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International Union of Pharmacology. XLVIII. 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 α_1 subunit of 190 to 250 kDa is the largest subunit, and it incorporates the conduction pore, the voltage sensor and gating apparatus, and most of the known sites of channel regulation by second messengers, drugs, and toxins. Like the α subunits of sodium channels, the α_1 subunit of voltage-gated calcium channels is organized in four homologous domains (I–IV), with six transmembrane segments (S1–S6) in each. The S4 segment serves as the voltage sensor. The pore loop between transmembrane segments S5 and S6 in each domain determines ion conductance and selectivity, and changes of only three amino acids in the pore loops in domains I, III, and IV will convert a sodium channel to calcium selectivity. An intracellular β subunit and a transmembrane, disulfide-linked $\alpha_2\delta$ 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 α_1 subunits (Hofmann et al., 1994).

Calcium Currents

Calcium currents recorded in different cell types have diverse physiological and pharmacological properties, and an alphabetical nomenclature has evolved for the distinct classes of calcium currents (Tsien et al., 1995). L-type calcium currents typically require a strong depolarization for activation, are long-lasting, and are blocked by the organic L-type calcium channel antagonists, including dihydropyridines, phenylalkylamines, and benzothiazepines. They are the main calcium currents recorded in muscle and endocrine cells, where they initiate contraction and secretion. L-type currents activating at lower voltages also exist predominantly in neurons and cardiac pacemaker cells. N-type, P/Q-type, and R-type calcium currents

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TABLE 1
Physiological function and pharmacology of calcium channels

Channel	Current	Localization	Specific Antagonists	Cellular Functions
$Ca_V1.1$	L	Skeletal muscle; transverse tubules	Dihydropyridines; phenylalkylamines; benzothiazepines	Excitation-contraction coupling
$Ca_V1.2$	L	Cardiac myocytes; smooth muscle myocytes; endocrine cells; neuronal cell bodies; proximal dendrites	Dihydropyridines; phenylalkylamines; benzothiazepines	Excitation-contraction coupling; hormone release; regulation of transcription; synaptic integration
$Ca_V1.3$	L	Endocrine cells; neuronal cell bodies and dendrites; cardiac atrial myocytes and pacemaker cells; cochlear hair cells	Dihydropyridines; phenylalkylamines; benzothiazepines	Hormone release; regulation of transcription; synaptic regulation; cardiac pacemaking; hearing; neurotransmitter release from sensory cells
$Ca_V1.4$	L	Retinal rod and bipolar cells; spinal cord; adrenal gland; mast cells	Dihydropyridines; phenylalkylamines; benzothiazepines	Neurotransmitter release from photoreceptors
$Ca_V2.1$	P/Q	Nerve terminals and dendrites; neuroendocrine cells	ω-Agatoxin IVA	Neurotransmitter release; dendritic Ca^{2+} transients; hormone release
$Ca_V2.2$	N	Nerve terminals and dendrites; neuroendocrine cells	ω-Conotoxin-GVIA	Neurotransmitter release; dendritic Ca^{2+} transients; hormone release
$Ca_V2.3$	R	Neuronal cell bodies and dendrites	SNX-482	Repetitive firing; dendritic calcium transients
$Ca_V3.1$	T	Neuronal cell bodies and dendrites; cardiac and smooth muscle myocytes	None	Pacemaking; repetitive firing
$Ca_V3.2$	T	Neuronal cell bodies and dendrites; cardiac and smooth muscle myocytes	None	Pacemaking; repetitive firing
Cav3.3	T	Neuronal cell bodies and dendrites	None	Pacemaking; repetitive firing

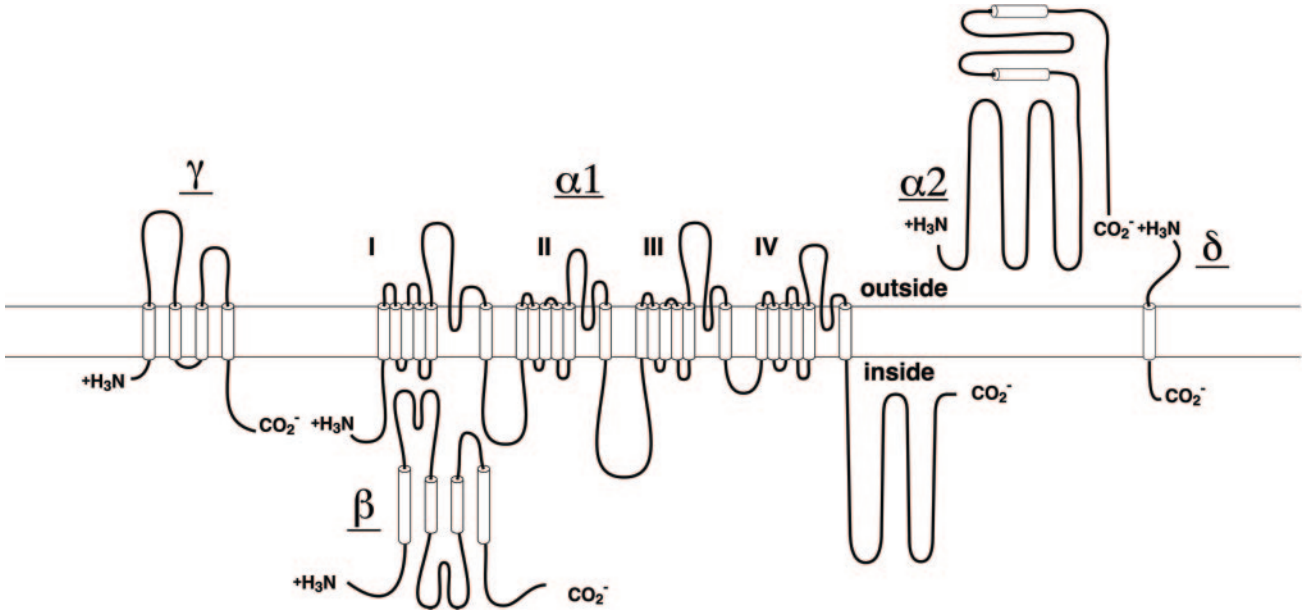

FIG. 1. Subunit structure of Ca_V1 channels. The subunit composition and structure of calcium channels purified from skeletal muscle are illustrated. The model is updated from the original description of the subunit structure of skeletal muscle calcium channels. This model fits available biochemical and molecular biological results for other Ca_V1 channels and for Ca_V2 channels. Predicted α helices are depicted as cylinders. The lengths of lines correspond approximately to the lengths of the polypeptide segments represented.

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 α_1 subunits are encoded by at least 10 distinct genes. Historically, various names have been given to the corresponding gene products, giving rise to

distinct and sometimes confusing nomenclatures. In 1994, a unified but arbitrary nomenclature was adopted in which α_1 subunits were referred to as α_{1S} for the original skeletal muscle isoform and α_{1A} through α_{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_V). The numerical identifier corresponds to the Ca_V channel α_1 subunit gene subfamily (1 to 3 at present) and the order of discovery of the α_1 subunit within that subfamily (1 through *n*). According to this nomenclature, the Ca_V1 subfamily ($Ca_V1.1$–$Ca_V1.4$) includes channels containing α_{1S}, α_{1C}, α_{1D}, and α_{1F}, which mediate L-type Ca^{2+} currents (Table 1). The Ca_V2 subfamily ($Ca_V2.1$–$Ca_V2.3$) includes channels containing α_{1A}, α_{1B}, and α_{1E}, which mediate P/Q-type, N-type, and R-type Ca^{2+} currents, respectively (Table 1). The Ca_V3 subfamily ($Ca_V3.1$–$Ca_V3.3$) includes channels containing α_{1G}, α_{1H}, and α_{1I}, which mediate T-type Ca^{2+} currents.

The complete amino acid sequences of these α_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 α_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_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.

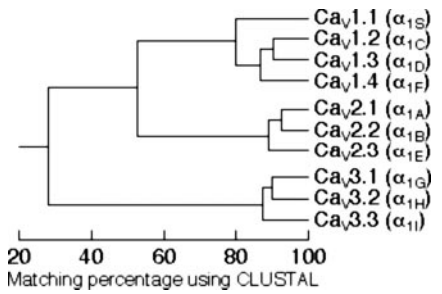

FIG. 2. Sequence similarity of voltage-gated calcium channel α_1 subunits. Phylogenetic representation of the primary sequences of the calcium channels. Only the membrane-spanning segments and pore loops (~350 amino acids) are compared. First, all sequence pairs were compared, which clearly defines three subfamilies with intrafamily sequence identities above 80% (Ca_V1, Ca_V2, and Ca_V3). Then a consensus sequence was defined for each subfamily, and these three sequences were compared to one another, with intersubfamily sequence identities of ~52% (Ca_V1 vs. Ca_V2) and 28% (Ca_V3 vs. Ca_V1 or Ca_V2).

The Ca_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 $Ca_V2.1$ channels are blocked specifically by ω-agatoxin IVA from funnel web spider venom. The $Ca_V2.2$ channels are blocked specifically by ω-conotoxin GVIA and related cone snail toxins. The $Ca_V2.3$ 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_V2 family of calcium channels.

The Ca_V3 subfamily of calcium channels are insensitive to both the dihydropyridines that block Ca_V1 channels and the spider and cone snail toxins that block the Ca_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 $Ca_V3.1$ and $Ca_V3.2$ channels. Development of more specific and high-affinity blockers of the Ca_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.

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TABLE 2
$Ca_V1.1$ channels

Channel name	$Ca_V1.1$
Description	Voltage-gated calcium channel α_1-subunit
Other names	α_{1s}, skeletal muscle L-type Ca^{2+} channel, skeletal muscle dihydropyridine receptor
Molecular information	Human: 1873aa, L33798 (PMID: 7713519), chr0.1q32, *CACNA1S*, LocusID: 779 Rat: 1146aa (partial sequence), L04684 (PMID: 1335956), chr. 13, Cacna1s, LocusID: 116652 Mouse: 1861aa, L06234 (PMID: 1281468), chr. 1, Cacna1s, LocusID: 12292 (see 'Comments')
Associated subunits	$\alpha_2\delta$, β, γ[1,2]
Functional assays	Patch-clamp (whole-cell, single-channel), calcium imaging, gating charge movement, skeletal muscle contraction
Current	$I_{Ca,L}$
Conductance	13–17pS (in 90–110 mM Ba^{2+})[3,4]
Ion selectivity	$Ca^{2+} > Sr^{2+} > Mg^{2+} > Ba^{2+}$ [5]
Activation	V_a = 8–14 mV, τ_a > 50 ms at +10 mV (10 mM Ca^{2+})[4,6]
Inactivation	V_h = −8 mV, 40% current inactivation after 5 s (−5 mV)[4]
Activators	BayK8644, dihydropyridine agonists, FPL64176[2,8,9]
Gating modifiers	Dihydropyridine antagonists (e.g., (+)- isradipine; IC_{50} = 13 nM at −90 mV and 0.15 nM at −65 mV)[9]
Blockers	Nonselective: cadmium (IC_{50} < 0.5 mM)[9]; selective for $Ca_V1.x$: verapamil, devapamil (IC_{50} < 1 μM) and other phenylalkylamines, (+)-*cis*-diltiazem (IC_{50} < 80 μM)[9]
Radioligands	(+)-[^{3}H]isradipine (K_d = 0.2–0.7 nM) and other dihydropyridines; (−)-[^{3}H]devapamil (K_d = 2.5 nM), (+)-*cis*-[^{3}H]diltiazem (K_d = 50 nM)[2]
Channel distribution	Skeletal muscle transverse tubules (tetramers)[10]
Physiological functions	Excitation-contraction coupling and Ca^{2+} homeostasis in skeletal muscle[11]
Mutations and pathophysiology	Point mutations cause hypokalemic periodic paralysis and malignant hyperthermia susceptibility in humans and muscular dysgenesis in mice (*mdg*/*mdg*)[12,13]
Pharmacological significance	Not established
Comments	The gene for $Ca_v1.1$ 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[14]

aa, amino acids; chr., chromosome; Bay K8644, methyl 1,4-dihydro-2,6-dimethyl-3-nitro-4-(2-trifluoromethylphenyl)-pyridine-5-carboxylate; FPL64176, methyl 2,5 dimethyl-4-[2-(phenylmethyl)benzoyl]-1*H*-pyrrole-3-carboxylate.

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TABLE 3
$Ca_V1.2$ channels

Channel name	$Ca_V1.2$
Description	Voltage-gated calcium channel α_1 subunit
Other names	α_{1C}, cardiac or smooth muscle L-type Ca^{2+} channel, cardiac or smooth muscle dihydropyridine receptor
Molecular information	Human: 2169aa, L29529 (cardiac; PMID: 8392192), 2138aa, Z34815 (fibroblast; PMID: 1316612); 2138aa, AF465484 (jejunum; PMID: 12176756); chr. 12p13.3, *CACNA1C*, LocusID: 775 Rat: 2169aa, M59786 (aortic smooth muscle; PMID: 2170396); 2140/2143aa, M67516/M67515 (brain; PMID: 1648941); chr. 4q42, Cacna1c, LocusID: 24239 Mouse: 2139aa, L01776 (brain; PMID: 1385406); chr. 6, Cacna1c, LocusID: 12288 (see 'Comments')
Associated subunits	$\alpha_2\delta$, β, γ[1,2]
Functional assays	Patch-clamp (whole-cell, single-channel), calcium imaging, cardiac or smooth muscle contraction hormone secretion
Current	$I_{Ca,L}$
Conductance	Ba^{2+} (25pS) > Sr^{2+} = Ca^{2+} (9pS)[3]
Ion selectivity	$Ca^{2+} > Sr^{2+} > Ba^{2+} \gg Mg^{2+}$ from permeability ratios
Activation	V_a = −17 mV (in 2 mM Ca^{2+}; HEK cells)[4]; −4 mV (in 15 mM Ba^{2+}; HEK cells) to −18.8 mV (in 5 mM Ba^{2+}; HEK cells and *Xenopus* oocytes)[5–7]; τ_a = 1 ms at +10 mV[5]
Inactivation	V_h = −50 to −60 mV (in 2 mM Ca^{2+}; HEK cells),[4] −18 to −42 mV (in 5–15 mM Ba^{2+}; HEK cells)[5,7,8,9]; τ_{fast} = 150 ms, τ_{slow} = 1100 ms; 61% inactivated after 250 ms in HEK cells[8] (at V_{max} in 15 mM Ba^{2+})[4]; ~70% inactivation after 1 s (at V_{max} in 2 mM Ca^{2+})[4]; inactivation is accelerated with Ca^{2+} as charge carrier (calcium-dependent inactivation: 86% inactivated after 250 ms[8,10])
Activators	BayK8644, dihydropyridine agonists, FPL64176[10,11]
Gating modifiers	Dihydropyridine antagonists (e.g., isradipine, IC_{50} = 7 nM at −60 mV; nimodipine, IC_{50} = 139 nM at −80 mV)[6,9]
Blockers	Nonselective: Cd^{2+} [12]; selective for $Ca_V1.x$: devapamil (IC_{50} = 50 nM in 10 mM Ba^{2+} at −60 mV) and other phenylalkylamines; diltiazem (IC_{50} = 33 μM in 10 mM Ba^{2+} at −60 mV and 0.05Hz)[12]
Radioligands	(+)-[^{3}H]isradipine (K_d < 0.1 nM) and other dihydropyridines; (−)-[^{3}H]devapamil (K_d = 2.5 nM), (+)-*cis*-[^{3}H]diltiazem (K_d = 50 nM)[11]
Channel distribution	Cardiac muscle, smooth muscle (including blood vessels, intestine, lung, uterus); endocrine cells (including pancreatic β-cells, pituitary); neurones[13]; subcellular localization: concentrated on granule-containing side of pancreatic β-cells[14]; neurons (preferentially somatodendritic)[15]
Physiological functions	Excitation-contraction coupling in cardiac or smooth muscle, action potential propagation in sinoatrial and atrioventricular node, synaptic plasticity, hormone (e.g., insulin) secretion[10,13,16,17]
Mutations and pathophysiology	Required for normal embryonic development (mouse, zebrafish)[18,19]; de novo G406R mutation in alternative exon 8A in 1 allele causes Timothy syndrome[20]
Pharmacological significance	Mediates cardiovascular effects of clinically used Ca^{2+} antagonists[17]; high concentrations of dihydropyridines exert antidepressant effects through $Ca_v1.2$ inhibition[17]
Comments	Tissue-specific splice variants exist—in addition to cardiac channels, smooth muscle and brain channels have been cloned[7,21,22]; the gene for $Ca_v1.2$ was first isolated and characterized in rabbit heart (2171aa, P15381, X15539)

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

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TABLE 4
$Ca_V1.3$ channels

Channel name	$Ca_V1.3$
Description	Voltage-gated calcium channel α_1 subunit
Other names	α_{1D}, "neuroendocrine" L-type Ca^{2+} channel
Molecular information	Human: 2161aa, M76558 (brain; PMID: 1309651); 2181aa, M83566 (pancreatic β-cells; PMID: 1309948); chr. 3p14.3, *CACNA1D*, LocusID: 776 Rat: 1646aa, M57682 (brain; PMID: 1648940); 2203aa, D38101 (pancreatic β-cells; PMID: 7760845); chr. 16p16, Cacna1d, LocusID: 29716 Mouse: 2144aa, AJ437291 (embryonic heart; PMID: 12900400); chr. 14, Cacna1d, LocusID: 12289 (see "Comments")
Associated subunits	Most likely at least α_2, β, and δ subunits
Functional assays	Patch-clamp (whole-cell, single-channel), calcium imaging
Current	$I_{Ca,L}$
Conductance	Not established
Ion selectivity	Not established
Activation	V_a = −15 to −20 mV (mouse cochlear hair cells; 10 mM Ba^{2+})[1,2]; −18 mV (in 15 mM Ba^{2+}; HEK cells) to −37 mV (5 mM Ba^{2+}; 2 mM Ca^{2+} HEK cells or *Xenopus* oocytes)[3,4]; $\tau_a < 1$ ms at +10 mV[3]
Inactivation	V_h = −36 to −43 mV[3,5]; τ_{fast} = 190 ms, τ_{slow} = 1700 ms (at V_{max} in HEK cells)[3]; calcium-induced inactivation is observed after expression in HEK cells[3] and in cochlear outer hair cells but not in inner hair cells[2]
Activators	BayK8644[1–5]
Gating modifiers	Dihydropyridine antagonists (e.g., isradipine, IC_{50} = 30 nM at −50 mV and 300 nM at −90 mV; nimodipine, IC_{50} = 3 μM at −80 mV)[3,4]
Blockers	Nonselective: Cd^{2+} [5]
Radioligands	(+)-[^{3}H]isradipine ($K_d < 0.5$ nM)[3]; in radioreceptor assays, HEK cell-expressed $Ca_v1.2$ and $Ca_v1.3$ channels bind (+)-[^{3}H]isradipine with indistinguishable K_D[3]; in functional experiments, however, $Ca_v1.2$ channels show higher DHP sensitivity—this discrepancy is explained by the slower inactivation of $Ca_v1.3$ decreasing the availability of inactivated channels for state-dependent DHP block
Channel distribution	Sensory cells (photoreceptors, cochlear hair cells[1,2]), endocrine cells (including pancreatic β-cells, pituitary, adrenal chromaffin cells, pinealocytes),[7–9] low density in heart (atrial muscle, sinoatrial and atrioventricular node)[1,7,10] and vascular smooth muscle[7]; neurones[6]; subcellular localization: on neurones 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,[1,10,12] mood behavior,[12] hormone secretion
Mutations and pathophysiology	Deafness, sinoatrial and atrioventricular node dysfunction,[1,10,12] no convincing evidence for contribution to pancreatic β-cell L-type currents and insulin secretion in mouse 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-cell and cochlear variants have been cloned; it is likely that $Ca_v1.3$ 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 $Ca_v1.2$ can also activate at more negative potentials

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

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TABLE 5
$Ca_V1.4$ channels

Channel name	$Ca_V1.4$
Description	Voltage-gated calcium channel α_1 subunit
Other names	α_{1F}
Molecular information	Human: 1966aa, AJ224874 (PMID: 9662399); chr. Xp11.23, *CACNA1F*, LocusID: 778 Rat: 1981aa, AF365975 (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 retinal neurons[1]
Functional assays	Patch-clamp (whole-cell, single-channel), calcium imaging
Current	$I_{Ca,L}$
Conductance	Preliminary evidence for very small single channel conductance (less than half of $Ca_v1.2$); $Ba^{2+} > Ca^{2+}$ [2,4,6]
Ion selectivity	Not established
Activation	$V_a = -2.5$ to -12 mV (2–20 mM Ca^{2+} or 15–20 mM Ba^{2+}; HEK cells)[3–6]; $\tau_a < 1$ ms at V_{max} (but slower components were also observed)[3,6]
Inactivation	$V_h = -9$ to -27 mV (10–20 mM Ba^{2+}, HEK cells)[4,6]; inactivation kinetics even slower than those of $Ca_v1.3$ with incomplete inactivation during 10-s depolarizations to V_{max}[3]; calcium-induced inactivation is not observed for $Ca_v1.4$ channels expressed in HEK cells[3,4,6] but after expression in *Xenopus* oocytes[2]
Activators	BayK8644[2–4,6]
Gating modifiers	Dihydropyridine antagonists: nifedipine (IC_{50} = 944 nM at -100 mV, ~300 nM at -50 mV[4]; isradipine: ~80% inhibition by 100 nM at -50 mV[3,6] and 1 μM at -90 mV)[3]; D-*cis*-diltiazem (IC_{50}=92 μM); verapamil: 69% inhibition at 100 μM (0.2 Hz, holding potential = -80 mV)[6]
Blockers	Nonselective: Cd^{2+} [2]
Radioligands	Unlike for $Ca_v1.2$ and $Ca_v1.3$, no high-affinity (+)-[^{3}H]isradipine binding detectable (HEK cells) (J. Striessnig, unpublished observations)
Channel distribution	Retinal photoreceptors and bipolar cells, spinal cord, lymphoid tissue (plasma and mast cells)[1,4,7–10]
Physiological functions	Neurotransmitter release in retinal cells
Mutations and pathophysiology	Mutations cause X-linked congenital stationary night blindness type 2[7,9,11,12]
Pharmacological significance	Not established
Comments	The biophysical properties of heterologously expressed $Ca_v1.4$ channels resemble those recorded in retinal neurons, suggesting that this channel type underlies retinal $I_{Ca,L}$—however, similar to $Ca_v1.4$, $Ca_v1.3$ 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.

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TABLE 6
$Ca_V2.1$ channels

Channel name	$Ca_V2.1$
Description	Voltage-gated calcium channel α_1 subunit
Other names	α_{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	$\alpha_2\delta$, β, possibly γ
Functional assays	Voltage-clamp, patch-clamp, calcium imaging, neurotransmitter release
Current	$I_{Ca,P}$, $I_{Ca,Q}$
Conductance	9, 14, 19pS (P-type, cerebellar Purkinje neurones)[4]; 16–17pS (for $\alpha_{1A}/\alpha_2\delta/\beta$ in *Xenopus* oocytes)[2,5,6]
Ion selectivity	$Ba^{2+} > Ca^{2+}$
Activation	$V_a = -5$ mV for native P-type, $V_a = -11$ mV for native Q-type (with 5 mM Ba^{2+} charge carrier)[7] $V_a = -4.1$ mV for rat $\alpha_{1A\text{-}a}/\alpha_2\delta/\beta_4$ $V_a = +2.1$ mV for rat $\alpha_{1A\text{-}b}/\alpha_2\delta/\beta_4$ (with 5 mM Ba^{2+} charge carrier)[6] $V_a = +9.5$ mV; $\tau_a = 2.2$ ms at +10 mV for human $\alpha_{1A\text{-}1}/\alpha_2\delta/\beta_{1b}$ in HEK293 cells (with 15 mM Ba^{2+} charge carrier)[3]
Inactivation	$V_h = -17.2$ mV for $\alpha_{1A\text{-}a}/\alpha_2\delta/\beta_4$; $V_h = -1.6$ mV for $\alpha_{1A\text{-}b}/\alpha_2\delta/\beta_4$ (with 5 mM Ba^{2+} charge carrier); $V_h = -17$ mV, $\tau_h = 690$ ms at +10 mV human $\alpha_{1A\text{-}1}/\alpha_2\delta/\beta_{1b}$ in HEK293 cells (with 15 mM Ba^{2+} charge carrier)[3]; $\tau_h > 1$ s at 0 mV native P-type (with 5 mM Ba^{2+} charge carrier)[7] (see "Comments")
Activators	None
Gating modifiers	ω-agatoxin IVA (P-type $K_d = 1$–3 nM[8]; Q-type $K_d \sim 100$–200 nM[5,9]), ω-agatoxin IVB[6]
Blockers	ω-conotoxin MVIIC[8]; other blockers include piperidines, substituted diphenylbutylpiperidines, piperazines, volatile anesthetics, gabapentin, mibefradil, and peptide toxins DW13.3 and ω-conotoxin SVIB[21–26] (see "Comments")
Radioligands	[^{125}I]ω-conotoxin MVIIC
Channel distribution	Neurons (presynaptic terminals, dendrites, some cell bodies), heart, pancreas, pituitary
Physiological functions	Neurotransmitter release in central neurons and neuromuscular junction; excitation-secretion coupling in pancreatic β-cells
Mutations and pathophysiology	Missense mutations in IS4-IS5, IIS4-IIS6, IIIS4-IIIS6, and IVS4-IVS6 cause FHM[27]; a common feature among FHM mutations is an apparent gain-of-function phenotype as a result of a shift in V_{50act} to more hyperpolarized potentials (an increased probability of opening at the single channel level)[28,29]; other effects include a decrease in maximal current density at the whole-cell level and alterations of synaptic transmission[28–31]; point mutations in IIS1, IIS6-IIIS2, IIIS5-IIIS6, and IVS1-IVS5 cause episodic ataxia type-2, a polyglutamine expansion in the carboxyl region causes spinocerebellar ataxia type-6, and mutation of IS5-IS6 and IVS6 causes episodic and progressive ataxia[10–12,27]
Pharmacological significance	Peptide toxins that selectively inhibit $Ca_V2.1$ channel block a significant portion of neurotransmission in the mammalian CNS[13]; block of $Ca_V2.1$ channels inhibits the late-phase formalin response and inflammatory pain but has no significant effect on mechanical allodynia or thermal hyperalgesia[14–17]; mice lacking a functional $Ca_V2.1$ gene exhibit cerebellar atrophy, severe muscle spasms, and ataxia and usually die by 3 to 4 weeks postnatal[18,19]
Comments	Rates of inactivation and V_h are differentially affected by coexpression with β_{1b}, β_{2a}, β_3, or β_4 subunits, as well as by alternative splicing of the α_{1A} subunit; identified regions of alternative splicing include the domain I-II linker, domain II-III linker, IVS3-IVS4, and the carboxyl terminus[1,2,6,32–34]; whole-cell currents with P-type kinetics seem to be conducted by the $\alpha_{1A\text{-}b}$ splice variant coexpressed with any of the β subunits or by the $\alpha_{1A\text{-}a}$ splice variant coexpressed with the β_{2a} subunit[6,7,20]; whole-cell currents with Q-type kinetics seem to be encoded by $\alpha_{1A\text{-}a}$ coexpressed with any of the β_{1b}, β_3, or β_4 subunits[6,20]; whole-cell currents with Q-type pharmacology seem to be encoded by α_{1A} splice variants containing Asp Pro residues in the domain IV S3-S4 linker, whereas whole-cell currents with P-type pharmacology seem to be conducted by α_{1A} splice variants missing Asp Pro residues in IV S3-S4 linker[3,6]; 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[26,32,36]

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

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TABLE 7
$Ca_V2.2$ channels

Channel name	$Ca_V2.2$
Description	Voltage-gated calcium channel α_1 subunit
Other names	N-type, α_{1B}; rbB-I, rbB-II (in rat),[1,2] BIII (in rabbit)[3]
Molecular information	Human: 2339aa, M94172, 2237aa, M94173,[4] chr. 9q34, *CACN1B* Rat: 2336aa, M92905[1] Mouse: 2329aa, NM007579, NP031605
Associated subunits	$\alpha_2\delta/\beta_1$, β_3, β_4,[5] possibly γ
Functional assays	Voltage-clamp, patch-clamp, calcium imaging, neurotransmitter release, ^{45}Ca uptake into synaptosomes
Current	$I_{Ca,N}$
Conductance	20pS (bullfrog sympathetic neurones)[6]; 14.3pS (rabbit BIII cDNA in skeletal muscle myotubes)[3]
Ion selectivity	$Ba^{2+} > Ca^{2+}$
Activation	V_a = +7.8 mV, τ_a = 3 ms at +10 mV (human $\alpha_{1B}/\alpha_2\delta/\beta_{1-3}$ in HEK293 cells, 15 mM Ba^{2+} charge carrier)[4,7]; V_a = +9.7 mV, τ_a = 2.8 ms at +20 mV (rat $\alpha_{1B\text{-}II}/\beta_{1b}$, in *Xenopus* oocytes, 40 mM Ba^{2+} charge carrier)[2]
Inactivation	V_h = −61 mV, τ_h ~200 ms at +10 mV (human $\alpha_{1B}/\alpha_2\delta/\beta_{1-3}$ in HEK293 cells, 15 mM Ba^{2+} charge carrier)[4,7]; V_h = −67.5 mV; τ_h = 112 ms at +20 mV (rat $\alpha_{1B\text{-}II}/\beta_{1b}$ in *Xenopus* oocytes, 40 mM Ba^{2+})[2]
Activators	None
Gating modifiers	None
Blockers	ω-conotoxin GVIA (1–2 μM, irreversible block), ω-conotoxin MVIIA (SNX-111, Ziconotide/Prialt), ω-conotoxin MVIIC[8]; other blockers include piperidines, substituted diphenylbutylpiperidines, long alkyl chain molecules, aliphatic monoamines, tetrandine, gabapentin, peptidylamines, volatile anesthetics, the peptide toxins SNX-325 and DW13.3, as well as the ω-conotoxins SVIA, SVIB, and CVID[20–34]
Radioligands	[^{125}I]ω-conotoxin GVIA (K_d = 55 pM, human $\alpha_{1B}/\alpha_2\delta/\beta_{1-3}$ in HEK293 cells)[4]
Channel distribution	Neurons (presynaptic terminals, dendrites, cell bodies)[9]
Physiological functions	Neurotransmitter release in central and sympathetic neurons[10]; sympathetic regulation of the circulatory system[11,35]; activity and vigilance state control[36]; sensation and transmission of pain (see "Pharmacological significance" and "Comments")
Mutations and pathophysiology	Differing reports exist: mice lacking a functional $Ca_V2.2$ gene exhibit a normal life span and no detectable behavioral modifications compared with wild type but possess an increase in basal mean atrial pressure and other functional alterations to the sympathetic nervous system[11]—however, in a different study, approximately 1/3 of the mice lacking a functional $Ca_V2.2$ 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 $Ca_V2.2$. gene have been reported to date
Pharmacological significance	In rats, intrathecal administration of ω-conotoxin GVIA or ω-conotoxin MVIIA shows strong effects on inflammatory pain, postsurgical pain, thermal hyperalgesia, and mechanical allodynia[13–15]; in humans, intrathecal administration of SNX-111 (Ziconotide/Prialt, synthetic ω-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[16]
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[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[1–4,37–39]; 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[43–45]

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

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TABLE 8
$Ca_V2.3$ channels

Channel name	$Ca_V2.3$
Description	Voltage-gated calcium channel α_1 subunit
Other names	R-type, α_{1E}; rbE-II (in rat)[1]; BII-1, BII-2 (in rabbit)[2]
Molecular information	Human: 2251aa, L29384, 2270aa, L29385,[3] chr0.1q25-q31, *CACNA1E* Rat: 2222aa,[1] GenBank accession no. L15453 Mouse: 2272aa, Q61290
Associated subunits	$\alpha_2\delta/\beta$, possibly γ
Functional assays	Voltage-clamp, patch-clamp, calcium imaging, neurotransmitter release
Current	$I_{Ca,R}$
Conductance	Not established
Ion selectivity	$Ba^{2+} \sim Ca^{2+}$ (rat)[4]; $Ba^{2+} > Ca^{2+}$ (human)[3]
Activation	V_a = +3.5 mV, τ_a = 1.3 ms at 0 mV (human $\alpha_{1E}/\alpha_2\delta/\beta_{1-3}$, 15 mM Ba^{2+} charge carrier in HEK293 cells)[3] V_a = −29.1 mV, τ_a = 2.1 ms at −10 mV (rat $\alpha_{1E}/\alpha_2\delta/\beta_{1b}$, 4 mM Ba^{2+} charge carrier in *Xenopus* oocytes)[1]
Inactivation	V_h = −71 mV, τ_h = 74 ms at 0 mV (human $\alpha_{1E}/\alpha_2\delta/\beta_{1-3}$, 15 mM Ba^{2+} charge carrier in HEK293 cells)[3]; V_h = −78.1 mV, τ_h = 100 ms at −10 mV (rat $\alpha_{1E}/\alpha_2\delta/\beta_{1b}$, 4 mM Ba^{2+} charge carrier in *Xenopus* oocytes)[1]
Activators	None
Gating modifiers	None
Blockers	SNX-482, Ni^{2+} (IC_{50} = 27 μM), Cd^{2+} (IC_{50} = 0.8 μM), mibefradil (IC_{50} = 0.4 μM),[10] volatile anesthetics[11]
Radioligands	None
Channel distribution	Neurons (cell bodies, dendrites, some presynaptic terminals), heart, testes, pituitary
Physiological functions	Neurotransmitter release, repetitive firing, long-term potentiation, post-tetanic potentiation, neurosecretion[12–14]
Mutations and pathophysiology	No point mutations in the native $Ca_v2.3$ gene have been reported; mice deficient for the $Ca_v2.3$ gene retain a substantial cerebellar R-type current,[5] suggesting that R-type currents actually reflect a heterogeneous mixture of channels; homozygous $Ca_v2.3$-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 $Ca_v2.3$ calcium channel in transmitting and/or the development of somatic inflammatory pain[6]
Pharmacological significance	See "Comments"
Comments	$Ca_v2.3$ has been variously reported to encode a novel type of calcium channel with properties shared between both low- and high-threshold calcium channels[1,4] or a type of high-threshold channel resistant to DHPs, ω-agatoxin-IVA, and ω-conotoxin-GVIA and called R-type (for "residual")[7] The tarantula toxin SNX-482 blocks exogenously expressed $Ca_v2.3$ currents[8] but is only partially effective on native cerebellar R-type currents,[9] suggesting that $Ca_v2.3$ does not always conduct a significant portion of the R-type current as originally defined[7]; identified regions of alternative splicing include the domain II-III linker and carboxyl terminus and have been shown to affect channel kinetics and Ca^{2+}-dependent stimulation[1–3,15,16]

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

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TABLE 9
$Ca_V3.1$ channels

Channel name	$Ca_v3.1$
Description	Voltage-gated calcium channel α_1 subunit
Other names	T-type, $\alpha_1 3.1$, α_{1G}
Molecular information	Human: 2377aa, O43497, NM_018896, chr. 17q22, *CACNA1G*[1] Rat: 2254aa, O54898, AF027984 Mouse: 2288aa, CAI25956, NM_009783 (see "Comments")
Associated subunits	No biochemical evidence, small changes induced by $\alpha_2\delta_1$[2] and $\alpha_2\delta_2$[3,4]
Functional assays	Voltage-clamp, calcium imaging
Current	$I_{Ca,T}$
Conductance	7.5pS[1]
Ion selectivity	$Sr^{2+} > Ba^{2+} = Ca^{2+}$
Activation	$V_a = -46$ mV, $\tau_a = 1$ ms at -10 mV[5,6]
Inactivation	$V_h = -73$ mV, $\tau_h = 11$ ms at -10 mV[5,6]
Activators	Not established
Gating modifiers	Kurtoxin, $IC_{50} = 15$ nM[7]
Blockers	No subtype-specific blocker[8]; selective for $Ca_v3.x$ relative to $Ca_v1.x$ and $Ca_v2.x$: mibefradil,[9,10] U92032,[11] penfluridol and pimozide[12]; nonselective: nickel ($IC_{50} = 250$ μM),[13] amiloride[14]
Radioligands	None
Channel distribution	Brain, especially soma and dendrites of neurons in olfactory bulb, amygdala, cerebral cortex, hippocampus, thalamus, hypothalamus, cerebellum, brain stem (human RNA blots,[1,5] rat in situ hybridization[15] and immunocytochemistry[16]); ovary, placenta, heart (especially sinoatrial node; mouse in situ hybridization[17])
Physiological functions	Thalamic oscillations[18]
Mutations and pathophysiology	Not established
Pharmacological significance	May mediate effect of absence antiepileptic drugs such as ethosuximide[19] and other thalamocortical dysrhythmias[20]
Comments	Splice variants that differ in their voltage dependence have been cloned[5]

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

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TABLE 10
$Ca_V3.2$ channels

Channel name	$Ca_v3.2$
Description	Voltage-gated calcium channel α_1 subunit
Other names	T-type, $\alpha_1 3.2$, α_{1H}
Molecular information	Human: 2353aa, O95180, AF051946, chr0.16p13.3, *CACNA1H*[1] Rat: 2359aa, AAG35187, AF290213 Mouse: 2365aa, NP_067390, NM_021415
Associated subunits	Not established
Functional assays	Voltage-clamp, calcium imaging
Current	$I_{Ca,T}$
Conductance	9pS[2]
Ion selectivity	$Ba^{2+} = Ca^{2+}$
Activation	$V_a = -46$ mV, $\tau_a = 2$ ms at -10 mV[3]
Inactivation	$V_h = -72$ mV, $\tau_h = 16$ ms at -10 mV[3]
Activators	None
Gating modifiers	Kurtoxin[4]
Blockers	$Ca_v3.2$ is more sensitive than $Ca_v3.1$ to block by nickel ($IC_{50} = 12$ μM)[5] and possibly phenytoin[6] and amiloride[2,7]; selective for $Ca_v3.x$ relative to $Ca_v1.x$ and $Ca_v2.x$: mibefradil,[8,9] U92032,[10] penfluridol and pimozide,[11] and amiloride[12]; nonselective: nimodipine,[2] anesthetics[5]
Radioligands	None
Channel distribution	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])
Physiological functions	Smooth muscle contraction,[17] smooth muscle proliferation,[18] aldosterone secretion,[19] cortisol secretion[20]
Mutations and pathophysiology	Single nucleotide polymorphisms associated with childhood absence epilepsy patients in a Chinese population[21]
Pharmacological significance	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]
Comments	Splice variation found in the linker connecting repeat 3 and 4[25]

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

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TABLE 11
$Ca_V3.3$ channels

Channel name	$Ca_v3.3$
Description	Voltage-gated calcium channel α_1 subunit
Other names	T-type, $\alpha_1 3.3$, α_{1I}
Molecular information	Human: 2251aa, AAM67414, AF393329, chr. 22q13.1, *CACNA1I* [1] Rat: 1835aa, AF086827, AAD17796 Mouse 2753aa: XP_139476, XM_139476
Associated subunits	No biochemical evidence, small changes induced by γ_2[2]
Functional assays	Voltage-clamp, calcium imaging
Current	$I_{Ca,T}$
Conductance	11pS[1]
Ion selectivity	$Ba^{2+} = Ca^{2+}$
Activation	$V_a = -44$ mV, $\tau_a = 7$ ms at -10 mV[4]
Inactivation	$V_h = -72$ mV, $\tau_h = 69$ ms at -10 mV[4]
Activators	Not established
Gating modifiers	None
Blockers	No subtype-specific blocker[5]; selective for $Ca_v3.x$ relative to $Ca_v1.x$ and $Ca_v2.x$: mibefradil,[6,7] U92032,[8] penfluridol,[9] pimozide[9]; nonselective: nickel ($IC_{50} = 216\ \mu M$)[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]

aa, amino acids; chr., chromosome.

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