The Role of Calcium Channels in Epilepsy

Sanjeev Rajakulendran and Michael G. Hanna

UCL–Institute of Neurology, MRC Centre for Neuromuscular Diseases, Queen Square, London WC1N 3BG, United Kingdom

Correspondence: m.hanna@ucl.ac.uk

A central theme in the quest to unravel the genetic basis of epilepsy has been the effort to elucidate the roles played by inherited defects in ion channels. The ubiquitous expression of voltage-gated calcium channels (VGCCs) throughout the central nervous system (CNS), along with their involvement in fundamental processes, such as neuronal excitability and synaptic transmission, has made them attractive candidates. Recent insights provided by the identification of mutations in the P/Q-type calcium channel in humans and rodents with epilepsy and the finding of thalamic T-type calcium channel dysfunction in the absence of seizures have raised expectations of a causal role of calcium channels in the polygenic inheritance of idiopathic epilepsy. In this review, we consider how genetic variation in neuronal VGCCs may influence the development of epilepsy.

Voltage-gated calcium channels (VGCCs) are widely expressed throughout the mammalian central nervous system (CNS), but also in nonexcitable cells of the immune system, in which their roles are less clearly defined. They are the evolutionary link between a single ancestral potassium channel from which they originated and sodium channels with which they share striking structural homology. Their fundamental importance has been underpinned by the identification of pathological processes associated with their dysfunction. Whereas three broad categories of neurological diseases are associated with inherited defects of VGCCs, epilepsy, migraine, and ataxia, it is their role in seizure disorders that has provoked much interest. This, in part, reflects the drive to understand the genetic basis of a common disorder, but also the need to design effective rational treatment.

From mediating action potential (AP) firing and membrane oscillations to facilitating intracellular signal transduction through to supporting neurotransmitter release, their biological roles are diverse and made possible by differences in the electrophysiological properties among subtypes of the VGCC superfamily. Their widespread effects on neuronal excitability have raised a fundamental question: Do alterations in their expression and biophysical characteristics predispose to epilepsy?

Although mounting data, particularly from animal studies, would suggest an answer in the affirmative, the story to date is not quite so simple or indeed complete. In this review, we focus on the physiological roles played by neuronal VGCCs from an epileptogenic viewpoint. We evaluate the animal models and human phenotypes, which arise from calcium channel dysfunction, and consider how such perturbations

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of channel function may lead to cortical excitability.

VGCCs: STRUCTURE, SUBTYPES, AND FUNCTION

Calcium Channels: A History of Discovery

The calcium channel narrative has its origins in the 1950s with the observation by Paul Fatt and Bernard Katz (Fatt and Katz 1953) that muscle cells bathed in a solution devoid of sodium ions were still electrically excitable. Subsequently, Harald Reuter's work on calcium currents in cardiac myocytes established a role for the channel in cardiac function (Reuter 1967). Since then, calcium channels have been identified in all electrically active cells (Table 1).

Pharmacological dissection using channel antagonists and blockers has played an important role in identifying the many calcium channel subtypes (Dolphin 2006). The use of dihydropyridines (DHPs) as a tool for calcium channel blockade led to the identification of a subtype as “long-lasting” or L-type as they show slow voltage-dependent inactivation. L-type channels are highly expressed in skeletal, cardiac, and smooth muscles (Hess et al. 1984), endocrine cells, in which they initiate the release of hormones (Milani et al. 1990; Yang and Berggren 2006), and neurons (Bean 1989a; Flavell and Greenberg 2008).

Studies of calcium currents in starfish eggs by Hagiwara, who pioneered much of the early work in invertebrate tissues (Hagiwara et al.

Table 1. Calcium channel subtypes, their localization roles, and association in disease states

Biophysical classification	Calcium channel type	Current type	Main localization	Function	Diseases
HVA	Ca _v 1.1	L	Skeletal muscle	E–C coupling Gene transcription	Hypokalaemic periodic paralysis
	Ca _v 1.2	L	Cardiac, smooth muscle neuronal, adrenal chromaffin cells	E–C coupling Gene transcription Hormone secretion, enzyme activity	Timothy syndrome
	Ca _v 1.3	L	Endocrine, neuronal, cardiac, adrenal chromaffin cells	Cardiac pacemaking hormone secretion auditory transduction	–
	Ca _v 1.4	L	Retina	Visual transduction	Night blindness
	Ca _v 2.1	P/Q	Neuronal	Neurotransmitter release	EA2, FHM1, SCA6, epilepsy
	Ca _v 2.2	N	Neuronal, endocrine	Neurotransmitter release	–
	Ca _v 2.3	R	Neuronal	Neurotransmitter release, rhythmic firing	–
	Ca _v 3.1	T	Neuronal, cardiac	Rhythmic firing/ pacemaking	Absence seizures
	Ca _v 3.2	T	Neuronal, cardiac	Rhythmic firing/ pacemaking	Absence seizures
IVA	Ca _v 3.3	T	Neuronal	Rhythmic firing/ pacemaking	–

The VGCC $\alpha 1$ subunit family. Timothy syndrome is a multisystem disease characterized by cardiac arrhythmias, dysmorphism, intermittent hypoglycemia, cognitive impairment, and autism (Splawski et al. 2004).

HVA, High-voltage activated; IVA, low-voltage activated; E–C, excitation–contraction; EA2, episodic ataxia type 2; FHM1, familial hemiplegic migraine type 1; SCA6, spinocerebellar ataxia type 6.

1975) and neurons (Llinas and Yarom 1981), showed calcium currents that had different biophysical properties to L-type channels. The “new” currents activated at more negative membrane potentials, inactivated rapidly, had smaller single-channel conductances, and were insensitive to DHPs. These “tiny” and “transient” currents were named T-type and this led to the classification of calcium channels into low- (T-type) and high-voltage-activated (HVA) (L-type) (Carbone and Lux 1984; Carbone et al. 1984; Fedulova et al. 1985; Nowycky et al. 1985). The HVA family of calcium channels was further subclassified according to their conductance, kinetics, and sensitivity to pharmacological blocking agents (Tsien et al. 1988; Hess 1990).

In presynaptic nerve terminals, a component of the calcium current was found to be insensitive to DHP, but was blocked by a peptide, ω -conotoxin GV1A, obtained from the cone shell, *Conus geographus* (Nowycky et al. 1985; McCleskey et al. 1987). This calcium current was named N-type for “Non-L” and “Neuronal.” Another calcium channel subtype was identified in cerebellar purkinje cells (Llinas et al. 1989) and was found to be insensitive to both DHP and ω -conotoxin GV1A (Hillman et al. 1991). These channels were termed P-type after “Purkinje” cells and, subsequently, were found to be sensitive to ω -agatoxin IVA, a peptide found in the venom of the American funnel web spider, *Agelenopsis aperta* (Mintz et al. 1992). A further component of the ω -agatoxin IVA-sensitive calcium current, albeit with lower affinity for the toxin, was identified in cerebellar granule cells and named Q-type. An R-type or “residual” calcium current has also been isolated on the basis of insensitivity to DHPs and the toxins that block N- and P/Q-type currents (Randall and Tsien, 1995). Although initially thought to involve distinct channels, the P- and Q-type channels are now often referred to as P/Q-type channels because they are thought to arise from either splice variants (Bourinet et al. 1999) or from different accessory subunit interactions (Richards et al. 2007) with the pore-forming component arising from the same gene.

Calcium Channel Structure

The Principal $\alpha 1$ Subunit

Calcium channels are multimeric membrane complexes and each consists of a principal $\alpha 1$ subunit, which defines the channel type. Ten different $\alpha 1$ subunits have been identified and, although each is capable of functioning as a channel when expressed alone, in the case of HVA channels at least, they coassemble with β , $\alpha 2\delta$, and possibly γ subunits. Current evidence suggests that low-voltage-activated (LVA) channels do interact with auxiliary subunits, a potentially unique feature among calcium and sodium channels. Although more detailed structure-functional relationships will emerge once the high-resolution crystal structure of the subunit has been solved, current understanding has highlighted a number of key features and domains of the channel.

The $\alpha 1$ subunit is a peptide of ~ 2000 amino acids. It is thought to have evolved through two duplications of an ancestral potassium channel and shares striking structural homology with voltage-gated sodium channels. Its membrane topology consists of four homologous domains (I–IV), each of which contains six transmembrane segments (designated S1–S6). The S4 segment of each domain is lined by positively charged amino acids and act as the voltage sensor. A group of conserved glutamate residues in the linker between segments S5 and S6, which loops back into the membrane to form the channel pore, confers the high selectivity for calcium ions (Yang et al. 1993). The amino and carboxyl termini are involved in trafficking and anchoring the $\alpha 1$ subunit to the membrane (Fig. 1A). The latter contains an IQ motif that interacts with Ca^{2+} /calmodulin, the effect of which is calcium-dependent facilitation (CDF) and calcium-dependent inactivation (CDI) (Cuttler et al. 1998; Lee et al. 1999, 2000, 2003; Van Petegem et al. 2005). The intracellular loop between domains II and III contains the interaction domain for G protein–coupled receptors and key motifs that interact with soluble N-ethylmaleimide-sensitive factor-activating protein receptor (SNARE) proteins important for vesicular docking before exocytosis (Rettig et al.

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Figure 1. Structure and function of voltage-gated calcium channels (VGCCs). (A) Membrane topology of the $\alpha 1$ subunit. The subunit consists of four domains (I–IV), each containing six transmembrane segments (S1–S6). The S4 segment of each domain is lined with positively charged amino acids and acts as the voltage sensor. The S5–S6 interlinker lines the pore of the channel. (B) Schematic of the channel complex for high-voltage-activated (HVA) and low-voltage-activated (LVA) calcium channels and their diverse biological roles. HVA channels consist of a principal $\alpha 1$ subunit, which forms the channel pore, a β subunit, which is cytoplasmic, an extracellular $\alpha 2\delta$ subunit, which is attached to the membrane via a glycosylphosphatidylinositol (GPI) anchor, and possibly a γ subunit. Alternative splicing gives rise to multiple isoforms of all the subunits. LVA channels do not appear to associate with accessory subunits. CaM, Calmodulin.

1996; Catterall 1999; Mochida et al. 2003a,b). Our understanding of the complex mechanisms underpinning CDI and CDF has advanced, although it remains incomplete and has already been covered in recent reviews (Zamponi 2003; Catterall 2011; Simms and Zamponi 2014) and so will not be discussed any further here; the role of calcium channels in neurotransmitter release

along with G protein modulation is discussed below.

Auxiliary Subunits: β , $\alpha 2\delta$, and γ

The $\alpha 1$ subunit of high-voltage calcium channels coassembles with an intracellular β subunit and an extracellular $\alpha 2\delta$ subunit in a 1:1:1 stoichiometry.

chiometry (Fig. 1B). The β subunit has predicted α -helices and is cytoplasmic with no transmembrane segments (Ruth et al. 1989). Four genes encode the β subunits ($\text{Ca}_v\beta 1$ – $\text{Ca}_v\beta 4$) and each is subject to alternative splicing (Ruth et al. 1989; Castellano et al. 1993a,b), thus increasing the number of potential isoforms with which α subunits associate. When expressed alone, $\alpha 1$ subunits are capable of producing functional calcium channels, but with attenuated current densities and altered biophysical properties (Perez-Reyes et al. 1989). Coexpression with β subunits enhances trafficking and expression of the $\alpha 1$ subunit at the plasma membrane by processes that involve both inhibition of channel degradation in proteosomes and a shift in the balance between exportation of the channel to the cell membrane and retention in the endoplasmic reticulum (ER) (Buraei and Yang 2010; Altier et al. 2011; Waithe et al. 2011). Depending on the particular isoform, $\text{Ca}_v\beta$ subunits may also induce a shift in the channel activation to more hyperpolarized potentials and increase the channel opening probability factors, which contribute to the increase in current density observed when the $\alpha 1$ and β subunits are coexpressed (Dolphin 2003a). The site of interaction between the two is the α interaction domain (AID), a highly conserved motif located in the cytoplasmic linker between domains I and II (Pragnell et al. 1994; Van Petegem et al. 2004). Mutations in *CACNB*, the gene that encodes the $\text{Ca}_v\beta 4$ subunit, in mice result in the “lethargic” phenotype (Burgess et al. 1997) of nonconvulsive seizures, ataxia, and dyskinesias (see below).

The $\alpha 2$ and δ subunits arise from transcription of a single gene, the product undergoing first posttranslational cleavage followed by disulfide-linkage (De Jongh et al. 1990; Jay et al. 1991). Four $\alpha 2\delta$ subunit genes have been identified, 1–4, and each is subjected to alternative splicing (Ellis et al. 1988; Gao et al. 2000; Barclay et al. 2001; Qin et al. 2002); $\alpha 2\delta$ -3 is highly expressed in neurons (Klugbauer et al. 2003). The $\alpha 2$ component is entirely extracellular and although the δ subunit was initially thought to span the membrane, recent evidence suggests that it, too, is extracellular and is anchored to

the membrane by glycosylphosphatidylinositol (GPI). All HVA calcium channels associate with a $\alpha 2\delta$ subunit, which increases the trafficking and density of the calcium channels at the plasma membrane, although the effects are generally small (Shistik et al. 1995; Felix et al. 1997; Gao et al. 2000).

On purification of the skeletal L-type calcium channel, a transmembrane γ subunit (stargazin) was isolated (Chang and Hosey 1988; Sharp and Campbell 1989; Arikath and Campbell 2003). The encoding gene is targeted in the *stargazer* mouse (Letts et al. 1998) and has been shown to be a modulator of α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors at postsynaptic membranes (Tomita et al. 2005; Bats et al. 2007; Matsuda et al. 2013). Seven different splice isoforms of the γ subunit have been identified in neurons (Klugbauer et al. 2000; Chen et al. 2007), and, although when heterologously expressed with $\text{Ca}_v 2.1$ (P/Q-type) channels, they exerted effects on channel physiology (Roussel et al. 2001), it is unclear whether they are genuine accessory subunits of the neuronal calcium channel complex in vivo (Ahlijanian et al. 1990; McEnery et al. 1991; Witcher et al. 1994; Martin-Moutot et al. 1995).

Physiological Roles of Calcium Channels in Neurons

In the nervous system, calcium channels support a host of biological processes, including gene expression, neuro-architectural development, intracellular signal propagation, membrane oscillation, and neurotransmitter release (Catterall 2011; Simms and Zamponi 2014). The variety of calcium channel types required to support such diversity of function is achieved by both extensive alternative splicing of subunit genes and the various combinations with which the subunits coassemble (Bourinet et al. 1999; Krovetz et al. 2000; Lipscombe 2005; Lipscombe and Raingo 2007; Lipscombe et al. 2013), the result being the generation of multiple channels with each showing finely tuned biophysical properties tailored to cell- and network-specific roles. Here, we focus on two functions that, in particular, have implications for seizure gen-

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eration, their presynaptic involvement in neurotransmitter release, and their role in burst firing.

P/Q-, N-, and R-Type Channels in Synaptic Transmission

Synaptic transmission in the mammalian CNS is mediated by the coordinated actions of multiple Ca_v channel types; $\text{Ca}_v2.1$ (P/Q-type) channels predominate at central synapses; $\text{Ca}_v2.2$ (N-type) channels appear to be more prominent in peripheral nerve terminals, such as those involved in sensory and autonomic function; $\text{Ca}_v2.3$ (R-type) channels also contribute to neurotransmission, albeit to a lesser extent (Uchitel et al. 1992; Luebke et al. 1993; Takahashi and Momiyama 1993; Turner et al. 1993; Wheeler et al. 1994; Reuter 1995; Reid et al. 1997; Catterall 1998; Wu et al. 1998; Trimmer and Rhodes 2004; Wadel et al. 2007; Neher and Sakaba 2008). Their localization within the active zones of presynaptic nerve terminals (Westenbroek et al. 1995) enables the coupling of calcium influx to vesicular exocytosis through a direct interaction with the SNARE protein complex comprising syntaxin, SNAP-25, and VAMP/synaptobrevin (Catterall 1999; Mochida et al. 2003a,b; Weiss and Zamponi 2012). The site of this interaction is the “synprint” (synaptic protein interaction) region located in the large intracellular linker between domains II and III of Ca_v (Sheng et al. 1994, 1996; Rettig et al. 1996) in the case of $\text{Ca}_v2.1$ and $\text{Ca}_v2.2$ channels; disruption of this motif reduces the efficacy of neurotransmission (Catterall 1999), although emerging evidence suggests that other mechanisms or regulatory proteins, such as CASK, Mint-1, and Rab3-interacting molecules (RIMs), may also facilitate the presynaptic organization of calcium channels (Kaneko et al. 2002; Maximov and Bezprozvanny 2002; Kiyonaka et al. 2007; Liu et al. 2011; Graf et al. 2012). In addition to facilitating neurotransmission, the SNARE proteins also exert inhibitory modulation on $\text{Ca}_v2.1$; syntaxin reduces Ca_v channel expression and inhibits its activity on heterologous expression (Bezprozvanny et al. 1995).

More recently, the role of Ca_v3 (T-type) channels in neurotransmitter release, specifically low-threshold exocytosis, has been a subject of interest with evidence from hippocampal neurons and dorsal root ganglion cells; in addition, all members of this family interact with SNARE proteins (Carbone et al. 2006a,b; Tang et al. 2011; Jacus et al. 2012; Weiss et al. 2012; Rozanski et al. 2013).

G Protein Modulation of Presynaptic Calcium Channels

Ca_v2 channels are subject to inhibitory modulation by G protein–coupled receptors, which typically results in a positive shift in the voltage dependence of activation, as well as a slowing of the rate channel activation as channels enter the “reluctant” state (Dunlap and Fischbach 1981; Dolphin and Scott 1986; Holz et al. 1986; Bean 1989b; Dolphin 1998, 2003b), an effect that can be relieved by strong depolarizations, which shifts the channel to a “willing” state (Ikeda 1991, 1996). This is a major mechanism of negative feedback whereby neurotransmitters can modulate the activity of presynaptic calcium channels via G protein pathways and, thus, influence neurotransmission. $\text{G}\beta\gamma$ subunits are the key elements involved in this process via an interaction with a site on the cytoplasmic linker between repeats I and II of the calcium channel α subunit (Herlitze et al. 1996a,b; Ikeda 1996; De Waard et al. 1997; Garcia et al. 1998; Zamponi and Snutch 1998), as well as domains in the amino- and carboxy-terminal regions (Swartz 1993; Zhang et al. 1996; Qin et al. 1997; Zamponi et al. 1997; Furukawa et al. 1998a,b; Page et al. 1998; Canti et al. 1999).

T-Type Channels in Neuronal Excitability and Burst Firing

Ca_v3 channels conducting T-type currents are particularly enriched in thalamic neurons, in which their biophysical characteristics are well suited for the rhythmic firing of APs and facilitation of network oscillations, which are thought to play a key role in circadian rhythms, including the sleep–wake cycle, but which may

reverberate inappropriately, resulting in absence seizures (Llinas 1988; Talley et al. 1999; McCormick and Contreras 2001; Perez-Reyes 2003; Lee et al. 2004). The key components of the thalamocortical network relevant to seizure propagation appear to consist of thalamic relay nuclei, cortical sensory neurons, and thalamic reticular neurons, which form a closed-loop circuit capable of self-propagating oscillations (Huguenard and Prince 1992; Meis et al. 1996; Pinault et al. 1998; Meeren et al. 2002; Slaght et al. 2002; Pinault 2003; Polack et al. 2007).

T-type channels are central to the phenomenon of “bursting,” in which hyperpolarization followed by depolarization ensures that a large fraction of T-type channels, which are inactivated at the typical resting membrane potential, recover to generate a low-threshold spike (LTS) or “calcium spike,” which triggers an AP (Ulrich and Huguenard 1997), so called “rebound bursting.” If the membrane is sufficiently depolarized, then the subsequent activation of both sodium and potassium channels can initiate high-frequency firing or “burst firing,” the proposed pathophysiological substrate for the spike and wave discharges (SWDs) seen on electroencephalographic (EEG) recordings, in which the “spike” represents AP firing and the “wave” corresponds to a period of relative neuronal inactivity (Coulter et al. 1989a; Turner et al. 1994; Kim et al. 2001; Chemin et al. 2002; Blumenfeld 2005; Molineux et al. 2006; Xu and Clancy 2008; Alvina et al. 2009; Cain and Snutch 2012). In addition, T-type channels generate “window currents,” in which, at certain potentials, a proportion of channels are open but not inactivated, leading to an inward calcium current, which contributes to membrane stability. It follows that changes in the channel milieu, which determine whether channels are open, closed, or inactivated, will influence the window current, which, in turn, will have consequences on neuronal excitability, a chain of events that may underlie seizure initiation (Williams et al. 1997; Perez-Reyes 2003; Crunelli et al. 2005; Contreras 2006; Cain and Snutch 2010). Finally, T-type channels also influence neuronal firing in a calcium-dependent manner by controlling intracellular calcium concentration and inter-

acting with calcium-activated potassium channels (Simms and Zamponi 2014).

HVA channels also appear to have postsynaptic roles in neuronal firing and bursting, particularly R-type channels, which activate at relatively lower thresholds than other members of the HVA family and may contribute to afterdepolarization (Randall and Tsien 1997; Metz et al. 2005). More recently, postsynaptic roles for $\text{Ca}_v2.1$ channels in bidirectional cerebellar plasticity in cerebellar Purkinje cells have also been shown (Jorntell and Hansel 2006; Higley and Sabatini 2008), which may have some relevance to the development of ataxia in those individuals with mutations in the channel (see the section Dominant Mutations in $\text{Ca}_v2.1$ Cause Episodic Ataxia Type 2 and Epilepsy).

$\text{Ca}_v2.1$ (P/Q-TYPE) CHANNEL AND EPILEPSY

The $\text{Ca}_v2.1$ channel and, in particular, variations in the *CACNA1A* gene have long been implicated as a susceptibility factor in the pathogenesis of idiopathic generalized epilepsy. Physiologically, $\text{Ca}_v2.1$ oversees the spike-driven calcium influx that acts as a trigger for vesicular exocytosis. Thus, its role in neurotransmission at CNS synapses makes it ideally placed to influence neuronal excitability. There are several lines of evidence, albeit indirect, to support a role for *CACNA1A* and $\text{Ca}_v2.1$ in epilepsy. The most compelling argument is based on the observation that dysfunction of various subunits of the $\text{Ca}_v2.1$ channel complex in rodents results in an epileptic phenotype of absence seizures often associated with SWD on EEG recordings.

Animal Models of Absence Epilepsy

$\text{Ca}_v2.1$ -Type Knockout Mouse

Jun and colleagues (1999) generated α_{1A} knockout mice to examine the effects of ablation of the $\text{Ca}_v2.1$ channel. Whereas heterozygote ($\alpha_{1A}^{+/-}$) mice had a normal phenotype, the homozygotes were healthy until ~ 10 days after birth when they developed a severe progressive ataxia, dystonia, and absence seizures character-

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ized by 3–5-Hz SWDs. The older mice also showed selective degeneration of the anterior vermis. P-type current in Purkinje cells and P/Q-type currents from cerebellar granule cells were abolished; however, currents from other calcium channel subtypes were elicited, but underwent changes in expression. Furthermore, recordings from hippocampal slices obtained from $\alpha 1A^{-/-}$ homozygote mice showed up-regulation of N- and R-type-mediated synaptic transmission (Jun et al. 1999; Fletcher et al. 2001; Urbano et al. 2003; Song et al. 2004).

Absence Seizures in Recessive Mutations of *Ca_v2.1* in Rodents

Several strains of inbred mice have been found to harbor recessive mutations in the *CACNA1A* gene. These mice show a complex phenotype consisting of epilepsy, ataxia, and motor dysfunction of varying degrees (Pietrobon 2005).

A proline to leucine substitution in the S5–S6 of the second transmembrane domain (P601L) underlies the *tottering* (*tg/tg*) mouse phenotype consisting of ataxia and absence seizures. In addition, a 5–7-Hz spike and wave pattern is demonstrable on EEG recording (Green and Sidman 1962; Noebels and Sidman 1979; Fletcher et al. 1996; Lorenzon et al. 1998; Fletcher and Frankel 1999; Fureman et al. 2002; Miki et al. 2008). When expressed, the mutation reduced calcium current in Purkinje cells by ~40% when compared with wild-type (WT) channels (Wakamori et al. 1998) and impaired neurotransmission at excitatory synapses with an increased reliance of N-type channels (Caddick et al. 1999; Ayata et al. 2000; Qian and Noebels 2000; Matsushita et al. 2002).

The *leaner* mouse mutant (*tg^{la}/tg^{la}*) is caused by truncation of the normal open reading frame of *CACNA1A* and expression of an aberrant carboxy-terminal sequence and has a similar phenotype to that of the *tottering* mouse, including absence seizures with SWD, but its ataxia is more severe, reflected by the very striking degeneration of cerebellar granule and Purkinje cells found in these mice (Fletcher et al. 1996). The *leaner* mouse also shows a profound reduction in calcium currents in cerebel-

lar Purkinje neurons (Dove et al. 1998; Lorenzon et al. 1998).

Although the ataxic *rolling Nagoya* (*tg^{rol}/tg^{rol}*) mouse, which harbors the R1262G mutation in the S4 segment of repeat III, does not have absence seizures (Mori et al. 2000), the *rocker* phenotype (*tg^{rkr}/tg^{rkr}*), which arises from a similar missense mutation (T1310K) does show absence-like seizures with generalized 5–7-Hz SWDs (Zwingman et al. 2001). The *rolling Nagoya* mouse shows a reduction in neuronal calcium current at lower voltages and also a depolarizing shift in the channel activation.

More recently, the recessive *CACNA1A^{tg-4J}* (*tg-4J*) mouse has been described and it shows ataxia, paroxysmal dyskinesias, and absence seizures similar to the original tottering mouse. The resultant *Ca_v2.1* channel showed altered kinetics of activation with a 7-mV positive shift in the voltage dependence of activation consistent with a loss of function (Miki et al. 2008).

A spontaneous recessive mutation in *CACNA1A* was identified in the *groggy* (GRY), which shows absence seizures similar to the tottering mouse series, ataxia, and paroxysmal dyskinesia. The mutation, M251K, located close to the ion selective pore is associated with a small cerebellum and abnormalities of Purkinje cells (Tokuda et al. 2007).

Mutations in Auxiliary Subunits and Absence Seizures in Rodents

Mutations in genes that encode all three auxiliary subunits of HVA channels are associated with absence seizures with SWD in animal models. A truncating mutation in *CACNB4*, which effectively knocks out the *Ca_vβ4* subunit, results in the “lethargic” phenotype (Burgess et al. 1997) of absence seizures with SWDs (2–4 Hz), ataxia, hypomotor behavior, and dyskinesias (Hosford et al. 1995; Aizawa et al. 1997). A reduction in excitatory neurotransmitter release has been reported in these mutants (Burgess et al. 1997). The *ducky* (*du*) and *ducky-2J* (*du^{2J}*) mice harbor mutations in $\alpha 2\delta 2$ subunits and phenotypically show seizures, behavioral arrest, and ataxia (Meier 1968; Barclay et al. 2001; Brodbeck et al. 2002; Donato et al. 2006). A third strain,

the *entla* (*ent*) mouse arises from an exonic duplication, which disrupts the disulfide bridge and renders the $\alpha 2\delta 2$ subunit nonfunctional (Brill et al. 2004). All three murine strains show absence seizures associated with SWD and have reduced $\text{Ca}_v 2.1$ current densities. Mutations in the $\gamma 2$ subunit (stargazin) underlie both the *stargazer* and *wagglers* murine models of epilepsy, in which the mice show absence seizures with SWD and head-tossing behavior (Letts et al. 2003, 1998), which, in the case of the *wagglers* mice, is exacerbated further by knockout of the $\gamma 4$ subunit (Letts et al. 2005). However, in view of the known postsynaptic effects of the $\gamma 2$ subunit on AMPA receptors, it is possible that this, rather than a reduction in P/Q-type channel activity, may be the cause of the phenotype.

The $\text{Ca}_v 2.1$ Channel and Human Epilepsy

Dominant Mutations in $\text{Ca}_v 2.1$ Cause Episodic Ataxia Type 2 and Epilepsy

The *CACNA1A* gene encodes the $\alpha 1$ subunit of $\text{Ca}_v 2.1$. Its other designation, P/Q-type, refers to the neuronal cell types from which its constituent currents were isolated and arise from alternative splicing; “P” for Purkinje and “Q” for granule cells of the cerebellum. Mutations in the gene are associated with three allelic disorders: episodic ataxia type 2 (EA2), familial hemiplegic migraine type 1 (FHM1), and Spinocerebellar ataxia type 6 (SCA6) (Ophoff et al. 1996; Jodice et al. 1997; Zhuchenko et al. 1997; Rajakulendran et al. 2012).

EA2 is a dominantly inherited disorder characterized by paroxysmal disturbance of the cerebellar-brainstem circuitry manifesting as attacks of ataxia, vertigo, vomiting, and nystagmus (Jen et al. 2004, 2007). The prevalence of epilepsy (Rajakulendran et al. 2010) and EEG abnormalities (Neufeld et al. 1996) in individuals with clinical and genetically confirmed EA2 is higher than the background population, suggesting that genetic variations in *CACNA1A* may be a potential susceptibility factor in human epilepsy.

The publication of two papers brought this possibility into sharp focus; Jouvenceau and

colleagues reported the case of a boy with a complex phenotype comprising primary generalized epilepsy, episodic ataxia, and learning difficulties in whom a point mutation (R1820X) in *CACNA1A*, which gave rise to a premature stop codon, was identified. When expressed in *Xenopus* oocytes, the mutation caused substantial impairment of calcium channel function supporting pathogenicity (Jouvenceau et al. 2001).

A further mutation in *CACNA1A* was identified in a family, in which five affected members over three generations had a phenotype of cerebellar ataxia and absence epilepsy. The identified E147K mutation segregated with the disease phenotype in the family (Imbrici et al. 2004). Functional heterologous expression of the E147K copy DNA (cDNA) in *Xenopus* oocytes showed only a modest impairment of $\text{Ca}_v 2.1$ channel function in terms of current density and slowing of inactivation, which was in stark contrast to the R1820X mutant (Jouvenceau et al. 2001), which resulted in a non-functional channel, and to previous EA2 mutations, which have all generally resulted in a profound perturbation of $\text{Ca}_v 2.1$ channel function (Guida et al. 2001).

There have also been other reports of individuals with EA2 and epilepsy, in which mutations in *CACNA1A* have been identified (Jen et al. 2004; Kaunisto et al. 2004). Finally, several mutations in FHM1, a severe variant of migraine with aura associated with hemimotor/sensory disturbance, are also associated with epilepsy, which can occur both in the setting of an attack and also separate to it (Ducros et al. 2001; Beauvais et al. 2004; Kors et al. 2004; Zangaladze et al. 2010; Chan et al. 2008), although, generally, the association is markedly less than with EA2 in keeping with its underlying gain-of-function pathophysiology (van den Maagdenberg et al. 2004).

Taken together, loss-of-function mutations in $\text{Ca}_v 2.1$ can result in both ataxia and epilepsy in rodents and humans. The mechanisms underlying this susceptibility potentially include loss of excitatory neurotransmission into inhibitory neurons leading to increased neuronal firing, and compensatory up-regulation of T-type channels (see the section Animal Models of

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T-Type Dysfunction). However, certain considerations need to be borne in mind. First, the murine models harbor recessive mutations, whereas EA2 and epilepsy in humans is dominantly inherited. Second, whereas seizures are an invariable part of the rodent phenotype, the majority of humans with EA2 do not have epilepsy. Two explanations may account for this discrepancy: (1) a more profound loss of $\text{Ca}_v2.1$ function may be required for epilepsy, as seen in the animal models. (2) There may be species-specific differences in the roles of $\text{Ca}_v2.1$, its expression in the thalamus, and in the resulting compensatory changes when its function is perturbed.

$\text{Ca}_v2.1$ and Common Subtypes of Idiopathic Generalized Epilepsy (IGE)

The common idiopathic epilepsies show strong, albeit non-Mendelian heritability. Despite evidence from animal models and individuals in whom epilepsy cosegregates with EA2, attempts at dissecting the genetic architecture of IGE have failed to establish a causal role for variations in *CACNA1A* in common subtypes, such as childhood absence epilepsies (CAEs), juvenile absence epilepsies (JAEs), and juvenile myoclonic epilepsies (JMEs). Although small studies have suggested allelic associations (Chioza et al. 2001, 2002), the results have generally not withstood replication in larger studies, including genome-wide association studies (GWAS) (Sander et al. 1998, 2002; Cavalleri et al. 2007; Klassen et al. 2011). One reason for this could be the historical emphasis of the importance of common variants in epilepsy genetics. In contrast, the “common disease, rare variant” (CDRV) model proposes that a large part of the inherited susceptibility to complex traits, such as epilepsy, may be a result of the cumulative burden of low-frequency variants in multiple genes, which, in concert, increase the relative risk of disease.

Ca_v3 (T-TYPE) CHANNEL AND EPILEPSY

Animal Models of T-Type Dysfunction

In the GAERS (Genetic Absence Epilepsy Rats of Strasbourg) model, the rats show absence sei-

zures with 7–9-Hz SWDs. An R1584P missense change in *CACNA1H*, which encodes $\text{Ca}_v3.2$, was identified in the rats, which when expressed in the appropriate splice variant (+exon 25), induced a gain of T-type channel function, which increased with age mirroring of temporal profile of epilepsy development in animals. Additionally, an increased expression of $\text{Ca}_v3.2$ messenger RNA (mRNA) in reticular thalamic neurons with a consequent enhancement of T-type currents has also been shown.

In the WAG/Rij (Wistar Albino Glaxo Rats from Rijswijk) model of absence epilepsy, increased $\text{Ca}_v3.1$ and $\text{Ca}_v3.3$ currents were observed in thalamic neurons, together with predicted smaller depolarizations required to generate burst-firing in the same cell types (Coenen and Van Luijcklaar 2003; Broicher et al. 2008). Furthermore, pharmacological blocking of $\text{Ca}_v3.1$ in this model results in a reduction of seizure activity (Rimoli et al. 2009). One further point of interest is that altered expression of a specific splice isoform arising from a change in the same seizure-related domain as that found in the GAERS model has also been noted in WAG/Rij rats (Broicher et al. 2007a).

Further support for a role of $\text{Ca}_v3.1$ in seizure generation comes from transgenic mice models, in which overexpression of this channel type results in SWDs associated with behavioral arrest (Ernst et al. 2009). Conversely, $\text{Ca}_v3.1$ knockout mice show a lack of thalamic burst firing along with a resistance to Baclofen-induced absence seizures (Kim et al. 2001). In addition, seizures in $\text{Ca}_v2.1$ null mice and indeed other models, including *tottering*, *leaner*, and *stargazin*, can be abolished by introducing a further ablation of $\text{Ca}_v3.1$, which presumably negates the compensatory increase in T-type channels in these strains (Zhang et al. 2002; Song et al. 2004). Of further interest is the observation of increased thalamic T-type currents in *Coloboma* mice, which preceded the development of SWD and seizures. These mice are deficient in one copy of the gene that encodes the presynaptic protein SNAP-25, which interacts with HVA channels. Finally, in the pilocarpine and electrical kindling models of limbic epilepsy, augmented T-type currents are ob-

served in CA1 hippocampal neurons, along with increased burst-firing and neuronal death, findings that are attenuated in $\text{Ca}_v3.2$ knockout mice (Faas et al. 1996; Hendriksen et al. 1997; Su et al. 2002; Becker et al. 2008; Graef et al. 2009).

T-Type Calcium Channel Mutations and Human Epilepsy

In contrast to P/Q-channels, the evidence implicating variations in T-type channels to idiopathic generalized epilepsy is more robust. A total of 12 variants in *CACNA1H*, which encodes $\text{Ca}_v3.2$, were identified in individuals with CAE (Chen et al. 2003) of Han ethnicity from North China and not in normal controls. When expressed, 11 of the variants altered T-type channel gating and seven were predicted to increase neuronal firing (Vitko et al. 2005). In another study, two variants resulted in channel openings at more hyperpolarized potentials, implying a gain of function (Khosravani et al. 2004). When the phenotypic spectrum was extended to include JAE, JME, and temporal lobe epilepsies, more new variants in *CACNA1H* were identified in affected individuals. When expressed, several of these variants altered T-type channel properties that would be predicted to augment calcium current (Khosravani et al. 2005; Peloquin et al. 2006; Heron et al. 2007) and increase surface expression (Vitko et al. 2007). More recently, when the C456S variant was expressed in neurons, it increased neuronal firing, lowered the threshold for rebound burst firing, and induced changes in gene expression (Eckle et al. 2014).

However, quite a few *CACNA1H* variants do not appear to alter T-type channel function. Several explanations exist. The variants may just be single nucleotide polymorphisms (SNPs) and not pathogenic mutations; they may need to be present in specific splice isoforms to exert an effect akin to some P/Q-type channel mutations (Adams et al. 2009); they may only induce effects in vivo that cannot be ascertained with in vitro expression studies or may require or interact with additional proteins. Alternatively, the findings may simply reflect the prevailing view of the complex polygenic inheritance of epilep-

sy, in which variations in multiple genes each contribute a small effect to the overall phenotype (Gargus 2003; Vadlamudi et al. 2004; Bodmer and Bonilla 2008).

Variants in *CACNA1G*, which encode $\text{Ca}_v3.1$, have also been identified in Japanese and Hispanic individuals with IGE, particularly JME (Singh et al. 2007), although their effects on channel properties were not statistically different to WT channels. Further studies are needed to establish a causal role for this channel in IGE. One further note of interest is that all three Ca_v3 channels have also been linked to autism spectrum disorders (Splawski et al. 2006; Strom et al. 2010; Lu et al. 2012), in which the variants identified have induced a gain of T-type function, although how this leads to the resulting neurobehavioral phenotype is unclear.

Altogether, it would appear that genetic variation in genes encoding T-type channels, along with up-regulation of their expression in thalamocortical circuits, predisposes to seizure generation. Of particular interest are the findings of augmented T-type channel expression in focal and temporal lobe models of epilepsy, suggesting a far wider role for this channel subtype in epileptogenesis. Although some of the T-type channel variants identified in humans with absence seizures result in only a modest effect on channel biophysics, other factors, such as alterations in channel expression, trafficking, and distribution within neurons, may be contributory.

ANTIEPILEPTIC DRUGS AND CALCIUM CHANNELS

Several antiepileptic drugs (AEDs) in current use may target neuronal N-, P/Q-, and T-type calcium channels as part of their action. Ethosuximide, one of the mainstays of treatment for childhood absence seizures, reduces T-type currents with resulting reduction in thalamocortical oscillation (Coulter et al. 1989b,c; Huguenard and Prince 1994; Leresche et al. 1998; Broicher et al. 2007b), although whether this alone accounts for its antiepileptic effects is a matter of some debate (Crunelli and Leresche 2002; Richards et al. 2003). Zonisamide, in ad-

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dition, is effective in the treatment of generalized tonic-clonic seizures and cortical myoclonus, and also blocks T-type channels (Suzuki et al. 1992; Biton 2007; Matar et al. 2009). Lev-
etiracetam, an antiepileptic with broad-spectrum activity, binds to the presynaptic vesicle protein SV2A (Lynch et al. 2004) and may block HVA channels either directly or indirectly (Lukyanetz et al. 2002; Lee et al. 2009). Antiepileptics of the gabapentinoid family bind to $\alpha 2\delta$ subunits and may exert their actions by inhibiting their trafficking functions, resulting in a reduction of calcium current density at the cell membrane with a consequent loss of synaptic transmission (Gee et al. 1996; Marais et al. 2001; Sills 2006; Hendrich et al. 2008). Other AEDs, such as sodium valproate, topiramate, lamotrigine, and phenytoin, have also been shown to block calcium channels (Twombly et al. 1988; Kelly et al. 1990; Stefani et al. 1996; Hainsworth et al. 2003; Kuzmiski et al. 2005). However, two points need to be borne in mind. First, AEDs generally have potentially widespread effects and multiple sites of action and, hence, their apparent antiepileptic action may not necessarily be a function of calcium channel blockade. Second, studies of in vitro calcium channel antagonism by AEDs may not accurately reflect the in vivo scenario, in which the concentration of the drug necessary to induce a clinical effect is unknown, as are the brain areas, in which it produces its effect.

CONCLUDING REMARKS

Whereas mutations in the P/Q-type channel, albeit recessive, are strongly associated with an epileptic phenotype in mice, whether such variation contributes to IGE in humans is less clear. Although the story is more convincing for T-type channels and absence seizures, the extent and significance of involvement in the various subtypes of epilepsy, together with the mechanisms by which their seemingly increased expression results in seizure generation, needs further clarification. The roles, if any, played by other calcium channel subtypes in epileptogenesis await elucidation. $\text{Ca}_v2.3$ (R-type) channels in the thalamus have been implicated in

burst firing and potentially proictogenic “plateau potentials” (Randall and Tsien 1997; Metz et al. 2005; Zaman et al. 2011) with $\text{Ca}_v2.3$ null mice showing an altered susceptibility to absence seizures, as well as resistance to pharmacologically induced limbic seizures, convulsions, and excitotoxic cell death (Weiergraber et al. 2006, 2007, 2008), tantalizing data that require further study.

The most significant strides in epilepsy genetics have, so far, been made in the rare monogenic forms, in which a combination of linkage studies, fine mapping, and a candidate gene approach have identified mutations in ion channel genes as the cause of a number of rare Mendelian epilepsy syndromes (Gourfinkel-An et al. 2004; Kullmann 2010). In contrast, disentangling the various genetic strands that underpin the development of idiopathic generalized epilepsy has proved challenging in the postgenomic era. In part, this reflects the complex polygenic nature of this heterogeneous group of disorders, in which multiple genetic variations in appropriate splice isoforms interact when expressed in certain neurons and networks to influence seizure development. Shedding light on this complex interplay, aided in the future by knowledge of the high-resolution crystal structure of the α subunits, combined with accurate modelling studies of epileptogenic networks, will advance our understanding of the role played by calcium channels and is also fundamental to the development of targeted and rational therapy.

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