conductance at rest<sup>1,10,12</sup> mood behavior,<sup>12</sup> hormone secretion

**Mutations and pathophysiology**
Deafness, sinoatrial and atrioventricular node dysfunction,<sup>1,10,12</sup> no convincing evidence for contribution to pancreatic β-cell L-type currents and insulin secretion in mouse models<sup>1,12,13</sup>

**Pharmacological significance**
Hypothetical drug targets for modulators of heart rate,<sup>1</sup> antidepressant drugs<sup>10</sup> and drugs for hearing disorders<sup>1</sup>

**Comments**
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<sub>V</sub>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<sub>V</sub>1.2 can also activate at more negative potentials

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

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

**Table 5**

**CaV1.4 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>Gating modifiers</th>
<th>Blockers</th>
<th>Radioligands</th>
<th>Channel distribution</th>
<th>Physiological functions</th>
<th>Mutations and pathophysiology</th>
<th>Pharmacological significance</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CaV1.4</td>
<td>Voltage-gated calcium channel $\alpha_1$ subunit</td>
<td>$\alpha_{1F}$</td>
<td>Human: 1966aa, AJ224874 (PMID: 9662399); chr. Xq11.23, CACNA1F, LocusID: 778</td>
<td>Not established</td>
<td>Preliminary functional evidence for $\beta_2$ association in incomplete X-linked congenital stationary night blindness</td>
<td>$I_{\text{Ca,L}}$</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>$V_a = -2.5$ to $-12$ mV (2–20 mM Ca$^{2+}$ or 15–20 mM Ba$^{2+}$; HEK cells); $\tau_a &lt; 1$ ms at $V_{\text{max}}$ (but slower components were also observed)</td>
<td>$V_i = -9$ 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 $V_{\text{max}}$; calcium-induced inactivation is not observed for CaV1.4 channels expressed in HEK cells but after expression in Xenopus oocytes</td>
<td>Dihydropyridine antagonists: nifedipine (IC$<em>{50}$ = 944 nM at $-100$ mV, ~300 nM at $-50$ mV$^4$; isradipine: ~80% inhibition by 100 nM at $-50$ mV$^4$, and 1 m$M$ at $-90$ mV$^3$); D-cis-diltiazem (IC$</em>{50}$ = 92 $\mu$M; verapamil: 69% inhibition at 100 $\mu$M (0.2 Hz, holding potential = $-80$ mV)$^6$</td>
<td>Noneselective: Cd$^{2+}$</td>
<td>Unlike for CaV1.2 and CaV1.3, no high-affinity (+)$^3$[3H]isradipine binding detectable (HEK cells) (J. Striessnig, unpublished observations)</td>
<td>Retinal photoreceptors and bipolar cells, spinal cord, lymphoid tissue (plasma and mast cells)$^3,4,7–10$</td>
<td>Neurotransmitter release in retinal cells</td>
<td>Mutations cause X-linked congenital stationary night blindness type 2$^7,9,11,12$</td>
<td>The biophysical properties of heterologously expressed CaV1.4 channels resemble those recorded in retinal neurons, suggesting that this channel type underlies retinal $I_{\text{Ca,L}}$; however, similar to CaV1.4, 1.4.3 channels also inactivate slowly and activate rapidly and may therefore also contribute to retinal $I_{\text{Ca,L}}$.</td>
<td></td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Channel name</th>
<th>Ca\textsubscript{v,1.2} channels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Voltage-gated calcium channel α\textsubscript{1A} subunit</td>
</tr>
<tr>
<td>Other names</td>
<td>α\textsubscript{1A}, P-type, Q-type, rβ\textsubscript{A-I} (in rat)\textsuperscript{1}, BL-1, BI-2 (in rabbit)\textsuperscript{2}</td>
</tr>
<tr>
<td>Molecular information</td>
<td>Human: 2510aa, AF004883, 2662aa, AF004884, chr. 1p13, CACNA1A&lt;br&gt;Rat: 2212aa, M64373&lt;br&gt;Mouse: 2165aa, NM007578, NP031604&lt;br&gt;Rabbit: 2273aa, X57476 (see “Comments”)</td>
</tr>
<tr>
<td>Associated subunits</td>
<td>α\textsubscript{δ}, β, possibly γ</td>
</tr>
<tr>
<td>Functional assays</td>
<td>Voltage-clamp, patch-clamp, calcium imaging, neurotransmitter release</td>
</tr>
<tr>
<td>Current</td>
<td>L\textsubscript{Ca-P}, L\textsubscript{Ca-Q}</td>
</tr>
<tr>
<td>Conductance</td>
<td>9, 14, 19ps (P-type, cerebellar Purkinje neurones)\textsuperscript{1}; 16–17ps (for α\textsubscript{1A}/α\textsubscript{δ}/β in Xenopus oocytes)\textsuperscript{2,5,6}</td>
</tr>
<tr>
<td>Ion selectivity</td>
<td>Ba\textsuperscript{2+} &gt; Ca\textsuperscript{2+}</td>
</tr>
<tr>
<td>Activation</td>
<td>(V_\text{a} = -5) mV for native P-type, (V_\text{a} = -11) mV for native Q-type (with 5 mM Ba\textsuperscript{2+} charge carrier)\textsuperscript{7}&lt;br&gt;(V_\text{a} = -4.1) mV for rat α\textsubscript{1A}/α\textsubscript{δ}/β\textsubscript{4}&lt;br&gt;(V_\text{a} = +9.5) mV; (\tau_2 = 2.2) ms at +10 mV for human α\textsubscript{1A}/α\textsubscript{δ}/β\textsubscript{1b} in HEK293 cells (with 15 mM Ba\textsuperscript{2+} charge carrier)\textsuperscript{3}</td>
</tr>
<tr>
<td>Inactivation</td>
<td>(V_\text{h} = -17.2) mV for α\textsubscript{1A}/α\textsubscript{δ}/β\textsubscript{4}; (V_\text{h} = -1.6) mV for α\textsubscript{1A}/α\textsubscript{δ}/β\textsubscript{4} (with 5 mM Ba\textsuperscript{2+} charge carrier); (V_\text{h} = -17) mV, (\tau_2 = 690) ms at +10 mV human α\textsubscript{1A}/α\textsubscript{δ}/β\textsubscript{1b} in HEK293 cells (with 15 mM Ba\textsuperscript{2+} charge carrier); (\tau_2 &gt; 1) s at 0 mV native P-type (with 5 mM Ba\textsuperscript{2+} charge carrier)\textsuperscript{7} (see “Comments”)</td>
</tr>
<tr>
<td>Activators</td>
<td>None</td>
</tr>
<tr>
<td>Gating modifiers</td>
<td>ω-agatoxin IVA (P-type, (K_A = 1–3) nM\textsuperscript{5}; Q-type (K_A = 100–200) nM\textsuperscript{5,9}); ω-agatoxin IVB\textsuperscript{6}</td>
</tr>
<tr>
<td>Blockers</td>
<td>ω-conotoxin MVIIIC\textsuperscript{6}; other blockers include piperidines, substituted diphenylbutylpiperidines, piperazines, volatile anesthetics, gabapentin, mibefradil, and peptide toxins DW13.3 and ω-conotoxin SVIB\textsuperscript{21–26} (see “Comments”)</td>
</tr>
<tr>
<td>Radioligands</td>
<td>[\textsuperscript{125}I]ju-conotoxin MVIIIC</td>
</tr>
<tr>
<td>Channel distribution</td>
<td>Neurons (presynaptic terminals, dendrites, some cell bodies), heart, pancreas, pituitary</td>
</tr>
<tr>
<td>Physiological functions</td>
<td>Neurotransmitter release in central neurons and neuromuscular junction; excitation-secretion coupling in pancreatic β-cells</td>
</tr>
<tr>
<td>Mutations and pathophysiology</td>
<td>Missense mutations in IS4-IS5, IS4-IS6, IIS4-IS6, and IIS4-IS6; and IVS4-IVS6 cause FHM\textsuperscript{27}, a common feature among FHM mutations is an apparent gain-of-function phenotype as a result of a shift in (V_{1/2}) to more hyperpolarized potentials (an increased probability of opening at the single channel level)\textsuperscript{28–29}; other effects include a decrease in maximal current density at the whole-cell level and alterations of synaptic transmission\textsuperscript{28–31}; point mutations in IIS1, IIS6-IIS2, IIS5-IIS6, and IVS1-IVS5 cause episodic ataxia type-2, a polyglutamine expansion in the carboxy region causes spinocerebellar ataxia type-6, and mutation of IIS5-IS6 and IVS6 causes episodic and progressive ataxia\textsuperscript{10–12,27}</td>
</tr>
<tr>
<td>Pharmacological significance</td>
<td>Peptide toxins that selectively inhibit Ca\textsubscript{v,2.1} channel block a significant portion of neurotransmission in the mammalian CNS\textsuperscript{21}; block of Ca\textsubscript{v,2.1} channels inhibits the late-phase formalin response and inflammatory pain but has no significant effect on mechanical allodynia or thermal hyperalgesia\textsuperscript{4–12}; mice lacking a functional Ca\textsubscript{v,2.1} gene exhibit cerebellar atrophy, severe muscle spasms, and ataxia and usually die by 3 to 4 weeks postnatal\textsuperscript{16,19}</td>
</tr>
<tr>
<td>Comments</td>
<td>Rates of inactivation and (V_\text{h}) are differentially affected by coexpression with β\textsubscript{2a}, β\textsubscript{2ao}, β\textsubscript{3}, or β\textsubscript{4} subunits, as well as by alternative splicing of the α\textsubscript{1A} subunit; identified regions of alternative splicing include the domain I-II linker, domain II-III linker, IVS3-IVS4, and the carboxy terminus\textsuperscript{1,2,6,22–34}; whole-cell currents with P-type kinetics seem to be conducted by the α\textsubscript{1A} subunit; the splice variant coexpressed with any of the β subunits or by the α\textsubscript{1Aα} splice variant coexpressed with the β\textsubscript{3} subunit\textsuperscript{6,20}; whole-cell currents with Q-type kinetics seem to be encoded by α\textsubscript{1A} or α\textsubscript{1Aβ} coexpressed with any of the β\textsubscript{1a}, β\textsubscript{3}, or β\textsubscript{4} subunits\textsuperscript{6,20}; whole-cell currents with Q-type pharmacology seem to be encoded by α\textsubscript{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\textsubscript{1A} splice variants missing Asp Pro residues in IV S3-S4 linker\textsuperscript{3}; 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\textsuperscript{26,32,36}.</td>
</tr>
</tbody>
</table>
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.


Sah DW and Bean BP (1994) Inhibition of P-type and N-type calcium channels by dopamine receptor antagonists. Mol Pharmacol 45:94–92.


### Channel name

**Ca$_{\alpha,2.2}$**

### Description

Voltage-gated calcium channel \(\alpha_1\) subunit

### Other names

N-type, \(\alpha_{1B}\); rbB-I, rbB-II (in rat); 1,2 BIII (in rabbit)

### Molecular information

- **Human**: 2339aa, M94172, 2237aa, M94173, chr. 9q34, CACNIB
- **Rat**: 2336aa, M929051
- **Mouse**: 2329aa, NM007579, NP031605

### Associated subunits

\(\alpha_2\delta\beta_1, \beta_3, \beta_4, \gamma\) possibly

### Functional assays

Voltage-clamp, patch-clamp, calcium imaging, neurotransmitter release, \(^{46}\text{Ca}\) uptake into synaptosomes

### Current

\(I_{\text{Ca,N}}\)

### Conductance

20pS (bullfrog sympathetic neurons); 14.3pS (rabbit BIII cDNA in skeletal muscle myotubes)

### Ion selectivity

\(Ba^{2+} > Ca^{2+}\)

### Activation

- \(V_a = +7.8 \text{ mV}, \tau_a = 3 \text{ ms at } +10 \text{ mV} \text{ (human } \alpha_{1B}/\alpha_2\delta\beta_1\beta_3\text{ in HEK293 cells, } 15 \text{ mM } Ba^{2+} \text{ charge carrier})^4,7; V_a = +9.7 \text{ mV}, \tau_a = 2.8 \text{ ms at } +20 \text{ mV} \text{ (rat } \alpha_{1B-II}/\beta_1\text{ in } \text{Xenopus} \text{ oocytes, } 40 \text{ mM } Ba^{2+} \text{ charge carrier})^2\)
- \(V_i = -61 \text{ mV}, \tau_i = -200 \text{ ms at } +10 \text{ mV} \text{ (human } \alpha_{1B}/\alpha_2\delta\beta_1\beta_3\text{ in HEK293 cells, } 15 \text{ mM } Ba^{2+} \text{ charge carrier})^4,7; V_h = -67.5 \text{ mV}, \tau_h = 112 \text{ ms at } +20 \text{ mV} \text{ (rat } \alpha_{1B-II}/\beta_1\text{ in } \text{Xenopus} \text{ oocytes, } 40 \text{ mM } Ba^{2+} \text{ charge carrier})^2\)

### Inactivation

None

### Gating modifiers

None

### Blockers

- \(\omega\)-conotoxin GVIA (1–2 \text{ pM, irreversible block})
- \(\omega\)-conotoxin MVIIA (SNX-111, Ziconotide/Prialt)
- \(\omega\)-conotoxin MVIIC
- Other blockers include piperidines, substituted diphenylbutylpiperidines, long alkyl chain molecules, aliphatic monoamines, tetrandine, gabapentin, peptidylamines, volatile carrier)
- \(\alpha\)-conotoxin MVIIC
- Other blockers include piperidines, substituted diphenylbutylpiperidines, long alkyl chain molecules, aliphatic monoamines, tetrandine, gabapentin, peptidylamines, volatile carrier)

### Radioligands

\([^{3}H]\text{-conotoxin GVIA} (K_d = 55 \text{ pM, human } \alpha_{1B}/\alpha_2\delta\beta_1\beta_3\text{ in HEK293 cells})^4\)

### Channel distribution

Neurons (presynaptic terminals, dendrites, cell bodies)

### Physiological functions

Neurotransmitter release in central and sympathetic neurons; sympathetic regulation of the circulatory system; activity and vigilance state control; sensation and transmission of pain

### Mutations and pathophysiology

Differing reports exist: mice lacking a functional \(Ca_{\alpha,2.2}\) 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 alternations to the sympathetic nervous system; however, in a different study, approximately 1/3 of the mice lacking a functional \(Ca_{\alpha,2.2}\) 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 responses; no point mutations in the native \(Ca_{\alpha,2.2}\) gene have been reported to date

### Pharmacological significance

In rats, intrathecal administration of \(\omega\)-conotoxin GVIA or \(\omega\)-conotoxin MVIIA shows strong effects on inflammatory pain, postsurgical pain, thermal hyperalgesia, and mechanical allodynia; 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 pain

### Comments

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 morphine; side effects of intrathecal administration of Ziconotide/Prialt include nystagmus, sedation, confusion, auditory and visual hallucinations, severe agitation, and unruly behavior; intravenous administration of \(\text{Ziconotide}\) to humans results in significant orthostatic hypotension; identified regions of alternative splicing include the domain I-II linker, domain II-III linker, IIIS3-IVS4, and the carboxyl terminus; 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 e37a splice isoform in dorsal root ganglia correlates with a subset of nociceptive neurons; alternative splicing also alters interactions with intracellular synaptic proteins such as Mint1, CASK, syntaxin, and SNAP-25

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\(\text{aa, amino acid; chr., chromosome; HEK, human embryonic kidney.}\)


calcium channel.

J Neurosci presynaptic proteins syntaxin and SNAP-25.


Biophys J 80:2690–2700.


### Table 8

**Ca$_{2,3}$ channels**

<table>
<thead>
<tr>
<th>Channel name</th>
<th>Ca$_{2,3}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Voltage-gated calcium channel α subunit</td>
</tr>
<tr>
<td>Other names</td>
<td>R-type, α$_{2,3}$; 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, chr1.1q25-31, CACNAJE</td>
</tr>
<tr>
<td>Associated subunits</td>
<td>α$_2$δβ, possibly γ</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$^{2+}$ = Ca$^{2+}$ (rat)(^2); Ba$^{2+}$ &gt; Ca$^{2+}$ (human)(^3)</td>
</tr>
<tr>
<td>Activation</td>
<td>$V_a$ = +3.5 mV, $t_a$ = 1.3 ms at 0 mV (human α$<em>{1d}/$δβ$</em>{1-3}$, 15 mM Ba$^{2+}$ charge carrier in HEK293 cells)(^3)</td>
</tr>
<tr>
<td>Inactivation</td>
<td>$V_i$ = -71 mV, $t_i$ = 74 ms at 0 mV (human α$<em>{1d}/$δβ$</em>{1-3}$, 15 mM Ba$^{2+}$ charge carrier in HEK293 cells)(^3)</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 μM), Cd$^{2+}$ (IC$</em>{50}$ = 0.8 μM), mibefradil (IC$_{50}$ = 0.4 μM),(^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>Pharmacological significance</td>
<td>See “Comments”</td>
</tr>
<tr>
<td>Comments</td>
<td>Ca$_{2,3}$ has been variously reported to encode a novel type of calcium channel with properties shared between low- and high-threshold calcium channels(^1)–(^3),(^15)–(^16) or a type of high-threshold channel resistant to DHPs, ω-agatoxin-IVA, and ω-conotoxin-GVIA and called R-type (for “residual”)(^7)</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(^5)–(^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(^6),(^8)</td>
</tr>
<tr>
<td>Physiological properties</td>
<td>Transmitter release, repetitive firing, long-term potentiation, post-tetanic potentiation, neurosecretion(^12)–(^14)</td>
</tr>
</tbody>
</table>

### Notes

Table 9

<table>
<thead>
<tr>
<th>Channel name</th>
<th>Ca₃.1 channels</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Voltage-gated calcium channel α₁ subunit</td>
</tr>
<tr>
<td>Other names</td>
<td>T-type, α₃.1, α₁G</td>
</tr>
<tr>
<td>Molecular information</td>
<td>Human: 2377aa, O43497, NM_018896, chr. 17q22, CACNA1G¹</td>
</tr>
<tr>
<td></td>
<td>Rat: 2254aa, O54898, AF027984</td>
</tr>
<tr>
<td></td>
<td>Mouse: 2288aa, CAI25956, NM_009783 (see “Comments”)</td>
</tr>
<tr>
<td>Associated subunits</td>
<td>No biochemical evidence, small changes induced by α₂δ₁² and α₂δ₃³⁴</td>
</tr>
<tr>
<td>Functional assays</td>
<td>Voltage-clamp, calcium imaging</td>
</tr>
<tr>
<td>Current</td>
<td>IᵥCaT</td>
</tr>
<tr>
<td>Conductance</td>
<td>7.3pS</td>
</tr>
<tr>
<td>Ion selectivity</td>
<td>Sr²⁺ &gt; Ba²⁺ &gt; Ca²⁺</td>
</tr>
<tr>
<td>Activation</td>
<td>Vᵐ = -46 mV, τₐ = 1 ms at -10 mV⁵.⁶</td>
</tr>
<tr>
<td>Inactivation</td>
<td>Vᵢₙ = -73 mV, τᵢₙ = 11 ms at -10 mV⁵.⁶</td>
</tr>
<tr>
<td>Activators</td>
<td>Not established</td>
</tr>
<tr>
<td>Gating modifiers</td>
<td>Kurtoxin, IC₅₀ = 15 nM⁷</td>
</tr>
<tr>
<td>Blockers</td>
<td>No subtype-specific blocker©; selective for Ca₃.3.x relative to Ca₁.x and Ca₂.x: mibefradil,⁹,¹⁰ U92032,¹¹ penfluridol and pimozone;¹² nonselective: nickel (IC₅₀ = 250 μM),¹³ amiloride¹⁴</td>
</tr>
<tr>
<td>Radioligands</td>
<td>None</td>
</tr>
<tr>
<td>Channel distribution</td>
<td>Brain, especially soma and dendrites of neurons in olfactory bulb, amygdala, cerebral cortex, hippocampus, thalamus, hypothalamus, cerebellum, brain stem (human RNA blots,¹⁵,¹⁶ rat in situ hybridization¹⁵ and immunocytochemistry¹⁶); ovary, placenta, heart (especially sinoatrial node; mouse in situ hybridization¹⁷)</td>
</tr>
<tr>
<td>Physiological functions</td>
<td>Thalamic oscillations¹⁸</td>
</tr>
<tr>
<td>Mutations and pathophysiology</td>
<td>Not established</td>
</tr>
<tr>
<td>Pharmacological significance</td>
<td>May mediate effect of absence antiepileptic drugs such as ethosuximide¹⁹ and other thalamocortical dysrhythmias;¹⁸¹²¹⁹</td>
</tr>
<tr>
<td>Comments</td>
<td>Splice variants that differ in their voltage dependence have been cloned²⁵</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Channel name</th>
<th>Ca$_{3.2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Voltage-gated calcium channel $\alpha_1$ subunit</td>
</tr>
<tr>
<td>Other names</td>
<td>T-type, $\alpha_{3.2}$, $\alpha_{1H}$</td>
</tr>
<tr>
<td>Molecular information</td>
<td>Human: 2353aa, O95180, AF051946, chr0.16p13.3, CACNAIH$^1$</td>
</tr>
<tr>
<td></td>
<td>Rat: 2359aa, AAG5187, AF290213</td>
</tr>
<tr>
<td></td>
<td>Mouse: 2365aa, NP_067390, NM_021415</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>$I_{Ca,T}$</td>
</tr>
<tr>
<td>Conductance</td>
<td>9pS$^2$</td>
</tr>
<tr>
<td>Ion selectivity</td>
<td>Ba$^{2+} = Ca^{2+}$</td>
</tr>
<tr>
<td>Activation</td>
<td>$V_a = -46$ mV, $\tau_a = 2$ ms at $-10$ mV$^3$</td>
</tr>
<tr>
<td>Inactivation</td>
<td>$V_h = -72$ mV, $\tau_h = 16$ ms at $-10$ mV$^3$</td>
</tr>
<tr>
<td>Activators</td>
<td>None</td>
</tr>
<tr>
<td>Gating modifiers</td>
<td>Kurtoxin$^4$</td>
</tr>
<tr>
<td>Blocks</td>
<td>Ca$<em>{3.2}$ is more sensitive than Ca$</em>{3.1}$ to block by nickel ($IC_{50} = 12 \mu M$) and possibly phenytoin$^4$ and amiloride$^5$; selective for Ca$<em>{3.3}$ relative to Ca$</em>{1.2}$ and Ca$_{2.2}$; mibefradil,$^6$ U92032,$^7$ penfluridol and pimozide,$^8$ and amiloride$^9$; nonselective: nimodipine,$^2$ anesthetics$^5$</td>
</tr>
<tr>
<td>Radioligands</td>
<td>None</td>
</tr>
<tr>
<td>Channel distribution</td>
<td>Kidney (human Northern$^1$), rat smooth muscle (RT-PCR$^{13}$), liver (human Northern$^1$), 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$^{15}$), and heart (especially sinoatrial node; mouse in situ hybridization$^{16}$)</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>

**TABLE 10**

Ca$_{3.2}$ channels

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


3. Klocker U, Lee JH, Cribbs LL, Daud A, Hesslefelder, J, Pervez, E, Perez-Reyes E, and Schneider T (1999) Comparison of the Ca$^{2+}$ currents induced by expression of three cloned $\alpha_1$ subunits, $\alpha_{1G}$,$^{1H}$ and $\alpha_{1P}$, of low-voltage-activated T-type Ca$^{2+}$ channels. Eur J Neurosci 11:4171–4178.


### Channel name

**Ca\textsubscript{3.3}**

### Description

Voltage-gated calcium channel \( \alpha \) subunit

### Other names

T-type, \( \alpha_{3.3} \), \( \alpha_{11} \)

### Molecular information

**Human:** 2251aa, AAM67414, AF393329, chr. 22q13.1, CACNAII \(^1\)

**Rat:** 1835aa, AF086827, AAD17796

**Mouse:** 2753aa: XP_139476, XM_139476

### Associated subunits

No biochemical evidence, small changes induced by \( \gamma_2 \)

### Functional assays

Voltage-clamp, calcium imaging

### Current

\( I_{\text{Ca,T}} \)

### Conductance

11pS\(^1\)

### Ion selectivity

\( \text{Ba}^{2+} = \text{Ca}^{2+} \)

### Activation

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

\( V_I = -72 \text{ mV}, \tau_I = 69 \text{ ms at } -10 \text{ mV} \)

### Activators

Not established

### Gating modifiers

None

### Blockers

No subtype-specific blocker\(^5\); selective for Cav3.x relative to Cav1.x and Cav2.x: mibefradil,\(^6,7\) U92032,\(^8\) penfluridol,\(^9\) pimozide; nonselective: nickel (IC\textsubscript{50} = 216 \mu M)\(^10\)

### Radioligands

None

### Channel distribution

Brain, especially olfactory bulb, striatum, cerebral cortex, hippocampus, reticular nucleus, lateral habenula, cerebellum (rat in situ hybridization,\(^11\) human Northern\(^12\))

### Physiological functions

Thalamic oscillations\(^13\)

### Mutations and pathophysiology

Not established

### Pharmacological significance

May mediate effect of absence antiepileptic drugs such as ethosuximide\(^14\) and other thalamocortical dysrhythmias\(^15\)

### Comments

Splice variants have been reported\(^16\)

### NOMENCLATURE AND RELATIONSHIPS OF VOLTAGE-GATED CALCIUM 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>Activators</th>
<th>Gating modifiers</th>
<th>Blockers</th>
<th>Channel distribution</th>
<th>Physiological functions</th>
<th>Mutations and pathophysiology</th>
<th>Pharmacological significance</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca\textsubscript{3.3}</td>
<td>Voltage-gated calcium channel ( \alpha ) subunit</td>
<td>T-type, ( \alpha_{3.3} ), ( \alpha_{11} )</td>
<td>Human: 2251aa, AAM67414, AF393329, chr. 22q13.1, CACNAII (^1)</td>
<td></td>
<td>Voltage-clamp, calcium imaging</td>
<td>( I_{\text{Ca,T}} )</td>
<td>11pS(^1)</td>
<td>( \text{Ba}^{2+} = \text{Ca}^{2+} )</td>
<td>( V_N = -44 \text{ mV}, \tau_a = 7 \text{ ms at } -10 \text{ mV} )</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Brain, especially olfactory bulb, striatum, cerebral cortex, hippocampus, reticular nucleus, lateral habenula, cerebellum (rat in situ hybridization,(^11) human Northern(^12))</td>
<td></td>
<td></td>
<td>May mediate effect of absence antiepileptic drugs such as ethosuximide(^14) and other thalamocortical dysrhythmias(^15)</td>
</tr>
</tbody>
</table>