

## Calcium Channels – An Overview

EMILIO CARBONE

Department of Neuroscience, NIS Center of Excellence, CNISM Research Unit, Torino, Italy

### Definition

► **Voltage-gated  $\text{Ca}^{2+}$  channels** are integral membrane proteins forming aqueous pores which open in response to cell depolarization.  $\text{Ca}^{2+}$  channels play a key role in controlling vital functions: they shape the ► **action potential** and membrane electrical oscillations and act as gate-controller of  $\text{Ca}^{2+}$ , the most ubiquitous ► **second messenger** [1]. As such,  $\text{Ca}^{2+}$  channels are implicated in cardiac, skeletal and smooth ► **muscle contraction** (► **excitation-contraction coupling**), ► **hormone** and neurotransmitter release (► **excitation-secretion coupling**) and  $\text{Ca}^{2+}$ -dependent processes that modulate short- and long-term cell activity and gene expression (► **excitation-transcription coupling**) [2–5].

### Characteristics

$\text{Ca}^{2+}$  channels have been grouped into two main classes, based on their threshold of activation: the ► **high voltage-activated (HVA) channels** and the ► **low voltage-activated (LVA) channels** [4]; although this classification could not be strictly applied since some of the HVA channels activate at significantly low voltages [2]. LVA channels activate “► **transiently**” during small depolarizations near ► **resting membrane potentials** (→ ► **Membrane potential – basics**) and are therefore commonly indicated as T-type channels. T-type channels are responsible for ► **low-threshold spikes**, oscillatory cell activity, muscle contraction, hormone release, cell growth, differentiation and proliferation [5]. The HVA channels require larger membrane depolarizations to open and are further subdivided into four types (► **L-, N-, P/Q- and R-type  $\text{Ca}^{2+}$  channels**) based on their structural, pharmacological and biophysical characteristics [2,3]. They are responsible for the sustained depolarizing phase of action potentials, muscle contraction, hormone and neurotransmitter release, gene expression and cell differentiation.

### Molecular Structure

The principal pore-forming subunit of both LVA and HVA channels is the  $\alpha_1$ -subunit, a high-molecular weight protein (190–250 kDa), which is structurally similar to the ►  **$\text{Na}^+$  channel  $\alpha$ -subunit** [1]. It is formed by four domains (I–IV) linked together in a single polypeptide chain and each domain contains six putative transmembrane segments (S1–S6), plus a loop (P) that dips partially into the pore to form the pore-lining region (Fig. 1). The cytoplasmic loops

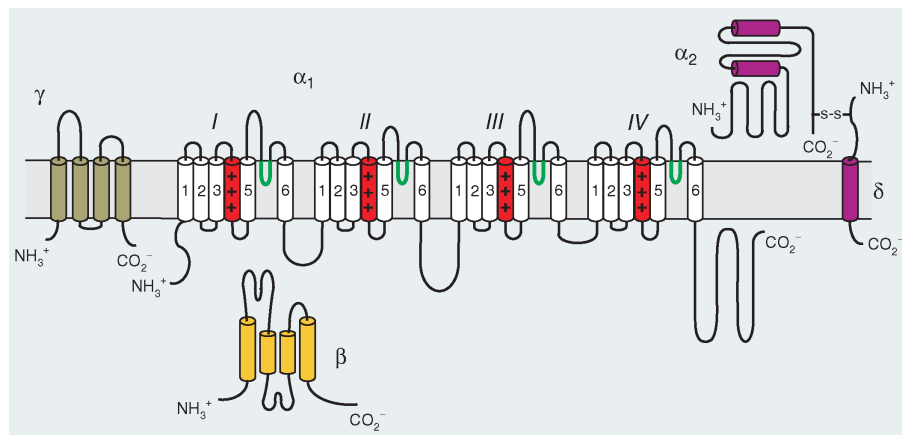
linking the four domains are structurally important for their interactions with  $\beta$ -subunits, second messengers, membrane binding proteins and channel ► **gating**.

Molecular cloning of  $\text{Ca}^{2+}$  channels has provided evidence for the existence of ten different pore-forming  $\alpha_1$  subunits with pharmacological and biophysical profiles similar to the endogenous  $\text{Ca}^{2+}$  channels expressed in most tissues. Alignment of their amino acid sequences suggests strong homologies and divergences between the various  $\text{Ca}^{2+}$  channel types (Fig. 2). Strong homologies exist between the four L-types (Cav1), the N-, P/Q- and R-type ( $\text{Ca}_v2$ ), and the three T-type ( $\text{Ca}_v3$ ) channels, while large divergences exist between the HVA and LVA subfamilies. Figure 2 reports the  $\text{Ca}^{2+}$  channel classifications most used in the literature [2,3].

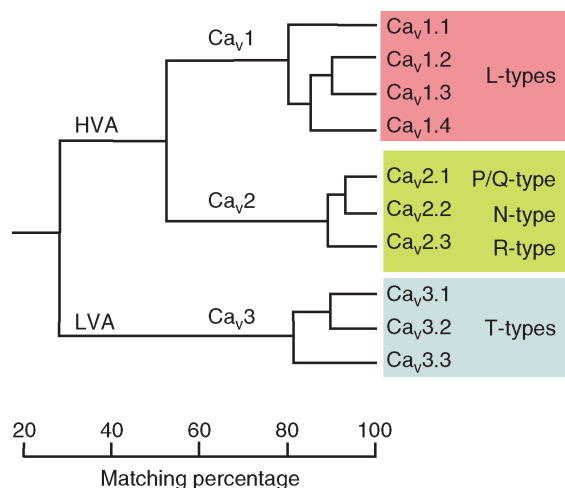
At variance with the T-type channels, whose  $\alpha_1$ -subunit is sufficient to warrant ► **activation** and ► **inactivation gating**, channel expression and membrane incorporation, the HVA channels are heteromultimeric protein complexes which comprise the  $\alpha_1$ -subunit in association with auxiliary  $\beta$ ,  $\alpha_2\text{-}\delta$  and  $\gamma$ -subunits (Fig. 3). Coexpression of  $\alpha_2\text{-}\delta$  with the  $\alpha_1$ -subunit ensures proper  $\text{Ca}^{2+}$  current kinetics and current densities. The same occurs with the co-expression of  $\beta$  and  $\alpha_1$ -subunits. Still vague is the role of  $\gamma$ -subunits ( $\gamma_1$  to  $\gamma_8$ ) which consist of four transmembrane domains and whose site of interaction with the  $\alpha_1$ -subunit is still unknown. The  $\alpha_2\text{-}\delta$ -subunit is formed by a membrane-spanning  $\delta$ -peptide (27 kDa) and an extracellular  $\alpha_2$ -peptide (143 kDa) bound together by a disulfide bridge (Fig. 1). Presently, four genes encoding for different  $\alpha_2\text{-}\delta$ -subunits ( $\alpha_2\text{-}\delta_1$  to  $\alpha_2\text{-}\delta_4$ ) have been identified with several additional splice variants. The up-regulation of the  $\alpha_2\text{-}\delta$  gene appears to correlate with the onset of ► **allodynia** (non-noxious stimuli eliciting pain) and ligands that target the  $\alpha_2\text{-}\delta$ -subunit, the gabapentins, are used for treatment of neuropathic pain. The four  $\beta$ -subunits ( $\beta_1$  to  $\beta_4$ ) and their splice variants so far identified are almost exclusively cytosolic. They possess a hydrophobic region containing SH3 and guanylate kinase domains, indicating that they belong to the membrane-associated guanylate kinase (MAGUK) family and as such may integrate multiple signaling pathways near the channel. The  $\beta$ -subunit has high-affinity for a conserved region within the domain I-II region of N- and PQ-type channels, termed the *alpha interaction domain* (AID).

### Activation-Inactivation Gating

As for other voltage-gated ion channels, the probability of  $\text{Ca}^{2+}$  channels opening is strictly voltage-dependent, i.e., the switch from a closed (non-conductive) to an open (conductive) configuration is strictly dependent on voltage, usually requiring 4–8 mV to change e-fold the probability of channel opening [6]. Structure-function



**Calcium Channels – An Overview. Figure 1** Subunit structure of voltage-gated  $\text{Ca}^{2+}$  channels: transmembrane topology of the  $\alpha_1$  and associated auxiliary subunits ( $\beta$ ,  $\alpha_2$ - $\delta$ ,  $\gamma$ ). Predicted  $\alpha$ -helices are depicted as cylinders. For the  $\alpha_1$ -subunit the transmembrane spanning  $\alpha$ -helices (1 to 6) are repeated in the four domains (I to IV). Red cylinders indicate the positively charged S4 segments (voltage sensors), and the thick green lines denote the pore loops (P) that line the permeation pathway for  $\text{Ca}^{2+}$ . The lengths of lines are not intended to represent the exact lengths of the polypeptide segments indicated. The same is for the size of various subunits. Adapted and redrawn from ref [2].



### Calcium Channels – An Overview.

**Figure 2** Phylogenetic tree of voltage-gated  $\text{Ca}^{2+}$  channels, showing the percentage of identity between the different cloned  $\text{Ca}^{2+}$  channels [5]. The first bifurcation occurs between HVA and LVA channels. The HVA family includes four genes encoding the L-type channels ( $\text{Ca}_v1.1$ – $\text{Ca}_v1.4$ ) and three genes encoding the P/Q ( $\text{Ca}_v2.1$ ), N- ( $\text{Ca}_v2.2$ ) and R-type ( $\text{Ca}_v2.3$ ) channels. The LVA family includes three genes encoding the  $\text{Ca}_v3.1$ – $\text{Ca}_v3.3$  channels. Adapted and redrawn from ref [5].

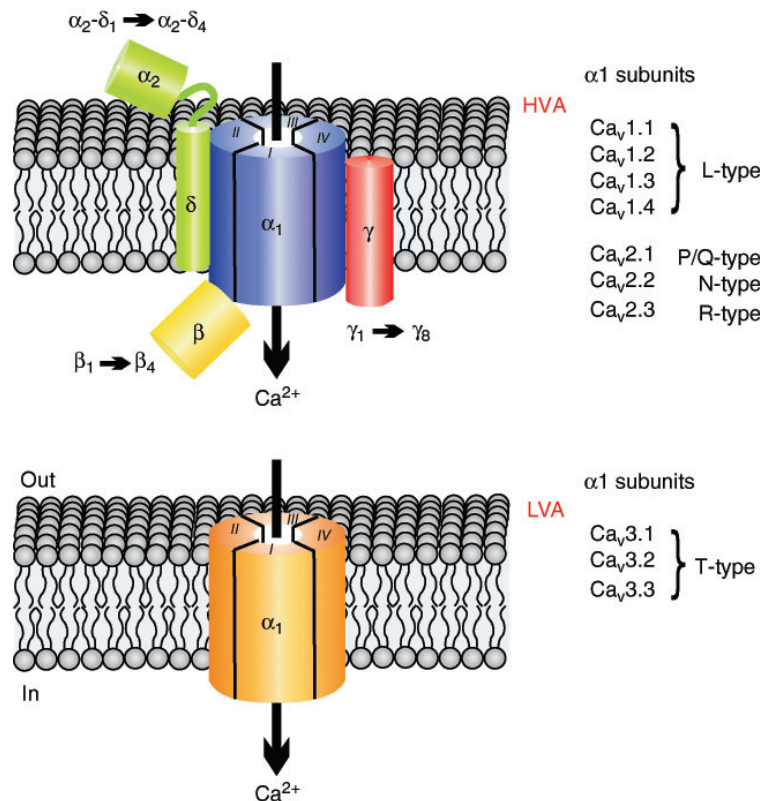
studies have associated this property to the presence of positively charged lysine and arginine residues distributed in the S4 transmembrane segment of each domain, which form the “**voltage sensor**” (Fig. 1). However, the exact location of the activation gates that

regulate the open and closed states of the pore remains unknown.

During maintained depolarization,  $\text{Ca}^{2+}$  channels tend to inactivate, but the speed and extent of channel inactivation may vary dramatically. In general,  $\text{Ca}^{2+}$  channels inactivate by either  $\text{Ca}^{2+}$ - or voltage-dependent mechanisms.  $\text{Ca}^{2+}$ -dependent inactivation is dominant for the cardiac  $\text{Ca}_v1.2$  L-type channel, but may also occur for other HVA channels. **Ca<sup>2+</sup>-dependent inactivation** is a **calmodulin**-dependent process, involving sites on the C-terminal domain of the  $\alpha_1$ -subunit. Voltage-dependent inactivation is a general term for inactivation that does not clearly depend on  $\text{Ca}^{2+}$ . **T-type Ca<sup>2+</sup> channels** tend to inactivate rapidly and almost completely, while inactivation of HVA channels is usually slow and incomplete. Spontaneous switch between inactivating and non-inactivating modes have been observed in single N-type channels, perhaps reflecting modulation by some intracellular signaling process. However, how  $\text{Ca}^{2+}$ -binding or membrane voltage affect the inactivation gate is still widely unknown [6].

### Channel Permeability

The present view of  $\text{Ca}^{2+}$  channel permeability is based on the existence of an intrapore binding site controlling both ion selectivity and channel block: the **selectivity filter**. This highly specialized region of  $\text{Ca}^{2+}$  channels consists of a ring of four negative charged groups inside the pore. In HVA channels, each of the four P loops contains a glutamate forming the EEEE locus, in T-type channels two glutamates are substituted by two aspartates in the corresponding position (EEDD locus). The spatial arrangement of the four negative charges



**Calcium Channels – An Overview. Figure 3** Schematic representation of the voltage-gated  $\text{Ca}^{2+}$  channel complex. On top is represented the heteromeric structure of the HVA  $\text{Ca}^{2+}$  channel, consisting of the pore forming  $\alpha_1$ -subunit (with the four domains I to IV) plus the  $\beta$ ,  $\gamma$  and  $\alpha_2\text{-}\delta$  auxiliary/regulatory subunits. To the bottom is represented the LVA  $\text{Ca}^{2+}$  channel consisting only of the pore forming  $\alpha_1$ -subunit. To the right are listed the different  $\alpha_1$ -subunits that correspond to different  $\text{Ca}^{2+}$  channel isoforms. Adapted and redrawn from ref [3].

in the P loops is postulated to closely coordinate two  $\text{Ca}^{2+}$  ions whose sequential entrance and subsequent interaction induce high  $\text{Ca}^{2+}$  fluxes while preserving high affinity for the pore-site [7]. Although this simple ion-ion interaction would explain the dual nature of  $\text{Ca}^{2+}$  as permeant ions at millimolar concentrations and as blockers of  $\text{Na}^+$  currents at micromolar concentrations, the complete understanding of  $\text{Ca}^{2+}$  channel permeability is likely to require a further hypothesis of ion-pore structure interactions. The recent availability of T-type channel clones [5] has allowed closer comparisons between LVA and HVA channel permeability properties, highlighting the role that the EEEE or EEDD locus play in the regulation of ion selectivity in the two channel groups.  $\text{Ca}_v3.1$  T-type channels have apparently a narrower pore size (5.1 Å diameter) compared to the  $\text{Ca}_v1.2$  L-type pore size (6.2 Å diameter) [7]. This structural difference may explain the different  $\text{Ca}^{2+}/\text{Ba}^{2+}$  selectivity and blocking action of  $\text{Cd}^{2+}$  and  $\text{Ni}^{2+}$  of the two channel families (LVA and HVA): the L-, N- and P/Q-type channels being more permeable to  $\text{Ba}^{2+}$  than  $\text{Ca}^{2+}$  and more sensitive to the block by  $\text{Cd}^{2+}$  and the T-type

channels being equally permeable to  $\text{Ca}^{2+}$  and  $\text{Ba}^{2+}$  and more sensitive to the block by  $\text{Ni}^{2+}$  (Table 1).

### Physiology, Pharmacology and Channelopathies

In the following paragraphs are described the tissue and cellular location, physiological role, pharmacology and related [channelopathies](#) associated to each  $\text{Ca}^{2+}$  channel type as summarized in Table 1.

L-type channels ( $\text{Ca}_v1$ ). L-type channels are widely expressed in many tissues and control a number of  $\text{Ca}^{2+}$ -dependent responses in excitable cells. In central neurons they are preferentially located on proximal dendrites and cell bodies and are involved in postsynaptic integration, neuronal plasticity, gene transcription and mood behavior. In sensory neurons ([cochlear hair cells and photoreceptors](#)), they directly control neurotransmitter release and sensory perception. The L-type family includes four  $\alpha_1$ -subunits ( $\text{Ca}_v1.1$  to  $\text{Ca}_v1.4$ ) with different structure-function characteristics but common blockers: [1,4-dihydropyridines \(DHPs\)](#), [phenylalkylamines](#) and [benzothiazepines](#). With the exception of  $\text{Ca}_v1.3$  and  $\text{Ca}_v1.4$ , which activate at

**Calcium Channels – An Overview. Table 1** Selective and often used blockers, distribution and established channelopathies [10] of the various voltage-gated  $\text{Ca}^{2+}$  channels

Channel		Blockers		Distribution	Channelopathies	
		Selective	Unselective (often used)		Gene	Diseases
L	Ca <sub>v</sub> 1.1	Dihydropyridines, phenylalkylamines, benzothiazepines	Cd <sup>2+</sup>	Skeletal muscles, transverse tubule	CACNA1S	Hypokalemic periodic paralysis & malignant hyperthermia in humans, muscular dysgenesis in mice
	Ca <sub>v</sub> 1.2	Dihydropyridines, phenylalkylamines, benzothiazepines	Cd <sup>2+</sup>	Cardiac & smooth muscle myocytes; endocrine cells, neuronal cell bodies & dendrites	CACNA1C	Timothy syndrome
	Ca <sub>v</sub> 1.3	Dihydropyridines, phenylalkylamines, benzothiazepines	Cd <sup>2+</sup>	Endocrine cells; neuronal cell bodies & dendrites, atrial myocytes & pacemaker cells, cochlear hair cells	CACNA1D	Deafness, sinoatrial & atrioventricular node dysfunction
	Ca <sub>v</sub> 1.4	Dihydropyridines, phenylalkylamines, benzothiazepines	Cd <sup>2+</sup>	Retinal rod & bipolar cells, spinal cord, adrenal gland, mast cells	CACNA1F	Congenital stationary night blindness type 2, X-linked cone-rod dystrophy type 3
P/Q	Ca <sub>v</sub> 2.1	ω-agatoxin IVA	Cd <sup>2+</sup>	Nerve terminals & dendrites, neuroendocrine cells	CACNA1A	Episodic ataxia type-2, spinocerebellar ataxia type-6, familial hemiplegic migraine
N	Ca <sub>v</sub> 2.2	ω-conotoxin VIA, SNX 111 (ziconotide)	Cd <sup>2+</sup>	Nerve terminals & dendrites, neuroendocrine cells	CACNA1B	
R	Ca <sub>v</sub> 2.3	SNX 482	Cd <sup>2+</sup> , Ni <sup>2+</sup>	Nerve terminals & dendrites, neuroendocrine cells, cardiac myocytes	CACNA1E	
T	Ca <sub>v</sub> 3.1	none	Ni <sup>2+</sup> , mibefradil	Neuronal cell bodies & dendrites, cardiac & smooth muscle myocytes	CACNA1G	
	Ca <sub>v</sub> 3.2	none	Ni <sup>2+</sup> , mibefradil	Neuronal cell bodies & dendrites, cardiac & smooth muscle myocytes, neuroendocrine cells	CACNA1H	Childhood absence epilepsy
	Ca <sub>v</sub> 3.3	none	Ni <sup>2+</sup> , mibefradil	Neuronal cell bodies & dendrites	CACNA1I	

relatively low voltages, the other Ca<sub>v</sub>1 channels activate at voltages much more positive than resting potential. Activation is fast and sharply voltage-dependent while inactivation is relatively slow in the presence of Ba<sup>2+</sup> but speeds-up in the presence of Ca<sup>2+</sup> (▶Ca<sup>2+</sup>-dependent inactivation). Deactivation (giving rise to ▶tail currents) is also fast, ensuring rapid closing of the channels on membrane repolarization to resting levels. L-type channels are distinguished from the other Ca<sub>v</sub> channels by their high sensitivity to DHPs. DHP antagonists (nifedipine, nitrendipine) reversibly block the channels and help quantifying the amount of L-type

channels expressed in a cell, while DHP agonists (Bay K 8644) prolong the open state of the channel, producing slow tail currents near resting potential. As such, DHP agonists allow measuring the ▶single channel activity of high conductance L-type channels in membrane patches, otherwise hardly detectable [8]. L-type channels can be often distinguished from the other Ca<sup>2+</sup> channels for their ▶cAMP/PKA-mediated up-regulation which causes increased mean open times and probability of openings at the single channel level and increased Ca<sup>2+</sup> current amplitude in whole-cell recordings [9]. Neuronal and neuroendocrine L-type

channels can be also inhibited by a fast **▶G-protein coupled receptor (GPCR)** mechanism activated by neurotransmitters which could be at the basis of an **▶autocrine feedback control** of hormone release.

P/Q-type channels ( $Ca_v2.1$ ). The  $Ca_v2.1$  family includes two  $Ca^{2+}$  channels which are nearly indistinguishable except for their different affinity to a common blocker: the spider venom  $\omega$ -agatoxin IVA. P-type channels are more sensitive to  $\omega$ -agatoxin IVA ( $K_d$  1–3 nM) than Q-type channels ( $K_d$  100–200 nM).  $Ca_v2.1$  channels are widely expressed in neurons but are also available in pancreatic, pituitary and chromaffin cells. Their main physiological function is to control neurotransmitter release in central neurons and mammalian **▶neuromuscular junctions** where they are highly expressed at the presynaptic sites. P/Q-type channels control also the excitation-secretion coupling in pancreatic and chromaffin cells.  $Ca_v2.1$  channels play a key role in neurotransmitter release due to their high-density of expression at the release sites of central synapses and share most of the modulatory properties of N-type channels described below. Similarly to the N-type channels they bind tightly to the **▶SNARE complex** proteins at the **▶synprint motif** of the II-III linker of the channel. P/Q-type channels are also effectively inhibited by the neurotransmitter activated GPCRs mechanism described below. Missense mutations of P/Q-type channels cause **▶familial hemiplegic migraine (FHM)** associated to an apparent gain of function as a result of an increased probability of channel openings and alteration of synaptic transmission (Table 1).

N-type channels ( $Ca_v2.2$ ).  $Ca_v2.2$  channels are widely expressed in the central and peripheral nervous system and chromaffin cells. They are highly expressed at the nerve terminals, where they control neurotransmitter release, and to a minor degree at the dendritic sites, where they are involved in  $Ca^{2+}$  signaling.  $Ca_v2.2$  channels control also hormone release in neuroendocrine cells. The channels activate at relatively high voltages. Maximal activation at positive potentials and deactivation on return to resting levels are both fast. Inactivation is variable but significantly faster than L-type channels and slower than T-type channels.  $Ca_v2.2$  channels are insensitive to DHPs but are selectively blocked by  $\omega$ -conotoxin GVIA and related cone snail toxins (Table 1).

N-type channels play a key role in neurotransmitter release due to their high-density of expression at the release sites and their tight binding to the SNARE complex of the vesicle release machinery (syntaxin 1A, SNAP-25, VAMP2/synaptobrevin and synaptotagmin). These proteins bind at the synprint motif of the II-III linker of the channel and the tight interaction affects the availability and gating of the channel. The SNARE complex in fact either steadily inactivates the channel or inhibits its activation through a  $G_{\beta\gamma}$  subunit.

Interestingly, N-type channels are effectively modulated by GPCRs activated by neurotransmitters and the mechanism is thought to be at the basis of **▶presynaptic inhibition**. Briefly, an activated  $G_{\beta\gamma}$  subunit binds directly to the pore-forming  $\alpha_1$ -subunit of the N-type channel and shifts the gating mode from “willing” (from which the channel readily opens) to “reluctant” (from which the channel opens less frequently). The **▶modulatory mechanism** is **▶membrane-delimited**, voltage-dependent and causes an increased delay of the channel opening which produces an overall slow activation of the “reluctant” channel. Strong depolarizations opening the channels reduce the affinity of  $G_{\beta\gamma}$  for the  $\alpha_1$ -subunit and the channel recovers its normal gating mode.

R-type channels ( $Ca_v2.3$ ).  $Ca_v2.3$  channels are widely expressed in the central nervous system at the cell bodies, dendrites and presynaptic terminals. They are also expressed in **▶motoneurons**, heart, pituitary and chromaffin cells. The  $Ca_v2.3$  channel has been originally reported to encode a  $Ca^{2+}$  channel type with biophysical properties between LVA and HVA channels, or usually as an HVA channel resistant to DHPs,  $\omega$ -toxins and thus called R-type (for “residual”).  $Ca_v3$  channels are likely to form a family of several channels with fast activation but variable inactivation that could be fast and comparable to the  $Ca_v3$  types or slow like the  $Ca_v1$  channels. They are involved in neurotransmitter and hormone release, repetitive firing ( $\rightarrow$  **▶Action potential**) and **▶long-term potentiation**. The tarantula toxin SNX-482 blocks exogenously expressed  $Ca_v2.3$  currents but is only partially or not effective on native R-type currents, suggesting that  $Ca_v2.3$  does not always conduct a significant portion of the R-type current which remains after blocking all the other **▶voltage-gated  $Ca^{2+}$  channels**.  $Ca_v2.3$  channels are also sensitive to small doses of  $Ni^{2+}$ . In some case the  $Ni^{2+}$  block has  $K_d$  comparable to that of the  $Ca_v3.2$  T-type channel described below.

T-type channels ( $Ca_v3$ ).  $Ca_v3$  channels ( $Ca_v3.1$  to  $Ca_v3.3$ ) are ubiquitously expressed and sustain key physiological functions which derive from their unique properties [4,5]: (i) they activate and inactivate at unusually negative voltages and are responsible for a window-current near resting potentials, (ii) they exhibit fast and complete inactivation during sustained depolarization and deactivate slowly on repolarization, (iii) they are equally or slightly more permeable to  $Ca^{2+}$  than  $Ba^{2+}$  and have small single channel conductance, (iv) they outlast **▶membrane-patch excision** and (v) they are preferentially blocked by low doses of mibefradil and  $Ni^{2+}$  (particularly the  $Ca_v3.2$ ) (Table 1). At present,  $Ca_v3$  channels are recognized to play a critical role in many physiological functions in which a low-threshold  $Ca^{2+}$  entry is required to trigger, or sustain, specific cell activities. This is particularly true for the generation of low-threshold spikes, pacemaking activity, hormone

secretion, cell growth and differentiation. T-type channels play also a critical role in several pathologies in which either their recruitment, overexpression, or altered gating cause cardiac hypertrophy, hypertension, heart failure, ►absence epilepsy, ►neurogenic pain, and ►Parkinson's disease. Most recently, T-type channels are shown to control the vesicular release of neurotransmitters in neurons, and very recent data indicate that they are involved in fast ►catecholamine release in adrenal chromaffin cells.

## References

- Hille B (2001) Ion channels of excitable membranes, 3rd edn. Sinauer, Sunderland, MA
- Catterall WA, Perez-Reyes E, Snutch TP, Striessnig J (2005) International union of pharmacology. XLVIII. Nomenclature and structure-function relationships of voltage-gated calcium channels. *Pharmacol Rev* 57:411–425
- Dolphin AC (2006) A short history of voltage-gated calcium channels. *Br J Pharmacol* 147:S56–S62
- Carbone E, Lux HD (1984) A low voltage-activated, fully inactivating Ca channel in vertebrate sensory neurones. *Nature* 310:501–502
- Perez-Reyes E (2003) Molecular physiology of low-voltage-activated T-type calcium channels. *Physiol Rev* 83:117–161
- Jones SW (2003) Calcium channels: unanswered questions. *J Bioenerg Biomembr* 35:461–475
- Talavera K, Staes M, Janssens A, Klugbauer N, Droogmans G, Hofmann F, Nilius B (2001) Aspartate residues of the Glu-Glu-Asp-Asp (EEDD) pore locus control selectivity and permeation of the T-type  $\text{Ca}^{2+}$  channel  $\alpha_{1G}$ . *J Biol Chem* 276:45628–45635
- Hess P, Lansman JB, Tsien RW (1984) Different modes of Ca channel gating behaviour favoured by dihydropyridine Ca agonists and antagonists. *Nature* 311:538–544
- Bean BP, Nowycky MC, Tsien RW (1984)  $\beta$ -adrenergic modulation of calcium channels in frog ventricular heart cells. *Nature* 307:371–375
- Lorenzon NM, Beam K (2005) Calcium channelopathies. In: Zamponi G (ed) *Voltage-Gated Calcium Channels*. Kluwer Academic, London, UK, pp 240–261

## Calcium Channels: Regulation of Gene Transcription

ADRIANO SENATORE, J. DAVID SPAFFORD  
B1–173, Department of Biology, University  
of Waterloo, Waterloo, ON, Canada

### Synonyms

Excitation-transcription coupling; Voltage-gated calcium channels/ligand-gated calcium channels and control of gene expression; Calcium-regulated nuclear signaling

### Definition

Nerve activity induces  $\text{Ca}^{2+}$  influx through voltage-gated calcium channels (►VGCCs), and activates vital functions such as ►neurotransmitter release (NT) and gene transcription. The latter function is often coupled to permanent changes to the structure of synapses (e.g., ►synaptic plasticity) and the survivability of neurons. Recent research indicate that the specificity of local nuclear signaling pathways depends upon the association of specific channel types to cytosolic  $\text{Ca}^{2+}$ -sensitive factors and not just  $\text{Ca}^{2+}$  influx *per se*. Indeed, it is only the L-type ( $\text{Ca}_v1.2$ ) channels which are critical for the transcriptional regulation of many genes and these contribute only to a fraction of the total  $\text{Ca}^{2+}$  influx during neural activity.  $\text{Ca}^{2+}$  influx by other means, such as the ►N-methyl-D-aspartate receptors (NMDA), also contribute to calcium-dependent gene expression changes and share many but not all of the same nuclear signaling pathways.

### Characteristics

#### Calcium as a Signaling Molecule

The nervous system relies on charged molecules to relay information. Whereas the relatively inert  $\text{Na}^+$  and  $\text{K}^+$  ions serve mostly to establish membrane potential and carry action potentials along excitable membranes,  $\text{Ca}^{2+}$  has properties that allow it to accomplish additional functions. First, it has a unique affinity for binding ligands containing oxygen-donating groups such as carboxyls, carbonyls, ethers, and alcohols. Second,  $\text{Ca}^{2+}$  is kept at low levels within the cytosol since it precipitates organic anions and is toxic to cells at high concentrations. These features likely lead to the exploitation of the calcium ion not only as a charge carrier but also as a signaling molecule.

#### Calcium-regulated Genes

Nerve activity promotes subcellular calcium “hotspots” or microdomains around individual channels, and collectively these active channels contribute to global cellular processes including synaptic plasticity and neuronal survival. An example is long-term memory which involves synaptic connectivity changes activated via ►long term-potential (LTP). Strengthening of synapses induced by LTP requires gene transcription mediated by calcium-sensitive signaling pathways [1]. Furthermore, activity-dependent neuronal survival, which is important during cognitive development, also requires calcium-dependent gene transcription [2].

“First responder” genes are termed ►immediate early genes (IEGs), whose transcription is upregulated without a requirement for newly synthesized proteins. The expression of IEGs is tightly regulated in space and time in active neurons by the summation of nerve inputs and local  $\text{Ca}^{2+}$  flux. ►Brain-Derived Neurotrophic Factor (BDNF) is a classical calcium-activated IEG