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Review

T-type calcium channels in burst-firing, network synchrony, and epilepsy ☆

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ABSTRACT

Low voltage-activated (LVA) T-type calcium channels are well regarded as a key mechanism underlying the generation of neuronal burst-firing. Their low threshold for activation combined with a rapid and transient calcium conductance generates low-threshold calcium potentials (LTCPs), upon the crest of which high frequency action potentials fire for a brief period. Experiments using simultaneous electroencephalography (EEG) and intracellular recordings demonstrate that neuronal burst-firing is a likely causative component in the generation of normal sleep patterns as well as some pathophysiological conditions, such as epileptic seizures. However, less is known as to how these neuronal bursts impact brain behavior, in particular network synchronization. In this review we summarize recent findings concerning the role of T-type calcium channels in burst-firing and discuss how they likely contribute to the generation of network synchrony. We further outline the function of burst-firing and network synchrony in terms of epileptic seizures. This article is part of a Special Issue entitled: Calcium channels.

Contents

1. T-type calcium channels and burst-firing

Calcium ion entry through voltage-activated calcium channels both depolarizes the cell membrane and regulates numerous intracellular signaling pathways. T-type calcium channels are known as low voltage-activated (LVA) channels as they first open at more hyperpolarized membrane potentials compared to high-voltage activated (HVA) calcium channels, such as the L-, P/Q-, N- and R-type channels [1]. The distinct properties of T-type calcium channels allow the conduction of inward current in response to smaller membrane depolarizations than those required to activate HVA calcium or even sodium channels [2]. In this regard, T-type calcium channels are first-responders to small depolarizations and their activity further depolarizes the cell to the point where HVA and sodium channels activate allowing both large scale calcium entry and the generation of action potentials [3,4]. Despite their lower threshold for activation, T-type channels inactivate at a fast rate, resulting in a transient surge in calcium entry. Under conditions in which there is sufficient depolarization to induce T-type activation and, additionally that there is sufficient density of T-type channels, a cascade depolarization can occur generating a LTCP upon the crest of which sodium and potassium channel-mediated action potentials fire [5]. Firing continues until the T-type channels inactivate in parallel with the activation of small conductance calcium-activated potassium channels,

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which repolarize the membrane back below the range of T-type channel activation [6,7]. Overall, the entire burst process takes approximately 100 to 200 ms limiting the frequency at which bursting can occur to around 5 to 10 Hz [3]. Of note, if multiple bursts occur out-of-phase with each other, burst-firing in distinct local areas can generate higher frequency output for an entire regional population of neurons [8]. The burst-firing mode is predicted to promote the synchronization of bursting and oscillations not only within particular neural nuclei of the brain, but also between interconnected loci in central nervous system (CNS) networks and to contribute to normal non-REM sleep and also to some types of epileptic seizures.

Three T-type calcium channel genes are expressed in mammalian tissues; $Ca_V3.1$, $Ca_V3.2$ and $Ca_V3.3$. The three isoforms are distinctly expressed throughout the central and peripheral nervous systems as well as in non-neuronal tissues and are predicted to play crucial roles in numerous physiological processes [2]. T-type calcium channels are most well known for their part in controlling neuronal excitability [3,9] and have been implicated in several pathophysiological disorders [10,11]. In both endogenous and exogenous systems the T-type calcium channel subtypes exhibit distinct biophysical properties concerning their rates and voltage dependences of activation and inactivation, recovery from inactivation (de-inactivation) and deactivation, allowing a wide array of cell-specific responses to be generated depending upon the expression of specific subtypes [3,12,13]. The spectrum of T-type calcium channel types is made more complex by the occurrence of multiple alternatively spliced isoforms, generating a large number of functional variants and potentially allowing for highly tailored excitability profiles. Overall, the LTCPs and the bursts that T-type calcium channels generate are predicted to vary in their voltage dependences and duration as well as rates of depolarization and repolarization [3]. The strength of burst-firing also varies in its sensitivity to depolarizing stimuli, with some bursts generating more action potentials in response to stronger stimuli and others displaying an all or nothing response, where maximal action potential numbers are seen with either threshold or supra-threshold stimuli [8]. Along these lines, it is predicted that depending upon the relative expression of particular T-type calcium channel isoforms burst-firing itself can vary, with specific burst types occurring in different neurons and in different pathophysiological states. As such, while many types of neurons exhibit burst-firing, it is important to understand the complement of T-type calcium channels expressed within particular neurons.

2. T-type calcium channels and network synchrony

It might be predicted that a high frequency burst of action potentials in a neuronal cell body would produce a similar effect at axon terminals, generating a powerful release of neurotransmitter onto the postsynaptic cell and therefore, a more pronounced effect than that produced by a more low frequency, tonic firing event. It is also likely that a key effect of a burst, at least on postsynaptic cells, may be the short-lived nature of the synaptic drive, inducing a momentary depolarization or hyperpolarization in response to strong yet brief neurotransmitter release.

Alternately, it is possible that a primary role for burst-firing may occur within the cell in which it is generated. When a burst is generated in a thalamocortical relay (TCR) neuron at any point, for example in a distal dendrite, proximal dendrite, or cell body, the LTCP is conducted not only to the soma, but also back-propagates throughout the entire dendritic tree. Contrastingly, the calcium signal generated by action potentials, as well as the action potentials themselves fail to back-propagate into more distal dendrites [14,15]. In this regard, the burst-firing process may act as a neuronal frequency filter, preventing the conduction of recent incoming postsynaptic activity to the soma, and thereby preventing other activities contributing to the neuronal output, at least until the LTCP abates or another burst occurs. In theory, this notion fits well with the bi-modal role of TCR neurons which act as relay cells for sensory information during wakefulness, but become locked in an oscillatory thalamocortical loop in some non-REM sleep states and absence seizures. In the relay state TCRs primarily fire in a tonic manner and can modulate firing frequency in response to incoming sensory or cortical activities [16–18]. The cell membrane potential does not reach the hyperpolarized potentials necessary to de-inactivate T-type calcium channels and therefore bursts do not occur. However, during sleep or epileptic seizures TCRs become locked in a self-propagating oscillatory loop along with corticothalamic pyramidal and reticular thalamic neurons, during which they primarily burst-fire due to a long lasting hyperpolarization that promotes T-type channel de-inactivation [5]. It is in this burst-firing state that TCRs do not conduct sensory information, predictably because incoming sensory activity is filtered out by the burst frequency-locked oscillation. Together, a neuronal burst may play a dual role, with high frequency action potentials creating a powerful output signal to the postsynaptic cell to propagate the network oscillation, whilst back-propagating LTCPs filter out incoming signals that occur outside the frequency of the membrane oscillation.

The network synchronization that is thought to occur as a result of burst-firing likely develops from diffuse projections to reciprocally connected CNS nuclei [19–22]. Bursts that start in one area of the initiating nucleus are predicted to generate bursts in multiple postsynaptic neurons in the projected nucleus through axonal arborization to multiple synapses. These bursting neurons will in turn recruit additional neurons in the reciprocally connected initiating nucleus and this amplification will progress on each cycle of the oscillation. Another possibility for the development of network synchronization may occur as a result of dendrite–dendrite interconnection. As a single burst in one dendrite is capable of generating an LTCP throughout the dendritic tree [14,15] and also given that T-type dependent dendrite–dendrite synaptic neurotransmission has been reported [23–25], it is feasible that dendrites are capable of transmitting burst activity to other dendrites. If this process indeed occurs, it would provide a regional mechanism of generating synchrony in a local area without the need for conventional axonic synapses in reciprocally connected neurons. In this regard, it is of note that gap junctions have been implicated in synchronizing TCR firing, at least at alpha and theta frequencies associated with wakeful relaxation and drowsy or light sleeping states, respectively [26].

3. T-type calcium channels and epilepsy

3.1. Human epilepsy mutations in T-type calcium channels

A number of single base changes have been identified in the genes encoding for the $Ca_V3.1$ and $Ca_V3.2$ T-type calcium channels in some patients with generalized epilepsies [10,11,27–31]. Of 13 *CACNA1G* (encoding $Ca_V3.1$) variants identified in one study of genetic generalized epilepsy patients, five resulted in amino acid substitutions, with one occurring in the domain I–II intracellular linker and the rest found in the domain II–III linker [27]. No statistically significant differences were identified in $Ca_V3.1$ functional properties when evaluated exogenously using heterologous expression systems, although moderately faster inactivation decay rates were noted with some mutations.

A large number of base changes have been identified in the *CACNA1H* gene in patients with childhood absence [28,30,32] as well as juvenile absence, juvenile myoclonic, myoclonic astatic, febrile and temporal lobe epilepsies [29], many of which result in amino acid substitutions. Childhood absence epilepsy mutations occur primarily in the $Ca_V3.2$ domain I–II linker with most of the remaining mutations found in the voltage-sensing, pore and carboxyl-terminal regions [10,11]. The mutations associated with other epilepsies display a fairly diverse distribution in their structural location [29]. Upon exogenous evaluation of $Ca_V3.2$ calcium channel biophysical properties many of the alterations were found to induce changes considered to be a gain-of-function (i.e., hyperpolarized shift in the voltage-dependence of activation),

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although some had no apparent effect and others displayed an apparent loss-of-function (such as reduced current density) [32–37]. While these varied effects may reflect the polygenic nature of epilepsy, some genetic variability may also represent single nucleotide polymorphisms (SNPs) unrelated to the epileptic condition. In addition, recent studies have shown that some genetic mutations in calcium channel isoforms exhibit splice variant-specific functional effects [38–40]. Therefore, it is important to consider when studying calcium channelopathies using cloned channels that the contextually relevant variants for a particular CNS region or even specific neuron type are likely crucial towards determining biophysical alterations in channel properties. The testing of splice variants insensitive to a particular mutation/SNP may exhibit a false negative result thus alterations that lack effects exogenously should not necessarily be discounted as irrelevant towards epileptogenesis.

3.2. T-type calcium channels and burst-firing in limbic epilepsy

Some of the most convincing data linking T-type calcium channels and burst firing to seizures come from rodent models of epilepsy wherein increased T-type calcium currents are often observed in parallel with enhanced burst-firing properties [41]. Systemic administration of pilocarpine is used in rats and mice as a model of complex-partial and temporal-lobe epilepsy, in the short- and long-term, respectively [42,43]. Animals that develop chronic seizures several days after pilocarpine treatment display up-regulated $Ca_V3.2$ expression and increased T-type calcium current density that correlates with increased burst-firing in dendrites of hippocampal CA1 pyramidal neurons [44–46]. Genetic ablation of $Ca_V3.2$ prevents the seizure-induced increase in T-type currents, as well as burst-firing, and also attenuates the neuronal damage observed in the CA1 and CA3 regions following initial status epilepticus [47]. In the same model, enhanced burst-firing is also observed in subiculum neurons [48], as well as in midline thalamic neurons that project to the hippocampal CA1 and entorhinal cortex in parallel with increased $Ca_V3.2$-mediated T-type calcium currents [49]. How this increased burst-firing activity affects network synchrony in the hippocampus and related structures is unknown. However, it could be postulated that bursting would increase cycling oscillatory activity within the limbic network as increasing numbers of neurons are recruited and as firing becomes synchronized in response to frequency filtering.

3.3. T-type calcium channels and burst-firing in absence epilepsy

Further evidence implicating burst-firing in seizures is observed in rodents with either genetically-induced or spontaneously-acquired epileptic phenotypes [41,50]. Genetically modified mice with HVA calcium channel dysfunction display absence seizures accompanied by enhanced T-type (likely $Ca_V3.1$-mediated) calcium currents in TCR neurons [51]. In support, the genetic enhancement of $Ca_V3.1$ currents in mouse TCR neurons, either directly via $Ca_V3.1$ channel overexpression or indirectly by knockout of phospholipase C β4, induces absence seizure-like phenotypes [52–54]. Furthermore, genetic ablation of $Ca_V3.1$ reduces sensitivity to some types of pharmacologically-induced absence seizures [55]. Interestingly, a recent study proposed that different splice variants of the mouse *Cacna1g* gene act as candidate modifiers for the severity of the epileptic phenotype induced by mutations in voltage-gated sodium channels [56].

In the Wistar Albino Glaxo Rats from Rijswijk (WAG/Rij) model of absence epilepsy that display spontaneously-acquired seizures [57,58], enhanced $Ca_V3.1$ and $Ca_V3.3$ currents have been observed in lateral geniculate and centrolateral TCR neurons [59]. Computer modeling suggests that the enhanced T-type current reduces the stimulus required to induce burst-firing in these neurons. In addition, a modest increase in $Ca_V3.2$ currents is observed in WAG/Rij reticular thalamic nucleus (RTN) neurons. Combined simultaneous multiunit, EEG and intracellular recordings show that TCR neurons from several TCR (e.g. centrolateral; Fig. 1D) areas as well as RTN neurons burst-fire during seizures and correlate with the spikes in spike-and-wave discharges (SWDs), a hallmark of absence seizures on surface EEG recordings [60–62]. It should be noted that not all thalamic regions exhibit recurrent burst-firing, as some only fire one or two action potentials, or infrequent bursts per EEG spike. However, spike frequency-locked membrane oscillations resembling low-level LTCPs are present in recordings from neurons that do not display burst-firing. In addition, while burst-firing in RTN neurons occurs at the same time as spikes in SWDs, action potential firing in other TCR (e.g., centrolateral, paracentral; Fig. 1D and E) areas is observed to lag EEG spikes.

In the Genetic Absence Epilepsy Rats from Strasbourg (GAERS) model [58,63], burst-firing occurs in RTN neurons and correlates closely with spike-timing in cortical EEG recorded SWDs (Fig. 1A) [64,65]. In this model, RTN neurons display increased T-type currents [66] via $Ca_V3.2$ channel up-regulation [67,68]. In addition, these animals possess a missense mutation in the gene encoding for $Ca_V3.2$ which increases the rate of channel recovery from inactivation and is predicted to enhance calcium conductance to RTN neurons during burst depolarizations [38]. While RTN neurons are GABAergic, the hyperpolarization they induce in TCR neurons can play an excitatory role. T-type (primarily $Ca_V3.1$) calcium channels in the relatively depolarized TCR neurons are predominantly inactive at rest and hyperpolarization induced by GABA release from RTN axon terminals drives their de-inactivation. On cessation of hyperpolarization, TCR neurons can then burst-fire; a process known as rebound burst-firing. However, at least in GAERS it appears that GABAergic drive to TCR neurons may not actually induce rebound bursts during absence seizures, but instead induce membrane oscillations [69]. Similar to some TCR regions in the WAG/Rij model, neurons in the GAERS ventrobasal thalamic nucleus (e.g., ventroposterior lateral) appear to display sub-threshold membrane oscillations in time with SWDs, but only fire single or double action potentials (if any) upon the crest of the depolarization (Fig. 1C) [70,71]. Neurons in a nearby TCR region; the ventromedial thalamic nucleus, do appear to occasionally burst-fire on the crest of membrane oscillations that occur in time with SWDs, however bursts do not occur on each depolarization, appearing almost sporadically with sometimes no action potentials or only one or two action potentials firing [71]. In both cases, neuronal rebound burst firing can be manually induced by direct hyperpolarizing current injection, however during SWDs bursting does not occur. If TCR burst-firing does not faithfully follow seizure activity in GAERS (as well as in some WAG/Rij TCR regions) it could be questioned whether TCR burst-firing is truly required for absence seizure propagation, contrary to the studies discussed above concerning genetically modified mice with altered $Ca_V3.1$ activity in TCR neurons.

3.4. Silencing neuronal output with membrane oscillations

GAERS cortical pyramidal neurons also display robust burst-firing that precedes spikes in the SWDs recorded on cortical EEGs (Fig. 1B) [69,72]. Without a reciprocal positive feedback from TCR neurons, how does cortical burst-firing continue to propagate? Corticothalamic pyramidal neurons project to TCR neurons, but also to the RTN (Fig. 2). Burst-firing in the RTN can only be conveyed back to the cortex via burst-firing TCR neurons, since the RTN has no direct connection to the cortex. Therefore, if TCR neurons do not burst faithfully in response to burst-firing in either the RTN or the cortex then this activity will not be propagated as thalamocortical network oscillations. In addition, as discussed in Section 2, for the oscillations to spread and recruit other cortical areas, in the classic theory of absence seizures, functional and bursting connections between TCR neurons and the cortex are required. If this network theory is correct then without positive feedback from burst-firing in the TCR neurons, regions outside the cortical epileptic focus cannot be recruited.

At least for GAERS, there appear to be three possible explanations for the lack of burst-firing observed in TCR neurons. In one scenario, simultaneous EEG and intracellular recordings may not yet have

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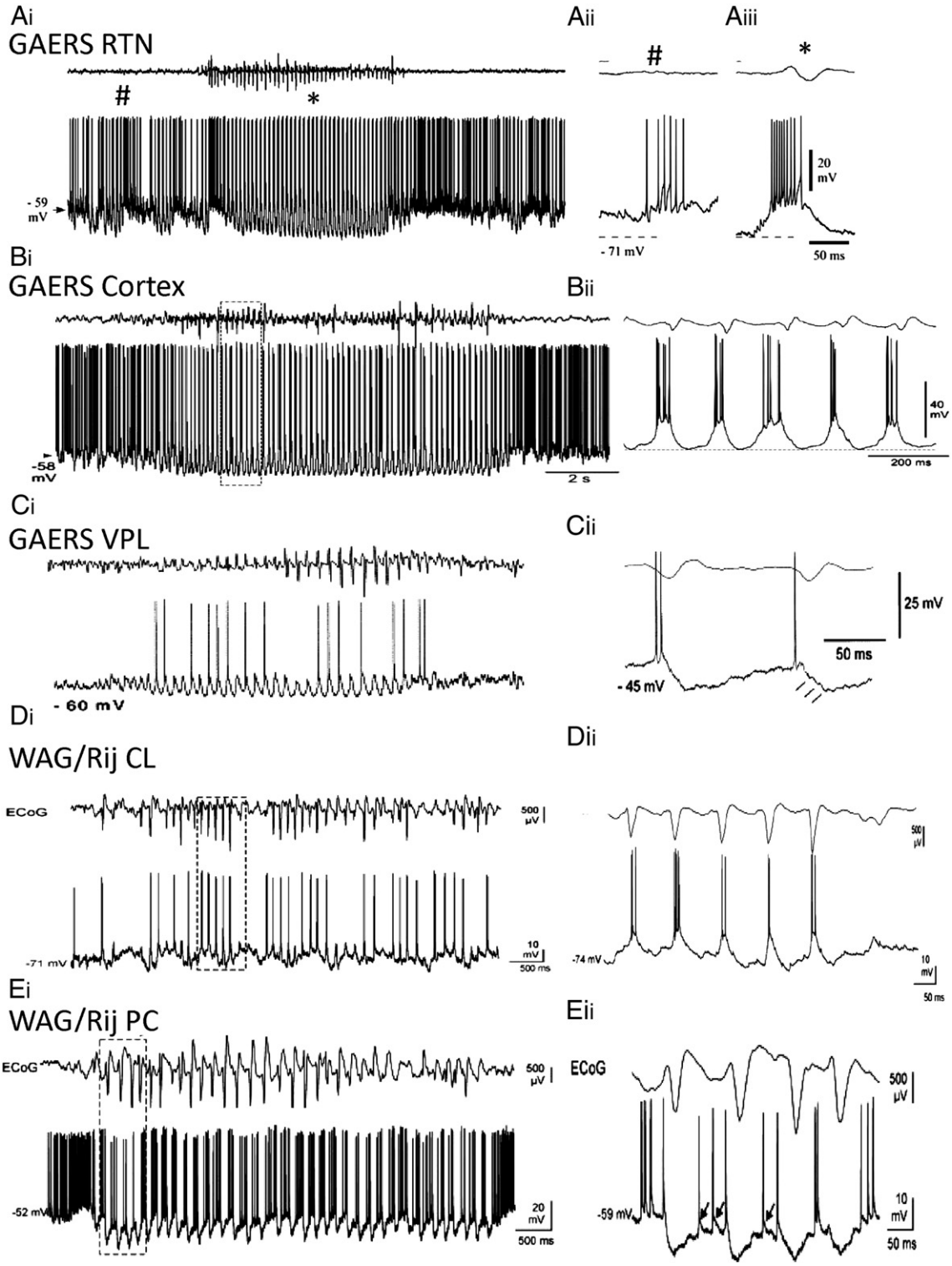

Fig. 1. Correlation between burst-firing and subthreshold membrane oscillations with SWDs. In each panel upper traces correspond to EEG/ElectroCorticoGram (ECoG) recordings while lower traces correspond to intracellular recordings from representative single neurons. Panels on the right hand side show expanded time scales from the panels on left hand side. (A) SWDs in GAERS correlate closely with burst-firing in RTN neurons (*Ai and Aiii) while non-burst action potentials do not correlate with SWDs (#Ai and Aii). (B) SWDs in GAERS also correlate with bursts in cortical layer V/VI pyramidal neurons (representative example from a layer VI neuron shown here). Note that bursts precede spikes in SWDs (Bii). (C) In GAERS VPL neurons SWDs correlate with subthreshold membrane oscillations with sporadic action potential firing but without bursting (Cii). (D) Contrastingly, in WAG/Rij CL neurons SWDs correlate with burst-firing (Dii), but also display single action potentials or subthreshold membrane oscillations (Di). (E) In WAG/Rij PC neurons SWDs correlate with subthreshold membrane oscillations with sporadic action potentials (Eii). Also note that action potential firing takes place out of synchrony with spike-timing in SWDs (Eii). VPL, CL and PC represent different types of TCR neurons. SWD = spike–wave discharge, RTN = reticular thalamic nucleus , VPL = ventroposterior lateral, CL = centrolateral, PC = paracentral. (*A*) *Reproduced from Reference* [64], (*B*) *Reproduced from Reference* [72], (*C*) *Reproduced from Reference* [70], (*D and E*) *Reproduced from Reference* [61].

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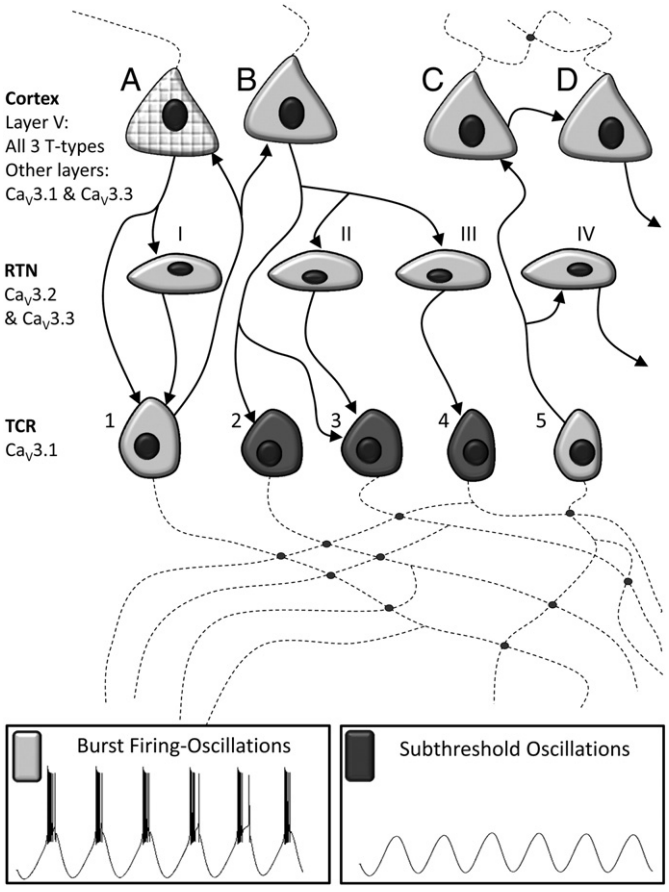

Fig. 2. Possible connectivity and synchronization mechanisms in the thalamocortical system. Schematic of three nuclei in the thalamocortical circuit implicated in burst-firing and seizures. Solid lines with arrows denote axonal projections from burst-firing neurons. Dotted lines represent dendrites. Dots represent dendritic synapses. Pyramidal neuron A (cross-hatched) is in an epileptic focus and generates paroxysmal oscillatory burst-firing, in turn inducing burst-firing in both RTN neuron I and TCR neuron 1. TCR neuron 1 bursts in response to incoming oscillatory drive, reciprocally inducing burst-firing in pyramidal neuron A, while also recruiting pyramidal neuron B via TCR axonal arborization. Pyramidal neuron B innervates TCR neurons 2 and 3, and also in RTN neurons II and III via axonal arborisation, in turn providing drive to TCR neurons 3 and 4. However, TCR neurons 2, 3 and 4 respond only with subthreshold membrane oscillations without burst-firing, therefore the no burst-firing signal is returned to the RTN or cortex. TCR neuron 5 receives oscillatory input from dendritic LTCPs occurring in TCR neurons 1, 2, 3 and 4, via dendrite–dendrite synapses, generating burst-firing in TCR neuron 5, which recruits RTN neuron IV (continuing recruitment propagation throughout the network) and cortical neuron C. Lastly, cortical neuron C recruits cortical neuron D via intracortical axonal and/or dendrite-dendritic synaptic connections and continues recruitment propagation throughout the network. The potential mechanisms illustrated could occur as different combinations of the individual connections described. RTN = reticular thalamic nucleus, TCR = thalamocortical relay.

been undertaken in the specific TCR neuronal region(s) in which burst-firing occurs in synchrony with spikes in SWDs. This seems plausible given the TCR nucleus-specific differences in burst-firing described above in the WAG/Rij model. Indeed, absence seizures may display a more focal as opposed to typically generalized nature, affecting only particular thalamocortical regions, which would fit with the finding that only particular areas of the thalamus propagate the burst-firing SWD activity [73].

A second possibility arises if the thalamocortical circuit can sustain network oscillatory activity without the requirement of burst-firing in TCR neurons. Since burst-firing appears to occur in cortical as well as RTN neurons during seizures, this would make the lack of bursting in TCR neurons an exception to the rule. In this circumstance could non-bursting yet membrane oscillatory activity in TCR neurons be sufficient to maintain oscillatory activity in the thalamocortical network? It may be that the one or two action potentials or sporadic bursts that occur on membrane oscillations are sufficient to propagate the seizure activity and recruit other cortical areas. However, it seems unlikely that such sporadic and low level activity would be sufficient to generate the drive required to recruit and amplify thalamocortical network oscillations.

A third possible scenario is that subthreshold membrane oscillations themselves, irrespective of action potentials, may be sufficient to induce the absence seizure phenotype (i.e. sensory shutdown). This would require sustained drive to occur from the cortex, without the need for TCR feedback in order for propagation of the seizure to occur. Subthreshold membrane oscillations observed in GAERS TCR neurons during seizures are proposed to occur as a result of interplay between GABA(A) receptor-mediated GABAergic (RTN) and glutamatergic (corticothalamic) synaptic activity [70,71,74]. It is thus feasible that these sub-threshold membrane oscillations could generate T-type channel-mediated calcium potentials that propagate throughout the cell body and dendritic tree, such as that occurs with LTCPs. In doing so this may allow TCR neurons to act as a frequency filter without increasing their action potential output. These membrane oscillations typically occur in the presence of a hyperpolarization that lasts for the duration of the oscillation [70,71] thus hyperpolarization of TCR neurons could promote enhanced T-type channel de-inactivation and support a role for calcium conductance during membrane oscillations. In addition, as discussed in Section 2, dendrite–dendrite synapses or gap junctions could spread such membrane oscillations through local TCR regions.

In this third hypothesis sporadic action potentials would be relatively irrelevant towards the role of TCR neurons during absence seizures. SWD activity has been shown to develop initially in the cortex via paroxysmal intrinsic oscillatory activity, which then recruits a potentially hyperexcitable RTN [72,75]. The driving force arriving from upstream cortical and RTN neurons may simply act to silence TCR output, while allowing the synchronization of their sub-threshold oscillations via LTCP-like oscillatory activity. This would have the effect of blocking afferent sensory input to the thalamus and therefore to the cortex, as well any efferent information from the cortex to the periphery. This hypothesis is likely only relevant if reciprocal feedback from TCR neurons to the cortex is not necessary to maintain and spread oscillatory activity in the thalamocortical network [17,76]. If cortical oscillations can be maintained in and spread to neighboring cortical areas from the epileptic focus then the theory becomes plausible.

Overall, we hypothesize it most likely that a combination of scenarios one and three is likely most relevant to the GAERS model and that as observed in WAG/Rij, there are region-specific roles for burst-firing and sub-threshold oscillations in TCR subregions (Fig. 2). If this is the case, primary TCR regions may burst-fire in phase with SWDs, which act to propagate the oscillatory activity and absence seizures, while secondary TCR regions generate subthreshold membrane oscillations that, although not directly participating in thalamocortical network oscillations, act to dampen and suppress the relay mode of TCR output and any sensory relay activity within secondary TCR regions.

4. Concluding remarks

While the link between T-type calcium channels and burst-firing is well established, the link between burst-firing and epilepsy is not as clearly understood. It is known that burst-firing increases network synchrony and recruitment, and that this contributes to seizure generation and propagation. In rodent models of limbic epilepsy, increased T-type activity and enhanced burst-firing has been observed in a number of hippocampal and thalamic regions, although the effects on network synchrony are less clear. In absence epilepsy, numerous studies have linked enhanced T-type activity to seizures associated with cortical, RTN and TCR regions of the thalamocortical network. While cortical areas of the epileptic focus and RTN neurons display bursting in synchrony with spikes in SWDs, a lack of correlation is seen in several TCR subregions. It is predicted that burst-firing acts to

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propagate and synchronize firing both locally and throughout the thalamocortical network, while also acting as a frequency filter preventing sensory information being relayed to the cortex. In the non-bursting regions it is possible that subthreshold oscillations are capable of performing a filtering task without increasing neuronal output. Subthreshold oscillations alone may allow particular neuronal areas to perform a silencing role during sleep and epileptic seizures, suppressing sensory relay to specific cortical areas. Contrastingly, bursting regions may spread network oscillations and recruit interconnected cortical areas, while simultaneously acting as a frequency filter.

As advances are made towards understanding the mechanisms of network synchronization, so too will our understanding of how burst-firing synchronizes both local and remote interconnected regions. Some questions can likely be approached more promptly, for example whether bursts or LTCPs can be propagated from neuron to neuron through dendrites could be established with calcium imaging studies. Similarly, why some TCR neurons burst-fire during SWDs while others do not, despite having the capability to do so may relate to the intrinsic resting membrane potential of the neurons involved [61,62] and/or to region-specific differences in T-type channel expression. With such information it may be possible to develop more specific drug treatments that target network oscillations at specific nuclei, thereby suppressing pathophysiological absence seizures without interfering with normal physiological, for example, relay activity. While ethosuximide is a front line absence epilepsy treatment with reported inhibitory effects on T-calcium channels, contradictory evidence suggests that it is primarily efficacious on the persistent sodium channel current [77–80]. Several novel small molecule treatment efforts aimed at the generation of high affinity selective T-type calcium channel blockers have recently been reported. These include the TTA compounds, which exhibit efficacy in suppressing seizures in the WAG/Rij model [81–83], although a secondary effect of enhancing slow-sleep has also been reported [84]. Another new promising agent is Z944 which inhibits cloned and native T-type currents and also suppresses both thalamic burst-firing and absence seizures in the GAERS model [85]. Z944 has successfully advanced through an early human phase 1 clinical trial thus the search for new and better epilepsy therapies is making headway.

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References

[1] W.A. Catterall, E. Perez-Reyes, T.P. Snutch, J. Striessnig, International Union of Pharmacology XLVIII Nomenclature and structure–function relationships of voltage-gated calcium channels, Pharmacol. Rev. 57 (2005) 411–425.
[2] E. Perez-Reyes, Molecular physiology of low-voltage-activated T-type calcium channels, Physiol. Rev. 83 (2003) 117–161.
[3] S.M. Cain, T.P. Snutch, Contributions of T-type calcium channel isoforms to neuronal firing, Channels 4 (2010) 44–51.
[4] J. Xu, C.E. Clancy, Ionic mechanisms of endogenous bursting in CA3 hippocampal pyramidal neurons: a model study, PLoS One 3 (2008) e2056.
[5] H. Jahnsen, R. Llinas, Voltage-dependent burst-to-tonic switching of thalamic cell activity: an in vitro study, Arch. Ital. Biol. 122 (1984) 73–82.
[6] H.H. Yazdi, M. Janahmadi, G. Behzadi, The role of small-conductance Ca2+-activated K+ channels in the modulation of 4-aminopyridine-induced burst firing in rat cerebellar Purkinje cells, Brain Res. 1156 (2007) 59–66.
[7] Y. Lee, J.-H. Han, C.-S. Lim, D.-J. Chang, Y.-S. Lee, H. Soh, C.-S. Park, B.-K. Kaang, Impairment of a parabolic bursting rhythm by the ectopic expression of a small conductance Ca2+-activated K+ channel in Aplysia neuron R15, Neurosci. Lett. 349 (2003) 53–57.
[8] D. Contreras, The role of T-channels in the generation of thalamocortical rhythms, CNS Neurol. Disord. Drug Targets 5 (2006) 571–585.
[9] M.C. Iftinca, G.W. Zamponi, Regulation of neuronal T-type calcium channels, Trends Pharmacol. Sci. 30 (2009) 32–40.
[10] S.M. Cain, T.P. Snutch, Voltage-gated calcium channels and disease, Biofactors 37 (2011) 197–205.
[11] P.J. Adams, T.P. Snutch, Calcium channelopathies: voltage-gated calcium channels, Subcell. Biochem. 45 (2007) 215–251.
[12] J. Chemin, A. Monteil, E. Perez-Reyes, E. Bourinet, J. Nargeot, P. Lory, Specific contribution of human T-type calcium channel isotypes (alpha(1G), alpha(1H) and alpha(1I)) to neuronal excitability, J. Physiol. 540 (2002) 3–14.
[13] A.S. Kozlov, F. McKenna, J.H. Lee, L.L. Cribbs, E. Perez-Reyes, A. Feltz, R.C. Lambert, Distinct kinetics of cloned T-type Ca2 + channels lead to differential Ca2 + entry and frequency-dependence during mock action potentials, Eur. J. Neurosci. 11 (1999) 4149–4158.
[14] A.C. Errington, J.J. Renger, V.N. Uebele, V. Crunelli, State-dependent firing determines intrinsic dendritic Ca2+ signaling in thalamocortical neurons, J. Neurosci. 30 (2010) 14843–14853.
[15] S.R. Williams, G.J. Stuart, Action potential backpropagation and somato-dendritic distribution of ion channels in thalamocortical neurons, J. Neurosci. 20 (2000) 1307–1317.
[16] J.R. Huguenard, Neuronal circuitry of thalamocortical epilepsy and mechanisms of antiabsence drug action, Adv. Neurol. 79 (1999) 991–999.
[17] J.P. Manning, D.A. Richards, N.G. Bowery, Pharmacology of absence epilepsy, Trends Pharmacol. Sci. 24 (2003) 542–549.
[18] H. Blumenfeld, Cellular and network mechanisms of spike–wave seizures, Epilepsia 46 (2005) 21–33.
[19] S. Kakei, J. Na, Y. Shinoda, Thalamic terminal morphology and distribution of single corticothalamic axons originating from layers 5 and 6 of the cat motor cortex, J. Comp. Neurol. 437 (2001) 170–185.
[20] A. Destexhe, T. Bal, D.A. McCormick, T.J. Sejnowski, Ionic mechanisms underlying synchronized oscillations and propagating waves in a model of ferret thalamic slices, J. Neurophysiol. 76 (1996) 2049–2070.
[21] P. Landry, M. Deschênes, Intracortical arborizations and receptive fields of identified ventrobasal thalamocortical afferents to the primary somatic sensory cortex in the cat, J. Comp. Neurol. 199 (1981) 345–371.
[22] D. Pinault, The thalamic reticular nucleus: structure, function and concept, Brain Res. Brain Res. Rev. 46 (2004) 1–31.
[23] X.B. Liu, C.N. Honda, E.G. Jones, Distribution of four types of synapse on physiologically identified relay neurons in the ventral posterior thalamic nucleus of the cat, J. Comp. Neurol. 352 (1995) 69–91.
[24] J.S. Isaacson, B.W. Strowbridge, Olfactory reciprocal synapses: dendritic signaling in the CNS, Neuron 20 (1998) 749–761.
[25] J. Johnston, K.R. Delaney, Synaptic activation of T-type Ca2+ channels via mGluR activation in the primary dendrite of mitral cells, J. Neurophysiol. 103 (2010) 2557–2569.
[26] S.W. Hughes, M. Lorincz, D.W. Cope, K.L. Blethyn, K.A. Kekesi, H.R. Parri, G. Juhasz, V. Crunelli, Synchronized oscillations at alpha and theta frequencies in the lateral geniculate nucleus, Neuron 42 (2004) 253–268.
[27] B. Singh, A. Monteil, I. Bidaud, Y. Sugimoto, T. Suzuki, S. Hamano, H. Oguni, M. Osawa, M.E. Alonso, A.V. Delgado-Escueta, Y. Inoue, N. Yasui-Furukori, S. Kaneko, P. Lory, K. Yamakawa, Mutational analysis of CACNA1G in idiopathic generalized epilepsy, Hum. Mutat. 28 (2007) 524–525.
[28] Y. Chen, J. Lu, H. Pan, Y. Zhang, H. Wu, K. Xu, X. Liu, Y. Jiang, X. Bao, Z. Yao, K. Ding, W.H. Lo, B. Qiang, P. Chan, Y. Shen, X. Wu, Association between genetic variation of CACNA1H and childhood absence epilepsy, Ann. Neurol. 54 (2003) 239–243.
[29] S.E. Heron, H. Khosravani, D. Varela, C. Bladen, T.C. Williams, M.R. Newman, I.E. Scheffer, S.F. Berkovic, J.C. Mulley, G.W. Zamponi, Extended spectrum of idiopathic generalized epilepsies associated with CACNA1H functional variants, Ann. Neurol. 62 (2007) 560–568.
[30] J. Liang, Y. Zhang, Y. Chen, J. Wang, H. Pan, H. Wu, K. Xu, X. Liu, Y. Jiang, Y. Shen, X. Wu, Common polymorphisms in the CACNA1H gene associated with childhood absence epilepsy in Chinese Han population, Ann. Hum. Genet. 71 (2007) 325–335.
[31] G.W. Zamponi, P. Lory, E. Perez-Reyes, Role of voltage-gated calcium channels in epilepsy, Pflugers Arch. 460 (2009) 395–403.
[32] I. Vitko, Y. Chen, J.M. Arias, Y. Shen, X.R. Wu, E. Perez-Reyes, Functional characterization and neuronal modeling of the effects of childhood absence epilepsy variants of CACNA1H, a T-type calcium channel, J. Neurosci. 25 (2005) 4844–4855.
[33] I. Vitko, I. Bidaud, J.M. Arias, A. Mezghrani, P. Lory, E. Perez-Reyes, The I–II loop controls plasma membrane expression and gating of Cav32 T-type Ca2+ channels: a paradigm for childhood absence epilepsy mutations, J. Neurosci. 27 (2007) 322–330.
[34] H. Khosravani, C. Altier, B. Simms, K.S. Hamming, T.P. Snutch, J. Mezeyova, J.E. McRory, G.W. Zamponi, Gating effects of mutations in the Cav32 T-type calcium channel associated with childhood absence epilepsy, J. Biol. Chem. 279 (2004) 9681–9684.
[35] H. Khosravani, C. Bladen, D.B. Parker, T.P. Snutch, J.E. McRory, G.W. Zamponi, Effects of Cav32 channel mutations linked to idiopathic generalized epilepsy, Ann. Neurol. 57 (2005) 745–749.
[36] J.B. Peloquin, H. Khosravani, W. Barr, C. Bladen, R. Evans, J. Mezeyova, D. Parker, T.P. Snutch, J.E. McRory, G.W. Zamponi, Functional analysis of Ca32 T-type calcium channel mutations linked to childhood absence epilepsy, Epilepsia 47 (2006) 655–658.
[37] J.L. Wang, C.Y. Han, Y.H. Jing, Y.C. Chen, N. Feng, J.J. Lu, Y.H. Zhang, H. Pan, H.S. Wu, K.M. Xu, Y.W. Jiang, J.M. Liang, L. Wang, X.L. Wang, Y. Shen, X.R. Wu, The effect of CACNA1H gene G773D mutation on calcium channel function, Chin. J. Med. Gen. 23 (2006) 369–373.
[38] K.L. Powell, S.M. Cain, C. Ng, S. Sirdesai, L.S. David, M. Kyi, E. Garcia, J.R. Tyson, C.A. Reid, M. Bahlo, S.J. Foote, T.P. Snutch, T.J. O'Brien, A Cav32 T-type calcium channel point mutation has splice-variant-specific effects on function and segregates with

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seizure expression in a polygenic rat model of absence epilepsy, J. Neurosci. 29 (2009) 371–380.
[39] P.J. Adams, E. Garcia, L.S. David, K.J. Mulatz, S.D. Spacey, T.P. Snutch, Ca(V)21 P/Q-type calcium channel alternative splicing affects the functional impact of familial hemiplegic migraine mutations: implications for calcium channelopathies, Channels 3 (2009) 110–121.
[40] P.J. Adams, R.L. Rungta, E. Garcia, A.M. van den Maagdenberg, B.A. Macvicar, T.P. Snutch, Contribution of calcium-dependent facilitation to synaptic plasticity revealed by migraine mutations in the P/Q-type calcium channel, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 18694–18699.
[41] S.M. Cain, T.P. Snutch, Voltage-Gated Calcium Channels in Epilepsy — Jasper's Basic Mechanisms of the Epilepsies, 4th ed. Oxford University Press, Bethesda, U.S.A., 2012.
[42] E.A. Cavalheiro, The pilocarpine model of epilepsy, Ital. J. Neurol. Sci. 16 (1995) 33–37.
[43] E.A. Cavalheiro, N.F. Santos, M.R. Priel, The pilocarpine model of epilepsy in mice, Epilepsia 37 (1996) 1015–1019.
[44] H. Su, D. Sochivko, A. Becker, J. Chen, Y. Jiang, Y. Yaari, H. Beck, Upregulation of a T-type Ca2+ channel causes a long-lasting modification of neuronal firing mode after status epilepticus, J. Neurosci. 22 (2002) 3645–3655.
[45] Y. Yaari, C. Yue, H. Su, Recruitment of apical dendritic T-type Ca2+ channels by backpropagating spikes underlies de novo intrinsic bursting in hippocampal epileptogenesis, J. Physiol. 580 (2007) 435–450.
[46] E.R. Sanabria, H. Su, Y. Yaari, Initiation of network bursts by Ca2+ - dependent intrinsic bursting in the rat pilocarpine model of temporal lobe epilepsy, J. Physiol. 532 (2001) 205–216.
[47] A.J. Becker, J. Pitsch, D. Sochivko, T. Opitz, M. Staniek, C.C. Chen, K.P. Campbell, S. Schoch, Y. Yaari, H. Beck, Transcriptional upregulation of Cav32 mediates epileptogenesis in the pilocarpine model of epilepsy, J. Neurosci. 28 (2008) 13341–13353.
[48] J. Wellmer, H. Su, H. Beck, Y. Yaari, Long-lasting modification of intrinsic discharge properties in subicular neurons following status epilepticus, Eur. J. Neurosci. 16 (2002) 259–266.
[49] J.D. Graef, B.K. Nordskog, W.F. Wiggins, D.W. Godwin, An acquired channelopathy involving thalamic T-type Ca2+ channels after status epilepticus, J. Neurosci. 29 (2009) 4430–4441.
[50] S.M. Cain, T.P. Snutch, Voltage-gated calcium channels in epilepsy, Epilepsia 51 (2010) 11-11.
[51] Y. Zhang, M. Mori, D.L. Burgess, J.L. Noebels, Mutations in high-voltage-activated calcium channel genes stimulate low-voltage-activated currents in mouse thalamic relay neurons, J. Neurosci. 22 (2002) 6362–6371.
[52] W.L. Ernst, Y. Zhang, J.W. Yoo, S.J. Ernst, J.L. Noebels, Genetic enhancement of thalamocortical network activity by elevating alpha 1g-mediated low-voltage-activated calcium current induces pure absence epilepsy, J. Neurosci. 29 (2009) 1615–1625.
[53] E. Cheong, Y. Zheng, K. Lee, J. Lee, S. Kim, M. Sanati, S. Lee, Y.S. Kim, H.S. Shin, Deletion of phospholipase C beta4 in thalamocortical relay nucleus leads to absence seizures, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 21912–21917.
[54] E. Cheong, S. Lee, B.J. Choi, M. Sun, C.J. Lee, H.-S. Shin, Tuning thalamic firing modes via simultaneous modulation of T- and L-type Ca2+ channels controls pain sensory gating in the thalamus, J. Neurosci. 28 (2008) 13331–13340.
[55] D. Kim, I. Song, S. Keum, T. Lee, M.J. Jeong, S.S. Kim, M.W. McEnery, H.S. Shin, Lack of the burst firing of thalamocortical relay neurons and resistance to absence seizures in mice lacking alpha(1G) T-type Ca2+ channels, Neuron 31 (2001) 35–45.
[56] N.A. Hawkins, J.A. Kearney, Confirmation of an epilepsy modifier locus on mouse chromosome 11 and candidate gene analysis by RNA-Seq, Genes Brain Behav. 11 (2012) 452–460.
[57] A.M. Coenen, E.L. Van Luijtelaar, Genetic animal models for absence epilepsy: a review of the WAG/Rij strain of rats, Behav. Genet. 33 (2003) 635–655.
[58] O. Akman, T. Demiralp, N. Ates, F.Y. Onat, Electroencephalographic differences between WAG/Rij and GAERS rat models of absence epilepsy, Epilepsy Res. (2010).
[59] T. Broicher, T. Kanyshkova, P. Meuth, H.C. Pape, T. Budde, Correlation of T-channel coding gene expression, IT, and the low threshold Ca2+ spike in the thalamus of a rat model of absence epilepsy, Mol. Cell. Neurosci. 39 (2008) 384–399.
[60] M. Inoue, J. Duysens, J.M. Vossen, A.M. Coenen, Thalamic multiple-unit activity underlying spike–wave discharges in anesthetized rats, Brain Res. 612 (1993) 35–40.
[61] A. Gorji, C. Mittag, P. Shahabi, T. Seidenbecher, H.-C. Pape, Seizure-related activity of intralaminar thalamic neurons in a genetic model of absence epilepsy, Neurobiol. Dis. 43 (2011) 266–274.
[62] T. Seidenbecher, H.C. Pape, Contribution of intralaminar thalamic nuclei to spike-and-wave-discharges during spontaneous seizures in a genetic rat model of absence epilepsy, Eur. J. Neurosci. 13 (2001) 1537–1546.
[63] C. Marescaux, M. Vergnes, A. Depaulis, Genetic absence epilepsy in rats from Strasbourg—a review, J. Neural Transm. Suppl. 35 (1992) 37–69.
[64] S.J. Slaght, N. Leresche, J.M. Deniau, V. Crunelli, S. Charpier, Activity of thalamic reticular neurons during spontaneous genetically determined spike and wave discharges, J. Neurosci. 22 (2002) 2323–2334.
[65] D. Pinault, N. Leresche, S. Charpier, J.M. Deniau, C. Marescaux, M. Vergnes, V. Crunelli, Intracellular recordings in thalamic neurones during spontaneous spike and wave discharges in rats with absence epilepsy, J. Physiol. 509 (Pt. 2) (1998) 449–456.
[66] E. Tsakiridou, L. Bertollini, M. de Curtis, G. Avanzini, H.C. Pape, Selective increase in T-type calcium conductance of reticular thalamic neurons in a rat model of absence epilepsy, J. Neurosci. 15 (1995) 3110–3117.
[67] E.M. Talley, L.L. Cribbs, J.H. Lee, A. Daud, E. Perez-Reyes, D.A. Bayliss, Differential distribution of three members of a gene family encoding low voltage-activated (T-type) calcium channels, J. Neurosci. 19 (1999) 1895–1911.
[68] E.M. Talley, G. Solorzano, A. Depaulis, E. Perez-Reyes, D.A. Bayliss, Low-voltage-activated calcium channel subunit expression in a genetic model of absence epilepsy in the rat, Brain Res. Mol. Brain Res. 75 (2000) 159–165.
[69] D. Pinault, Cellular interactions in the rat somatosensory thalamocortical system during normal and epileptic 5–9 Hz oscillations, J. Physiol. 552 (2003) 881–905.
[70] S. Charpier, N. Leresche, J.M. Deniau, S. Mahon, S.W. Hughes, V. Crunelli, On the putative contribution of GABA(B) receptors to the electrical events occurring during spontaneous spike and wave discharges, Neuropharmacology 38 (1999) 1699–1706.
[71] J.T. Paz, M. Chavez, S. Saillet, J.M. Deniau, S. Charpier, Activity of ventral medial thalamic neurons during absence seizures and modulation of cortical paroxysms by the nigrothalamic pathway, J. Neurosci. 27 (2007) 929–941.
[72] M. Chipaux, S. Charpier, P.-O. Polack, Chloride-mediated inhibition of the ictogenic neurones initiating genetically-determined absence seizures, Neuroscience 192 (2011) 642–651.
[73] H. Blumenfeld, Consciousness and epilepsy: why are patients with absence seizures absent? Prog. Brain Res. 150 (2005) 271–286.
[74] C.E. Landisman, B.W. Connors, VPM and PoM nuclei of the rat somatosensory thalamus: intrinsic neuronal properties and corticothalamic feedback, Cereb. Cortex 17 (2007) 2853–2865.
[75] P.O. Polack, S. Mahon, M. Chavez, S. Charpier, Inactivation of the somatosensory cortex prevents paroxysmal oscillations in cortical and related thalamic neurons in a genetic model of absence epilepsy, Cereb. Cortex 19 (2009) 2078–2091.
[76] L. Danober, C. Deransart, A. Depaulis, M. Vergnes, C. Marescaux, Pathophysiological mechanisms of genetic absence epilepsy in the rat, Prog. Neurobiol. 55 (1998) 27–57.
[77] V. Crunelli, N. Leresche, Block of thalamic T-type Ca(2+) channels by ethosuximide is not the whole story, Epilepsy Curr. 2 (2002) 53–56.
[78] T.R. Browne, F.E. Dreifuss, P.R. Dyken, D.J. Goode, J.K. Penry, R.J. Porter, B.G. White, P.T. White, Ethosuximide in the treatment of absence (peptit mal) seizures, Neurology 25 (1975) 515–524.
[79] R. Gulhan Aker, K. Tezcan, N. Carcak, E. Sakalli, D. Akin, F.Y. Onat, Localized cortical injections of ethosuximide suppress spike-and-wave activity and reduce the resistance to kindling in genetic absence epilepsy rats (GAERS), Epilepsy Res. 89 (2009) 7–16.
[80] J.P. Manning, D.A. Richards, N. Leresche, V. Crunelli, N.G. Bowery, Cortical-area specific block of genetically determined absence seizures by ethosuximide, Neuroscience 123 (2004) 5–9.
[81] Z.Q. Yang, J.C. Barrow, W.D. Shipe, K.A. Schlegel, Y. Shu, F.V. Yang, C.W. Lindsley, K.E. Rittle, M.G. Bock, G.D. Hartman, V.N. Uebele, C.E. Nuss, S.V. Fox, R.L. Kraus, S.M. Doran, T.M. Connolly, C. Tang, J.E. Ballard, Y. Kuo, E.D. Adarayan, T. Prueksaritanont, M.M. Zrada, M.J. Marino, V.K. Graufelds, A.G. DiLella, I.J. Reynolds, H.M. Vargas, P.B. Bunting, R.F. Woltmann, M.M. Magee, K.S. Koblan, J.J. Renger, Discovery of 1,4-substituted piperidines as potent and selective inhibitors of T-type calcium channels, J. Med. Chem. 51 (2008) 6471–6477.
[82] W.D. Shipe, J.C. Barrow, Z.Q. Yang, C.W. Lindsley, F.V. Yang, K.A. Schlegel, Y. Shu, K.E. Rittle, M.G. Bock, G.D. Hartman, C. Tang, J.E. Ballard, Y. Kuo, E.D. Adarayan, T. Prueksaritanont, M.M. Zrada, V.N. Uebele, C.E. Nuss, T.M. Connolly, S.M. Doran, S.V. Fox, R.L. Kraus, M.J. Marino, V.K. Graufelds, H.M. Vargas, P.B. Bunting, M. Hasbun-Manning, R.M. Evans, K.S. Koblan, J.J. Renger, Design, synthesis, and evaluation of a novel 4-aminomethyl-4-fluoropiperidine as a T-type Ca2+ channel antagonist, J. Med. Chem. 51 (2008) 3692–3695.
[83] V.N. Uebele, C.E. Nuss, S.V. Fox, S.L. Garson, R. Cristescu, S.M. Doran, R.L. Kraus, V.P. Santarelli, Y. Li, J.C. Barrow, Z.Q. Yang, K.A. Schlegel, K.E. Rittle, T.S. Reger, R.A. Bednar, W. Lemaire, F.A. Mullen, J.E. Ballard, C. Tang, G. Dai, O.B. McManus, K.S. Koblan, J.J. Renger, Positive allosteric interaction of structurally diverse T-type calcium channel antagonists, Cell Biochem. Biophys. 55 (2009) 81–93.
[84] R.L. Kraus, Y. Li, Y. Gregan, A.L. Gotter, V.N. Uebele, S.V. Fox, S.M. Doran, J.C. Barrow, Z.Q. Yang, T.S. Reger, K.S. Koblan, J.J. Renger, In vitro characterization of T-type calcium channel antagonist TTA-A2 and in vivo effects on arousal in mice, J. Pharmacol. Exp. Ther. 335 (2010) 409–417.
[85] E. Tringham, K.L. Powell, S.M. Cain, K. Kuplast, J. Mezeyova, M. Weerapura, C. Eduljee, X. Jiang, P. Smith, J.-L. Morrison, N.C. Jones, E. Braine, G. Rind, M. Fee-Maki, D. Parker, H. Pajouhesh, M. Parmar, T.J. O'Brien, T.P. Snutch, T-type calcium channel blockers that attenuate thalamic burst firing and suppress absence seizures, Sci. Transl. Med. 4 (2012) 121ra19.

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