Voltage-Gated Calcium Channels and Idiopathic Generalized Epilepsies

HOUMAN KHOSRAVANI AND GERALD W. ZAMPONI

Department of Physiology and Biophysics, Hotchkiss Brain Institute, University of Calgary, Calgary, Canada

Khosravani, Houman, and Gerald W. Zamponi. Voltage-Gated Calcium Channels and Idiopathic Generalized Epilepsies. *Physiol Rev* 86: 941–966, 2006; doi:10.1152/physrev.00002.2006.—The idiopathic generalized epilepsies encompass a class of epileptic seizure types that exhibit a polygenic and heritable etiology. Advances in molecular biology and genetics have implicated defects in certain types of voltage-gated calcium channels and their ancillary subunits as important players in this form of epilepsy. Both T-type and P/Q-type channels appear to mediate important contributions to seizure genesis, modulation of network activity, and genetic seizure susceptibility. Here, we provide a comprehensive overview of the roles of these channels and associated subunits in normal and pathological brain activity within the context of idiopathic generalized epilepsy.

I. INTRODUCTION: IDIOPATHIC GENERALIZED EPILEPSIES

Epilepsy is a disorder of recurrent spontaneous seizures and is among the most common neurological conditions, accounting for 0.5% of the whole burden of diseases worldwide (164). One in 10 persons with a normal life span can expect to experience at least 1 seizure (83). Epileptic seizures are characterized as abnormal hyperexcitable, hypersynchronous neuronal population activity and manifest themselves in different ways depending on their site of origin and subsequent spread (85). The clinical diversity observed in epileptic seizure disorders is a reflection of the numerous cellular and network routes to seizure genesis. Seizures can originate in different brain structures that are responsible for motor, sensory, cognitive, and autonomic systems. The transition to seizure activity can be considered as a disruption of normal brain function. This transformation to pathological activity can be manifested by changes that occur at the level of single neurons (e.g., molecular alterations in ion channels, complements thereof, and regulatory proteins), local circuitry (e.g., alterations in cell-to-cell coupling via chemical and electrical synapses as well as ephaptic communication), or at the level of anatomically defined neuronal networks (e.g., structural changes and alteration between excitatory and inhibitory neuronal, interneuronal, and glial elements) (191). This notion is complicated by the fact that intrinsic neuronal properties can feedback to alter network dynamics, and vice versa. Moreover, activity at the network level can trigger alterations in gene expression that can affect the firing properties of individual neurons.

A. Classification of Seizures and Epilepsies

From a clinical perspective, seizures can be classified into two broad categories (107). Focal (or partial) seizures are localized to one hemisphere and involve only a

small brain region such as an area within the motor cortex that can result in motor seizures. Partial epileptic seizures may also arise from focal brain lesions caused, for example, by traumatic brain injury (116). However, it is now known that certain focal epilepsies can have a genetic origin (287). The second category comprises generalized seizures, which are characterized by virtually simultaneous onset of seizure activity over both brain hemispheres as seen using field potential recordings (Fig. 1). These generalized epileptic syndromes can further be classified as either symptomatic or idiopathic. Symptomatic generalized epilepsy is thought to be caused by identifiable factors such as anoxia and infection, which can result in widespread brain damage. In contrast, idiopathic generalized epilepsies have no clear etiology and may be at least partly caused by defects at the genetic level (20, 202). Data gathered from several cohort studies suggest that the frequency of idiopathic generalized epilepsies in the general epilepsy population is between 15 and 20% (reviewed in Ref. 130). As outlined above, although epileptic disorders span a continuum of conditions, we focus here predominantly on idiopathic generalized epilepsies to highlight recent developments implicating the involvement of voltage-gated calcium channels in this spectrum of epilepsy disorders.

Absence-type epilepsies account for 3–4% of all seizure disorders (63). As classified by the International League Against Epilepsy (ILAE) (3), typical absence seizures are a defining attribute of several of the idiopathic generalized epilepsies (Table 1). Seizure episodes are typified by a sudden impairment in consciousness, behav-

TABLE 1. *Clinical attributes of generalized idiopathic epilepsy*

Childhood absence epilepsy
  Absence seizures manifest between ages 4 and 8
  More common in females
  Respond well to antiepileptic drugs
Juvenile absence epilepsy
  Onset around puberty
  No sex predominance
  Atypical absence seizures
  Often have other seizure types (generalized tonic-clonic, myoclonic, and atonic seizures)
  Patients may be intellectually impaired
Juvenile myoclonic epilepsy
  Seizure onset between ages 8 and 18
  Have generalized tonic-clonic and myoclonic seizures
  Myoclonic seizures are characterized by sudden jerks of the neck, shoulders, and arms that may be repetitive without losing awareness
  Patients may exhibit photosensitivity
  Most common form of idiopathic generalized epilepsy
Generalized tonic-clonic seizures alone
  Seizures occur upon awakening
  Seizures can occur during sleep
  Time of seizure occurrence may not be linked to any external factors

Generalized seizures show bilateral and synchronous onset observed in electroencephalographic (EEG) recordings. Seizures in idiopathic generalized epilepsy are usually one of several types: generalized tonic-clonic, myoclonic, absence, or atypical absence. Idiopathic generalized epilepsy is a subtype of generalized epilepsy that has a genetic predisposition and includes the epileptic disorders (3) shown in the table.

ioral arrest, and may be accompanied by facial clonus or other subtle physical manifestations. These seizures are generally short in duration (lasting typically <10 s) and terminate suddenly without any postseizure alterations in
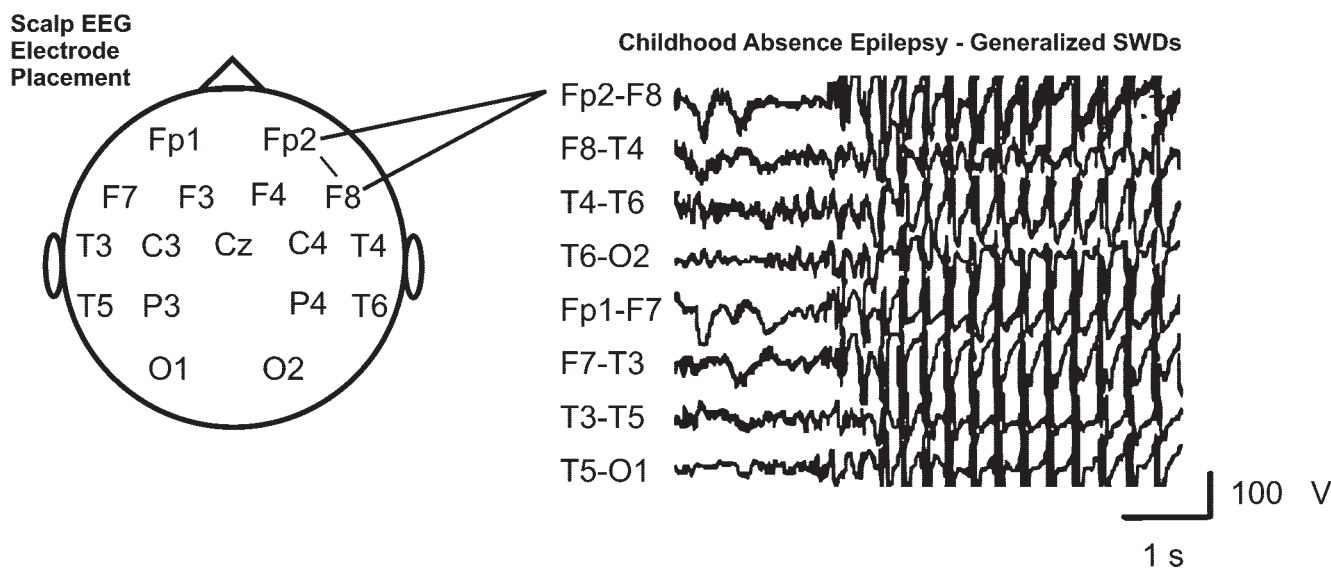
FIG. 1. Spike-wave discharges in human absence epilepsy. Typical 3- to 4-Hz spike-wave discharges observed over the entire brain, a hallmark of generalized epilepsy. Electroencephalographic (EEG) recordings are presented for a selection of electrodes placed over the scalp covering the entire head. Placement of EEG electrodes is depicted on a head model. Voltage tracings are presented in a bipolar manner with potentials, originally recorded in reference to a noninvolved electrode, represented as a subtraction from two neighboring electrodes to produce a single tracing. [Adapted from Yoshinaga et al. (312).]

behavior. The electrographic hallmark of absence seizures are spike-wave discharges (SWDs) that can be recorded using electroencephalography (EEG). These discharges typically arise synchronously over both brain hemispheres with a frequency of ~3–4 Hz and are maximal over frontal midline regions with minimal involvement of posterior brain regions (85, 122, 234). In generalized epilepsy, SWDs are principally mediated by interactions between thalamic and cortical networks (19) and are known to involve the activity of voltage-gated calcium channels. It must be noted that although absence seizures are always associated with SWDs, the converse is not true as SWDs are observed in other forms of epilepsy (85). This is a relevant point when considering subsequent discussion on models of spike-wave epilepsy.

B. Features of Idiopathic Generalized Epilepsy

Patients affected by idiopathic generalized epilepsy commonly present with their first seizure between the ages of 3 and 16 (107); however, adult onset has also been reported (187). Patients with idiopathic epilepsy syndromes exhibit no underlying structural or brain lesions when assayed by radiological imaging and are otherwise neurologically normal (84, 107). In the case where absence seizures are the predominant epileptic seizure type (84), childhood absence epilepsy and juvenile absence epilepsy encompass the two main idiopathic epilepsy subtypes. Patients with childhood absence epilepsy are typically neurologically normal. On the other hand, juvenile absence epilepsy patients often have intellectual impairment and they have atypical absence seizures, characterized by a longer duration, less abrupt onset, loss of postural tone, and often the co-occurrence of other seizure types (Table 1). Two other idiopathic generalized epilepsy seizure types, juvenile myoclonic epilepsy and idiopathic generalized epilepsy with tonic-clonic seizures alone (4) (Table 1), are recognized by the international classification (3). Specific diagnosis of different idiopathic generalized epilepsy types occurs best when both clinical and EEG data are available. It is interesting to note that generalized tonic-clonic seizures in idiopathic generalized epilepsy usually occur after awakening, particularly from a brief period of sleep when preceded by sleep deprivation. This relation is particularly clear in patients with juvenile myoclonic epilepsy and implicates the thalamocortical network, which is known to be involved in both sleep rhythm and SWD generation.

Of the absence-type idiopathic generalized epilepsy disorders, childhood absence epilepsy is perhaps the one that has been most extensively studied at the genetic level. Patients with childhood absence epilepsy can have a family history of epilepsy that is inherited in an autosomal dominant manner, with concordances of up to 85%

reported in monozygotic twins (15). However, genetic studies have also identified individuals with mutant genes who do not exhibit the epileptic phenotype (244). Moreover, the precise identification of gene loci is complicated by the presence of a large number of genetic polymorphisms in the childhood absence epilepsy population (241). Therefore, it is not entirely clear what the relative contributions of external or endogenous factors (such as involvement of multiple genes) are in bringing about the spectrum of epileptic seizure types observed in idiopathic generalized epilepsies. Nonetheless, there is substantial evidence implicating a genetic component in idiopathic generalized epilepsy, and in particular in absence-type seizure disorders (120). Genetic association studies have identified mutations in a number of different types of voltage- and ligand-gated ion channels, including GABA$_A$ receptors, as well as voltage-dependent sodium, potassium, and chloride channels, resulting in either a gain or loss of function (102, 201, 285) (see Table 2).

In the context of idiopathic epilepsies, the two brain structures that have received the most attention are the neocortex and the thalamus. The normal connectivity of these two brain structures differs at the level of neuronal/interneuronal cell types and at the level of network organization. Interactions between the thalamus and neocortex bring about synchronized oscillations that, under normal conditions, serve physiological roles such as the generation of sleep spindles, which occur in early stages of sleep (262). During spike-wave seizures, the normal function of this circuitry is somehow altered in a manner that results in the generation of SWDs. As such, voltage-gated calcium channels have increasingly emerged as important players in the generation of SWDs in both humans and in experimental models of epilepsy. In this article, we review the current state of knowledge concerning the role of these channels and their auxiliary subunits in idio-

TABLE 2. *Other voltage- and ligand-gated ion channel genes carrying mutations that have been linked to generalized epilepsies*

Gene	Channel/Subunit	Epilepsy Disorder	Reference Nos.
KCNA1	$K_v 1.1$	EA1	28, 319
KCNQ2	$K_v 7.2$	BFNC, myokymia	59
KCNQ3	$K_v 7.3$	BFNC	42, 252
CLCN2	CLC-2	CAE	113
SCN1A	$Na_v 1.1$	GEFS+, SMEI	50, 89
SCN2A	$Na_v 1.2$	GEFS+, BFNIS	117, 272
SCN1B	β_1	GEFS+	295
GABRA1	GABA$_A$ (α_1)	JME	53
GABRG2	GABA$_A$ (γ_2)	GEFS+, FS, CAE	12, 294
GABRD	GABA$_A$ (δ)	GEFS+	71

EA, episodic ataxia; BFNC, benign familial neonatal convulsions; CAE, childhood absence epilepsy; GEFS+, generalized epilepsy with febrile seizures plus; SMEI, severe myoclonic epilepsy of infancy; BFNIS, benign familial neonatal and infantile seizures; JME, juvenile myoclonic epilepsy; FS, febrile seizures.

pathic generalized epilepsy and related pathophysiologies. Specifically, we focus predominantly on T-type and P/Q-type channels because these are the major calcium channel subtypes that have been implicated in seizure disorders in both humans and animal models of epilepsy, in particular in the context of idiopathic generalized epilepsies.

II. MOLECULAR PHYSIOLOGY OF VOLTAGE-GATED CALCIUM CHANNELS AND ASSOCIATED ANCILLARY SUBUNITS

A. Subtypes and Physiological Roles of Voltage-Gated Calcium Channels

Voltage-gated calcium channels are key mediators of calcium entry into neurons in response to membrane depolarization. Calcium influx via these channels mediates a number of essential neuronal responses, such as the activation of calcium-dependent enzymes, gene expression (72, 93, 273), the release of neurotransmitters from presynaptic sites (247, 258, 302), and the regulation of neuronal excitability (217). The nervous system expresses a number of different calcium channels with unique cellular and subcellular distributions and specific physiological functions. They have been classified into two major categories (41): low voltage-activated (LVA) calcium channels (i.e., T-type channels) and high voltage-activated (HVA) channels, although this classification should not be applied rigidly, as some of the HVA channel subtypes can, under certain circumstances, be activated at relatively negative voltages (308). As outlined in greater detail below, LVA channels are activated by small depolarizations near typical neuronal resting membrane potentials and are key contributors to neuronal excitability. Their functional identification is aided by their sensitivities to blockers such as nickel ions (95, 161), mibefradil (190), and the scorpion venom-derived peptide kurtoxin (49, 250); however, the above blockers cannot be considered as truly selective for T-type channels. HVA channels require larger membrane depolarizations to open and can be further subdivided, based on pharmacological and biophysical characteristics, into L-, N-, R-, P-, and Q-types. L-type channels are slow to activate and inactivate with barium as the charge carrier and are defined by their sensitivities to dihydropyridine agonists and antagonists (95). They are typically found on cell bodies where they participate, among other functions, in the activation of calcium-dependent enzymes and in calcium-dependent gene transcription events (8, 72, 298). N-type channels produce inactivating currents that are selectively and potently inhibited by ω-conotoxins GVIA and MVIIA, two peptides isolated from fish-hunting marine snails (2, 91, 212, 230). P- and Q-type channels are identified by their

differential sensitivities to the American funnel web spider toxin ω-agatoxin IVA (2), and like N-type channels, they are concentrated at presynaptic nerve terminals where they are linked to the release of neurotransmitters (300, 301). In the context of neurotransmitter release, N-type and P/Q-type channels do not appear to be created equally, as N-type channels tend to support inhibitory neurotransmission, whereas the P/Q-type channels have more frequently been linked to the release of excitatory neurotransmitters but can also support inhibitory release (32, 33, 76, 163, 225). R-type channels were originally termed as such because of their resistance to the above blockers (229). These channels are rapidly inactivating and activate at somewhat more hyperpolarized potentials compared with the other HVA calcium channel subtypes (257). They can potently, albeit not totally selectively, be inhibited by SNX-482, a peptide toxin isolated from tarantula venom (23, 206). R-type channels are distributed in proximal dendrites and presynaptic nerve termini (288, 311, 316). Their precise physiological function remains enigmatic; however, there is evidence that these channels underlie carbachol-dependent plateau potentials in hippocampal CA1 neurons (152) and may mediate neurotransmitter release at select synapses (296).

B. Molecular Structure of Voltage-Gated Calcium Channels

HVA calcium channels are heteromultimers that are formed through association of α_1-, β-, α_2-δ-, and γ-subunits (Fig. 2). In contrast, LVA channels may contain only the α_1-subunit; however, this remains an area of controversy. While effects of ancillary subunit coexpression on T-type channel function have been reported in certain expression systems (75, 79, 121), antisense knockdown of calcium channel β-subunits in neurons does not appear to affect T-type channel function (155, 169). Moreover, a biochemical association between T-type channel α_1- and ancillary subunits has not been demonstrated (79).

The principal pore-forming subunit of both LVA and HVA calcium channels is the α_1-subunit, which contains the key structural moieties that are required for a functional calcium channel, and which is the sole determinant of the calcium channel subtype. To date, nine different types of neuronal calcium channel α_1-subunits have been identified and shown to fall into three major classes: Ca_v1, Ca_v2, and Ca_v3 (Fig. 2). The Ca_v1 family encodes different isoforms of L-type channels (149, 193, 197, 282, 304). Among the Ca_v2 family, alternate splice isoforms of $Ca_v2.1$ encode P- and Q-type channels (22), $Ca_v2.2$ represents N-type channels (80), and $Ca_v2.3$ corresponds to R-type channels (229, 257, 305) (for review, see Ref. 254). Finally, the Ca_v3 family represents three different types of T-type channels (i.e., $Ca_v3.1$, $Ca_v3.2$, and $Ca_v3.3$) with
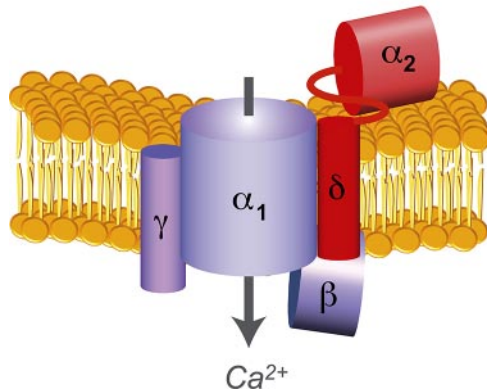
Ancillary subunits

$\beta_1, \beta_2, \beta_3, \beta_4$
γ_1 through γ_8
α_2-δ_1 through α_2-δ_4

Neuronal α_1 subunits

HVA
$Ca_v1.2$
$Ca_v1.3$ } L-type
$Ca_v1.4$

$Ca_v2.1$ P/Q-type
$Ca_v2.2$ N-type
$Ca_v2.3$ R-type

LVA
$Ca_v3.1$
$Ca_v3.2$ } T-type
$Ca_v3.3$

FIG. 2. Subunit assembly and subtypes of voltage-gated calcium channels. Graphic representation of the high voltage-activated calcium channel complex consisting of the main pore forming α_1-subunit plus ancillary, β-, γ-, and α_2-δ-subunits. Low voltage-activated calcium channels may consist of only the α_1-subunit (not separately shown). Different neuronal α_1-subunits correspond to different calcium channel isoforms identified in native neurons.

distinct kinetic properties (43, 56, 145, 160, 194, 198, 199, 216). These different types of calcium channel α_1-subunits support specific physiological functions, as evident from findings obtained from calcium channel knockout mice (Table 3), and by studying genetic abnormalities in calcium channels in disease states (for review, see Ref. 219).

C. Structural Basis of Calcium Channel Function

To provide a context for the effects of mutations in calcium channel genes that have been linked to the etiologies of neurological disorders such as epilepsy, we will briefly touch on the structural determinants of calcium

channel function. The α_1-subunits are comprised of four major transmembrane domains that are structurally homologous to those found in voltage-gated sodium and potassium channels (reviewed in Refs. 39, 40; see Fig. 2). Each domain consists of six transmembrane helices, with intracellularly localized NH_2 and $COOH$ termini. The fourth membrane-spanning α-helix (S4 segment) contains positively charged arginine and lysine residues every three to four amino acids. Mutagenesis and crystallization studies involving potassium channels have confirmed early suggestions that this region forms the voltage sensor (38), a structural element that translocates within the membrane in response to changing membrane potential

TABLE 3. *Phenotypic consequences of calcium channel α_1- and ancillary subunit knockout studies*

Channel Subunit	Phenotype	Reference Nos.
$Ca_v1.1$	Mice die at birth due to asphyxiation, due to lack of skeletal muscle contraction (including diaphragm).	270
$Ca_v1.2$	Phenotype is lethal, mice die around *day 12* postcoitum, isolated myocytes spontaneously beat until *day 14* postcoitum.	248
$Ca_v1.3$	Mice are deaf due to loss of cochlear synaptic transmission and also exhibit cardiac arrhythmias.	223
$Ca_v1.4$	Mice are blind due to loss of rod vision.	185
$Ca_v2.1$	Mice show ataxia and absence seizures and die ~4 wk after birth.	135, 256
$Ca_v2.2$	Mice are hyposensitive to neuropathic and inflammatory pain, show reduced levels of anxiety, and show altered state of vigilance and reduced ethanol consumption.	16, 112, 128, 142, 207, 239
$Ca_v2.3$	Mice exhibit altered sensitivity to pain.	240
$Ca_v3.1$	The phenotype is behaviorally normal, mice are resistant to certain types of seizures including other genetic models of absence seizures and can rescue the epileptic phenotype of $Ca_v2.1$ mice. They also exhibit altered sleep structure. These mice may experience hyperperception of visceral pain.	143, 144, 256
$Ca_v3.2$	Mice are unusually small and show developmental deformities (i.e., trachea). Also, relaxation of vascular smooth muscle is impaired giving rise to deficient control of blood pressure.	44
β_1	Mice die at birth due to lack of skeletal muscle contraction.	106, 270
β_2	Embryonic lethal.	9
β_3	Mice appear visibly normal.	58, 205
β_4	De facto knockout due to premature stop; mice show absence seizures and ataxia.	31
α_2-δ_2	De facto knockout due to premature stop; mice have absence seizures.	26
γ_1	Mice appear normal.	96
γ_2	De facto knockout due to premature stop; mice have absence seizures and other features such as ataxic gait, paroxysmal dyskinesia.	166

(77, 132, 176) and mediates channel opening. The reentrant P-loops between S5 and S6 segments are believed to line the pore of the channel to allow for the passage of permeant ions. The P-loops each contain a critical glutamic acid residue (4 in total) that together form a ring of negative charge and allow for selectivity of divalent cations over monovalent ions (82, 307, 309). However, other amino acid residues in the outer vestibule of the pore are likely to contribute to ion permeation and selectivity (92, 242). The α_1-subunits also contain the key structural elements that allow the channel to inactivate upon prolonged membrane depolarization. Voltage-dependent inactivation, a key feature that regulates availability of a calcium channel to open, is thought to involve a physical occlusion of the channel pore by a cytoplasmic gating particle. This inactivation gate appears to be formed at least in part by the cytoplasmic domain I-II linker region. However, other regions of the channel, in particular the S6 helices, are also important (reviewed in Ref. 267), perhaps by forming a docking site for the inactivation gate (268). The COOH terminus region of the α_1-subunit contains the key loci responsible for calcium-dependent inactivation, a process that is observed only when calcium is used as the charge carrier. Originally thought to occur only with L-type channels, more recent evidence indicates that all types of high voltage-activated channels are subject to this type of regulation by calcium ions. Mechanistically, this process involves a dynamic interaction of the calcium binding protein calmodulin with the COOH-terminal region of the α_1-subunit (158, 170, 218, 320).

The cytoplasmic linker regions of various types of calcium channel α_1-subunits form key interaction sites for regulatory proteins and may be substrates for phosphorylation events. For example, the I-II linker regions of $Ca_v2.1$ and $Ca_v2.2$ subunits interact with G protein $\beta\gamma$-subunits (for review see Refs. 70, 74, 315); the II-III linker regions of these two channels interact with a number of synaptic proteins (for review, see Refs. 40, 259). The domain II-III linker region of $Ca_v3.2$ interacts with $G\beta_2$-subunits (306) and is a substrate for calmodulin-dependent protein kinase phosphorylation (299). These are but a few examples, as the list of calcium channel interacting proteins is too extensive to comprehensively review here. Nonetheless, in the context of epilepsy-associated genetic mutations, it is important to consider that their physiological effects may manifest themselves by interfering with calcium channel regulatory mechanisms, without necessarily causing alterations in the biophysical properties of the channels per se.

D. Ancillary Subunits of Calcium Channels

While calcium channel α_1-subunit is sufficient to form functional channels, the association of HVA channel α_1-subunits with ancillary β- (73), α_2-δ- (5, 35, 147), and γ-subunits (18) is known to result in altered functional properties and/or increased plasma membrane expression.

The α_2-δ-subunit is translated as a single gene product, and then posttranslationally cleaved into a membrane-spanning δ-peptide (27 kDa) and extracellular α_2-peptide (143 kDa) (60), which are subsequently relinked via disulfide bonds. Expression studies have shown that the α_2-δ-protein alters current kinetics and current densities when coexpressed with HVA α_1-subunits, although to different degrees with different channels (147, 310). The α_2-δ-subunit is the only known calcium channel ancillary subunit to interact with a clinically active drug compound, in that its association with gabapentin mediates analgesia (251). To date, four genes encoding for different α_2-δ-proteins (α_2-δ_1, α_2-δ_2, α_2-δ_3, α_2-δ_4) have been identified, with several potential additional splice variants (146).

Four different types of β-subunits (β_1 through β_4), along with various splice variants (reviewed in Refs. 73, 232), have been identified and characterized. Unlike α_2-δ proteins, β-subunits appear to be exclusively cytosolic in nature, with the exception of β_{2a}, which can become palmitoylated and thus membrane anchored (90, 228). The β-subunit core resembles membrane-associated guanylate kinase homologs with conserved interacting SH3 and guanylate kinase (GK) domains (275). Residues in the GK domain participate in the formation of a hydrophobic groove that is involved in the high-affinity binding to a conserved region within the domain I-II linker region of HVA calcium channels, termed alpha interaction domain (AID) (47, 291). Recently published crystal structure data have revealed that binding of the β-subunit to the channel is critically dependent on a functional association of the SH3 and GK regions (47, 213, 291), which is stabilized by the beta interaction domain, a short amino acid stretch that was originally thought to directly interact with the calcium channel AID region (291). The functional consequences of β-subunit coexpression include increased plasma membrane expression of the α_1-subunit (17, 48, 226) as well as altered channel kinetics (90, 310) (reviewed in Ref. 5). Consistent with an important role in calcium channel function, knockout of individual β-subunit genes results in severe physiological consequences (see Table 3).

Eight different types of γ-subunits have been identified (γ_1 through γ_8) (5). The γ-subunits are comprised of four transmembrane domains with intracellular NH_2 and COOH termini (Fig. 2), but the mutual sites of interaction with the α_1-subunit remain unknown. While it has been observed that some of the γ-subunits have the propensity to alter the functional characteristics of HVA calcium channels (238) (reviewed in Ref. 18), the precise action of these subunits on HVA calcium channels remains to be

completely understood, and there is evidence that these subunits can interact with other membrane proteins such as AMPA receptors (45).

Considering the important roles of these subunits in regulating calcium channel function, one may perhaps expect that naturally occurring mutations in calcium channel subunit genes may have the propensity to alter normal physiological responses in animals and humans. As we will outline below, this does indeed occur within the context of idiopathic generalized epilepsies.

III. VOLTAGE-GATED CALCIUM CHANNELS AND ANCILLARY SUBUNITS IN IDIOPATHIC GENERALIZED EPILEPSY

A. T-Type Calcium Channels and Spike-Wave Seizures

1. T-type channel physiology

T-type channels mediate a spectrum of physiological roles including pacemaker activity and various forms of physiological and pathophysiological neuronal oscillations (99, 217). Moreover, it was recently demonstrated that T-type channel activity can result in calcium-induced calcium release in neurons of the paraventricular nucleus of the thalamus and other midline neurons associated with the thalamocortical system (233). [Note that calcium-induced calcium release is known to occur in thalamocortical neurons but it does not involve the action of T-type channels (29).] This novel role for T-type channels in the thalamocortical system putatively lends itself to numerous calcium-dependent signaling pathways that extend the role of these channels beyond their biophysical attributes and into complex processes such as synaptic plasticity (237).

T-type channels display several unique biophysical features compared with HVA channels. They activate and inactivate near the resting membrane potential of neurons (approximately -60 mV), display more rapid inactivation kinetics, and deactivate more slowly to produce pronounced tail currents (30). There is also an increased overlap in the voltage dependences of activation and inactivation, which gives rise to a phenomenon termed the "window current." At membrane voltages where the window current is operational, a small fraction of T-type channels never fully inactivates and can be rapidly recruited for calcium influx upon depolarization. Interactions between the window current and the K^+ leak current in thalamic (reticular and thalamocortical) and possibly cortical neurons can result in membrane bistability (57). This T-type-mediated potential can interact with other active currents (e.g., I_h) to modulate neuronal output between nonoscillatory and oscillatory modes that

have different physiological correlates such as the slow (<1 Hz) sleep rhythm (57, 124). In response to a membrane hyperpolarization, a large fraction of T-type channels is recovered from the inactivated state, thus priming them for opening events. The ensuing calcium entry is thought to mediate a low-threshold calcium potential, a transient membrane depolarization that is sufficiently large to trigger a succession of sodium spikes (62, 157, 188, 245, 314). This feature is commonly referred to as "rebound bursting" and has been shown to occur in various neuronal subtypes including thalamocortical relay neurons, thalamic reticular neurons (54, 69, 126, 174), and a subpopulation of neocortical cells (61).

2. T-type calcium channel distribution

It is important to note that the precise biophysical characteristics of T-type calcium channels in relation to their physiological roles vary with Ca_v3 channel subtype and can be dramatically affected by alternate splicing of a given T-type channel gene (203). Their unique gating kinetics in addition to their specific regional distribution allows for these channels to be used by different neuronal subtypes to generate a variety of network dynamics. The exact distribution and protein expression levels of T-type calcium channels in the brain are not well understood, with most of the current knowledge having been derived from in situ hybridization studies in rat brain slices (55, 138, 276). Although T-type channel mRNA has been detected across all brain regions including the cerebellum, we focus predominantly on the major brain structures thought to be involved in spike-wave seizures, i.e., the thalamus and neocortex. All three T-type isoforms are expressed at relatively high levels in the hippocampus (276), with $Ca_v3.1$ being the dominantly expressed subtype in thalamocortical neurons (276). In contrast, $Ca_v3.2$ and $Ca_v3.3$ appear to be expressed more prominently in the thalamic reticular nucleus (276). Cells in this nucleus are primarily GABAergic interneurons that play a key role in synchronizing thalamic outputs onto thalamocortical neurons that then project to the cortex (262). Diffuse mRNA levels have been detected for $Ca_v3.1$ and $Ca_v3.3$ in most cortical areas (276). Transcript levels of $Ca_v3.2$ in the cortex typically occur at lower levels, except in layer V cortical pyramidal neurons (276). It should be noted, however, that it is not clear whether presence of mRNA correlates well with protein expression levels in the plasma membrane, and what particular splice isoform of the channel may be present (105).

In most types of neurons, the specific subcellular distribution of T-type channels has not yet been identified by immunocytochemical means. However, concordant evidence from numerous electrophysiological and functional imaging studies suggests that they are located both on and near the soma (136), and generally at more distal

dendritic sites (129, 137, 139, 182, 188, 200). Moreover, a recent study using electrophysiological and pharmacological investigation of reticular cells in thalamic brain slices indicates the presence of a slowly inactivating T-type current in the dendrites and a fast inactivating current at the soma (133). Pharmacological manipulations have suggested that the fast inactivating current is likely to be carried by $Ca_v3.2$ channels, whereas the slow T-type current may be mediated by $Ca_v3.3$ channels. These results are supported by data from in situ hybridization studies for reticular neurons where mRNA expression of both isoforms has been detected (276). The subcellular distribution (e.g., soma vs. dendrites) is likely subject to further heterogeneity when considering the different T-type channel isoforms, splice variants, and developmental changes in the lifetime of the organism. For example, previous reports in reticular thalamic neurons have reported differences in the rates of inactivation of T-type currents in intact slices (66) (slow) compared with acutely dissociated neurons (126) (fast).

3. T-type channels and the thalamocortical network

The thalamocortical circuit is the primary link between peripheral sensory systems and the cerebral cortex. This circuitry is also one of the most studied in the context of neurophysiological rhythm generation and encompasses structures responsible for the regulation of brain states such as arousal and slow-wave sleep, a hallmark thalamocortical oscillation (263). From a simplistic anatomical perspective, this circuit consists of a network of reticular, thalamocortical (also referred to as relay), and neocortical neurons. Cortical neurons directly innervate reticular and thalamocortical neurons, whereas the reticular neurons provide GABAergic projections onto each other and onto thalamocortical neurons, which in turn synapse onto neocortical neurons (Fig. 3). Indeed, although the thalamus receives many sensory inputs, the primary source of excitatory synapses onto it comes from the cortex (86, 87, 172, 173), which exemplifies the influence of neocortical activity on thalamic information processing. Both neocortical and thalamocortical cells have excitatory projections back onto reticular neurons, and the activity of the circuit is further regulated via thalamic (local circuit) and neocortical interneurons (189, 249). The intraconnectivity between reticular neurons is believed to be a form of lateral inhibition (286) and central to the role of this local network in modulating overall thalamic outputs to cortical areas during both physiological and seizure activity (100, 255).

Thalamic neuronal firing can be broadly categorized into tonic-mode and burst-mode firing. The later involves the action of T-type calcium channels in the thalamocortical circuitry and is highlighted by their contribution to the propagation of thalamically generated spindles to the neocortex. Bursting in reticular neurons is mediated by low-threshold calcium potentials (126) in response to corticofugal volleys from neocorticofugal inputs (52). The bursts are preceded by prolonged hyperpolarizing potentials (263) that are triggered by the activity of G protein-coupled inward rectifier potassium channels (101) and lead to the activation of T-type currents in dendrites of reticular neurons (126). Modeling studies have demonstrated a sensitive link between the compartmental distribution of T-type conductances and the ability of thalamocortical and, more so, reticular neurons to fire in burst mode (69). Specifically, for a fixed burst threshold in a model of reticular neurons, GABAergic conductances are required to be relatively larger if the T-type current is localized to the soma versus dendrites.

The low-threshold calcium potential-induced bursts of action potentials occur in a subpopulation of reticular neurons and are manifested as tonic firing with burstlike modulation due to membrane bistability (100). The GABAergic activity of reticular neurons (involving both $GABA_A$ and $GABA_B$) results in hyperpolarization and subsequent low-threshold calcium potential-mediated rebound bursting in thalamocortical neurons, which faithfully track the bursts in the reticular network and manifest themselves as sleep spindles (263). There is some evidence from in vivo studies that burst-mode firing in thalamic neurons can occur during wakefulness (109, 110); however, this is not a common occurrence, and this interpretation may be complicated by an intermediate state of brain activity such as drowsiness (264).

Absence-type seizures occur preferentially during drowsiness or slow-wave sleep, which highlights the involvement of common synchronizing elements (such as the reticular network) underlying certain sleep and seizure states. However, unlike the state when sleep spindles are generated (101), the presence and interaction with the cortex is critical for the generation of SWDs (266). During cortically generated SWDs the GABAergic reticular neurons faithfully follow the cortical bursting activity and are synchronized with the activity recorded in the cortex (Fig. 4). In contrast, thalamocortical neurons undergo a sustained hyperpolarization in response to phasic inhibitory postsynaptic potentials (IPSPs), which are however incapable of recovering a sufficiently large fraction of T-type channels. Consequently, thalamocortical neurons do not exhibit rebound bursts during the epoch when SWDs are observed in the cortex (265) (Fig. 4). Reticular neurons are thus driven by the activity in the cortex, which leads to the inhibition of thalamocortical neurons, and prevents the feedback to cortical areas. Therefore, in one possible scenario, increased T-type channel (i.e., $Ca_v3.2$ and $Ca_v3.3$) activity could result in increased burst-mode firing in thalamic reticular neurons. The persistent activity of reticular neurons during SWDs causes increased membrane conductance in thalamocortical neurons in the form of steady inhibition, which may perhaps explain the
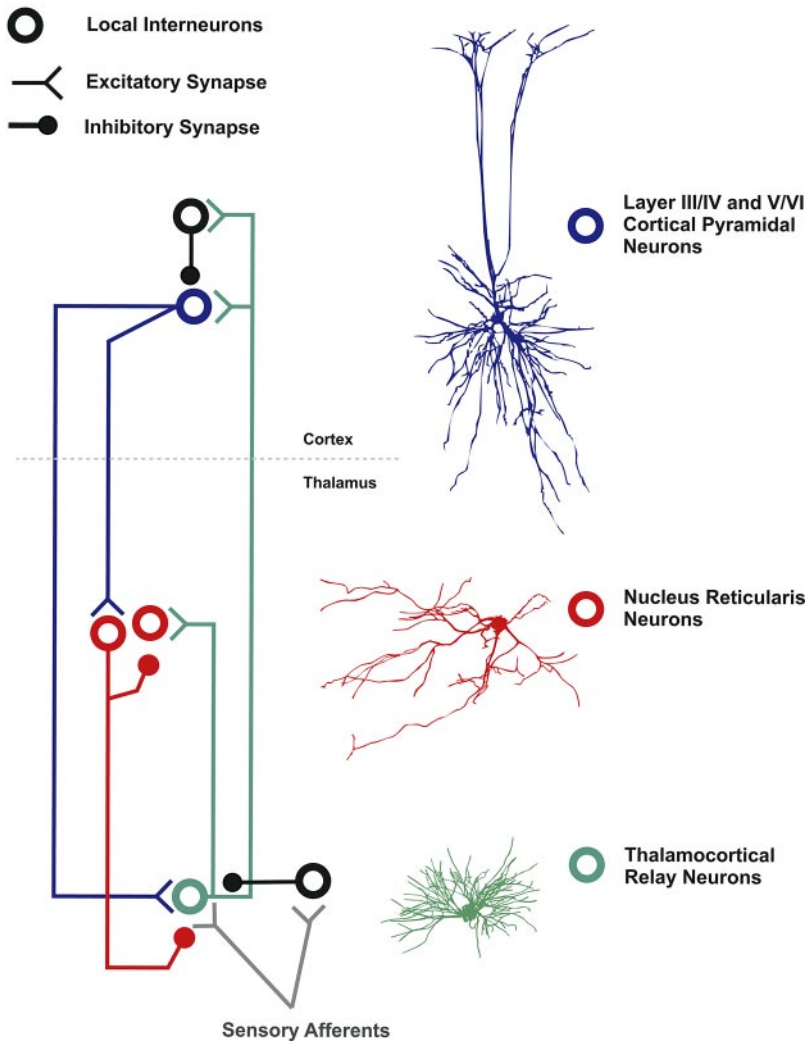
Thalamocortical Circuit

FIG. 3. The simplified thalamocortical circuit involved in the generation of spike-wave discharges. *Left*: neuronal circuitry implicated in the generation of spike-wave seizures. For simplicity, local-circuit interneurons in the thalamus and cortex are not illustrated. Neurons are indicated in the form of color-coded circles that correspond to neuronal phenotypes obtained from staining experiments in cats that were used in modeling studies (51, 66, 67). Thalamic relay neurons (green) receive sensory inputs and project onto cortical pyramidal neurons in layers III/IV and V/VI in the cerebral cortex (blue). Sensory inputs can also project onto thalamic inhibitory interneurons (black, thalamus) that can in turn modulate the firing of relay neurons. Thalamocortical relay neurons can also synapse onto cortical inhibitory interneurons (black, cortex). Corticothalamic projections from layer VI of the cortex can reciprocally synapse onto relay neurons in addition to neurons in the thalamic reticular nucleus (red). The GABAergic reticular neurons are highly interconnected both via chemical and electrical synapses and form a pacemaker subcircuit within the thalamus. Both reticular and relay neurons express T-type calcium channels and can exhibit rebound bursts.

unconsciousness during absence seizures caused by inhibition of synaptic transmission of signals from the outside world (263). It should be noted that there are a large number of modeling studies in which underlying ionic currents and network dynamics are explored in the context of both physiological and epileptiform thalamocortical oscillations. Although review of these works is beyond the scope of this manuscript, a concise review by Destexhe and Sejnowski (68) is available.

The rhythmic activity that is observed in EEG recordings during an epileptic seizure is a reflection of cortical and thalamic network interactions. In a number of rodent models of epilepsy, the frequencies of SWDs are typically faster than the 3–4 Hz observed with the common form of human absence seizures, which may hint at interspecies differences in these network interactions, or perhaps somewhat different pathways for seizure generation. Indeed, the frequency of SWDs in these rodent models is complicated by the notion that some of the observed thalamocortical oscillations may be part of normal physiological activity (221, 303). Historically, there has been much debate with regard to the site of initiation for SWD-based seizures (reviewed in Refs. 195, 263); specifically, the question pertaining to which structure, cortex versus thalamus, is the key anatomical substrate for initiating SWDs. Initial evidence for the involvement of both structures came from human studies undergoing invasive intracranial EEG monitoring (reviewed in Ref. 21), which is now deemed unethical for generalized forms of epilepsy due to a consensus that large networks in the brain are involved. However, a body of evidence from in vivo experiments in rats and cats suggests that the cortex may be the minimal substrate for generating spike-wave seizures (reviewed in Ref. 263). Moreover, recent studies utilizing multisite recordings in two accepted rat genetic models of absence epilepsy, the Genetic Absence Epilepsy Rat from
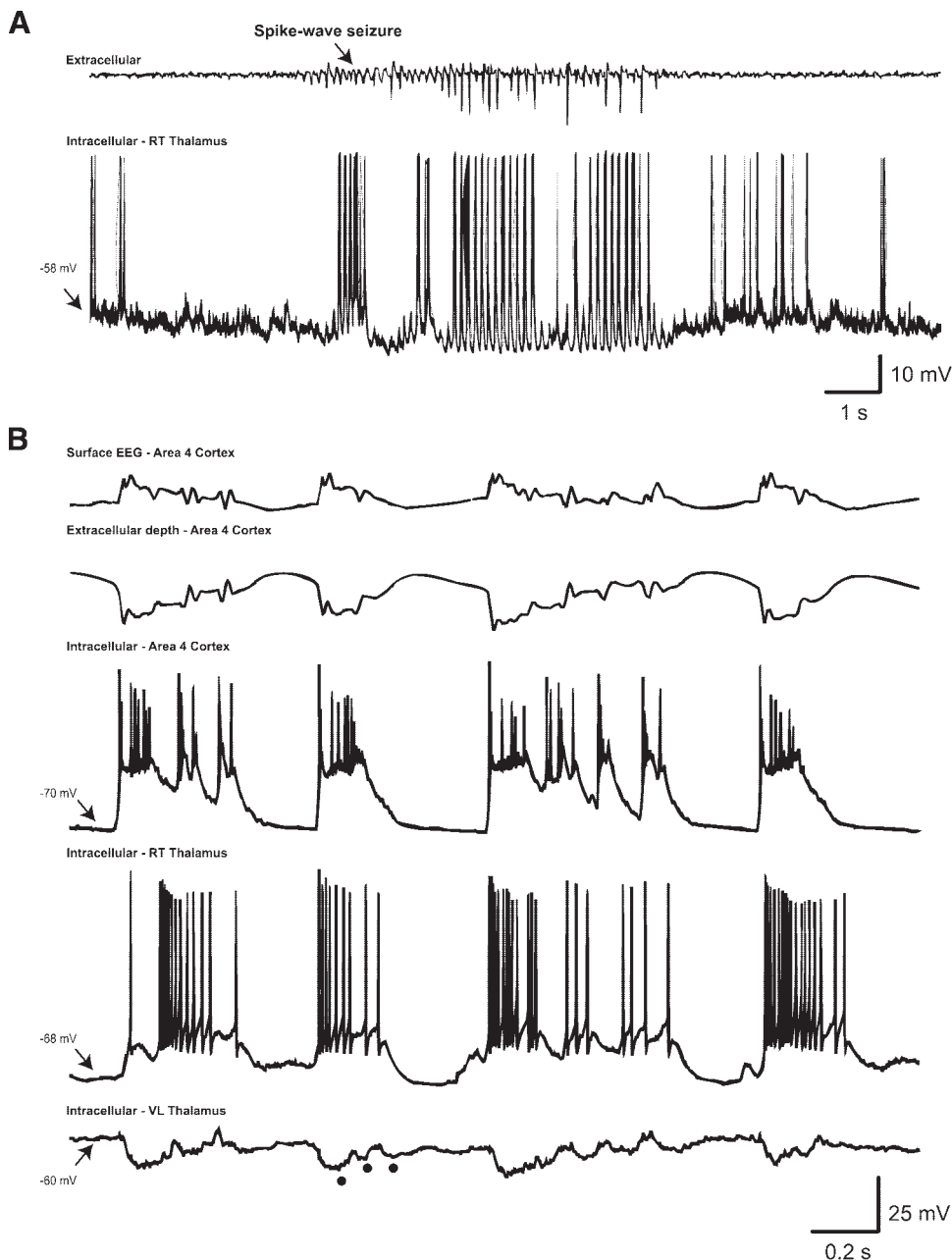
FIG. 4. Firing patterns of thalamic and cortical elements in animal models of spike-wave seizures. *A*: simultaneous extracellular and intracellular recording of absence seizure activity in an adult genetic absence epilepsy rat from Strasbourg (GAERS). The intracellular recording is from a thalamic reticular neuron, which exhibits bursting activity in synchrony with spike-wave discharges recorded extracellularly. [Adapted from Slaght et al. (253).] *B*: simultaneous electroencephaolographic (EEG), extracellular field, and intracellular recordings of cortical and thalamic neurons during an epoch of spontaneous polyspike-wave seizure activity in a cat under ketamine-xylazine anesthesia. Cortical and thalamocortical (in the ventrolateral nucleus, VL) recordings were obtained simultaneously, and reticular neurons were recorded later and superimposed due to the repeatability of the oscillation. Cortical neurons exhibit bursting during each of the paroxysmal depolarizing shifts (191). This activity is closely tracked by reticular neurons that exhibit T-type mediated bursting activity. The GABAergic influence of reticular neurons on thalamocortical cells can be seen by the series of inhibitory postsynptic potentials (see dots), which result in tonic hyperpolarization of these neurons for the duration of the spike-wave activity. Similar observations have been reported during spike-wave seizures in the GAERS rat (222). Whether thalamocortical neurons exhibit rebound spikes is a function of their membrane potential caused by inputs from reticular and cortical neurons. A large fraction of these cells, however, cannot fire, which is believed to result in disruption of information flow to the cortex resulting in the absence phenotype during seizures. [Adapted from Steriade (263) and Steriade and Contreras (265).]

Strasbourg (GAERS) and the Wistar Albino Glaxo rats, bred in Rijswijk (WAG/Rij), have suggested that neocortical cell firing temporally precedes (on the order of milliseconds) the activity in the thalamus (195, 221). Taken together, these studies imply that complex interactions involving the entire thalamocortical network are necessary in generating rhythmic activity under both physiological and pathophysiological states, with T-type channels playing a key role in modulating the firing properties of neuronal elements.

3. Genetic animal models

Animal studies have provided insights as to whether T-type expression is altered via epileptic activity, or whether increased T-type expression is a requirement for the development of seizure activity. For example, the GAERS rat exhibits 7- to 11-Hz SWDs, usually after 30 days of life. In this rat model of absence epilepsy, an increase in T-type currents in reticular neurons has been reported after the second postnatal week (284). This increase in T-type currents is putatively mediated by elevated $Ca_v3.2$ expression in reticular neurons, which as the animal develops to exhibit absencelike seizures, is also accompanied by elevated expression of $Ca_v3.1$ in relay neurons (277). This suggests that an increase in T-type channel expression can precede the development of seizures, perhaps by altering network dynamics via mecha-

nisms that affect potentiation. In support of this notion, a modeling study employing a strictly thalamic network has demonstrated differential effects on network activity in response to an augmented T-type conductance in reticular neurons (279). Although rebound spiking number in individual reticular neurons was relatively unchanged, the increase in T-type conductance resulted in increased network synchrony by introducing a phase-lag between reticular and thalamocortical firing. It should be noted that a similar effect on synchrony was observed for increased calcium-activated potassium conductance in the model. Nonetheless, a degree of caution is warranted when attempting to interpret these results in relation to in vivo recordings that take place in the context of larger and more complexly connected networks. Presently, a precise causal connection between increased T-type channel activity and subsequent development of seizures remains to be established. It is conceivable that developmental causes involving either modulation of the channels, their redistribution with other isoforms, and alternate splicing may be contributing factors. Indeed, such developmental effects occur in the heart where $Ca_v3.1$ and $Ca_v3.2$ undergo differential developmental expression (208). Such alterations resulting in an epileptic phenotype represent gradual neurophysiological changes over time. In converse to these more slowly developing processes of epileptogenesis, it has been shown that even a single episode of status epilepticus in rat hippocampal brain slices can result in a selective increase in T-type channel activity, indicating that epileptic seizures per se may have the propensity to rapidly alter T-type currents (271), thus potentially lowering the threshold for subsequent seizure events.

Recent in vivo studies involving T-type ($Ca_v3.1$) knock-out (KO) mice have provided additional insights into the role of T-type channels in the generation of SWDs and absencelike seizure episodes (144). Ablation of the $Ca_v3.1$ gene in mice abolishes rebound spiking in dissociated adult thalamocortical neurons but does not alter their ability to fire tonically. Deep thalamic recordings from $Ca_v3.1$ KO mice also revealed a lack of synchronized activity. In vivo recordings from the cortical surface in these mice demonstrated a resistance to baclofen-induced 3- to 5-Hz SWDs that could be induced in control animals. This resistance could be due to a loss of rebound bursting in thalamocortical neurons, which are known to express high levels of $Ca_v3.1$ channels and to receive strong GABAergic inputs. Intriguingly, these mice are not resistant to SWDs induced by bicuculline, and tonic-clonic seizures were inducible in both KO and control animals with 4-aminopyridine injection. A possible explanation of why these mice experience bicuculline-induced seizures may be due to cortical involvement. Indeed, previous work has shown that the isolated cortex is able to generate bicuculline-induced SWDs, suggesting that the cortex can act as the seizure-generating zone (266). An alternative explanation for lack of protection against seizures in some models versus others may involve the reticular neurons that are known to predominantly express $Ca_v3.2$ and $Ca_v3.3$ T-type channels rather than $Ca_v3.1$. Therefore, it is conceivable that other T-type calcium channel isoforms (for example, $Ca_v3.2$) may be involved in the generation of hypersynchronous activity in some models of epilepsy without requiring the action of $Ca_v3.1$ channels in thalamocortical neurons. The findings obtained with $Ca_v3.1$ KO mice also indicate that full-blown convulsive seizures may recruit different mechanistic pathways. Moreover, consistent with the functional link between T-types and intrathalamic rhythm generation, $Ca_v3.1$ KO mice show altered sleep architecture, with markedly diminished thalamic delta (1–4 Hz) waves and sleep spindles (7–14 Hz) (159). Intriguingly, the slow (<1 Hz) rhythms that can be sustained by the cortex remained relatively intact in KO animals.

More recently, it has been demonstrated that $Ca_v3.1$ KO rescues the epileptic phenotypes seen in a number of murine models of absence seizures, including $Ca_v2.1$ knockout mice, which (as we discuss in detail in sect. IIIB1) display severe absence seizures (256). Thalamocortical neurons isolated from $Ca_v2.1$ KO mice were shown to exhibit an ~50% increase in T-type currents (predominantly due to $Ca_v3.1$). In contrast, $Ca_v2.1^{-/-}/Ca_v3.1^{+/-}$ mice exhibited a 25% reduction in T-type currents, yet they continued to exhibit SWDs with no changes in seizure frequency or duration. Thalamic mRNA transcript levels for $Ca_v3.1$ were not different between $Ca_v2.1^{+/+}$ and $Ca_v2.1^{-/-}$ mice. These findings suggest that, under certain conditions, even reduced levels of T-type channel activity are capable of sustaining SWDs. Overall, these results indicate that complete KO of $Ca_v3.1$ channels can play a protective role against SWDs in these genetic models of absence epilepsy, as well as in a subset of pharmacological seizure models (Fig. 5).

4. T-type channel mutations in epileptic patients

Ion channel defects are considered to be one of the primary etiological causes of idiopathic generalized epilepsy (244). T-type channels have always been likely candidates due to their eminent presence in cortical and thalamic structures and their established physiological role in modulating neuronal firing. Moreover, clinically active antiepileptic drugs have been associated with T-type calcium channel inhibition (see below). However, although long suspected, a direct link involving T-type channels and the generalized spike-wave epilepsies in humans was only recently established. A number of missense mutations have now been identified in the $Ca_v3.2$ calcium channel gene in patients diagnosed with childhood absence epilepsy and other forms of idiopathic gen-
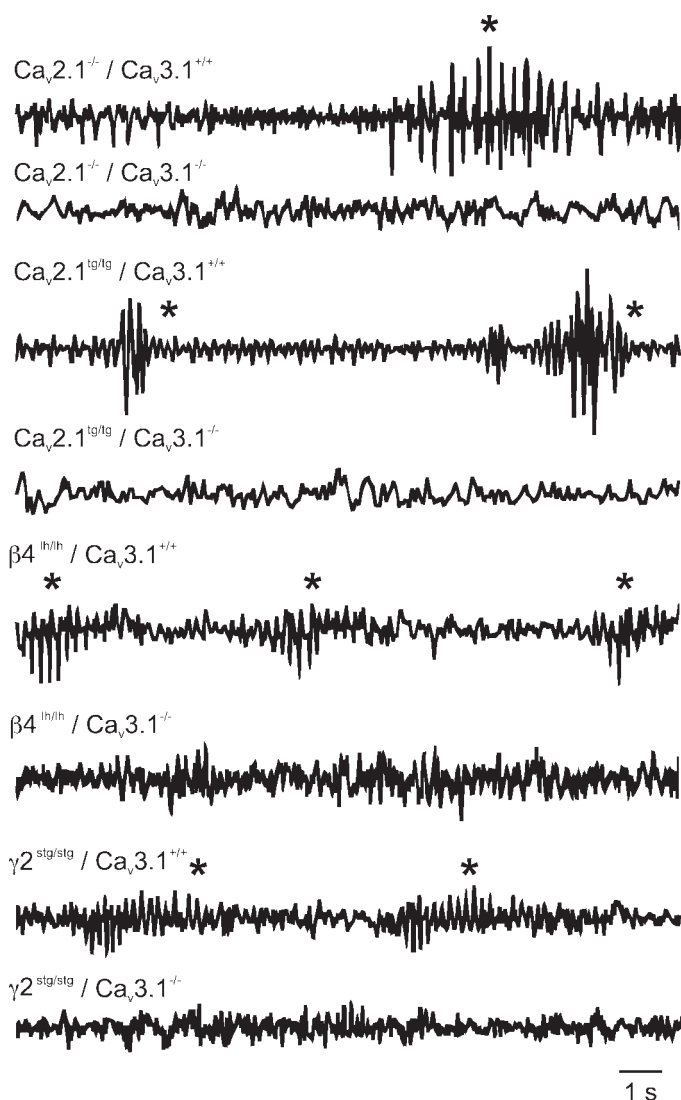
FIG. 5. Ablation of $Ca_v3.1$ T-type calcium channels can rescue several genetic models of absence seizures from the epileptic phenotype. Electroencephalographic recordings (15 s) are shown from the cortex of $Ca_v2.1^{-/-}$, $Ca_v2.1^{tg/tg}$ (tottering), $\beta4^{lh/lh}$ (lethargic), and $\gamma2^{stg/stg}$ (stargazer) mice with or without the ablation of $Ca_v3.1$ channels, during spike-wave discharges corresponding to absence seizures (asterisks). In each genetic model, a complete ablation ($Ca_v3.1^{-/-}$) is required to rescue the animal from the epileptic phenotype. [Adapted from Song et al. (256).]

eralized epilepsy (Fig. 6). The first genetic study involved 118 patients with childhood absence epilepsy, and point mutations were detected in 14 of these patients, but not in 230 control individuals (46). Intriguingly, none of the affected individuals had a family history of epilepsy, but carriers inherited a mutant copy of the gene in a heterozygous manner from one parent. A large number of polymorphisms were also reported that were identified in both childhood absence epilepsy and control groups. Of the identified 12 mutations, only two were found in more than one affected individual. A second study investigated a heterogeneous population of patients with idiopathic gen-

eralized epilepsy (including childhood absence epilepsy, juvenile myoclonic epilepsy, and febrile convulsions) and identified three additional missense mutations and one nonsense mutation that occurred in 9 of 192 individuals (118). None of these new mutations segregated with a specific epilepsy phenotype, and their presence was not associated with a single subtype of idiopathic generalized epilepsy. It is important to note that every single one of the reported $Ca_v3.2$ mutations could also be found in seizure-free individuals.

The consequences of the entire set of missense mutations on $Ca_v3.2$ channel function have recently been examined in transient expression systems (140, 141, 215, 292). Several of these mutations were found to result in small changes in the gating characteristics of both rat and human $Ca_v3.2$ channels in a manner consistent with a gain of function (i.e., increased T-type channel activity). Specifically, some of the mutations resulted in a hyperpolarizing shift in the voltage dependence of activation, while others resulted in increased channel availability due to decreased steady-state inactivation. However, the majority of the mutations did not significantly affect the biophysical characteristics of the channel (141, 215), which is intriguing considering that most of the mutations are localized within the domain I-II linker of the channel, a region thought to be involved in voltage-dependent inactivation (at least in HVA calcium channels).

It should be noted that alterations in biophysical properties of mutant channels are not expected to be the sole mechanism for the generation of pathophysiology. It is conceivable that processes such as neuronal development, targeting of channels to appropriate subcellular compartments, and/or cumulative effects from multiple mutations can all contribute to the etiology of idiopathic generalized epilepsies. Moreover, as outlined earlier, it is well known that many intracellular proteins interact with voltage-gated calcium channels and perhaps a number of these "biophysically silent" mutations might, given their localization on intracellular linkers, disrupt important intracellular signaling pathways that bring about, or contribute to, the epileptic phenotype (see also NOTE ADDED IN PROOF). Ultimately, it may prove necessary to perform conditional and region-specific knockin animal studies (both in isolation and combinations thereof) to elucidate their exact functional role in seizure genesis. From a clinical point of view, it appears as if mutant channels with large biophysical changes compared with wild-type channels account for only a small fraction of affected individuals. This is supported by the low incidence of mutations that segregate with idiopathic generalized epilepsy phenotypes (34, 278). Nonetheless, genetically identified mutations in patients and investigation of their function have served to further implicate T-type channels as important players in the idiopathic generalized epilepsies.
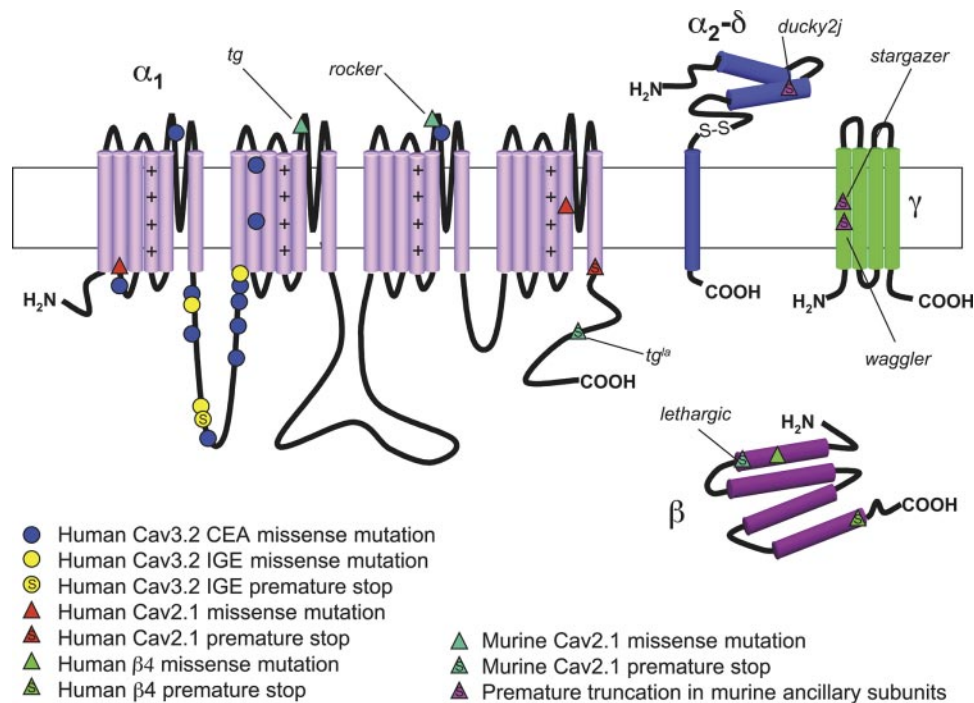
FIG. 6. Transmembrane topology of the calcium channel α_1- and associated ancillary subunits with locations of identified mutations linked to epilepsy. The pore-forming α_1-subunit that is comprised of four homologous transmembrane domains, flanked by cytoplasmic NH_2 and COOH termini and connected by intracellular linker regions. Each of the four domains consists of six transmembrane spanning α-helices (termed S1 through S6, indicated by cylindrical segments) and a pore-loop structure that lines the permeation pathway for calcium (see reentrant loop between fifth and sixth transmembrane region in each domain). The S4 segments of each domain carry positively charged amino acid residues in every third position and are thought to form the voltage sensor of the channel (see "+" symbols for voltage sensor). Locations of mutations in $Ca_v3.2$ that have been linked to idiopathic generalized epilepsy (circles, idiopathic generalized epilepsy) and epilepsy mutations in $Ca_v2.1$ channels in animals and humans (triangles) are indicated. Calcium channel β-subunits are cytoplamic proteins that tightly associate with the α_1-subunit domain I-II linker region (232). The α_2-δ-subunit is translated as a single protein, which is posttranslationally cleaved into α_2- and δ-subunits that are subsequently relinked via disulfide bonds (5, 147). The δ-subunit contains a single transmembrane region connected to the extracellular α_2-portion. The γ-subunits contain four transmembrane spanning helices flanked by cytoplasmic NH_2 and COOH termini. Approximate locations of mutations in ancillary calcium channel subunits linked to absence seizures in mice and humans (triangles) are also indicated. CAE, childhood absence epilepsy.

Collectively, these findings support the notion that idiopathic generalized epilepsies comprise complex forms of epilepsy where numerous susceptibility alleles can appear and disappear in an individual's genome through factors such as meiotic reshuffling and chance events. Thus these alleles may not segregate in a Mendelian manner and in isolation do not appear to cause a sufficiently large perturbation to the functioning of brain networks to results in the disease phenotype. Instead, they could give rise to a genetic susceptibility by which their effects can combine with other alleles, perhaps involving the same or other proteins, to cause the epileptic condition in affected individuals (201). However, it is possible that future genetic linkage studies may identify calcium channel mutations that clearly segregate, in a Mendelian manner, with an epileptic phenotype.

B. P/Q-Type Channel Defects and Spike-Wave Seizure Disorders

Central to the mechanisms of spindle and SWD generation are oscillatory rhythms, specifically in the tha-

lamic reticular network (99), which along with bursting activity in areas of the cortex affect the entire thalamocortical circuitry and modulate the firing of thalamocortical neurons (263). Although electrical synapses have recently been implicated in synchronizing the activities of reticular neurons (98, 156, 175), chemical synaptic transmission remains a primary mode of synchronizing the neuronal ensembles required for the generation of SWDs in both the thalamus and cortex. Because $Ca_v2.1$ (P/Q-type) calcium channels are key mediators of synaptic transmission in most central and peripheral neurons, alterations in $Ca_v2.1$ channel function therefore have the propensity to affect both cellular and network behavior.

1. $Ca_v2.1$ channels and murine models of absence epilepsy

The first evidence implicating $Ca_v2.1$ channels in the generation of spike-wave seizures came from several mouse strains that showed absence-like seizure activity. The *tottering* (*tg*) mouse was originally identified based on observations of cerebellar ataxia and intermittent paroxysmal dyskinesis (211). Subsequent examinations re-

vealed the presence of EEG abnormalities that corresponded to absencelike seizures with SWDs in the range of 5–7 Hz (94, 211). Electrophysiological recordings have revealed that CA3 hippocampal pyramidal neurons in *tg* mice are prone to increased burst firing caused by paroxysmal depolarizing shifts when exposed to a high extracellular K^+ model of in vitro seizures, consistent with hyperexcitability (114, 115). The *leaner* (tg^{la}) mice display cortical spike-and-wave discharges that also resemble absence seizures. These mice are reported to be severely ataxic and often have a short survival postweaning (94, 177). Finally, the *Rocker* mice show spontaneous bilateral SWDs in the 6- to 7-Hz range while awake at a frequency of about one episode per minute, and which are always accompanied by behavioral arrest (321). These three mouse genotypes and their seizure disorders are recessively inherited and characterized by mild to severe ataxia and, in the case of tg^{la}, significant loss of cerebellar Purkinje and granular neurons (119).

All three mouse lines show defects in the gene encoding $Ca_v2.1$ channels (11) (Fig. 6). In *tg* mice, a proline residue normally found in the domain II S5-S6 region of $Ca_v2.1$ is replaced by leucine (78, 94). This amino acid substitution reportedly results in decreased levels of P/Q-type current levels in native mouse neurons, as well as in transient expression studies (293), whereas the gating characteristics of the mutant channel do not appear to be significantly altered. Given that the mutation is located near the pore region of the channel, this decrease in current activity could perhaps be due to reduced single-channel amplitude, although this has not been confirmed experimentally. The reduction of P/Q-type channel activity in *tg* mice is paralleled by a dysfunction in neurotransmitter release in neocortical neurons (7) and a switch to N-type channel-mediated synaptic transmission (227). Moreover, this aberrant P/Q-type channel function may also account for reduced evoked excitatory synaptic potentials evoked in ventrobasal thalamic neurons (33).

The $Ca_v2.1$ calcium channel gene of tg^{la} mice contains a nucleotide substitution in the COOH-terminal region that results in its premature truncation (78, 94). It has been reported that the tg^{la} mutation causes altered P/Q-type channel currents and, like the *tg* mutation, reduces neurotransmitter release at neocortical synapses (7). It is unlikely that this mutation would affect single-channel conductance, suggesting that the reduced whole cell currents may either be due to a reduced probability of channel opening, or perhaps due to less effective targeting of the channel to the plasma membrane (i.e., reduced channel numbers). The *Rocker* mutation results in the replacement of a lysine residue (T1310K) in the domain III S5-S6 region with threonine (321) (Fig. 6). Its consequences on channel function in neurons or in transient expression systems remain to be determined, although the location near the pore site may again suggest possible effects on

ion permeation. The common theme in the genetic absence models of *tg* and tg^{la} mice appears to be a reduction in P/Q-type channel-mediated calcium entry, and hence synaptic release. This would be consistent with findings showing that complete genetic ablation of P/Q-type channels in mice results in absence seizures with behavioral arrests (256). However, it is important to note that the absence phenotype in these animal models does not occur in isolation, but rather is accompanied by other neurophysiological defects (i.e., ataxia, cerebellar atrophy), and this complicates our ability to link altered P/Q-type channel activity to the occurrence of seizures (see also sect. v).

2. $Ca_v2.1$ channelopathies in humans

In humans, a number of mutations in P/Q-type calcium channels have been associated with conditions such as episodic ataxia type 2 (64, 65, 97, 108, 131, 214, 246, 313) and familial hemiplegic migraine (214; reviewed in Ref. 220). In a few instances, patients carrying these mutations appear to exhibit absence seizures in addition to their ataxic phenotype. For example, a truncation mutation in the COOH-terminal region of $Ca_v2.1$ has been identified in a juvenile patient diagnosed with episodic ataxia type 2 and afflicted with childhood episodes of absence epilepsy and primary generalized seizures (134). This mutation results in a nonfunctional channel (Fig. 6), which in turn promotes a dominant-negative inhibition of wild-type channels. The same group of investigators recently reported on a family in which five patients exhibit absence epilepsy in combination with cerebellar ataxia (127). A novel point mutation in domain I-S2 region of the $Ca_v2.1$ calcium channel was identified, shown to segregate with the epileptic/ataxic phenotype, and to result in impairment of channel function. The significance of this study is the apparent association between absence seizures and reduced P/Q-type channel function, which is again consistent with findings in *tg* and tg^{la} mice. However, it is important to point out that the occurrence of absence seizures in episodic ataxia type 2 patients with P/Q-type channel mutations appears to be rare. Similarly, although familial hemiplegic migraine mutations in P/Q-type channels have been linked with the occurrence of seizures in several case studies (14, 81, 148), these seizures were not classified as absence. Hence, the majority of P/Q-type channel mutations identified in humans, unlike in the rodent counterparts, do not seem to give rise to absence epilepsy.

Considering that loss of P/Q-type channel activity can contribute to the development of absence seizures, one may perhaps speculate that the mutations that give rise to the familial hemiplegic migraine might not result in reduced P/Q-type currents. The functional effects of a number of the familial hemiplegic migraine mutations have been examined following transient expression in systems

such as *Xenopus* oocytes (150, 151), HEK293 cells (111, 283), cultured cerebellar granule neurons (283), and cultured hippocampal neurons (36); however, no clear-cut trend has emerged as to whether these mutations produce gains or loss of P/Q-type function. Most recently, the direct functional consequences of the four original familial hemiplegic migraine mutations (214) on excitatory (36) and inhibitory (37) synaptic transmission have been investigated. In the case of excitatory synaptic transmission, it was observed that all four mutant channels resulted in reduced current densities and diminished current influx for supporting synaptic transmission when compared with constituted wild-type channels in $Ca_v2.1$ KO cultured hippocampal neurons (36, 37). In the case of inhibitory synaptic transmission, expression of these mutant channels in inhibitory neurons cultured from $Ca_v2.1$ KO neurons reduced the contribution of these channels to supporting postsynaptic GABAergic currents compared with wild-type channels (37). The reduction in P/Q-type channel activity contrasts with the gain of channel function that is observed when certain familial hemiplegic migraine mutations were introduced into a mouse background (289). Given these conflicting results, it remains difficult to say whether the lack of absence seizures seen in familial hemiplegic migraine patients is related to the possibility that P/Q-type channel activity is increased, rather than the type of decrease observed in the case of most episodic ataxia type 2 mutations and in mouse genetic models of absence epilepsy (Fig. 6).

C. Involvement of Ancillary Subunits of Voltage-Gated Calcium Channels in Seizure Disorders

Ancillary calcium channel subunits are important regulators of HVA calcium channel function. Murine and/or human mutations associated with seizure activity have been identified in all three classes of ancillary subunits (Fig. 6). A frame-shift mutation resulting in a functional knockout of the calcium channel β_4-subunit gives rise to the *lethargic* (*lh*) mouse phenotype, which is known to exhibit absence seizures and ataxia (31). In thalamic neurons isolated from these mice, excitatory, but not inhibitory, neurotransmitter release is reduced similar to what has been observed with *tg* mice (33). In humans, both missense and truncation mutations in the β_4-subunit have been found in idiopathic generalized epilepsy patients (88). Considering that the β_4-subunit is the primary subtype associated with P/Q-type channels, it is possible that these mutations may mediate their physiological effects by altering P/Q-type calcium channel function or targeting; however, since other types of calcium channel α_1-subunits can also associate with β_4, such a link is not equivocal. There may also be precedent for changes in calcium channel function via altered β-subunit expression patterns in (focal) temporal lobe epilepsy as has been shown in a single study (171).

To our knowledge, mutations in either γ- or α_2-δ-subunits have so far not been linked to epilepsy in humans; however, there are several mouse phenotypes associated with these subunits. Two different mutations in the calcium channel α_2-δ_2 subunit (CACNA2D2 gene) result in loss of the full-length proteins giving rise to the *ducky* mouse, with the two identified forms being designated as *du* and du^{2J}. Both mouse strains are characterized by behavioral arrest, bihemispheric spike-wave seizures with a frequency of ~5–7 Hz, and ataxia and paroxysmal dyskinesia (10, 210). Coexpression of the mutant α_2-δ_2-gene in COS cells diminishes $Ca_v2.1$ currents (26). Moreover, morphological differences have been observed in Purkinje cells from *du/du* mice, which show reduced size and complexity of dendritic processes rendering these neurons to appear as if they were developmentally immature (26). However, it is important to note that Purkinje cells are not lost as is the case for some of the other genetic epilepsy models that show cerebellar defects (e.g., tg^{la} mice). Duplication of exon 3 of the α_2-δ_2-subunit prevents the disulfide linkage between α_2 and δ_2, the *entla* mouse (25). These mice show seizure activity in the 2- to 4-Hz range in cortical and hippocampal regions and exhibit reduced $Ca_v2.1$ channel activity in the hippocampus. Although these mutations in the CACNA2D2 gene seem to result in reduced P/Q-type channel activity, the precise mechanism by which they result in absence-like seizure activity in the thalamocortical system remains open for investigation.

The spontaneous *Stargazer* (*stg*) and *Waggler* mouse strains arise from disruptions in the calcium channel γ_2-subunit. These mice exhibit head tossing and absencelike seizures, with SWDs occurring about once per minute (166, 167). In *Waggler* mice, seizures are dramatically exacerbated by targeted mutations in the calcium channel γ_4-subunit, suggesting that γ_4 may compensate against some of the deleterious effects that result from compromised γ_2-function in these mice (168). As with the α_2-δ-subunits, the *stg* mutation reportedly results in inhibition of P/Q-type calcium channel activity by a subtle reduction in channel availability (18). However, the γ_2-subunit also interacts with AMPA receptors (45), which are responsible for fast glutamatergic synaptic transmission and are involved in synaptic plasticity (24, 183). This interaction with the γ_2 subunit is involved in the targeting of these receptors to synaptic sites (204, 290) and has recently been shown to modulate AMPA receptor function per se (281). Considering that AMPA receptors are known to undergo modification under epileptic processes (1), it remains unclear as to whether the physiological consequences of the *stg* mutation are due to actions on calcium channels, AMPA receptors, or both.

A role of HVA calcium channel interacting proteins is also exemplified in the case of juvenile myoclonic epilepsy patients that carry a mutation in the calcium binding protein EFHC1 that under normal conditions enhances R-type channel activity, an effect that is abolished by the mutations in this protein (274). However, mice deficient of R-type channels do not display seizure activity (162), and hence, it is not clear if the clinical manifestation of the EFHC1 mutation is directly related to the activity of R-type channels.

Taken together, a common theme in the effects of mutations in ancillary subunits appears to be an inhibition of P/Q-type channel activity, although it is by no means proven that their physiological effects are indeed mediated exclusively by these channels.

D. Antiepileptic Drugs and Calcium Channel Pharmacology

A number of clinically used antiepileptic drugs have been shown to block LVA and/or HVA calcium channels; however, it is not clear to what extent their inhibition is linked to the clinical efficacy of these drugs. A number of antiepileptic drugs are also used in the treatment of other nonepileptic neurological disorders including migraines and depression (236). Although many patients are seizure-controlled on antiepileptic drugs, their effectiveness can depend on the type of seizure disorder, their history of seizures before initiating treatment, and the efficacy achieved after first treatment (153, 154). The therapeutic benefit of antiepileptic drugs involves elevating seizure threshold for neurons and neuronal networks.

A number of antiepileptic drugs block calcium entry via HVA calcium channels. Gabapentin, a drug used in the treatment of generalized tonic-clonic seizures, is known to physically interact with the calcium channel α_2-δ-subunit (186) to block presynaptic calcium channel activity (13), although this mechanism of action does not seem to apply in all regions of the nervous system (27). Lamotrigine, a drug given to patients with absence, tonic-clonic, and partial seizures, has been shown to inhibit N- and P/Q-type channels (260, 297) without affecting T-type channels (318). However, due to the fact that $GABA_A$ receptors are also a major target for this drug, it is difficult to attribute its anticonvulsive effects unequivocally to calcium channel block. The antiepileptic drug levetiracetam may also block some HVA channels with its main effects exhibited on N-type channels (179). Recently, it was demonstrated that this compound can also effectively bind to the synaptic vesicle protein SV2A in brain-derived membrane and vesicle isolates (181). This interaction was found to be specific to the SV2A isoform (i.e., no binding was observed to its related proteins SV2B or C). Presently, it is not known if this compound could

mediate its effect on N-type channels indirectly via binding to SV2A. One of the many actions of the antiepileptic drug topiramate, commonly used to treat partial and generalized seizures, is to block cholinergic-dependent plateau potentials by blocking R-type channels (152). This might suggest that R-type channel inhibition could potentially protect against seizure activity. The common theme among some of these drugs is an inhibition of calcium channels at presynaptic sites, which is in some ways counterintuitive considering that knockout or decreased expression of P/Q-type channels gives rise to an epileptic phenotype, indicating that acute inhibition of these channels is not functionally equivalent to long-term gene knockdown.

In the case of LVA calcium channels, ethosuximide is an effective and commonly used antiepileptic drug for the treatment of absence seizures in the pediatric population (107). The pharmacological effects of this drug have been a matter of recent debate (125). Despite the known role of T-type channels in rebound bursting (specifically in the thalamus), it has been questioned as to whether the therapeutic effects of ethosuximide are derived from its action on these channels, since no block of LVA calcium currents in rat and cat thalamocortical neurons could be observed (165). On the other hand, in expression systems, ethosuximide reportedly blocks all three cloned human T-type channel isoforms (104). These different observations may perhaps be explained by the apparent state dependence of ethosuximide block that gives rise to an ~10-fold higher affinity inhibition of inactivated channels (note that T-type channels accumulate inactivation during prolonged bursting and spike-wave activity). Alternatively, the conflicting findings could be due to interspecies differences in channel structure in addition to putative cortical action of this drug (231, 266). The antiepileptic drug valproic acid is highly effective in the treatment of absence epilepsy (103). However, whether the clinical action of this drug is due to T-type channel block remains unresolved (235) given that studies have reported only a moderate amount of current block at therapeutic levels (243, 280).

Collectively, these findings indicate that HVA and LVA calcium channels are targeted by antiepileptic drugs; however, it is not clear to what extent their inhibition is linked to the clinical efficacy of these drugs.

IV. CONCLUSIONS

Epilepsy is one of the most prominent neurological disorders, and its spectrum of etiologies is a reflection of the many routes to seizure onset in brain networks. A growing body of evidence firmly establishes P/Q-type and T-type channels as important contributors to seizure genesis through modulation of neuronal properties that act to

shape network function, whereas other types of calcium channels do not appear to contribute to the development of seizure activity. Collectively, clinical and basic science studies point to new and exciting avenues for research directed toward dissecting the roles of these channels in different seizure disorders and associated neurological problems such as episodic ataxia.

Evidence from rat and mouse models of absence epilepsy, knockout mice, and characterization of functional effects of mutations found in patients all point to the fact that inhibition of P/Q-type channel activity somehow alters neurons and neuronal networks to result in seizure activity. This may also apply for variants of ancillary subunits that can act to reduce P/Q-type channel function. Conversely, however, it has been suggested that some of the clinically active antiepileptic drugs act by inhibiting presynaptic calcium channels. It is important to reiterate that acute inhibition of these channels is not functionally equivalent to long-term gene knockdown. Alternatively, the possibility that the therapeutic action of these drugs may be unrelated to calcium channel inhibition cannot be excluded.

The precise mechanism by which changes in $Ca_v2.1$ channel function result in absence-like seizures has remained unclear. Indeed, interpretations of animal and clinical studies in the context of common forms of absence epilepsy are complicated by the fact that some of the murine P/Q-type channel mutations are associated with other neurological defects such as ataxia and cerebellar atrophy and that the absence phenotype in humans carrying P/Q-type channel mutations appears to be accompanied by primary generalized epilepsy. Furthermore, it is important to consider the perspective that the rodent models involving P/Q-type channel mutations may not be sufficiently focal in their brain defects to allow for a causal interpretation of their phenotype in relation to the human disorder. For example, these mice have cerebellar defects and experience mild to severe ataxia, a condition that is not observed in patients with absence epilepsy (19). However, similar to patients, these genetic models of absence epilepsy involve the thalamocortical circuitry, respond to clinically used antiepileptic drugs such as ethosuximide and valproic acid (123, 256), and do experience absencelike behavioral changes (209).

There are several potential avenues by which reduced P/Q-type channel activity could affect network properties that give rise to seizure activity. First, there is evidence that P/Q-type channel defects preferentially affect excitatory synaptic transmission. Such a disruption may well result in decreased input onto inhibitory neurons. Because inhibitory networks are known to play an important role in synchronizing ensembles of neurons, any inappropriate synaptic input onto the inhibitory network may contribute to pathological synchronization that is incompatible with normal network functioning (6, 261).

Second, it has been shown that P/Q-type channel activity is directly linked to calcium-dependent gene transcription via the CREB pathway (273), and therefore, reduced P/Q-type channel activity may compromise appropriate gene regulation and expression. This may be consistent with abnormal neuronal morphology that is observed with human and murine P/Q-type channel mutations (Fig. 6). Finally, it is important to note that T-type calcium channel activity appears to be increased in at least four different mouse models of absence epilepsy (i.e., $Ca_v2.1$ KO, *tg*, *lh*, *stg*) (256, 317); therefore, it is conceivable that the epileptic phenotypes associated with compromised P/Q-type channel function may arise indirectly from enhanced neuronal excitability mediated by T types (Fig. 5).

In contrast to P/Q-type channels, the appearance of enhanced T-type currents elevates the propensity for seizure activity. T-type channels mediate the rebound bursts in cortical and thalamic reticular neurons that are the physiological substrates for SWDs. Therefore, increased T-type channel expression (such as in the GAERS rat) or activity (as seen with gain-of-function mutations found in humans) can contribute to seizure genesis. It should, however, be noted that increased T-type calcium channel activity does not necessarily have to result from increased T-type channel expression. For example, alterations in ionic currents that interact with T-type currents, such as the H current (I_h), which is mediated by HCN channels, can result in absence seizures (180, 224). This was recently demonstrated in the case of HCN2 (found primarily in the thalamus)-deficient mice, which exhibit spontaneous 5-Hz SWDs with absencelike episodes (178). Similarly, the WAG/Rij rat, which exhibits spontaneous absencelike seizures of neocortical origin (196), has been shown to have reduced levels of HCN1 protein expressed in the cortex; interestingly, mRNA levels for HCN1 were unaffected, and protein expression levels did not seem to differ from control animals for the three other HCN genes (269).

Given that cortical, thalamocortical relay, and reticular thalamic neurons express different complements of T-type channel isoforms, all three channel subtypes are potential contributors to the epileptic phenotype, but may do so in a regional- or cell type-specific manner. In this regard, it is interesting to note that in the GAERS rat, intrathalamic administration of ethosuximide (a known T-type blocker, see sect. IIID) is only effective in reducing seizures by 70% at concentrations well beyond those known to be effective in blocking T-type channels (231). However, intracortical administration of ethosuximide has been shown to be much more effective is halting seizure activity (184), which further supports the notion that T-type-mediated SWD generation is not exclusively a thalamic phenomenon. This notion is further supported by the observation that specific knockout of one given channel subtype (i.e., $Ca_v3.1$ which is expressed predom-

inantly in thalamocortical relay neurons) is not universally effective in protecting against all pharmacologically induced generalized seizures. The susceptibility of the KO mice to bicuculline-induced seizures indicates that rebound bursting in thalamocortical relay neurons may not be required for this form of seizure activity and serves as a reminder of the many complex routes to seizure genesis (reviewed in Refs. 191, 192). On the other hand, reticular neurons express Ca$_v$3.2 and Ca$_v$3.3, and it would thus be interesting to explore seizure susceptibility in knockout mice deficient of these channel subtypes. It also remains to be determined whether knockout or downregulation of Ca$_v$3.1 could provide a protective role against absence seizures induced by the putative gain of function in Ca$_v$3.2 such as those found in humans with idiopathic generalized epilepsy.

Historically, epilepsy has been a disorder through which much has been learned about the central nervous system and brain function in general. Exploration of voltage-gated calcium channels in epilepsy has proven to be both a challenging and rewarding endeavor. Future work promises to unlock many of the mysteries of how intrinsic cellular properties can interact in a complex network to bring about the intricacies of brain function in health and disease.

NOTE ADDED IN PROOF

A recent study by Zhong et al. (317a) has demonstrated that the CACNA1H (Ca$_v$3.2) T-type calcium channel gene can undergo extensive alternative gene splicing. The authors reported that several of the reported idiopathic generalized epilepsy mutations in this gene, although not mediating changes in channel function when introduced into any given cDNA, interfere with splicing events. As a consequence, certain splice isoforms that may have unique biophysical properties can no longer be formed in vivo. We propose that this might be a possible mechanism by which these mutations could affect seizure threshold in certain neurons. Thus the findings of Zhong et al. (317a) further support the concept that the reported mutations can manifest their effects in numerous ways beyond direct biophysical changes.

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