

Calcium Channels

Key References

- Arikathe, J. and Campbell, K.P., Auxiliary subunits: essential components of the voltage-gated calcium channel complex., *Curr. Opin. Neurobiol.*, **13**, 298-307 (2003).
- Ertel, E.A., et al., Nomenclature of voltage-gated calcium channels., *Neuron*, **25**, 533-535 (2000).
- Jaggannathan, S., et al., Voltage-operated calcium channels in male germ cells., *Reproduction*, **123**, 203-215 (2002).
- Kochegarov, A.A., Pharmacological modulators of voltage-gated calcium channels and their therapeutic application., *Cell Calcium*, **33**, 145-162 (2003).
- Lorenzon, N.M. and Beam, K.G., Calcium channelopathies., *Kidney Int.*, **57**, 794-802 (2000).
- McDonough, S.I., Editor., Calcium Channel Pharmacology., Kluwer Academic/Plenum, New York (2004).
- Miljanich, G.P. and Ramachandran, J., Antagonists of neuronal calcium channels: Structure, function and therapeutic implications., *Annu. Rev. Pharmacol. Toxicol.*, **35**, 707-734 (1995).
- Ophoff, R.A., et al., Genetics and pathology of voltage-gated Ca²⁺ channels., *Histol. Pathol.*, **13**, 827-836 (1998).
- Perez-Reyes, E., Molecular physiology of low-voltage-activated T-type calcium channels., *Physiol. Rev.*, **83**, 117-161 (2003).
- Scott, R.H., et al., Cellular actions of gabapentin and related compounds on cultured sensory neurons., *Current Neuropharmacol.*, **1**, 219-235 (2003).
- Shorofsky, S.R. and Balke, C., Calcium currents and arrhythmias: Insights from molecular biology., *Am. J. Med.*, **110**, 127-140 (2001).
- Triggle, D.J., et al., Calcium channel ligands: structure-function relationship of the 1,4-dihydropyridines., *Med. Res. Revs.*, **9**, 123-180 (1989).

Overview

The voltage-gated calcium channels constitute one group of a superfamily of ion channels that also includes sodium and potassium channels and among which exists functional, sequence and topological similarities. These channels provide a major route of calcium translocation across the plasma membranes of excitable cells and serve to support multiple functions, including muscle contraction, hormone and neurotransmitter release, cell motility, cell growth and regulation, cell damage and death and finally cell survival.

There are at least six classes of voltage-gated calcium channels that are differentially distributed according to cell type and location and that may be distinguished by electrophysiological, pharmacological and structural characteristics. Several therapeutically effective drugs, including verapamil, nifedipine, diltiazem and second-generation 1,4-dihydropyridine analogs of nifedipine, interact at the L-type channel and are widely used in the treatment of hypertension and certain cardiovascular disorders.

The voltage-gated calcium channel is a hetero-multimer being composed of α_1 , α_2 - δ , and β subunits and, for skeletal muscle, the γ subunit. The α_1 subunit is the major functional unit of the channel, expressing the permeation and gating functions and, at least in the case of the L-type channels, the drug binding sites. However, the other subunits, notably the β subunit, have significant impact on the expression and electrophysiological characteristics of the channel. Additionally, the α_2 - δ subunit may also be involved in drug binding, notably for gabapentin. There are 10 α_1 subunits (Ca_v1.1-1.4, formerly α_{1S} , α_{1C} , α_{1D} and α_{1F} ; Ca_v2.1-2.3, formerly α_{1A} , α_{1B} and α_{1E} ; Ca_v3.1-3.3, formerly α_{1G} , α_{1H} and α_{1I}) and four β

subunits (β_1 - β_4) known with splice variants of each. The α_1 subunits are large membrane proteins composed of four homologous domains, I-IV, with each domain composed of six transmembrane helices and a pore region between helices five and six. The S4 segments contain specific arrays of positive charges that are assigned to a voltage-sensing function. The Ca_v1.2-1.4 genes code for the α -subunits of the L-type channels of the cardiac and neuronal/endocrine types and Ca_v1.1 codes for the L-type channels of skeletal muscle. The Ca_v2.1-2.3 genes code for the N-, P/Q and R-type channels. The functional properties and expression of the α subunits are substantially modified by the presence of β subunits. It is likely that channel subclasses are produced by α - β subunit interactions as well as by splice variations. The Ca_v3.1-3.3 subunits code for the T-type channel, the most recently cloned channel.

Although electrophysiological differences do exist between the channel classes, the most obvious distinctions are between the T- and the other types. T-type channels need only small depolarizations to be activated and are known as low-voltage-activated (LVA) and they deactivate slowly. In contrast, the other classes all require larger depolarizations to be activated and are known as high-voltage-activated (HVA) channels. Although there are electrophysiological distinctions among the HVA channels, they are not sufficiently precise as to permit unambiguous differentiation solely by these criteria. Additionally, it is likely that subclasses of each of these channel types exist with different biophysical properties. At present, pharmacological differentiation is the best route for differentiating the HVA channels.

The L-type channels are well characterized by small synthetic ligands – verapamil, nife-

dipine and diltiazem – and the T-type channel is described as preferentially blocked by mibefradil, a structurally distinct entity that was in clinical use albeit it was recently withdrawn. All of these entities interact with their channel targets in a voltage-dependent manner, with the greater affinity being exhibited for the open and inactivated states of the channel. The N-, P- and Q-type channels are sensitive to peptide toxins from molluscs and spiders, including the conotoxins and the agatoxins. The conotoxins GVIA and MVIIA interact with the N-type channels with nanomolar potencies; MVIIIC interacts with both N and P/Q types and agatoxin IVA interacts selectively with the P/Q types of channel. No small organic ligands are clinically available for other than the L-type channel, although there are a number of experimental compounds for the T- and N-type channels.

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TYPES OF CURRENT	L	T	N	P	Q	R
CALCIUM CHANNELS	Ca _v 1.1 – 1.4	Ca _v 3.1 – 3.3	← Ca _v 2.1-2.3 →			
CONDUCTANCE, pS^a	~25	~8	~10-20	~9-19	16	—
ACTIVATION THRESHOLD	High	Low	High	High	High	High
DEACTIVATION RATE	Fast	Slow	Fast	Fast	Fast	Fast
INACTIVATION RATE	Slow	Fast	Moderate	Very slow	Moderate	Fast
PERMEATION	Ba ²⁺ > Ca ²⁺	Ba ²⁺ = Ca ²⁺	Ba ²⁺ > Ca ²⁺	Ba ²⁺ > Ca ²⁺	Ba ²⁺ > Ca ²⁺	Ba ²⁺ = Ca ²⁺
FUNCTION	E-C coupling CV system, smooth muscle, gene expression endocrine cells, neurotrans. release (eye and ear)	Cardiac sino atrial node spiking, repetitive activity in neurons and endocrine cells, smooth muscle	Neuronal only	← Neurotransmitter release →		Neuronal
PHARMACOLOGY^b						
1,4-Dihydropyridines [activators/antagonists] (e.g. Bay K 8644 (B133) /Nimodipine (N149))	Sensitive	Insensitive	Insensitive	Insensitive	Insensitive	Insensitive
Phenylalkylamines (e.g. Verapamil (V4629))	Sensitive	Insensitive	Insensitive	Insensitive	Not known	Insensitive
Benzothiazepines (e.g. Diltiazem (D2521))	Sensitive	Insensitive	Insensitive	Insensitive	Not known	Insensitive
Benzimidazoles (e.g. Mibefradil (M5441))	Insensitive	Sensitive (not selective) ^c	Not known	Not known	Not known	Not known
ω-Conotoxin GVIA (C9915)	Insensitive	Insensitive	Sensitive	Insensitive	Insensitive	Insensitive
ω-Conotoxin MVIIc (C4188)	Insensitive	Insensitive	Sensitive	Sensitive	Sensitive	Insensitive
ω-Agatoxin IVA (A6719)	Insensitive	Insensitive	Sensitive	Sensitive	Sensitive	Insensitive
ω-Agatoxin IIIA	Sensitive	Insensitive	Sensitive	Sensitive	Sensitive	Sensitive
Calciseptine	Sensitive (not skeletal muscle)	Insensitive	Insensitive	Insensitive	Insensitive	Insensitive
Calcicludine (C2836)	Sensitive (not skeletal muscle)	Sensitive	Sensitive	Sensitive	Sensitive	Sensitive
Cd ²⁺ block	Potent	Weak	Potent	Potent	Potent	Potent
Ni ²⁺ block	Weak	Potent	Weak	Intermediate	Potent	Potent
RADIOLIGANDS OF CHOICE	[³ H]-cis-(+)-Diltiazem [³ H]-Desmethoxyverapamil [³ H]-PN 200-110 (Isradipine)	Not known	[¹²⁵ I]-ω-Conotoxin MVIIa [¹²⁵ I]-ω-Conotoxin GVIA [¹²⁵ I]-ω-Conotoxin MVIIc	Not known	Not known	Not known
TISSUE EXPRESSION	Widespread: CV system, neurons, endocrine, sk. muscle	Neurons, sm. muscle, sa node	Neurons	Neurons	Neurons	Neurons
DISEASE RELEVANCE	Hypertension, angina, cardiac arrhythmias, malignancy, hyperthermia, hypokalemic periodic paralysis	Arrhythmias, epilepsy, fertility?	Pain	Migraine? Epilepsy	Migraine? Epilepsy	Diabetes?

FOOTNOTES

a ~100 mM Ba²⁺ as charge carrier.

b Sensitive refers to concentrations < 1 μM; insensitive refers to concentrations > 1 μM.

c Mibefradil is not very selective for T-type currents; ethosuximide and congeners may be more selective, although of lower affinity.