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The Physiology, Pathology, and Pharmacology of Voltage-Gated Calcium Channels and Their Future Therapeutic Potential

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ABBREVIATIONS: ABT-639, 5-[(8*aR*)-3,4,6,7,8,8*a*-hexahydro-1*H*-pyrrolo[1,2-*a*]pyrazine-2-carbonyl]-4-chloro-2-fluoro-*N*-(2-fluorophenyl) benzenesulfonamide; AID, α-interaction domain; APA, aldosterone-producing adenoma; ASD, autism spectrum disorder; AVN, atrioventricular node; BayK8644, 1,4-dihydro-2,6-dimethyl-5-nitro-4-[2-(trifluoromethyl)phenyl]-3-pyridinecarboxylic acid methyl ester; BPN-4689, Cp8, 1-(3-chlorophenethyl)-3-cyclopentylpyrimidine-2,4,6-trione; CaM, calmodulin; CaMKII, calmodulin kinase II; CCB, Ca^{2+} channel blocker; CDI, Ca^{2+}-dependent inactivation; CNS, central nervous system; CREB, cAMP/calcium response element binding protein; CTM, C-terminal modulatory structure; CSNB2, congenital stationary night blindness type 2; DCRD, distal C-terminal regulatory domain; DHP, dihydropyridine; DRG, dorsal root ganglion; DM, myotonic dystrophy; FHM, familial hemiplegic migraine; FPL 64167, 2,5-dimethyl-4-[2-(phenylmethyl)benzoyl]-1*H*-pyrrole-3-carboxylic acid methyl ester; GIRK, G protein–coupled K$^+$ channel; GPCR, G protein–coupled receptor; GWAS, genome-wide association study; HCN, hyperpolarization-activated cyclic nucleotide-gated channel; HypoPP, hypokalemic periodic paralysis; LTCC, L-type calcium channel; LTP, long-term potentiation; MH, malignant hyperthermia; miR, microRNA; NMP-7, (9-pentylcarbazol-3-yl)-piperidin-1-ylmethanone; NNC55-0396, (1*S*,2*S*)-2-[2-[[3-(1*H*-benzimidazol-2-yl)propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl cyclopropanecarboxylate dihydrochloride; OMIM, Online Mendelian Inheritance in Man; PCRD, proximal C-terminal regulatory domain; PD, Parkinson's disease; PIP$_2$, phosphatidylinositol 4,5-bisphosphate; PKA, protein kinase A; RyR, ryanodine receptor; SAN, sinoatrial node; SDZ202-791, propan-2-yl (4*R*)-4-(2,1,3-benzoxadiazol-4-yl)-2,6-dimethyl-5-nitro-1,4-dihydropyridine-3-carboxylate; SNc, substantia nigra pars compacta; SNP, single nucleotide polymorphism; SR, sarcoplasmic reticulum; ST101, spiro[imidazo[1,2-*a*]pyridine-3,2-indan]-2(3*H*)-one; TROX-1, (3*R*)-5-(3-chloro-4-fluorophenyl)-3-methyl-3-(pyrimidin-5-ylmethyl)-1-(1*H*-1,2,4-triazol-3-yl)-1,3-dihydro-2*H*-indol-2-one; TS, Timothy syndrome; TTA-A2, (*R*)-2-(4-cyclopropylphenyl)-*N*-(1-(5-(2,2,2-trifluoroethoxy)pyridin-2-yl)ethyl) acetamide; TTA-P2, 3,5-dichloro-*N*-[1-(2,2-dimethyl-tetrahydro-pyran-4-ylmethyl)-4-fluoro-piperidin-4-ylmethyl]-benzamide; Z944, *N*-[[1-[2-(*tert*-butylamino)-2-oxoethyl]piperidin-4-yl]methyl]-3-chloro-5-fluorobenzamide.

Abstract——**Voltage-gated calcium channels are required for many key functions in the body. In this review, the different subtypes of voltage-gated calcium channels are described and their physiologic roles and pharmacology are outlined. We describe the current uses of drugs interacting with the different calcium channel subtypes and subunits, as well as specific areas in which there is strong potential for future drug development. Current therapeutic agents include drugs targeting L-type $Ca_V1.2$ calcium channels, particularly 1,4-dihydropyridines, which are widely used in the treatment of hypertension. T-type (Ca_V3) channels are a target of ethosuximide, widely used in absence epilepsy. The auxiliary subunit $\alpha_2\delta$-1 is the therapeutic target of the gabapentinoid drugs, which are of value in certain epilepsies and chronic neuropathic pain. The limited use of intrathecal ziconotide, a peptide blocker of N-type ($Ca_V2.2$) calcium channels, as a treatment of intractable pain, gives an indication that these channels represent excellent drug targets for various pain conditions. We describe how selectivity for different subtypes of calcium channels (e.g., $Ca_V1.2$ and $Ca_V1.3$ L-type channels) may be achieved in the future by exploiting differences between channel isoforms in terms of sequence and biophysical properties, variation in splicing in different target tissues, and differences in the properties of the target tissues themselves in terms of membrane potential or firing frequency. Thus, use-dependent blockers of the different isoforms could selectively block calcium channels in particular pathologies, such as nociceptive neurons in pain states or in epileptic brain circuits. Of important future potential are selective $Ca_V1.3$ blockers for neuropsychiatric diseases, neuroprotection in Parkinson's disease, and resistant hypertension. In addition, selective or nonselective T-type channel blockers are considered potential therapeutic targets in epilepsy, pain, obesity, sleep, and anxiety. Use-dependent N-type calcium channel blockers are likely to be of therapeutic use in chronic pain conditions. Thus, more selective calcium channel blockers hold promise for therapeutic intervention.**

I. Introduction

Voltage-gated calcium channels are required for key functions in excitable cells, including transmitter release and hormone secretion (Catterall et al., 2013), excitation-transcription coupling (Wheeler et al., 2012), and excitation-contraction coupling (Bannister and Beam, 2013). To determine which calcium channels are involved in specific processes, we can employ a range of selective drugs as blockers of the different channels, as part of the armory of experimental tools. This is particularly important if we are to infer potential therapeutic uses of selective blockers from such experiments.

The first voltage-gated calcium channel complex to be studied was that from skeletal muscle, where it is present in great abundance in the transverse tubules. After purification of the complex, it was found to contain five components: α_1 (approximately 170 kDa), α_2 (approximately 150 kDa), β (approximately 52 kDa), δ (approximately 17–25 kDa), and γ (approximately 32 kDa) in an approximately stoichiometric ratio (Takahashi et al., 1987; Tanabe et al., 1987) (Fig. 1). The α_1 subunit was found to bind the calcium channel blockers 1,4-dihydropyridines (DHPs), and thus was established as the pore-forming subunit. From these seminal studies came the cloning of 10 mammalian α_1 subunits, four β subunits, and four or more $\alpha_2\delta$ subunits. This diversity provides a wealth of sites for selective pharmacological modification (Schroeder et al., 2000; Catterall and Swanson, 2015), which are outlined in Fig. 1. This review concentrates on the actual and potential pharmacology of these voltage-gated calcium channels throughout the body.

II. Ca_V1 Channel Family

A. Genes Encoding Ca_V1 Pore-Forming $\alpha1$ Subunits

The Ca_V1 Ca^{2+} channel family is also known as the so-called L-type Ca^{2+} channels (LTCCs). In early studies in cardiac myocytes (Nilius, 1986) and neurons (Carbone and Lux, 1984; Nowycky et al., 1985), they were designated “L” due to their long-lasting inward currents during depolarization, which allowed them to be distinguished from rapidly decaying Ca^{2+} currents, termed transient or T-type channels (see section IV on Ca_V3 channels). A feature that distinguishes L-type channels from all other Ca^{2+} channels is their high sensitivity for organic L-type Ca^{2+} channel blockers (CCBs), also known as Ca^{2+} antagonists. These drugs serve not only as essential pharmacological tools to isolate L-type current components in vitro, but they have also been used clinically for decades to treat cardiovascular diseases. Radioactive derivatives of CCBs were subsequently used to reversibly label LTCCs in the brain, heart, and smooth and skeletal muscle. The density of L-type channels was an order of magnitude higher in skeletal muscle than in other tissues, which allowed purification of the channel complex, biochemical characterization of its subunits, and cloning of its pore-forming $\alpha1$ subunit. The skeletal muscle L-type channel, formed by $Ca_V1.1$ $\alpha1$ subunits, is encoded by the *CACNA1S* gene (Catterall et al., 2005). This genetic information subsequently allowed homology cloning of $Ca_V1.2$ (*CACNA1C*) and $Ca_V1.3$ $\alpha1$ subunits (*CACNA1D*). Much later, human genetics finally identified the retinal $Ca_V1.4$ channel (*CACNA1F*) as the fourth member of the LTCC family (Bech-Hansen et al., 1998; Strom et al., 1998).

As we outline below, the four LTCC isoforms possess similar pharmacological properties but differ regarding their tissue distribution and biophysical properties. Moreover, they all undergo extensive alternative splicing that can affect their activity and interaction with other modulatory proteins. This functional heterogeneity allows Ca^{2+} signals to be adjusted to individual cellular requirements. Human genetic diseases leading to gain or loss of function have been described for all four L-type channel isoforms.

B. Physiology of Ca_V1 Channels

1. Physiologic Roles of Ca_V1 Calcium Channels. Tissue expression of $Ca_V1.1$ and $Ca_V1.4$ is more restricted than that of $Ca_V1.2$ and $Ca_V1.3$ (Fig. 2). $Ca_V1.1$

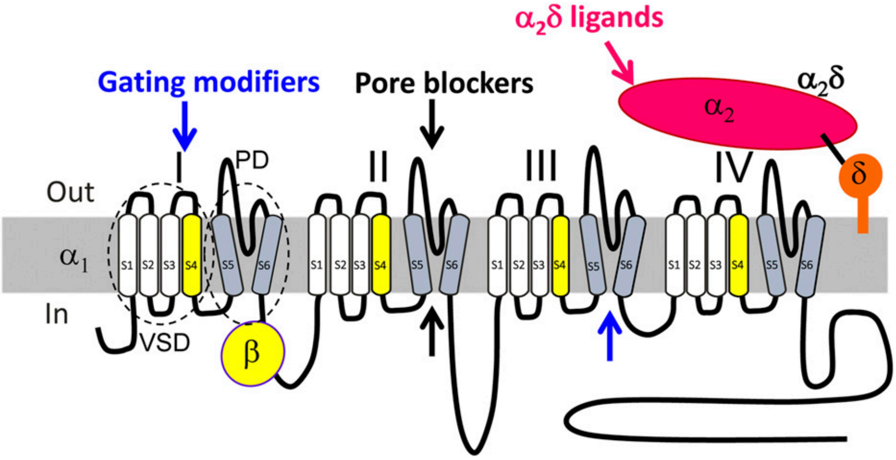

Fig. 1. Diagram of voltage-gated calcium channel subunit topology. Voltage-gated calcium channel subunit topology showing major drug binding mechanisms. Channel inhibition can be induced by modification of channel gating (blue arrows, gating modifiers) by interaction with extracellular regions within one or more of the four voltage-sensing domains (VSDs) (e.g., peptide toxins, such as ω-agatoxin IVA; section III.D.2), or within the activation gates of the pore domain (PD) channel, formed by all four S5–S6 helices together (e.g., DHP LTCC blocker; section III.D). Direct block of the pore from the extracellular side (by peptide toxins such as ω-conotoxin GVIA; section II.D.2) or small molecules (with access from the cytoplasmic side) can also target regions within the ion conducting pathway and obstruct permeation through the pore (black arrows; pore blockers). Some drugs also act through both mechanisms (e.g., phenylalkylamine LTCC blockers; section II.D.1). For structural features, also see Fig. 4. The $\alpha_2\delta$ ligands (magenta arrow) can modify channel trafficking.

is mainly expressed in skeletal muscle and is essential for skeletal muscle contraction. $Ca_V1.4$ is primarily restricted to the retina and is required for normal visual function. $Ca_V1.1$ and $Ca_V1.4$ $\alpha1$ transcripts are not found at significant levels in the brain, although expression in a limited subset of neurons cannot be excluded (Sinnegger-Brauns et al., 2009). By contrast, in most electrically excitable cells, $Ca_V1.2$ and/or $Ca_V1.3$ are expressed and both isoforms are often even expressed in the same cell, such as in neurons (Olson et al., 2005; Chan et al., 2007; Dragicevic et al., 2014), adrenal chromaffin cells (Marcantoni et al., 2010), and sinoatrial node (SAN) and atrial cardiomyocytes (Mangoni et al., 2003). Both channels are required for normal brain function and serve different roles in the cardiovascular system and in endocrine functions. Transcripts for all L-type channel isoforms have also been detected in lymphocytes, although their functional role in these cells remains unknown.

a. $Ca_V1.1$. $Ca_V1.1$ is expressed in skeletal muscle within the junctional membranes of the T-tubule system. $Ca_V1.1$ channels interact physically with ryanodine-sensitive Ca^{2+} release channels [ryanodine receptors (RyRs) such as RyR1] in the sarcoplasmic reticulum (SR), where they trigger rapid Ca^{2+} release and contraction (Tanabe et al., 1987). The direct $Ca_V1.1$-RyR1 conformational coupling has been shown to involve the $Ca_V1.1$ $\alpha1$-subunit II–III intracellular loop (Block et al., 1988; Nakai et al., 1998; Grabner et al., 1999). The $Ca_V1.1$ channel expressed in adult muscle conducts a very small amplitude, slow-activating Ca^{2+} current with a very right-shifted voltage sensitivity, making this channel a truly atypical Ca^{2+} channel (for review, see Bannister and Beam, 2013). Typical intramembrane charge movements (gating currents), voltage-gated SR Ca^{2+} release, and tetrad formation can all be restored upon reexpression of $Ca_V1.1$ $\alpha1$ subunits in $Ca_V1.1$ $\alpha1$-deficient skeletal muscle myotubes (Tanabe et al., 1988; Takekura et al., 1994), demonstrating the essential role of $Ca_V1.1$ in skeletal muscle. RyR1 influences essential properties of skeletal LTCCs and enhances channel function (Nakai et al., 1996; Avila and Dirksen, 2000). The direct mechanical coupling mechanism and small amplitude Ca^{2+} influx can explain the absence of pharmacological effects of CCBs at therapeutic doses in muscle. Although these drugs bind to $Ca_V1.1$ with nanomolar affinity (Glossmann and Striessnig, 1990) and can inhibit Ca^{2+} inward current in skeletal muscle myocytes in vitro (Benedetti et al., 2015), they do not efficiently inhibit the fast voltage-dependent conformational changes in $Ca_V1.1$ $\alpha1$ subunits that trigger SR Ca^{2+} release.

b. $Ca_V1.2$ and $Ca_V1.3$. As outlined above, both isoforms are expressed in the heart, brain, and endocrine cells. Since they differ only slightly in their sensitivity toward CCBs, their contribution to individual cellular processes and physiologic functions could not be dissected using pharmacological means but required the generation of $Ca_V1.2$- and $Ca_V1.3$-deficient mice (for reviews, see Striessnig and Koschak, 2008; Hofmann et al., 2014).

i. L-Type Ca^{2+} Channels in the Heart. $Ca_V1.2$ and $Ca_V1.3$ are expressed in the heart but their contribution to L-type current varies in different regions. In cardiomyocytes, $Ca_V1.2$ predominates and triggers contraction. By contrast, in the SAN and atrioventricular node (AVN), $Ca_V1.3$ is the predominant LTCC isoform. In $Ca_V1.3^{-/-}$ mice, resting heart rate is reduced and arrhythmic, spontaneous SAN pacemaker frequency is slowed and irregular, and diastolic depolarization is prolonged (Zhang et al., 2002; Mangoni et al., 2003). In humans, normal pacemaking function also requires $Ca_V1.3$ channels because loss-of-function mutations in the $Ca_V1.3$ $\alpha1$-subunit gene (*CACNA1D*) also lead to bradyarrhythmia in humans (Baig et al., 2011). They work in a complex pacemaker network of sarcolemmal electrogenic molecules—including $Ca_V3.1$, the hyperpolarization-activated cyclic nucleotide-gated channels (HCNs) HCN-4 and HCN-2, delayed rectifier K^+ channels, and the Na/Ca exchanger—and in conjunction with intracellular rhythmic sarcoplasmic Ca^{2+} oscillations (supported by SR Ca^{2+} release through RyRs and SR Ca^{2+} uptake through sarcoplasmic/endoplasmic reticulum calcium transport-ATPase -2) (for a recent review, see Striessnig et al., 2014). Therefore, knockout or pharmacological inhibition of $Ca_V1.3$ alone reduces heart rate and induces irregular SAN action but does not completely prevent pacemaking (Striessnig et al., 2014).

SAN cells are an excellent example to demonstrate why both $Ca_V1.2$ and $Ca_V1.3$ channel isoforms are required for proper function. Differences in their biophysical properties as well as subcellular localization enable them to support SAN activity during different time points of the action potential cycle. $Ca_V1.3$ channels activate at more negative membrane potentials than $Ca_V1.2$ in SAN (and other) cells (Lipscombe, 2002; Mangoni et al., 2003, 2006; Marcantoni et al., 2010; Bock et al., 2011; Christel et al., 2012). They can therefore sustain Ca^{2+} entry at threshold potentials and during the diastolic depolarization phase. $Ca_V1.3$ also closely colocalizes with sarcomeric RyRs (Christel et al., 2012), which may allow it to contribute to RyR-mediated Ca^{2+} release during diastolic depolarization (Lakatta and DiFrancesco, 2009). $Ca_V1.2$ activates at more positive potentials and colocalizes less with sarcomeric RyRs (Christel et al., 2012). It therefore seems to contribute little to this intracellular Ca^{2+} release. However, its biophysical properties allow $Ca_V1.2$ to support the SAN action potential. $Ca_V1.3$ is also the prominent L-type channel in AVN cells and contributes to AVN conduction and pacemaking (Platzer et al., 2000; Marger et al., 2011b).

In the working myocardium, the $Ca_V1.2$ channels predominate. They tightly associate with signaling molecules involved in cAMP and protein kinase A (PKA) signaling (Balijepalli et al., 2006) and mediate cardiac

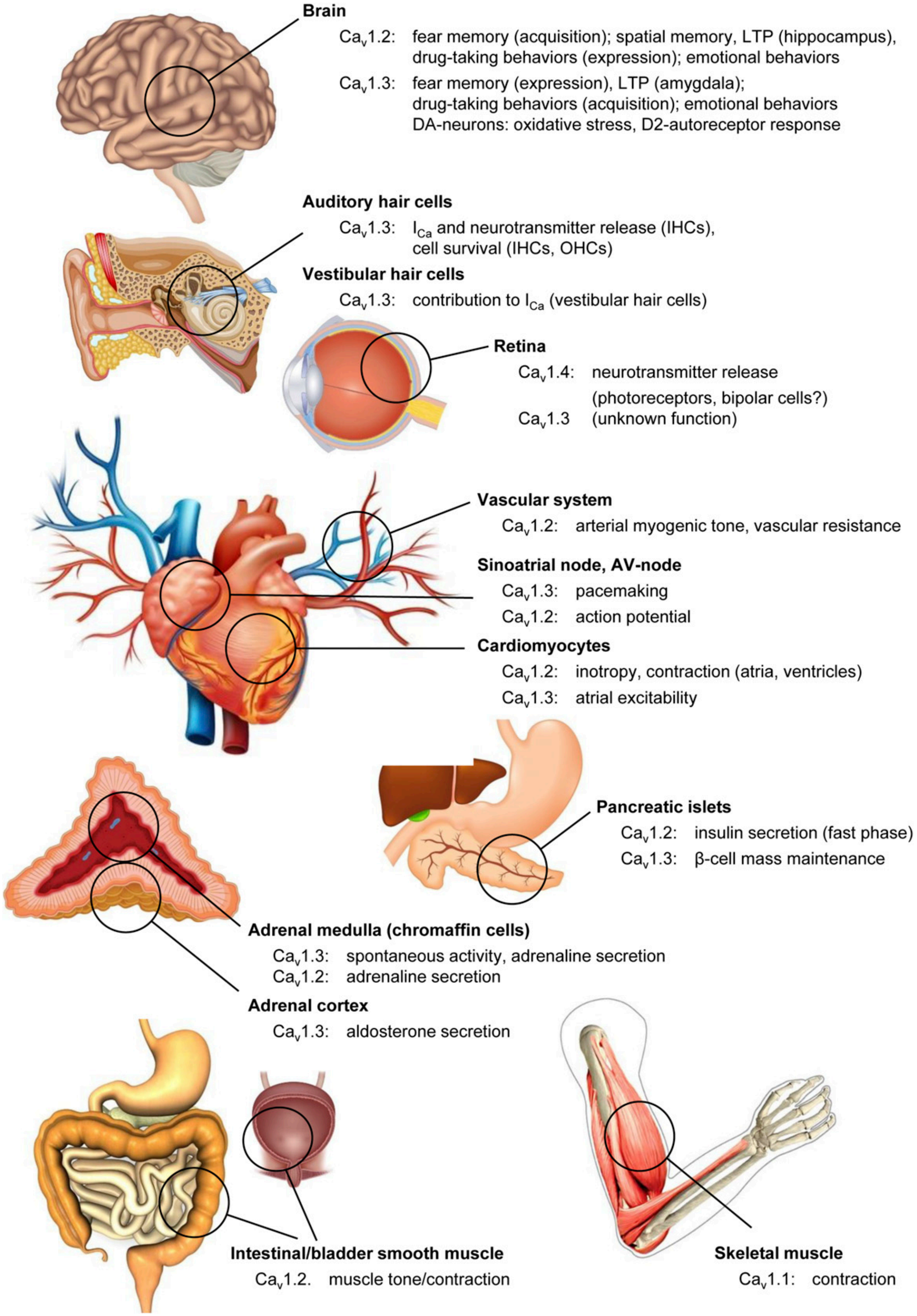

Fig. 2. The most important physiologic functions of the different LTCC isoforms. Except for skeletal muscle Ca^{2+} channels (a complex of Ca$_V$1.1 α1 associated with β1a, $\alpha_2\delta$-1, and γ1 subunits) and the working myocardium (Ca$_V$1.2 α1 associated with primarily β2 and $\alpha_2\delta$-1 subunits), their subunit composition is not known for other tissues. These sites represent actual and potential sites for action of selective LTCC blockers. DA, dopamine; IHC, inner hair cells; OHCs, outer hair cells.

inotropy (Sinnegger-Brauns et al., 2004). No Ca$_V$1.3 expression is found in ventricular muscle and only low expression is found in the atria. Ca$_V$1.2 activation supplies Ca^{2+} to trigger Ca^{2+}-induced Ca^{2+} release from the SR RyRs for contraction. Ca$_V$1.2 α1-subunit knockout mice die in utero (Seisenberger et al., 2000); therefore, homozygous loss-of-function mutations are likely lethal in humans as well. As shown in knockout mice, even a less than 50% reduction of I_{Ca} can lead to heart failure and enhanced lethality (Goonasekera et al., 2012). Cardiac disease can result not only from permanent loss of Ca$_V$1.2 activity but also from enhanced Ca$_V$1.2 activity. In transgenic mice overexpressing accessory β subunits, the sustained increase in Ca^{2+} current amplitude (without major kinetic changes) induces cardiac hypertrophy (Chen et al., 2011). As discussed below, de novo mutations in the Ca^{v}1.2 α1 gene (*CACNA1C*) or its auxiliary subunits also cause human cardiac disease.

ii. L-Type Ca^{2+} Channels in the Brain. Fast presynaptic neurotransmitter release in neurons depends on the close coupling of presynaptic Ca$_V$2 channels to the release machinery. By contrast, Ca$_V$1.3 and Ca$_V$1.2 are located postsynaptically predominantly on the cell soma and in the spines and shafts of dendrites in neurons (Di Biase et al., 2008; Jenkins et al., 2010). There they shape neuronal firing and activate Ca^{2+}-dependent pathways involved in control of gene expression, termed excitation-transcription coupling (Ma et al., 2013). By supporting neuronal plasticity, they participate in different forms of learning and memory, drug addiction, and neuronal development (for review, see Striessnig et al., 2014). Channel-bound calmodulin (CaM) and calmodulin kinase II (CaMKII) are essential biochemical elements decoding voltage-induced alterations in channel activity (Wheeler et al., 2008; Christel and Lee, 2012; Ma et al., 2013). Approximately 90% of the LTCCs in the brain are Ca$_V$1.2 and only 10% are Ca$_V$1.3 (Hell et al., 1993; Sinnegger-Brauns et al., 2009), and they often reside within the same neuron (Olson et al., 2005; Chan et al., 2007; Dragicevic et al., 2014).

Studies of the role of Ca$_V$1.2 and Ca$_V$1.3 in different brain functions in vivo are complicated by the fact that LTCC blockers preferentially act on vascular rather than neuronal LTCCs in vivo, and supratherapeutic doses may be required to effectively inhibit brain channels (see below) (Helton et al., 2005). The quantification of L-type current components is difficult due to the substantial contribution of Ca$_V$2 channels to total Ca^{2+} current in most neurons. Even more complexity is introduced by the fact that Ca$_V$1.2 and Ca$_V$1.3 α1 subunits can associate with all four β subunits (Pichler et al., 1997) and undergo alternative splicing (Bock et al., 2011; Huang et al., 2013b); Ca$_V$1.3 can also undergo RNA editing (Huang et al., 2012). At antihypertensive doses, organic CCBs (e.g., nimodipine, isradipine, or diltiazem) do not affect brain function in humans during chronic treatment. However, subtle central nervous system (CNS) effects of LTCC blockers can be detected in experimental clinical studies in healthy volunteers as changes in corticospinal metaplasticity (Wankerl et al., 2010). Unfortunately, experimental in vivo doses used in animal experiments are usually very high and cause pronounced Ca$_V$1.2-mediated cardiovascular effects, which seriously compromises the interpretation of behavioral outcomes of such studies (Waltereit et al., 2008; Busquet et al., 2010).

Genetically modified mice have been instrumental in revealing the physiologic role of the two brain LTCC isoforms (Striessnig and Koschak, 2008; Hofmann et al., 2014; Striessnig et al., 2014). Hippocampal function depends mainly on Ca$_V$1.2. This isoform is required for hippocampal spatial memory formation (Moosmang et al., 2005a; White et al., 2008) for protein synthesis-dependent, NMDA receptor–independent late-phase long-term potentiation (LTP) in CA3-CA1 synapses, and for activation of the microtubule-associate protein kinase/cAMP/calcium response element binding protein (CREB) signaling cascade (Moosmang et al., 2005a). In contrast with Ca$_V$1.2, Ca$_V$1.3 does not contribute to CA3-CA1 hippocampal LTP and the spatial memory encoding in the Morris water maze appeared normal in Ca$_V$1.3-deficient mice (McKinney and Murphy, 2006).

These two LTCCs also contribute in different ways to other types of memory, such as fear memory and memory associated with drug-taking behaviors. Ca$_V$1.3 is not required for acquisition and extinction of conditioned contextual fear memory (Moosmang et al., 2005a; Busquet et al., 2008) but is required for its consolidation (McKinney et al., 2009). Impaired consolidation in Ca$_V$1.3$^{-/-}$ mice was associated with significantly reduced LTP in the basolateral amygdala synapse receiving input from the entorhinal cortex and enhanced excitability of basolateral amygdala neurons (McKinney et al., 2009). Ca$_V$1.2 seems to carry most of the measurable L-type current in lateral amygdala neurons and their acute pharmacological inhibition reduces thalamolateral amygdala LTP and auditory cued fear memory acquisition (Langwieser et al., 2010).

Ca$_V$1.2 and Ca$_V$1.3 deficiency also affects anxiety- and depression-like behaviors. Reduced Ca$_V$1.2 activity in mouse forebrain enhances anxiety-like behaviors (Lee et al., 2012a). In one study, enhanced anxiety was only observed in females (Dao et al., 2010) and was associated with an antidepressant phenotype in both sexes. Ca$_V$1.3 deficiency induces antidepressant-like behaviors not explained by deafness (Busquet et al., 2010). Conversely, selective stimulation of Ca$_V$1.3 channels in vivo by the LTCC activator BayK8644 (1,4-dihydro-2,6-dimethyl-5-nitro-4-[2-(trifluoromethyl) phenyl]-3-pyridinecarboxylic acid methyl ester) induces depression-like behavior (Sinnegger-Brauns et al., 2004). Genetic defects resulting in enhanced activity of Cav1.2 (*CACNA1C* gene mutations) cause Timothy syndrome (TS), which is characterized not only by severe cardiac arrhythmias but also by neurologic and neuropsychiatric abnormalities (see section II.C below).

Neuronal plasticity associated with drug dependence involves signaling cascade controlled by $Ca_V1.2$ and $Ca_V1.3$ LTCC activity in a different manner. When using locomotor sensitization as a model for psychostimulant-induced long-term plasticity, $Ca_V1.3$ mediates the development of sensitization, whereas $Ca_V1.2$ is responsible for expression of the sensitized response (Giordano et al., 2010). Signaling pathways involved in acute psychostimulant treatment and activated during development of sensitization have been identified (Schierberl et al., 2011; Striessnig et al., 2014).

LTCCs also appear to contribute to the high vulnerability of substantia nigra pars compacta (SNc) dopamine neurons to cell death in Parkinson's disease (PD) (Surmeier et al., 2011). In these permanently active neurons, they mediate activity-dependent dendritic Ca^{2+} transients that contribute to oxidative stress. Transcripts for both $Ca_V1.2$ and $Ca_V1.3$ have been detected in these cells (Chan et al., 2007; Dragicevic et al., 2014). LTCCs appear to have only a minor stabilizing role for pacemaking itself (Guzman et al., 2009; Dragicevic et al., 2014), but $Ca_V1.3$ Ca^{2+} channels regulate SNc firing rates through dopamine D2 autoreceptors activated by dendritic dopamine release in a negative feedback loop through activation of G protein–coupled K^+ channels (GIRKs) such as GIRK2 (*KCNJ6*) (Dragicevic et al., 2014).

$Ca_V1.3$ LTCCs also play a role in maintenance of normal synaptic connectivity. On D2 receptor–expressing striatopallidal medium spiny neurons, they are required for synaptic pruning induced by dopamine depletion (Olson et al., 2005; Fieblinger et al., 2014). A role for $Ca_V1.3$ in synaptic refinement has been described in the auditory pathway during development (Hirtz et al., 2012). Together these data point to an important role of $Ca_V1.3$ for the generation and maintenance of neuronal connectivity.

iii. L-Type Ca^{2+} Channels in Endocrine Cells. LTCCs are present in many endocrine cells but are best characterized in pancreatic islet cells, adrenal chromaffin cells, and aldosterone-producing cells in the adrenal cortex. In mouse pancreatic β cells, $Ca_V1.2$ LTCCs control the fast phase of insulin secretion (Barg et al., 2001; Schulla et al., 2003; Sinnegger-Brauns et al., 2004). β-cell–specific ablation of $Ca_V1.2$ impairs insulin secretion and glucose tolerance (Schulla et al., 2003). In mice, the $Ca_V1.3$ channels do not couple to insulin secretion (Barg et al., 2001; Sinnegger-Brauns et al., 2004) but are required for β-cell proliferation and maintenance of normal β-cell number (Namkung et al., 2001). In contrast with mice, $Ca_V1.3$ transcripts seem to predominate in human β cells (Rorsman and Braun, 2013). Therefore, species differences with respect to isoform expression cannot be excluded. In mice, the late phase of insulin secretion is more dependent on $Ca_V2.3$ (Jing et al., 2005). Glucagon-secreting α cells express both $Ca_V1.2$ and $Ca_V1.3$, in addition to Ca_V2 channels (Vignali et al., 2006). High doses of CCBs (achieved during intoxication) reduce insulin secretion and cause hyperglycemia, supporting the important role of LTCCs for insulin secretion in humans (Levine et al., 2007). However, the therapeutic (vasodilating) plasma concentrations of DHPs that lower blood pressure do not cause a clinically relevant inhibition of pancreatic LTCCs or hormone secretion in the endocrine pancreas.

In mouse chromaffin cells, $Ca_V1.2$ and $Ca_V1.3$ together carry about 50% of the total Ca^{2+} current, each isoform contributing equally to the L-type current component. Although Ca_V2 and Ca_V3 channels are also present (Marcantoni et al., 2010), LTCCs are those coupled most tightly to catecholamine secretion during long depolarizing stimuli (Marcantoni et al., 2010). Although non-LTCCs contribute about one-half of the total inward Ca^{2+} current during square pulse depolarizations, they only contribute about 20% of the total Ca^{2+} charge during a train of action potentials (Vandael et al., 2012). The lower activation voltage range of $Ca_V1.3$, compared with $Ca_V1.2$, allows them to be active at threshold voltages and sustain a pacemaker current responsible for the spontaneous activity of chromaffin cells (Marcantoni et al., 2010). $Ca_V1.3$ channels also engage in a complex coupling to Ca^{2+}-activated large and small conductance Ca^{2+}-activated potassium channels. Accordingly, these K^+ currents are reduced in $Ca_V1.3$-deficient cells, resulting in changes in the cell's firing properties. $Ca_V1.3$ not only drives action potential pacemaking but also serves as a brake for mouse chromaffin cell firing by activating small conductance Ca^{2+}-activated potassium channels and inducing spike frequency adaptation. This could be of physiologic significance upon high-frequency stimulation of chromaffin cells during stress responses (Vandael et al., 2012).

A recent surprising discovery was that $Ca_V1.3$ Ca^{2+} channels can play a central role for aldosterone secretion in humans. Primary aldosteronism is a common cause of secondary hypertension. In most cases it is attributable to either unilateral aldosterone-producing adenoma (APA) or to bilateral adrenal hyperplasia. Several steps of aldosterone synthesis are controlled by intracellular Ca^{2+} (Azizan et al., 2013). Therefore, mutations in different ion channels and ATPases, which directly or indirectly increase intracellular Ca^{2+} signaling, enhance aldosterone production in APAs. These are somatic mutations in the plasma membrane Ca^{2+} pump PMCA3 (*ATP2B3*) (Beuschlein et al., 2013), or mutations that depolarize the cell and activate LTCCs. This also includes mutations in GIRK4 K^+ channels (*KCNJ5*) (Choi et al., 2011) and in the Na^+/K^+-ATPase (*ATP1A1*) (Azizan et al., 2013; Beuschlein et al., 2013). Many recurrent mutations were also found in the pore-forming

α1 subunit of Ca$_V$1.3 (*CACNA1D*) (Azizan et al., 2013; Scholl et al., 2013; Fernandes-Rosa et al., 2014). All of the functionally tested Ca$_V$1.3 α1 mutations exhibit a clear gain-of-function phenotype (Azizan et al., 2013; Scholl et al., 2013). This provided direct evidence that Ca$_V$1.3 plays a major role for APA-induced aldosteronism. In the human adrenal cortex, *CACNA1D* transcripts are the most abundant Ca^{2+} channel subunits (Scholl et al., 2013), suggesting that Ca$_V$1.3 channels are also important for regulation of physiologic aldosterone secretion. Despite this important role of LTCCs, CCBs lower blood pressure but do not effectively lower plasma aldosterone levels in most patients with primary hyperaldosteronism (Stimpel et al., 1988; Carpenè et al., 1989). This may be explained by the contribution of other Ca^{2+} channels to aldosterone secretion, as recently reported for T-type channels in humans (Scholl et al., 2015) and rodents (Hu et al., 2012).

iv. L-Type Ca^{2+} Channels in Auditory and Vestibular Hair Cells. Ca$_V$1.3 channels play an essential role for hearing and Ca$_V$1.3 deficiency leads to deafness in both mice (Platzer et al., 2000) and in humans (Baig et al., 2011). Whereas Ca$_V$2 channels form part of the presynaptic active zones of neurons, Ca$_V$1 channels are associated with the specialized presynaptic structures providing highly localized Ca^{2+} signals for neurotransmitter release at ribbon synapses in sensory cells, such as cochlear inner hair cells (Ca$_V$1.3) and photoreceptors (mainly Ca$_V$1.4). Patch clamp recordings in Ca$_V$1.3$^{-/-}$ hair cells revealed that these channels carry 80% to >90% (depending on the hair cell position along the longitudinal axis of the cochlea) of the total Ca^{2+} current in both inner and outer hair cells (for review, see Koschak et al., 2013).

c. Ca$_V$1.4. In the retina, immunoreactivity for Ca$_V$1.4 α1 has been localized in the synapses of the outer and inner plexiform layer, as well as on photoreceptor cell bodies (Morgans, 2001; Regus-Leidig et al., 2009; Busquet et al., 2010; Mercer and Thoreson, 2011). These channels are predominantly expressed at release sites located in close vicinity to the typical horseshoe-shaped ribbon synapses. Retinal photoreceptors are highly specialized, light-sensing cells. Sustained release of glutamate from their ribbon synapses is Ca^{2+} dependent and LTCCs serve as the predominant source for Ca^{2+} entry. Heterologously expressed Ca$_V$1.4 currents show rapid activation, open at more negative membrane potentials compared Ca$_V$1.2, and inactivate slowly. These properties allow the channel to conduct sustained Ca^{2+} currents at voltages negative to −40 mV (for review, see Koschak et al., 2013). Whereas only a minor fraction of channels might be available at this potential (approximately 10%–15% at −35 mV), the resulting Ca^{2+} influx is expected to be sufficient to trigger neurotransmitter release. Like Ca$_V$1.3, Ca$_V$1.4 is slightly less sensitive to block by DHP CCBs than Ca$_V$1.2 at negative holding potentials (see also section II.D below). This intermediate DHP sensitivity of Ca$_V$1.4 and Ca$_V$1.3 is in good accordance with data obtained in retinal cells, in which relatively high concentrations of DHPs are required to efficiently block L-type Ca^{2+} currents (Wilkinson and Barnes, 1996). In some individuals, nifedipine altered the so-called "light rise" of the electro-oculogram presumably by inhibiting LTCCs (most likely Ca$_V$1.3) on the basolateral surface of the retinal pigment epithelium, thereby preventing the slow rise in intracellular Ca^{2+} required to generate the light rise (Constable, 2011). Thus far, there have been no reports of obvious visual dysfunction in patients receiving CCB medication. Some LTCC blockers have been reported to delay the progression of visual deficits in degenerative retinitis pigmentosa (Barabas et al., 2010; Nakazawa, 2011). However, these findings were not reproduced in all studies, and it remains unclear whether this potential photoreceptor-protective effect is due to block of retinal LTCCs.

2. Ca$_V$1 Family Splice Variants. Alternative splicing is a key mechanism for regulating both the functional properties of Cav1 channels as well as their subcellular targeting to specialized cellular structures. Best understood is the C-terminal splicing of Ca$_V$1.3 α1 subunits, which gives rise to fundamentally different channels. These "long" and "short" Ca$_V$1.3 channels differ with respect to not only their Ca^{2+}- and voltage-dependent gating properties (Bock et al., 2011; Tan et al., 2011) but also their association with modulatory signaling scaffolds (Olson et al., 2005). Some of the splicing-induced effects influence Ca$_V$1.3 channel modulation by CaM (Liu et al., 2010; Bock et al., 2011). CaM preassociates with all Ca$_V$1 and Ca$_V$2 α1 subunits, even at low intracellular Ca^{2+} concentrations (Ben Johny et al., 2013). Calcium-induced conformational changes allow CaM to promote inactivation [i.e., Ca^{2+}-dependent inactivation (CDI)], which involves interaction with C- and N-terminal effector sites (for review, see Christel and Lee, 2012; Simms et al., 2014). CDI and voltage-dependent inactivation during depolarization involve conformational rearrangements of the intracellular channel mouth (Tadross et al., 2010). By restraining Ca^{2+} influx through the channel, CDI prevents excessive Ca^{2+} influx. Several mechanisms regulate the strength of CaM binding and therefore the effectiveness of CDI. Among those are competing CaM-like Ca^{2+} binding proteins, which do not support CDI (Yang et al., 2006; Cui et al., 2007) and RNA editing (Huang et al., 2012). Ca$_V$1 channels also contain a modulatory domain within the C terminus itself. In Ca$_V$1.3 and Ca$_V$1.4 channels, a C-terminal modulatory structure (CTM) is formed by noncovalent interaction of a proximal and a distal C-terminal regulatory domain (PCRD and DCRD, respectively) and putative α helices (Singh et al., 2006, 2008). This structure can compete with CaM binding (Liu et al., 2010). It thereby weakens CDI, reduces open probability, and also shifts the voltage dependence of channel activation to more positive voltages (Singh et al., 2006, 2008). As discussed below, this C-terminal intramolecular interaction is also conserved in Ca$_V$1.2 channels and is a target for channel modulation by PKA. Proteolytic processing has not yet been reported in Ca$_V$1.3, but alternative splicing creates multiple short splice variants that lack the DCRD and therefore allow robust modulation by CaM (Bock et al., 2011; Tan et al., 2011). Accordingly, "short" channel variants exhibit much more pronounced CDI, a more negative activation range, and higher open probability (Bock et al., 2011). Almost complete C-terminal inhibition of CDI also occurs in Ca$_V$1.4 (Singh et al., 2006) and thereby enables permanent Ca^{2+} influx underlying photoreceptor signaling (Singh et al., 2006).

Alternative splicing can also affect the pharmacological properties of LTCCs. Extensive alternative splicing outside the C-terminal tail has been described for Ca$_V$1.2 α1 subunits. As outlined below, tissue-specific splicing occurs. Arterial smooth muscle variants can activate and inactivate at more negative membrane potentials than splice variants predominantly found in cardiomyocytes (Liao et al., 2009). Alternative splicing may also change in disease states. For example, this has been reported in hypertrophied rat and human failing hearts, in rat myocardial infarction models, and in human atherosclerotic blood vessels (for an extensive review, see Liao and Soong, 2010).

In Ca$_V$1.1 α1 subunits, only 4 of 13 splice variants are likely to encode functional channels (Perez-Reyes et al., 1990; Tuluc et al., 2009). However, one variant is abundantly expressed in mouse and human myotubes but is not in differentiated muscle and may therefore play a special role in developing and regenerating muscle (Tuluc et al., 2009). This variant differs from the adult variant only in the length of the domain IV S3–S4 linker due to skipping of exon 29 (Ca$_V$1.1Δ29) (Tuluc et al., 2009). Upon expression in dysgenic myotubes, the Ca$_V$1.1Δ29 splice variant is normally targeted into triads and supports skeletal muscle type excitation-contraction coupling, but there is a drastically increased voltage sensitivity and open probability of the channel (Tuluc et al., 2009). Interestingly, the pathogenesis of myotonic dystrophy (DM) types 1 and 2 (DM1 and DM2, respectively)—an autosomal dominant disorder characterized by skeletal myopathy, cardiac arrhythmia, cataracts, hypogonadism, hypersomnolence, insulin resistance, and other symptoms—has been related to the aberrant splicing of several genes, including Ca$_V$1.1 (Tang et al., 2012). A marked repression of exon 29 in DM1 and DM2 patients was found. In DM1, the extent of exon 29 skipping was also correlated with muscle strength of the patients. Small interfering RNA studies in mice suggested that two splicing factors previously implicated in DM1, MBNL1, and CUGBP1 (Philips et al., 1998; Lin et al., 2006), regulate exon 29 splicing. Together these findings indicated that DM-associated splicing defects alter Ca$_V$1.1 function, with a potential for exacerbation of myopathy. Differences in intracellular Ca^{2+} entry observed for myotubes from DM1 and DM2 patients might at least in part be related to changes in the expression of the embryonic mRNA isoform lacking exon 29 (Santoro et al., 2014).

In Ca$_V$1.4 α1 subunits, a transcript scanning approach identified 19 alternative splice variants (Tan et al., 2012). It is currently unclear how, and to what extent, these naturally occurring alternative splice variants add to the properties of native Ca$_V$1.4 currents (Von Gersdorff and Matthews, 1996; Rabl and Thoreson, 2002) or whether their expression is differentially regulated under pathophysiological conditions in the retina. However, one of the splice variants found in 14% of the full-length transcripts screened can be predicted to affect Ca$_V$1.4 channel gating. It is generated by inclusion of an alternative exon 43* and inserts a stop codon that truncates the C terminus. This mutation would remove its CTM, which prevents Ca$_V$1.4 from undergoing CDI, (see above, Singh et al., 2006). This could lead to expression of channel species undergoing more pronounced inactivation. Overall, alternative splicing in the C terminus was shown to produce at least four splice variants resulting in different lengths of the C-terminal tail (Tan et al., 2012).

C. Ca$_V$1 Channel Pathophysiology

1. Ca$_V$1.1.

a. Hypokalemic Periodic Paralysis. Hypokalemic periodic paralysis (HypoPP) is an heterogeneous autosomal dominant disorder, with missense mutations of a Ca^{2+} channel (Ca$_V$1.1, HypoPP-1) or a sodium channel (Na$_V$1.4, HypoPP-2) accounting for 60% and 20% of cases, respectively (Jurkat-Rott et al., 2002). HypoPP symptoms generally manifest around the second decade of life, and they are characteristically exhibited with hypotonia as well as attacks of local or generalized skeletal muscle weakness or paralysis. Muscle fibers of HypoPP patients show a paradoxical, long-lasting depolarization in response to low extracellular K$^+$, which leads to Na$^+$ channel inactivation, loss of membrane excitability, and paralysis, independent of whether Na$^+$ or Ca^{2+} channels are affected (Jurkat-Rott et al., 2000; Ruff, 2000). S4 arginine mutations of Na$_V$1.4 associated with HypoPP induced a hyperpolarization-activated cationic leak through the voltage sensor of the skeletal muscle Na$_V$1.4 (Sokolov et al., 2007; Struyk et al., 2008), referred to as gating pore current or omega current (Jurkat-Rott et al., 2012). Recently, fibers from a mouse model for HypoPP carrying the mutation Ca$_V$1.1 R528H also elicited a small anomalous inward current at the resting potential (Wu et al., 2012), similar to observations in a Na$_V$1.4 HypoPP mouse model (Wu et al., 2011). Therefore, the gating pore current may be a common mechanism for paradoxical depolarization and susceptibility to HypoPP arising from missense mutations in the S4 voltage sensor of either Ca^{2+} or Na$^+$ channels.

b. Malignant Hyperthermia. Malignant hyperthermia (MH) is a potentially fatal pharmacogenetic disorder in which susceptible individuals experience a life-threatening hypermetabolic reaction of skeletal muscle after exposure to certain anesthetics or skeletal muscle relaxants (e.g., succinylcholine). This uncontrolled increase in the concentration of free myoplasmic Ca^{2+} released from the SR Ca^{2+} stores underlies this phenotype (Jurkat-Rott et al., 2002). Up to 70% of all MH cases are caused by mutations in RyR1 (MHS1), whereas only approximately 1% of cases result from $Ca_V1.1$ $\alpha1$ mutations (MHS5). For deeper insights into both $Ca_V1.1$ structure/function and the pathophysiological mechanisms of MH from the functional analysis of $Ca_V1.1$ mutants, see Yarotskyy and Dirksen (2013).

2. $Ca_V1.2$.

a. Timothy Syndrome. TS is an autosomal dominant condition caused by de novo gain-of-function mutations in the pore-forming $\alpha1$ subunit of $Ca_V1.2$ [*CACNA1C*; Online Mendelian Inheritance in Man (OMIM) number 601005]. It is a multiorgan disease characterized by both cardiac and extracardiac symptoms. The underlying mutations reduce voltage-dependent inactivation (Splawski et al., 2004; Barrett and Tsien, 2008). This enhances Ca^{2+} influx and delays cardiomyocyte repolarization with increased risk of severe ventricular arrhythmias. Lethal tachycardias are the primary cause of death and of reduced average life expectancy (2.5 years). Typical extracardiac features include dysmorphic facial features, syndactyly, and mental retardation (Marks et al., 1995; Splawski et al., 2005; Gillis et al., 2012). Older patients are likely to develop autism (Splawski et al., 2005). TS mutations are located in the S6 segment of the first homologous repeat (IS6; Fig. 1), which forms part of the activation gate. This segment is alternatively spliced (exon 8, 8a). Classic TS type 1 results from a recurrent de novo *CACNA1C* mutation, G406R in exon 8a. An atypical form (TS type 2) is caused by mutations in G406R or G402S in exon 8. In two patients reported thus far, the G402S mutation shows a stronger cardiac phenotype but without syndactyly (Splawski et al., 2005; Hiippala et al., 2015). Since the original publications of the typical TS mutations in IS6, a number of other *CACNA1C* mutations have been identified in constitutively expressed exons showing a gain-of-function phenotype with enhanced current amplitudes or slowing of voltage-dependent inactivation and/or enhanced inward currents at negative voltages (Fukuyama et al., 2014; Hennessey et al., 2014; Boczek et al., 2015; Wemhöner et al., 2015). Intriguingly, most of them were identified in patients presenting with long QT and arrhythmias without obvious extracardiac symptoms (Fukuyama et al., 2014; Hennessey et al., 2014; Hiippala et al., 2015; Wemhöner et al., 2015). On the other hand, patients with mutations outside IS6 (I1166T and A1473G in the repeat III and IV activation gates, G1911R in the long C-terminal tail) (Gillis et al., 2012; Hennessey et al., 2014; Boczek et al., 2015) showed additional extracardiac symptoms (e.g., seizures, craniofacial features, developmental delay, microcephaly, dentition abnormalities), including syndactyly in A1473G. *CACNA1C* mutations can also underlie sudden unexpected infant death (Hennessey et al., 2014). Despite the finding of a $Ca_V1.2$ gain of function, CCBs are not established as therapy for TS. The TS type 1 mutation is less sensitive to block by DHPs than wild-type channels (Splawski et al., 2004).

Loss-of-function (missense) mutations in $Ca_V1.2$ $\alpha1$ (*CACNA1C*), $Ca_V1.2$ $\beta2$ (*CACNB2*), and $Ca_V1.2$ $\alpha_2\delta$-1 (*CACNA2D1*) genes have also been associated with different types of cardiac arrhythmias, including Brugada syndrome (Napolitano and Antzelevitch, 2011; Fukuyama et al., 2014). Together these data indicate that cardiac $Ca_V1.2$ must operate within a narrow activity range to ensure normal cardiac excitability.

The role of $Ca_V1.2$ dysfunction for extracardiac developmental and neurologic symptoms of TS has also been studied. Craniofacial abnormalities and syndactyly in TS patients can be explained by a role of $Ca_V1.2$ during development. For example, $Ca_V1.2$ is expressed in pharyngeal arches within the subset of cells that give rise to jaw primordia. Ca^{2+} influx through $Ca_V1.2$ regulates jaw development and affects cellular hypertrophy and hyperplasia in the mandible (Ramachandran et al., 2013).

b. Neuropsychiatric Disease. Given the expression of $Ca_V1.2$ in most brain regions, the gain-of-function phenotype can also alter neuronal function and neuronal development. Autism often develops in older TS patients who survive from arrhythmias. Autistic behavioral traits are replicated in mice expressing a human TS mutation (Bader et al., 2011). Activity-dependent dendrite retraction was observed in induced pluripotent stem cell–derived neurons produced from TS patients (Krey et al., 2013), indicating that normal $Ca_V1.2$ activity is essential for synaptic development. On the basis of our current knowledge about the role of $Ca_V1.2$ channels for brain physiology (see section II.B), this suggests that $Ca_V1.2$ dysfunction may also contribute to human neuropsychiatric disease risk. Indeed, large-scale genome-wide association studies (GWASs) revealed a strong association between susceptibility for various psychiatric disorders, including bipolar disease, schizophrenia, and major depression, and single nucleotide polymorphisms (SNPs) in the *CACNA1C* gene. These are located within intronic regions (Bhat et al., 2012). SNP rs1006737, a common intronic risk haplotype, is one of the most consistent associations in psychiatric genetics (Bhat et al., 2012; Yoshimizu et al., 2015). It also has an impact on task-based human behaviors and human brain morphology, such as gray matter volume of specific regions (for references, see Yoshimizu et al., 2015). Interestingly, this SNP leads to increased $Ca_V1.2$ $\alpha1$ subunit mRNA expression and L-type current density in fibroblast-derived induced neurons (Yoshimizu et al., 2015). This fits well with the observation that autism associated with TS is also caused by gain-of-function *CACNA1C* mutations.

3. $Ca_V1.3$.

a. Parkinson's Disease. As described above, LTCCs serve as an important Ca^{2+} source in spontaneously active SNc neurons, which preferentially degenerate in PD. In some reports, DHPs were found to protect SNc neurons in neurotoxin-based models of PD in rodents and nonhuman primates (Kupsch et al., 1995, 1996; Chan et al., 2007; Ilijic et al., 2011). This was achieved at low doses of DHPs, considered therapeutic in humans. Further support for a potential therapeutic role for DHPs comes from case-control and cohort studies. These studies reported a significantly reduced risk for a first-time diagnosis of PD in users of brain-permeable CCBs (odds or rate ratios of 0.71–0.78) (Becker et al., 2008; Ritz et al., 2010; Pasternak et al., 2012; Lang et al., 2015). Neuroprotection by CCBs, in particular by DHPs, can be rationalized by inhibition of dendritic Ca^{2+} entry during action potentials of rhythmic activity or during burst firing (Putzier et al., 2009), which occurs in response to reward-predicting stimuli (Liss and Roeper, 2008). In addition, these drugs may reduce α-synuclein–dependent L-DOPA–induced degeneration of SNc-dopamine neurons (Mosharov et al., 2009).

b. Hearing and Cardiac Dysfunction. Like in knockout mice, the major symptoms of $Ca_V1.3$ deficiency in humans are SAN dysfunction (bradycardia and arrhythmia) and deafness. This has been described in two Pakistani families with autosomal recessive sinoatrial node dysfunction and deafness syndrome (Baig et al., 2011). Thus far, it is unclear to what extent other *CACNA1D* mutations or polymorphisms contribute risk for hearing disorders or for SAN dysfunction. Despite a normal life span, $Ca_V1.3^{-/-}$ mice also appear more vulnerable to ventricular extrasystoles (Matthes et al., 2004) and atrial fibrillation due to reduced L-type currents and impaired intracellular Ca^{2+} handling in atrial myocytes (Zhang et al., 2002; Mancarella et al., 2008).

c. Neuropsychiatric Disease. As for $Ca_V1.2$, human genetics also strongly point to an important role of $Ca_V1.3$ LTCCs in the pathophysiology of neuropsychiatric disease, including autism spectrum disorders (ASDs). As described above, somatic $Ca_V1.3$ $\alpha1$-subunit (*CACNA1D*) gain-of-function mutations cause aldosteronism through excess aldosterone production in APAs (Azizan et al., 2013). Interestingly, two of these mutations were also found as germline de novo mutations in two patients with a severe congenital syndrome presenting not only with primary aldosteronism but also with neurodevelopmental deficits and seizures at early age (PASNA, OMIM number 615474) (Scholl et al., 2013). In addition, de novo *CACNA1D* mutations have also been reported as high-risk mutations in two patients with sporadic autism and intellectual disability (Iossifov et al., 2012; O'Roak et al., 2012). For both mutations, functional studies also revealed a strong channel gain of function (Pinggera et al., 2015) very similar to the biophysical changes observed for mutations in APAs (Azizan et al., 2013; Scholl et al., 2013). Given the important role of $Ca_V1.3$ for many brain functions (see above) and the causal role of $Ca_V1.2$ gain of function in autism associated with TS, these data do not prove, but strongly suggest, a direct causal role of the two de novo mutations in the ASD patients (Pinggera et al., 2015). Moreover, these observations prompt several clinically relevant questions: Would patients with ASD and patients with primary aldosteronism with seizures and neurologic abnormalities with *CACNA1D* mutations benefit from therapy with LTCC blockers? Is aldosterone secretion also enhanced in the two ASD patients or do they show any other symptoms that could result from enhanced Cav1.3 function?

These findings also raise the important question of to what extent more subtle functional changes in $Ca_V1.3$ function in known *CACNA1D* polymorphisms can also contribute to overall neuropsychiatric disease risk.

4. $Ca_V1.4$.

a. Congenital Stationary Night Blindness Type 2. $Ca_V1.4$ channels are the most predominant LTCCs in retinal neurons. Their importance is well supported by the fact that *CACNA1F* gene mutations cause several forms of human retinal diseases (OMIM numbers 300071, 300476, and 300600). The majority of $Ca_V1.4$ mutations were identified in patients with congenital stationary night blindness type 2 (CSNB2). Typical symptoms of CSNB2 are low visual acuity, myopia, nystagmus, strabismus, photophobia, and night blindness (Bech-Hansen et al., 1998). The severity of night blindness is a variable symptom, and in some cases, it was not even reported. Because of the X-linked nature of $Ca_V1.4$ channel dysfunction, CSNB2 mainly involves male individuals but heterozygote female individuals can also be affected (Hope et al., 2005; Michalakis et al., 2014).

Structural aberrations identified in CSNB2 patients comprise $Ca_V1.4$ $\alpha1$-subunit missense or truncation mutations in addition to insertions or deletions, which can be categorized by their functional effects as loss or gain of function or impairment of the CTM (see above) (Stockner and Koschak, 2013). The complete absence of channel function or altered gating properties is expected to eliminate or decrease $Ca_V1.4$-mediated Ca^{2+} entry required for normal photoreceptor signaling. Both loss of channel function and a strong gain of function can also lead to alterations in photoreceptor synapse formation. This has been demonstrated in mice lacking $Ca_V1.4$ ($Ca_V1.4^{-/-}$) and mutant mice ($Ca_V1.4$ $\alpha1$ containing the I745T mutation, which induces a gain-of-function phenotype with activation at more hyperpolarized voltages and slowed inactivation) (Tom Dieck, 2013). These data demonstrated the importance of proper $Ca_V1.4$ function for efficient photoreceptor synapse maturation, and that dysregulation of $Ca_V1.4$ channels in CSNB2 may have synaptopathic consequences. Thus far, no comparable human data are available regarding retinal morphology. However, inner and outer retinal layers were shown to be thinned in CSNB2 patients when evaluated with spectral domain optical coherence tomography (Chen et al., 2012). These animal data suggest that altered Ca^{2+} signaling in CSNB2 may result in changes in retinal morphology early in development and may contribute to the overall dysfunction of retinal transmission. Potential pharmacotherapeutic interventions might therefore have to be applied early in disease. Such interventions also depend on mechanistic insights into the aberrations caused by the individual mutations. Gene therapeutic approaches focus on recombinant viral vectors as promising vehicles for therapeutic gene delivery to the retina (for reviews, see Boye et al., 2013; Lipinski et al., 2013). Gene replacement strategies may be applicable in patients carrying null mutations (full channel) or with impaired CTM function (C-terminal truncations) (Burtscher et al., 2014). The recent finding that some mutations (e.g., L860P; Burtscher et al., 2014) reduce the expression of functional channels by decreasing protein stability also suggests alternative approaches, such as pharmacochaperoning with ligands that stabilize folding intermediates and reduce endoplasmic reticulum–associated degradation. Valproic acid has been suggested to act as a pharmacological chaperone for unfolded proteins and is being explored in an ongoing clinical trial in patients with autosomal dominant retinitis pigmentosa (ClinicalTrials.gov identifier NCT01233609). Direct pharmacological activation of $Ca_V1.4$ channels with known LTCC activators (e.g., BayK8644) is not feasible for clinical application in human retinal disorders due to toxic side effects resulting from activation of $Ca_V1.2$ and $Ca_V1.3$ in other tissues as outlined below.

D. Pharmacology of Ca_V1 Channels

1. Molecular Pharmacology. Clinically used CCBs belong to different chemical classes. The most widely used are DHPs, such as amlodipine, felodipine, or nifedipine (Fig. 3). Like verapamil (a phenylalkylamine) and diltiazem (a benzothiazepine), they interact with overlapping high-affinity drug binding domains close to the pore and to the proposed activation gate of LTCC $\alpha1$ subunits (Fig. 4) (Hockerman et al., 1997; Striessnig et al., 1998; Tikhonov and Zhorov, 2009; Catterall and Swanson, 2015). Binding is reversible, stereoselective and, in isolated membranes at zero membrane potential, occurs with dissociation constants in the nanomolar range (0.1–50 nM) (Glossmann and Striessnig, 1990). Bound drugs interfere with the normal voltage-dependent cycling of the channel through its resting, open, and inactivated states (modulated receptor model) (Bean et al., 1986; Berjukow and Hering, 2001). The uncharged DHPs primarily stabilize and induce inactivated channel states. They possess much higher affinity for the inactivated channel conformation and thus their IC_{50} decreases with increased availability of inactivated channel states at more depolarized membrane potentials (voltage-dependent block) (Bean et al., 1986; Hamilton et al., 1987; Berjukow and Hering, 2001; Koschak et al., 2001). Access of phenylalkylamines and benzothiazepines is favored by the open channel state. Direct pore block together with stabilization of inactivated channel states with slowed recovery from inactivation results in pronounced frequency- or use-dependent inhibition (Shabbir et al., 2011). Ca^{2+} channel activators, such as the DHPs (−)-BayK8644 and (+)-SDZ202-791 [propan-2-yl (4*R*)-4-(2,1,3-benzoxadiazol-4-yl)-2,6-dimethyl-5-nitro-1,4-dihydropyridine-3-carboxylate], also exist (see below).

The sensitivity of LTCCs for DHP CCBs varies in different tissues for several reasons. One explanation is the variable contribution of these LTCCs to total L-type current. $Ca_V1.3$ and $Ca_V1.4$ exhibit about 5- to 10-fold lower sensitivity to DHPs than $Ca_V1.2$, as demonstrated in heterologous expression systems at negative membrane potentials (Koschak et al., 2001, 2003; Xu and Lipscombe, 2001). This can explain the relatively weak inhibition of L-type pacemaker currents in the SAN, which are dominated by $Ca_V1.3$ (Mangoni and Nargeot, 2001). Another factor affecting DHP sensitivity of L-type currents is alternative splicing of $\alpha1$ subunits. For $Ca_V1.2$, it has been demonstrated that DHPs inhibit currents in arterial smooth muscle at lower concentrations than in the working myocardium. A detailed analysis of $Ca_V1.2$ $\alpha1$ splice variants in the heart and smooth muscle revealed the presence of more DHP-sensitive splice variants predominantly expressed in arterial smooth muscle. Some of these splice variants activate at slightly more negative voltages (Liao et al., 2004; Cheng et al., 2009) and are therefore expected to preferentially contribute to a steady-state Ca^{2+} inward current (window current) close to the smooth muscle resting potential that controls myogenic tone. The more depolarized resting membrane potential in smooth muscle (≥ -60 mV) compared with cardiomyocytes (or most neurons) favors inactivated channel states preferentially blocked by DHPs. Some of these splice variants are also prone to more pronounced steady-state inactivation, which also enhances DHP sensitivity (Liao et al., 2007). There is also evidence that alternative splicing of $Ca_V1.2$ $\alpha1$ affects the molecular architecture of the drug binding domain and thus the access of DHPs for inactivated channel states (Welling et al., 1993). Alternative splicing (in the C terminus) also slightly affects the DHP sensitivity of $Ca_V1.3$ (Huang et al., 2013b).

2. Clinical Pharmacology. LTCC blockers have been licensed for decades for the treatment of hypertension and myocardial ischemia, and they belong to the most widely prescribed drugs worldwide. DHPs are arterial

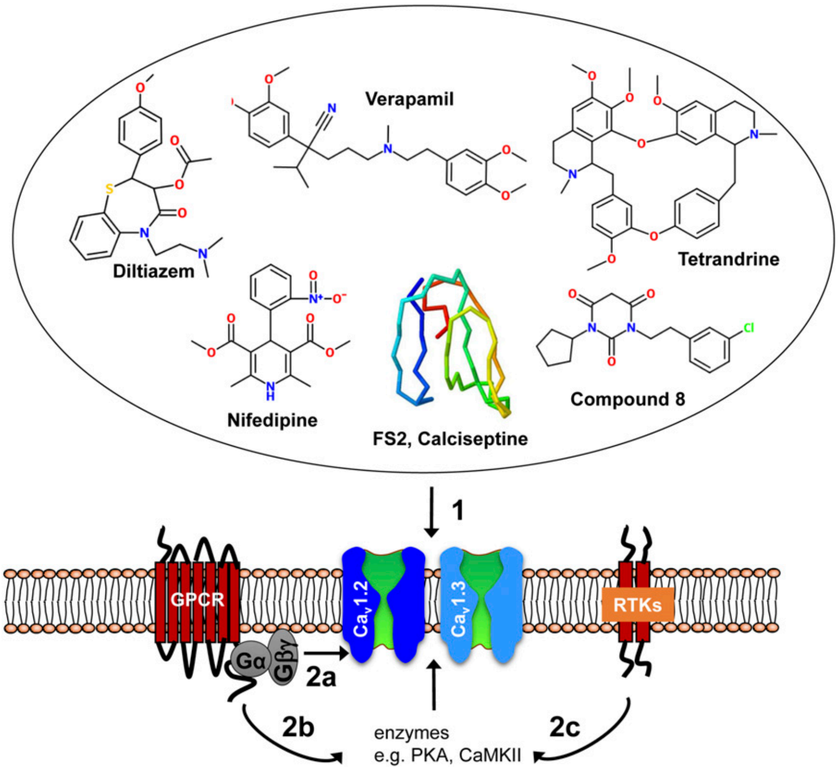

Fig. 3. Modulation of L-type channels by drugs, toxins, and signaling pathways. (Pathway 1) The major pharmacologically relevant classes of LTCC active drugs are shown. DHPs (prototype nifedipine) are the most selective LTCC blockers. Verapamil and diltiazem also block non- LTCCs at higher concentrations (Diochot et al., 1995; Ishibashi et al., 1995). Tetrandrine is a bis-benzylisoquinoline alkaloid. It was isolated from the Chinese medicinal herb *Stephania tetrandra* used in China to treat hypertension and angina (King et al., 1988). In addition to LTCCs, it also blocks non–L-type current components (Weinsberg et al., 1994). Note that the apparent potency of classic L-type channel blockers strongly depends on membrane potential and/or stimulation frequency and action potential length. (Pathway 2) L-type channels are modulated by a variety of different signaling pathways either through membrane-delimited actions of activated G proteins (pathway 2a) or enzymes activated by GPCR (pathway 2b) or receptor tyrosine kinase (RTK) (pathway 2c) signaling (for details, see text). The FS2 structure (very similar to calciseptine) was drawn according to PDB ID 1TFS (chain trace, disulfide bonds not shown).

vasodilators reducing arterial muscle tone, peripheral vascular resistance, and vasospasms in coronary or peripheral arteries. By lowering arterial blood pressure and afterload, DHPs also reduce cardiac oxygen demand. Together with their spasmolytic effect, this explains most of the antianginal actions of DHPs. At therapeutic doses, DHPs lack negative inotropic actions and do not directly affect SAN and AVN function. In addition to their antihypertensive, vasodilating, and spasmolytic properties, verapamil and diltiazem are also negative chronotropic, dromotropic, and inotropic and thus inhibit exercise-induced increases in heart rate and myocardial oxygen consumption (similar to β-adrenoceptor antagonists). These direct cardiodepressant effects make them suitable for the treatment of angina pectoris in hypertensive patients (Bangalore et al., 2008).

Unwanted effects at therapeutic doses, such as flushing, headache, dizziness, and hypotension, are mostly related to the vasodilating effects of CCBs. Peripheral edema and ankle swelling is often the therapy-limiting side effect upon long-term use of DHPs (Parkinson Study Group, 2013). Constipation is a frequent side effect of verapamil and can be explained by LTCC inhibition in intestinal smooth muscle (Moosmang et al., 2005b). Verapamil (and to a lesser degree, diltiazem) can cause bradycardia, atrioventricular block, or a decrease in left ventricular function, especially in patients who are taking β-adrenoceptor blockers or who have preexisting heart disease. DHPs can also worsen angina, most likely due to a redistribution of coronary blood flow to the nonischemic myocardium in the absence of direct cardiodepressant effects.

At therapeutic doses, CCBs cause no relevant side effects in other tissues where LTCCs serve important functions. There is no evidence for muscle weakness from block of $\mathrm{Ca_V}1.1$ channels in skeletal muscle, increased hearing thresholds from inhibition of $\mathrm{Ca_V}1.3$ in cochlear inner hair cells, visual impairment from block of $\mathrm{Ca_V}1.4$ in retinal photoreceptors, or CNS disturbances from block of $\mathrm{Ca_V}1.2$ and or $\mathrm{Ca_V}1.3$ in the brain. Suppression of insulin secretion and hyperglycemia occur only at toxic plasma levels after CCB overdose (Levine et al., 2007). However, this side effect plays no role at therapeutic doses in clinical practice.

3. L-Type Calcium Channels as Potential Targets for Other Indications. Our increasing understanding regarding the physiologic and pathophysiological role of

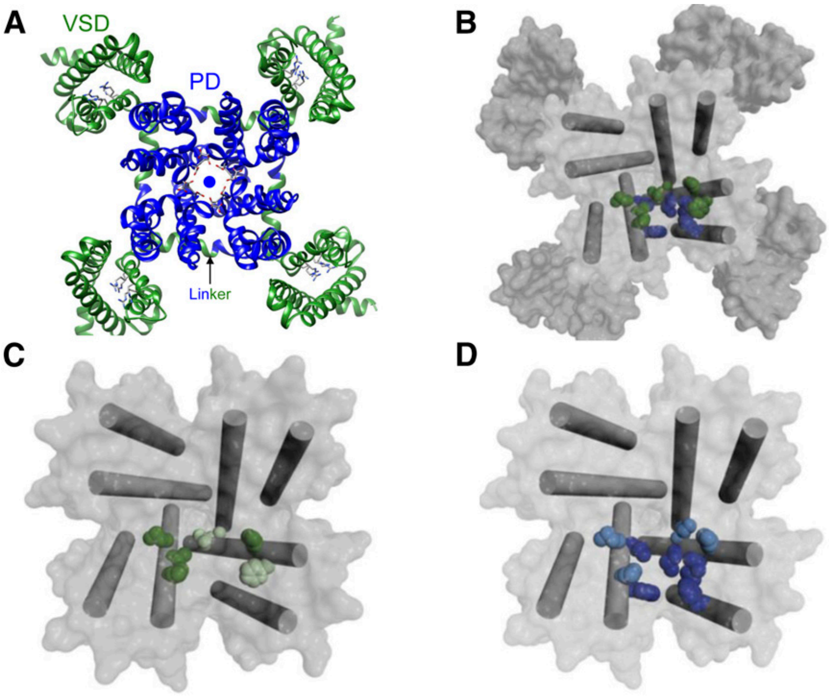

Fig. 4. Calcium channel structure and ligand binding sites. (A) Extracellular view of the overall structure of Ca_VAb (preopen state; PDB ID 4MVQ), a homotetrameric voltage-dependent and calcium-selective channel generated by introducing three negatively charged aspartate residues (side chains in the pore are illustrated) (Tang et al., 2014). The four homologous domains of the $\alpha 1$ subunits of voltage-gated calcium channels likely possess a very similar architecture. Each domain contributes a voltage-sensing domain (VSD) (green, segments S1–S4) and a pore-forming domain, which together form the pore domain (PD) with a central ion conducting pathway for calcium ions (sphere). Each voltage sensor contains four positively charged arginines (side chains illustrated) that sense transmembrane voltage changes. Voltage-sensor movements are transmitted to the PD through a linker (arrow indicates one of them) between helices S4 and S5. (B) Top view of the pore module of Ca_VAb (pore-forming S5 and S6 helices are shown as cylinders) in the preopen state, with amino acid side chains analogous to those implicated in phenylalkylamine binding (green) and amino acid side chains specific for DHP binding illustrated in blue. The Ca_VAb structure has been used to illustrate how the analogs of amino acid residues important for drug binding in mammalian channels may form drug binding domains (Catterall and Swanson, 2015).The overlapping binding pocket can explain noncompetitive interactions observed in binding experiments in different tissues (Striessnig et al., 1998). (C) Top view of the Ca_VAb pore module in the preopen state, with the S5 and S6 segments illustrated as cylinders and amino acid side chains analogous to those implicated in phenylalkylamine binding illustrated in dark green for $Ca_V1.2$-specific residues and in light green for Ca_V-conserved residues. (D) Representation of DHP binding residues as in (C) for phenylalkylamines. Images in (B) to (D) were reproduced from Catterall and Swanson (2015), with permission.

LTCCs also outside the cardiovascular system raises the important question about the pharmacotherapeutic potential of LTCC block in other tissues. A particularly challenging question relates to the efficient inhibition of LTCCs in the brain. As outlined above, a number of therapeutically highly relevant pharmacological effects can be postulated from findings in mutant mice and from human mutations. This includes neuroprotection in PD as well as treatment of neuropsychiatric disorders, ASDs, and febrile seizures. Since CCBs are well established for clinical use in cardiovascular disease, they could be “repurposed” for other indications.

a. Parkinson’s Disease Neuroprotection. Based on the strong preclinical findings regarding a key role of LTCC-mediated Ca^{2+} load in SNc neurons, a phase 3 clinical trial (ClinicalTrials.gov identifier NCT02168842) has already been initiated to study the neuroprotective potential of the DHP isradipine in early PD. Isradipine is currently licensed for the treatment of high blood pressure. At present, the preclinical in vivo findings from neurotoxin-induced PD models do not allow us to predict whether $Ca_V1.2$, $Ca_V1.3$, or both isoforms contribute to the proposed Ca^{2+} toxicity. In clinical trials, $Ca_V1.2$-mediated side effects, such as hypotension and/or peripheral edema, limit long-term treatment of PD with higher doses of DHPs (Parkinson Study Group, 2013), providing a strong argument for efforts to discover $Ca_V1.3$-selective inhibitors that are not yet available (see below). However, it is currently unknown whether $Ca_V1.3$-selective inhibitors would miss a neuroprotective component mediated by $Ca_V1.2$ channels.

b. Neuropsychiatric Disease. As described above, GWASs have revealed a strong association of intronic SNPs in *CACNA1C* and the susceptibility for psychiatric disorders, including bipolar disease, schizophrenia, major depression, and ADs. It is one of the most consistent associations reported in psychiatric genetics (Dao et al., 2010; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013; Ripke et al., 2013). The recent findings that one of these SNPs (rs1006737) leads to increased $Ca_V1.2$ function (Yoshimizu et al., 2015), and that gain-of-function *CACNA1C* mutations cause autism in TS, strongly motivate the reevaluation of CCBs for the treatment of bipolar disease, schizophrenia, and major depression. In contrast with earlier clinical studies (Hollister and Trevino, 1999; Post et al., 2000), future trials could stratify patients according to risk alleles to define cohorts who may benefit most from the addition of CCBs to standard therapy (Ostacher et al., 2014; Lencz and Malhotra, 2015). Nonselective brain-permeable CCBs, such as isradipine, are expected to block both $Ca_V1.2$ and $Ca_V1.3$. On the basis of the preclinical findings discussed above, the inhibition of $Ca_V1.3$ may contribute antidepressant effects.

c. Febrile Seizures. $Ca_V1.2$ channels appear to contribute critically to the generation of febrile seizures. This has been shown using patch clamp recordings from hippocampal pyramidal cells in acute rat pup brain slices (Radzicki et al., 2013). Nimodipine could block hyperthermia-induced abnormal spontaneous firing of these neurons in vitro as well as in an in vivo model. Nimodipine was applied intraperitoneally, acutely at a dose of 2.5 mg/kg, which was carefully selected to prevent side effects, but it is expected to reach much higher plasma concentrations than during therapeutic dosing in humans. Nimodipine, unlike other CCBs, is also a potent inhibitor of adenosine uptake (Striessnig et al., 1985); therefore, a contribution of this mechanism to the observed in vivo protection of febrile seizure cannot be excluded. Irrespective of these considerations, this study provided compelling evidence for a role of $Ca_V1.2$ in febrile seizures and for clinical trials to stop or prevent seizures triggered by high fever and to reduce the risk for long-term neurologic consequences. Parenteral nimodipine is already licensed for the treatment of subarachnoid hemorrhage and is thus already available for interventional studies.

d. Cardiovascular Disease. The recent discovery that $Ca_V1.3$ plays a key role in aldosterone secretion may be one of the reasons why therapeutic doses of the DHP CCBs, which preferentially block $Ca_V1.2$ in arterial resistance vessels, show no robust inhibitory effects on aldosterone secretion in humans. This may be achieved in the future with potent $Ca_V1.3$-selective inhibitors. They are unlikely to affect cardiac inotropy due to their absence in ventricular myocardium but are expected to cause a bradycardic effect (Platzer et al., 2000; Baig et al., 2011). This combined mechanism of action could be therapeutically meaningful in patients with heart failure, in which heart rate (due to enhanced sympathetic drive) and aldosterone (due to secondary aldosteronism) are both elevated. High heart rate is a risk factor in heart failure, and selective lowering of heart rate, with the HCN (I_f) channel blocking bradycardic agent ivabradine, improves cardiovascular outcomes (Böhm et al., 2010). However, in this patient cohort, a troublesome side effects of these drugs may be atrial fibrillation risk, which has been shown to be increased in $Ca_V1.3$-deficient mice (see above).

4. Pharmacological Targeting of L-Type Calcium Channels in the Brain. Effective block of LTCCs in the brain is complicated by the fact that negative resting membrane potentials in most neurons and short action potential durations do not favor high sensitivity for DHPs due to their state-dependent action (Helton et al., 2005). At the same time, alternative splicing and more depolarized potentials render $Ca_V1.2$ channels highly DHP sensitive in arterial resistance vessels (see above). To minimize cardiovascular side effects and maximize therapeutic actions in the brain, two strategies can be pursued. One consists of the development of $Ca_V1.3$-selective drugs. However, if inhibition of neuronal $Ca_V1.2$ channels is also desired, then higher CNS activity may be achieved by enhancing brain delivery of CCBs to the brain.

a. $Ca_V1.3$-Selective L-Type Calcium Channel Blockers. In radioligand binding studies, isradipine binds to $Ca_V1.2$ and $Ca_V1.3$ channels with indistinguishable affinities (Koschak et al., 2001). However, in functional studies, isradipine inhibits recombinant $Ca_V1.2$ channel currents with about 5- to 10-fold lower IC_{50} values (Koschak et al., 2001), indicating differences in the effect of voltage on drug sensitivity. Evidence for more potent inhibition of $Ca_V1.2$ by isradipine also comes from experiments in isolated SAN cells, in which 70% of the L-type current is $Ca_V1.3$ mediated. In a previous study, 50 nM isradipine inhibited only 26% of the wild-type current (mostly $Ca_V1.3$) but 72% of the $Ca_V1.2$ component remaining in $Ca_V1.3^{-/-}$ SAN cells. This implies an IC_{50} for $Ca_V1.3$ well above 50 nM (Mangoni et al., 2003).

Thus far, only one study has described $Ca_V1.3$-selective blockers. A detailed structure-activity relationship has been reported for novel pyrimidine-2,4,6-triones (Kang et al., 2012, 2013). The most selective candidate, BPN-4689 [1-(3-chlorophenethyl)-3-cyclopentylpyrimidine-2,4,6-trione; also referred to as compound 8 (Cp8)] (Kang et al., 2012), showed a more than 600-fold selectivity for $Ca_V1.3$ compared with $Ca_V1.2$ in a fluorescent imaging plate reader assay. Whole-cell patch clamp recordings in human embryonic kidney 293 cells stably expressing LTCC complexes revealed an IC_{50} of 24.3 μM for $Ca_V1.3$ inhibition, whereas $Ca_V1.2$ Ba^{2+} currents were nearly unaffected. A follow-up study (Huang et al., 2014) confirmed the inhibitory activity of Cp8 on transiently expressed LTCC Ca^{2+} currents in whole-cell patch clamp recordings. However, neither high potency nor relevant $Ca_V1.3$ selectivity was confirmed. These experiments also revealed a dependence of the Cp8-mediated effect on the coexpressed auxiliary β subunit. With palmitoylated β2a, $Ca_V1.2$ Ca^{2+} currents were even more sensitive to Cp8 than $Ca_V1.3$ currents. A third study found an even more complex modulation of LTCC Ba^{2+} and Ca^{2+} currents by Cp8 (Ortner et al., 2014). In whole-cell patch clamp recordings on transiently expressed LTCCs in tsA201 cells, Cp8 induced a pronounced time-dependent change in gating kinetics characterized by a slowing of the activation, inactivation, and deactivation time course and thus closely resembled the activity of known LTCC activators. This effect was also confirmed for native $Ca_V1.2$- and $Ca_V1.3$-current components in mouse chromaffin cells (Ortner et al., 2014). Taken together, these studies suggest that the $Ca_V1.3$ selectivity of Cp8 and related pyrimidine-2,4,6-triones is highly dependent on experimental conditions and that these drugs may even cause channel-activating effects. Therefore, $Ca_V1.3$-selective blockers, for use as $Ca_V1.3$-selective pharmacological tools and suitable for further clinical development, still remain to be discovered.

b. L-Type Channel Activators as Therapeutics. In addition to selective blockers, activators of LTCCs have also been successfully used to study the role of LTCCs for cellular signaling and LTCC physiology in vivo. The most widely used experimental compounds are the DHPs (−)-BayK8644 and (+)-SDZ202-791 (Glossmann and Striessnig, 1990) as well as the benzoyl pyrrole FPL 64167 (methyl 2,5-dimethyl-4-[2-(phenylmethyl)benzoyl]-1*H*-pyrrole-3-carboxylate) (Zheng et al., 1991). The stereoselective activation of a voltage-gated Ca^{2+} current component by these drugs is currently the most specific proof for the presence of an L-type current. These compounds exert their activating properties by increasing current amplitudes, shifting activation voltage to more negative voltages, slowing of inactivation, and increasing and slowing tail currents (Tsien et al., 1986; McDonough et al., 2005). Despite their invaluable role in studying the molecular pharmacology of LTCCs in vitro, they are not suitable for clinical use. They activate all four LTCC isoforms and in vivo effects are largely determined by toxic effects through activation of $Ca_V1.2$ in the brain and cardiovascular system. BayK8644 increases cardiac contractility (Pelc et al., 1986), induces cardiac arrhythmias (Zhou et al., 2013), and elevates arterial blood pressure (Bourson et al., 1989). Activation of brain LTCCs by BayK8644 induces a severe neurobehavioral dystonic syndrome, including self-biting, mostly due to $Ca_V1.2$ activation (Sinnegger-Brauns et al., 2004; Hetzenauer et al., 2006). It is associated with enhanced release of dopamine, glutamate, and other neurotransmitters as well as massive neuronal activation in most brain regions (Sinnegger-Brauns et al., 2004; Hetzenauer et al., 2006). These pharmacological effects preclude the chronic administration of LTCC activators. However, it is currently unclear whether short-term administration of low doses in a controlled clinical setting could lead to long-term changes in brain function, such as those induced by electroconvulsive therapy.

c. Peptide Toxins Inhibiting L-Type Calcium Channels. As for non-LTCCs, peptides selectively inhibiting L-type channels have been discovered. Calciseptine and FS2 (Fig. 3) are structurally highly related 60–amino acid polypeptides, isolated from venom of the black mamba (*Dendroaspis polylepis polylepis*). Similar to DHPs, they selectively block LTCCs, and this explains their smooth muscle relaxant and cardiodepressant properties (De Weille et al., 1991; Watanabe et al., 1995). Glacontryphan-M (11 amino acid residues) isolated from the venom of the marine snail *Conus marmoreus* (Hansson et al., 2004) is also present in the wings of a butterfly, apparently serving as predator defense (Bae et al., 2012). In pancreatic β cells, it inhibits only L-type currents with low nanomolar IC_{50} values and does not inhibit other (Ca_V2) Ca^{2+} channels (Hansson et al., 2004). Selective but less potent inhibition of neuronal LTCCs has also been reported for a peptide, CSTX-1, isolated from the venom of a spider, *Cupiennius salei* (Kubista et al., 2007). Calcicludine is a 60–amino acid polypeptide from the venom of *Dendroaspis angusticeps* structurally related to dendrotoxins (Schweitz et al., 1994). In addition to neuronal L-type currents, it also blocks native N-type and other high voltage–activated Ca^{2+} channels at low nanomolar concentrations (Schweitz et al., 1994). In contrast with N-type CCBs (ziconotide, see section III.D.2 on Ca_V2 channels), peptide toxins blocking LTCCs have not been developed for clinical use thus far.

5. Indirect Modulation of Ca_V1 Calcium Channels. The activity of LTCCs is modulated by neurotransmitters, enzymes, and alternative splicing and protein interactions in a number of ways.

a. cAMP-Dependent Protein Kinase (Protein Kinase A). Activation of cardiac ($Ca_V1.2$) LTCCs by adrenergic stimulation in the "fight-or-flight" response and upon therapy with β-adrenergic receptor agonists is the classic example of ion channel regulation by a signaling pathway (Fig. 3). During the fight-or-flight response, PKA phosphorylates $Ca_V1.2$ LTCC currents in cardiomyocytes, and this contributes to increased heart rate and contractility. Modulation requires the proteolytic cleavage of the C-terminal tail by post-translational proteolytic processing. The resulting C-terminal fragment remains noncovalently attached with the remainder of the long C-terminal tail through interaction of two putative α-helices (PCRD and DCRD, see above) (Fuller et al., 2010; Fu et al., 2013). Binding of the C-terminal fragment to the cleaved $\alpha1$ subunit inhibits channel activity. PKA is anchored to the C-terminal fragment by A kinase–anchoring proteins. PKA phosphorylates two $Ca_V1.2$ $\alpha1$ residues, serine 1700 and threonine 1704, within the PCRD helix (Fuller et al., 2010; Fu et al., 2013). This interferes with PCRD–DCRD interaction, relieves inhibition by the C-terminal fragment, and increases $Ca_V1.2$ current. In mutant mice carrying these mutations, the important role of the phosphorylation of these residues for β-adrenergic modulation of $Ca_V1.2$ channels in the heart was recently confirmed in vivo (Fu et al., 2013). C-terminally attached phosphatases (including protein phosphatase 2A and 2B/calcineurin) ensure rapid dynamics for regulation by phosphorylation/dephosphorylation in the heart and brain (Murphy et al., 2014).

A kinase–anchoring proteins are also found in a complex with native $Ca_V1.3$ channels (Marshall et al., 2011) and are stimulated by PKA. This has been shown in adrenal chromaffin cells (Mahapatra et al., 2012) and in the SAN (Mangoni et al., 2003). For $Ca_V1.3$, the molecular details for PKA regulation are less well studied but seem to also involve phosphorylation sites within the C-terminal tail (Liang and Tavalin, 2007; Ramadan et al., 2009).

b. Membrane Phospholipids. Various G protein–coupled receptors (GPCRs) (e.g., muscarinic acetylcholine receptors) can inhibit voltage-gated calcium channels, including LTCCs (Suh and Hille, 2005; Hille et al., 2015), through activation of phospholipase C. Phosphatidylinositol 4,5-bisphosphate (PIP_2) seems to stabilize active channel conformations by tethering cytoplasmic domains, bound to its inositol phosphates, to the plasma membrane to which PIP_2 is anchored through its fatty acid side chains (Suh et al., 2012). This can explain the reduction of Ca^{2+} channel currents by receptor-mediated PIP_2 depletion. In superior cervical ganglion neurons, extracellularly applied arachidonic acid can also inhibit Ca^{2+} channel activity (Heneghan et al., 2009). Current models predict that arachidonic acid released after phospholipase C activation and activation of Ca^{2+}-sensitive phospholipase A2 can occupy the fatty acid binding site of PIP_2 and interfere with PIP_2 stabilization of the channel. Channel-lipid interactions at the inner leaflet of the membrane bilayer which reduce rather than stabilize channel activity have also been identified (Kaur et al., 2015).

As for Ca_V2 channels, inhibition of LTCCs by GPCR activation through direct G protein–mediated, membrane-delimited pathways (Fig. 3, pathway 2a) has also been reported (Gilon et al., 1997; Pérez-Garci et al., 2013) but is less well understood on the molecular level.

c. Receptor Tyrosine Kinases. Activation of receptor tyrosine kinases (e.g., by insulin-like growth factor-1) can activate $Ca_V1.2$ and $Ca_V1.3$ LTCC function, involving phosphorylation of their pore-forming $\alpha1$ subunits (Bence-Hanulec et al., 2000; Gao et al., 2006) (Fig. 3, pathway 2c).

d. Protein Interactions with L-Type Calcium Channels. For a discussion of confirmed protein interaction partners, see separate reviews by Calin-Jageman and Lee (2008) and Striessnig et al. (2014). Protein–protein interactions, as described for LTCCs in the brain and heart, can serve as scaffold proteins, stabilize channel gating, recruit enzymes (e.g., PKA, CaMKII; see above) to the channel, or guide the channel to defined subcellular compartments. In principle, modulation of LTCC may also be achieved by interference with modulatory proteins, including accessory subunits. For example, genetically encoded CCBs can be obtained by anchoring known $\alpha1$-subunit protein interaction partners (e.g., CaM or CaMKII) to the plasma membrane (Yang et al., 2013).

e. Novel Modulatory Mechanisms. Since maintenance of LTCC channel activity within a narrow activity range seems to be a prerequisite especially for normal brain and heart function, close control of its activity and expression is required. Recent studies have identified novel modulatory mechanism beyond the usual signaling pathways. Among those are microRNAs (miRs), which have been identified as potential regulators of $Ca_V1.2$. For example, miR-1 targets the $Ca_V1.2$ $\alpha1$-subunit gene (*CACNA1C*) and reduces its expression (Rau et al., 2011). In DM (DM1, DM2) miR-1 is lost, which may account for the observed upregulation of heart $Ca_V1.2$ $\alpha1$ protein and the resulting cardiac pathology in affected individuals (Rau et al., 2011).

E. Conclusion

The recent discovery of important physiologic functions controlled by different LTCC isoforms (particularly $Ca_V1.2$ and $Ca_V1.3$) identifies these LTCCs as new drug targets. This is especially attractive because nonselective channel blockers have been in clinical use for decades and could therefore be repurposed for novel indications. In addition, a high therapeutic potential for several indications, including neuropsychiatric diseases, can also be predicted for novel, $Ca_V1.3$-selective CCBs.

III. Ca_V2 Channel Family

A. Genes, Gene Products, and Splice Variants

Like the LTCCs described in the preceding section, members of the Ca_V2 family are heteromultimeric assemblies of a pore-forming $Ca_V\alpha1$ subunit plus ancillary $Ca_V\beta$ and $Ca_V\alpha_2\delta$ subunits, with the former defining the channel subtype. The Ca_V2 family is encoded by three genes (*CACNA1A*, *CACNA1B*, and *CACNA1E*) that encode $Ca_V\alpha1$ subunits $Ca_V2.1$, $Ca_V2.2$, and $Ca_V2.3$, respectively (Mori et al., 1991; Dubel et al., 1992; Williams et al., 1992). $Ca_V2.1$ channels give rise to both P-type and Q-type currents that were described in neurons, with this distinction likely being caused by a combination of associated the $Ca_V\beta$ subunit (Richards et al., 2007) and alternative splice events in the $Ca_V2.1$ subunit per se (see below). $Ca_V2.2$ and $Ca_V2.3$ underlie neuronal N-type and R-type currents, respectively.

Each of the Ca_V2 channel family members can undergo alternative splicing, thus creating a wide spectrum of Ca_V2 currents with specific biophysical and pharmacological properties. For example, alternative splicing of $Ca_V2.1$ channels in the domain I–II linker region can drastically alter voltage-dependent inactivation, whereas an insertion of asparagine-proline motif in the domain IV S3–S4 loop region drastically alters sensitivity of the channels to the spider toxin ω-agatoxin-IVA (Bourinet et al., 1999). Alternative splicing of exon 37, in the $Ca_V2.1$ C-terminal region, results in altered calcium-dependent inactivation and facilitation of the channel (Soong et al., 2002; Chaudhuri et al., 2004; Chang et al., 2007). Alternative splicing of the C-terminal region also affects channel biophysics and functional regulation by the $Ca_V\beta$ subunit (Sandoz et al., 2001). It is interesting to note that splice variation in $Ca_V2.1$ channels has been shown to alter the functional effects of mutations linked to familial hemiplegic migraine (FHM) (Adams et al., 2009), such that biophysical consequences of several of these pathologic mutations are weakened in $Ca_V2.1$ channels containing exon 47.

Alternative splicing of $Ca_V2.2$ channels has also been described. Splicing of sequences in domain III S3–S4 and domain IV S3–S4 gives rise to variants with different biophysical properties and tissue distribution (Lin et al., 1997, 1999). Along these lines, alternative splicing of exon 18 in the intracellular domain II–III linker region alters voltage-dependent inactivation of the channels (Pan and Lipscombe, 2000; Thaler et al., 2004), and splice variants of the human $Ca_V2.2$ channel that lack large portions of the II–III linker display very large shifts in the half-inactivation potential of the channel and distinct subcellular distributions in neurons, in addition to preventing the association of the channel with synaptic proteins such as syntaxin 1A (Kaneko et al., 2002; Szabo et al., 2006). Interestingly, similar deletion variants in the $Ca_V2.1$ II–III linker have also been described (Rajapaksha et al., 2008). Alternative splicing of exon 31 in the $Ca_V2.2$ voltage sensor produces channels with different activation kinetics (Lin et al., 2004). Perhaps the splice event that has gathered the most attention involves exon 37 of the channel. Alternative splicing of this exon (which encodes sequences in the $Ca_V2.2$ C terminus) alters current densities, second messenger regulation, and tissue distribution, with the exon 37a–expressing variants being more expressed in small nociceptive neurons (Bell et al., 2004; Castiglioni et al., 2006; Raingo et al., 2007; Andrade et al., 2010). Remarkably, the variant containing exon 37a contributed most prominently to nociceptive signaling (Altier et al., 2007). The effects of splicing of exon 37 on current densities could be correlated with alterations in the ubiquitination state of the channel (Marangoudakis et al., 2012). Truncated forms of $Ca_V2.1$ and $Ca_V2.2$ channels that lack entire transmembrane domains have also been reported (Scott et al., 1998; Raghib et al., 2001). Coexpression of these truncated forms mediates dominant negative effects on full-length channels due to the activation of unfolded protein response pathways (Page et al., 2004).

Interestingly, splicing of exons 24 and 31 in $Ca_V2.1$ and $Ca_V2.2$ channels appears to be controlled by the splicing factor Nova-2 (Allen et al., 2010), suggesting a common cellular mechanism for fine-tuning the expression/properties of these two channel subtypes, and perhaps explaining why analogous splice variants are observed in these two calcium channels subtypes (as noted above, large deletions in the domain II–III linker region have been described for both $Ca_V2.1$ and $Ca_V2.2$ channels; Kaneko et al., 2002; Rajapaksha et al., 2008).

In contrast with $Ca_V2.1$ and $Ca_V2.2$, investigations into alternate splicing of $Ca_V2.3$ channels have been more limited. Six major splice isoforms of $Ca_V2.3$ have been identified and shown to differ in their tissue distribution (Marubio et al., 1996; Vajna et al., 1998; Schramm et al., 1999) and in their pharmacological properties (Tottene et al., 1996, 2000).

Overall, the three members of the Ca_V2 family can give rise to a large number of different types of ionic conductances through alternate splicing of various exons. This diversity is further enhanced by coassembly with the various ancillary $Ca_V\beta$ and $Ca_V\alpha_2\delta$ subunits, and their splice variants, thus providing tremendous control of calcium entry in specific tissues at specific times during development. The existence of multiple variants of a single calcium channel type is potentially important for drug design. For example, in the context of developing new analgesics, the ability to selectively target $Ca_V2.2$ channels containing exon 37a, although downregulated in experimental neuropathic pain conditions (Altier et al., 2007), might allow for selective inhibition of $Ca_V2.2$ channels expressed in nociceptive neurons while sparing channels expressed in other regions of the nervous system.

B. Physiologic Roles of Ca_V2 Calcium Channels

Ca_V2 channels are primarily thought of as the drivers of evoked synaptic transmission (Wheeler et al., 1994). Although these channels are expressed at various subcellular loci, they are targeted to presynaptic nerve terminals where they open in response to incoming action potential (Westenbroek et al., 1992, 1995). The ensuing entry of calcium ions then triggers the fusion of synaptic vesicles, culminating in the release of neurotransmitters into the synaptic cleft. The three major Ca_V2 channel isoforms support not only rapid neurotransmitter release but also hormone release from secretory cells such as chromaffin cells (Santana et al., 1999; Albillos et al., 2000; Wykes et al., 2007; Álvarez et al., 2013).

To facilitate effective coupling between the neurotransmitter release machinery and calcium entry, these $Ca_V2.1$ and $Ca_V2.2$ channels contain a synaptic protein interaction (synprint) site that interacts with syntaxin 1A and SNAP25 (Sheng et al., 1994, 1996; Rettig et al., 1996). This is one mechanism by which channels can be localized in proximity to synaptic vesicles. It also allows for regulation of calcium channel activity by these synaptic proteins. In particular, syntaxin 1A is a potent regulator of $Ca_V2.1$ and $Ca_V2.2$ channel availability (Bezprozvanny et al., 1995); furthermore, syntaxin 1A facilitates G protein inhibition of $Ca_V2.2$ channels (Jarvis et al., 2000; Jarvis and Zamponi, 2001; for review, see Zamponi, 2003). Several considerations suggest that this syntaxin 1A–mediated regulation of channel activity, rather than coupling to the release apparatus, may be the physiologically more important function of the synaptic protein interaction site. First, invertebrate Ca_V2 channels do not possess a synprint motif, yet they perfectly support synaptic transmission (Spafford et al., 2003). Second, although they are able to bind to syntaxin 1A in vitro, $Ca_V2.3$ calcium channels do not have a synprint-like motif. Finally, work from several groups has identified postsynaptic density protein PSD95, *Drosophila* disc large tumor suppressor Dlg1, and Zona occludens-1 protein–containing proteins such as Rab3-interacting molecule and MINT-1 as critical anchors between Ca_V2 channels and synaptic vesicles (Maximov and Bezprozvanny, 2002; Han et al., 2011, 2015; Kaeser et al., 2011; Wong et al., 2013, 2014), with the interactions being critically dependent on the C-terminal region of the channel.

In addition to supporting vesicle release, members of the Ca_V2 channel family also fulfill other signaling functions. For example, $Ca_V2.1$ and $Ca_V2.2$ channels interact physically with large conductance calcium-activated potassium channels and provide the calcium influx needed to efficiently activate these channels (Berkefeld et al., 2006; Berkefeld and Fakler, 2008). This in turn allows Ca_V2 channels to regulate neuronal excitability by altering potassium conductances (Loane et al., 2007). In addition, Ca_V2 channel activity has been linked to CREB-dependent gene transcription via activation of Ca^{2+}-CaMKII (Wheeler et al., 2012) as well as to the activation of nuclear factor of activated T cells (Hernández-Ochoa et al., 2007). Along these lines, the expression of syntaxin 1A appears to be initiated by activation of $Ca_V2.1$ calcium channels (Sutton et al., 1999), again via a CREB-dependent pathway.

These fundamental roles of Ca_V2 channels for neuronal function and communication manifest themselves in many critical physiologic functions in the whole animal, ranging from motor control to the transmission of sensory information. These roles are exemplified by many pathologic conditions that occur as a result of calcium channel dysfunction, as we discuss in the ensuing section.

C. Ca_V2 Channel Pathophysiology

Notwithstanding the possibility of compensation, Ca_V2 channel knockout mouse lines can provide compelling insights into the function of a particular Ca_V2 channel isoform. This is readily apparent when considering the phenotype of $Ca_V2.1$ null mice. These mice exhibit ataxia and absence seizures and die around 4 weeks after birth (Jun et al., 1999). Although $Ca_V2.1$ channels control neuromuscular synaptic transmission under normal circumstances, these mice are not paralyzed, likely because of compensation from $Ca_V2.2$ and $Ca_V2.3$ channels (Jun et al., 1999; Urbano et al., 2003). It is interesting to note that postnatal deletion of the $Ca_V2.1$ encoding gene results in a much slower onset of the neurologic deficits (Mark et al., 2011).

In contrast with $Ca_V2.1$ null mice, $Ca_V2.2$ deficiency leads to only mild consequences, which include reduced pain hypersensitivity in models of inflammatory and neuropathic pain (Hatakeyama et al., 2001; Kim et al., 2001a; Saegusa et al., 2001), hyperactivity (Beuckmann et al., 2003), reduced anxiety (Saegusa et al., 2001), a reduction of voluntary alcohol intake (Newton et al., 2004), and problems with blood pressure control (Mori et al., 2002). The effects of $Ca_V2.2$ channel deletion on pain are consistent with the notion that $Ca_V2.2$ channels are critical for neurotransmitter release from afferent terminals in the spinal dorsal horn (for review, see Bourinet et al., 2014), and these findings validate $Ca_V2.2$ channels as potential targets for analgesics. The link between $Ca_V2.2$ channels and behaviors related to addiction and anxiety is less clearly understood. Similar to $Ca_V2.2$ channel knockout mice, mice lacking $Ca_V2.3$ are viable and show reduced pain sensitivity (Saegusa et al., 2002). These mice are also resistant to certain types of chemically induced seizures, suggesting a role of these channels in thalamocortical network excitability or communication (Weiergräber et al., 2007); these mice also show deficits in hippocampal theta oscillation architecture (Müller et al., 2012). Finally, it has been reported that these $Ca_V2.3$ null mice show deficits in second-phase insulin release (Jing et al., 2005).

Another source for insights into the physiologic and pathophysiological roles of channels is derived from channelopathies in both animals and humans. To our knowledge, no mouse mutations in $Ca_V2.2$ and $Ca_V2.3$ channels have been linked to a disease phenotype, perhaps consistent with the absence of a severe phenotype on the corresponding null mice. However, there is a recent report of an apparent gain-of-function human point mutation in the $Ca_V2.2$ gene, leading to a myoclonus-dystonia phenotype (Groen et al., 2015).

A different picture emerges with regard to $Ca_V2.1$ channels. There are several mouse lines with mutations in $Ca_V2.1$ channels that give rise to ataxic and epileptic phenotypes. This includes “leaner,” “tottering,” and “rocker,” which were previously reviewed in detail (Pietrobon, 2002; Khosravani and Zamponi, 2006). Mutations in $Ca_V2.1$ channels have been described in patients with various forms of ataxia, as well as in patients with FHM. Spinal cerebellar ataxia type 6 is a disorder in which there is a polyglutamine expansion within the channel’s C-terminal region (Jodice et al., 1997). The cellular mechanisms by which these expansions trigger the disease phenotype remain a topic of investigation. When introduced into $Ca_V2.1$ channels and studied in heterologous systems, the polyglutamine expansions have been shown to cause hyperpolarizing shifts in the half-inactivation potential of the channels (Matsuyama et al., 1999). When introduced into a mouse model, however, channel function in cerebellar Purkinje cells does not appear to be compromised in Purkinje cells (Saegusa et al., 2007). A similar lack of effects on channel biophysics was observed in another mouse model; nontheless, an age-dependent neuronal dysfunction was observed, and there was an accumulation of $Ca_V2.1$ aggregates (Watase et al., 2008). Altogether, these data suggest that it is the formation of these aggregates, rather than alterations in channel function, that underlies the clinical phenotype in spinal cerebellar ataxia type 6.

Episodic ataxia type 2 is another form of movement disorder that has been linked to $Ca_V2.1$ channel mutations (for review, see Pietrobon, 2010). These mutations include missense mutations, splice site mutations, and frame shifts the lead to the truncation of the $Ca_V2.1$ protein junctions and typically lead loss of channel function (Wappl et al., 2002; Kipfer et al., 2013). In addition, dominant negative effects of mutated channels on normal $Ca_V2.1$ channels have been reported (Jouvenceau et al., 2001; Jeng et al., 2008; Mezghrani et al., 2008; Page et al., 2010). Consistent with what has been observed with $Ca_V2.1$ null mice, loss of function of $Ca_V2.1$ due to a premature truncation of the protein has been shown to give rise to absence seizures in one patient with episodic ataxia (Jouvenceau et al., 2001). The observation that loss of $Ca_V2.1$ function is linked to adverse events such as movement disorders and seizures suggests that therapeutics with off-target actions on $Ca_V2.1$ channels may result in pathophysiological side effects.

On the other hand, gain-of-function mutations in the gene encoding $Ca_V2.1$ channels have been associated with FHM (Tottene et al., 2009). Numerous FHM-1 mutations in *CACNA1A* have been discovered, and a number of these have been examined in both heterologous expression systems and in knock-in mouse models. It has become clear that expression of such mutants in heterologous systems is not ideal, because these mutations appear to manifest themselves differently when the channels are present in a native neuronal environment [compare Hans et al. (1999) with Van den Maagdenberg et al. (2004)]. The various mutations can lead to drastic differences in disease severity consistent with the notion that FHM-1 has a wide spectrum of clinical phenotypes (Pietrobon and Moskowitz, 2013). A mouse model of one of the mutations (S218L) recapitulates the clinical phenotype observed in humans (Van den Maagdenberg et al., 2010), including ataxia, seizures, and brain edema after head trauma. Remarkably, a small organic molecule (*tert*-butyl dihydroquinone) that normalizes the gain-of-function phenotype of these mutant channels has been shown to counteract the effects of the equivalent of the S218L mutation on *Drosophila* synaptic physiology (Inagaki et al., 2014). It remains to be determined whether this compound may mediate similar protection in S218L knock-in mice.

Overall, among the Ca_V2 channel family members, $Ca_V2.1$ appears to be the main subtype compromised by multiple genetic mutations. That said, one could speculate that $Ca_V2.2$ channel and $Ca_V2.3$ channel dysfunction may be more subtle in many cases, except for the gain-of-function mutation recently reported in $Ca_V2.2$ (Groen et al., 2015), and could contribute to disorders such as pain hypersensitivity, addiction, or seizures, perhaps via dysregulation by cellular signaling processes rather than genetic abnormalities in the channels themselves.

D. Molecular Pharmacology of Ca_V2 Channels

1. $Ca_V2.1$ and $Ca_V2.3$ Channels and Their Potential Roles as Targets for Therapeutics. Various types of voltage-gated calcium channels can be potently inhibited by peptide toxins isolated from the venoms of a variety of predatory organisms, such as fish-hunting molluscs, scorpions, and spiders. For example, $Ca_V2.1$ channels are potently inhibited by ω-agatoxin IVA, a large polypeptide that is isolated from the venom of the North American funnel web spider *Agenelopsis aperta* (Adams et al., 1993) (for review, see Olivera et al., 1994). However, as noted above, unless they are carefully modulated with compounds that normalize aberrant gain of function (see Inagaki et al., 2014), $Ca_V2.1$ channels are not broadly considered as good pharmacological targets. $Ca_V2.3$ channel inhibitors could potentially have a beneficial effect in seizure disorders (Dibué et al., 2013) and as pain therapeutics (Matthews et al., 2007); however, these channels do not have a particularly rich pharmacology and selective small organic inhibitors of $Ca_V2.3$ channels are lacking (Schneider et al., 2013). They are inhibited by the spider toxin SNX-482 (Newcomb et al., 1998); however, this toxin also targets $Ca_V1.2$ LTCCs (Bourinet et al., 2001) and A-type K^+ currents (Kimm and Bean, 2014) and is thus not selective.

2. $Ca_V2.2$ Channels and Their Roles as Targets for Therapeutics. In contrast with the $Ca_V2.1$ and $Ca_V2.3$ channels, there is an extensive body of literature pertaining to N-type calcium channel inhibitors. There are four principal means by which $Ca_V2.2$ channel–mediated cellular events can be regulated for therapeutic purposes: 1) direct block of $Ca_V2.2$ channel peptides and small organic molecules, 2) activation of a range of GPCRs, 3) interference with $Ca_V2.2$ channel trafficking, and 4) direct interference with the coupling of the channels to downstream effectors (Fig. 5). Here, we provide a brief overview of these four mechanisms.

a. Direct $Ca_V2.2$ Channel Blockers. $Ca_V2.2$ channels are potently inhibited by peptide toxins isolated from the venoms of a variety of predatory organisms. In particular, they are selectively and potently inhibited by ω-conotoxin GVIA, a peptide toxin isolated from the fish-hunting cone snail *Conus geographus* (Olivera et al., 1984) (Fig. 5, pathway 2). Indeed, ω-conotoxin GVIA and ω-agatoxin IVA have been used extensively as experimental tools to help distinguish native N-type and P/Q-type currents in various types of neurons, and this has been made possible largely by the high degree of target selectivity by these peptides. Furthermore, these two toxins also exemplify two major modes of action: pore block and gating modification. ω-Conotoxin GVIA is a small 27–amino acid peptide with a backbone that is constrained by three disulfide bonds and it can be physically lodged into the permeation pathway of the channel, thus acting as a pore blocker (Reynolds et al., 1986; Ellinor et al., 1994; Feng et al., 2001). The unblocking rate constant is quite low, leading to virtually irreversible block (at least over the time course of tens of minutes) unless the plasma membrane is strongly hyperpolarized (Stocker et al., 1997; Feng et al., 2003). To our knowledge, all of the known ω-conotoxins that act on Ca_V2 channels fall into this category. By contrast, ω-agatoxin IVA is a much larger (83 amino acid) peptide that acts by blocking voltage sensor movement, rather than occluding the pore of the channel (Mintz et al., 1992). It too produces poorly reversible inhibition, unless the membrane is repetitively depolarized—an action that allows the voltage sensors of the channel to dislodge the bound toxin (Mintz et al., 1992). Several other spider toxins fall into the category of gating inhibitors, including α-grammotoxin SIA, a peptide that is isolated from the venom of the tarantula *Grammostola spatulata* and inhibits both $Ca_V2.2$ and $Ca_V2.1$ channels (Lampe et al., 1993; McDonough et al., 1997), and the $Ca_V2.3$ channel blocker SNX-482 from the tarantula *Hysterocrates gigas* (Bourinet et al., 2001).

Fish-hunting molluscs have proven to yield a particularly rich palette of Ca_V2 calcium channel blockers, in many cases with selectivity for $Ca_V2.2$ channels. A 25–amino acid $Ca_V2.2$ channel pore-blocking toxin, ω-conotoxin MVIIA, has been isolated from the *Conus magus* snail and mediates potent analgesia after intrathecal delivery to rodents (Chaplan et al., 1994; Bowersox and Luther, 1998; Wang et al., 2000; Scott et al., 2002) and human patients with persistent cancer pain (Atanassoff et al., 2000; Miljanich, 2004; Staats et al., 2004; Thompson et al., 2006; Wallace et al., 2006; Ver Donck et al., 2008). This fits with the important role of $Ca_V2.2$ channels in neurotransmitter release from afferent terminals. *C. magus* also yields a number of other Ca_V2 channel inhibitors such as ω-conotoxins MVIIB, MVIIC, and MVIID (Olivera et al., 1994). Along these lines, peptides isolated from other types of snails such as *Conus striatus*, *Conus fulman,* and *Conus catus* produce various Ca_V2 channel blocking peptides. These peptides generally share a similar disulfide bridge arrangement and act as pore blockers. Although most of them act selectively on $Ca_V2.2$ channels (e.g., ω-conotoxins SIA, FVIA, or CVID) (Smith et al., 2002; Adams et al., 2003; Lee et al., 2010), others also block $Ca_V2.1$ channels (e.g., ω-conotoxins SIB and MVIIC) (Hillyard et al., 1992; Adams et al., 1993; Woppmann et al., 1994). Some of these ω-conotoxins are effective systemically in a mouse model of inflammatory pain (Sadeghi et al., 2013). Of note, ω-conotoxin CVID has been tested as an analgesic in clinical trials (Schroeder et al., 2006).

The blocking site for ω-conotoxin GVIA and MIIVA in the $Ca_V2.2$ subunit has been investigated via the construction of chimeric channels (Ellinor et al., 1994) and by site-directed mutagenesis (Feng et al., 2001, 2003). These studies have revealed that the large extracellular domain III S5–S6 region is a key determinant of ω-conotoxin GVIA block, and that mutagenesis of a single glycine residue in this region at position 1326 to proline dramatically enhances the reversibility of ω-conotoxin GVIA and MVIIA block. A subsequent study showed that coexpression of the $Ca_V\alpha_2\delta$ subunit alters both the kinetics and extent of inhibition of the channels by ω-conotoxin CVID and MVIIA (Mould et al., 2004), but it is not clear whether this is due to a steric hindrance of toxin access or an allosteric effect.

Although peptide toxins can be highly selective high-affinity blockers of various Ca_V2 channel subtypes, their clinical use is limited because they do not cross the blood–brain barrier. Furthermore, many of the pore-blocking conotoxins do not act effectively as state-dependent blockers (Feng et al., 2003), which can be a desirable feature in clinically active compounds, as seen with anticonvulsants and local anesthetics (Hille, 1977; Willow et al., 1985; Ragsdale et al., 1991; Zamponi et al., 1993). Both of these issues are overcome with the development of small organic blockers, but often at the expense of selectivity and affinity. Although there are, to our knowledge, no selective small organic inhibitors of $Ca_V2.1$ and $Ca_V2.3$ channels, several small organic molecules that preferentially block $Ca_V2.2$ channels have been identified, likely because of the importance of the latter channel subtype for pain transmission. The peptidylamines are one such class, and they are designed to mimic the pore-blocking actions of the larger conotoxin molecules and are formed by linking *N,N*-di-substituted leucine acid to a tyrosine amine (Hu et al., 1999b,c; Ryder et al., 2000). High-affinity (approximately 40 nM) block of $Ca_V2.2$ channels has been reported in the literature (Ryder et al., 1999). The same authors also identified phenylalanine and benzoxyaniline derivatives as high-affinity (<1 μM) $Ca_V2.2$ channel blockers with efficacy in pain (Hu et al., 1999a,d).

Another distinct class of $Ca_V2.2$ channel blockers is derived from compounds that are related to D2 dopamine receptor–blocking antipsychotics (and a subclass of ion channel blockers such as fomocaine and flunarizine; Benjamin et al., 2006; Ye et al., 2011) (Fig. 5, pathway 2). These types of compounds contain a core piperidine, morpholine, or piperazine structure, often linked to one or two diphenyl moieties via alkyl chains, and they have long been known to block N-type channels (Tytgat et al., 1991; Zamponi et al., 1996). Extensive structure-activity work in this compound class has been reported (Zamponi et al., 2009; Pajouhesh et al., 2010, 2012). Furthermore, several lead compounds in

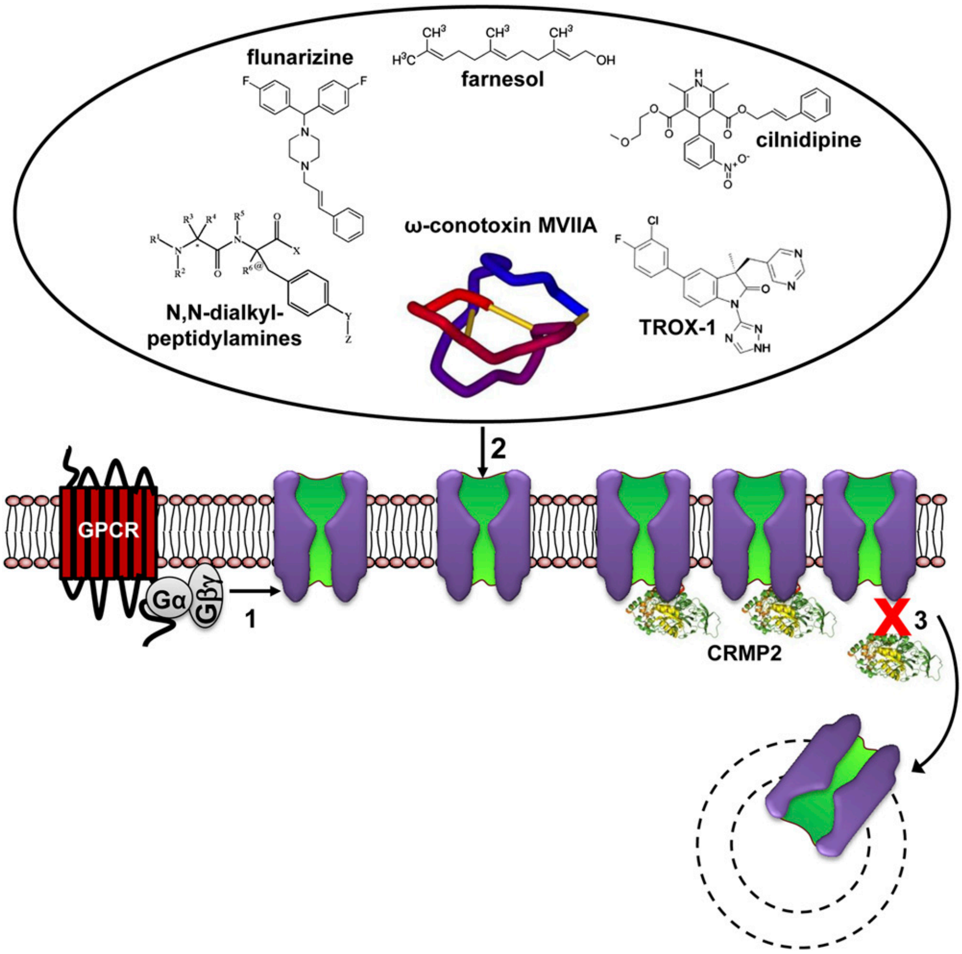

Fig. 5. Modulation of N-type channels by drugs, toxins, and signaling pathways. The major pharmacologically relevant classes of N-type calcium channel active drugs and toxins are shown in pathway 2. This includes pore-blocking peptide toxins such as *ω*-conotoxin MVIIA, as well as a series of different types of small organic molecules that include piperazines and piperidines, DHPs, and long-chain carbon molecules. N-type channels are modulated by a variety of different signaling pathways either through membrane-delimited actions of activated G proteins activated by GPCRs (pathway 1), or by interfering with scaffolding proteins such as CRMP-2 (pathway 3) (for details, see the text). The image of *ω*-conotoxin MVIIA is reproduced from Wikipedia (https://en.wikipedia.org/wiki/Ziconotide).

this class have been validated in animal models of pain. For the derivatives with a mixed action on $Ca_V2.2$ and Ca_V3 channels, the addictive and intoxicating narcotic properties of ethanol were also abrogated (Newton et al., 2008). Other derivatives in this class include pyrazolpiperidines (Subasinghe et al., 2012) and aminopiperidine sulfonamide (Shao et al., 2012), both of which have analgesic properties by virtue of N-type channel blocking action.

Although most typically thought of as blockers of LTCCs, there is evidence that some DHPs can also block N-type calcium channels with high affinity. One such example is cilnidipine (Uneyama et al., 1997; Kato et al., 2002), which has analgesic properties in rats (Koganei et al., 2009) in addition to being kidney protective and antihypertensive in human patients (Hatta et al., 2012; Kario et al., 2013). These beneficial effects may be attributable to the actions of this compound on N-type channels in the sympathetic nervous system (Takahara, 2009).

Finally, other examples of $Ca_V2.2$ channel blockers that have been described in the literature include an oxindole compound termed TROX-1 [(3*R*)-5-(3-chloro-4-fluorophenyl)-3-methyl-3-(pyrimidin-5-ylmethyl)-1-(1*H*-1,2,4-triazol-3-yl)-1,3-dihydro-2*H*-indol-2-one] (Abbadie et al., 2010; Swensen et al., 2012), which is a state-dependent inhibitor that has analgesic properties. In addition, long carbon chain molecules such as aliphatic monoamines (Beedle and Zamponi, 2000) and farnesol (Roullet et al., 1999) block $Ca_V2.2$ channels with high affinity (albeit not selectively) and exhibit preferential block of inactivated channels. There are likely many other classes of $Ca_V2.2$ channel–inhibiting pharmacophores, altogether indicating that these channels show a rich pharmacology. It is worth reiterating that many of the compounds described above mediate state-dependent block of $Ca_V2.2$ channels, which is seen as a leftward shift in the steady-state inactivation curve of the channel and frequency-dependent inhibition of current activity. This contrasts with the tonic blocking action that is typically observed with pore-blocking toxins. Also in contrast with the action of peptide toxins, the blocking sites for the vast majority of small organic

$Ca_V2.2$ channel blockers are not known. Although the nature of the coexpressed $Ca_V\beta$ subunit and point mutations in the domain I–II region of $Ca_V2.1$ both affect piperidine block (Benjamin et al., 2006), it is not clear whether this region is the physical interaction site for these compounds.

b. G Protein Inhibition of $Ca_V2.2$ Channels. Many types of GPCRs are functionally linked to $Ca_V2.2$ calcium channels (for reviews, see Dolphin, 2003; Tedford and Zamponi, 2006) (Fig. 5, pathway 1). Activation of these receptors initiates nucleotide exchange in the associated $G\alpha$ subunit, producing active signaling molecules ($G\alpha$-GTP and $G\beta\gamma$). The $G\beta\gamma$ subunits physically associate with the Cav2.2 channel to mediate a potent voltage-dependent inhibition of channel activity (Herlitze et al., 1996; Ikeda, 1996), which arises from a stabilization of the channel's closed conformation (Jones et al., 1997). $Ca_V2.1$ channels are regulated in an analogous manner, but they undergo a much smaller degree of inhibition (Arnot et al., 2000). Although the majority of clinically used drugs act via various GPCRs, these receptors are coupled to many downstream effector systems; hence, the extent to which the clinical action of receptor agonists and antagonists involves Ca_V2 calcium channels is unclear. However, opioid receptors are one example in which the clinical action of a receptor agonist is linked closely to $Ca_V2.2$. The μ-opioid receptor agonist morphine is a potent clinically used analgesic that interacts with μ-opioid receptors (Mizoguchi et al., 2012), which then inhibits $Ca_V2.2$ channels in dorsal horn synapses (Heinke et al., 2011), along with concomitant activation of G protein–coupled inward rectifier potassium channels (Marker et al., 2005). The receptor-induced inhibition of $Ca_V2.2$ channels is thought to reduce presynaptic calcium levels, which in turn reduces synaptic transmission between these afferent nerve terminals (Kondo et al., 2005; Beaudry et al., 2011). Morphine also acts at μ-opioid receptors that are expressed in the CNS (Diaz et al., 1995; Goodchild et al., 2004), where a clear correlation between physiologic effects and modulation of $Ca_V2.2$ channels is more difficult to establish. Although morphine is considered selective for μ-opioid receptors, selective agonists of the other three members of the extended opioid receptor family (i.e., δ- and κ-opioid receptors, and nociceptin receptors) also functionally inhibit $Ca_V2.2$ channels (Gross and Macdonald, 1987; Moises et al., 1994; Motin et al., 1995; Morikawa et al., 1998; Toselli et al., 1999; Larsson et al., 2000; Yeon et al., 2004; Ruiz-Velasco et al., 2005; Evans et al., 2010). As in the case of μ-opioid receptors, their activation induces analgesia in various animal models of pain (King et al., 1997; Darland et al., 1998; Field et al., 1999; Mika et al., 2001; Courteix et al., 2004; Nozaki et al., 2012). Although there are no clinically approved δ-opioid– and nociceptin receptor–targeting analgesics, there is at least one κ-opioid receptor agonist (pentazocine) that is used in humans as an analgesic.

$GABA_B$ receptors are another class of receptors that inhibit $Ca_V2.2$ calcium channels in dorsal horn synapses (Terrence et al., 1985); however, the associated CNS side effects typically preclude clinical use of systemic $GABA_B$ agonists such as baclofen (Schuele et al., 2005; Bortolato et al., 2010). Nevertheless, intrathecal baclofen is used in patients to treat spasticity and associated central pain after brain or spinal cord injury (Slonimski et al., 2004). Interestingly, the α-conotoxin Vc1.1 and the structurally related peptide Rg1A have been shown to activate peripheral $GABA_B$, leading to $Ca_V2.2$ channel inhibition and analgesia when delivered intrathecally or intramuscularly (Callaghan et al., 2008; Callaghan and Adams, 2010; Klimis et al., 2011; Cuny et al., 2012; Berecki et al., 2014). To enhance oral bioavailability, a cyclized version of the Vc1.1 has been designed (Carstens et al., 2011); however, it is unclear whether these cyclized peptides could lead to similar central nervous side effects.

Altogether, $Ca_V2.2$ channels are important effectors of 7-transmembrane-helix receptors, with the physiologic significance of this regulation being most clearly exemplified in the primary afferent pain pathway. Although it is likely that agonists of other GPCRs mediate their downstream effects via Ca_V2 calcium channels in many other physiologic processes (see Kisilevsky et al., 2008), systematic studies of the effects of GPCR agonists in $Ca_V2.2$ null mice would be required to ascertain the importance of Ca_V2 channels as physiologic effectors.

c. Inhibition of $Ca_V2.2$ Channel Trafficking. $Ca_V2.2$-type calcium channels have been shown to associate with collapsin response mediator protein 2 (CRMP-2; Chi et al., 2009) (Fig. 5, pathway 3). This interaction stabilizes the channels in the plasma membrane, presumably by slowing the rate of channel internalization, and this in turn facilitates $Ca_V2.2$ channel–mediated release of neurotransmitters such as calcitonin gene–related peptide (Chi et al., 2009). Conversely, disruption of Cav2.2 channel interactions with CRMP-2 can be achieved by using interfering peptides, attached to cell penetrating sequences such as TAT. TAT peptides reduce $Ca_V2.2$ channel density in the plasma membrane, thereby mediating analgesic effects in various pain models (Brittain et al., 2011; Ripsch et al., 2012; Wilson et al., 2012). This is an example of how $Ca_V2.2$-mediated calcium entry can be regulated by targeting the mechanism that controls channel density in the plasma membrane without blocking channel function per se. A search for small molecular mimetics of these TAT peptides is ongoing. Another mechanism that is critical for $Ca_V2.2$ channel trafficking is the association of these channels with the ancillary $Ca_V\alpha_2\delta$ subunit. This mechanism can also be exploited for therapeutic intervention, as discussed in detail in later sections of this review.

d. Interference with $Ca_V2.2$ Coupling to the Synaptic Vesicle Release Machinery. As noted earlier, $Ca_V2.2$ channels physically associate with proteins that are involved in fast synaptic transmission (Sheng et al., 1994). It has been shown that competitive disruption of $Ca_V2.2$ interactions with syntaxin 1A by using synthetic synprint peptides blocks $Ca_V2.2$ channel–mediated synaptic transmission (Mochida et al., 1996). This constitutes an example of how $Ca_V2.2$ channel–mediated physiologic processes can be pharmacologically manipulated without alteration of $Ca_V2.2$ channel function or density. As with regulators of $Ca_V2.2$ channel trafficking, it may be possible to identify small organic mimetics of these synprint peptides that can be used to target $Ca_V2.2$ channel–mediated synaptic transmission as a potential approach toward treating conditions such as pain.

E. Conclusion

Altogether, among the Ca_V2 channel family members, $Ca_V2.2$ and to a lesser extent $Ca_V2.3$ channels have potential as therapeutic targets. Although $Ca_V2.3$ channels may potentially be explored as targets for epileptic seizures and analgesics, $Ca_V2.3$ (thus far) has a relatively limited pharmacology that can be exploited for therapeutic purposes. By contrast, substantial efforts have been made in identifying novel classes of $Ca_V2.2$ channel blockers with high affinity and selectivity. This effort may have been boosted by the U.S. Food and Drug Administration approval of Prialt (the commercial name of ω-conotoxin MVIIA or ziconotide; Jazz Pharmaceuticals, Dublin, Ireland) and the phenotype of the $Ca_V2.2$ null mouse. Beyond their application as analgesics, $Ca_V2.2$ channel blockers may well be effective in conditions such as drug dependence and anxiety.

IV. Ca_V3 Channel Family

A. Genes, Gene Products, and Splice Variants

T-type calcium channels are represented by three genes (*CACNA1G*, *CACNA1H*, and *CACNA1I*) that encode three different types of $Ca_V3\alpha1$ subunits: $Ca_V3.1$ (Perez-Reyes et al., 1998), $Ca_V3.2$ (Cribbs et al., 1998), and $Ca_V3.3$ (Lee et al., 1999a). Expression of these subunits gives rise to T-type currents with distinct electrophysiological and pharmacological properties (Mcrory et al., 2001; Santi et al., 2002). Unlike members of the high voltage–activated channel Ca_V1 and Ca_V2 families, Ca_V3 calcium channels do not require coassembly with auxiliary calcium channel subunits. Nonetheless, these channels can be functionally regulated by these ancillary subunits. Coexpression of $Ca_V\alpha_2\delta$ subunits has been shown to increase current density of T-type calcium channels; however, no biochemical complexes have been identified (Dolphin et al., 1999; Dubel et al., 2004). Furthermore, $Ca_V\gamma6$ subunits can depress $Ca_V3.1$ channel current density (Hansen et al., 2004), and this is due to a physical interaction with the $Ca_V3.1$ subunit (Lin et al., 2008). Its effect can be mimicked by small peptide sequences derived from $Ca_V\gamma6$. Both $Ca_V\alpha_2\delta$-2 and $Ca_V\gamma5$ subunits alter gating currents of $Ca_V3.1$ channels, which is again indicative of direct functional modulation (Lacinová and Klugbauer, 2004). Nonetheless, these functional interactions do not have the hallmarks of the universal auxiliary subunit regulation of Ca_V1 and Ca_V2 calcium channels.

The three Ca_V3 subunits have all been shown to undergo alternative splicing, which serves to increase functional diversity (Swayne and Bourinet, 2008). Alternative splicing events in the domain I–II linker of $Ca_V3.1$, leading to exclusion of exon 8, result in enhanced cell surface expression and thus elevated current densities (Shcheglovitov et al., 2008), indicating that this region may be involved in either endoplasmic reticulum retention or cell surface trafficking. A $Ca_V3.1$ splice isoform isolated from the mouse inner ear, including exons 14, 25A, 34, and 35, displays unique permeation characteristics (Nie et al., 2008). Multiple splice isoforms of $Ca_V3.1$ in the domain III–IV linker region that arise from different combinations of exons 25A, 25B, and 26 have been identified and shown to exhibit altered activation and inactivation kinetics, as has splicing of exon 14 in the II–III linker region (Chemin et al., 2001a). Notably, the expression of the III–IV linker splice isoforms is altered in samples from human glioma and in retinoblastoma cells, suggesting a possible role of particular $Ca_V3.1$ isoforms in tumor growth (Latour et al., 2004; Bertolesi et al., 2006). Alternative splicing has also been described for $Ca_V3.2$ channels. Splicing of exons 25 and 26 in the domain III–IV linker of this channel results in changes in activation and inactivation kinetics (Ohkubo et al., 2005). Furthermore, exon 25 influences the functional effects of $Ca_V3.2$ channel mutations that have been linked to the development of seizures in a rat model of absence epilepsy (Powell et al., 2009) and may be linked to the development of cardiac hypertrophy (David et al., 2010). Altogether, in $Ca_V3.2$ channels, as many as 14 different sites for splice variation have been identified, some of which are capable of producing nonfunctional channels (Zhong et al., 2006). Finally, splicing events in $Ca_V3.3$ channels have also been shown to give rise to variants with distinct biophysical properties. Splicing of exon 9 in the domain I–II linker and exons 33 and 34 in the C-terminal region of the channel are important determinants of channel properties (Murbartián et al., 2002, 2004).

In summary, different splice isoforms of all three Ca_V3 channel subtypes can give rise to a large array of different types of T-type channel conductances that may be expressed in a region-specific manner and can also be developmentally regulated. Understanding which specific splice isoforms contribute to particular physiologic functions is an important consideration for drug discovery.

B. Physiologic Roles of Ca_V3 Calcium Channels

T-type calcium channels are ideally suited to regulate neuronal excitability, due to their hyperpolarized range of activation and inactivation. At a typical neuronal resting membrane potential, T-type calcium channels are partially inactivated. A brief membrane hyperpolarization (e.g., inhibitory postsynaptic event) can be sufficient to recover channels from inactivation, thus increasing the fraction of the channel that is available for opening (Coulter et al., 1989; Huguenard and Prince, 1992). This in turn facilitates membrane depolarization and thus neuronal firing to give rise to a phenomenon termed "rebound bursting" (McCormick and Huguenard, 1992). This is of particular importance in thalamocortical circuitry (Ulrich and Huguenard, 1997) but also in many other brain circuits such as in the cerebellum (Molineux et al., 2006; Tadayonnejad et al., 2010). In addition, as a result of the overlap between activation and inactivation curves, T-type channels support a window current that is active near neuronal resting membrane potentials, which also contributes to the regulation of neuronal excitability (Chevalier et al., 2006; Dreyfus et al., 2010). In the SAN, Ca_V3 channels also contribute to pacemaker activity (Mangoni et al., 2006). Finally, T-type calcium channels have been shown to be associated physically and functionally with members of voltage- and calcium-activated potassium channels (Anderson et al., 2010, 2013; Engbers et al., 2012, 2013; Rehak et al., 2013). These associations confer T-type channel–mediated calcium-dependent control of potassium channel activity, which in turn regulates neuronal firing patterns (Turner and Zamponi, 2014). $Ca_V3.2$ channels have also been associated functionally with inhibition of K_V7 channels to control axonal firing (Martinello et al., 2015) and with HCN channels to regulate presynaptic function at specific cortical synapses (Huang et al., 2011).

In addition to regulating neuronal excitability, T-type calcium channel activity has been linked to evoked hormone secretion, such as the release of catecholamines from chromaffin cells (Carabelli et al., 2007). In addition, T-type calcium channels have been linked to neurotransmitter release from presynaptic afferent nerve terminals in the spinal cord dorsal horn (Jacus et al., 2012; García-Caballero et al., 2014). This function may rely in part on the association of these Ca_V3 channels with the synaptic vesicle release proteins syntaxin 1A and SNAP25, which in turn have been shown to modulate Cav3 channel activity (Weiss et al., 2012). Furthermore, T-type channels, particularly $Ca_V3.1$, are important in sleep-wake cycles and feeding behavior (Uebele et al., 2009).

T-type calcium channel activity is also important for the function of the cardiovascular system and the renin-angiotensin system (Hansen, 2015). Angiotensin results in the upregulation of T-type calcium channels, which then triggers an increase in aldosterone secretion (Chen et al., 1999). This process appears to involve the activation of CaMKII and its phosphorylation of the domain II–III linker region in $Ca_V3.2$ channels (Yao et al., 2006). As a result, T-type calcium channels are considered excellent potential targets for the development of novel antihypertensive drugs (Oshima et al., 2005; Perez-Reyes et al., 2009). Aldosterone, in turn, has been shown to upregulate T-type channel expression in cultured cardiac myocytes, thereby altering beating frequency (Lalevée et al., 2005). This highlights the function of T-type calcium channels as regulators of pacemaking in the heart (Mesirca et al., 2014, 2015). A recent study revealed that $Ca_V3.2$ T-type calcium channels are also critically important for relaxation of cerebral arteries by contributing to a negative feedback loop that involves calcium-induced calcium release from RyRs and subsequent activation of calcium-dependent potassium conductances (Harraz et al., 2014, 2015). This then would suggest that T-type calcium channel blockers could act in some cases as vasoconstrictors. By contrast, $Ca_V3.3$ in human cerebral arteries contributes to smooth muscle cell contraction in cooperation with $Ca_V1.2$. (Harraz et al., 2015)

T-type calcium channel activity has also been linked to gene transcription. Activation of T-type channels has been shown to activate nuclear factor of activated T cells in cartilage tissue (Lin et al., 2014) and during the development of cardiac hypertrophy (Hsu et al., 2013; Huang et al., 2013a). T-type channels have also been linked to activation of CREB in cardiomyocytes in response to aldosterone (Ferron et al., 2011). Unlike in the case of Ca_V1 and Ca_V2 calcium channels (Wheeler et al., 2012), the mechanism by which T-type calcium channels modulates gene expression remains poorly understood.

C. Ca_V3 Channel Pathophysiology

Knockout mouse lacking the three Ca_V3 calcium channel isoforms have been created and examined in detail. Mice lacking the $Ca_V3.1$ subunit are viable and have a relatively mild behavioral phenotype. They are resistant to baclofen-induced seizures (Kim et al., 2001b), whereas mice overexpressing $Ca_V3.1$ present with absence epilepsy (Ernst et al., 2009). They also show resistance to chemically induced tremor (Park et al., 2010), but the latter is accompanied by increased cerebellar atrophy and a loss of motor coordination (Chang et al., 2011). $Ca_V3.1$ knockout mice also appear to show increased visceral pain sensation due to alterations in thalamic neuron firing (Kim et al., 2003), and these mice present with bradycardia (Mangoni et al., 2006), which is consistent with the role of these channels in cardiac pacemaker activity. Furthermore, $Ca_V3.1$ knockout mice show resistance to high-fat diet–induced weight gain (Uebele et al., 2009).

$Ca_V3.2$ null mice show abnormal development of the trachea and reduced relaxation of vascular tissue in response to acetylcholine (Chen et al., 2003a), the latter fitting with the observations described in the preceding section. These mice also show reduced sensitivity to certain types of peripheral painful stimuli (Choi et al., 2007), as well as heightened anxiety and impaired memory (Gangarossa et al., 2014). $Ca_V3.3$ null mice exhibit an increased susceptibility to drug-induced spike and wave discharges (Lee et al., 2014) but appear otherwise normal.

A number of channelopathies linked to Ca_V3 channels have been described in humans. Although there is no consistent linkage of mutations in human $Ca_V3.1$ and $Ca_V3.3$ channels to pathophysiology, mutations in $Ca_V3.2$ channels have been associated with seizure disorders, autism, and hyperaldosteronism. Many single nucleotide mutations in $Ca_V3.2$ have been reported in patients with childhood absence epilepsy and other types of idiopathic generalized epilepsies (Chen et al., 2003b; Heron et al., 2004, 2007). Functional studies in which these mutations were introduced into transiently expressed $Ca_V3.2$ channels revealed that a subset of the mutations caused gains of function in channel gating and increases in cell surface expression, whereas others appeared to have no effects on the biophysical properties of the channels (Khosravani et al., 2004, 2005; Vitko et al., 2005, 2007; Peloquin et al., 2006; Heron et al., 2007). The absence of biophysical effects of some of the mutations is curious; however, a recent study examining the consequences of a $Ca_V3.2$ mutation in a rat model of absence epilepsy revealed that the biophysical effect of the mutation depended critically on the use of a specific splice variant backbone of the channel (Powell et al., 2009). Gain-of-function mutations in $Ca_V3.2$ have also been linked to a genetic form of autism (Splawski et al., 2006), although how these changes in channel function lead to an autistic phenotype is not understood. Gain-of-function mutations in *CACNA1H* have also recently been associated with early onset hypertension and hyperaldosteronism (Scholl et al., 2015), in agreement with the known role of $Ca_V3.2$ in aldosterone secretion from zona glomerulosa cells in the adrenal cortex (Guagliardo et al., 2012).

Dysregulation of T-type calcium channels has been associated with chronic pain in animal models. In particular, the dorsal root ganglion (DRG) subtypes expressing $Ca_V3.2$ have recently been characterized in molecular detail (Reynders et al., 2015; Usoskin et al., 2015). In primary afferent fibers, $Ca_V3.2$ channels regulate neuronal excitability and synaptic transmission in the dorsal horn (Jacus et al., 2012; Waxman and Zamponi, 2014). Therefore, enhancement of $Ca_V3.2$ channel expression/activity contributes to pain hypersensitivity. Although no mutations in $Ca_V3.2$ that result in increased pain in humans have been reported in the literature, peripheral nerve injury or inflammation (Jagodic et al., 2008; García-Caballero et al., 2014), diabetes (Jagodic et al., 2007; Messinger et al., 2009), and colonic inflammation (Marger et al., 2011a) all give rise to increased DRG neuron T-type calcium currents in rodents. At least two mechanisms appear to contribute to this phenomenon: an enhancement of $Ca_V3.2$ channel trafficking, due to glycosylation in the case of diabetic pain (Orestes et al., 2013; Weiss et al., 2013), and stabilization of these channels as a result of enhanced deubiquitination (García-Caballero et al., 2014). Inhibiting $Ca_V3.2$ channels pharmacologically thus mediates analgesia (François et al., 2014). The recent development of a floxed $Ca_V3.2$–green fluorescent protein mouse line revealed that this channel is expressed in sensory neurons specialized in detecting mechanical stimuli, termed low-threshold mechanoreceptors. Conditional knockout of the channel in this subtype of DRGs further shows that $Ca_V3.2$ is implicated in allodynia linked to neuropathic pain (François et al., 2015).

As noted above, $Ca_V3.2$ channels also play a role in pressure overload-induced cardiac hypertrophy (Chiang et al., 2009). They appear to be a contributor to abnormal growth of ventricular cells (Martínez et al., 1999) and may dispose hypertrophic tissue to arrhythmias (Nuss and Houser, 1993). Finally, there is accumulating evidence that T-type calcium channels may also participate in the growth of certain cancers (Ohkubo and Yamazaki, 2012; Rim et al., 2012; Zhang et al., 2012; Das et al., 2013; Gackière et al., 2013; Dziegielewska et al., 2014).

Altogether, it appears as if aberrant expression and function of T-type calcium channels is a factor in multiple disorders. Conversely, targeting these channels pharmacologically may provide a spectrum of therapeutic benefits. Below, we highlight aspects of T-type calcium channel pharmacology.

D. Molecular Pharmacology of Ca_V3 Channels

1. Inorganic Ions. One of the key distinguishing features of T-type calcium channels is their sensitivity to extracellularly applied nickel ions (Fox et al., 1987). $Ca_V3.2$ calcium channels display a greater affinity for nickel ions compared with $Ca_V3.1$ and $Ca_V3.3$ channels, by approximately one order of magnitude (Lee et al., 1999b). This is due to the fact that $Ca_V3.2$ channels express a unique histidine residue at position 191 within the domain I S3–S4 loop (Kang et al., 2006; Nosal et al., 2013). It was subsequently shown that the same residue also acts as a major redox modulation site in the channel, which leads to inhibition of channel activity by ascorbate (Nelson et al., 2007) and upregulation of channel function in the presence of L-cysteine (Nelson et al., 2005). Differential regulation of Ca_V3 isoforms also occurs in the presence of another metal ion, zinc. $Ca_V3.2$ channels are inhibited more strongly by zinc ions compared with the other two Ca_V3 isoforms (Traboulsie et al., 2007). Interestingly, under certain circumstances, zinc ions can act as agonists of $Ca_V3.3$ channels by slowing the rate of deactivation, giving rise to ultraslow tail currents (Traboulsie et al., 2007; Reynders et al., 2015). By contrast, the deactivation kinetics of $Ca_V3.2$ channels is enhanced by zinc ions (Noh et al., 2010). Finally, magnesium ions also appear to modulate T-type channel activity. Importantly, it was shown that differential magnesium blocking affinity in external barium- and calcium-containing solutions underlies the apparent differences in the magnitude of $Ca_V3.1$ currents carried by calcium and barium (Serrano et al., 2000).

In addition to divalent metal ions, T-type channels are also potently blocked by trivalent metal ions (Mlinar and Enyeart, 1993). Specifically, for cloned human $Ca_V3.1$ channels, yttrium was the most potent of the lanthanides, with an affinity of around 30 nM (Beedle et al., 2002). However, block was greatly attenuated upon increasing the concentration of permeant ions, suggesting that trivalent ions act by physically occluding the pore of the channel.

Altogether, metal ions can be potent inhibitors of T-type calcium channel activity, also showing some selectivity. However, these ions are predominantly useful as research tools, rather than as a therapeutic approach.

2. Peptide Toxins. Like in the case of inorganic ions, peptide toxins are not particularly useful therapeutic agents because they cannot be administered orally and do not cross the blood–brain barrier. Kurtoxin, a peptide isolated from the venom of the scorpion species *Parabuthus transvaalicus*, was first reported to inhibit $Ca_V3.1$ calcium channels with high affinity (Chuang et al., 1998). This compound acts as a gating modifier in a manner akin to that described for the P-type channel blocker ω-agatoxin IVA (Sidach and Mintz, 2002). However, kurtoxin also targets other calcium channel isoforms, including both N and L types (Sidach and Mintz, 2002), and also has effects on sodium channels (Zhu et al., 2009). The solution structure of kurtoxin has been solved and shown to resemble those of α-scorpion toxins, but nonetheless with unique surface properties that could explain its action on T-type channels (Lee et al., 2012b). KLI and KLII are additional *P. transvaalicus* scorpion toxins with blocking effects on T-type calcium channels. Both toxins block T-type channels and sodium channels, with only a weak effect on transiently expressed $Ca_V3.3$ channels (Olamendi-Portugal et al., 2002).

Protoxins I and II are peptides isolated from the *Thrixopelma pruriens* tarantula, and they were originally described as sodium channel inhibitors (Schmalhofer et al., 2008). Both peptides were subsequently shown to block Ca_V3 channels in a subtype-dependent manner (Edgerton et al., 2010). Protoxin I preferentially blocks $Ca_V3.1$ channels over $Ca_V3.3$ and even more so over $Ca_V3.2$ (Ohkubo et al., 2010; Bladen et al., 2014b). Protoxin II appears to act as a gating modifier, with the highest affinity for $Ca_V3.2$ channels (Edgerton et al., 2010; Bladen et al., 2014b). Another spider toxin that blocks T-type calcium channels is PsPTx3, a peptide isolated from *Theraphosidae* tarantula that has apparent selectivity for $Ca_V3.2$ calcium channels (French patent application FR2940973).

Overall, compared with N-type calcium channels for which there is a rich peptide toxin pharmacology (in particular in marine snails), peptide toxin inhibitors of Ca_V3 channels remain relatively scant and derive mostly from arachnids. It should be noted, however, that peptide blockers of T-type calcium channels need not be confined to those derived from venomous species. For example, monocyte chemoattractant protein-1, which is an endogenous agonist of the chemokine receptor CCR2, directly and potently inhibits $Ca_V3.2$ T-type calcium channels (You et al., 2010).

3. Small Organic Molecules. Compared with peptide toxins, there is no dearth of small organic T-type calcium channel blockers. A number of different classes of T-type calcium channel blockers have been identified (Fig. 6). One of the first recognized blockers of T-type calcium channels is the diuretic amiloride (Tang et al., 1988). It blocks $Ca_V3.2$ channels with about one order of magnitude higher affinity compared with $Ca_V3.1$ and $Ca_V3.3$ channels (Lopez-Charcas et al., 2012); however, this compound is by no means a selective T-type calcium channel inhibitor (Kleyman and Cragoe, 1988; Manev et al., 1990). The succinimides are also a group of relatively simple compounds that include the antiepileptic agent ethosuximide (Huguenard, 2002). This compound is a low-affinity blocker of all three Ca_V3 channel isoforms and displays state-dependent inhibition (Gomora et al., 2001).

Mibefradil is a compound that initially generated significant excitement in the field, due to its purported selective inhibition of T-type calcium channels (Mishra and Hermsmeyer, 1994; Ertel and Clozel, 1997). This compound was approved by the U.S. Food and Drug Administration for the treatment of hypertension, but it had to be withdrawn from the market because of metabolism by cytochrome P450 and drug–drug interactions (Mullins et al., 1998). Furthermore, this compound was by no means a selective inhibitor of T-type channels. A more recent derivative of mibefradil (NNC55-0396 [(1*S*,2*S*)-2-[2-[[3-(1*H*-benzimidazol-2-yl) propyl]methylamino]ethyl]-6-fluoro-1,2,3,4-tetrahydro-1-(1-methylethyl)-2-naphthalenyl cyclopropanecarboxylate dihydrochloride]) has much lower interactions with CYP3A4 (Bui et al., 2008).

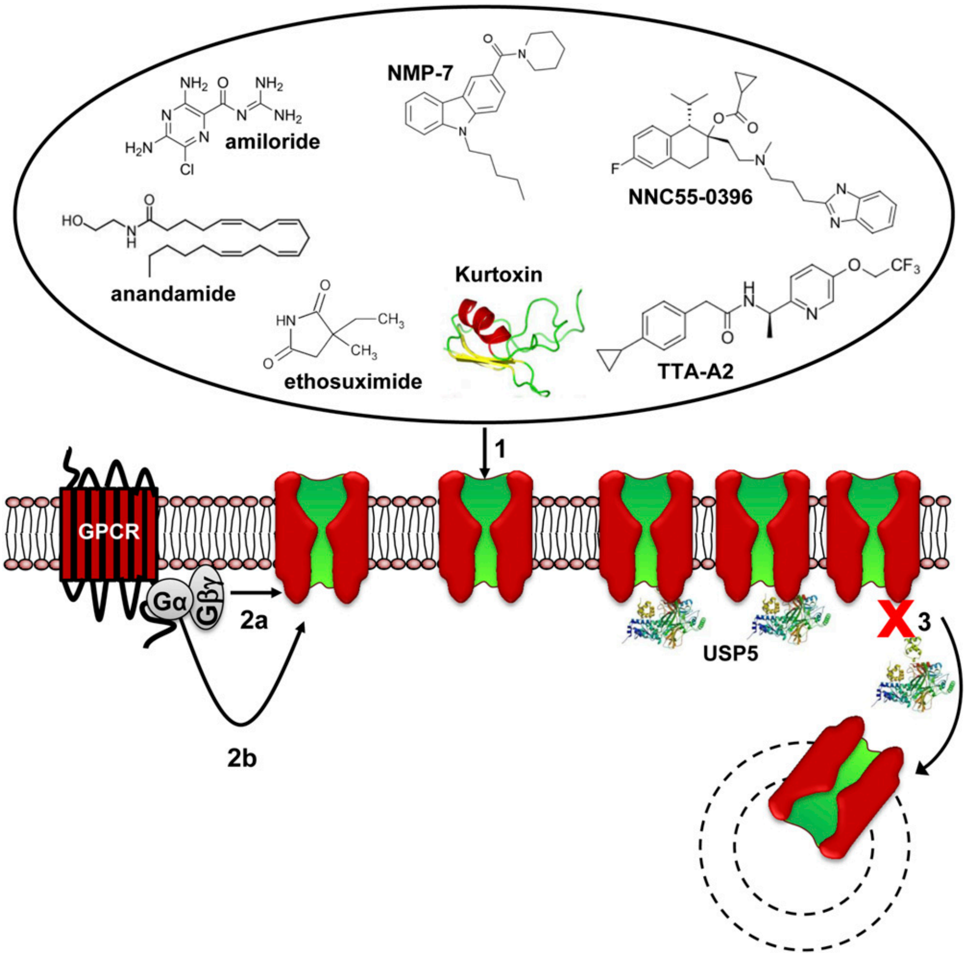

Fig. 6. T-type calcium channel regulators. Examples of classes of blockers known to inhibit T-type calcium channels, including small organic molecules and the peptide toxin kurtoxin. The inhibitors either physically block the pore, or bind to the gating machinery (pathway 1). T-type calcium channels can also be regulated by activation of GPCRs, either directly by G protein $\beta\gamma$ subunits (pathway 2a), or indirectly via protein kinases such as Rho kinase, protein kinase C, or CaMKII (pathway 2b). T-type calcium channel expression in the plasma membrane is regulated by ubiquitination and deubiquitinating. The deubiquitinase USP5 removes ubiquitin groups, thus increasing channel stability in the plasma membrane. Interfering with USP5 binding to the channel (pathway 3) leads to channel internalization and degradation. The kurtoxin image is reproduced from the Orientations of Proteins in Membranes database (Lomize et al., 2006; http://opm.phar.umich.edu/protein.php?pdbid=1t1t).

T-type calcium channels also interact with endocannabinoids and synthetic cannabinoid receptor ligands. Anandamide and its derivative Na-Gly (arachidonyl glycine) mediate potent inhibition of Ca$_{V}$3 calcium channels (Chemin et al., 2001b; Barbara et al., 2009). NMP-7 [(9-pentylcarbazol-3-yl)-piperidin-1-ylmethanone] is a synthetic carbazole derivative that acts as an agonist of cannabinoid receptors. This compound and several of its derivatives also potently block T-type calcium channels (You et al., 2011; Gadotti et al., 2013).

Diphenyl-butyl piperidines are a class of neuroleptic drugs that are well known for their actions as D2 dopamine receptor antagonists (Seeman, 1980). Several members of this class of compounds, including pimozide and penfluridol, potently inhibit Ca$_{V}$3 channels in a subtype-dependent manner (Enyeart et al., 1990; Santi et al., 2002). Rational drug discovery efforts centered around the piperidine core pharmacophore have resulted in the discovery of a number of selective and highly potent T-type channel inhibitors, including a compound termed Z944 (*N*-[[1-[2-(*tert*-butylamino)-2-oxoethyl]piperidin-4-yl]methyl]-3-chloro-5-fluorobenzamide) (Tringham et al., 2012). This compound has completed phase1b clinical trials for pain and is being advanced into phase 2 trials. A series of compounds that combine the carbazole core of NMP-7 and features of Z944 also mediate potent Ca$_{V}$3 channel inhibition without off-target effects on cannabinoid receptors and with efficacy in several in vivo models of pain (Bladen et al., 2015). Another series of compounds that incorporates features of Z944 includes TTA-A2 [(*R*)-2-(4-cyclopropylphenyl)-*N*-(1-(5-(2,2,2-trifluoroethoxy) pyridin-2-yl)ethyl) acetamide] and TTA-P2 [3,5-dichloro-*N*-[1-(2,2-dimethyl-tetrahydro-pyran-4-ylmethyl)-4-fluoro-piperidin-4-ylmethyl]-benzamide] (Choe et al., 2011; Francois et al., 2013), both of which mediate state-dependent inhibition of T-type currents with a preference for Ca$_{V}$3.2. TTA-A2 increased sleep and prevented high-fat diet–induced weight gain in mice (Uebele et al., 2009).

T-type calcium channels also have the propensity to interact with certain types of DHPs. LTCC-blocking DHPs such as nimodipine and niguldipine also potently block T-type channels (Stengel et al., 1998). Several types of DHP with preferential blocking action on T-type channels over L-type channels have since been identified (Kumar et al., 2002; Bladen et al., 2014a). In contrast with these inhibitors, another compound, ST101 (spiro[imidazo[1,2-*a*]pyridine-3,2-indan]-2(3*H*)-one), exhibits a channel-activating response, and this may be useful to further unravel the role of T-type channels. Its use in vivo showed cognitive-enhancing effects (Moriguchi et al., 2012).

It is interesting to note that many of the classes of compounds described above have been tested in various rodent models of inflammatory and neuropathic pain and have shown to mediate analgesia. Furthermore, we are aware of at least two T-type channel blockers that are being tested in humans for safety and efficacy in pain: Z944 (Lee, 2014) and ABT-639 [5-[(8*aR*)-3,4,6,7,8,8*a*-hexahydro-1*H*-pyrrolo[1,2-*a*]pyrazine-2-carbonyl]-4-chloro-2-fluoro-*N*-(2-fluorophenyl) benzenesulfonamide] (Ziegler et al., 2015). This underscores the importance of T-type calcium channels (particularly $Ca_V3.2$) in the primary afferent pain pathway. On the other hand, as noted earlier, T-type calcium channels are important targets for treating absence seizures, with ethosuximide being one of the archetypal T-type channel blocking antiepileptic drugs. Other clinically used antiepileptic drugs with at least partial action on T-type calcium channels include zonisamide (Matar et al., 2009) and valproic acid (Todorovic and Lingle, 1998).

4. Interference with Ca_V3 Channel Regulation. T-type calcium channels can be regulated by extracellular signaling molecules, and this can potentially be exploited for therapeutic purposes. For example, it has been shown that T-type channels (most notably $Ca_V3.2$ channels) are regulated by redox modulation. Ascorbate inhibits $Ca_V3.2$ channel activity via metal catalyzed oxidization (Nelson et al., 2007), whereas L-cysteine increases $Ca_V3.2$ current amplitudes (Nelson et al., 2005; Joksovic et al., 2006) through redox activity. This redox modulation occurs at a specific residue (His-191) (Nelson et al., 2007), which is also involved in Ni^{2+} block of these channels (Kang et al., 2006) and results in hyperalgesia (Pathirathna et al., 2006). Along these lines, hydrogen sulfide induces hyperalgesia via actions on $Ca_V3.2$ calcium channels (Maeda et al., 2009). In this context, it is interesting to note that administration of polaprezinc can mediate analgesia in a model for interstitial cystitis, presumably through its antioxidant activity (Murakami-Nakayama et al., 2015).

Another means of altering Ca_V3 channel activity is via intracellular messenger regulation. This includes effects of protein kinases (Welsby et al., 2003; Yao et al., 2006; Iftinca et al., 2007), direct binding of G proteins (Wolfe et al., 2003), and phosphatases (Huang et al., 2013a). A detailed description of second messenger regulation of T-type channels has been the focus of several previous review articles (Huc et al., 2009; Iftinca and Zamponi, 2009). Here, we focus on one example in which T-type channel regulation can potentially be exploited as a therapeutic strategy for pain. As noted earlier, $Ca_V3.2$ channels are under control by ubiquitinating and deubiquitinating enzymes. The deubiquitinase USP5 is upregulated after injury or inflammation, leading to increased T-type channel activity and thus chronic pain. Uncoupling USP5 from the channel via interfering TAT peptides reverses the pain phenotype (García-Caballero et al., 2014), as do small organic mimetics (Gadotti et al., 2015) (Fig. 6). This is reminiscent of the approach described above for the interaction between $Ca_V2.2$ channels and CRMP-2 (Ripsch et al., 2012) and supports the idea of therapeutic interventions that are not targeted at blocking channel activity, but instead interfere with channel trafficking.

E. Conclusion

T-type channels are important regulators of neuronal firing and neuronal communication, and they play important roles in the cardiovascular system. Their dysregulation can give rise to conditions such as epilepsy, pain, cardiac hypertrophy, and cancer; consequently, they are potential drug targets for these conditions. However, despite the fact that there are many classes of potential T-type channel blocking small organic molecules, their clinical use to date has been restricted largely to the treatment of absence seizures.

V. Auxiliary $\alpha_2\delta$ and β Subunits

Purification of the channel complexes showed the $Ca_V1.1$ and $Ca_V1.2$ channels, as well as the $Ca_V2.1$ and $Ca_V2.2$ channels, to be associated with auxiliary $\alpha_2\delta$ and β subunits (Takahashi et al., 1987; Tanabe et al., 1987; Witcher et al., 1993; Liu et al., 1996). Subsequent expression studies have shown that the other Ca_V1 and Ca_V2 channels also require these subunits for cell surface and functional expression (see sections II and III). However, from purification studies, the association of the $\alpha_2\delta$ subunit with the complex was found to be looser than that of the β subunit and was dependent on the solubilization conditions used to extract the channel complex from the lipid bilayer (Müller et al., 2010). Whether the T-type channels are associated with auxiliary $\alpha_2\delta$ subunits is still under investigation (see section IV). This section concentrates on $\alpha_2\delta$ subunits, because of their important role as an established therapeutic target; however, the function of β subunits is also discussed briefly below (section V.F), because they are functionally very important in Ca_V1 and Ca_V2 calcium channel complexes and also since disruption of the interaction between $\alpha 1$ and β subunits has been the subject of drug discovery projects.

A. $\alpha_2\delta$ Subunit Genes and Gene Products

Four mammalian genes encoding $\alpha_2\delta$ subunits have been cloned (*CACNA2D1–CACNA2D4*). A further gene was also identified by homology (Whittaker and Hynes, 2002). The first to be cloned was $\alpha_2\delta$-1, after purification of the protein as part of the skeletal muscle calcium channel complex. *CACNA2D1* encodes $\alpha_2\delta$-1, whose distribution is fairly ubiquitous in excitable cells and some other cell types. In addition to being present in skeletal muscle, it is also found in cardiac and smooth muscle as well as in both the central and peripheral nervous systems and in secretory tissue. In skeletal, cardiac, and smooth muscle, $\alpha_2\delta$-1 is associated with the LTCCs $Ca_V1.1$ in skeletal muscle and $Ca_V1.2$ in cardiac and smooth muscle (Ellis et al., 1988; Jay et al., 1991; Klugbauer et al., 1999; Wolf et al., 2003; Walsh et al., 2009). *CACNA2D2* and *CACNA2D3*, encoding $\alpha_2\delta$-2 and $\alpha_2\delta$-3, were identified by homology with *CACNA2D1*. They are expressed in neurons and some other tissues (Klugbauer et al., 1999; Barclay et al., 2001). *CACNA2D4*, encoding $\alpha_2\delta$-4, is present in retinal neurons and elsewhere (Qin et al., 2002; Wycisk et al., 2006b). The exon structure is similar in all $\alpha_2\delta$ subunit genes; for example, *CACNA2D1* has 39 exons.

Several other related genes have been found bioinformatically to have a comparable domain structure. A gene incorrectly termed *CACNA2D5* in an article by Whittaker and Hynes (2002) has the sequence of $\alpha_2\delta$-4 (*CACNA2D4*), and the more remotely related gene, erroneously termed *CACNA2D4* in that review corresponds to the more distantly related *CACHD1*, and has not yet been characterized. Homologous genes are also found in *Drosophila melanogaster* and *Caenorhabditis elegans* (Dickman et al., 2008; Saheki and Bargmann, 2009) and have been characterized to affect both calcium channel and presynaptic functions. Furthermore, proteins of the *CLCA* gene family, which have a related domain structure, have been identified to be auxiliary subunits of calcium-activated chloride channels (Yurtsever et al., 2012).

1. $\alpha_2\delta$ Subunit Splice Variants. It was noted that the cDNA sequence of $\alpha_2\delta$-1 subunit isoforms expressed in rat brain and skeletal muscle showed some divergence (Kim et al., 1992). Three regions, termed A, B, and C, were later identified to be alternatively spliced, with $\Delta A + B + C$ being the major splice variant in brain and in peripheral DRG neurons (Angelotti and Hofmann, 1996; Lana et al., 2014). A change in $\alpha_2\delta$-1 splicing was recently found in rat DRG neurons, after spinal nerve ligation. Increased expression was observed of a minor splice variant ($\Delta A + B\Delta C$), particularly in small DRG neurons, and this showed a lower affinity for gabapentin (Lana et al., 2014). There are also splice variants of the other $\alpha_2\delta$ subunits, but their expression has not been studied in detail (Klugbauer et al., 1999; Barclay and Rees, 2000; Qin et al., 2002).

B. Physiologic Roles of $\alpha_2\delta$ Proteins

1. Roles in Calcium Channel Function. The $\alpha_2\delta$ subunits were originally described as transmembrane proteins, but evidence suggests they are glycosylphosphatidylinositol anchored (Davies et al., 2010) (Fig. 1). In coexpression studies, the $\alpha_2\delta$-1 to $\alpha_2\delta$-4 subunits results in increased currents formed by high voltage–activated calcium channels (Ca_V1 and Ca_V2 families). The current density is markedly increased, and there are also a number of effects on biophysical parameters of the current, including hyperpolarization of inactivation and increase in inactivation kinetics as well as an increase in the coupling of channel opening to changes in voltage (Gurnett et al., 1996, 1997; Qin et al., 1998; Wakamori et al., 1999; Barclay et al., 2001; Brodbeck et al., 2002; Klugbauer et al., 2003; Yasuda et al., 2004; Cantí et al., 2005; Tuluc et al., 2007). Several of these studies show that $\alpha_2\delta$ and β subunits produce synergistic effects on current density for several channel subtypes (see Yasuda et al., 2004). For the $Ca_V1.1$ channel complex in skeletal muscle, $\alpha_2\delta$-1 was also found to have a functional role in excitation-coupled entry of Ca^{2+} into skeletal myotubes, although not in the formation of the $Ca_V1.1$ tetrad structure or in excitation-contraction coupling (Obermair et al., 2005; Gach et al., 2008). In mice in which $\alpha_2\delta$ subunits were depleted, there was a reduction of calcium currents in relevant cell types (Barclay et al., 2001; Fuller-Bicer et al., 2009; Patel et al., 2013; Pirone et al., 2014).

It was recently shown that $\alpha_2\delta$-1 subunits increased the expression of Ca_V2 channels in the plasma membrane (Cassidy et al., 2014); therefore, at least part of the effect of $\alpha_2\delta$ subunits on current density relates to trafficking of channel complexes. The effect of $\alpha_2\delta$-1 was largely dependent on the additional presence of a β subunit that produced a marked increase of the density of channels in the plasma membrane (Cassidy et al., 2014). However, no effect of $\alpha_2\delta$-1 was found on the rate of endocytosis of $Ca_V2.2$ (Cassidy et al., 2014), making it likely that $\alpha_2\delta$ subunits increase plasma membrane expression by enhancing forward trafficking of the channel complexes. In agreement with an effect of $\alpha_2\delta$ subunits on trafficking, $\alpha_2\delta$-1 knockdown, using short hairpin RNA, reduced plasma membrane expression of $Ca_V1.2$ in smooth muscle cells (Bannister et al., 2009) and reduced $Ca_V2.1$ levels in synaptic boutons (Hoppa et al., 2012).

Several studies also found a small enhancement of T-type (Ca_V3) channel expression by $\alpha_2\delta$ subunits (Dolphin et al., 1999; Dubel et al., 2004), although these channels express very well without $\alpha_2\delta$ subunits. This leaves open the possibility that Ca_V3 channel trafficking and function may be enhanced by auxiliary subunit expression.

2. Structural Roles of $\alpha_2\delta$-1 Subunits. The $\alpha_2\delta$ subunits have a similar domain structure to many proteins involved in extracellular matrix and extracellular protein–protein interactions (Whittaker and Hynes, 2002). Indeed, $\alpha_2\delta$-1 has been reported to interact with thrombospondins and to have a structural role in synapse formation (Eroglu et al., 2009), and the $\alpha_2\delta$ proteins in *Drosophila* have been shown to have an effect on presynaptic morphology (Dickman et al., 2008; Kurshan et al., 2009), as is also the case for $\alpha_2\delta$-3 in an auditory system synapse (Pirone et al., 2014). Since $\alpha_2\delta$ subunits are involved in calcium channel trafficking as well as function, it may be difficult to tease apart their roles independent of calcium channels.

C. Pathophysiological Roles of the $\alpha_2\delta$ Subunits in Disease

1. Cardiac Dysfunction. Human mutations in *CACNA2D1* have been associated with cardiac dysfunction in a small number of patients, including Brugada (Burashnikov et al., 2010) and short QT (Templin et al., 2011; Bourdin et al., 2015) syndromes. Furthermore, knockout of *cacna2d1* in mice resulted in a cardiac phenotype; the mice had compromised cardiac function and smaller cardiac calcium channel current density (Fuller-Bicer et al., 2009).

2. Epilepsies and Cerebellar Ataxia. Mutations in *cacna2d2* give rise to a phenotype of cerebellar ataxia and absence epilepsy in the spontaneously arising mouse mutants *ducky* and *ducky*^{2J} (Barclay et al., 2001; Brodbeck et al., 2002; Donato et al., 2006). *Entla* is another mouse strain with a mutation in *cacna2d2*, and these mice display ataxia and tonic-clonic epilepsy (Brill et al., 2004). This is also seen in the targeted knockout of *cacna2d2* (Ivanov et al., 2004). These mutations are all recessive, with the heterozygotes showing no significant behavioral effects (Barclay et al., 2001). Interestingly, ataxia is one of the adverse events reported when gabapentin and pregabalin are used therapeutically (Beal et al., 2012; Zaccara et al., 2012).

The ataxic phenotype is thought to result from the loss of $\alpha_2\delta$-2 from cerebellar Purkinje cells, in which it is normally strongly expressed (Barclay et al., 2001). Mutations in *CACNA2D2* in humans have been described to cause rare cases of recessive epileptic encephalopathy and mental retardation (Edvardson et al., 2013; Pippucci et al., 2013; Vergult et al., 2015). Family members with one mutated copy of this gene were unaffected. Regarding the role of $\alpha_2\delta$-1 in epilepsy, in two rat models of epileptic seizures, no upregulation of brain $\alpha_2\delta$-1 was observed, although there were regions of dysregulated $\alpha_2\delta$-1 distribution associated with neuronal cell loss (Nieto-Rostro et al., 2014).

3. Neuropathic Pain. Peripheral nerve injury has, as one consequence, an increase of $\alpha_2\delta$-1 mRNA in damaged DRG neurons, as evidenced by in situ hybridization (Newton et al., 2001), microarray analysis (Wang et al., 2002), and quantitative polymerase chain reaction (Bauer et al., 2009; Lana et al., 2014). This results in an increase of $\alpha_2\delta$-1 protein in DRGs and their terminals within the spinal cord (Luo et al., 2001; Bauer et al., 2009). Furthermore, $\alpha_2\delta$-1–overexpressing mice show a neuropathic phenotype (tactile allodynia and hyperalgesia) in the absence of nerve injury (Li et al., 2006), indicating that $\alpha_2\delta$-1 regulates the excitability of DRG neurons. In agreement with this, *cacna2d1* knockout mice showed a phenotype of reduced sensitivity to mechanical stimulation and delayed onset of neuropathic mechanical hypersensitivity after peripheral nerve injury (Patel et al., 2013). It has been found that expression of $\alpha_2\delta$-1 reduced the on rate of ω-conotoxins including MVIIA and CVID as well as their apparent affinity for $\mathrm{Ca_V}2.2$ in the oocyte expression system (Mould et al., 2004). Given that $\alpha_2\delta$-1 is upregulated in damaged sensory neurons in neuropathic pain models, this may limit the efficacy of these toxins.

A role for $\alpha_2\delta$-3 in central pain processing in mice and humans has also been elucidated, on the basis of a *Drosophila* screen that identified the importance of straightjacket (*stj*), the *Drosophila* homolog of $\alpha_2\delta$-3, in thermal nociception (Neely et al., 2010).

4. Psychiatric Disorders. SNPs in the $\alpha_2\delta$ subunit and other calcium channel genes have been associated with a spectrum of psychiatric diseases in a five-disorder meta-analysis of GWASs (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). The data were gathered from patients with bipolar disorder, schizophrenia, major depressive disorder, ASD, and attention-deficit disorder. In this study, SNPs in the $\alpha_2\delta$ genes *CACNA2D2* and *CACNA2D4* (as well as other calcium channel genes *CACNA1C, CACNA1S, CACNA1D, CACNA1E*, and *CACNB2*) were found to show significant association with illness, across these disorders. SNPs in *CACNA1I* were also recently associated with schizophrenia (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). In a more recent study, an excess of several rare disruptive mutations in *CACNA2D1, CACNA2D2*, and *CACNA2D3*, as well as other calcium channel genes and a variety of other genes involved in synaptic function, were found in schizophrenic patients (Purcell et al., 2014). Furthermore, a splice site mutation in *CACNA2D3* was identified previously as a "likely gene-disrupting mutation" in ASDs (Iossifov et al., 2012).

5. Night Blindness. It was initially found that *CACNA2D4*, encoding $\alpha_2\delta$-4, was distributed in a limited number of cell types, including the pituitary gland, adrenal gland, and colon, suggesting that it might have a role in secretory tissue (Qin et al., 2002). However, widespread distribution of $\alpha_2\delta$-4 transcripts was observed in mouse tissue (Wycisk et al., 2006a). Mutation in the *CACNA2D4* can lead to dysfunction of photoreceptors, causing certain forms of night blindness.

These include spontaneous mutation in the mouse, as well as human mutations (Wycisk et al., 2006a,b). These mutations are both associated with autosomal recessive cone dystrophy and night blindness. It is possible that the phenotype resulting from $\alpha_2\delta$-4 loss or dysfunction is confined to the retina because of a unique role in photoreceptors and lack of compensation by other $\alpha_2\delta$ subunits.

6. Hearing. A role for $\alpha_2\delta$-3 in hearing has been identified using a knockout mouse for $\alpha_2\delta$-3 (Pirone et al., 2014). This study identified reduced presynaptic Ca^{2+} channels and smaller auditory nerve fiber terminals synapsing on cochlear nucleus bushy cells to be associated with a specific hearing impairment resulting from the loss of $\alpha_2\delta$-3.

D. Pharmacology of $\alpha_2\delta$ Ligands

1. Ligand Binding Sites on $\alpha_2\delta$ Subunits. The $\alpha_2\delta$-1 and $\alpha_2\delta$-2 subunits (but not $\alpha_2\delta$-3 or $\alpha_2\delta$-4) possess a binding site for the antiepileptic drugs gabapentin (2-[1-(aminomethyl)-cyclohexyl] acetic acid) and pregabalin [*S*(+)-3-isobutyl GABA].

Other related compounds include 4-methylpregabalin and similar molecules (Ohashi et al., 2008; Corrigan et al., 2009). These compounds were not designed as drugs with $\alpha_2\delta$ binding in mind; rather, they were intended to increase $GABA_A$ receptor activation. They were synthesized to be rigid lipophilic analogs of GABA (Belliotti et al., 2005; Silverman, 2008). However, it was identified that gabapentin did not affect GABA receptors or GABA levels, despite being effective in various forms of experimental epilepsy models and in some human epilepsies (for review, see Taylor et al., 2007). To unravel the function of gabapentin, a key step was to purify and identify its binding sites in the brain by using radiolabeled gabapentin and proteomic approaches (Gee et al., 1996). By these means, the primary binding site was found to be $\alpha_2\delta$-1. ^{3}H-gabapentin was then observed to also bind to $\alpha_2\delta$-2 but not $\alpha_2\delta$-3 (Klugbauer et al., 1999; Gong et al., 2001). It is worth emphasizing that $\alpha_2\delta$ subunits, as accessory proteins of voltage-gated calcium channels, would not have been considered as drug targets. Indeed, until $\alpha_2\delta$-1 was identified as the binding site of gabapentin, the $\alpha_2\delta$ proteins were not considered to have any ligand binding sites. A single affinity binding site was observed, and the Hill coefficient was reported as near to 1, indicating a lack of binding cooperativity (Dissanayake et al., 1997).

In the initial studies in which $\alpha_2\delta$-1 was identified as the binding site for gabapentin, the apparent affinity for gabapentin binding showed a sequential increase during the steps of purification of $\alpha_2\delta$ from pig brain, from 92 nM in membranes to 9.4 nM for purified $\alpha_2\delta$-1 protein (Brown et al., 1998). In our studies, a marked increase in gabapentin binding affinity was observed for both $\alpha_2\delta$-1 and $\alpha_2\delta$-2 purified in detergent-resistant membrane (lipid raft) fractions compared with total membrane fractions (Davies et al., 2006; Lana et al., 2014). For example, the binding of ^{3}H-gabapentin to $\alpha_2\delta$ from membranes from mouse cerebellum (predominantly $\alpha_2\delta$-2, which is strongly expressed in Purkinje neurons) gave a K_D of approximately 385 nM, whereas the K_D was approximately 80 nM in detergent-resistant membranes from the same tissue (Davies et al., 2006). For $\alpha_2\delta$-2 expressed in Cos-7 cells, the K_D was approximately 470 nM in membranes and approximately 50 nM in the lipid raft fraction (Davies et al., 2006). The affinity of ^{3}H-gabapentin binding to $\alpha_2\delta$-1 was similarly found to increase 3-fold on dialysis of brain membranes, and this was attributed to the removal of diffusible factor of molecular mass < 12 kDa (Dissanayake et al., 1997). These results could indicate that there may be an endogenous ligand that occupies this site, although its function still remains obscure and its nature remains unknown; however, many endogenous amino acids, including L-leucine, are able to bind to $\alpha_2\delta$ subunits (Brown et al., 1998). Structure-function studies showed that C-terminal truncation of $\alpha_2\delta$-1 abrogated binding to ^{3}H-gabapentin (Brown and Gee, 1998). Subsequently, residues were identified in $\alpha_2\delta$-1, which were essential for gabapentin binding, particularly the third arginine (R) in an RRR motif (Wang et al., 1999). Mutation of RRR to RRA in both $\alpha_2\delta$-1 and $\alpha_2\delta$-2 consistently reduced the functionality of the $\alpha_2\delta$-1 and $\alpha_2\delta$-2 subunits, both in terms of calcium current enhancement (Field et al., 2006; Hendrich et al., 2008) and calcium channel trafficking (Tran-Van-Minh and Dolphin, 2010; Cassidy et al., 2014). Whether this suggests that binding of the endogenous "agonist" ligand is necessary for full functionality of the $\alpha_2\delta$ subunits remains unclear, because the mutation itself could reduce $\alpha_2\delta$ function. However, in this scenario, gabapentinoid drugs acting as "antagonists" would displace the "endogenous agonist." Although a number of endogenous small molecules have been shown to bind to $\alpha_2\delta$-1 and $\alpha_2\delta$-2, including L-leucine (Gee et al., 1996; Dissanayake et al., 1997), it has not been shown that they fulfill an endogenous agonist role.

The RRR motif is situated just upstream of the VWA domain, and it is therefore predicted to sit structurally at the base of the VWA domain, between it and the first chemosensory-like domain (Dolphin, 2012). Mutation of RRR to RRA reduced the affinity of gabapentin binding, for both $\alpha_2\delta$-1 (Wang et al., 1999) and $\alpha_2\delta$-2 (Davies et al., 2006). Knock-in mice were created with the same point mutation in either $\alpha_2\delta$-1 or $\alpha_2\delta$-2, such that gabapentin binding affinity was markedly reduced (Field et al., 2006; Lotarski et al., 2011). Using the $\alpha_2\delta$-1 knock-in mouse model, it was found that binding of gabapentin and pregabalin to the $\alpha_2\delta$-1 subunit is essential for their therapeutic effect, both in neuropathic pain and in several epilepsy models (Field et al., 2006; Lotarski et al., 2014). Furthermore, anxiolytic-like effects of pregabalin in mice were also mediated by drug binding to $\alpha_2\delta$-1 rather than $\alpha_2\delta$-2 (Lotarski et al., 2011). Nevertheless, gabapentin and pregabalin show similar affinities for $\alpha_2\delta$-1 and $\alpha_2\delta$-2 (Gong et al., 2001; Li et al., 2011); therefore, $\alpha_2\delta$-1–selective ligands might show an improved side effect profile.

Using ligand binding assays, it has been possible to identify many compounds that displace ^{3}H-gabapentin or ^{3}H-pregabalin, some with greater affinity for $\alpha_2\delta$-1 or with selectivity toward $\alpha_2\delta$-1 relative to $\alpha_2\delta$-2, as well as with improved pharmacokinetics (Cundy et al., 2004; Mortell et al., 2006; Field et al., 2007; Rawson et al., 2011); however, none are yet in clinical use, except extended-release prodrugs of gabapentin. Ataxia is reported to be one of the side effects of gabapentin that might be mediated via binding to $\alpha_2\delta$-2, arguing that selective $\alpha_2\delta$-1 ligands could be therapeutically useful (Field et al., 2007). Many other gabapentin-like compounds have also been found to bind to $\alpha_2\delta$-1 (Blakemore et al., 2010)

It is interesting to speculate whether ligands (endogenous or otherwise) might also bind to and modulate the function of $\alpha_2\delta$-3 (and $\alpha_2\delta$-4), neither of which possess an RRR motif, and whether drugs binding to the fairly ubiquitous $\alpha_2\delta$-3 subunits might have therapeutic potential, if they could be identified. Development of an assay for such drugs would be challenging, but structural and modeling studies will have a part to play.

2. Binding of Gabapentin to $\alpha_2\delta$-1 Splice Variants. The minor splice variant of $\alpha_2\delta$-1 (ΔA + BΔC), whose relative expression was increased after nerve injury in DRG neurons, showed a reduced affinity for gabapentin (Lana et al., 2014). This finding points toward the possibility that variation in the relative expression level of this splice variant in patients with neuropathic pain may influence the therapeutic efficacy of these drugs.

3. Mechanism of Action of $\alpha_2\delta$ Ligands. In terms of molecular mechanism of action (downstream of binding to $\alpha_2\delta$ subunits), most studies indicate that gabapentin and pregabalin produce very little or no acute inhibition of calcium currents in transfected cells or in neuronal cell bodies in most studies (Rock et al., 1993; Davies et al., 2006; Hendrich et al., 2008), although some studies reported small acute inhibitory effects (Stefani et al., 1998; Martin et al., 2002; Sutton et al., 2002). It was also found that although gabapentin did not inhibit calcium currents in wild-type mouse DRG neurons, the currents in DRGs from $\alpha_2\delta$-1–overexpressing mice were inhibited by gabapentin (Li et al., 2006). It was then found that chronic but not acute application of gabapentin markedly reduced calcium currents formed by several different $\alpha1/\beta/\alpha_2\delta$ subunit combinations (Hendrich et al., 2008). This effect occurred when using either $\alpha_2\delta$-1 or $\alpha_2\delta$-2; however, it did not occur in the absence of $\alpha_2\delta$ subunits or when $\alpha_2\delta$-3 or mutant $\alpha_2\delta$ subunits that bind gabapentin very poorly were used in the experiments (Hendrich et al., 2008), strongly pointing to the view that effects of gabapentin were indeed occurring via binding to $\alpha_2\delta$ subunits. More recently, it has been found that chronic gabapentin reduces the cell surface expression of $\alpha_2\delta$-1, $\alpha_2\delta$-2, and the associated α1 subunits Ca$_V$2.1 and Ca$_V$2.2 (Hendrich et al., 2008; Tran-Van-Minh and Dolphin, 2010; Cassidy et al., 2014), by disrupting the recycling process (Tran-Van-Minh and Dolphin, 2010). In agreement with the hypothesis that gabapentinoid drugs reduce trafficking of these $\alpha_2\delta$ subunits, it was also found that chronic in vivo pregabalin application reduced the amount of $\alpha_2\delta$-1 in presynaptic terminals in the dorsal horn of the spinal cord, interpreted as an effect on trafficking from DRG cell bodies (Bauer et al., 2009).

Other potential mechanisms of action of gabapentin have been put forward. Thrombospondins are secreted extracellular matrix proteins that promote synaptogenesis via binding to a postsynaptic receptor, which was identified to be $\alpha_2\delta$-1 (Eroglu et al., 2009). Gabapentin was found to disrupt this interaction between $\alpha_2\delta$-1 and thrombospondins (Eroglu et al., 2009) and has been found to interfere with synaptogenesis, while at the same time not affecting the stability of preformed synapses (Eroglu et al., 2009). Thrombospondins are elevated during synaptogenesis associated with development and are also elevated after nerve injury. However, thrombospondins promote formation of nonfunctional silent synapses (Christopherson et al., 2005), and thrombospondins destabilize postsynaptic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid glutamate receptors (Hennekinne et al., 2013). The involvement of gabapentin in these processes remains unclear.

As mentioned above, it is possible that selective ligands of $\alpha_2\delta$-1 might be of therapeutic use, with fewer side effects, because the therapeutic antiepileptic, anxiolytic, and antihyperalgesic effects in animal models of gabapentin and pregabalin were via binding to $\alpha_2\delta$-1 (Field et al., 2006; Lotarski et al., 2011, 2014). Nevertheless, $\alpha_2\delta$-2 binds these drugs with similar affinity and is expressed in brain regions associated with movement and other behaviors (Barclay et al., 2001).

4. Role of Amino Acid Transporters in the Action of Gabapentin. Pregabalin and gabapentin do not inhibit the transport of GABA in vitro (Su et al., 2005) However, both gabapentin and pregabalin are zwitterions at neutral pH and use the large neutral amino acid transporter "system L" for uptake across cell membranes (Belliotti et al., 2005; Su et al., 2005; Dickens et al., 2013).

5. Effects of $\alpha_2\delta$ Ligand Drugs on Synaptic Transmission and Transmitter Release. $\alpha_2\delta$-1 subunits are strongly expressed in presynaptic terminals (Taylor and Garrido, 2008; Bauer et al., 2009). Indeed, chronic effects of gabapentinoid drugs have been observed in pain pathways (Biggs et al., 2014). Acute effects of gabapentinoid drugs to inhibit transmitter release and synaptic transmission have been observed in some, but not all, in vitro systems (reviewed in Davies et al., 2007; Taylor et al., 2007). It is possible that, despite their lack of acute effect on somatic calcium currents in several systems (for review, see Dolphin, 2013), the gabapentinoid drugs might have differential effects on calcium currents in presynaptic terminals compared with cell bodies, resulting in more rapid inhibition. It is also possible that calcium channel turnover is higher in presynaptic terminals than in somata, so that effects on calcium channel trafficking are observed more acutely. Thus, gabapentinoid drugs might act rapidly or more slowly, depending on the interplay between these different processes, and possibly also depending on presynaptic sensitization, such as by activation of protein kinase C (Maneuf and McKnight, 2001). However, gabapentin had no effect on transmitter release at hippocampal synapses in culture (Hoppa et al., 2012).

6. Effects of Gabapentinoids in Preclinical Animal Models.

a. Seizure Models. Gabapentin and pregabalin are effective in several models of anticonvulsant action (Welty et al., 1993; Vartanian et al., 2006). By contrast, pregabalin did not reduce the incidence of spontaneous absence seizures in a genetic rat model of absence seizures (Vartanian et al., 2006). The effect of these drugs in several epilepsy models has been shown to result from binding to $\alpha_2\delta$-1, rather than $\alpha_2\delta$-2 (Lotarski et al., 2014), although there was no widespread upregulation of brain $\alpha_2\delta$-1 in two epilepsy models studied (Nieto-Rostro et al., 2014). It is possible that gabapentin has its effect by preventing new synapse formation as previously described (Eroglu et al., 2009), giving rise to the possibility that gabapentin might be protective against epileptogenesis by these means (Radzik et al., 2015).

b. Pain Models. The effect of the gabapentinoid drugs is said to be “state dependent,” meaning they have no effect on normal acute pain perception in naive animals, whereas they are efficacious in chronic pain models (Dickenson et al., 2005). Some behavioral effects of gabapentinoid drugs on pain phenotypes may be observed acutely (Field et al., 2006), but chronic treatment is generally more effective (Hao et al., 2000; Fox et al., 2003; Xiao et al., 2007). In agreement with this, it was observed that the effect of pregabalin increased with time of chronic treatment (Bauer et al., 2009).

E. Therapeutic Uses of $\alpha_2\delta$ Ligands

1. Epilepsy. Gabapentin was first developed as a GABA analog; although it is now known that this does not represent its mechanism of action, it was shown to be effective as an antiepileptic drug in clinical trials. Gabapentin was approved for use as an adjunct drug to improve control of partial seizures (Crawford et al., 1987; Marson et al., 2000). Pregabalin is also effective as adjunct therapy for partial seizures (French et al., 2003). It is possible that gabapentin also has a protective mechanism against seizure development (Rossi et al., 2013).

2. Neuropathic Pain. Gabapentin and pregabalin are widely used in neuropathic pain treatment, including diabetic neuropathy, chronic neuropathic pain induced by chemotherapeutic and other drugs, as well as postherpetic and trigeminal neuralgia (Rosenstock et al., 2004; Richter et al., 2005; Stacey et al., 2008; O’Connor and Dworkin, 2009; Moore et al., 2009, 2014). These drugs have relatively slow onsets of action and no effect on acute pain (Moore et al., 2009). Their efficacy is low in terms of numbers of patients that must be treated to observe a therapeutic response in one patient (e.g., 4.4 in postherpetic neuralgia), but the efficacy of gabapentin is consistent with that of other drug therapies in postherpetic neuralgia and painful diabetic neuropathy (Moore et al., 2014; Johnson and Rice, 2014).

Fibromyalgia is a poorly understood pain syndrome, including persistent, widespread pain and tenderness, sleep problems, and fatigue. Although gabapentin and pregabalin are used in this condition (Traynor et al., 2011; Wiffen et al., 2013), a systematic review of clinical trials for gabapentin concluded that there was currently insufficient evidence to confirm its efficacy (Moore et al., 2014).

3. Other Indications. Restless legs syndrome, also known as Willis–Ekbom disease, is a common neurologic disorder with an approximate adult prevalence of 1.9–15.0%. Disruption of sleep due to symptoms of restless legs syndrome may result in fatigue and depression. Gabapentin and the longer-acting prodrug gabapentin enacarbil have been found to have some efficacy in the treatment of this disorder (Happe et al., 2003; Garcia-Borreguero et al., 2013). Pregabalin has also been examined for use in generalized anxiety disorder (Wensel et al., 2012).

F. Physiologic and Potential Pharmacological Roles of $\mathrm{Ca_V}\beta$ Subunits

1. $\mathrm{Ca_V}\beta$ Subunit Biochemistry. $\mathrm{Ca_V}\beta$ subunits were first identified in the purified skeletal muscle voltage-gated calcium channel complex and the gene for $\mathrm{Ca_V}\beta1$ was then cloned (Ruth et al., 1989). Three more $\mathrm{Ca_V}\beta$ subunit genes were then identified by homology: $\mathrm{Ca_V}\beta2$, $\mathrm{Ca_V}\beta3$, and $\mathrm{Ca_V}\beta4$ (for reviews, see Dolphin, 2003; Buraei and Yang, 2010). The $\mathrm{Ca_V}\beta$ subunits are cytoplasmic proteins that bind with high affinity to the part of the intracellular loop between domains I and II of the $\mathrm{Ca_V}1$ and $\mathrm{Ca_V}2$ α_1 subunits. This binding motif is an 18–amino acid region in the proximal part of the I–II linker, termed the α-interaction domain (AID) (Pragnell et al., 1994).

$\mathrm{Ca_V}\beta$ subunits were found by homology modeling to contain a conserved *src* homology-3 domain and a guanylate kinase-like domain, linked by a flexible loop

(Hanlon et al., 1999). However, the guanylate kinase-like domain has no kinase activity, because there are mutations in the active site. Three studies solved the crystal structure of the conserved domains in several β subunits (Chen et al., 2004; Opatowsky et al., 2004; Van Petegem et al., 2004). They showed that the interaction site of the AID peptide is in a groove in the guanylate kinase-like domain (Van Petegem et al., 2004). In the intact I–II loop, the α-helical structure of the AID, which is imposed by binding to the Ca$_V\beta$-subunit, is predicted to continue to the end of S6 in transmembrane domain I (Opatowsky et al., 2004). Thus, β subunits may be considered as chaperones to induce correct folding of the α1 subunit.

2. Physiology of Ca$_V\beta$ Subunits. Ca$_V\beta$ subunits increase the functional expression and influence the biophysical properties of the Ca$_V$1 and Ca$_V$2 channels, and at least two processes have been proposed to account for this. All of the Ca$_V\beta$ subunits increase the maximum single channel open probability, which will increase current through individual channels, and will thus result in increased macroscopic current density (Matsuyama et al., 1999; Meir et al., 2000; Neely et al., 2004). However, Ca$_V\beta$ subunits also increase the amount of channel protein in the cell membrane, as measured by imaging, gating charge determination, or various biochemical means (Josephson and Varadi, 1996; Kamp et al., 1996; Brice et al., 1997; Bichet et al., 2000; Altier et al., 2002; Cohen et al., 2005; Leroy et al., 2005; Cassidy et al., 2014). Ca$_V\beta$ subunits were postulated to mask an endoplasmic reticulum retention signal in the I–II linker of Ca$_V\alpha$1 subunits (Bichet et al., 2000; Cornet et al., 2002), although no specific motif was identified (Cornet et al., 2002). It was then found that a mutation (W391A) in the I–II loop of Ca$_V$2.2 disrupts functional interaction with Ca$_V\beta$ subunits (Leroy et al., 2005), and this was used this to probe the mechanism of action of Ca$_V\beta$ subunits. Ca$_V$2.2 (W391A) was found to have a more rapid rate of degradation than wild-type Ca$_V$2.2, and this was blocked by proteasomal inhibitors (Waithe et al., 2011). A similar conclusion was reached for the effects of Ca$_V\beta$ subunits on LTCCs (Altier et al., 2011); these findings may represent a general function of Ca$_V\beta$ subunits in protecting the α1 subunit from endoplasmic reticulum–associated proteasomal degradation and thus promoting forward trafficking of the channels to the plasma membrane.

Moreover, calcium channel–independent functions of β subunits have also been reported. Several studies demonstrated targeting of β_4 subunits into the nucleus, suggesting a direct function in activity-dependent gene regulation (Colecraft et al., 2002; Hibino et al., 2003; Subramanyam et al., 2009; Tadmouri et al., 2012). Isoform-specific functions of β_4 splice variants were recently observed in neurons (Etemad et al., 2014). Although many aspects of the regulation and function of this new signaling pathway are still controversial, a lack of this nonconventional β_4 function could contribute to the ataxic phenotype in patients and mice with mutations in the β_4 gene.

3. Pathophysiology and Potential Pharmacology Involving Ca$_V\beta$ Subunits. Ca$_V\beta$ subunit pathology has been implicated in epilepsy, cardiac dysfunction, and other diseases (for review, see Buraei and Yang, 2010). It has been hypothesized that development of a drug targeting the groove within Ca$_V\beta$ into which the AID peptide is inserted could inhibit the interaction between the Ca$_V\alpha$1 and β subunits and thus reduce calcium channel function, which could be beneficial in certain conditions such as hypertension and chronic pain. Indeed, such a lead molecule was identified (Young et al., 1998). However, since the interaction between Ca$_V\beta$ and the AID region is of very high affinity and involves a number of residues, it is difficult to identify first how a small molecule would compete for binding and second how selectivity between the different Ca$_V\alpha$1 and β subunits would be obtained. Nevertheless, the use of cell-permeant peptides described above to interfere with the interaction between Ca$_V$2.2 and CRMP-2 (Ripsch et al., 2012) might also be employed to disrupt the α1–β interaction.

VI. Conclusions

The identification of specific roles for different calcium channel isoforms, as well as their different splice variants and auxiliary subunits, has been aided by knockout mouse models and the existence of human mutations in many of these channels and their auxiliary subunits. For example, the recent discovery of important physiologic functions differentially controlled by Ca$_V$1.2 and Ca$_V$1.3 identifies both channels as potentially novel drug targets, if selectivity can be achieved. Nonselective blockers of these channels (DHPs and other CCBs) have been of use in the treatment of hypertension for many years and their side effect profile has been well studied. Some selectivity of DHPs is nevertheless achieved in vivo for targeting vascular Ca$_V$1.2 because of the depolarized potentials found in this tissue, since DHPs bind with higher affinity to inactivated channels. If selective drugs can be developed, there is a strong therapeutic potential for selective Ca$_V$1.3 blockers for several indications, including neuropsychiatric diseases, PD neuroprotection, and resistant hypertension associated with hyperaldosteronism.

For the Ca$_V$2 channel family members, Ca$_V$2.2 has particular potential as a therapeutic target. Major effort has been put into identifying novel classes of Ca$_V$2.2 channel blockers with high affinity, selectivity, and use dependence. This effort has been spurred on by the success, albeit limited, of ziconotide (the peptide ω-conotoxin MVIIA) as an intrathecally administered drug for use in intractable pain, as well as the phenotype of the Ca$_V$2.2 knockout mouse. Beyond their application as analgesics, $\mathrm{Ca_V}2.2$ channel blockers may well be effective in conditions such as drug dependence and anxiety.

T-type ($\mathrm{Ca_V}3$) channels are important regulators of neuronal firing and pacemaker activity, and they play important roles in the cardiovascular system. Their dysregulation contributes to a number of chronic conditions, including epilepsy and pain; consequently, they are both potential and actual (ethosuximide) drug targets for these conditions. However, despite the fact that many classes of potential T-type channel blocking small organic molecules have been developed and studied, their clinical use to date has been restricted largely to the prophylaxis of absence seizures by ethosuximide.

Of the $\mathrm{Ca_V}$ auxiliary subunits, $\alpha_2\delta$-1 is a well established drug target for the drugs gabapentin and pregabalin, used in chronic neuropathic pain and in combination with other drugs in several forms of epilepsy. These drugs also bind to $\alpha_2\delta$-2, but not $\alpha_2\delta$-3. Whether a selective or more potent $\alpha_2\delta$-1 ligand would have fewer side effects and whether a similar ligand targeting $\alpha_2\delta$-3 might be of therapeutic use remain to be determined. Although targeting the interaction between α_1 and β might be of therapeutic relevance in principle, this has not yet proven possible.

In conclusion, it is clear that selective calcium channel blockers are likely to hold great promise for therapeutic intervention in the future.

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Authorship Contributions

Wrote or contributed to the writing of the manuscript: Zamponi, Striessnig, Koschak, Dolphin.

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