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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 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 α2δ 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 (Tseïn 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

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TABLE 1  
**Physiological function and pharmacology of calcium channels**

<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; benzoiazepines</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; benzoiazepines</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; benzoiazepines</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; benzoiazepines</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-Bungarotoxin IVA</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-GVIA</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>

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**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\( \alpha \)). The numerical identifier corresponds to the \( \alpha_1 \) subunit gene subfamily (1 to 3 at present) and the order of discovery of the \( \alpha_1 \) subunit within that subfamily (1 through 6). According to this nomenclature, the \( \alpha_{1A} \) subfamily (Ca\( \alpha_1.1 \)–Ca\( \alpha_1.4 \)) includes channels containing \( \alpha_{1S} \), \( \alpha_{1C} \), \( \alpha_{1D} \), and \( \alpha_{1F} \), which mediate L-type \( \text{Ca}^{2+} \) currents (Table 1). The \( \alpha_{1B} \) subfamily (Ca\( \alpha_1.2 \)–Ca\( \alpha_1.3 \)) 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 \( \alpha_{1C} \) subfamily (Ca\( \alpha_{1.3.1} \)–Ca\( \alpha_{1.3.3} \)) 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\( \alpha_{1} \) 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\( \alpha_{2} \) 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\( \alpha_{2.1} \) channels are blocked specifically by \( \omega \)-agatoxin IVA from funnel web spider venom. The Ca\( \alpha_{2.2} \) channels are blocked specifically by \( \omega \)-conotoxin GIVA and related cone snail toxins. The Ca\( \alpha_{2.3} \) channels are blocked specifically by the synthetic peptide toxin SNX-482 derived from tarentula venom. These peptide toxins are potent blockers of synaptic transmission because of their specific effects on the Ca\( \alpha_{2} \) family of calcium channels.

The Ca\( \alpha_{3} \) subfamily of calcium channels is insensitive to both the dihydropyridines that block Ca\( \alpha_{1} \) channels and the spider and cone snail toxins that block the Ca\( \alpha_{2} \) 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 kurtxin inhibits the activation gating of Ca\( \alpha_{3.1} \) and Ca\( \alpha_{3.2} \) channels. Development of more specific and high-affinity blockers of the Ca\( \alpha_{3} \) 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>Channel name</th>
<th>Ca2+L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Voltage-gated calcium channel α1-subunit</td>
</tr>
<tr>
<td>Other names</td>
<td>α1L, skeletal muscle L-type Ca2+ channel, skeletal muscle dihydropyridine receptor</td>
</tr>
<tr>
<td>Molecular information</td>
<td>Human: 1873aa, L33798 (PMID: 7713519), chr.1q32, CACNA1S, LocusID: 779</td>
</tr>
<tr>
<td>Associated subunits</td>
<td>αδ, β, γ, δ</td>
</tr>
<tr>
<td>Functional assays</td>
<td>Patch-clamp (whole-cell, single-channel), calcium imaging, gating charge movement, skeletal muscle contracture</td>
</tr>
<tr>
<td>Current Conductance</td>
<td>ICa,L</td>
</tr>
<tr>
<td>Ion selectivity</td>
<td>Ca2+ &gt; Sr2+ &gt; Mg2+ &gt; Ba2+</td>
</tr>
<tr>
<td>Activation</td>
<td>VA = 8–14 mV, tA &gt; 50 ms at +10 mV (10 mM Ca2+ γ)</td>
</tr>
<tr>
<td>Inactivation</td>
<td>VA = 8–14 mV, 40% current inactivation after 5 s (~5 mV)</td>
</tr>
<tr>
<td>Activators</td>
<td>BayK8644, dihydropyridine agonists, FPL64176</td>
</tr>
<tr>
<td>Gating modifiers</td>
<td>Dihydropyridine antagonists (e.g., (+)-isradipine; IG50 = 13 nM at ~90 mV and 0.15 nM at ~65 mV)</td>
</tr>
<tr>
<td>Blockers</td>
<td>Nonselective: cadmium (IC50 &lt; 0.5 mM), selective for Ca2+L.x: verapamil, dicipamil (IC50 &lt; 1 μM) and other phenylalkylamines, (+)-cis-diltiazem (IC50 &lt; 80 μM)</td>
</tr>
<tr>
<td>Radioligands</td>
<td>(+)-(6)[H]isradipine (Kd = 0.2–0.7 nM) and other dihydropyridines; (+)-(6)[H]devapamil (Kd = 2.5 nM), (+)-cis-[H]diltiazem (Kd = 50 nM)</td>
</tr>
<tr>
<td>Channel distribution</td>
<td>Skeletal muscle transverse tubules (tetramers)</td>
</tr>
<tr>
<td>Physiological functions</td>
<td>Excitation-contraction coupling and Ca2+ homeostasis in skeletal muscle</td>
</tr>
<tr>
<td>Mutations and pathophysiology</td>
<td>Point mutations cause hypokalemic periodic paralysis and malignant hyperthermia susceptibility in humans and muscular dysgenesis in mice (mdg/mdg)</td>
</tr>
<tr>
<td>Pharmacological significance</td>
<td>Not established</td>
</tr>
<tr>
<td>Comments</td>
<td>The gene for Ca2+L.1 was first isolated and characterized in rabbit (1873aa, M23919, X05921); several groups reported three-dimensional structures of the purified skeletal muscle calcium channel complex determined using electron cryomicroscopy and single-particle averaging</td>
</tr>
</tbody>
</table>

aa, amino acids; chr., chromosome; Bay K8644, methyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-trifluoromethyl phenyl)pyridine-5-carboxylate; FPL64176, methyl 2,5 dimethyl-4-(2-phenylalkylamine)-1H-pyrole-3-carboxylate.


11. CACNA1S; Online Mendelian Inheritance in Man (OMIM) no. 114208.

TABLE 3
Ca_{1.2} channels

<table>
<thead>
<tr>
<th>Channel name</th>
<th>Ca_{1.2}</th>
<th>Description</th>
<th>Voltage-gated calcium channel α1 subunit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other names</td>
<td>α1C, α1D</td>
<td>cardiac or smooth muscle L-type Ca^{2+} channel, cardiac or smooth muscle dihydropyridine receptor</td>
<td></td>
</tr>
<tr>
<td>Molecular information</td>
<td>Human: 2169aa, L29529 (cardiac; PMID: 8392192), 2138aa, Z34815 (fibroblast; PMID: 1316612); 2138aa, AP465484 (jejunum; PMID: 12176756); chr. 12p13.3, CACNA1C, LocusID: 775; Rat: 2169aa, M09578 (sortic smooth muscle; PMID: 2107036); 2140/2143aa, M67516/M67515 (brain; PMID: 1648941); chr. 4q42, Cacna1c, LocusID: 24239</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Associated subunits</td>
<td>αδβ, αδγβ, αδγβδ</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional assays</td>
<td>Patch-clamp (whole-cell, single-channel), calcium imaging, cardiac or smooth muscle contraction hormone secretion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>I_{Ca}^{L} (25pS) &gt; Sr^{2+} = Ca^{2+} (9pS)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conductance</td>
<td>Ba^{2+} = -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)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ion selectivity</td>
<td>Ca^{2+} &gt; Sr^{2+} &gt; Ba^{2+} &gt;&gt; Mg^{2+} from permeability ratios</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activation</td>
<td>V_{h} = -50 to -60 mV (in 2 mM Ca^{2+}; HEK cells), -18 to -42 mV (in 5-15 mM Ba^{2+}; HEK cells)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inactivation</td>
<td>t_{inact} = 150 ms, t_{dyn} = 1100 ms; 61% inactivated after 250 ms in HEK cells (at V_{max} in 15 mM Ba^{2+}); 70% inactivation after 1 s (at V_{max} in 2 mM Ca^{2+}); inactivation is accelerated with Ca^{2+} as charge carrier (calcium-dependent inactivation: 86% inactivated after 250 ms)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activators</td>
<td>BayK8644, dihydropyridine agonists, FP64176</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gating modifiers</td>
<td>Dihydropyridine antagonists, e.g., isradipine, I_{C0} = 7 nM at -60 °C; nimodipine, I_{C0} = 139 nM at -60 °C</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blockers</td>
<td>Nonselective: Cd^{2+} 12, selective for Ca_{1.2}: devapamil (I_{C0} = 50 nM in 10 mM Ba^{2+} at -60 mV) and other phenylalkylamines; diltiazem (I_{C0} = 33 µM in 10 mM Ba^{2+} at -60 mV and 0.5Hz2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radioligands</td>
<td>(+)^{3}H]sradipine (K_{D} = 0.1 nM) and other dihydropyridines; (+)^{3}H]devapamil (K_{D} = 2.5 nM)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Channel distribution</td>
<td>Cardiac muscle, smooth muscle (including blood vessels, intestine, lung, uterus); endocrine cells (including pancreatic β-cells, pituitary); neurons13; subcellular localization: concentrated on granule-containing side of pancreatic β-cells14; neurons (preferentially somatodendritic)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physiological functions</td>
<td>Excitation-contraction coupling in cardiac or smooth muscle, action potential propagation in motor neurons</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mutations and pathophysiology</td>
<td>Required for normal embryonic development (mouse, zebrafish)18,19; de novo G406R mutation in CACNA1C gene determine the tissue-specific expression of the neuronal class C and class D L-type calcium channel alpha 1 subunits</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pharmacological significance</td>
<td>Mediates cardiovascular effects of clinically used Ca^{2+} antagonists17; high concentrations of dihydropyridines exert antidepressant effects through Ca_{1.2} inhibition</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Comments</td>
<td>Tissue-specific splice variants exist—in addition to cardiac channels, smooth muscle and brain channels have been cloned21,22; the gene for Ca_{1.2} was first isolated and characterized in rabbit heart (2171aa, P15581, X15539)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

20. CACNA1C: OMMID no. 114205.
Table 4
Ca\(_{\text{v}}\)1.3 Channels

<table>
<thead>
<tr>
<th>Channel name</th>
<th>Ca(_{\text{v}})1.3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Description</td>
<td>Voltage-gated calcium channel α1 subunit</td>
</tr>
<tr>
<td>Other names</td>
<td>α(_{\text{D}}), “neuroendocrine” L-type Ca(^{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</td>
</tr>
<tr>
<td>Rat: 1646aa, M57682 (brain; PMID: 1648940); 2203aa, D38101 (pancreatic β-cells; PMID: 7760845); chr. 16p16, Cacna1d, LocusID: 29716</td>
<td></td>
</tr>
<tr>
<td>Mouse: 2144aa, A4J437291 (embryonic heart; PMID: 12900400); chr. 14, Cacna1d, LocusID: 12289</td>
<td></td>
</tr>
</tbody>
</table>

| Associated subunits | Most likely at least α\(_{\text{D}}\), β, and δ subunits |
| Functional assays | Patch-clamp (whole-cell, single-channel), calcium imaging |
| Current | I\(_{\text{Ca,L}}\) |
| Ion selectivity | Not established |

**Activation**

\[ V_{\text{a}} = -15 \text{ to } -20 \text{ mV (mouse cochlear hair cells); } 10 \text{ mM Ba}^{2+} \text{; } -18 \text{ mV (in } 15 \text{ mM Ba}^{2+}; \text{ HEK cells) to } -37 \text{ mV (5 mM Ba}^{2+}; \text{ 2 mM Ca}^{2+} \text{ HEK cells or Xenopus oocytes) } \]

\[ \tau_{\text{a}} < 1 \text{ ms at } +10 \text{ mV} \]

**Inactivation**

\[ V_{\text{h}} = -36 \text{ to } -43 \text{ mV}^{3,5}; \text{ } \tau_{\text{inact}} = 190 \text{ ms, } \tau_{\text{slow}} = 1700 \text{ ms (at } V_{\text{max}} \text{ in HEK cells)} \]

**Activators**

BayK8644 \(^1\)–\(^5\)

**Gating modifiers**

Dihydropyridine antagonists (e.g., isradipine, IC\(_{50} = 30 \text{ nM at } -50 \text{ mV and } 300 \text{ nM at } -90 \text{ mV}; \text{ nimodipine, IC}_{50} = 3 \mu \text{M at } -80 \text{ mV}^{3,4} |

**Blockers**

Nonselective: CD\(^{2+}\) \(^5\)

**Radioligands**

\( (+)\text{H} \text{isradipine (}
\text{K}_{\text{d}} < 0.5 \text{ mM)}^{2}; \text{ in radioreceptor assays, HEK cell-expressed Ca}_{\text{v}}1.2 \text{ and Ca}_{\text{v}}1.3 \text{ channels bind } (+)\cdot \text{H} \text{isradipine with indistinguishable } \text{K}_{\text{d}}\text{; in functional experiments, however, Ca}_{\text{v}}1.2 \text{ channels show higher DHP sensitivity—this discrepancy is explained by the slower inactivation of Ca}_{\text{v}}1.3 \text{ decreasing the availability of inactivated channels for state-dependent DHP block) |

**Channel distribution**

Sensory cells (photoreceptors, cochlear hair cells\(^1\)–\(^3\)), endocrine cells (including pancreatic β-cells, pituitary, adrenal chromaffin cells, pinealocytes,\(^7\)–\(^9\) low density in heart (atrial muscle, sinoatrial and atrioventricular node)\(^7\)–\(^10\) and vascular smooth muscle\(^5\), neurons\(^6\), subcellular localization: on neurons preferentially located on proximal dendrites and cell bodies\(^6\) |

**Physiological functions**

Neurotransmitter release in sensory cells, control of cardiac rhythm and atrioventricular node conductance at rest\(^1\),\(^3\)–\(^10\) mood behavior,\(^12\) hormone secretion |

**Mutations and pathophysiology**

Deafness, sinoatrial and atrioventricular node dysfunction,\(^1\),\(^3\)–\(^10\) no convincing evidence for contribution to pancreatic β-cell L-type currents and insulin secretion in mice models\(^1\),\(^12\),\(^13\) |

**Pharmacological significance**

Hypothetical drug targets for modulators of heart rate,\(^1\) antidepressant drugs\(^10\) and drugs for hearing disorders\(^1\) |

**Comments**

Tissue-specific and developmental (exon 1b) splice variants exist—in addition to brain, pancreatic β-cells, and atrioventricular node)\(^7\); neurones\(^6\); subcellular localization: on neurons preferentially located on proximal dendrites and cell bodies\(^6\) |


\(^7\) Takimoto K, Li D, Nerboune JM, and Levitan ES (1997) Distribution, splicing and glucocorticoid-induced expression of cardiac \(\alpha_{\text{D}}\) and \(\alpha_{\text{D}}\)\(_D\) voltage-gated calcium channel mRNAs. J Mol Cell Cardiol 29:3055–3062.


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

**TABLE 5 Ca_{1.4} channels**

<table>
<thead>
<tr>
<th>Channel name</th>
<th>Description</th>
<th>Other names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ca_{1.4}</td>
<td>Voltage-gated calcium channel α_{1} subunit</td>
<td>α_{1F}</td>
</tr>
</tbody>
</table>

**Molecular information**
- **Human**: 1966aa, AJ224874 (PMID: 9662399); chr. Xp11.23, CACNA1F, LocusID: 778
- **Rat**: 1981aa, AF369575 (PMID: 11526344); chr. Xq22, Cacna1f, LocusID: 114493
- **Mouse**: 1985aa, AF192497 (PMID: 10873387); chr. X, Cacna1f, LocusID: 54652

**Associated subunits**
Not established; preliminary functional evidence for β_{2} association in incomplete X-linked congenital stationary night blindness.

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

**Current**
I_{Ca,L}

**Conductance**
Premise for very small single channel conductance (less than half of Ca_{1.2}); Ba^{2+} > Ca^{2+}

**Ion selectivity**
Not established

**Activation**
V_{0} = -2.5 to -12 mV (2–20 mM Ca^{2+} or 15–20 mM Ba^{2+}; HEK cells)\textsuperscript{3–6}, \tau_{a} < 1 ms at V_{m} (but slower components were also observed)\textsuperscript{3,6}

**Inactivation**
V_{0} = -9 to -27 mV (10–20 mM Ba^{2+}; HEK cells)\textsuperscript{3,6}; inactivation kinetics even slower than those of Ca_{1.3} with incomplete inactivation during 10-s depolarizations to V_{m}; calcium-induced inactivation is not observed for Ca_{1.4} channels expressed in HEK cells\textsuperscript{3,4,6} but after expression in *Xenopus* oocytes\textsuperscript{2}

**Activators**
BayK8644\textsuperscript{2,4,6}

**Gating modifiers**
Dihydropyridine antagonists: nifedipine (IC_{50} = 944 nM at -100 mV, -300 nM at -50 mV\textsuperscript{4}; isradipine: \textsim80% inhibition by 100 nM at -50 mV\textsuperscript{3,6} and 1 \mu M at -90 mV); d-cis-diltiazem (IC_{50}=92 \mu M); verapamil: 69% inhibition at 100 \mu M (0.2 Hz, holding potential = -80 mV\textsuperscript{8})

**Blockers**
Nonselective: Cd\textsuperscript{2+}

**Radioligands**
Unlike for Ca_{1.2} and Ca_{1.3}, no high-affinity (+)\textsuperscript{[3H]}isradipine binding detectable (HEK cells)

**Channel distribution**
Retinal photoreceptors and bipolar cells, spinal cord, lymphoid tissue (plasma and mast cells)\textsuperscript{3,4,7–10}

**Physiological functions**
Neurotransmitter release in retinal cells

**Mutations and pathophysiology**
Mutations cause X-linked congenital stationary night blindness type 2\textsuperscript{7,9,11,12}

**Pharmacological significance**
Not established

**Comments**
The biophysical properties of heterologously expressed Ca_{1.4} channels resemble those recorded in retinal neurons, suggesting that this channel type underlies retinal I_{Ca,L}—however, similar to Ca_{1.4}, Ca_{1.3} channels also inactivate slowly and activate rapidly and may therefore also contribute to retinal I_{Ca,L}

---

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


11. CACNA1F; OMIM no. 300110.

**Channel name**  
Ca\(\text{v}_{2.1}\)

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

**Other names**  
\(\alpha_{1A}\) P-type, Q-type, rbA-I (in rat)\(^1\); BI-1, BI-2 (in rabbit)\(^2\)

**Molecular information**  
Human: 2510aa, AF004883, 2662aa, AF004884, chr. 19p13, CACNA1A  
Rat: 2212aa, M64373  
Mouse: 2165aa, NM007578, NP031604  
Rabbit: 2273aa, X57476 (see “Comments”)

**Associated subunits**  
\(\alpha_\delta, \beta, \) possibly \(\gamma\)

**Functional assays**  
Voltage-clamp, patch-clamp, calcium imaging, neurotransmitter release

**Current**  
\(I_{\text{Ca},P}, I_{\text{Ca},Q}\)

**Conductance**  
9, 14, 19pS (P-type, cerebellar Purkinje neurones)\(^4\); 16–17pS (for \(\alpha_{1A}\)/\(\alpha_\delta/\beta_4\))

**Ion selectivity**  
\(E_{\text{rev}}^{\text{Ca}} > E_{\text{rev}}^{\text{Ba}^{2+}}\)

**Activation**  
\(V_a = -5 \text{ mV for native P-type, } V_a = -11 \text{ mV for native Q-type (with } 5 \text{ mM } \text{Ba}^{2+} \text{ charge carrier)}\)\(^7\)  
\(V_{i1} = -4.1 \text{ mV for rat } \alpha_{1A}/\alpha_\delta/\beta_4\)  
\(V_{i2} = +1.4 \text{ mV for rat } \alpha_{1A}/\alpha_\delta/\beta_4\) (with 5 mM \(\text{Ba}^{2+}\) charge carrier)\(^6\)  
\(V_{i3} = +9.5 \text{ mV; } \tau_1 = 2.2 \text{ ms at } +10 \text{ mV for human } \alpha_{1A}/\alpha_\delta/\beta_1\) in HEK293 cells (with 15 mM \(\text{Ba}^{2+}\) charge carrier)\(^3\)

**Inactivation**  
\(V_{h1} = -17.2 \text{ mV for } \alpha_{1A}/\alpha_\delta/\beta_4\); \(V_{h2} = -1.6 \text{ mV for } \alpha_{1A}/\alpha_\delta/\beta_4\) (with 5 mM \(\text{Ba}^{2+}\) charge carrier); \(V_{h3} = -17 \text{ mV; } \tau_1 = 690 \text{ ms at } +10 \text{ mV human } \alpha_{1A}/\alpha_\delta/\beta_1\) in HEK293 cells (with 15 mM \(\text{Ba}^{2+}\) charge carrier); \(\tau_1 > 1 \text{ s at } 0 \text{ mV native P-type (with } 5 \text{ mM } \text{Ba}^{2+} \text{ charge carrier)}\)

**Radioligands**  
\(^{[125]}\text{I}-\text{conotoxin MVIIIC}\)\(^{21–26}\); other blockers include piperidines, substituted diphenylbutylpiperidines, piperazines, volatile anesthetics, gabapentin, mibefradil, and peptide toxins DW13.3 and \(^{[125]}\text{I}-\text{conotoxin MVIIC}\)

**Channel distribution**  
Neurons (presynaptic terminals, dendrites, some cell bodies), heart, pancreas, pituitary

**Pharmacological significance**  
Peptide toxins that selectively inhibit \(\text{Ca}_{\text{v}}.2.1\) channel block a significant portion of neurotransmitter release in the mammalian CNS\(^1\); block of \(\text{Ca}_{\text{v}}.2.1\) channels inhibits the late-phase formalin response and inflammatory pain but has no significant effect on mechanical allodynia or thermal hyperalgesia\(^4,14–17\); mice lacking a functional \(\text{Ca}_{\text{v}}.2.1\) gene exhibit cerebellar atrophy, severe muscle spasms, and ataxia and usually die by 3 to 4 weeks postnatal\(^16,19\)

**Comments**  
Rates of inactivation and \(V_h\) are differentially affected by coexpression with \(\beta_2\), \(\beta_2\alpha\), \(\beta_3\), or \(\beta_4\) subunits, as well as by alternative splicing of the \(\alpha_{1A}\) subunit. Identified regions of alternative splicing include the domain I-II linker, domain II-III linker, IVS3-IVS4, and the carboxyl terminus\(^1,3,6,9,22–24\); whole-cell currents with P-type kinetics seem to be conducted by the \(\alpha_{1A}\)/\(\beta_2\alpha\) splice variant coexpressed with any of the \(\beta\) subunits or by the \(\alpha_{1A}/\beta_2\alpha\) splice variant coexpressed with the \(\beta_2\alpha\) subunit\(^6,20\); whole-cell currents with Q-type kinetics seem to be encoded by \(\alpha_{1A}/\beta_4\) coexpressed with any of the \(\beta_4\) subunits\(^6,20\); whole-cell currents with Q-type pharmacology seem to be encoded by \(\alpha_{1A}\) 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 \(\alpha_{1A}\) splice variants missing Asp Pro residues in IV S3-S4 linker\(^3,6\); alternative splicing also alters current density, current-voltage relations, calcium/calmodulin-dependent facilitation, and sensitivity to mibefradil, and binding to intracellular synaptic proteins such as Mint1, CASK, syntaxin, and SNAP-25\(^20,32,36\).
hemiplegic migraine and episodic ataxia type-2 are caused by mutations in the calcium channel gene CACNL1A4.


<table>
<thead>
<tr>
<th>Channel name</th>
<th>( \alpha_{2.2} )</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_{1B} ); rB-II, rB-II (in rat), ( \alpha_{III} ) (in rabbit)</td>
</tr>
<tr>
<td><strong>Molecular information</strong></td>
<td>Human: 2339aa, M91472, 2327aa, M94173, ch. 9q34, CACNB1</td>
</tr>
<tr>
<td><strong>Rat</strong></td>
<td>2336aa, M92905</td>
</tr>
<tr>
<td><strong>Mouse</strong></td>
<td>2329aa, NM007579, NP031605</td>
</tr>
<tr>
<td><strong>Associated subunits</strong></td>
<td>( \alpha_2\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, ( ^{46}\text{Ca} ) 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 BIII cDNA in skeletal muscle myotubes)(^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_a = +7.8 \text{ mV}, \tau_a = 3 \text{ ms} \text{ at } +10 \text{ mV (human } \alpha_{1B}/\alpha_2\delta\beta_1-3 \text{ in HEK293 cells, 15 mM Ba}^{2+} \text{ charge carrier)}^{4,5,7}; V_h = +9.7 \text{ mV}, \tau_h = 2.8 \text{ ms} \text{ at } +20 \text{ mV (rat } \alpha_{1B-II}/\beta_1 \text{ in Xenopus oocytes, 40 mM Ba}^{2+} \text{ charge carrier)}^{2} )</td>
</tr>
<tr>
<td><strong>Inactivation</strong></td>
<td>( V_i = -61 \text{ mV}, \tau_i = -200 \text{ ms} \text{ at } +10 \text{ mV (human } \alpha_{1B}/\alpha_2\delta\beta_1-3 \text{ in HEK293 cells, 15 mM Ba}^{2+} \text{ charge carrier)}^{4,5,7}; V_h = -67.5 \text{ mV}, \tau_h = 112 \text{ ms} \text{ at } +20 \text{ mV (rat } \alpha_{1B-II}/\beta_1 \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 M, irreversible block), ( \omega)-conotoxin MVIIA (SNX-111, Ziconotide/Prialt), ( \omega)-conotoxin MVIIC; other blockers include piperidines, substituted diphenylbutylpiperidines, long alkyd chains, monoamines, tetrandine, gabapentin, peptideosomes, volatile anesthetics, the peptide toxins SNX-111, Ziconotide/Prialt, synthetic ( \omega)-conotoxins MVIIC, and CVID ( ^{20–34} )</td>
</tr>
<tr>
<td><strong>Radioligands</strong></td>
<td>( [\text{^{125}I}]\omega)-conotoxin GVIA (( K_d = 55 \text{ pM, human } \alpha_{1B}/\alpha_2\delta\beta_1-3 \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 neurons(^10); sympathetic regulation of the circulatory system(^1,3,5); activity and vigilance state control(^36); sensation and transmission of pain (see &quot;Pharmacological significance&quot; and &quot;Comments&quot;)</td>
</tr>
<tr>
<td><strong>Mutations and pathophysiology</strong></td>
<td>Differing reports exist: mice lacking a functional ( \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 arterial pressure and other functional alterations to the sympathetic nervous system(^1) however, in a different study, approximately 1/3 of the mice lacking a functional ( \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(^12); no point mutations in the native ( \alpha_{2.2} ) gene have been reported to date</td>
</tr>
<tr>
<td><strong>Pharmacological significance</strong></td>
<td>In rats, intracerebroventricular administration of ( \omega)-conotoxin GVIA or ( \omega)-conotoxin MVIIC shows strong effects on inflammatory pain, postsurgical pain, thermal hyperalgesia, and mechanical allodynia(^13–15); in humans, intracerebroventricular administration of SNX-111 (Ziconotide/Prialt, synthetic ( \omega)-conotoxin MVIIC) 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(^16)</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 morphine(^17); side effects of intrathecal administration of Ziconotide/Prialt include nystagmus, sedation, confusion, auditory and visual hallucinations, severe agitation, and unruly behavior(^18); intravenous administration of Ziconotide to humans results in significant orthostatic hypotension(^19); identified regions of alternative splicing include the domain I-II linker, domain II–III linker, IIIS3–IIIS4, IVS3–IVS4, and the carboxyl terminus(^4,37–39); 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 e37a splice isoform in dorsal root ganglia correlates with a subset of nociceptive neurons(^40–42); alternative splicing also alters interactions with intracellular synaptic proteins such as Mint1, CASK, syntaxin, and SNAP-25(^33–45)</td>
</tr>
</tbody>
</table>

---

**TABLE 7**

<table>
<thead>
<tr>
<th>( \alpha_{2.2} ) channels</th>
</tr>
</thead>
</table>

---

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


### Channel name

CaV2.3

### Description

Voltage-gated calcium channel α1 subunit

### Other names

R-type, α1E; rbE-II (in rat); BII-1, BII-2 (in rabbit)

### Molecular information

Human: 2251aa, L29384, 2270aa, L29385, chr.1q25-q31, CACNAIE

Mouse: 2272aa, Q61290

### Associated subunits

α2δβ, possibly γ

### Functional assays

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

### Current

ICaL

### Conductance

Not established

### Ion selectivity

Ba2+ = Ca2+ (rat); Ba2+ > Ca2+ (human)

### Activation

V50 = +3.5 mV, t50 = 1.3 ms at 0 mV (human α1E/α2δββ1-3, 15 mM Ba2+ charge carrier in HEK293 cells)3

V50 = -29.1 mV, t50 = 2.1 ms at -10 mV (rat α1E/α2δββ1-1, 4 mM Ba2+ charge carrier in Xenopus oocytes)1

### Inactivation

V50 = -71 mV, t50 = 74 ms at 0 mV (human α1E/α2δββ1-3, 15 mM Ba2+ charge carrier in HEK293 cells)3; V50 = -78.1 mV, t50 = 100 ms at -10 mV (rat α1E/α2δββ1-1, 4 mM Ba2+ charge carrier in Xenopus oocytes)1

### Activators

None

### Gating modifiers

None

### Blockers

SNX-482, Ni2+ (IC50 = 27 μM), Cd2+ (IC50 = 0.8 μM), mibebradil (IC50 = 0.4 μM), volatile anesthetics

### Radioligands

None

### Channel distribution

Neurons (cell bodies, dendrites, some presynaptic terminals), heart, testes, pituitary

### Physiologic functions

Neurotransmitter release, repetitive firing, long-term potentiation, post-tetanic potentiation, neuroscretion

### Mutations and pathophysiology

No point mutations in the native Ca2.3 gene have been reported; mice deficient for the Ca2.3 gene retain a substantial cerebellar R-type current, suggesting that R-type currents actually reflect a heterogeneous mixture of channels; homozygous Ca2.3-null mice survive to adulthood, reproduce, and are apparently behaviorally normal; mutant mice exhibit an increased resistance to formalin-induced pain, supporting an involvement of the Ca2.3 calcium channel in transmitting and/or the development of somatic inflammatory pain

### Pharmacological significance

See “Comments”

### Comments

Ca2.3 has been variously reported to encode a novel type of calcium channel with properties shared between both low- and high-threshold calcium channels or a type of high-threshold channel resistant to DHPs, ω-agonotoxin-IVA, and ω-conotoxin-GVIA and called R-type (for “residual”). The tarantula toxin SNX-482 blocks exogenously expressed Ca2.3 currents but is only partially effective on native cerebellar R-type currents, suggesting that Ca2.3 does not always conduct a significant portion of the R-type current as originally defined; identified regions of alternative splicing include the domain II-III linker and carboxyl terminus and have been shown to affect channel kinetics and Ca2+-dependent stimulation

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

TABLE 9
Ca\textsubscript{3.1} 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>Activators</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>Ca\textsubscript{3.1}</td>
<td>Voltage-gated calcium channel (\alpha) subunit</td>
<td>T-type, (\alpha\textsubscript{3.1}, \alpha\textsubscript{1G})</td>
<td>Human: 2377aa, O43497, NM_018896, chr. 17q22, CACNA1G\textsuperscript{1}</td>
<td>No biochemical evidence, small changes induced by (\alpha\textsubscript{2}\delta\textsubscript{2}) and (\alpha\textsubscript{2}\delta\textsubscript{3}) \textsuperscript{3,4}</td>
<td>Voltage-clamp, calcium imaging</td>
<td>(I_{\text{CaT}})</td>
<td>7.5pS</td>
<td>(S_{\text{Ba}^{2+}}&gt;S_{\text{Ca}^{2+}})</td>
<td>(V_{a} = -46 \text{ mV}, \tau_{a} = 1 \text{ ms} \text{ at } -10 \text{ mV}\textsuperscript{5,6}</td>
<td>(V_{a} = -73 \text{ mV}, \tau_{a} = 11 \text{ ms} \text{ at } -10 \text{ mV}\textsuperscript{5,6}</td>
<td>Not established</td>
<td>Kurtoxin, IC\textsubscript{50} = 15 nM</td>
<td>None</td>
<td>Brain, especially soma and dendrites of neurons in olfactory bulb, amygdala, cerebral cortex, hippocampus, thalamus, hypothalamus, cerebellum, brain stem (human RNA blots, \textsuperscript{1,5} rat in situ hybridization\textsuperscript{15} and immunocytochemistry\textsuperscript{16}); ovary, placenta, heart (especially sinoatrial node; mouse in situ hybridization\textsuperscript{17})</td>
<td>Thalamic oscillations\textsuperscript{18}</td>
<td>Not established</td>
<td>May mediate effect of absence antiepileptic drugs such as ethosuximide\textsuperscript{19} and other thalamocortical dysrhythmias\textsuperscript{20}</td>
<td>Splice variants that differ in their voltage dependence have been cloned\textsuperscript{5}</td>
<td></td>
</tr>
</tbody>
</table>

### Table 10: Ca₃.2 channels

<table>
<thead>
<tr>
<th>Channel name</th>
<th>Ca₃.2</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, α₃.2, α₃H</td>
</tr>
<tr>
<td>Molecular information</td>
<td>Human: 2353aa, O95180, AF051946, chr0.16p13.3, CACNAIH¹</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>9pS²</td>
</tr>
<tr>
<td>Ion selectivity</td>
<td>Ba²⁺ = Ca²⁺</td>
</tr>
<tr>
<td>Activation</td>
<td>Vₐ = -46 mV, τₐ = 2 ms at -10 mV³</td>
</tr>
<tr>
<td>Inactivation</td>
<td>Vᵦ = -72 mV, τᵦ = 16 ms at -10 mV³</td>
</tr>
<tr>
<td>Activators</td>
<td>None</td>
</tr>
<tr>
<td>Gating modifiers</td>
<td>Kurtxin⁴</td>
</tr>
<tr>
<td>Blockers</td>
<td>Cat, Ca₃, Ca₉, and amiloride²; selective for Ca₃.x relative to Ca₁.x and Ca₂.x: mibebradil,⁸⁻⁹ U92032,¹⁰ penfluridol and pimozone,¹¹ and amiloride¹²; nonselective: nimodipine,²³ anesthetics⁵</td>
</tr>
<tr>
<td>Radioligands</td>
<td>None</td>
</tr>
<tr>
<td>Channel distribution</td>
<td>Kidney (human Northern¹), rat smooth muscle (RT-PCR¹⁵), liver (human Northern¹), adrenal cortex (rat, bovine; in situ hybridization and RT-PCR¹⁴), brain (especially in olfactory bulb, striatum, cerebral cortex, hippocampus, reticular thalamic nucleus; rat in situ hybridization¹⁶), and heart (especially sinoatrial node; mouse in situ hybridization¹⁶)</td>
</tr>
<tr>
<td>Physiological functions</td>
<td>Smooth muscle contraction,¹⁷ smooth muscle proliferation,¹⁸ aldosterone secretion,¹⁹ cortisol secretion²⁰</td>
</tr>
<tr>
<td>Mutations and pathophysiology</td>
<td>Single nucleotide polymorphisms associated with childhood absence epilepsy patients in a Chinese population²¹</td>
</tr>
<tr>
<td>Pharmacological significance</td>
<td>May mediate effect of absence antiepileptic drugs such as ethosuximide²² and other thalamocortical dysrhythmias²³; potential drug target in hypertension and angina pectoris²⁴</td>
</tr>
<tr>
<td>Comments</td>
<td>Splice variation found in the linker connecting repeat 3 and 4²⁵</td>
</tr>
</tbody>
</table>

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

TABLE 11
Ca,3.3 channels

<table>
<thead>
<tr>
<th>Channel name</th>
<th>Description</th>
<th>Other names</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Voltage-gated calcium channel α subunit</td>
<td>T-type, α3.3, α11</td>
</tr>
<tr>
<td>Molecular information</td>
<td>Human: 2251aa, AAM67414, AF393329, chr. 22q13.1, CACNAII 1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rat: 1835aa, AF086827, AAD17796</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mouse 2753aa: XP_139476, XM_139476</td>
<td></td>
</tr>
<tr>
<td>Associated subunits</td>
<td>No biochemical evidence, small changes induced by γ2 2</td>
<td></td>
</tr>
<tr>
<td>Functional assays</td>
<td>Voltage-clamp, calcium imaging</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>I_{Ca,T}</td>
<td></td>
</tr>
<tr>
<td>Conductance</td>
<td>11pS</td>
<td></td>
</tr>
<tr>
<td>Ion selectivity</td>
<td>Ba^{2+} = Ca^{2+}</td>
<td></td>
</tr>
<tr>
<td>Activation</td>
<td>V_{an} = -44 mV, τ_{an} = 7 ms at -10 mV^4</td>
<td></td>
</tr>
<tr>
<td>Inactivation</td>
<td>V_{tr} = -72 mV, τ_{rr} = 69 ms at -10 mV^4</td>
<td></td>
</tr>
<tr>
<td>Activators</td>
<td>Not established</td>
<td></td>
</tr>
<tr>
<td>Gating modifiers</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Blockers</td>
<td>No subtype-specific blocker; selective for Ca,3.x relative to Ca,1.x and Ca,2.x: mibefradil, 6,7</td>
<td></td>
</tr>
<tr>
<td>Radioligands</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>Channel distribution</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>
</tr>
<tr>
<td>Physiological functions</td>
<td>Thalamic oscillations 13</td>
<td></td>
</tr>
<tr>
<td>Mutations and pathophysiology</td>
<td>Not established</td>
<td></td>
</tr>
<tr>
<td>Pharmacological significance</td>
<td>May mediate effect of absence antiepileptic drugs such as ethosuximide 14 and other thalamocortical dysrhythmias 15</td>
<td></td>
</tr>
<tr>
<td>Comments</td>
<td>Splice variants have been reported 16</td>
<td></td>
</tr>
</tbody>
</table>

aa, amino acids; chr., chromosome.