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Voltage-Gated Calcium Channels in Epilepsy

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Voltage-gated calcium channels mediate calcium influx that both controls neuronal excitability and regulates calcium-sensitive intracellular signalling pathways. While the substrates underlying epileptic seizures remain to be fully understood, burst-firing in the thalamocortical circuitry is known to be evoked by activation of low-voltage-activated (T-type) calcium channels and is thought to give rise to spike-wave discharges associated with absence epilepsy. Naturally occurring rodent genetic models of absence epilepsy have revealed that at least the $Ca_V3.1$ and $Ca_V3.2$ T-type channel isoforms play critical roles in disease etiology. Additionally, altered expression of several calcium channel subtypes has been observed and gain-of-function mutations have been identified in calcium channel genes from both epilepsy patients and animal models of epilepsy further providing useful tools for elucidating the underlying involvement of calcium channels towards disease pathophysiology. A number of the currently prescribed anti-epileptic drugs have been shown to inhibit calcium channel activity although these agents typically interact with multiple molecular targets. Given their unique distributions and contributions to higher brain functions, the selective pharmacological blockade of T-type calcium channel subtypes may provide attractive targets for the development of future therapeutic treatments.

Voltage-gated calcium channels are integral membrane proteins that form calcium-selective pores in the plasma membrane (Figure 1). Calcium ions flowing into the cell are driven by an electro-chemical gradient generated by a high concentration of calcium outside the cell to a low calcium concentration inside. In neurons the rapid influx of calcium depolarizes the cell membrane potential due to its divalent positive charge and mediates biophysical processes such as action potential firing and membrane potential oscillations. A second effect of calcium ion influx is to regulate the intracellular signaling pathways and biochemical machinery required for physiological functions such as neurotransmitter release. Cells contain numerous calcium sensitive proteins, such as enzymes and DNA transcription factors that can be up or down-regulated by the binding of calcium ions. Due to the highly complex and widespread effects of calcium channels, even small alterations in their expression or biophysical properties can induce pathophysiological changes in the brain with the potential to induce epileptic seizures.

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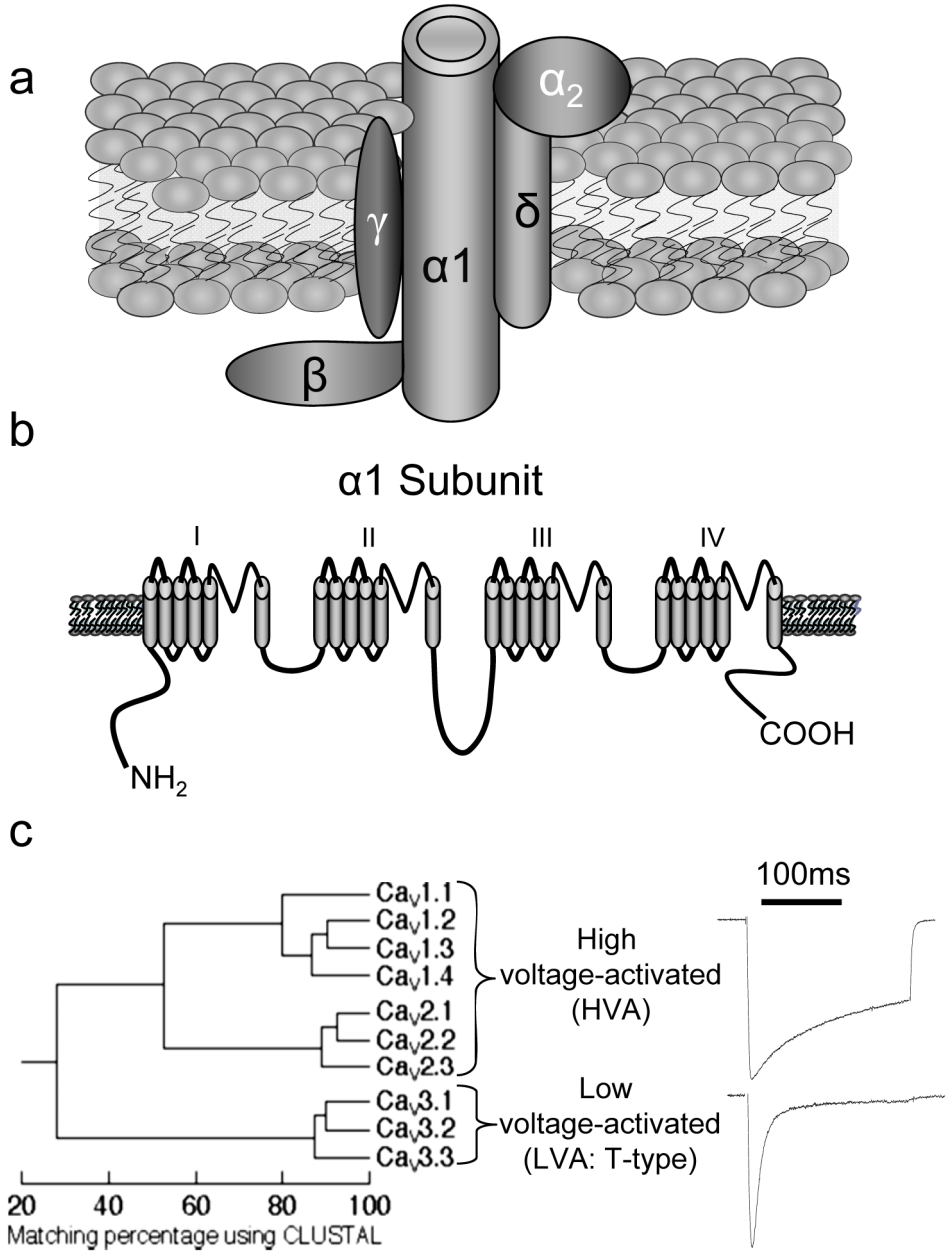

Figure 1. Voltage-gated calcium channels. (a) Schematic illustrating the topography of the high voltage-activated calcium channel complex showing the main pore-forming α_1 subunit and ancillary subunits. The α_1 and δ subunits are integral membrane proteins, the β subunit is intracellular and binds directly to the α_1, while the α_2 subunit is thought to be largely extracellular. (b) Schematic diagram showing structure of the calcium channel α_1 subunit with its four domain structure. (c) The left panel shows the phylogenic relationship between the ten known calcium channel α_1 subunits. Ca_V1 subunits form the L-type subfamily, Ca_V2 channels the P/Q-type, N-type and R-type, and the Ca_V3 subunits form the low voltage-activated T-type calcium channels. The right panel shows representative traces of calcium currents recorded from reticular thalamic neurons in response to depolarization of the membrane potential. The upper trace shows a slow inactivating high voltage-activated current and the lower trace shows the fast inactivating low voltage-activated current.

CALCIUM CHANNEL NOMENCLATURE

Calcium channels are generally classed as either high voltage-activated (HVA) or low voltage-activated (LVA), depending on whether they open at more positive (e.g. −40mV) or more negative (e.g. −60 mV) membrane potentials, respectively (Figure 1).[1, 2] High voltage-activated channels can be further classified according to their

pharmacological sensitivities and genetic α_1 subunit protein (Ca_V) composition into L-type ($Ca_V1.1$-$Ca_V1.4$), P/Q-type ($Ca_V2.1$), N-type ($Ca_V2.2$) and R-type ($Ca_V2.3$). Low voltage-activated channels, also known as "T-type", for their comparatively "tiny" or "transient" currents are further classified to according to their α_1 subunit composition ($Ca_V3.1$-$Ca_V3.3$).[1] Additional structural and functional variants of each Ca_V subtype can be generated by alternative splicing to produce a large number of different "splice variants" and therefore increase the repertoire and complexity of calcium channel properties. It should be noted that $Ca_V1.3$ L-type and $Ca_V2.3$ R-type channels can exhibit characteristics of "mid-voltage-activated" channels, opening at membrane potentials that are more negative than HVA channels and more positive than LVA channels. For simplicity in this chapter, $Ca_V3.1$-$Ca_V3.3$ will be referred to as "T-type channels" and all other calcium channels will be referred to as "HVA channels".

While each calcium channel α_1 subunit contains the molecular machinery necessary to conduct calcium ions (calcium-selective pore, voltage sensing and gating mechanisms), a number of ancillary proteins (β, $\alpha_2\delta$ and γ subunits) are associated with the HVA channel types and which modify channel biophysical properties and expression (Figure 1).[2] Four β subunit genes (β1-β4), four $\alpha_2\delta$ subunit genes ($\alpha_2\delta_1$ - $\alpha_2\delta_4$) and eight γ subunit genes (γ1-γ8) have been identified in vertebrates. There is no firm biochemical evidence as yet that T-type calcium channels require ancillary subunits for native functioning. Nine of the ten of calcium α_1 subunits (all but $Ca_v1.1$) are widely expressed in the central and peripheral nervous systems and several have been implicated in contributing to epilepsy pathophysiology.

CALCIUM CHANNEL BIOPHYSICAL PROPERTIES

From their closed/resting state calcium channels open once the membrane potential depolarizes to a threshold point, at which the internal voltage sensor moves and the channel conformation changes to an open-pore calcium conducting state. Calcium channels only conduct ions in the open state and with ongoing depolarization an internal inactivation mechanism induces additional conformational changes to prevent further conduction. Once in the inactivated state, the channels can only be reopened by re-polarization to hyperpolarized membrane potentials, allowing the voltage sensor to return to its original closed conformation and the inactivation machinery to return to its de-inactivated position. Only from this state can further membrane depolarization reopen the channels to their ion conducting state. The membrane potentials and rates at which these steps occur varies between the calcium channel subtypes and splice variants, producing channel variants with widely differing conducting properties.[2–4]

Calcium channels are generally slower at opening (activation) and closing (deactivation) than typical voltage-activated sodium channels. Amongst the calcium channel subtypes, HVA channels generally display slower activation and faster deactivation that LVA channels. Further, HVA channels generally inactivate much more slowly than LVA channels. Together these properties result in HVA channels generating longer lasting calcium influxes upon sustained depolarizations with T-type channels conducting more rapid and shorter calcium influxes under both brief and sustained depolarizations (Figure 1). Of particular note, T-type channels also exhibit a distinct overlap of the membrane potentials at which they both activate and inactivate, uniquely enabling them to regulate subthreshold excitability including mediating intrinsic oscillatory behaviours and firing rates.

CALCIUM CHANNELS AND EXCITABILITY

T-type channels and excitability

T-type calcium channels and burst-firing

T-type channels typically open at membrane potentials around −70 to −50 mV, more negative than that required to open both typical HVA calcium channels and sodium channels (~−40 to −30 mV).[4] The comparatively

smaller depolarization required to open T-type channels from resting bestows a particular importance with regard to cellular excitability. Small depolarizations induced by, for example, NMDA receptor activation, can cause T-type calcium channels to open leading to further membrane depolarization and which in turns leads to the opening of additional T-type calcium channels[5–7]. If the expression of these channels is of a sufficient density, this cascade depolarization induces a "calcium spike" also known as a "Low Threshold Spike" (LTS), similar to an action potential, but slower in activation and inactivation rate and peaking at more hyperpolarized membrane potentials (~−45 to −35mV).[8, 9]

This calcium spike can depolarize the membrane to a level whereby sodium channels and potassium channels then open and initiate high frequency action potential (AP) firing on the crest of the LTS. The AP firing can continue until the T-type calcium channels inactivate and the membrane is repolarized by small conductance Ca-activated potassium (sK) channels. This type of event is known as a "burst" and burst-firing is thought to underlie the spike-and-wave discharges (SWDs) that are both the hallmark of absence epilepsy seizures on electroencephalography (EEG) recordings and that can also be observed in some other generalized and partial epilepsies (Figure 2).[10, 11] The "spikes" in these events are thought to correspond to summated neurotransmission, whereas the "wave" complexes are predicted to correspond to a period of neural quiescence. Together, they represent the oscillatory nature of absence seizures as they progress and resonate in the brain.

Different T-type channel subtypes contribute to particular parts of the burst due to their differing activation / inactivation kinetics (*fastest* $Ca_V3.1$>$Ca_V3.2$>>$Ca_V3.3$ *slowest*), deactivation kinetics (*fastest* $Ca_V3.3$>$Ca_V3.1$>$Ca_V3.2$ *slowest*) and rate of recovery from inactivation (*fastest* $Ca_V3.1$>$Ca_V3.3$>$Ca_V3.2$ *slowest*).[8, 12] $Ca_V3.1$ channels are predicted to generate very fast activating, short lasting bursts, $Ca_V3.2$ to generate fast activating, longer-lasting bursts and $Ca_V3.3$ slow activating and very long lasting bursts. Neuronal bursting properties likely depend on the relative proportion of the three T-subtypes that are expressed within a given neuron.

T-type calcium channels and slow oscillations

In addition to the oscillations generated by burst-firing, T-type calcium channels are involved in generating a number of other types of oscillations, especially in the thalamocortical network and which are of particular importance in some epileptic disorders. The membrane potentials at which T-type channel variants open, close, inactivate and de-inactivate are known to overlap and vary between subtypes. At potentials of overlap in conducting and non-conducting states some percentage of channels are always open, although the entire population is constantly shifting between open, closed and inactivated states. This produces a constant inward calcium current known as a "window current".[4, 8, 13, 14] Whether a given neuron is at a membrane potential where the window current is "on" or "off" can have great effect on excitability, and the switching between these states, controlled by different leak, hyperpolarization-activated depolarizing and cation-activated depolarizing conductances, is thought to underlie a number of neural rhythms and oscillations.[15–19] While burst-firing is a critical propagator of seizure activity, intrinsic oscillations within cells and networks potentially underlie the actual initiation of seizures.[20] This can be observed by artificial enhancement of T-type channel expression in inferior olivary neurons using computer modeling combined with patch clamp (known as "dynamic clamp"), and is sufficient to induce spontaneous oscillations.[21] This likely occurs since subtle changes in T-type channel current density can lead to large changes in electrophysiological oscillatory behavior.[21, 22] For example, overexpression of the $Ca_V3.3$ channel alone in neuroblastoma cells induces spontaneous oscillatory activity and low threshold firing.[23]

HVA calcium channels and excitability

HVA channels are intrinsically involved in many different aspects of neuronal excitability and a comprehensive discussion is beyond the scope of this chapter. However, some of their roles relative to epilepsy are of particular note. Postsynaptically expressed HVA channels generate large, long lasting depolarization and modification to

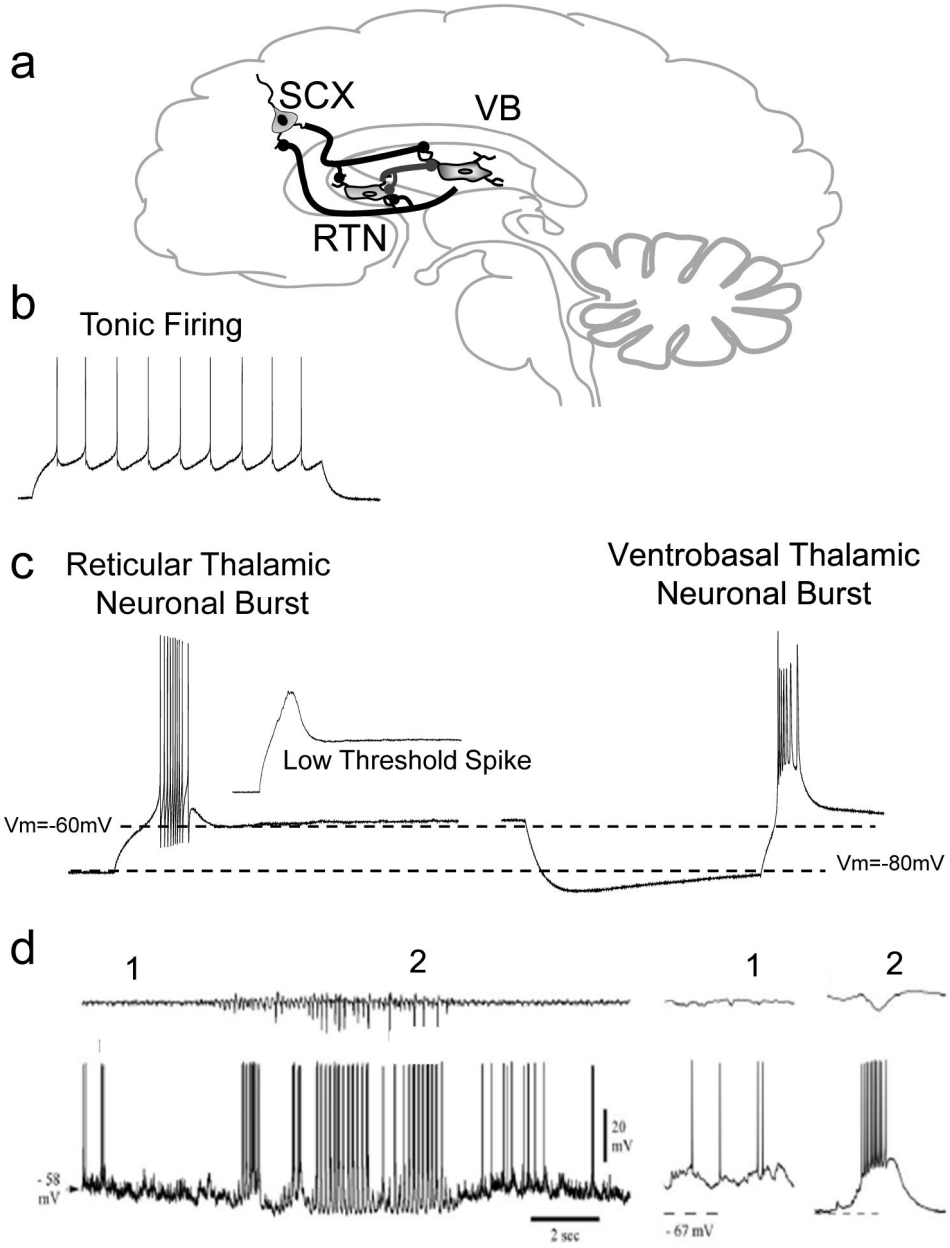

Figure 2. The thalamocortical network and burst-firing. (a) Diagram of the thalamocortical network showing connections between the somatosensory cortex (SCX), the sensory relay neurons of the ventrobasal posterior thalamic groups (VB) and the reticular thalamic nucleus (RTN). (b) Under normal physiological conditions as sensory signals from the periphery are relayed to the cortex the VB and RTN neurons fire tonically in response to depolarization. In this state there is minimal T-type calcium channel activity. During epileptiform activity burst-firing becomes predominant (c) and the thalamocortical network becomes locked in a self-propagating oscillatory loop (Vm=membrane potential). (*c: Inset)* In the absence of sodium channel (600nM tetrodotoxin applied) activity the low threshold spike that underlies burst-firing is evident. (d) Burst-firing in the RTN of the GAERS epileptic rat model of absence epilepsy correlates with burst-firing in the RTN. Upper panels in show EEG recordings and lower panels show corresponding intracellular recordings in an RTN neuron with expanding timescales from on right side. Note that tonic neuronal firing does not correspond to spikes in the EEG trace (1), however burst-firing correlates closely with spikes observed on the EEG trace during spike-wave discharges (2).

their biophysical properties or expression can have substantial effects on the intrinsic firing properties of neurons. While HVA channels all play a role in low threshold burst-firing in that they conduct large amounts of calcium during bursts, especially during action potentials, they do not appear crucial for bursting activity to occur.[6, 24] R-type channels however, are becoming increasingly linked to a role in burst-firing as they have a

lower threshold for activation than typical HVA channels, are capable of transient surges of current and are linked to after-depolarization, which is required for repetitive bursting.[25, 26] Furthermore, R-type channels may be involved in generating adequate activation of sK channels to ensure sufficient repolarization following a burst, which is a requirement for T-type de-inactivation over a series of multiple bursts. In addition, R-type channels have been proposed to contribute to sustained depolarizations, known as "plateau potentials", which have been implicated in pro-epileptic neuronal activity.[27]

A number of the HVA calcium channel subtypes are also expressed presynaptically and are critically involved in neurotransmitter release.[28–30] With an absolute dependence of neural functions on synaptic neurotransmission, it follows that even small alterations in the biophysical properties of presynaptic calcium channels could have a significant impact on the firing properties of nerve cells and neural networks with the potential to lead to epileptic seizure activity.

CALCIUM CHANNELS IN ABSENCE EPILEPSY

T-type calcium channels in the thalamocortical network and absence seizures

The thalamocortical network components involved in absence seizures appear comprised of three primary nuclei; sensory relay neurons including those located in the ventrobasalposterior thalamic groups, the corticothalamic pyramidal neurons in layers V-VI of the sensory cerebral cortex (SCX) and the reticular thalamic nucleus (RTN; Figure 2). In this network, glutamatergic axonal efferents from the SCX synapse on VB neurons, which send reciprocal glutamatergic projections back to the SCX. The RTN forms a shell around the dorsal-anterior face of the thalamus and as axons from SCX and VB neurons also project to pass through the RTN they synapse upon RTN neurons inducing depolarization. RTN neurons are GABAergic and send projections both to VB neurons and to other RTN neurons, inducing hyperpolarization in both neuronal types. Ventrobasal thalamic neurons are thought to respond more faithfully to hyperpolarizing inputs via the RTN than directly from depolarizing inputs from the SCX.[31]

During wakefulness or seizure-free periods, VB neurons act as a simple relay by forwarding sensory signals from the periphery to the cortex. In this mode thalamic neurons are relatively depolarized and T-type channels in both VB and RTN neurons are, in general, inactivated. In this state, thalamic neurons follow a generally "tonic" or repetitive firing pattern of variable frequency with regular action potentials and little bursting (Figure 2).

However, during absence seizures (which follow a similar pattern to non-REM sleep) the SCX, VB and RTN neurons become locked in a self propagating oscillatory loop. During this state RTN neurons are more hyperpolarized allowing burst-firing to occur via the de-inactivation of $Ca_V3.2$ and $Ca_V3.3$ T-type channels expressed in these cells in response to depolarization from VB and SCX collaterals (Figure 2).[32–35] Close correlation is observed between the timing of burst-firing in neurons of the RTN and the spikes observed in SWDs on EEG recordings during absence seizures in the Genetic Absence Epilepsy Rats from Strasbourg (GAERS) model of absence epilepsy (Figure 2).[36, 37] Burst-firing in the RTN induces hyperpolarization of VB neurons via $GABA_A$ and/or $GABA_B$ receptor activation, de-inactivating $Ca_V3.1$ T-type channels and as hyperpolarization-activated channels (HCN; I_h) and corticothalamic inputs depolarize the neuron back toward the resting potential, a "rebound burst" is induced by opening of the de-inactivated $Ca_V3.1$ channels (Figure 2).[33, 38] This process in turn induces depolarization in the SCX, which send excitatory signals back to the thalamus and the absence seizure propagates.[18, 39] Overall, despite RTN neurons being GABAergic, they actually drive excitatory behavior in their burst-firing state by de-inactivating the T-type calcium channels expressed in VB neurons

The role of T-type calcium channels in the SCX is less clear. All three T-subtypes exist in the cortex, with $Ca_V3.1$ and $Ca_V3.3$ being expressed throughout, but with greatest expression in layer V; also the only layer to express

$Ca_V3.2$.[33] While oscillatory activity and low-threshold spiking has been identified in the cortex, burst-firing is generally uncommon in cortical neurons.[40–44] Correspondingly, T-type currents are generally either absent or of small magnitude in cortical neurons, while HVA calcium channels are abundant. [45–50] However, evidence from genetic rat models of absence epilepsy, suggests that seizures actually initiate in the SCX, which then recruits the thalamus and spreads to other cortices.[43, 51–53] Whether intrinsic normal oscillatory activity in this region recruits a hyperexcitable thalamus to induce seizures, or pathophysiological hyperexcitablity in the cortex is responsible for inducing seizures directly is as yet unknown.[20, 54, 55]

Calcium channels in human epilepsy

T-type calcium channel mutations in human epilepsy

A number of apparent mutations have been identified in the human *CACNA1G* ($Ca_V3.1$) and *CACNA1H* ($Ca_V3.2$) genes within subpopulations of idiopathic generalized and childhood absence epilepsy patients.[56–59] Some of the alterations in $Ca_V3.2$ have been shown to induce altered biophysical properties or increase channel expression when examined in exogenous expression systems. However, some have no apparent effect, potentially reflecting the polygenic nature of idiopathic generalized epilepsies and/or that a subset of the changes represent single nucleotide polymorphisms.[60–65] Details of these results have been comprehensively reviewed (see refs [66, 67, 68]), however these findings provide a strong indication that T-type calcium channels play a role in human idiopathic generalized epilepsies, supporting a large volume of data provided by experiments on animal models.

P/Q-type calcium channel mutations in human epilepsy

The $Ca_V2.1$ subunit encodes both P-type and Q-type channels through an alternate splicing mechanism.[69] These channels are highly expressed presynaptically where they are critically involved in neurotransmission and synaptic efficacy and therefore have a great influence on neuronal excitability.[70, 71] This aspect is reflected by a number of mutations in the $Ca_V2.1$ gene identified in patients suffering from severe neurological disorders including ataxias and congenital migraine.[66] While instances wherein HVA channel mutations have been identified in human absence epilepsy patients are rare, such cases do exist for $Ca_V2.1$. Within three generations of a single family, five members suffered from a combination of absence seizures / episodic ataxia and were found to possess a missense mutation (*E147K*) in the $Ca_V2.1$ subunit gene.[70] In another study, an eleven year old boy was identified with primary generalised epilepsy, episodic and progressive ataxia, and mild learning difficulties. Analysis of his genome revealed a truncation mutation (*R1820*-stop) in the $Ca_V2.1$ channel.[73] Both of these distinct mutations result in a loss in P/Q-type channel function. Another missense mutation (*I712V*) has been reported in the $Ca_V2.1$ subunit gene of an 11-year-old girl suffering from episodes of seizures, ataxia and other neural disorders, although no functional effects have yet been observed on the channel properties.[74] Furthermore, a small proportion of patients with familial hemiplegic migraine type-1 and with underlying mutations in the $Ca_V2.1$ channel also display both generalized and complex partial seizures.[66, 67, 75–79]

T-type calcium channels in absence epilepsy animal models

Genetic Absence Epilepsy Rats from Strasbourg (GAERS)

Genetic rodent models of epilepsy have been useful as tools in understanding the mechanisms that underlie absence seizures. Some of these models are generated by inbreeding rats that have developed epilepsy naturally to produce fully epileptic strains. The GAERS inbred Wistar rat model displays spontaneous absence seizures with similar characteristics to the human condition, with the exception that SWDs occur at a higher frequency (3–4 Hz in humans *vs* 7–9 Hz in GAERS).[80, 81] Calcium channels have been implicated in SWDs in GAERS since an early experiment wherein the injection of cadmium into the RTN at a concentration that blocks all calcium channel subtypes (1 mM) was found to abolish SWDs.[82] An increase in T-type current density has been found in the RTN neurons of GAERS with a corresponding increase in expression of $Ca_V3.2$ but not $Ca_V3.3$

mRNA.[83, 84] Furthermore, GAERS has been shown to possess a missense mutation (R1584P) in the *Cacna1h* gene encoding $Ca_V3.2$ and which correlates closely with seizure expression when the GAERS rats are outcrossed with non-epileptic control rats (Figure 3).[85] The R1584P mutation induces a gain-of-function in a particular $Ca_V3.2$ splice variant (+exon 25), increasing the rate at which channels recover from inactivation and allowing enhanced charge conduction during high frequency depolarizations such as those which occur during burst-firing. Since a greater number of $Ca_V3.2$ channels will recover from inactivation during multiple bursting in GAERS, the LTS magnitude is predicted to decrease less over a series of bursts. As LTS magnitude has been shown to correlate directly with number of action potentials per burst,[86] the resultant effect in GAERS RTN neurons is that over a series of multiple bursts, the number of APs per burst decreases to a lesser degree throughout a burst train. In addition to the R1584P mutation effect on $Ca_V3.2$ channel biophysical properties, the thalamic expression of the affected splice variant (+exon 25) also increases with development, potentially exacerbating hyperexcitability and underlying the temporal nature of seizure expression in GAERS animals.

Wistar Albino Glaxo Rats from Rijswijk (WAG/Rij)

Wistar Albino Glaxo Rats from Rijswijk (WAG/Rij) are another well studied genetic absence epilepsy model that display spontaneous seizures.[87] Like GAERS, these rats also display upregulation of T-type calcium channel expression, although in WAG/Rij this involves the $Ca_V3.1$ subtype in thalamic centrolateral and lateral geniculate (visual cortex projecting) neurons and with $Ca_V3.3$ in centrolateral and RTN neurons (Figure 3).[88] Despite increased T-type currents in all three neuron types, no differences have been observed in the number of APs generated per burst. However, modeling studies predict that smaller depolarizations would be required to induce burst-firing in lateral geniculate neurons of WAG/Rij animals. In addition, as with the $Ca_V3.2$ T-type in GAERS, alterations in the expression of specific splice variants of $Ca_V3.1$ have been noted in the WAG/Rij model, which is of particular interest since this occurs in the same domain III-IV linker region that seizure-related splice variation was observed with $Ca_V3.2$ in GAERS (exon 25–26).[89] In support of the involvement of $Ca_V3.1$ channels in seizure generation in this model, specific block of $Ca_V3.1$ using indomethacin-related compounds has been shown to attenuate seizures in WAG/Rij.[90] Interestingly, the systemic administration of the L-type calcium channel blocker, nimodipine, apparently exacerbates seizures in this model.[91]

Manipulation of $Ca_V3.1$ channels and absence seizures

In support of a role for $Ca_V3.1$ T-type channels in absence seizures, genetic enhancement of $Ca_V3.1$ expression in mice results in spontaneous bilateral SWDs (Figure 3).[92] Accordingly, genetic knockout of the $Ca_V3.1$ channel in mice generates a phenotype whereby thalamic relay neurons cannot burst-fire and *in vivo* the mice show resistance to classic pharmacologically-induced absence seizures using $GABA_B$ agonists, baclofen and butyrolacetone (a prodrug of γ-hydroxybutyric acid).[38]

Overall, it appears that an increase in the activity of any of the three T-type channel subtypes in the thalamocortical system may have the effect of enhancing or inducing absence seizures as a direct result of increased burst-firing in any of the thalamocortical regions, whether it occurs from increased expression or increased function of a T-type calcium channel subtype. Certainly, enhancement of either $Ca_V3.1$ or $Ca_V3.2$ channels seems to have strong pro-epileptic effects in the thalamocortical system.

HVA channels in absence epilepsy animal models

HVA channels in Wistar Albino Glaxo Rats from Rijswijk

In the WAG/Rij model of absence epilepsy, as well as an increase in T-type currents, an increase in the expression of P/Q-type channel protein occurs in the RTN.[93] This expression appears to occur presynaptically although experiments have yet to be conducted to determine the functional significance of this expression change on synaptic neurotransmission and absence seizure activity.

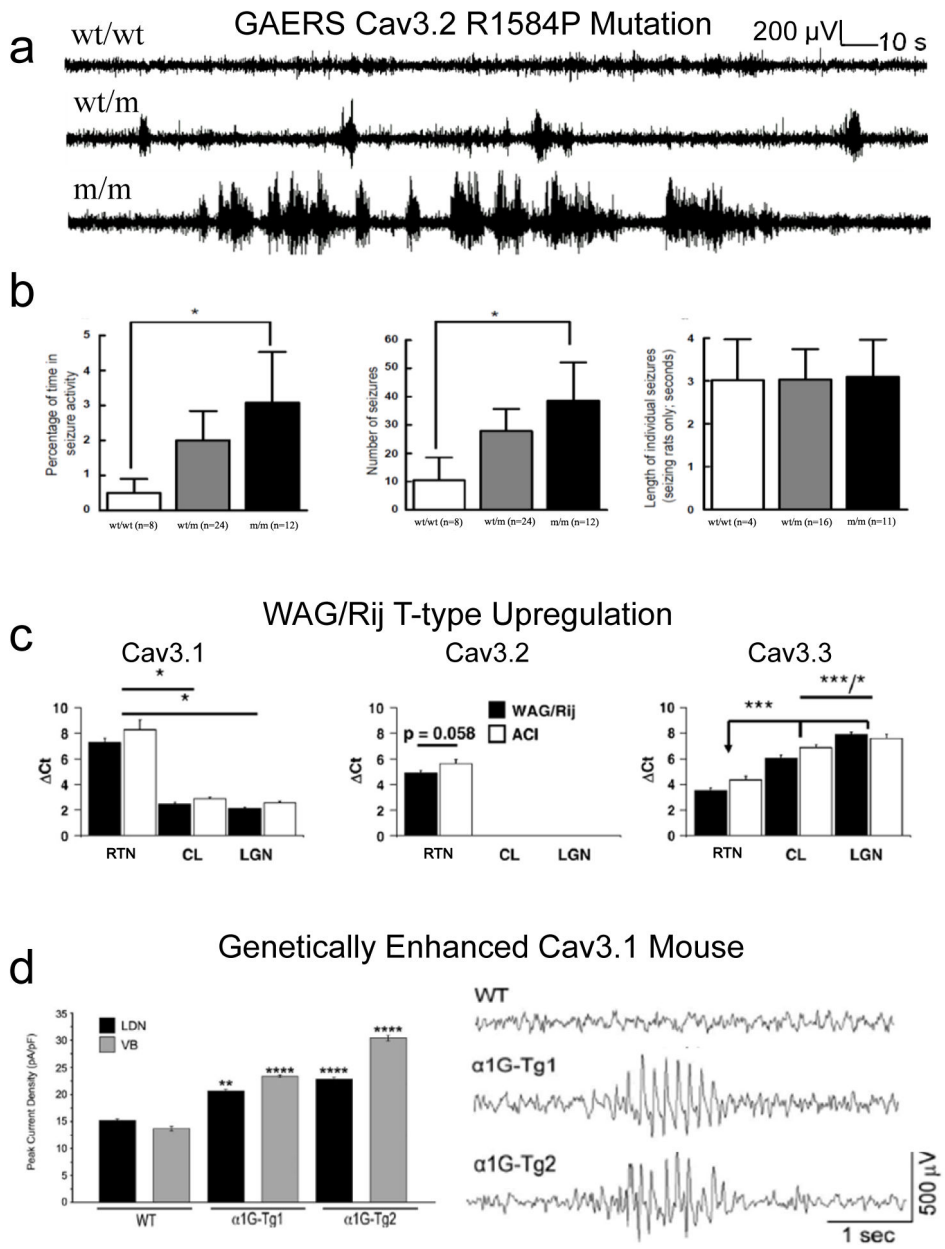

Figure 3. T-type calcium channels and absence epilepsy. (a-b) In the GAERS rodent model of absence epilepsy an arginine to proline missense mutation at position 1584 (R1584P) correlates with the expression of seizure activity. Mating GAERS with a non-epileptic strain (NEC) through two generations produces offspring that have no copies (wt/wt), one copy (wt/m) or two copies (m/m) of the R1584P mutation in an otherwise similar genetic background. Animals with two copies of the mutation spend increased time in seizure activity and experience more seizures than animals with no copies of the R1584P mutation. The missense GAERS mutation does not affect either the duration or morphology of individual seizures. (c) The WAG/Rij model of absence epilepsy displays increased expression of the $Ca_V3.1$ T-type calcium channel in thalamic centrolateral (CL) and lateral geniculate (LGN) neurons and of the $Ca_V3.3$ T-type in CL and RTN neurons. (d) In mice with a genetically enhanced expression of $Ca_V3.1$ channels (*Tg1* and *Tg2*) larger T-type currents are observed in lateral dorsal (LDN) and ventrobasal (VB) thalamic neurons and the mice display spontaneous bilateral spike-wave discharges in EEG recordings.

HVA channels in absence epileptic mice models

Mice generated or identified with mutations that suppress P/Q-type channel function exhibit many features of absence epilepsy. $Ca_V2.1$ gene knock-out mice suffer from severe ataxia and seizures and die in early life following massive neuronal damage, in particular in the cerebellum where P/Q-type channels play a vital role in

movement control.[66, 67, 94–97] *Tottering* mice ($Ca_V2.1$ *P601L*) display absence and motor seizures, whereas *Leaner* (C-terminal truncation) and *Rolling Nagoya* mice (*R1262G*) display absence seizures only.[98–100] Each of these mutations results in decreased P/Q-type current density and a number of other biophysical alterations, generally considered as loss-of-function.[68, 101] The reduced activity can be observed physiologically as attenuated excitatory synaptic neurotransmission in cortical and thalamic neurons.[102, 103] Similarly, *Rocker* mice (*T1310K*) display absence-like seizures, however the effects on channel biophysics are not currently known.[104] It should be noted that all of these mouse models display ataxia, likely due to the critical role of cerebellar P/Q-type channels in movement control, although which may have pro-epileptic downstream effects concerning the production of secondary seizures. In this regard, it should be noted that with the *Tottering* mouse an increase is observed in the T-type currents ($Ca_V3.1$) in thalamic relay neurons.[105]

Of further note, seizures in $Ca_V2.1$ knockout mice can be abolished by introducing a second mutation to also knockout $Ca_V3.1$ T-type channel function.[106] Although similar investigations have not been reported for the other absence model mice carrying $Ca_V2.1$ mutations, this implies that decreased activity of P/Q-type channels may lead to a compensatory increase in T-type currents, which may be responsible for the absence seizures observed. However, since in the WAG/Rij model an *increase* in P/Q-type channel expression is observed in conjunction with increased T-type activity, a compensatory decrease in P/Q-type / increase in T-type model cannot be accepted as absolute. In addition, combined knock-out studies must be treated with caution since the absence seizures observed in $Ca_V2.1$ knockout mice can be abolished by a second mutation to knockout shaker-like potassium channels, which normally increases excitability.[107] Thus, it might be argued that any number of mutations that interfere with excitability in the thalamocortical network may block the epileptic phenotype caused by a first mutation.

The mid-voltage activated R-type channel has been shown to play a role in modulating thalamocortical rhythmicity, altering the frequencies displayed during pharmacologically-induced SWD.[108] Mice lacking $Ca_V2.3$ channels do not display spontaneous absence seizures, however, they do exhibit increased susceptibility to the absence seizures and motor arrest induced by systemic administration of γ-hydroxybutyrolactone.[106] This is of particular interest since these mice also demonstrate resistance to generalized convulsive and limbic seizures (discussed in "CaV2.3 R-type channels in the kainic acid-Induced limbic epilepsy model" and "Generalized seizures in CaV2.3 transgenic mice").[110, 111]

Calcium channel ancillary subunits in absence epilepsy models

The β, $\alpha_2\delta$ and γ ancillary calcium channel subunits that modulate the biophysical properties and expression of the HVA α_1 subunits have also been implicated in absence epilepsy.[112] Mice containing a mutation that genetically deletes the β4 subunit, known as *lethargic*, express SWDs and ataxia, along with defects in presynaptic function.[113] In addition, two strains of mice with mutations in the $\alpha_2\delta_2$ subunit, known as *ducky* and *ducky^{2J}*, both also display SWDs and ataxia. [114, 115] Furthermore, a mutation that renders the $\alpha_2\delta_2$ subunit non-functional (the *entla* mouse) has also been linked to SWDs.[116] All three $\alpha_2\delta_2$ mutated mice models possess reduced P/Q-type currents and display similar absence and/or ataxia phenotypes to that for the $Ca_V2.1$ gene knockout / mutated mice described above, suggesting that at least part of the mechanism by which they induce seizures may be due to attenuated $\alpha_2\delta_2$ -mediated modulation of the $Ca_V2.1$ P/Q-type calcium channel. A similar mechanism may underlie the β4 knockout *lethargic* mice since β subunits are essential for P/Q-type channel function.

Mutations in the γ_2 subunit protein, also known as "stargazin", have been found in *stargazer* and *waggler* mouse epilepsy models and result in increased inactivation of P/Q-type channels.[117, 118] These mice both display SWDs as well as a head tossing behavior, which are exacerbated in *waggler* mice due to an additional knockout of the γ_4 subunit.[119] As a note of caution, in addition to the modulatory role of this subunit on HVA calcium channels, stargazin is known to be involved in the synaptic trafficking and biophysical modulation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. Therefore some or all of the

phenotype associated with mutations in these mice could alternately involve AMPA-mediated signaling. This may also be reflected in the GAERS model where the stargazin subunit is upregulated in both the SCX and thalamus; key areas involved in absence seizures, although no alterations in P/Q-type channel activity have yet been reported in this model.[120]

CALCIUM CHANNELS IN TEMPORAL LOBE / COMPLEX PARTIAL EPILEPSY

T-type calcium channels in the pilocarpine model of temporal lobe epilepsy/complex partial epilepsy

In the pilocarpine model of temporal lobe epilepsy (TLE) status epilepticus is induced by systemic administration of the muscarinic receptor agonist, pilocarpine.[121, 122] During an initial "acute" phase lasting up to approximately 24 hours rodents suffer from seizures resembling temporal lobe epilepsy. Following this, a seizure-free period lasting from a few days to weeks occurs until a "chronic" phase resembling complex-partial seizures develops (Figure 4). Immediately after the acute phase significant pathophysiological damage can be observed in hippocampal, thalamic, cortical and striatal structures. During this period $Ca_V3.2$ expression is upregulated and a corresponding upregulation of T-type currents is thought to occur in the apical dendrites of hippocampal CA1 neurons.[123–126] Some small changes have also been observed in the biophysical properties of the T-type currents in these neurons.[126] Burst-firing is increased in CA1 neurons after the induction of status epilepticus, as would be expected with increased T-type conductance, and can be reversed by specific blockade of $Ca_V3.2$ channels (Figure 4). Furthermore, in $Ca_V3.2$ knock-out mice, the number of seizures is attenuated, burst-firing is abolished and neuronal damage in the CA1 region (cell loss and mossy fiber sprouting) is reduced.[125] Therefore, T-type channels, specifically $Ca_V3.2$, appear to be upregulated by temporal lobe seizures and/or have a strong influence on development of complex-partial seizures in the pilocarpine model. In addition, there is a direct correlation between seizure-induced neuronal damage and upregulated expression of $Ca_V3.2$ channels; although whether increased $Ca_V3.2$ expression induces neuronal damage or if damage itself increases the expression of $Ca_V3.2$ is unknown.

T-type channels in electrical kindling model of limbic epilepsy

Seizure "kindling" is another established model for studying epilepsy in both rodents and higher animals.[127] In this model, low intensity focal electrical stimulation of a particular area of the brain is used to induce seizures, which increase in intensity and duration as the induction is repeated, due to the phenomenon that seizures lower the threshold for further seizures. For example, electrical stimulation of limbic structures can induce temporal lobe epilepsy. In rats, similar to what is seen for the pilocarpine model, kindling increases T-type currents in CA1 hippocampal neurons following stimulation applied to CA3 hippocampal efferents (Schaffer collaterals) which innervate the CA1.[128] The increase in T-type currents remains six weeks following the cessation of kindling stimulation. Simultaneous increases in neuronal hyperexcitability and damage are also observed in this model, implying that increased T-type currents may drive neurons into a pathophysiological, hyperexcitable state wherein over-excitability induces neuronal damage. Conversely, and again similar to the pilocarpine model, the reverse may be true whereby seizure-induced damage leads to an upregulation of T-type currents.

HVA channels in electrical kindling models of limbic epilepsy

In the same electrical kindling model using rats, HVA currents increase by ~50% in comparison to controls in hippocampal CA1 neurons.[128] Correspondingly, $Ca_V1.3$, $Ca_V2.1$ and $Ca_V2.3$ channel mRNA is increased in the CA1 and dentate gyrus hippocampal regions in the initial stages of epileptogenesis as seizures are developing.[129] Contrastingly, at these stages the expression of $Ca_V2.2$ N-type channel mRNA is decreased. However, once kindling is fully developed a significant *increase* is observed in expression of the $Ca_V2.2$ subtype alone.

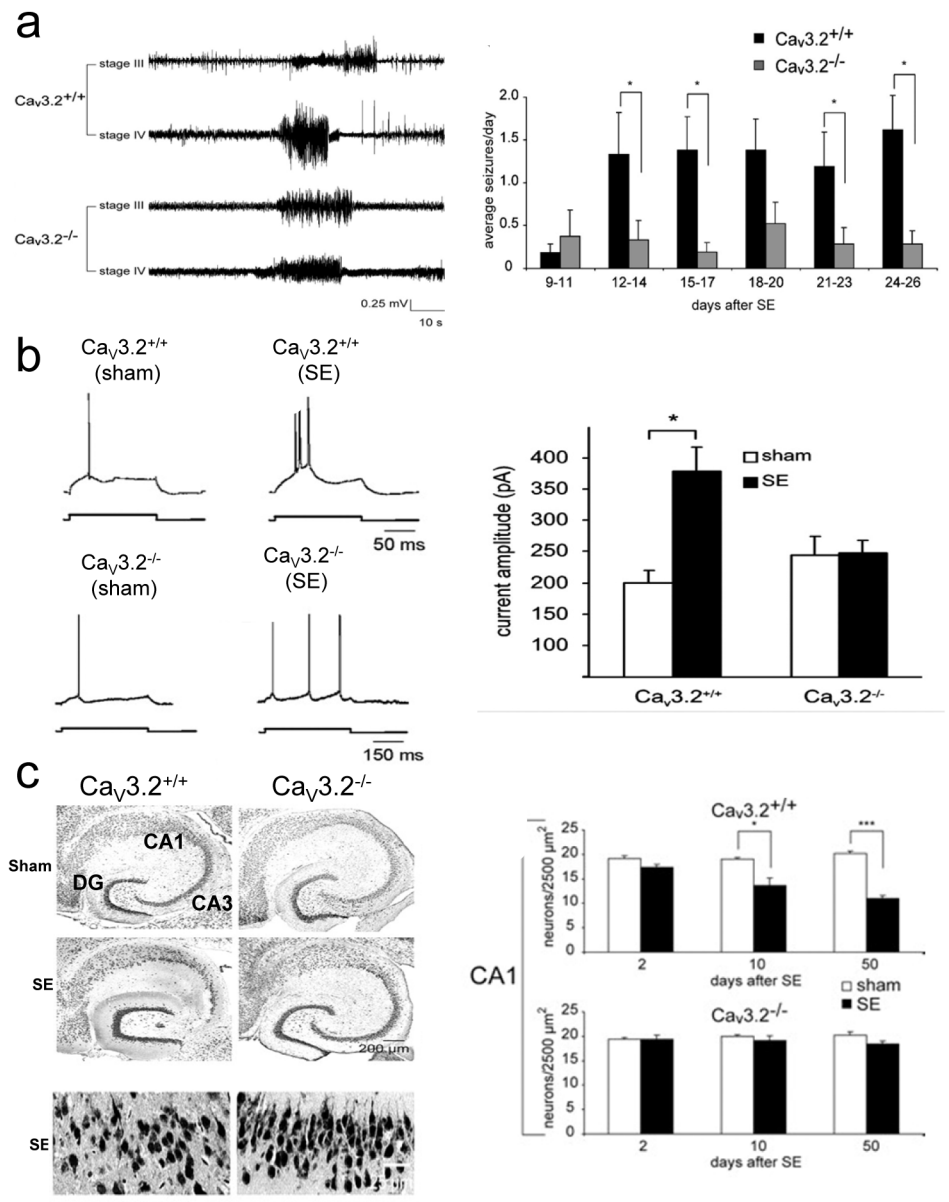

Figure 4. T-type Ca channels in temporal lobe / complex partial epilepsy. (a) Systemic injection of pilocarpine in mice induces the development of complex-partial seizures as observed with EEG recording. Seizure morphology and duration is similar in wild-type ($Ca_V3.2^{+/+}$) and $Ca_V3.2$ gene knockout mice ($Ca_V3.2^{-/-}$), however $Ca_V3.2^{-/-}$ mice display fewer seizures per day than $Ca_V3.2^{+/+}$ mice following status epilepticus (SE). (b) CA1 hippocampal neurons do not display burst-firing activity in response to depolarization in sham-treated $Ca_V3.2^{+/+}$ mice (top left panel), however in $Ca_V3.2^{+/+}$ mice displaying pilocarpine-induced seizures 7–15 days after SE (top right panel) clear burst-firing is observed. Conversely, in $Ca_V3.2^{-/-}$ mice burst-firing is not observed in either sham-treated (bottom left panel) or pilocarpine-treated (bottom right panel) animals. (b; far right panel) Increased T-type tail currents are detected in CA1 neurons of $Ca_V3.2^{+/+}$ mice treated with pilocarpine but not in CA1 neurons of sham-treated controls or $Ca_V3.2^{-/-}$ mice. (c) Neuronal cell loss occurs via a $Ca_V3.2$-dependent mechanism. Representative hippocampal sections from sham-control and SE-experienced $Cav3.2^{+/+}$ and $Cav3.2^{-/-}$ mice stained with an antibody directed against the neuron-specific epitope NeuN 50 days after treatment. Note the pronounced neuronal cell loss in CA1 and CA3 areas after SE in Cav3.2 mice but not in $Cav3.2^{-/-}$ mice. The higher-magnification micrographs of representative CA1 subfields of SE-experienced animals highlight the substantial neuronal degeneration in $Cav3.2^{+/+}$ but not $Cav3.2^{-/-}$ mice (bottom). Neuronal cell loss is quantified in the right panel.

Therefore, alterations in both HVA and T-type calcium channel expression occurs at different levels and rates in the kindling model in a subtype-specific manner making elucidation of the specific role of each subtype somewhat complicated. Nonetheless, there is a clear correlation of calcium channel expression with the development and maintenance of seizures in this limbic epilepsy model.

$Ca_V2.3$ R-type channels in kainic acid-induced limbic epilepsy model

$Ca_V2.3$ knockout mice exhibit altered susceptibility to absence seizures, and decreased susceptibility to generalized seizures as discussed in detail in "HVA channels in absence epileptic mice models" and in "Generalized Seizures in $Ca_V2.3$ transgenic mice" and are thought to contribute toward epileptogenic plateau potentials in CA1 hippocampal neurons.[108-111] Further studies have revealed that $Ca_V2.3$ deficient mice are also resistant to limbic seizures and secondary generalized seizures induced by systemic administration of the glutamate receptor agonist, kainic acid.[110] It should be noted that this only applies to the more severe stages of seizure in this model and that lower severity seizures actually display signs of increased sensitivity as has been suggested for absence seizures in these mice.[108] In addition, these mice show reduced neuronal cell loss and neurodegeneration within the CA3 region in response to seizures and their survival rate is significantly improved.

CALCIUM CHANNELS IN GENERALIZED CONVULSIVE SEIZURES

HVA calcium channels in Genetic Epilepsy Prone Rats

Genetic Epilepsy Prone rats (GEPRs) are inbred Sprague-Dawley strains that develop either moderate (GEPR-3) or severe (GEPR-9) predisposition to, and expression of spontaneous as well as audiogenic and kindling-induced complex-partial seizures leading to secondary tonic-clonic seizures. Seizures are thought to originate from the forebrain and/or brainstem circuitry as well as the inferior colliculus.[130, 131] HVA calcium currents have been shown to be increased in inferior colliculus neurons of the less severe seizure expressing GEPR-3 strain.[132] Corresponding increases in $Ca_V1.3$ L-type and $Ca_V2.3$ R-type protein levels are observed in neurons from this region in GEPR-3 rats which have not yet suffered seizures.[133] Following a single audiogenic seizure GEPR-3 rats display a further increase in the expression of both $Ca_V1.3$ and $Ca_V2.3$ calcium channels and also an increase in the expression of the $Ca_V2.1$ P/Q-type. Interestingly, these are the same calcium channel types upregulated in limbic electrical kindling models, further supporting their role in epileptic susceptibility.

Generalized seizures in $Ca_V2.3$ transgenic mice

The $Ca_V2.3$ knockout mouse model displays altered susceptibility to pharmacologically-induced absence and limbic seizures.[108, 109, 110] While these mice display no spontaneous seizures, it has been demonstrated that $Ca_V2.3$ knockout mice show resistance to generalized convulsive seizures and reduced lethality induced by systemic administration of the GABA receptor antagonist pentylenetetrazol.[111] However, these mice do not show any altered susceptibility to seizures induced administration of the potassium channel blocker, 4-aminopyrridine.

Calcium channels ancillary subunits in genetic convulsive animal models

In addition to the alterations in HVA channel α_1 subunit expression in GEPRs, expression abnormalities of the calcium channel ancillary subunits have also been observed in this model. Expression of the β_3 subunit is increased in seizure-naïve GEPR-3 rats and increases further following induction of a single audiogenic seizure.[133] Contrastingly, expression of the $\alpha_2\delta$ subunit is decreased in seizure-naïve GEPR-3 rats and decreases further following induction of a single audiogenic seizure. The overall affect on calcium currents remains difficult to establish due to the altered expression of the HVA channel subunits that also occurs in GEPRs.

CONCLUSIONS

A number of currently used anti-epileptic drugs (AEDs) have been shown to block calcium channels.[134] These include front line absence treatments such as ethosuximide[49, 135–150] and valproic acid[49, 138, 151–152], zonisamide[153–157] and leviteracetam[160, 172–173] in the treatment of partial-onset and generalized seizures,

lamotrigine[49, 158–163] and gabapentin/pregabalin[174–182] for partial seizures and primary/secondary generalized convulsive seizures and phenytoin[49, 164], carbamazepine[47, 165,166]and topiramate[150, 167–170] to control complex-partial and tonic-clonic seizures. In many cases the exact relevance of the *in vitro* pharmacological findings are difficult to interpret since the cells in which the AEDs have been tested *in vitro* are often not from the region where the drug has its intended effect *in vivo*. Further difficulties arise from the drug concentrations used since the accurate measurement of clinical AED concentrations in specific human brain areas is often not possible, resulting in the drug concentrations for *in vitro* testing being estimated from human plasma concentrations combined with animal cerebral spinal fluid concentration to plasma concentration ratios. The result is often that higher or lower concentrations may be tested in comparison to those existing in the brains of epileptic patients. Within these limitations, in most *in vitro* studies 100% block of calcium channel activity is rarely observed with clinical concentrations of AEDs. Despite this, convincing evidence for the involvement of subtype-selective calcium channels in AED pharmacology is mounting for some of the currently used AEDs. As a result, calcium channels are more commonly being viewed as attractive targets for novel epileptic therapies. While small molecules with the ability to specifically block individual calcium channel subtypes are not presently available, considerable effort is ongoing towards developing new and selective calcium channel blocking compounds aimed at the treatment of epilepsy.[183]

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