

Calcium Channels

Key References

- Bergsman, J.B. et al. "Classification and function of voltage-gated calcium channels." *Handbook of Experimental Pharmacology, Vol 147, Pharmacology of Ionic Channel Function: Activators and Inhibitors*, pp. 55-85, Springer-Verlag, Berlin Heidelberg (2000).
- De Waard, M. et al. "Structural and functional diversity of voltage-activated calcium channels." in *Ion Channels*, Volume 4 (T. Narahashi, Ed.), pp. 41-87, Plenum Press, NY (1996).
- Ertel, E.A. et al. "Nomenclature of voltage-gated calcium channels." *Neuron* **25**, 533-535 (2000).
- Ertel, S.I. et al. "T-type calcium channels and pharmacological blockade: Potential pathophysiological relevance." *Cardiovas. Drugs Therap.* **11**, 723-739 (1997).
- Lorenzon, N.M., Beam, K.G. "Calcium Channelopathies." *Kidney Int.* **57**, 794-802 (2000).
- Miljanich, G.P., 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).
- Randall, A.D. "The molecular basis of voltage-gated Ca²⁺ channel diversity: Is it time for T?" *J. Memb. Biol.* **161**, 207-213 (1998).
- Shorofsky, S.R., Balke, C.W. "Calcium currents and arrhythmias: Insights from molecular biology." *Am. J. Med.* **110**, 127-140 (2001).
- Striessnig, J. et al. "Structural basis of drug binding to L-type Ca²⁺ channels." *Trends Pharmacol. Sci.* **19**, 108-115 (1998).
- Triggle, D.J. "The pharmacology of ion channels: With particular reference to voltage-gated Ca²⁺ channels." *Eur. J. Pharmacol.* **375**, 311-325 (1999).
- Triggle, D.J. et al. "Ca²⁺ 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 amongst which exists functional, sequence and topological similarities. These channels are 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. 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_{1-4}) 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, nifedipine 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.

Calcium Channels

TYPES	L	T	N	P	Q	R
α-SUBUNIT NOMENCLATURE	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, endocrine cells, some neurons	Cardiac sino atrial node spiking, repetitive activity in neurons and endocrine cells, smooth muscle	Neuronal only	Neuronal only	Neuronal	Neuronal
			←————— Neurotransmitter release —————→			
PHARMACOLOGY^b						
1,4-Dihydropyridines [activators/antagonists] (e.g. Bay K 8644 (B-133) /Nimodipine (N-149))	Sensitive	Insensitive	Insensitive	Insensitive	Insensitive	Insensitive
Phenylalkylamines (e.g. Verapamil (V 4629))	Sensitive	Insensitive	Insensitive	Insensitive	—	Insensitive
Benzothiazepines (e.g. Diltiazem (D 2521))	Sensitive	Insensitive	Insensitive	Insensitive	—	Insensitive
Benzimidazoles (e.g. Mibefradil (M 5441))	Insensitive	Sensitive	—	—	—	—
ω-Conotoxin GVIA (C 9915) ω-Conotoxin MVIIC (C 4188)	Insensitive Insensitive	Insensitive Insensitive	Sensitive Sensitive	Insensitive Sensitive	Insensitive Sensitive	Insensitive Insensitive
ω-Agatoxin IVA (A 6719) ω-Agatoxin IIIA	Insensitive Sensitive	Insensitive Insensitive	Insensitive Sensitive	Sensitive Insensitive	Sensitive Sensitive	Insensitive Sensitive
Calciseptine	Sensitive (not skeletal muscle)	Insensitive	Insensitive	Insensitive	Insensitive	Insensitive
Calcicludine (C 2836)	Sensitive (not skeletal muscle)	Sensitive	Sensitive	Sensitive	Sensitive	Sensitive
Cd ²⁺ block Ni ²⁺ block	Potent Weak	Weak Potent	Potent Weak	Potent Intermediate	Potent	Potent Potent
RADIOLIGANDS OF CHOICE	[³ H]- <i>cis</i> -(+)-Diltiazem [³ H]-Desmethoxyverapamil [³ H]-PN 200-110 (Isradipine)	—	[¹²⁵ I]-ω-Conotoxin MVIIA [¹²⁵ I]-ω-Conotoxin GVIIA [¹²⁵ I]-ω-Conotoxin MVIIC	—	—	—

FOOTNOTES

a ~100 mM Ba²⁺ as charge carrier.

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