Presnaptic Calcium Channels: Structure, Regulators, and Blockers

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Abstract The central and peripheral nervous systems express multiple types of ligand and voltage-gated calcium channels (VGCCs), each with specific physiological roles and pharmacological and electrophysiological properties. The members of the Ca_v2 calcium channel family are located predominantly at presynaptic nerve terminals, where they are responsible for controlling evoked neurotransmitter release. The activity of these channels is subject to modulation by a number of different means, including alternate splicing, ancillary subunit associations, peptide and small organic blockers, G-protein-coupled receptors (GPCRs), protein kinases, synaptic proteins, and calcium-binding proteins. These multiple and complex modes of calcium channel regulation allow neurons to maintain the specific, physiological

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window of cytoplasmic calcium concentrations which is required for optimal neurotransmission and proper synaptic function. Moreover, these varying means of channel regulation provide insight into potential therapeutic targets for the treatment of pathological conditions that arise from disturbances in calcium channel signaling. Indeed, considerable efforts are presently underway to identify and develop specific presynaptic calcium channel blockers that can be used as analgesics.

1 Subtypes and Physiological Functions of Calcium Channels

The entry of calcium ions into the cytosol mediates a wide range of cellular responses, including the activation of calcium dependent enzymes, gene transcription, and the initiation of calcium triggered membrane fusion – a key aspect of vesicular neurotransmitter release (Dolmetsch et al. 2001; Fields et al. 2005; Martin-Moutot et al. 1996; Reid et al. 2003; Sutton et al. 1999; Wheeler et al. 1994). Calcium may enter cells by a number of different mechanisms, including ligand and voltage-gated calcium channels (VGCCs). The nervous system expresses a number of different types of VGCCs, each with specific physiological functions and electrophysiological and pharmacological properties (Table 1). These include the L-type ($Ca_v1.1$-1.4), P/Q-type ($Ca_v2.1$), N-type ($Ca_v2.2$), R-type ($Ca_v2.3$), and T-type ($Ca_v3.1$-3.3) channels, which are broadly classified into low- and high-voltage activated channels (LVA and HVA channels, respectively) (Catterall 2000). LVA (a.k.a. T-type) calcium channels activate in response to small membrane depolarizations, display rapid gating kinetics, exhibit a small unitary conductance, and play a major role in neuronal pacemaker activity (Mangoni et al. 2006; Nelson et al. 2006). In contrast, HVA channels require larger membrane depolarizations in order to open and can be further categorized, based on their functional characteristics, into N-, P-, Q-, R-, and L-types. These HVA calcium channel subtypes are distinguished by their pharmacological profiles: L-type channels are sensitive to dihydropyridines (Fox et al. 1987), N-type channels are selectively inhibited by ω-conotoxins GVIA, MVIA, and CVID (Adams et al. 1993; Feng et al. 2003; Olivera et al. 1984; Reynolds et al. 1986), and P- and Q-type channels are differentially sensitive to ω-agatoxin IVA (Adams et al. 1993). R-type channels were originally identified based on their resistance to these pharmacological tools (Randall and Tsien 1995) but have since been shown to be potently inhibited by the spider toxin SNX-482 (Bourinet et al. 2001; Newcomb et al. 1998). These calcium channel subtypes also support distinct physiological functions and exhibit specific subcellular distributions (Table 1). For example, L-type calcium channels are expressed on cell bodies and support calcium-dependent gene transcription (Bading et al. 1993; Dolmetsch et al. 2001; Weick et al. 2003), while both N-type and P/Q-type channels are expressed at presynaptic nerve terminals, where they control evoked neurotransmitter release (Ishikawa et al. 2005; Westenbroek et al. 1992; Westenbroek et al. 1995). Recent evidence also implicates R-type calcium channels in the release of neurotransmitters at certain synapses (Kamp et al. 2005). For the purposes of this chapter, we will focus predominantly on these presynaptic VGCC subtypes.

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Table 1 Comparison of the physiological, pharmacological, and electrophysiological characteristics of voltage-gated calcium channel subunit subtypes

	Channel Family	Calcium Current	Subunit	(Sub)-Cellular Distribution	Physiological Function	Pharmacological Sensitivity	Knockout Phenotype
	$Ca_v1.1$	L-type	α_{1S}	skeletal muscle	excitation-contraction coupling, gene transcription	dihydropyridines (DHPs)	lethal
	$Ca_v1.2$	L-type	α_{1C}	cardiac muscle, endocrine cells	excitation-contraction coupling, hormone secretion	DHPs	lethal
	$Ca_v1.3$	L-type	α_{1D}	cochlear neurons, endocrine cells	tonic neurotransmitter release, hormone secretion	DHPs	cardiac arrythmias, deaf
HVA	$Ca_v1.4$	L-type	α_{1F}	retinal neurons, immune cells	tonic neurotransmitter release, T lymphocyte activation	DHPs	blind
	$Ca_v2.1$	P/Q-type	α_{1A}	presynaptic nerve terminals	evoked neurotransmitter release	ω-agatoxin IVA, IIIA ω-grammotoxin SIVA	ataxic, absence seizures
	$Ca_v2.2$	N-type	α_{1B}	presynaptic nerve terminals	evoked neurotransmitter release	ω-conotoxin GVIA, MVIIA and CVID, ω-grammotoxin SIVA, farnesol, peptidylamines	hyponociceptive, reduced anxiety, reduced withdrawal symptoms

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Table 1 Continued

	Channel Family	Calcium Current	Subunit	(Sub)-Cellular Distribution	Physiological Function	Pharmacological Sensitivity	Knockout Phenotype
	$Ca_v2.3$	R-type	α_{1E}	dendrites, presynaptic nerve terminals	evoked neurotransmitter release, neuronal excitability	SNX-482	seizure resistant, hyponociceptive
	$Ca_v3.1$	T-type	α_{1G}	neurons, cardiac tissue	pacemaker activity, burst firing, oscillatory	Kurtoxin, ethosuximide, nickel (low sensitivity)	seizure resistant, increased visceral pain perception
LVA	$Ca_v3.2$	T-type	α_{1H}	neurons, cardiac tissue, endocrine cells, smooth muscle	behaviour, hormone secretion, smooth muscle contraction	Kurtoxin, ethosuximide, nickel (high sensitivity)	compromised vascular function, reduced pain sensitivity
	$Ca_v3.3$	T-type	α_{1I}	neurons		Kurtoxin, nickel (low sensitivity)	–
ancillary subunits	common to all α_1 subunits		β	common to α_1 subunit distribution	membrane targeting, alteration of channel kinetics	–	lethal ($\beta_{1,2a}$), reduced neuronal function (β_3), ataxic and absence seizures (β_4)
			α_2-δ		and current densities	gabapentin, pregabalin	ataxic, absence seizures

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2 Molecular Structure of Voltage-Gated Calcium Channels

HVA calcium channels are formed by association of a multimeric protein complex that is comprised of α_1, β, and $\alpha_2 - \delta$ subunits, with, as far as we know, a 1:1:1 stoichiometry (Figure 1) (Catterall 2000). In addition, although its presence remains controversial, some types of HVA calcium channels appear to contain an additional γ subunit (Kang and Campbell 2003; Moss et al. 2002). The α_1 subunit is the major pore-forming subunit and is by itself sufficient to form a functional channel. However, the ancillary subunits are important for proper membrane targeting, and alteration of the functional characteristics of α_1 (Bichet et al. 2000; Stea et al. 1993; Walker and De Waard 1998; Zamponi et al. 1996). All α_1 subunits share a common architecture of four major transmembrane domains (I through IV), connected by cytosolic linker regions and cytoplasmic N- and C-termini. Each major domain contains six membrane spanning helices (S1 through S6) and a re-entrant p-loop that is thought to contain the amino acids that line the pore and form the ion

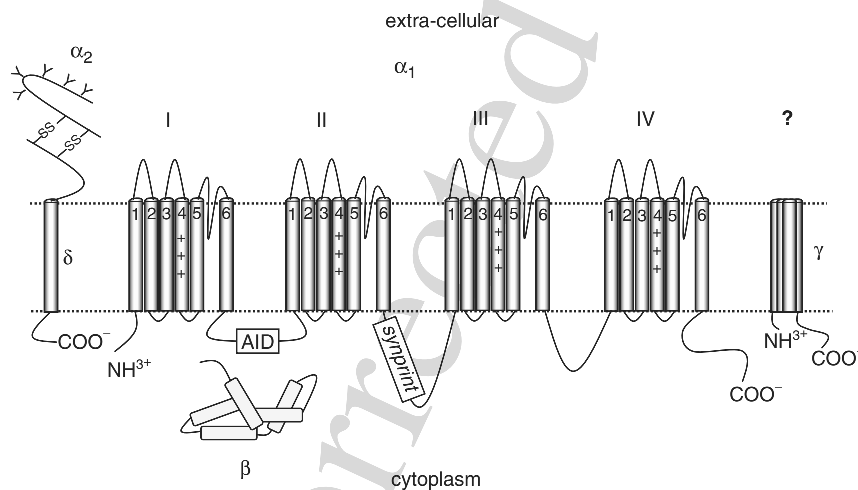

Fig. 1 Topology of the voltage-gated calcium channel protein complex. The main pore-forming subunit, α_1, is composed of four homologous domains (I through IV), connected by cytosolic linkers and flanked by cytosolic N- and C-termini. Each domain consists of six membrane-spanning helices (S1 through S6) and a p-loop between the S5 and S6 segments. The S4 segment contains several positively charged amino acids which act as the voltage sensor. The II-III linker contains a *synprint* region which is important for interactions with synaptic proteins essential for neurotransmitter release. The calcium channel β subunit is a cytoplasmic protein that associates with the α_1 subunit on the I–II linker alpha interaction domain (AID). The calcium channel α_2-δ subunit is composed of the membrane-spanning δ-subunit, connected via di-sulfide linkages to the heavily glycosylated α_2 subunit. Finally, the calcium channel γ subunit is comprised of four transmembrane helices with cytoplasmic N- and C-termini. The presence of this subunit in synaptic calcium channels is controversial, hence it is depicted with a question mark (?) overhead. The auxiliary calcium channel subunits are important for proper membrane targeting of the channel as well as for alteration of channel function.

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selectivity filter (Fig. 3.1) (Catterall 2000). Moreover, it is the calcium channel α_1 subunit that defines the calcium channel subtype. To date, 10 different α_1 subunits have been identified and shown to correspond to the native calcium channel isoforms when expressed functionally. They fall into three gene families, Ca_v1, Ca_v2, and Ca_v3 (Table 3.1). The Ca_v1 family encodes four different L-type channel isoforms (Koschak et al. 2003; Mikami et al. 1989; Tomlinson et al. 1993; Williams et al. 1992), the Ca_v3 family encodes three different T-type channel isoforms (Cribbs et al. 1998; Klockner et al. 1999; Lee et al. 1999b; McRory et al. 2001; Monteil et al. 2000; Perez-Reyes et al. 1998), and most relevant to this chapter, the Ca_v2 family includes the synaptic calcium channel subtypes. $Ca_v2.2$ and $Ca_v2.3$, respectively, correspond to N-type and R-type channels (Dubel et al. 1992; Soong et al. 1993; Williams et al. 1994), and different splice isoforms of $Ca_v2.1$ give rise to P- and Q-type channels (Bourinet et al. 1999). Each of the other types of calcium channel α_1 subunits undergoes alternate splicing, often producing calcium channel isoforms with very distinct electrophysiological properties (Lipscombe et al. 2002), and in the case of N-type calcium channels, differential cellular expression patterns (Bell et al. 2004).

The mammalian brain expresses four different types of β subunits (β_1 through β_4), which can undergo alternate splicing (Dolphin 2003a; Richards et al. 2004). They share a similar structural arrangement with two highly conserved regions (C1 and C2) of high overall sequence homology (75% and 85%, respectively), separated and flanked by a total of three variable regions (V1 through V3) of much lower homology (35%-55%) (Walker and De Waard 1998). These subunits are cytoplasmic proteins, with the exception of β_{2a}, whose N-terminus contains a pair of cysteine residues that can be palmitoylated, thus leading to membrane insertion of some splice isoforms of this subunit (Qin et al. 1998). Each of the four β subunits physically binds to a region within the α_1 subunit domain I-II linker, which is highly conserved among all HVA calcium channels and is termed the alpha interaction domain (AID) (Figure 1) (Pragnell et al. 1994). In addition, there have been reports of a second calcium channel β subunit interaction site within the C-terminus of α_1 (Qin et al. 1997), however, this role of this site remains unclear. The functional effects of β subunit co-expression include changes in channel kinetics and, depending on the channel subtype, an increase in current densities (Bichet et al. 2000; Chien et al. 1995; Yasuda et al. 2004). The latter observation has been linked to the masking of an endoplasmic reticulum (ER) retention signal on the calcium channel α_1 subunit (Bichet et al. 2000); however, our recently published work indicates that, at least in mammalian expression systems, the calcium channel α_1 subunit can give rise to robust current activity even when expressed alone (Yasuda et al. 2004). Perhaps the most obvious effect of the different β subunits is their regulation of channel inactivation rates, with β_{2a} dramatically slowing inactivation, and β_3 and β_{1b} accelerating inactivation (Arikkath and Campbell 2003; Yasuda et al. 2004).

The calcium channel β subunit is the only calcium channel subunit for which there is crystal structure information. The core of this subunit is homologous to membrane-associated guanylate kinases (MAGUKs), with conserved, interacting SH3 and guanylate kinase (GK) domains (Takahashi et al. 2004). Residues in the

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GK domain form a hydrophobic groove for high-affinity binding of HVA calcium channels. Binding of the β subunit to the AID region is critically dependent on functional association of the SH3 and GK regions (Opatowsky et al. 2003; Van Petegem et al. 2004). The functional significance of the intramolecular SH3-GK interaction is supported by electrophysiological data showing that coexpression of separate cDNA constructs that encode the SH3 and GK domains, respectively, results in normal β subunit function, whereas either one of the regions alone is incapable of regulating channel activity (Takahashi et al. 2005).

There are also four different types of calcium channel α_2-δ subunits, each of which is encoded by a single gene that is postranslationally cleaved into α_2 and δ peptides which are then reconnected via a disulfide bond (De Jongh et al. 1990; Klugbauer et al. 2003). The α_2 subunit is extracellular and can be heavily glycosylated, whereas the δ subunit spans the plasma membrane with a single helix (Figure 1).

It has been known for a long time that the skeletal muscle L-type calcium channel complex also contains a γ subunit – a four transmembrane helix with cytoplasmic N- and C-termini (Arikkath and Campbell 2003). Seven additional potential candidates for neuronal calcium channel γ subunits have been identified; however, it is not clear if these are bona fide calcium channel subunits. Indeed, the first identified neuronal calcium channel γ subunit "stargazin" has also been linked to AMPA receptor trafficking and pharmacology (Chen et al. 2000; Tomita et al. 2005). Hence, it remains unclear to what extent these subunits associate with the calcium channel complex in neurons.

Calcium channel α_1 and β subunits are subject to further heterogeneity due to alternate splicing, thus giving rise to a potentially vast number of different types of calcium channel molecules whose expression and distribution may be dynamically regulated to suit a particular physiological function. It is important to bear this in mind when comparing native calcium channel currents to data obtained in transient expression systems.

3 Consequences of Calcium Channel Gene Knockout

The differential physiological roles of individual calcium channel subunits are perhaps best highlighted by knockout (KO) mouse experiments (Table 1). KO animals lacking each of the major calcium channel α_1 and β subunits have been characterized in detail. KO of the $Ca_v1.1$ channel is lethal due to inability of mice to contract their diaphragm (Strube et al. 1996). KO of the $Ca_v1.2$ channel is embryonic lethal due to compromised cardiac function (Seisenberger et al. 2000). Mice lacking $Ca_v1.3$ exhibit cardiac arrhythmias and are deaf (Platzer et al. 2000), whereas mice lacking $Ca_v1.4$ are blind (Mansergh et al. 2005). These two calcium channel subtypes, respectively, control tonic glutamate release at ribbon synapses in cochlear hair cells and photoreceptors – this type of neurotransmitter release thus differs from the N- and P/Q-type channel mediated action potential evoked release, which

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is transient. Mice lacking $Ca_v3.1$ channels are resistant to certain types of pharmacologically induced seizures and may have an altered perception of visceral pain (Kim et al. 2001b), whereas mice lacking $Ca_v3.2$ channels are subject to compromised vascular function (Chen et al. 2003). $Ca_v2.3$ KO mice behave normally but show reduced pain responses, as well as resistance to certain types of epileptic seizures (Saegusa et al. 2000; Weiergraber et al. 2006). Although both N-type and P/Q-type channels control neurotransmitter release, they are clearly not created equal. Mice lacking the N-type ($Ca_v2.2$) channel are hyposensitive to pain and show reduced ethanol reward behavior (Hatakeyama et al. 2001; Kim et al. 2001a; Newton et al. 2004). Other than a slightly compromised control of blood pressure, these mice are behaviorally normal and viable. In contrast, mice lacking $Ca_v2.1$ channels are severely ataxic and show absence seizures (Jun et al. 1999). These mice usually die before reaching maturity, which is in stark contrast to the findings with $Ca_v2.2$ KO mice. The ataxic and epileptic phenotype of the $Ca_v2.1$ KO mice is consistent with data from several mouse lines with missense and frame shift mutations (Doyle et al. 1997; Wakamori et al. 1998), or polyglutamine expansions (Zhuchenko et al. 1997), in $Ca_v2.1$, as well as with several $Ca_v2.1$ human mutations found in patients with episodic ataxia type 2 (Denier et al. 2001; Friend et al. 1999; Guida et al. 2001; Ophoff et al. 1996) (see Section 4).

KO of the calcium channel β_1 subunit is lethal due to skeletal muscle paralysis that results from reduced membrane targeting of the $Ca_v1.1$ channel (Gregg et al. 1996; Strube et al. 1996). KO of the β_{2a} subunit is also lethal due to compromised development of the cardiac vasculature (Ball et al. 2002). Mice lacking the β_3 subunit are viable but show reduced neuronal L-type and N-type channel activity (Namkung et al. 1998). In the context of synaptic physiology, KO of the calcium channel β_4 subunit is of interest. *Lethargic* is a mouse line with a mutation in the calcium channel β_4 subunit that leads to a premature stop codon and *de facto* elimination of this subunit. The consequences of this KO are strikingly similar to those observed with KO or mutated $Ca_v2.1$ animals (Burgess et al. 1997), hinting at a potential common effect of these subunits on synaptic function. Similar considerations apply to α_2-δ subunits where a frameshift mutation leads to the elimination of this subunit in the *ducky*^{2j} mouse strain – again, as with $Ca_v2.1$ KO animals, these mice are ataxic and have absence seizures (Brodbeck et al. 2002). These observations suggest that KO of either β_4 or α_2-δ may lead to altered P/Q-type channel targeting and/or function.

The notion that N-type and P/Q-type channel knockout mice are phenotypically distinct suggests that these two calcium channel subtypes contribute to different aspects of synaptic function. Indeed, is has been reported that P/Q-type channels are more frequently linked to excitatory transmission, whereas N-type channels may contribute more often to inhibitory transmission (Potier et al. 1993). This is an important point to consider in the context of channel modulation as outlined below.

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4 Calcium Channelopathies Involving P/Q-Type Calcium Channel α_1 Subunits

Mutations in the α_1 subunits of voltage gated calcium channels have been linked to a number of disorders. These include hypokalemic periodic paralysis ($Ca_v1.1$) (Lapie et al. 1997), Timothy syndrome ($Ca_v1.2$ and $Ca_v3.2$) (Splawski et al. 2005; Splawski et al. 2004; Splawski et al. 2006), congenital stationary night blindness ($Ca_v1.4$) (Bech-Hansen et al. 1998; Hoda et al. 2005), and various forms of absence epilepsy ($Ca_v3.2$) (Khosravani and Zamponi 2006), none of which we will elaborate on further. Mutations in P/Q-type calcium channels of both mice and humans are also associated with a number of pathological conditions. As mentioned earlier, point mutations in $Ca_v2.1$ have been associated with episodic ataxia type 2, as well as with familial hemiplegic migraine (FHM) in humans (Ophoff et al. 1996). When introduced into recombinant channels and expressed in either transient expression systems or neurons, FHM mutations tend to result in decreased channel function (Pietrobon and Striessnig 2003). In contrast, data from knock-in mice carrying certain FHM mutations are consistent with a gain of function mediated by these mutations. To date, this issue has not been resolved. Similarly, patients with spinocerebellar ataxia type 6 show an ataxic phenotype due to a polyglutamine expansion in the $Ca_v2.1$ C-terminus (Zhuchenko et al. 1997) but, as in the case of FHM mutations, it is unclear whether this is due to increased or decreased P/Q-type channel activity. However, in general terms, any alteration in P/Q-type channel function is expected to produce pronounced effects on neurotransmitter release and synaptic function. Thus, increases and decreases in P/Q-type channel activity may well produce similar alterations in neuronal network function depending on whether inhibitory or excitatory inputs are affected.

There are also a number of murine models of P/Q-type channelopathies. *Leaner*, *Tottering, rolling Nagoya*, and *Rocker* mice all carry mutations in the $Ca_v2.1$ calcium channel α_1 subunit that result in either the substitution of individual amino acids or premature truncations of the channel protein. These mice tend to show an ataxic phenotype and, in some cases, absence seizures (Lorenzon et al. 1998; Mori et al. 2000; Noebels and Sidman 1979; Zwingman et al. 2001). In addition, several of these mutations cause cerebellar atrophy (Herrup and Wilczynski 1982). When introduced into recombinant channels, these mutations tend to reduce channel activity which is consistent with reduced P/Q-type currents in neurons isolated from these mouse lines.

To our knowledge, there are no identified N-type or R-type calcium channelopathies, which is consistent with the mild phenotype observed upon KO of the $Ca_v2.2$ or $Ca_v2.3$ genes.

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5 Calcium Channel Pharmacology

5.1 Peptide Blockers

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As mentioned earlier, the pharmacological profile of a given calcium channel is a key means of identifying a particular calcium channel subtype. While small organic molecules such as dihydropyridines have been used to definitively characterize L-type calcium channels (Bean 1984), peptide toxins isolated from fish-hunting marine snails, spiders, scorpions, and snakes have been an invaluable source of selective inhibitors of synaptic calcium channels (Doering and Zamponi 2005). The archetypal N-type calcium channel inhibitor is ω-conotoxin GVIA, a peptide isolated from the fish-hunting cone snail *Conus geographus*. This toxin docks at the outer vestibule of the channel and physically occludes the channel pore, thus preventing calcium entry (Ellinor et al. 1994). Block occurs with high affinity and selectivity over other types of calcium channels and is poorly reversible upon washout (Feng et al. 2001b). ω-Conotoxins MVIIA and CVID are isolated, respectively, from the venoms of *Conus magus* and *Conus catus*, and they too selectively inhibit N-type calcium channels via a pore blocking mechanism (Feng et al. 2001b; Fox 1995; Monje et al. 1993; Olivera et al. 1984). Compared with MVIIA, CVID has even higher selectivity for N-type over P/Q-type calcium channels. Both MVIIA and CVID have been used clinically to treat pain, via intrathecal injection, underscoring the importance of N-type calcium channels in synaptic transmission in the dorsal horn of the spinal cord. Although multiple structural domains likely contribute to conotoxin block, efforts to map the contoxin interaction site on the N-type calcium channel indicate that the domain III S5-S6 region is critical (Ellinor et al. 1994; Feng et al. 2001b). In addition, the ancillary α_2-δ subunits have been shown to reduce the affinity of N-type calcium channels for MVIIA and CVID (Mould et al. 2004).

Perhaps the best known peptide blocker of P/Q-type calcium channels is ω-agatoxin IVA, a peptide isolated from the venom of the North American funnel web spider *Agelenopsis aperta*. Unlike the conotoxins which are pore blockers, aga IVA functions as a gating inhibitor (McDonough et al. 1997). Application of aga IVA at concentrations as low as several nanomolars causes rapid inhibition of P-type channel activity and typically does not reverse upon washout (Adams et al. 1993; Turner et al. 1992). However, application of strong membrane depolarizations removes aga IVA block so that the channel effectively undergoes a large depolarizing shift in half activation potential – in essence, the toxin prevents activation gating but can be dislodged from its binding site by membrane depolarization (Mintz et al. 1992). The site of action of aga IVA appears to involve extracellular regions within domain IV of the $Ca_v2.1$ subunit (Winterfield and Swartz 2000). Indeed, alternate splicing of an asparagine-proline motif within the domain IV S3-S4 linker accounts for a 50-fold difference in aga IVA affinity between P-type and Q-type calcium channels (Bourinet et al. 1999). Other examples of peptide gating inhibitors include ω-grammotoxin SIVA (an N- and P/Q-type channel blocker) and SNX-482 (an R-type channel blocker), both isolated from different species of

tarantula. Interestingly, the effects of aga IVA and grammotoxin on P/Q-type channel activity are additive, indicating that they bind to separate sites on the channel (McDonough et al. 2002).

The 78 amino acid ω-agatoxin IIIA blocks P/Q-type channels with nanomolar affinity, but also potently inhibits L-type and N-type channels (Mintz 1994; Mintz et al. 1991). This toxin is much larger than the ω-conotoxins (which are typically 25–30 amino acids in length), but nonetheless acts by a pore blocking mechanism and is thus distinct in action from aga IVA (Mintz 1994). Yet, pore block by this peptide is incomplete suggesting that toxin-bound channels can still conduct a small amount of calcium. Due to its nonselective nature, and its failure to elicit complete channel block, this toxin is not very useful experimentally.

Aga IVA and ω-conotoxin GVIA are standard tools in elucidating the roles of P/Q-type and N-type calcium channels in synaptic transmission. In many types of synapses, application of either toxin may mediate moderate inhibition of neurotransmitter release, whereas co-application of both blockers may almost abolish synaptic transmission due to the nonlinear dependence of synaptic release on intracellular calcium concentration. On a final note, we should add that there are many other species of cone snails and spiders that produce active toxins which selectivity inhibit specific calcium channel subtypes (for example, ω-conotoxins GVIB, GVIC, GVIIA, SVIA, SVIB), and it is likely that many more remain to be discovered (Olivera et al. 1994).

5.2 Small Organic Compounds Blocking N-type Channels

Besides peptide toxins, presynaptic calcium channels can also be inhibited by divalent metal ions such as cadmium, and by a number of different classes of small organic molecules (Doering and Zamponi 2005). While there are, to our knowledge, no selective small organic inhibitors of P/Q-type calcium channels, substantial efforts are being made to develop small organic N-type channel blockers for use as analgesics which can be administered orally. Such compounds include 4-benzyloxyaniline piperidine derivatives, fatty acid like compounds such as farnesol, and peptidylamines (Hu et al. 1999a; Hu et al. 1999b; Hu et al. 1999c; Roullet et al. 1999) . High throughput screening continues to identify novel compounds which block N-type channel activity and which show efficacy as analgesics. However, in many cases the degree of selectivity of these compounds for N-type channels over other calcium channel subtypes is much less than that observed for peptide toxins.

The anticonvulsant gabapentin (1-(aminomethyl) cyclohexaneacetic acid) and its second-generation cousin pregabalin are highly effective as analgesics in rats and humans (Cheng and Chiou 2006; Zareba 2005). These compounds are unique in that they bind to the calcium channel α_2-δ subunit (Gee et al. 1996). Transgenic animals in which the putative gabapentin binding site on this subunit has been eliminated are resistant to the effects of gabapentin. It remains controversial as to whether the

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gabapentin-α_2-δ interaction does indeed reduce voltage gated calcium currents, or whether the analgesic effects of gabapentin are mediated by a different mechanism.

6 Regulation by G Protein–Coupled Receptors

It is well established that activation of G protein–coupled receptors (GPCRs), in particular those that couple to the $G\alpha_{i/o}$ subunit, can result in potent inhibition of both N-type and P/Q-type calcium channels (Figure 2) (Beech et al. 1992; Bernheim et al. 1991; Caulfield et al. 1994; Dunlap and Fischbach 1981; Golard and Siegelbaum 1993; Ikeda 1992; Ikeda and Schofield 1989; Lipscombe et al. 1989; Mintz and Bean 1993; Shapiro and Hille 1993; Zhu and Ikeda 1993). The physio-

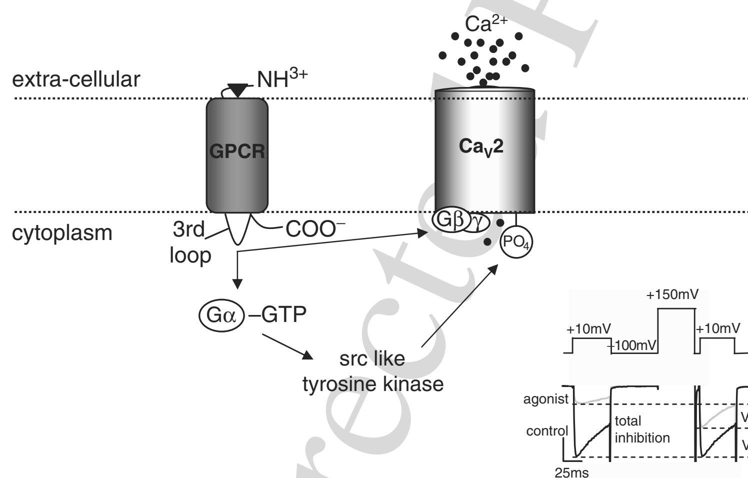

Fig. 2 Voltage-dependent (VD) and voltage-independent (VI) G-protein mediated inhibition of synaptic calcium channels. In the absence of agonist, the heterotrimeric G-proteins, Gαβγ, bind GDP and associate with the third intracellular loop of seven trans-membrane helix spanning G-protein coupled receptors (GPCRs). Agonist (▼) activation of the receptor results in an exchange of GDP for GTP on the G protein α-subunit. This exchange leads to dissociation of Gα-GTP and Gβγ subunits, which are subsequently free to act on downstream effectors such as enzymes or ion channels. Gβγ, which remains associated with the plasma membrane, binds to N- and P/Q-type calcium channels on the α_1 subunit, stabilizing the closed conformation of the channel and resulting in loss of current activity which is voltage-dependent (VD). Liberated Gα-GTP is cytoplasmic and activates enzymes such as adenylyl cyclase. Subsequent phosphorylation of synaptic calcium channels on the α_1 subunit leads to voltage-independent (VI) inhibition of channel activity. **Inset**: In the presence of GPCR agonist (grey trace), a step to +10 mV results in inhibition of control current (black trace). VD and VI inhibition can be separated by applying a strong, depolarizing pre-pulse (i.e. +150 mV) immediately prior to the test pulse. This pre-pulse relieves Gβγ-mediated VD inhibition, by physical removal of Gβγ from the channel, and remaining current inhibition can thus be attributed to VI inhibition.

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logical significance of this modulation is underscored by the action of opiates in the pain pathway, where activation of μ-opioid receptors by morphine mediates analgesia in part by inhibition of N-type calcium channel activity (Altier and Zamponi 2004). GPCR-mediated inhibition may have both voltage-dependent (VD) and voltage-independent (VI) components (Figure 2). VD inhibition involves the binding of G protein βγ subunits to a cytoplasmic site on the calcium channel α_1 subunit, thereby stabilizing the closed conformation of the channel (Figure 2) (Herlitze et al. 1996; Ikeda 1996). This inhibition is referred to as VD because it is favored at hyperpolarized potentials and can be relieved by strong membrane depolarizations or rapid trains of action potentials, thus allowing for activity-dependent dis-inhibition (Bean 1989; Hille 1994; Zamponi and Snutch 1998a, 1998b). The degree of VD inhibition depends on the calcium channel subtype, with N-type channels typically undergoing a larger degree of inhibition than P/Q-types (Currie and Fox 1997), and on the G protein β subunit isoform (Arnot et al. 2000; Garcia et al. 1998; Ruiz-Velasco and Ikeda 2000; Zhou et al. 2000). There may also be a subtle G protein γ subunit dependent component to N-type channel regulation (Ruiz-Velasco and Ikeda 2000). Furthermore, distinct Gβ subunit structural determinants appear to underlie modulation of these two channel types (Doering et al. 2004; Ford et al. 1998; Mirshahi et al. 2002a; Mirshahi et al. 2002b; Tedford et al. 2006). With different types of GPCRs coupling to specific subsets of G protein βγ subunits, differing degrees of VD inhibition of both calcium channel subtypes can thus be elicited. In addition, the extent of VD inhibition of both N- and P/Q-type channels appears to be dependent on the type of β subunit that is present in the calcium channel complex (Barrett and Rittenhouse 2000; Bourinet et al. 1996; Canti et al. 2000; Feng et al. 2001a). While many of the molecular details governing this regulation have been described over the past decade and have been reviewed in recent literature (Dolphin 2003b) new and important details concerning the structural underpinnings of VD inhibition are still emerging. For example, although both the calcium channel domain I-II linker and N-terminal regions have long been implicated in G protein modulation, it is now known that an interaction between these two regions is necessary for VD modulation (Agler et al. 2005). It is not completely resolved as to whether G protein βγ subunits facilitate the interaction between the N-terminus and the I-II linker region, or whether this interaction is needed to allow Gβγ binding to the channel. It has also been recently demonstrated that the C-terminal region of N-type calcium channels serves to enhance the affinity of the channel for Gβγ (Li et al. 2004), suggesting that a complex interplay among multiple cytoplasmic regions of the channel underlies VD inhibition. The aforementioned calcium channel β subunit dependence of VD G protein modulation may be due to the close proximity of the calcium channel β subunit interaction site and putative G protein binding sites within the domain I-II linker region (De Waard et al. 1997; Zamponi et al. 1997). However, the underlying mechanism remains subject to investigation. Indeed, there are differing views as to whether G protein βγ subunits compete with the calcium channel β subunit for binding, and whether or not G protein interactions with the channel cause dissociation of the calcium channel β subunit from the channel complex. However, irrespective of these molecular details, it is clear that G protein βγ subunits interact with cyto-

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plasmic regions of the calcium channel α_1 subunit resulting in a reduction of N- and P/Q-type channel activity that culminates in reduced calcium entry into the cell and thus reduced neurotransmitter release.

VD G protein modulation can be fine tuned by activation of other intracellular signaling cascades. For example, the activation of protein kinase C (PKC), which regulates channel activity directly, also interferes with the ability of N-type channels to undergo VD inhibition (Barrett and Rittenhouse 2000; Swartz 1993; Swartz et al. 1993). Intriguingly, this effect is dependent on the G protein $\beta\gamma$ subunit subtype, so that only $G\beta_1$-mediated responses are antagonized (Cooper et al. 2000). This is due to a unique pair of asparagine residues localized to the N-terminal helix of the $G\beta_1$ subunit (Doering et al. 2004). The structural basis for this effect has been resolved, as it has been shown that a single threonine residue located in the putative G protein $\beta\gamma$ subunit interaction site is the key locus for PKC-mediated effects (Hamid et al. 1999). In essence, this cross talk allows the channel to integrate two separate second messenger pathways in order to modulate current activity in a kinase- and $G\beta$ subunit-specific manner. The complexity of VD G protein modulation may allow synapses to precisely regulate the amount of calcium entering cells, and thus to adjust synaptic output.

In addition to VD $G\beta\gamma$ mediated inhibition of N-type channel activity, GPCR-induced VI modulation has been described for N-type calcium channels (Figure 2) (Beech et al. 1992; Beedle et al. 2004; Bernheim et al. 1991; Delmas et al. 1998a; Delmas et al. 1998b; Kammermeier et al. 2000; Schiff et al. 2000; Shapiro et al. 1999; Surmeier et al. 1995). VI inhibition is insensitive to membrane depolarizations and occurs over a slower time course than VD inhibition, implicating intracellular signaling cascades such as tyrosine kinase activation in this process. Furthermore, for P/Q-type channels, a form of VI modulation has been shown to involve an association of the G protein α_o subunit with the $Ca_v2.1$ C-terminus (Kinoshita et al. 2001). More recently, two studies have revealed a novel form of VI inhibition of N-type calcium channels that involves physical removal of calcium channels from the plasma membrane. N-type calcium channels and nociceptin (or ORL1) receptors have been shown to form stable, physical signaling complexes (Beedle et al. 2004). Prolonged agonist application results in internalization of the entire receptor-channel complex and to its subsequent degradation in lysosomes (Altier et al. 2006). The resultant loss of channel numbers in the plasma membrane and reduced current densities are, in effect, a form of VI inhibition. Channel internalization has also been shown to occur in response to $GABA_B$ receptor activation, although by an entirely different molecular mechanism that involves tyrosine kinase activity and cytoskeletal elements (Tombler et al. 2006). Moreover, this effect spontaneously reverses with receptor desensitization. That said, as in the case of nociceptin receptor activation, numbers of channels in the plasma membrane are reduced. It is likely that other types of GPCRs show similar receptor-mediated channel trafficking, and that this mechanism may emerge as a novel means of regulating N-type channels and thus synaptic activity.

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7 Regulation of Calcium Channels by Synaptic Proteins

The activity of N-type and P/Q-type calcium channels is also regulated by proteins that form part of the synaptic vesicle release machinery (Figure 3). These channel subtypes contain a specific synaptic protein interaction site (termed *synprint*) in the

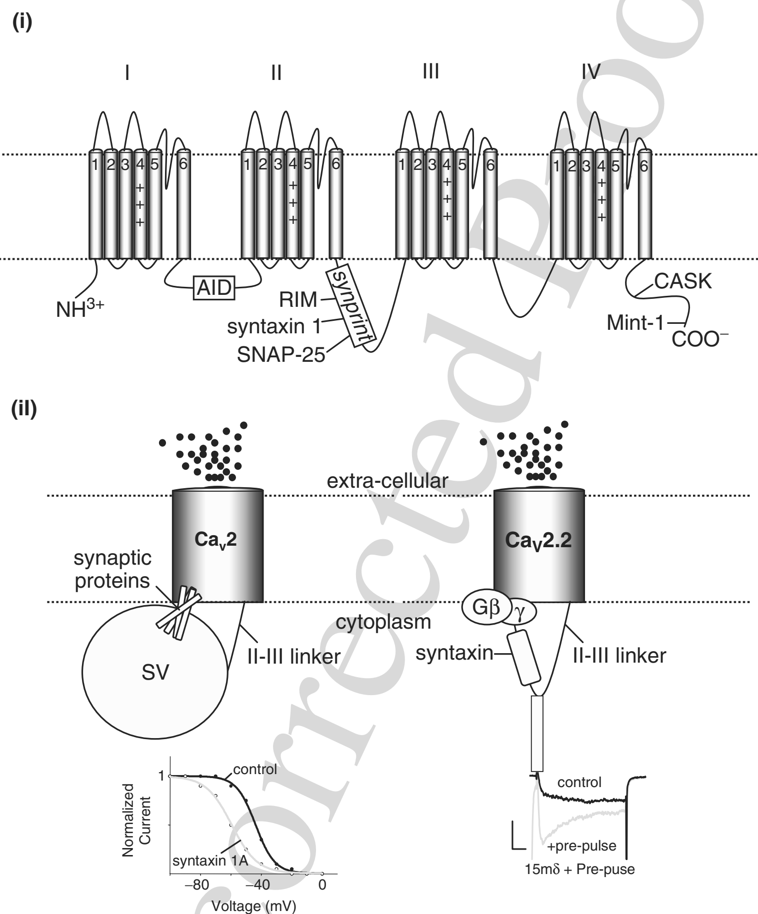

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Fig. 3 Regulation of calcium channels by synaptic proteins. (i) Putative interactions sites of synaptic and adaptor proteins with Ca_v2 channels are indicated on the calcium channel α_1 subunit. RIM, syntaxin 1, and SNAP-25 are believed to interact with synaptic calcium channels on the II-III linker *synprint* region, while CASK and Mint-1 are thought to interact with the α_1 C-terminus. **(ii)** The physical associations between calcium channels and synaptic proteins are believed to colocalize synaptic vesicles (SVs) to sources of cellular calcium entry (left). In addition, several of these Ca_v2-synaptic protein interactions are believed to reduce channel activity directly by shifting half-inactivation channel kinetics to more hyperpolarized potentials (bottom, left). In the absence of GPCR activation, N-type calcium channel interactions with syntaxin 1A are speculated to result in tonic, Gβγ-mediated channel inhibition. This tonic, Gβγ-mediated inhibition is evident following its removal by a strong depolarizing pre-pulse (bottom, right).

intracellular loop linking domains II and III (Sheng et al. 1994). However, it is important to note that there are channel splice variants that lack this region and that, although invertebrates are capable of neurotransmission, no equivalent *synprint* region is found in invertebrate synaptic calcium channel homologs (Spafford and Zamponi 2003; Zamponi 2003). In the case of the N-type calcium channel, the *synprint* region is known to bind syntaxin 1, SNAP-25, and Rim (Coppola et al. 2001; Jarvis and Zamponi 2001b; Sheng et al. 1994; Sheng et al. 1997). The P/Q-type channel *synprint* region also interacts with syntaxin 1 and SNAP-25, however, unlike the N-type channel, it also binds synaptotagmin 1 (Charvin et al. 1997). The *synprint* motif in these channels appears to serve multiple functions. It has been suggested that the interactions between the *synprint* region and the synaptic proteins help to co-localize synaptic vesicles to sources of calcium entry (Figure 3ii) (Zamponi 2003). There is also evidence that the *synprint* region is involved in targeting calcium channels to presynaptic sites, as substitutions or deletions to this region lead to a loss of presynaptic localization of both N- and P/Q-type channels (Harkins et al. 2004; Mochida et al. 2003). However, it should be noted that other regions of the channels, such as the C-terminus by virtue of its interactions with the adaptor proteins Mint-1 and CASK, appear equally critical for synaptic targeting (Maximov and Bezprozvanny 2002; Spafford et al. 2003). Finally, the *synprint* region appears to serve as an important modulatory site that allows synaptic proteins to regulate channel activity *per se*. In both transient expression systems and neurons, binding of syntaxin 1 and SNAP-25 results in a hyperpolarizing shift in the half-inactivation potential of both P/Q-type and N-type calcium channels, thus reducing channel availability (Figure 3ii) (Bezprozvanny et al. 1995; Jarvis and Zamponi 2001a; Stanley 2003). This negative shift is ablated in the concomitant presence of both proteins (and in the case of P/Q-type channels, in the presence of synaptotagmin) (Zhong et al. 1999), is abolished in the presence of munc-18, and does not occur when syntaxin is in its "open" conformation. Because the association between syntaxin 1 and munc-18, as well as the conformational state of syntaxin, vary during the vesicle release cycle, channel availability can be dynamically regulated at various stages in the neurotransmitter release process. This in turn may help to ensure the appropriate amount of calcium entering the nerve terminal during neurotransmission.

Our group also identified a second action of syntaxin 1A (but not 1B) on N-type calcium channels. Co-expression of this protein with N-type calcium channels results in a tonic G protein–mediated inhibition of channel activity that does not involve receptor activation (Jarvis et al. 2000). This appears to be due to a syntaxin-mediated co-localization of the channel and Gβγ that ultimately culminates in tonic channel inhibition (Figure 3ii). Indeed, syntaxin 1A binds to Gβγ *in vitro* on a region that is distinct from the Gβγ site involved in interactions with the *synprint* motif. These data are consistent with the idea of a sandwich formed by the channel, syntaxin and Gβγ (Jarvis et al. 2002). Intriguingly, although syntaxin 1B can also bind to Gβγ *in vitro*, no tonic G protein inhibition of channel activity ensues (Lu et al. 2001). This suggests that, compared with syntaxin 1A, syntaxin 1B adopts a slightly different channel-bound conformation. The syntaxin-mediated effect on G protein inhibition appears to be much more robust than the effect on channel

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availability as it occurs when syntaxin is in the open conformation and is maintained upon coexpression of SNAP-25. Furthermore, although binding of syntaxin 1A to the *synprint* region is destabilized upon activation of PKC (Yokoyama et al. 2005; Yokoyama et al. 1997), the functional effects of PKC activation are limited to elimination of syntaxin-mediated channel availability and not to G protein inhibition (Jarvis and Zamponi 2001a, 2005). For completeness, we note that a similar SNARE protein dis-inhibition of P/Q-type calcium channels is observed for cyclin-dependent kinase 5, which has been shown to increase P/Q-type channel activity by blocking interactions of the channel with SNAP-25 (Tomizawa et al. 2002).

It is worth noting that the binding interaction between synaptic proteins and $G\beta\gamma$ may allow G proteins to regulate synaptic activity independently of N-type channel activity. Taken together, the interactions between calcium channels, G proteins, kinases, and synaptic proteins such as syntaxin provide for complex mechanisms that regulate N-type calcium channel activity both in expression systems and in neurons.

8 Regulation of Presynaptic Calcium Channel Activity by Protein Kinases

Many types of kinases have been shown to regulate calcium channel activity, and this topic in itself would be sufficient for a free-standing chapter. Here, we will give only a few select examples of the major pathways of this type of presynaptic calcium channel regulation.

PKC is an important regulator of presynaptic calcium channel activity. PKC activity has been shown to upregulate R-type calcium channels (Kamatchi et al. 2000; Shekter et al. 1997; Stea et al. 1995), as well as to increase N-type calcium channel activity (Hamid et al. 1999; Stea et al. 1995). This, in addition to the aforementioned antagonistic effects of PKC on syntaxin and VD G protein inhibition of N-type channels, produces an increase in N-type current activity in response to PKC activation. It has recently been shown that the PKC binding protein, enigma homolog (ENH) serves to co-localize PKC-ε and N-type channels to facilitate PKC-dependent phosphorylation of the $Ca_v2.2$ subunit (Maeno-Hikichi et al. 2003), indicating the formation of a macromolecular signaling complex. In contrast, there is little direct PKC regulation of P/Q-type calcium channels (Wu et al. 2002).

Protein kinase A (PKA) has been reported to increase P/Q-type channel activity in both neurons (Huang et al. 1998) and in transient expression systems (Fournier et al. 1993; Fukuda et al. 1996; Kaneko et al. 1998). In contrast, N-type calcium channels appear to be relatively insensitive to PKA. PKA has been shown to regulate P/Q-type calcium channel activity indirectly by interfering with phosphatidylinositol 4,5 biphosphate (PIP_2) mediated regulation (Wu et al. 2002). Under normal circumstances, PIP_2 slows rundown of P/Q-type channel activity and produces VD current inhibition. Activation of PKA selectively antagonizes the VD inhibition mediated by PIP_2, perhaps by preventing PIP_2 binding to the inhibitory site on the channel while sparing PIP_2 action on the site linked to current rundown. Once again,

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this cross talk underscores the ability of voltage-gated calcium channels to integrate multiple signaling pathways.

Calcium channel β subunits are also targets for phosphorylation events. It was recently reported that a phosphatidylinositol 3-kinase dependent elevation of phosphatidyl-inositol-4,5 triphosphate (PIP_3) is critical for the ability of the calcium channel β_{2a} subunit to promote N-type calcium channel trafficking to the plasma membrane (Viard et al. 2004). Increased levels of PIP_3 result in activation of protein kinase B, which phosphorylates β_{2a} and allows for trafficking of N-type channels to the plasma membrane. Along similar lines, it has been shown that Ras/extracellular signal–regulated kinase (ERK) phosphorylation of both the α_1 and the β_{1b} subunit mediates an upregulation of $Ca_v2.2$ current activity (Martin et al. 2006). Collectively, these findings clearly underscore the importance of ancillary calcium channel subunits as targets for second messenger regulation.

9 Feedback Regulation by Calcium Binding Proteins

Another important regulatory mechanism of calcium channel activity is via calcium binding proteins such as calmodulin (Figure 4) (Halling et al. 2005). It is well established that L-type calcium channels undergo robust calcium-dependent inactivation (CDI) – a reduction of current activity in response to elevated intracellular calcium levels which serves to protect cells form calcium overload (Imredy and Yue 1994). In the absence of calcium ions, calmodulin is pre-associated with the C-terminus of the channel at a highly conserved region containing pre-IQ and IQ motifs. Upon calcium entry into the cell, calmodulin binds Ca^{2+}, accelerating the inactivation kinetics of the channel. CDI in L-type channels requires the high-affinity calcium binding sites of calmodulin, thus being relatively resistant to standard calcium buffers (Soldatov 2003). Although CDI was once believed to be a unique property of L-type channels, it was subsequently shown that all types of HVA channels are subject to this process (Lee et al. 1999a; Liang et al. 2003). However, unlike L-type channels, R-, N-, and P/Q-type channels undergo CDI only when calcium is weakly buffered (Figure 4) (Liang et al. 2003). Indeed, the CDI process in these channels involves the low-affinity calcium binding sites of calmodulin. This key difference means that calcium entry through an individual L-type channel is sufficient to induce CDI, whereas CDI in non-L-type HVA channels requires global rises in intracellular calcium, increases generated by calcium entry though numerous channels.

P/Q-type channels undergo a second calcium-dependent process whereby current activity increases following a strong membrane depolarization or a train of action potentials. This increase is only observed in the presence of external calcium, is insensitive to calcium buffers, and requires the high-affinity calcium binding sites on calmodulin (Chaudhuri et al. 2004; DeMaria et al. 2001). This process, termed calcium-dependent facilitation (CDF), is not observed with N-type or R-type channels and is $Ca_v2.1$ channel splice isoform dependent (Chaudhuri et al. 2004). The

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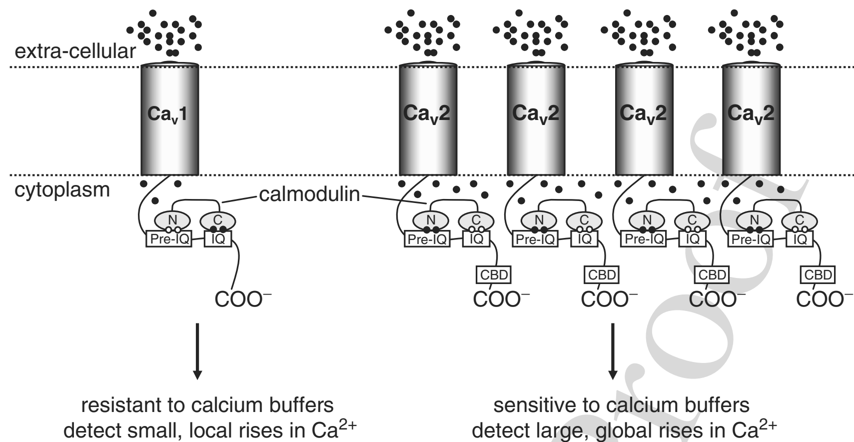

Fig. 4 Modulation of calcium channels by calcium binding proteins. Calcium-dependent inactivation (CDI) in L-type channels (Ca_V1) involves binding of calcium ions (•) to the high-affinity binding sites located on the C-lobe of calmodulin. In contrast, CDI in synaptic calcium channels involves binding of calcium ions to the low-affinity binding sites located on the N-lobe of calmodulin. Both types of CDI result in a loss of current activity, in response to calcium, as the inactivation kinetics of the channel are accelerated. However, because of the difference in occupation of low- versus high-affinity calcium binding sites, between channel types, different forms of CDI exhibit different properties. In the case of L-type channels, CDI is resistant to calcium buffers and detects small, local rises in calcium generated by a single ion channel (left), whereas, in the case of synaptic channels, CDI is sensitive to standard calcium buffers and detects large, global rises in calcium which require calcium entry through numerous channels (right). P/Q-type channels are also subject to calcium-dependent facilitation (CDF), and to modulation by the calcium binding proteins, calcium binding protein 1 (CaBP1) and visin-like protein 2 (VILIP-2). Both of these proteins bind to the calcium binding domain (CBD) on the channel's C-terminus. In contrast to calmodulin, CaBP1 antagonizes calcium channel opening in a calcium-independent manner, and VILIP-2 slows the inactivation kinetics of the channel.

distinct roles of the high- and low-affinity sites of calmodulin in CDF and CDI may thus manifest themselves in an initial upregulation of P/Q-type channel activity, followed by negative feedback inhibition as intracellular calcium concentration is increased.

We now know of other types of calcium binding proteins that mediate similar feedback regulation of P/Q-type calcium channels, including calcium binding protein 1 (CaBP1) and visin-like protein 2 (VILIP-2). Both of these proteins bind to the calcium binding domain (CBD) within the channel C-terminus and, compared with calmodulin, differentially regulate channel activity. CaBP1 antagonizes channel opening in a calcium-independent manner (Lee et al. 2002), whereas VILIP-2 slows the inactivation kinetics of the channel (Lautermilch et al. 2005). Both proteins must undergo myristoylation in order to mediate their effects (Few et al. 2005). To our knowledge, this type of regulation has only been described for P/Q-type calcium channels.

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Overall, the regulation of presynaptic calcium channels by different types of calcium binding proteins may provide for mechanisms by which neurons can fine tune the amount of calcium entering presynaptic nerve terminals, shift the relative contributions of N-type and P/Q-type channels to calcium entry, and thus regulate the amount of neurotransmitter that can be released from the synapse.

10 Summary

The entry of calcium into neurons via presynaptic calcium channels is a key step in evoked neurotransmitter release. Compromised calcium channel function can lead to severe neurological consequences, and yet the pharmacological inhibition of specific calcium channel subtypes can be beneficial in the treatment of conditions such as neuropathic pain. Because of the importance of these channels, neurons have evolved complex means for regulating calcium channel activity, including activation of second messenger pathways by G protein coupled receptors and feedback inhibition by calcium binding proteins. By these means, neurons are able to maintain the fine balance of cytoplasmic calcium levels that is required for optimal neurotransmitter release.

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