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Review

Neuronal Voltage-Gated Calcium Channels: Structure, Function, and Dysfunction

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Voltage-gated calcium channels are the primary mediators of depolarization-induced calcium entry into neurons. There is great diversity of calcium channel subtypes due to multiple genes that encode calcium channel α1 subunits, coassembly with a variety of ancillary calcium channel subunits, and alternative splicing. This allows these channels to fulfill highly specialized roles in specific neuronal subtypes and at particular subcellular loci. While calcium channels are of critical importance to brain function, their inappropriate expression or dysfunction gives rise to a variety of neurological disorders, including, pain, epilepsy, migraine, and ataxia. This Review discusses salient aspects of voltage-gated calcium channel function, physiology, and pathophysiology.

Introduction

The electrical activity of neurons and other excitable cells relies on a number of different types of voltage- and ligand-gated ion channels that are permeable to inorganic ions such as sodium, potassium, chloride, and calcium. While the former three ions support a predominantly electrogenic role, calcium ions are different in that they can not only alter membrane potential but also serve as important signaling entities (Clapham, 2007). Under normal resting conditions, intracellular calcium concentrations lie in the 100 nM range due to calcium-buffering molecules and sequestration into intracellular calcium stores (Clapham, 2007). Opening of voltage-gated calcium channels results in calcium influx along the electrochemical gradient, thus giving rise to a localized elevation of intracellular calcium into the high micromolar range (Wadel et al., 2007). This in turn triggers a wide range of calcium-dependent processes that include gene transcription, neurotransmitter release, neurite outgrowth, and the activation of calcium-dependent enzymes, such as calmodulin-dependent protein kinase II (CaMKII) and protein kinase C (PKC) (Wheeler et al., 1994, 2008, 2012) (for review, see Clapham, 2007). On the other hand, prolonged elevation of intracellular calcium levels is cytotoxic (Stanika et al., 2012) and, as a result, the activities of voltage-gated and other types of calcium-permeable channels are tightly regulated both by intrinsic gating processes, as well as by cell signaling pathways that control channel activity and trafficking to and from the plasma membrane (Simms and Zamponi, 2012). Dysregulation of these processes and associated alterations in calcium channel activity have been linked to various types of neurological disorders, including epilepsy, migraine, and chronic pain (for review, see Cain and Snutch, 2011). Therefore, voltage-gated calcium channels are important pharmacological targets for these and other conditions (Belardetti and Zamponi, 2012). Here, we will provide an overview of the physiological and pathophysiological roles of voltage-gated calcium channels in the central and peripheral nervous systems and highlight selected aspects of their structure, function, and modulation.

Subtypes, Pharmacology, and Structure of Voltage-Gated Calcium Channels

Voltage-gated calcium channels fall into two major categories: high voltage-activated (HVA) channels that open in response to large membrane depolarizations and low voltage-activated (LVA) channels that are activated by smaller voltage changes (Armstrong and Matteson, 1985; Bean, 1985) near typical neuronal resting membrane potentials. Based on biochemical and molecular analyses (Curtis and Catterall, 1984), we now know that HVA channels are heteromultimeric protein complexes that are formed through the coassembly of a pore-forming Cavα1 subunit, plus ancillary Cavβ and Cavα2δ subunits, whereas LVA channels appear to lack these ancillary subunits (Catterall et al., 2005). The Cavα1 subunit is the key determinant of calcium channel subtype. There are three major families of Cavα1 subunits (termed Cav1, Cav2, and Cav3), each of which have several members (Catterall et al., 2005). The Cav1 channel family encodes three different neuronal L-type channels (termed Cav1.2, Cav1.3, and Cav1.4) plus a skeletal muscle-specific isoform, Cav1.1 (Bech-Hansen et al., 1998; Mikami et al., 1989; Tanabe et al., 1987; Williams et al., 1992b). These channels display slow voltage-dependent gating characteristics and are sensitive to a number of different dihydropyridine (DHP) antagonists and agonists (Randall and Tsien, 1995). The Cav2 channel family includes three members (Cav2.1, Cav2.2, and Cav2.3). Through alternative splicing and assembly with specific ancillary subunits, Cav2.1 gives rise to P- and Q-type channels (Bourinet et al., 1999; Richards et al., 2007), which are both blocked (albeit with different affinities) by ω-agatoxin IVA—a peptide isolated from American funnel web spider venom (Adams et al., 1993). Cav2.2 encodes N-type channels (Dubel et al., 1992; Williams et al., 1992a) that are selectively inhibited by ω-conotoxins GVIA and MVIIA, toxins isolated from the venom of marine fish-hunting mollusks *Conus geographus* and *Conus magus*, respectively (McCleskey et al., 1987; Olivera et al., 1987). Cav2.3 corresponds to R-type channels (Soong et al., 1993) that can be inhibited by SNX-482, a peptide from *Hyristocrates Gigas* Tarantula venom (Bourinet et al., 2001; Newcomb et al.,

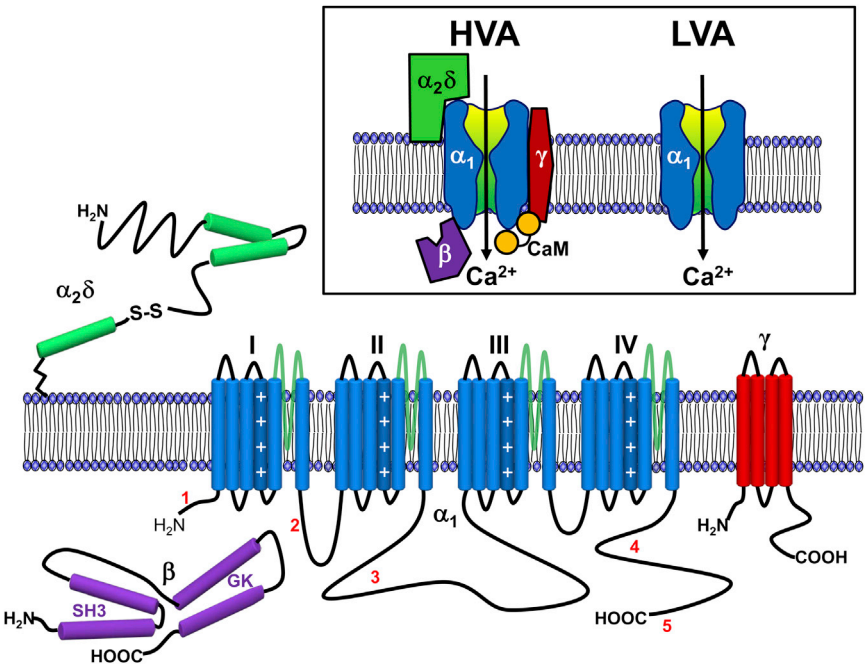

Figure 1. Subunit Composition and Transmembrane Topology of Voltage-Gated Calcium Channel Subunits

HVA channels are heteromultimers comprised of a pore-forming Cavα1 subunit that coassembles with ancillary Cavβ, Cavα2δ, and possibly Cavγ subunits, plus calmodulin (CaM); LVA channels on the other hand function as Cavα1 subunit monomers. The Cavα1 subunit is comprised of four major transmembrane domains (I–IV) that are connected by cytoplasmic linkers. Each of these domains contains six membrane-spanning helices, plus a re-entrant pore loop (shown in green). The fourth transmembrane segment in each domain contains positively charged amino acids in every third position and forms the voltage sensor. Key protein interaction sites with the Cavα1 subunits are indicated by numbers: (1) N-terminal calmodulin association site in L-type channels, (2) Cavβ interaction domain in all HVA channels, (3) synaptic protein interaction site (synprint) present in Cav2 channels, (4) PreIQ-IQ and IQ motifs in Cav1 and Cav2 channels that associate with calmodulin, and (5) scaffolding protein interaction sites in Cav2 channels. The Cavα2δ subunit is attached to the extracellular leaflet of the plasma membrane via a GPI anchor. The Cavβ subunit contains conserved interacting GK and SH3 domains that are separated by regions that are more variable among different Cavβ subunit isoforms. The Cavγ subunit contains four membrane-spanning helices; CaM has been omitted for simplicity.

1998). There are three types of Cav3 channels (Cav3.1, Cav3.2, and Cav3.3), all of which represent T-type calcium channels (Cribbs et al., 1998; Lee et al., 1999b; Perez-Reyes et al., 1998). Cav3 channels can be distinguished by their sensitivity to nickel and relative resistance to block by cadmium ions, which block all HVA channels in the low micromolar range (for review, see Perez-Reyes, 2003).

All ten Cavα1 subunits share a common transmembrane topology of four major transmembrane domains, each of which contain six membrane-spanning helices (termed S1–S6), a positively charged S4 segment that controls voltage-dependent activation (Catterall, 2010), and a re-entrant P loop motif between S5 and S6 that forms the permeation pathway (Figure 1). Each of the P loop regions contains highly conserved negatively charged amino acid residues (in the case of HVA channels, glutamic acids) that cooperate to form a pore that is highly selective for permeant cations such as calcium (Ellinor et al., 1995; Tang et al., 2014; Yang et al., 1993), barium, and strontium (Bourinet et al., 1996) and that interact with non-permeant divalents such as cadmium (Lansman et al., 1986). Different types of calcium channels display different single-channel conductances that vary over one order of magnitude, with Cav1.4 channels showing the smallest conductance (Doering et al., 2005; Fox et al., 1987; Weber et al., 2010). The major membrane domains are connected by large cytoplasmic linker regions and are bracketed by cytoplasmic N and C termini (Catterall et al., 2005). These cytoplasmic regions show the greatest sequence variation among channel subtypes and not only are important for second messenger regulation of channel function but also contain important sites for protein-protein interactions with regulatory elements, such as G proteins and protein kinases (Dai et al., 2009; Hall et al., 2013; Zamponi et al., 1997). Each of the known Cavα1 subunits can undergo alternative splicing, which may occur in a tissue- and age-dependent manner (Chaudhuri et al., 2004; Liao et al., 2005; Lipscombe, 2005; Lipscombe et al., 2013; Tan et al., 2011, 2012). Furthermore, RNA editing has been reported for Cav1.3 channels (Bazzazi et al., 2013; Huang et al., 2012), thus giving rise to additional functional diversity.

There are four known genes that encode Cavβ subunits (Cavβ1–Cavβ4), again with multiple alternative splice transcripts (for review, see Buraei and Yang, 2010). They are cytoplasmic proteins that contain conserved GK and SH3 domains and associate with the Cavα1 subunit at the domain I-II linker (Opatowsky et al., 2004; Pragnell et al., 1994; Van Petegem et al., 2004) (Figure 1). This results in alterations of the gating properties of the Cavα1 subunit, and perhaps more importantly, in increased cell surface trafficking (Brice and Dolphin, 1999; Buraei and Yang, 2010). The latter phenomenon is due to an inhibition of ubiquitination and degradation of the channels in the proteasome and perhaps in part due to masking of intrinsic ER retention signals in the Cavα1 subunit (Altier et al., 2011; Bichet et al., 2000; Waithe et al., 2011). In addition, it has been suggested that the Cav1.2 domain I-II linker contains an ER export signal that facilitates membrane expression (Fang and Colecraft, 2011) and that the Cavβ subunits act as a switch that shifts the balance between the export mechanism and ER retention signals in other parts of the channel, such as the C terminus (Altier et al., 2011).

There are also four different types of Cavα2δ subunits (Cavα2δ1–Cavα2δ4) that are each transcribed and translated as a single protein, posttranslationally cleaved, and then reconnected by a disulfide bond (for review, see Dolphin, 2013). It was originally thought that the Cavδ portion spanned the plasma

membrane, but more recent evidence indicates that the entire Cavα2δ subunit is attached to the extracellular leaflet of the plasma membrane via a glycophosphatidylinositol (GPI) anchor (Davies et al., 2010; Kadurin et al., 2012) (Figure 1). While there appears to be only a small effect of Cavα2δ on channel function (Yasuda et al., 2004), its coexpression typically results in augmented channel cell surface density. These changes in channel cell surface density are critically dependent on a metal ion binding site located within a von Willebrand factor domain of the α2 portion of this subunit (Cantí et al., 2005). In neurons, increased expression of Cavα2δ results in improved synaptic targeting of voltage-gated calcium channels and enhanced release probability, which occurs independently of the trafficking effect (Hoppa et al., 2012). Recent evidence indicates that Cavα2δ subunits act as thrombospondin receptors and it is possible that interactions with thrombospondin are involved in the aforementioned modulation of synaptic release (Eroglu et al., 2009).

Skeletal muscle L-type channels also contain an ancillary Cavγ subunit that contains four transmembrane helices (Arikkath and Campbell, 2003; Sharp and Campbell, 1989). As many as seven potential Cavγ isoforms have been identified in neuronal tissue, including Cavγ2, which is also known as "*stargazin*" (Chen et al., 2007; Chu et al., 2001). However, while certain types of Cavγ subunits can have profound effects on whole-cell current density, it is not clear whether they should be considered true neuronal calcium channels subunits (Letts et al., 1998; Rousset et al., 2001). Moreover, subunits such as *stargazin* have been associated with other cellular functions such as AMPA receptor trafficking (Bats et al., 2007; Matsuda et al., 2013; Tomita et al., 2005). There is however considerable evidence that all HVA channels associate with calmodulin (CaM), suggesting that CaM should be considered as the fourth calcium channel subunit (Minor and Findeisen, 2010; Peterson et al., 1999; Zühlke et al., 1999). Given the importance of ancillary subunits for HVA channels, it is surprising that the trafficking and overall biophysical properties of Cav3 channels in heterologous expression systems are reconstituted well with only the Cavα1 subunit (Perez-Reyes, 2003). Whether T-type channels include specific membrane-targeting motifs that are absent in HVA channels or lack ER retention and proteasomal-targeting motifs remains to be determined.

The majority of the structure/function information about voltage-gated calcium channels has been deduced from site-directed mutagenesis and generation of chimeric calcium channel subunits. Based on the crystal structures of potassium channels, several homology models of Cavα1 subunits have been constructed and used to model drug interactions, in particular with L-type channels (Huber et al., 2000; Lipkind and Fozzard, 2003; Zamponi et al., 2003). Cryo-EM structures have revealed crude structural information about this channel subtype (Serysheva et al., 2002; Walsh et al., 2009a, 2009b; Wolf et al., 2003), however, not at a resolution high enough to gain insights into the structural basis of channel function. Unlike potassium and bacterial sodium channels, it has not yet been possible to obtain crystal structure information concerning entire mammalian Cavα1 subunits. Crystal structures of the Cavβ subunit bound to a fragment of the Cavα1 subunit I-II linker have been solved by multiple groups, however (Chen et al., 2004; Opatowsky et al., 2004; Van Petegem et al., 2004). Furthermore, cocrystal structure studies and even NMR structures of calmodulin bound to Cav1.2 and Cav2.1 have been reported (Fallon et al., 2005, 2009; Kim et al., 2008, 2010; Liu and Vogel, 2012; Mori et al., 2008; Van Petegem et al., 2005). While these works have provided some advance in our understanding of subunit regulation of voltage-gated calcium channels, it remains to be determined whether the observed interactions are relevant to actual conformations in holochannels or perhaps modified by the presence of transmembrane regions and other intracellular domains.

Determinants of Calcium Channel Inactivation

To prevent calcium overload in response to prolonged membrane depolarization, voltage-gated calcium channels possess voltage- and/or calcium-dependent inactivation mechanisms. Voltage-dependent inactivation (VDI) is a property that is common to all voltage-gated calcium channel subtypes, although the extent of voltage-dependent inactivation varies with calcium channel isoform and is potently modulated in HVA channels by the Cavβ subunit (for review, see Stotz et al., 2004). Unlike voltage-gated potassium and sodium channels where there is evidence of a pore blocking, inactivation gating particle for N-type inactivation mechanisms (i.e., "ball and chain" and "hinged-lid") (Hoshi et al., 1990; West et al., 1992), it has proven somewhat more difficult to identify the mechanistic basis of VDI in calcium channels. Numerous studies have identified amino acid residues that appear to modulate inactivation, and many of them are found in either the domain I-II linker region or in the S6 regions of the major transmembrane domains (Berrou et al., 2001; Herlitze et al., 1997; Kraus et al., 1998; Stotz and Zamponi, 2001a). Based on extensive mutagenesis and chimeric work on HVA channels (Spaetgens and Zamponi, 1999; Stotz et al., 2000; Stotz and Zamponi, 2001b), we proposed a model in which the S6 segments undergo structural rearrangement in response to prolonged membrane depolarization (Figure 2). This then may expose a docking site for the domain I-II linker to act as a hinged-lid-like gating particle (Stotz et al., 2004). In Cav1.3 channels, this docking process may be modulated by an additional inhibitory element, termed the inactivation shield (Tadross et al., 2010). Interestingly, Cav3 (T-type) channels appear to be different from HVA channels with regard to VDI, such that the domain III-IV linker and C terminus appear to be important structural determinants in this channel family (Hamid et al., 2006; Ohkubo et al., 2005; Staes et al., 2001). It is thus possible that Cav3 channels contain a domain III-IV linker inactivation particle analogous to what is seen with sodium channel VDI. Whether these channels also contain an inactivation shield remains to be determined. Ultimately, crystal structure information will be required to gain precise insights into how calcium channels inactivate in response to voltage. Understanding how inactivation works at the molecular level is particularly important given that many clinically used drug compounds, such as DHPs and antiepileptics, show strong inactivated state dependences of block (Berjukow et al., 2000; Gomora et al., 2001).

A much more complete picture has emerged in the area of calcium-dependent inactivation (CDI), although it is by no means less complicated. CDI becomes apparent when comparing

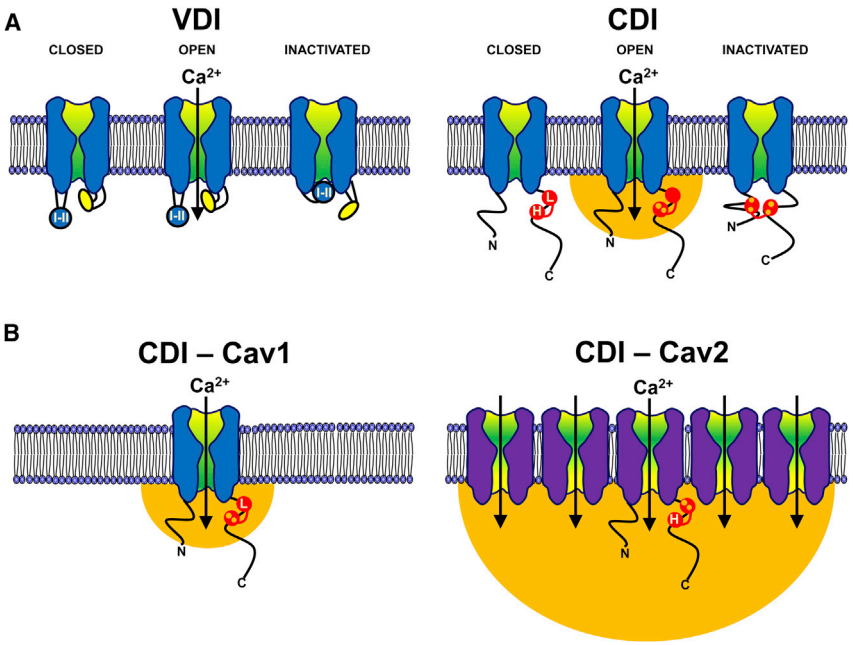

Figure 2. Schematic Representation of Possible Voltage-Dependent Inactivation and Calcium-Dependent Inactivation Mechanisms in HVA Channels

(A) Left: membrane depolarizations trigger a conformational change in the channel that results in a transition from closed to open (i.e., calcium-conducting state). Prolonged membrane depolarization triggers a further change in channel conformation (potentially mediated by the S6 segments in the four membrane domains, not shown). This may reposition a channel structure termed an "inactivation shield" (yellow), thus exposing a docking site for the inactivation gate that is formed by the domain I-II linker (blue ball-like structure). The inactivation gate then physically obstructs calcium entry. Right: calcium influx upon membrane depolarization also created a calcium domain near the inner mouth of the pore. Calcium binds to calmodulin (CaM, indicated by dumbbell structure in red with its high- [H] affinity and low- [L] affinity calcium binding sites) that is preassociated with the C terminus of the channel, which in turn causes molecular repositioning of CaM in the C terminus region and additional interactions with sites in the N terminus region of the channel when fully loaded with calcium (small orange dots). This leads to an inactivated (nonconducting) conformation of the channel.

(B) Calcium influx though an individual Cav1 channels creates a calcium nanodomain that is sufficient to activate the high-affinity sites on calmodulin, which in turn goes on to cause CDI (this process is EGTA insensitive). In contrast, for Cav2 channels, a concerted opening of multiple channels gives rise to a calcium microdomain that activates the low-affinity binding sites of CaM to trigger CDI (this can be blocked by EGTA).

channel current kinetics in the presence of barium to that of calcium, with the latter charge carrier imparting pronounced speeding of current decay kinetics (Imredy and Yue, 1994). This effect is critically dependent on CaM and blocked by overexpressing a dominant-negative mutant of CaM that lacks the ability to bind calcium (Lee et al., 1999a; Peterson et al., 1999; Zühlke et al., 1999). From a mechanistic standpoint, it is believed that calcium-free CaM is preassociated or anchored to the C terminus of the channel such that the C-terminal lobe of CaM interacts with the "IQ" domain and the N-terminal lobe with an upstream EF-hand region (Ben Johny et al., 2013; Liu et al., 2010) (Figure 2). Upon a rise in intracellular calcium, channel-anchored CaM binds calcium, which in turn promotes a conformational change in the C terminus/CaM complex and gives rise to CDI (Ben Johny et al., 2013; Erickson et al., 2001, 2003; Peterson et al., 2000) (Figure 2). For many years CDI was thought to only occur with L-type channels because no calcium-induced speeding of current decay kinetics was observed with native or cloned N-, R-, or T-type channels. However, whole-cell recordings during this era were typically performed with 10 mM EGTA in the patch pipette, which produces significant reduction in intracellular calcium. On the other hand, when intracellular calcium buffering is made less stringent with 0.5 mM EGTA, CDI also becomes apparent for the three members of the Cav2 channel family (Liang et al., 2003). In other words, CDI of Cav1.2 and Cav1.3 channels is supported by a local rise in calcium near the inner mouth of the pore, or rather, calcium entry through an individual channel is sufficient to mediate its own CDI (Zamponi, 2003a). In contrast, CDI of Cav2 channels requires a global rise in intracellular calcium, which is supported by the concerted calcium influx of a population of channels, hence explaining the EGTA sensitivity of this process (Dick et al., 2008; Erickson et al., 2003; Tadross et al., 2008; Zamponi, 2003a). This differential sensitivity to local and global calcium rises is due to the differential involvement of the high- and low-affinity calcium binding lobes on the CaM molecule, respectively, as revealed by site-directed mutagenesis of the calcium binding sites on CaM.

There are several additional twists to CDI: first, although Cav1.4 channels can bind calmodulin, they lack CDI (McRory et al., 2004), the latter because of an autoinhibitory domain in the distal C terminus that occludes upstream CaM binding sequences (Griessmeier et al., 2009; Singh et al., 2006; Wahl-Schott et al., 2006). From a mechanistic point of view, this autoinhibitory domain appears to act like an enzyme competitive inhibitor that regulates the affinity of calcium-free calmodulin for the channel (Liu et al., 2010). The resulting resistance to inactivation is probably necessary because these channels support tonic glutamate release in photoreceptor synapses (Morgans, 2000) and must therefore show sustained activity at depolarized potentials. Second, there is a curious absence of CDI for native Cav1.3 currents in auditory hair cells. This absence appears to be due to calcium-binding protein 4 (CaBP4), a CaM homolog with reduced calcium binding ability that is expressed in these cells and antagonizes the CDI process (Yang et al., 2006). It was originally suggested, based on studies on channel fragments, that competition between CaBP4 and CaM for the C terminus of Cav1.2 may lay at the root of the disruption of CDI by CaBP (Findeisen et al., 2013; Oz et al., 2013). However, more recent evidence based on work in intact channels indicates that CaBP may modulate CaM affinity by an allosteric mechanism (Yang et al., 2014). Third, recent evidence shows that CDI of Cav1.2 channels requires two different CaM molecules bound to the C terminus (Kim et al., 2010). Fourth, Cav1.3 shows

distinct modes of CDI that differentially depend on the high- (C-lobe) and low- (N-lobe) affinity calcium binding sites of CaM (Ben Johny et al., 2013). Cav1 channel CDI that depends on the high-affinity C-lobe of CaM appears to require only C-terminal regions of the channel, while low-affinity N-lobe CDI involves interactions of CaM with several N-terminal regions, as well as the C terminus (Dick et al., 2008; Simms et al., 2013) (Figure 2). Fifth, crystal structure information reveals that CaM interacts with the Cav2.1 C terminus in an opposite orientation compared to Cav1.2 (Kim et al., 2008), whereas Cav2.3 and Cav2.1 seem to bind CaM in the same orientation (Mori et al., 2008). The physiological significance of this finding is unclear.

Finally, Cav2.1 channels show a second form of calcium regulation (calcium-dependent facilitation [CDF]) that involves the high-affinity sites on CaM (DeMaria et al., 2001; Lee et al., 2003). Single-channel recording demonstrates that unlike CDI of these channels, which requires global calcium increase, calcium entry through an individual Cav2.1 channel is sufficient to promote CDF (Chaudhuri et al., 2007). Furthermore, this example highlights how Cav2.1 channels can be differentially regulated by two opposing calcium-dependent processes while using the same calcium sensor, CaM. Interestingly, L-type channels can exhibit CDF but only with substantial C-terminal mutations in the same region that natively promotes CDF of Cav2 channels (Hudmon et al., 2005; Zühlke et al., 1999) and appears to be stronger for channels expressed in oocytes compared to mammalian cells. Whether CDF and CDI are mediated by distinct binding conformations, orientations of CaM, or separate CaM molecules bound at different regions of Cav1 and Cav2 channels remains to be determined.

Altogether, CDI and VDI are important processes that limit excessive calcium entry into the cytosol. While VDI is intrinsic to the channel and only depends on voltage, CDI is a tunable process that provides feedback inhibition in response to rising intracellular calcium levels.

Role of Voltage-Gated Calcium Channels in Synaptic Transmission

Voltage-gated calcium channels are important mediators of depolarization-evoked release of neurotransmitters. To ensure efficient coupling of calcium influx to rapid vesicle release, calcium channels must be localized within the active zones of presynaptic nerve terminals. Most CNS synapses rely on Cav2.2 and Cav2.1 calcium channels for fast synaptic transmission (Wheeler et al., 1994) and both of these channel subtypes contain a synaptic protein interaction (synprint) site within the intracellular domain II-III linker region. This synprint site interacts with proteins of the synaptic vesicle release complex, such as syntaxin 1 and SNAP-25, thus placing the channels in close proximity to synaptic vesicles (Rettig et al., 1996; Sheng et al., 1994, 1996). Interaction of the vesicle release complex with the channels alters calcium channel function by promoting voltage-dependent inactivation and G$\beta\gamma$ modulation (Bezprozvanny et al., 1995; Jarvis and Zamponi, 2001). Cav2.3 channels are also capable of interacting with synaptic vesicle release proteins, however, with different channel and syntaxin structural determinants (Davies et al., 2011). The interactions between Cav2 channels and SNARE proteins have been subject to numerous reviews (Weiss and Zamponi, 2012; Zamponi, 2003b) and, hence, we will not further belabor the molecular details. It is however interesting to note that invertebrate Cav2 channels do not possess a synprint-like motif (Spafford et al., 2003), and splice isoforms of mammalian Cav2.2 and Cav2.1 channels that lack the synprint have been reported (Kaneko et al., 2002; Rajapaksha et al., 2008). Hence, it appears as if there are redundant or perhaps more important mechanisms that localize Cav2 channels to presynaptic sites. Indeed, adaptor proteins such as Mint-1 and CASK (Maximov and Bezprozvanny, 2002; Spafford et al., 2003), Rab3-interacting molecules (RIMs) (Graf et al., 2012; Kaeser et al., 2011; Kiyonaka et al., 2007), and RIM binding proteins such as DRBP (Liu et al., 2011) all are important for organizing Cav2 channels within active zones. Whether this is mediated through direct binding of these proteins to the Cav2 channel has, however, been subject to some debate (Wong and Stanley, 2010).

At the majority of CNS synapses, Cav1 channels are localized postsynaptically rather than presynaptically (Tippens et al., 2008) and may be anchored to postsynaptic sites via adaptor proteins such as Shank (Zhang et al., 2005). Cav1.3 and Cav1.4 channels are, however, important players on the presynaptic side of ribbon synapses in cochlear hair cells and in photoreceptor terminals (Striessnig, 2013), where their functions are modulated by other interacting proteins such as CaBP4 (Haeseleer et al., 2004). Unlike the Cav2 family, Cav1 channels do not possess a synprint-like motif for interactions with SNARE proteins, and they lack the Mint-1 and CASK interaction domains present in Cav2 channels. Instead, the organization of Cav1 channels in these synapses is critically dependent on bassoon (Frank et al., 2010; Jing et al., 2013). This different molecular organization may reflect the fact that the requirement for calcium channel function in postsynaptic photoreceptor nerve termini compared with, for example, a presynatpic cortical synapse, are fundamentally different. In the latter case, calcium channels need to open transiently in response to an incoming action potential to generate a large but temporally precise calcium influx, for which N-type channels with their high single-channel conductance are particularly well suited (Weber et al., 2010). In contrast, photoreceptors are depolarized in the dark where they tonically release glutamate (Morgans, 2000), requiring sustained calcium channel activity that is terminated upon light-induced membrane hyperpolarization. Not only does this require calcium channels to be noninactivating (as ensured by autoinhibitory elements and interactions with calcium binding proteins, see preceding section), but it may also demand a completely different architecture of calcium channels and associated synaptic, anchoring proteins. This underscores the importance for mammalian neurons to have a palette of different calcium channels and interacting partners that are tailored for specific neurophysiological functions.

L-type calcium channels are also important in hormone secretion. This has been particularly well studied in adrenal chromaffin cells where calcium entry via Cav1.2 and Cav1.3 drives much of the release of catecholamines (for review, see Vandael et al., 2013). An interesting twist to the role of calcium channels in secretion has been observed in these cells (Hagalili et al., 2008). Hagalili and colleagues reported that Cav1.2 channel

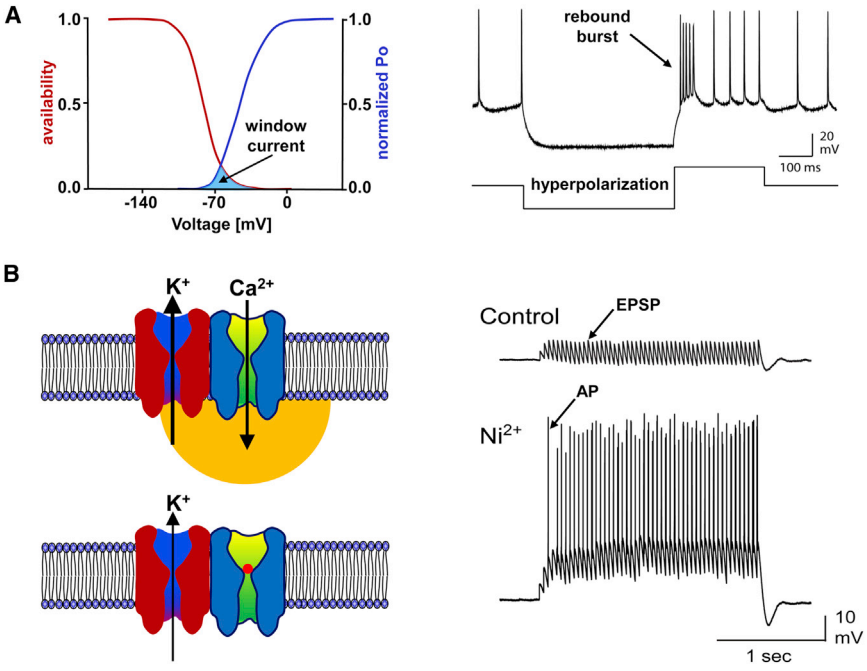

Figure 3. T-type Channel-Mediated Regulation of Neuronal Excitability

(A) Schematic representation of steady-state activation and inactivation curves for a T-type calcium channel. Note the overlap between these two curves that gives rise to a "window current" (indicated in blue). Note also that the exact position of the window current depends on neuronal subtype. At a typical neuronal resting potential of −70 mV, a large fraction of T-type channels are inactivated and thus unavailable for opening. A transient hyperpolarization will recover these channels from inactivation, thus increasing their availability. An ensuing depolarization will then activate a greater number of channels, thereby giving rise to a rebound burst. Such rebound bursting is exemplified in this current-clamp recording from a Golgi cell, which was mediated by Cav3.1 (taken from Molineux et al., 2006) (copyright by the National Academy of Sciences). (B) Calcium influx via T-type channels (blue) generates a local calcium domain (orange). KCa3.1 channels that are physically associated with T-type channels are activated by this rise in intracellular calcium. This hyperpolarization inhibits the temporal summation of parallel fiber excitatory postsynaptic potentials (EPSPs; reflected in a small upward spike in the current-clamp recording, see arrow) in Purkinje neurons, thus preventing action potential firing. Blocking T-type channel activity with nickel (indicated by red dot inside the channel pore) prevents calcium influx and thus reduces KCa3.1 channel activity. This allows temporal summation of parallel fiber EPSPs to trigger action potential (AP) discharges (see bottom current-clamp trace). These recordings were taken from Engbers et al. (2012) (copyright by the National Academy of Sciences).

mutants that are impermeant to calcium ions can partake in catecholamine release by direct coupling of the channel activation machinery to the vesicle release apparatus (see also Marom et al., 2010). Whether this mechanism is specific to chromaffin cells or perhaps also applicable to nerve terminals is unclear.

There is also increasing evidence that Cav3 calcium channels can contribute to exocytosis, specifically catecholamine release from chromaffin cells (Carabelli et al., 2007). They have also been implicated in neurotransmitter release in both the retina and olfactory bulb (Egger et al., 2003; Pan et al., 2001) (for review, see Carbone et al., 2006) and may contribute to synaptic transmission in hippocampal interneurons (Tang et al., 2011). More recent evidence has implicated T-type calcium channels in spontaneous synaptic release in dorsal horn synapses (Jacus et al., 2012) and in *trans*-glial chemical communication between dorsal root ganglion neurons (Rozanski et al., 2013). T-type calcium channels are particularly well suited for supporting low-threshold exocytosis because of their biophysical characteristics (specifically their low voltage dependence of activation and inactivation), which give rise to a small window current near resting neuronal membrane potentials (Figure 3). This in turn allows calcium entry via these channels in response to small voltage changes and hence activation of the release machinery.

Like Cav2 channels, all members of the Cav3 calcium channel family associate with the SNARE proteins syntaxin 1 and SNAP25; however, they do so via their C terminus, rather than the domain III-IV linker region (Weiss et al., 2012). Interestingly, coexpression with syntaxin 1A mediates a strong hyperpolarizing shift in half inactivation potential that is abolished upon coexpression with SNAP25, or alternatively when syntaxin is locked in its "open" conformation (Weiss et al., 2012). The significance of modulating channel availability in this manner is not clear, although it suggests that channels that are associated exclusively with syntaxin 1A, rather than the full complement of t-SNAREs, are less likely to support calcium entry and, thus, vesicle release. Exogenous expression of Cav3.2 channels in a chromaffin cell line induces low-threshold release, which can be blocked by coexpressing a peptide corresponding to the syntaxin interaction domain of the channel (Weiss et al., 2012). This indicates that physical association of Cav3.2 with syntaxin is of critical importance for T-type channel-mediated, low-threshold exocytosis.

Altogether, it is remarkable that all known types of neuronal calcium channels have been implicated in supporting secretion/neurotransmitter release, with specific roles being fulfilled by all major classes of calcium channels (i.e., fast synaptic transmission for Cav2 channels, tonic and slower release by Cav1 channels, and low-threshold exocytosis by Cav3 channels).

Calcium Channels and Neuronal Firing

Both HVA and LVA channels are important regulators of neuronal firing properties. As noted earlier, T-type channels are activated by small membrane depolarizations. At typical neuronal resting membrane potentials, however, a large fraction of T-type channels are inactivated (i.e., unavailable for opening) (Coulter et al., 1989). A transient membrane hyperpolarization can be sufficient to recover T-type channels from their inactivated state (Figure 3), such that an ensuing depolarization activates a larger population of T-type channels, leading to a dramatic

augmentation in whole-cell T-type current amplitude. This causes a low-threshold calcium potential that facilitates the activation of voltage-gated sodium channels to give rise to a burst of action potentials (Alviña et al., 2009; Destexhe et al., 1998). This phenomenon is termed ''rebound bursting'' and is of critical importance for the output of many different types of neurons (Molineux et al., 2006), perhaps most notably in thalamocortical relay neurons and in thalamic reticular neurons (Huguenard, 1998; Ulrich and Huguenard, 1997) (Figure 3). It should also be noted that Cav1.3 calcium channels display a relatively hyperpolarized range of activation (Xu and Lipscombe, 2001), and given their dendritic localization, it is possible that these channels could act like T-type channels in regulating postsynaptic activity.

There are other ways by which voltage-gated calcium channels can control neuronal firing frequency, and these are related to their calcium permeability rather than their electrogenic function. In cerebellar stellate cells and perhaps other types of neurons, all types of Cav3 channels are able to associate with Kv4.2 calcium-activated potassium channels into a large macromolecular signaling complex that also includes K channel-interacting protein 3 (KChIP3) (Anderson et al., 2010a, 2010b). This interaction bestows calcium sensitivity onto Kv4.2 inactivation, leading to increased Kv4.2 channel availability upon T-type current activation and a decrease in output gain (Anderson et al., 2010a). This phenomenon is exquisitely calcium sensitive such that the Kv4.2/Cav3/KChIP3 complex can act as a detector of extracellular changes in calcium concentration (Anderson et al., 2013) and mediate adaptive changes to maintain synaptic fidelity under conditions where extracellular calcium drops into the submillimolar range. Similarly, Cav3 channels can physically and functionally interact with intermediate conductance calcium-activated potassium channels (KCa3.1) in cerebellar Purkinje neurons. Calcium entry via Cav3 channels activates KCa3.1, which helps control temporal summation of synaptic inputs (Engbers et al., 2012) (Figure 3). Cav3 channels also form physical signaling complexes with large conductance calcium-activated potassium (KCa1.1) channels in medial vestibular neurons (Rehak et al., 2013). In these neurons calcium entry via T-type channels helps activate KCa1.1 channels to slow firing frequency. Along these lines, it has been reported that calcium entry via T-type channels modulates small conductance calcium-activated potassium (KCa2.1) channels in thalamic reticular neurons (Cueni et al., 2008) to regulate oscillatory behavior. This suggests that thalamic reticular neurons exhibit both electrogenic (i.e., rebound burst) and calcium-dependent mechanisms by which T-type channels shape their firing properties. Finally, the ability to regulate neuronal output via calcium-dependent activation of potassium conductances is also observed with members of the HVA calcium channel family. For example, Cav1.2, Cav2.1, and Cav2.2 channels physically associate with KCa1.1 channels to shape action potential repolarization (Berkefeld and Fakler, 2008; Berkefeld et al., 2006; Müller et al., 2010) and, in the case of chromaffin cells, pacemaking (Vandael et al., 2012). Hence, members of all three major classes of calcium channels are important regulators of neuronal firing properties, by virtue of their control over calcium-sensitive potassium channels.

Calcium Channels and Gene Transcription

It is well established that increases in intracellular calcium contribute to the initiation of gene transcription. As voltage-gated calcium channels are a major source of calcium influx, it is not surprising that these channels contribute to gene regulation. However, they do so in an intricate and regulated manner and in some cases independently of calcium influx. Below, we give an overview of the role of Cavα1 and Cavβ subunits in this process.

Cav1 Channels

L-type calcium channels were the first voltage-gated channels shown to regulate gene transcription and there is an extensive body of literature on this topic. L-type channel agonists and antagonists were shown to, respectively, promote and inhibit gene transcription of immediate early genes over 20 years ago in cortical neurons (Murphy et al., 1991). CaM kinase was recognized shortly thereafter as a critical signaling intermediate between L-type channels at the cell membrane and gene transcription in the nucleus (Bading et al., 1993). A brief KCl-induced depolarization of hippocampal neurons (i.e., 1 min) promotes translocation of calmodulin to the nucleus (Deisseroth et al., 1998), which in turn promotes the phosphorylation and activation of CREB (Thompson et al., 1995). Both the translocation of calmodulin and CREB activation are perturbed by L-type calcium channel blockers (Eickelberg et al., 1999; Wheeler et al., 2006). Interestingly, neuronal depolarization activates CREB gene transcription by two temporally distinct signaling cascades. Brief depolarization (1–10 min) activates CREB through a CaM/CaM kinase-dependent pathway, while sustained depolarization ($\geq$30 min) was shown to recruit a secondary Ras/MAPK pathway (Wu et al., 2001).

Additional evidence for L-type channel involvement in CREB transcription came from LTP studies in hippocampal neurons that demonstrated that CREB transcription critically depended on L-type calcium channel activity, with relatively little involvement from AMPA and NMDA receptors (Impey et al., 1996; Rajadhyaksha et al., 1999). This was recently confirmed with a conditional hippocampus/neocortex Cav1.2 knockout mouse that demonstrates an essential role of Cav1.2 in CREB signaling during LTP and spatial learning (Moosmang et al., 2005). NMDA receptors can however induce excitatory cell death by promoting transcription of genes controlled by another transcription factor, C/EBPβ, a process opposed by L-type calcium channels (Marshall et al., 2003). L-type channels also oppose nicotinic signaling to CREB in ciliary ganglion neurons, although the underlying mechanism is unclear (Chang and Berg, 2001). This suggests that L-type channels can both promote and antagonize aspects of gene transcription.

By expressing exogenous DHP-insensitive Cav1.2 channel variants in hippocampal neurons, while at the same time eliminating the contributions from the endogenous channels with DHPs, Dolmetsch and colleagues were able to examine the channel structural determinants that underlie the coupling between Cav1.2 channels and CREB activation (Dolmetsch et al., 2001). An extended depolarization (30 min) supported CREB gene transcription via the aforementioned Ras/MAPK pathway whose activation was shown to depend on the IQ domain that anchors CaM to the C terminus of the channel (Figure 4). This

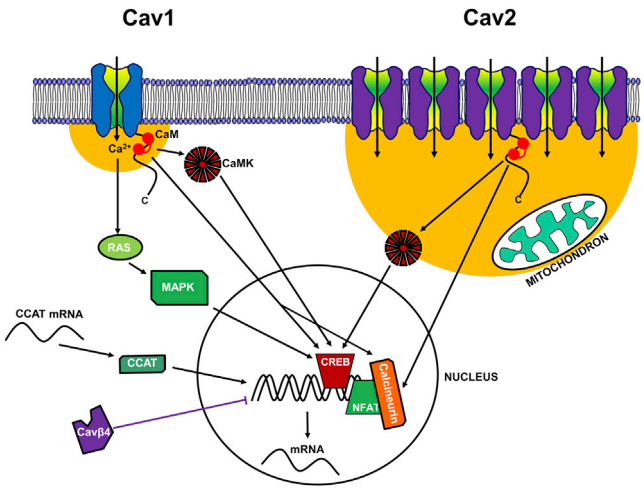

Figure 4. Pathways Involved in Calcium Channel Induced Changes in Gene Transcription

Prolonged calcium influx via Cav1 channels activates gene transcription via Ras and MAP kinase. In addition, brief calcium activation of calmodulin (CaM) stimulates CREB activation though direct signaling to the nucleus, or via activation of CaM kinase that is located in close proximity of the channel. The C terminus of Cav1.2 channels contains a transcription factor (CCAT) that can be expressed independently of full-length calcium channels and that can translocate to the nucleus. In contrast, Cav2 channel-mediated gene activation requires the concerted action of multiple channels to give rise to a larger calcium microdomain that is augmented by calcium release from mitochondria and ER (not shown). This directly activates more distantly localized CaM kinase clusters that in turn stimulate CREB. A calmodulin-mediated activation of NFAT has been shown to occur via calcineurin. Cavβ subunits can also be targeted to the nucleus where they appear to act as transcriptional repressors.

allows CaM to be situated close to the source of calcium influx, and after channel opening, CaM is thought to translocate to the nucleus to promote CREB activation (Deisseroth et al., 1998). How exactly CaM translocates to the nucleus in response to channel opening vis a vis the role of this interaction in CDI of the channel is unclear. It was subsequently shown that Cav1.3 channels couple to CREB more effectively than Cav1.2 channels in hippocampal neurons, especially during brief periods of neuronal activity, whereas they appear to be the exclusive driver of CREB activation in striatal medium spiny neurons (Zhang et al., 2006). In the nucleus accumbens, acute cocaine treatment activates CREB via Cav1.3 channels, but when mice are sensitized to cocaine, Cav1.2 overrides Cav1.3-mediated CREB activity (Giordano et al., 2010). The functional redundancy (and occasionally competition) of L-type channel signaling to CREB underscores the importance of this process for neuronal function.

While CaM promotes CREB-mediated gene transcription in response to prolonged neuronal activity, CaM kinase appears to underlie a more rapid L-type channel-mediated signaling process (Wu et al., 2001). Brief periods of channel activity result in the translocation of CaM kinase puncta to the vicinity of the channel, which then rapidly signal to the nucleus to activate CREB (Wheeler et al., 2008). This phenomenon appears to be tightly linked to the open probability of the channels rather than a mere rise in bulk intracellular calcium, suggesting that specific associations with L-type channels are necessary to support this signaling process.

Another twist in understanding L-type channel-mediated gene transcription is the observation that the Cav1.2 C terminus region can translocate to the nucleus and act as a transcription factor that was termed CCAT (calcium channel-associated transcription) (Gomez-Ospina et al., 2006). CCAT modulates transcription of gap junction proteins, NMDA and potassium channel subunits, and regulatory proteins such as kinases and chemokine ligands (Gomez-Ospina et al., 2006). Furthermore, CCAT promotes neurite outgrowth (Gomez-Ospina et al., 2013). Initially believed to result from proteolytic cleavage of the Cav1.2 C terminus, similar to what had been reported in cardiac cells (Hulme et al., 2006), CCAT is actually controlled by a cryptic promoter in exon 46 of the Cav1.2 gene (Gomez-Ospina et al., 2013). Expression analysis shows that CCAT is present in cortex, cerebellum, and diencephalon and, more importantly, can be expressed independently of full-length Cav1.2 mRNA (Gomez-Ospina et al., 2013). This unexpected, nonelectrogenic function needs to be borne in mind when considering the effects of mutations in Cav1.2 channels that are linked to human disease.

Although L-type channel-mediated activation of CREB has received perhaps the most attention, these channels also promote activation of other transcription factors. This includes activation of NFAT (specifically the NFATc4 isoform) in hippocampal neurons and is mediated by the calcium-dependent phosphatase calcineurin (Graef et al., 1999). This process is improved by AKAP79/150 expression in part because of enhanced calcineurin targeting to the channels (Oliveria et al., 2007) and also because AKAP can regulate release of calcineurin more effectively (Li et al., 2012). Whether the CaM/IQ interaction is involved in calcineurin/NFAT-mediated gene transcription is unknown, although the distal C terminus of Cav1.2 is known to bind calcineurin (Tandan et al., 2009).

Cav2 Channels

Cav2 channels also promote NFAT- and CREB-mediated gene transcription, although the molecular underpinnings are not well understood. One overriding theme for Cav2-mediated gene transcription is the requirement for a global calcium rise (reminiscent of Cav2 CDI), which is not the case for Cav1-mediated gene transcription. For instance, Cav2.1 channels promote expression of syntaxin 1A by a CaM kinase-, PKA-, and MAPK-sensitive pathway (likely CREB), but not if cytosolic calcium is buffered with EGTA (Sutton et al., 1999). Syntaxin 1A expression can also be triggered by thapsigargin, or caffeine in the presence of ω-agatoxin IVA, suggesting that although Cav2.1 channels can promote syntaxin 1A expression, a global rise in calcium from other sources is as effective (Sutton et al., 1999). N-type calcium channels have been shown to promote NFAT (NFATc1 isoform) nuclear localization in sympathetic ganglion neurons in response to 10 Hz stimulation (Hernández-Ochoa et al., 2007). A slower 1 Hz stimulation was not sufficient to promote NFAT translocation to nucleus, probably because global calcium did not reach sufficiently high levels (Hernández-Ochoa et al., 2007).

The most thorough investigation into Cav2-mediated gene transcription has been reported by Wheeler and colleagues (2012), who showed that Cav2 channels promote CREB activation, via CaM kinase, but that this occurs much more slowly compared with L-type calcium channels and that this process

requires much stronger membrane depolarizations (Wheeler et al., 2012). This group also showed that Cav2 signaling to CREB can be interrupted by calcium chelation and that efficiency of Cav2/CREB signaling is intimately tied to mitochondrial and ER calcium buffering (Wheeler et al., 2012). Although we are only beginning to understand Cav2-mediated gene transcription, it appears that global calcium elevation from vigorous neuronal activity, such as trains of action potentials, is required for Cav2 channel-mediated CREB activation.

Cavβ Subunits

Cavβ3/4 subunits have also emerged as transcriptional regulators, independently of their abilities to regulate calcium influx via the Cavα1 subunit. Cavβ3 was recently identified as a binding partner for a novel isoform of the transcription factor Pax6 (Zhang et al., 2010). The Pax6(S) isoform is transcriptionally active, but its function is suppressed by Cavβ3 in the nucleus (Zhang et al., 2010). The physiological relevance of this interaction is not yet known, but it is suspected to be important early in embryonic development.

The Cavβ4c splice isoform was first identified as a transcriptional regulator after yeast two-hybrid assays from chicken brain and cochlea, and later human vestibular neurons (Xu et al., 2011), and shows a strong interaction with the gene silencing protein CHCB2/HP1γ (Hibino et al., 2003). Coexpression of CHCB2/HP1γ recruits Cavβ4c to the nucleus, leading to disruption of CHCB2/HP1γ-mediated gene silencing (Hibino et al., 2003). Another isoform, Cavβ4b, is found in the nucleus of cerebellar granule and Purkinje cells and is exported from the nucleus following calcium influx or neuronal excitation (Subramanyam et al., 2009). On the other hand, a recent study by Tadmouri and colleagues (2012) in hippocampal neurons found that Cavβ4 is imported to the nucleus in an activity-dependent manner alongside a regulatory subunit of PP2A phosphatase. Once in the nucleus, association of Cavβ4/PP2A with HP1γ and the thyroid hormone receptor α (αTH) leads to the repression of thyroid hormone production (Tadmouri et al., 2012). This association of Cavβ4 and PP2A is ablated in a prematurely truncated Cavβ4 isoform that has been associated with juvenile myclonic epilepsy (Tadmouri et al., 2012). Interestingly, the thyroid hormone derivative thyroxine exacerbates absence seizures in juvenile myclonic epileptic patients (Obeid et al., 1996); altogether suggesting that Cavβ4 can suppress seizure activity by downregulating thyroid hormone levels. This highlights an example in which dysfunction in an ancillary calcium channel subunit can affect human disease independently of calcium channel function, per se.

From the data available to date, it appears that Cavβ subunits act as repressors of gene transcription, in contrast with the roles of various calcium channel α1 subunits that tend to promote gene activation by supporting a rise in intracellular calcium.

Calcium Channel Knockouts and Pathophysiology

A number of knockout mouse lines that lack specific calcium channel subunits have been constructed and their behavioral phenotypes analyzed. Moreover, a number of genetic abnormalities in calcium channels have been identified in both rodents and humans and have revealed important insights into the roles of these channels in both physiology and pathophysiology.

Cav1 Family

Mice lacking the skeletal muscle Cav1.1 isoform die at birth due to asphyxiation, as Cav1.1 null pups cannot contract their diaphragms (Tanabe et al., 1988). This severe phenotype underscores the importance of the Cav1.1 channel for skeletal muscle function and the fact that its highly specific role in excitation contraction coupling cannot be compensated by other calcium channels subtypes. In humans, mutations in the Cav1.1 channel have been linked to hypokalemic periodic paralysis, a transient form of paralysis that is triggered by low serum potassium and characterized by interepisode muscle weakness (Fouad et al., 1997; Ptácek et al., 1994). These mutations are typically localized to the voltage sensor regions in domains II, III, or IV (Fouad et al., 1997; Hirano et al., 2011) and appear to alter the voltage dependence of activation of the channels (Morrill et al., 1998; Morrill and Cannon, 1999), which in turn affects excitation contraction coupling and hence muscle function. A recently developed mouse model of hypokalemic periodic paralysis carrying an R528H mutation in the domain II voltage sensor recapitulates the human disease phenotype and reveals an abnormal gating pore current that appears to lie at the root of skeletal muscle dysfunction for this mutant channel (Wu et al., 2012) and that was first suggested by Sokolov and colleagues (Sokolov et al., 2007).

Cav1.2 null mice die in utero at day 14.5 post coitum, as this calcium channel subtype is critical for cardiac muscle contraction (Seisenberger et al., 2000). It is not clear to what extent brain development is also altered in these animals. This issue has been addressed with a conditional knockout mouse that lacks Cav1.2 in both hippocampus and cortex. This mouse shows impairment of spatial memory (White et al., 2008) and produces anxiety-like behavior (Lee et al., 2012). Interestingly, Cav1.2 conditional knockouts do not learn from fearful stimuli, a behavior attributed to L-type channel function in the amygdala (Jeon et al., 2010; Langwieser et al., 2010).

Mutations in the human CACNA1C gene have been linked to Timothy syndrome, a debilitating condition that includes mental retardation, lethal cardiac arrhythmias, various developmental abnormalities, and autism (Splawski et al., 2004, 2005). This is due to mutations at the beginning of the domain I-II linker region that interfere with both VDI and CDI (Barrett and Tsien, 2008; Depil et al., 2011) and is consistent with the role of this linker as a possible inactivation particle as outlined earlier in this Review. The autism phenotype associated with Timothy syndrome has been successfully recapitulated in a mouse model (Bader et al., 2011). Furthermore, isolation of pluripotent stem cells from Timothy syndrome patients has been used to examine the effect of these mutations on neural development (Krey et al., 2013; Paşca et al., 2011). These authors found that mutant channels from Timothy syndrome patients produce activity-dependent retraction of neuronal processes via a RhoA pathway, thus suggesting that Cav1.2 channels are critical for proper neuronal circuit formation that may be compromised in autistic patients. The role of Cacv1.2 channels in mental health is further supported by findings that SNPs located in *CACNA1C* are linked to development of other psychiatric disorders such as bipolar disorder, Schizophrenia, and depression (Dao et al., 2010; Green et al., 2010; He et al., 2014; Strohmaier et al., 2013) (for review,

see Giusti-Rodríguez and Sullivan, 2013). fMRI studies in patients with the noncoding *CACNA1C* risk allele Rs1006737 indicate altered amygdala function (Tesli et al., 2013), which fits with the phenotype of the Cav1.2 conditional KO mouse.

Mice deficient for Cav1.3 are deaf (Platzer et al., 2000), as this channel subtype is critical for auditory hair cell synaptic transmission. These mice also show abnormal auditory brain stem development (Hirtz et al., 2011), perhaps due to lack of auditory inputs. Independently of compromised hearing, these animals exhibit reduced immobility in forced swimming tests, suggesting that they are somewhat resistant to depression and implicating these channels in hippocampal function (Busquet et al., 2010). Cav1.3 channels expressed in the ventral tegmental area have been linked to the development of cocaine-induced long-term behavioral changes (Schierberl et al., 2011, 2012). In the nucleus accumbens, cocaine appears to activate CREB via Cav1.3 channels, which in turn gives rise to locomotor sensitization (Giordano et al., 2010). Interestingly, in animals that are pre-exposed to cocaine, there is switch from Cav1.3 to Cav1.2 channels that ablates the CREB activation. These data indicate an important role for Cav1.3 channels in neurological responses to psychoactive drugs and underscore the importance of L-type channels in gene regulation as discussed earlier. It is tempting to speculate that mutations in Cav1.3 channels in the human population could affect susceptibility to substances such as cocaine. A clear link between Cav1.3 channels and human disease has been established for two families with familial deafness. These individuals carry a glycine insertion mutation near the Cav1.3 pore that results in nonconducting channels (Baig et al., 2011). Affected individuals also display sinoatrial node dysfunction, consistent with the importance of this channel in cardiovascular function; however, no information is available about the neurological phenotype of these patients. It is also worth noting that Cav1.3 channel expression is upregulated in brains of early-stage Parkinson's patients (Hurley et al., 2013); however, it is not clear if this is coincident with disease or an epiphenomenon. Nonetheless, Cav1.3 calcium channel blockers have been suggested as a potential therapeutic for Parkinson's disease (Kang et al., 2012), in part based on earlier observations showing that Cav1.3 channels regulate the pacemaking of dopaminergic neurons in the substantia nigra in an age-dependent manner, with older neurons increasingly relying on this channel type (Chan et al., 2007). Interestingly, blocking Cav1.3 channels was sufficient to "reset" neurons to their juvenile state. Altogether, data from mice and humans confirm a critical role of Cav1.3 channels in audition but also suggest an involvement of this channel type in other neurophysiological functions, in particular in the dopaminergic system.

Mice lacking Cav1.4 are blind due to the importance of this channel in rod photoreceptor synaptic transmission (Chang et al., 2006; Lodha et al., 2010). These mice also show defects in ribbon synapse structure (Liu et al., 2013). Interestingly, mice deficient in CaBP4 have a phenotype that is qualitatively similar to those of Cav1.4 null mice (Haeseleer et al., 2004), consistent with the notion that CaBP4 is an essential functional regulator of Cav1.4 channels. Many different mutations in the *CACNA1F* gene that encodes Cav1.4 have been identified in human patients with congenital stationary night blindness-2 (for review, see Lodha et al., 2012). In some cases, these mutations lead to a loss of functional protein (Bech-Hansen et al., 1998), in others the mutations result in gain of function (Hemara-Wahanui et al., 2005), and yet another set of mutations causes a clinical phenotype, without any discernible effects on the biophysical properties of the channel (McRory et al., 2004). How such a variety of Cav1.4 mutations produce essentially the same clinical phenotype is not clear; however, insights may be gleaned from transgenic mouse models that recapitulate human congenital night blindness-2 (Knoflach et al., 2013).

Cav2 Family

Mice with a deletion of the gene encoding Cav2.1 display severe ataxia and develop absence seizures before they die approximately 4 weeks postnatal (Jun et al., 1999). The ataxic phenotype observed with these animals is consistent with the importance of P-/Q-type channels in cerebellar physiology. In hippocampal neurons and motor neuron endplates, there is functional compensation by Cav2.2 and Cav2.3 channels that allows for continued synaptic transmission (Jun et al., 1999; Urbano et al., 2003), although the notion that these animals experience seizures indicates that this compensation is incomplete. Several mouse lines with mutations in Cav2.1 channels have been identified, including "leaner," "tottering," and "rocker" mice, which have overlapping phenotypes that include ataxia and absence seizures (for review, see Pietrobon, 2002), in many ways similar to those observed with knockout of the entire gene. Mice in which Cav2.1 channels are selectively knocked out in Purkinje cells (postnatal) do not initially present with the full spectrum of neurological dysfunctions but instead develop them during adulthood (Mark et al., 2011). This suggests an important role of these channels in early development.

In humans, alterations of Cav2.1 channels produce a range of phenotypes. Gain-of-function mutations in the *CACNA1A* gene have been linked to familial hemiplegic migraine (Tottene et al., 2009), with mutation loci determining a wide range of disease severity (Pietrobon and Moskowitz, 2013). Two representative mutations have been incorporated into mouse models and recapitulate remarkably well the human disease phenotype and severity (van den Maagdenberg et al., 2004, 2010). Of particular note is a recent study that showed that the pathophysiological effects of the S218L mutation can be offset by tert-butyl dihydroquinone, a compound that counteracts the gain-of-function effects of this mutation on channel gating (Inagaki et al., 2014). In contrast, loss-of-function mutations in Cav2.1 including some that lead to truncations, frame shifts, and aberrant splicing (Kipfer et al., 2013) have been identified in patients with episodic ataxia-type 2 (Pietrobon, 2010). Several of these loss-of-function mutations result in dominant-negative effects on normal Cav2.1 channels (Jeng et al., 2006) through a direct protein degradation mechanism (Mezghrani et al., 2008) that is dependent on an 11 amino acid stretch in the channel N terminus (Page et al., 2010). One episodic ataxia patient bearing a Cav2.1 mutation that causes a premature truncation of the channel protein also experienced seizures (Jouvenceau et al., 2001). This is reflective of what is observed with Cav2.1-deficient mice and is in line with more recent reports that identified Cav2.1 channels as a risk allele for seizures (albeit via complex interactions with other genes) (Klassen et al., 2011). Overall, it appears that mutations

that decrease Cav2.1 channel function/expression produce episodic ataxia and/or absence seizures, while gain-of-function mutations lead to spreading cortical depression and migraine.

A different from of cerebellar ataxia (spinal cerebellar ataxia type 6) is caused by polyglutamine expansions in the Cav2.1 C terminus (Jodice et al., 1997). There are conflicting reports on the functional effects of these expansions in various heterologous systems. In Purkinje cells, the channels appear to function normally (Saegusa et al., 2007) and yet in a mouse model, they seem to give rise to progressive neuronal dysfunction (Watase et al., 2008). Neuronal defects can occur by mechanisms that are similar to polyglutamine expansion disorders (i.e., through the formation of aggregates) but perhaps require specific biological conditions not currently understood.

In contrast with Cav2.1, mice lacking the other major presynaptic channel Cav2.2 show a much milder phenotype. They are hyposensitive to inflammatory and neuropathic pain (Hatakeyama et al., 2001; Kim et al., 2001a; Saegusa et al., 2001), which fits with the importance of these channels in synaptic transmission between sensory fibers and dorsal horn neurons. These mice also show deficits for sympathetic control of heart rate and blood pressure (Mori et al., 2002) and are hyperactive (Beuckmann et al., 2003). Most interestingly, these animals exhibit reduced voluntary ethanol intake and reduced hypnotic response to alcohol (Newton et al., 2004). Cav2.3 null mice also have a mild phenotype that includes hyposensitivity to pain (Saegusa et al., 2002) and resistance to chemically induced seizures (Weiergräber et al., 2007). We are not aware of any mutations in Cav2.2 or Cav2.3 in humans and this is likely because mutations in these channels generate only mild, medically undetected phenotypes.

Cav3 Family

Cav3.1 null mice show bradycardia due to slowing of sinoatrial node pacemaking and reduced atrioventricular conduction (Mangoni et al., 2006). Their nervous system phenotype includes a resistance to baclofen-induced seizures (Kim et al., 2001b). Furthermore, ablation of this channel isoform also protects from seizures in Cav2.1 null or mutant mice such as "tottering" (Song et al., 2004). This fits well with the known role of T-type channels in the thalamocortical circuitry. The key function of Cav3 channels in thalamic neurons is underscored by the observations that targeted deletion of Cav3.1 in the thalamus results in increased arousal and altered sleep/wake patterns (Anderson et al., 2005) and that Cav3.3 null mice exhibit compromised sleep spindles in thalamic reticular neurons (Astori et al., 2011).

Cav3.2 null mice show compromised coronary function due to a permanent constriction of coronary arterioles (Chen et al., 2003). These mice also show reduced sensitivity to noxious pain (consistent with the expression of these channels in a subset of afferent pain fibers), but not chronic neuropathic pain (Choi et al., 2007). This contrasts with the potent analgesic actions of intrathecally delivered Cav3.2 channel blockers in neuropathic pain models, suggesting that there is compensation from other types of (calcium) channels in the afferent fibers of Cav3.2 null mice that maintain pain transmission. On the flip side, mice subjected to nerve injury, colonic inflammation (Jagodic et al., 2008; Marger et al., 2011), or chronic diabetic conditions (Jagodic et al., 2007) show increased T-type channel conductance in sensory neurons, which then contributes to the development of chronic pain. The underlying mechanisms for this remain to be elucidated but may involve posttranslational modification of the channels (Orestes et al., 2013). In this regard, T-type calcium channels serve as a unique example where disorders can be triggered by misregulation of channel expression, rather than mutations in the channels.

In humans, a number of mutations in Cav3.2 have been linked to generalized epilepsies (Heron et al., 2004, 2007). When introduced into recombinant channels, the vast majority of these mutations have only small effects on channel biophysics and cell surface density (Khosravani et al., 2004, 2005; Vitko et al., 2005). However, when expressed in neurons, at least one of these mutations (C456S) increased neuronal firing by reducing the threshold for rebound bursting (Eckle et al., 2014). The C456S channel mutant also enhances neurite outgrowth and dendritic arborization (Eckle et al., 2014), possibly explaining why some mutations appear to lack disease phenotypes in recombinant systems. One study reported Cav3.1 polymorphisms in families with juvenile myoclonic epilepsy (Singh et al., 2007), but no detailed linkage analysis was performed and it is thus not unclear if these mutations truly segregate with phenotype.

Finally, all three Cav3 channels have been linked to autism spectrum disorders (Lu et al., 2012; Splawski et al., 2006). The functional consequence of three autism mutations in the *CACNA1H* gene have been examined in heterologous systems and shown to result in reduced T-type currents (Splawski et al., 2006). How this contributes to autism, and if interactions with other autism risk alleles are necessary, remains to be determined.

Altogether, Cav3 channels appear to play important roles in regulating neuronal excitability, whereas their elimination (and inhibition) protects from hyperexcitability disorders such as absence epilepsy and certain forms of pain.

Ancillary Calcium Channel Subunits

Several knockout mouse lines lacking ancillary calcium channels have been generated. Mice lacking the Cavβ1 subunit display a phenotype that is similar to that of Cav1.1 knockout mice (Gregg et al., 1996; Strube et al., 1996), as this subunit is essential for skeletal muscle L-type calcium channel function. Along these lines, deletion of the Cavβ2 subunit produces an embryonic lethal phenotype due to reduced expression of Cav1.2 channels in the heart (Meissner et al., 2011; Weissgerber et al., 2006). These are two examples in which the absence of an ancillary subunit is directly associated with compromised function of an interacting Cavα subunit. Mice in which Cavβ1 or Cavβ2 deletion is limited to the CNS are viable, allowing some insights into the function of these subunits in the nervous system. Findings with this region-specific Cavβ2 mouse reveals malformation of the outer plexiform layer of the retina (Ball et al., 2002), suggesting that this subunit may be an important regulator of retinal L-type calcium channels. Cavβ3 knockout mice show improved glucose homeostasis (Berggren et al., 2004), and increased epinephrine release from the adrenal gland (Ohta et al., 2010). Targeted deletion of Cavβ3 subunits in neurons yields no overall behavioral or gross morphological phenotype but results in alterations of N-type and P-/Q-type currents in superior cervical

ganglion neurons (Namkung et al., 1998). In contrast, deletion of Cavβ4 results in a phenotype termed the "lethargic mouse" (Burgess et al., 1997). Here, a naturally occurring mutation produces a premature stop codon and a de facto knockout of the subunit. This results in the development of absence seizures and ataxia, similar to what is observed upon deletion of Cav2.1 channels, suggesting that Cavβ4 could be a specific and necessary component of P-/Q-type calcium channel complexes (Mich and Horne, 2008). While there is partial functional compensation from other Cavβ subunits in these mice (Burgess et al., 1999), this does not appear to be able to overcome the absence of Cavβ4.

Ducky 2J mice carry a mutation in the Cavα2δ2 subunit-encoding gene that leads to a premature stop codon and thus a truncated protein. These mice show severe seizure activity, ataxia, and uncoordinated gait, as well as compromised dendritic arborization of their cerebellar Purkinje neurons (Barclay et al., 2001). The Ducky 2J mouse phenotype must be considered with some reservation, however, because a truncated Cavα2δ2 is still produced and, therefore, is not a bona fide knockout animal (Brodbeck et al., 2002). Knockout of Cavα2δ1 is embryonic lethal to our knowledge, perhaps because this subunit is essential for targeting multiple types of calcium channels in various tissues to the plasma membrane. However, a recent targeted deletion of this subunit in the heart results in reduced cardiac L-type channel amplitude and decreased contractility (Fuller-Bicer et al., 2009). Finally, loss-of-function mutations in mouse Cavγ2 (*stargazin*) give rise to absence seizures (Letts et al., 1998) and although *stargazin* has small effects on Cav2.1 channel function, it is likely that the epileptic phenotype of the mouse is related to alterations in AMPA receptor expression (Payne et al., 2006; Ryu et al., 2008).

In humans, variations in coding and noncoding regions of Cavβ4 have been associated with juvenile myoclonic epilepsy (Escayg et al., 2000). One of these mutations produces a short C-terminal truncation in the Cavβ4 protein, and its coexpression with Cav2.1 channels results in altered gating kinetics of the channel. As discussed earlier, the association of Cavβ4 with Ppp2r5d, a regulatory subunit of phosphatase 2A, results in translocation of this complex to the nucleus in order to regulate gene expression, for which this process is compromised with truncated Cavβ4 subunits (Tadmouri et al., 2012). The gene encoding Cavβ2 has been linked to bipolar disorder in the Chinese Han population (Lee et al., 2011), hypertension (Lin et al., 2011), and cardiac conduction disease (Hu et al., 2010). Finally, a single nucleotide change in Cavα2δ4 has been associated with cone dystrophy in humans (Wycisk et al., 2006). This mutation introduces a premature stop codon that leads to truncation of the full-length protein by about 30%. Progressive cone dystrophy has also been observed with Cav1.4 channel mutations that lead to truncated channels (Jalkanen et al., 2006), suggesting that the Cavα2δ4 mutation may result in altered Cav1.4 currents in cones, which ultimately mediates the dystrophic phenotype.

Altogether, there is growing body of literature that reveals an association between mutations of various calcium channel subunits and a wide spectrum of neurological and nonneurological diseases that range from mild to extremely severe. Below, we shall discuss some additional considerations pertaining to the mechanisms by which mutations in these subunits generate the observed phenotypes.

Additional Considerations and Caveats

Information gained from knockout mouse models and genetic abnormalities in humans can provide important insights into the physiological roles and functions of calcium channels and their ancillary subunits. For some calcium channelopathies, there is a clear understanding of how mutations perturb channel function at the molecular level to give rise to a disease phenotype. For example, Cav1.2 Timothy syndrome mutations can disable the putative inactivation gate hinge of the channel (Barrett and Tsien, 2008; Depil et al., 2011). This then slows both calcium and voltage-dependent inactivation, leading to persistent L-type currents that alter the cardiac action potential and produce tonic calcium entry into neurons. The latter process can then affect neuronal excitability and augment calcium-dependent gene transcription. Along these lines, a mutation in the domain IIS6 region of Cav1.4 linked to night blindness dramatically slows inactivation, while concomitantly enhancing activation gating of the channel. The net functional result is an altered window current that affects tonic glutamate release in the dark and ultimately vision (Hemara-Wahanui et al., 2005). In other words, some calcium channel mutations create compelling links between channel biophysics and physiological output.

In other cases, however, channel biophysics do not equate well with the physiological outcome. Several Cav3.2 absence epilepsy mutations, for instance, have mild biophysical abnormalities yet somehow impart profound changes in neuronal excitability, especially in thalamic neurons. While these mutant channels should increase seizure activity in neurons, it is unclear how they do this at the molecular level. Some of the mutations may not affect Cav3.2 channel function at all but instead modulate interactions with other regulatory proteins or ion channels, such as the calcium-activated potassium channel family, which secondarily affect neuronal firing (Anderson et al., 2010a; Engbers et al., 2012). Another potential explanation is that some Cav3.2 mutations are only functionally relevant when present in a specific splice isoform (Powell et al., 2009), and thus choosing the correct channel backbone for phenotypic evaluation is critical. This idea may also explain why gain-of-function mutations in Cav3.2, which are linked to absence seizures, do not produce hyperexcitability in other nervous system regions, such as afferent pain fibers. Splice isoform-specific unmasking of mutant phenotypes has also been demonstrated for Cav2.1 (Adams et al., 2009) and may very well apply to other calcium channels subunits. Finally, it is important to reiterate that mutations in calcium channels and their ancillary subunits that are linked to gene transcription may result in complex changes in protein expression that ultimately determine the disease phenotype. This is true for mouse lines such as "lethargic" or "tottering" where mutations in ancillary subunits somehow result in increased thalamic T-type currents and absence seizures (Zhang et al., 2002). This cautionary example, along with the possibility of compensatory changes in channel expression, is a reminder that any observed phenotype may not be directly related to the gene in question.

Concluding Remarks

Since the discovery of calcium currents nearly half a century ago, tremendous progress has been made in understanding the structure, function, and physiology of voltage-gated calcium channels. Since the groundbreaking work of Katz and Miledi (1967), Hagiwara and Nakajima (1966), and Reuter (1967), there have been many memorable milestones. This includes the identification of multiple native calcium channel subtypes (Nowycky et al., 1985), evidence that HVA calcium channels are multimeric protein complexes (Curtis and Catterall, 1984), the cloning and expression of the first calcium channel gene (Tanabe et al., 1987, 1988), and the generation of various calcium channel knockout mouse lines and the crystallization of the Cavβ subunit (Chen et al., 2004; Opatowsky et al., 2004; Van Petegem et al., 2004). We now have an in-depth understanding of calcium channel pharmacology (for review, see Doering and Zamponi, 2005), their regulation by second messengers such as G proteins and protein kinases (Fuller et al., 2010; Tedford and Zamponi, 2006), and, as discussed here, their roles in neuronal physiology and pathophysiology. Future milestones may include the crystallization of a Cavα1 subunit (perhaps Cav3, as it does not associate with ancillary subunits), in-depth analysis of splice variations, and the roles of these variants in specific areas of the nervous system. Future research should also bring a better understanding of mechanisms underlying calcium channel dysregulation during disease, with perhaps a focus on posttranslational modifications and alterations in channel trafficking. Generation of novel mouse models that allow inducible and region-specific changes in calcium channel expression would also elevate our understanding of calcium channel physiology in the central and peripheral nervous systems.

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