Biochimica et Biophysica Acta 1828 (2013) 1560–1571

Contents lists available at SciVerse ScienceDirect

Biochimica et Biophysica Acta

journal homepage: www.elsevier.com/locate/bbamem

Review

T-type Ca^{2+} channels in absence epilepsy☆,☆☆

Eunji Cheong [a,*], Hee-Sup Shin [b,*]

[a] Department of Biotechnology, Translational Research Center for Protein Function Control, College of Life Science and Biotechnology, Yonsei University, Seoul, Republic of Korea
[b] Center for Cognition and Sociality, Institute for Basic Science, Daejeon, Republic of Korea

ARTICLE INFO

Article history:
Received 27 September 2012
Received in revised form 15 January 2013
Accepted 1 February 2013
Available online 13 February 2013

Keywords:
T-type Ca^{2+} channel
Absence epilepsy
Thalamocortical circuit
Burst firing
Oscillations

ABSTRACT

Low-voltage-activated T-type Ca^{2+} channels are highly expressed in the thalamocortical circuit, suggesting that they play a role in this brain circuit. Indeed, low-threshold burst firing mediated by T-type Ca^{2+} channels has long been implicated in the synchronization of the thalamocortical circuit. Over the past few decades, the conventional view has been that rhythmic burst firing mediated by T-type channels in both thalamic reticular nuclie (TRN) and thalamocortical (TC) neurons are equally critical in the generation of thalamocortical oscillations during sleep rhythms and spike-wave-discharges (SWDs).

This review broadly investigates recent studies indicating that even though both TRN and TC nuclei are required for thalamocortical oscillations, the contributions of T-type channels to TRN and TC neurons are not equal in the genesis of sleep spindles and SWDs. T-type channels in TC neurons are an essential component of SWD generation, whereas the requirement for TRN T-type channels in SWD generation remains controversial at least in the GBL model of absence seizures. Therefore, a deeper understanding of the functional consequences of modulating each T-type channel subtype could guide the development of therapeutic tools for absence seizures while minimizing side effects on physiological thalamocortical oscillations. This article is part of a Special Issue entitled: Calcium channels.

Contents

☆ This article is part of a Special Issue entitled: Calcium channels.

☆☆ Grants: This work was supported by a fund from the Institute for Basic Science, and Translational Research Center for Protein Function Control (2012-0000880) and the Basic Science Research Program (2012-0004313) and Pioneer Research Center Program (2012-0001087), funded by the Ministry of Education, Science and Technology in Korea.

* Corresponding authors. Tel.: +82 2 958 6931 or +82 2 2123 5885; fax: +82 2 958 6919 or +82 2 2123 8284.
E-mail addresses: eunjicheong@yonsei.ac.kr (E. Cheong), shin@ibs.re.kr (H.-S. Shin).

0005-2736/$ – see front matter
http://dx.doi.org/10.1016/j.bbamem.2013.02.002

1. Introduction

T-type Ca^{2+} channels mediate low-threshold Ca^{2+} spikes in neurons, leading to burst firing and rhythmic oscillations [1–3]. These channels are considered to be low-voltage-activated (LVA) Ca^{2+} channels, as they require much lesser membrane depolarization for opening. They exhibit smaller single-channel amplitudes than high-voltage-activated (HVA) channels and produce a transient current that decays as soon as the current peaks at the whole-cell level, leading to their designation as "T-type" for "transient" and "tiny" [4]. LVA currents have slower deactivating tail currents, show relatively equivalent conductance for Ca^{2+} and Ba^{2+} in the absence of Mg^{2+}, and exhibit whole-cell currents with fast inactivation kinetics [5–7]. Furthermore, most T-type channels are tonically inactivated, leaving only a small fraction available for "window" currents (see below) at typical neuronal resting membrane potentials [8–12]. However, a larger fraction of T-type channels avoid inactivation in TRN neurons which have a relatively hyperpolarized resting membrane potential [13].

This unusual voltage sensitivity of T-type Ca^{2+} channels renders them able to regulate cellular excitability and oscillatory behavior near the resting membrane potential. In TC neurons with a relatively depolarized resting membrane potential, a transient membrane hyperpolarization arising from inhibitory postsynaptic potentials (IPSPs) or the activation of certain types of potassium channels can de-inactivate T-type Ca^{2+} channels. The subsequent rebound of the membrane potential triggers their opening, and the resulting Ca^{2+} entry further depolarizes the membrane potential to reach the threshold for voltage-gated Na^{+} channels, thus initiating a train of action potentials. This phenomenon, which is called "rebound burst firing," represents a paradoxical enhancement of neuronal firing following the reception of inhibitory inputs. It is often observed under normal physiological conditions, such as sleep [14–17], and in pathophysiological conditions, such as epilepsy [18,19]. In TRN neurons with a relatively hyperpolarized resting membrane potential, depolarizing current injection or EPSPs were shown to trigger burst firing mediated by T-type Ca^{2+} channels [13,20]. These properties highlight the physiological significance of T-type channels in regulating neuronal firing patterns [21].

Since the first observations of low-threshold Ca^{2+} spikes mediated by T-type Ca^{2+} channels [4,22], these events have been studied in isolated neurons and slices from various brain regions, including the inferior olivary nucleus [3,23] and the thalamus [24,25], where neurons display intrinsic oscillatory activities. Dysfunction of T-type channels has been strongly implicated in various neurological disorders, including sleep disorders, absence epilepsy, neuropathic pain, Parkinson's disease-associated tremor, and neuropsychiatric disorders [26]. The functional implications of T-type channels in the oscillatory activities of neurons and the prominent expression of T-type channels in the thalamocortical circuit strongly suggest that they may be involved in the thalamocortical oscillations observed during sleep and absence epilepsy.

Absence epilepsy refers to generalized non-convulsive seizures that are characterized by a brief and sudden impairment of consciousness accompanied by spike-and-wave discharges (SWDs) in the electroencephalogram (EEG) [17,27–29]. Abnormal hyper-synchronized oscillatory activities in the thalamocortical network have been implicated as an underlying mechanism for the generation of SWDs [30–34]. Numerous studies have supported the hypothesis that SWDs arise from recurrent oscillatory activities in the network between the thalamic reticular nucleus (TRN) and the thalamocortical (TC) relay nucleus [17,33–36], whereas others have suggested that the cortex plays a leading role in the generation of SWDs [37–40]. Thalamocortical network oscillations are often accompanied by a shift in the firing pattern of both TRN and TC neurons from tonic to burst firing, leading to the hypothesis that low-threshold T-type Ca^{2+} channels are a critical component in sustaining the oscillations during SWDs [17,33,41]. However, there is still some controversy on this point [29,42]. In this review, we seek to provide a comprehensive overview of the role of T-type Ca^{2+} channels in absence epilepsy.

1.1. Three subtypes of T-type channels

Three subtypes of T-type channels have been identified; designated $Ca_V3.1$, $Ca_V3.2$ and $Ca_V3.3$, they correspond to complexes containing the pore-forming α1 subunits, α1G, α1H and α1I, respectively [8,43,44]. The electrophysiological properties of the three T-type channel subtypes have been examined by expressing cloned α1 subunits in a variety of heterologous expression systems [43,45]. The currents mediated by α1 subunits in heterologous systems are similar to those of native channels [43,45–47]. The T-type currents recorded from the three recombinant Ca_V3 channels share typical T-type channel characteristics: low voltage activation, negative steady-state inactivation, strongly voltage-dependent activation and inactivation, and slow deactivation [47], but exhibited characteristic voltage dependencies and kinetics of activation and inactivation depending on the subtypes [48]. They differ in their kinetics of inactivation, recovery from steady-state inactivation, and pharmacology [46,49,50]. All three subtypes are known to generate the steady-state component of T-type Ca^{2+} currents called the "window" current, which is defined as the overlap between the activation and steady-state inactivation curves. $Ca_V3.3$ channels are predicted to have a larger window current, probably due to a shift in their steady-state inactivation curve to relatively depolarized membrane potentials [8].

The kinetics of recovery from inactivation are critical to the ability of T-type channels to trigger rebound low-threshold spikes (LTS), because the fast recovery of T-type channels during an inhibitory postsynaptic potential (IPSP) leads to de-inactivation of the channels followed by channel openings as the membrane rebounds to its resting potential. The time course for recovery is highly variable, ranging from 100 to 3300 ms depending on the membrane potential and the durations of the inactivating and test pulses [46]. Of the three subtypes, $Ca_V3.1$ channels recover the fastest (~120 ms), $Ca_V3.2$ channels are the slowest (showing a recovery rate more than 3-fold slower than $Ca_V3.1$ channels), and $Ca_V3.3$ channels show an intermediate recovery rate [43,45,46].

Although most T-type currents display rapid inactivation (<30 ms) compared to HVA Ca^{2+} currents, subtype-specific variability has been noted, with $Ca_V3.1$ and $Ca_V3.2$ exhibiting fast inactivation while $Ca_V3.3$ displays relatively slow inactivation [46]. The differences in the electrophysiological properties of the T-type channels suggest that the firing patterns of neurons may depend on the expression levels of the various T-type channels. Thus, the biophysical heterogeneity and functional diversity of T-type Ca^{2+} currents [43,46] arise from the differential expression and colocalization of the channel subtypes [51]. This highlights the need to understand the expression patterns of the three subtypes in given brain regions or neurons, and to examine differences in their electrophysiological properties as a prerequisite for understanding their associated neuronal activities.

2. Low-threshold T-type Ca^{2+} channels in the thalamocortical circuit

Numerous groups have identified LTS in neurons of the thalamocortical circuit [20,52,53], suggesting the existence of LVA T-type Ca^{2+} channels in these neurons. The influx of Ca^{2+} through LVA Ca^{2+} channels engenders low-threshold Ca^{2+} spikes, which in turn trigger a burst of action potentials mediated by voltage-gated Na^{+} channels. The addition of tetrodotoxin, a blocker of Na^{+} channels, eliminates the fast spikes while leaving the slow component of LTS intact. Numerous studies have demonstrated that slow LTS are mediated by Ca^{2+} conductance, based on the observations that they are not generated in Ca^{2+}-free external solutions or in the presence of divalent cations such as Co^{2+} or Ni^{2+}, which block Ca^{2+} channel conductance [52].

2.1. Expression pattern of T-type channels in the thalamocortical circuit

$Ca_V3.1$, $Ca_V3.2$ and $Ca_V3.3$ are highly expressed in the thalamocortical circuit, suggesting that they play a prominent role in this circuit [51]. Notably, the three subtypes display a largely complementary expression pattern in the thalamus: $Ca_V3.1$ is exclusively expressed in TC regions, whereas $Ca_V3.2$ and $Ca_V3.3$ are abundant in GABAergic neurons of the TRN [54]. The slow decay and depolarized membrane potential range for activation of the low-threshold Ca^{2+} currents in the TRN [13] reflect the predominant contribution of $Ca_V3.3$ channels over $Ca_V3.2$ channels to the total T-type current in TRN neurons. This is supported by observations that $Ca_V3.3$ mRNA levels are much higher than $Ca_V3.2$ mRNA levels in these neurons [54–56]. Furthermore, T-type currents are drastically reduced in TRN neurons following deletion of the $Ca_V3.3$ T-type channel, strongly supporting the idea that the $Ca_V3.3$ channel is the predominant contributor to T-type currents in TRN neurons [57]. However, one study proposed that $Ca_V3.2$ channels mediate a substantial portion of T-type currents in TRN neurons. The authors showed that oxidizing agents, such as 5,5′dithio-bis(2-nitrobenzoic acid) (DTNB; which inhibits $Ca_V3.2$ but not $Ca_V3.1$ or $Ca_V3.3$), inhibit T-currents in TRN neurons by ~50% in rats and ~40% in mice [56]. This discrepancy should be investigated further.

In situ hybridization experiments have demonstrated substantial and widespread expression of mRNA signals for the three subtypes in the cortex; Cav3.1 and $Ca_V3.3$ appear to be expressed throughout all layers of the cortex, while Cav3.2 is predominantly found in layer V [51]. However, the differential distribution of subtypes among cortical layers or in different types of neurons has not been fully elucidated. A study on the subcellular distribution of Ca_V3 subtypes in rat brain cortical neurons showed that $Ca_V3.1$ T-type channels are prominent in the soma and proximal dendritic regions; $Ca_V3.2$ channels are expressed in the soma and proximal-mid dendrites; and $Ca_V3.3$ channels are distinctly localized to the soma and dendritic arbor of specific cell types [58]. These distribution patterns suggest that T-type channels may contribute to multiple neuronal activities.

3. The classical model for the role of thalamocortical oscillatory circuits in absence epilepsy

Oscillatory activities have been observed among neurons synchronized in the thalamocortical circuit during normal sleep-related oscillations and pathological paroxysmal oscillations [20,33,35,53]. Extensive feedforward and feedback connections between the thalamus and the cortex (summarized in Fig. 1) contribute significantly to strengthening the synchronization of oscillatory activities in the thalamocortical circuit, generating and maintaining both physiological and pathological oscillations [17,33,36,59].

Although researchers generally agreed that the synchronized activities among neurons in the thalamus and cortex are critical to the generation of oscillations within the thalamocortical circuit, there has been debate over which nucleus leads the generation of oscillations. Some studies have shown that cortical GABAergic interneurons constitute complex functional networks that generate cortical oscillations related to several behavioral functions [60–63]. However, it has also been suggested that reciprocal connections between the thalamic reticular and relay nuclei within the thalamus establish a core oscillatory unit [33]. Regardless, thalamocortical and corticothalamic innervations between the cortex and the thalamus integrate these intra-thalamic oscillations into larger thalamocortical networks to produce sleep spindles and the SWDs of absence epilepsy (i.e., normal and pathological oscillations, respectively) [17,33,35,64,65].

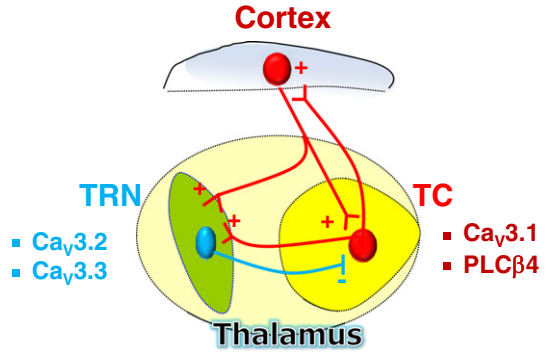

Fig. 1. Schematic representation of the thalamocortical circuit and T-type Ca^{2+} channel expression. The three subtypes of T-type Ca^{2+} channels are differentially expressed in the thalamocortical circuit involved in SWD generation. $Ca_V3.1$ channels are highly expressed in TC neurons but not in TRN neurons, whereas $Ca_V3.2$ and -3.3 channels are mainly expressed in TRN neurons. PLCβ4 is highly expressed in TC neurons and modulates the propensity for burst firing in TC neurons via controlling the Ca^{2+} currents mediated by $Ca_V3.1$ T-type channels.

3.1. TRN and TC neurons in thalamic synchrony

The thalamic circuit is composed of excitatory TC neurons and the inhibitory neurons of the TRN (Fig. 1). Extensive synaptic connections link the TC and TRN neurons, which together create a reciprocally innervated intra-thalamic circuit. The degree of synchrony within this intra-thalamic circuit has been thought to determine whether physiological or pathological oscillations occur [17]. It has been shown that inhibitory inputs from the TRN [20,53] or other brain regions [66] to TC neurons are followed by a post-inhibitory response, in which a rebound of the membrane potential induces burst firing of TC neurons. This, in turn, is believed to activate TRN neurons. Therefore, burst firing of thalamic neurons mediated by T-type Ca^{2+} currents is important for recurrent intra-thalamic oscillatory activities [67].

The TRN forms a shell-like structure that encompasses the anterior and lateral parts of the dorsal thalamus and provides inhibitory inputs to TC neurons [68]. TRN neurons display rhythmic burst activities that generate spontaneous oscillations within the reticular nucleus [20,69] and have long been hypothesized to act as pacemakers of thalamocortical oscillations, including sleep spindles and SWDs [14,70,71]. Intra-reticular inhibition has been proposed as an important component of thalamic synchrony. TRN neurons inhibit both TC neurons and other TRN neurons [72–74]. It has been suggested that recurrent inhibition within the TRN (intra-reticular inhibition) serves to reduce synchrony during spindle rhythms or the SWDs of generalized absence seizures [34,75], whereas electrical coupling via gap junctions synchronizes activities among TRN neurons [17,76].

Thalamic oscillatory activity is accompanied by low-threshold spikes, often corresponding to low-threshold burst firing of TC neurons [20,53]. Llinas and Jahnsen provided the first report of a Ca^{2+}-dependent low-threshold spike that is activated only after membrane hyperpolarization in TC neurons [52]. Since then, studies have shown than an LTS generates a long-lasting depolarization of membrane potential, triggering a burst of action potentials that ride the crest of the plateau [77]. This property of T-type Ca^{2+} channels in TC neurons is responsible for their unique ability to promote network oscillations in which neural inhibition leads to a paradoxical rebound spiking. Although inputs from inhibitory neurons in the TRN form the major driving force for the burst firing of TC neurons, a recent study proposed that inhibitory inputs from the substantia nigra pars reticulata (SNR) to the ventral medial (VM) nucleus in the TC region also play a crucial role in the ability of the basal ganglia to control absence seizures [66].

3.2. T-type Ca^{2+} channels in absence seizures

It has long been suggested that generalized absence seizures are accompanied by hyperexcitable oscillatory activities in the thalamocortical network [29,33,78]. The observation that succinimide and

related anticonvulsants block thalamic T-type channels [79,80] led researchers to speculate that T-type Ca^{2+} channels might be related to the pathogenesis of SWDs in generalized absence seizures [81].

Ethosuximide and valproate, two antiepileptic drugs used to treat generalized absence epilepsy [82], were reported to obstruct T-type Ca^{2+} channels in TC neurons at therapeutically relevant concentrations [79,83,84]. Other anticonvulsant drugs have also been shown to substantially suppress thalamic burst spikes [85–87]. These findings prompted researchers to study T-type Ca^{2+} channels for their potential to help explain the cellular and molecular mechanisms of SWD generation and absence seizures. However, T-type channel antagonists were shown to dampen SWDs in human absence seizure patients and in rodent models of absence seizures [88]. Furthermore, some studies have found that neither valproic acid [79] nor ethosuximide [65] acts on T-type Ca^{2+} channels, providing limited support for the idea that T-type Ca^{2+} channels are involved in absence epilepsy.

Recently, a series of piperidine-based molecules were shown to block recombinant T-type channels but not HVA Ca^{2+} channels [89]. One such compound, TTA-A2, potently blocked T-type currents in HEK293 cells expressing human $Ca_V3.1$, $Ca_V3.2$ or $Ca_V3.3$ T-channels, and suppressed the active wake state and promoted slow-wave sleep in mice [90], whereas it suppressed the absence epilepsy in WAG/Rij rat models [91]. TTA-P2, another piperidine-based molecule, also blocked endogenous T-currents in TC and TRN neurons, revealing the impact of window currents in these neurons [92] and the contribution of T-currents on EPSP-driven spike probability in TC neurons [93]. In addition, the piperazine-based compounds, Z941 and Z944, blocked T-type channels, attenuating thalamic burst firing and suppressing absence seizures [94].

Recent advances in genetic tools have contributed significantly to elucidating the role of T-type Ca^{2+} channels and thalamic bursts in the pathogenesis of absence epilepsy. A variety of genetic approaches have been employed to study the role of T-type channels in vivo, including ablation of T-type Ca^{2+} channel genes in mice [16,41,95], analysis of T-type channels in animal models of absence epilepsy [96–98], and analysis of putative candidate genes in human patients [99–102]. The following section summarizes recent achievements in genetic studies and new insights into the differential roles of T-type Ca^{2+} channels in TC versus TRN neurons in the genesis of absence epilepsy.

4. TC neurons in absence epilepsy

4.1. $Ca_V3.1$ T-type channels in TC neurons are required for SWD genesis

Paroxysmal oscillations of the thalamocortical network during SWDs are frequently observed upon a switch in the firing pattern of TC neurons from tonic to burst firing [103]. It has been proposed that low-threshold burst firing driven by $Ca_V3.1$ T-type channels in TC neurons is a crucial element in sustained oscillations during SWDs [17,33,41]. However, some controversies remain [29,42].

The spontaneous absence seizure in $\beta4^{lh/lh}$ mice, an animal model of absence seizure, was suppressed by $GABA_BR$ antagonist and exacerbated by $GABA_BR$ agonists, which suggested the enhanced $GABA_B$ receptor-mediated synaptic responses underlie the seizures [104]. However, a subsequent study reported that $\beta4^{lh/lh}$ or $\alpha1A^{tg/tg}$ mice with mutations in the genes encoding β4 and α1A subunits, respectively, revealed reduced excitatory synaptic transmission, but normal inhibitory synaptic transmission onto thalamocortical neurons by affecting P/Q type channel function [105]. These studies, although somewhat inconsistent, imply that the alteration in the balance between excitatory and inhibitory inputs onto TC neurons may underlie the absence seizures in these animal models. These data suggest that a propensity for membrane hyperpolarization (i.e., greater de-inactivation of T-type channels) could effectively escalate the opening probability of T-type Ca^{2+} channels, thereby reinforcing SWDs even without an increase in T-type expression. Further studies are needed to determine how malfunctions in P/Q-type channels can lead to the membrane hyperpolarization of TC neurons.

4.1.1. $Ca_V3.1$ knockout mice are resistant to $GABA_BR$-mediated absence seizure

An analysis of knockout mice lacking the $Ca_V3.1$ subunit of the α1G subtype revealed that this subunit plays an essential role in absence epilepsy [41]. In the thalamus, $Ca_V3.1$ is predominantly expressed in TC neurons [51]. Therefore, the $Ca_V3.1$-knockout ($Ca_V3.1^{-/-}$) mouse provides an important tool for exploring the function of T-type Ca^{2+} channels in TC neurons.

Consistent with the predominant expression of $Ca_V3.1$ in TC neurons [51], $Ca_V3.1^{-/-}$ mice fail to show low-threshold burst firing, confirming that LTS in TC neurons, which uniformly express high levels of $Ca_V3.1$ [51], critically depend on this subtype of T-type channels (Fig. 2 modified from [41]). As noted above, $Ca_V3.1$ channels remain inactive around the resting membrane potential of TC neurons, but they recover rapidly from inactivation (time constant, ~100 ms), allowing TC neurons to participate in post-inhibitory rebound burst firing. The results obtained to date have led researchers to propose that T-type currents and the resulting LTS in TC neurons are essential for the genesis of generalized SWDs, although they may not be critical for initiation of the oscillations [41,106]. Notably, $Ca_V3.1^{-/-}$ mice are resistant to SWD seizures specifically induced by $GABA_BR$ agonists. Baclofen and γ-hydroxybutyrate, two $GABA_BR$ agonists, have been shown to reliably induce absence seizure phenotypes in animals, with characteristic behavioral arrest synchronized with SWDs on EEG [107]. These $GABA_BR$ agonists evoked distinct paroxysmal 3–4 Hz SWDs on EEG recordings accompanied by behavioral arrest in wild-type mice, but induced only very weak and intermittent SWDs in $Ca_V3.1^{-/-}$ mice (Fig. 3 modified from [41]).

In contrast to this phenotype of $Ca_V3.1^{-/-}$ mice, studies on rat models of absence seizures suggest that the cortex, not the thalamus, leads the genesis of SWDs [37–40]. In studies using the GAERS and WAG/Rij strains (two rat models of absence epilepsy), the generation of SWDs was suggested to originate from the cortex [40,108], with cortical infusion of ethosuximide found to substantially block SWDs in the GAERS model [40]. However, another study found that the $Ca_V3.1$ T-type channel in the mediodorsal thalamus (MD) plays a crucial role in frontal lobe-specific seizures [109]. Insofar as the TC network comprises reciprocal feedback circuits among thalamic nuclei and the cortex, the question of where the seizure discharge is initiated may not be an important issue.

Many studies have corroborated the hypothesis that recurrent oscillatory activities in the network between the TRN and the TC relay nucleus generate thalamic synchrony, which is further propagated throughout the thalamocortical circuit [17,33–36]. SWDs induced by baclofen, a $GABA_BR$ agonist, rely on the thalamus; in contrast, bicuculline, a $GABA_AR$ antagonist, was shown to initially induce cortex-originating seizure spikes that subsequently evolve to highly synchronous SWDs throughout the thalamocortical circuit [107,110]. Interestingly, $Ca_V3.1^{-/-}$ mice are vulnerable to bicuculline-induced seizures [41]. After systemic injection of bicuculline, both mutant and wild-type mice exhibited a variety of epileptic symptoms; behavioral changes were accompanied by characteristic EEG patterns, comprising SWDs, single high-amplitude spikes, and a variety of epileptic patterns. Similarly, a potassium channel antagonist known to increase neuronal excitability (4-aminopyridine) also induced tonic–clonic seizures to a similar degree in both wild-type and $Ca_V3.1^{-/-}$ mice [41].

4.1.2. Absence epilepsy in P/Q-type channel deficient ($Ca_V2.1^{-/-}$) mice requires $Ca_V3.1$

Spontaneous absence epilepsy phenotypes have been observed in mice harboring mutations in various subunits of voltage gated Ca^{2+} channels known to affect the P/Q-type Ca^{2+} channel function. These

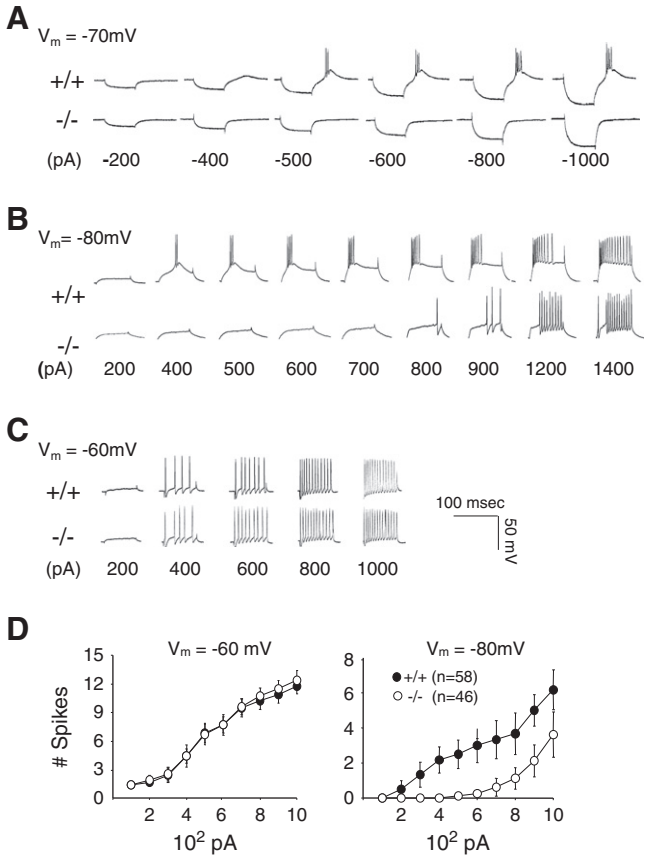

Fig. 2. Intrinsic firing properties of TC neurons located at the ventrobasal complex. (A) Burst firing patterns elicited by 100-ms pulses of negative step-current inputs at −70 mV. Holding membrane potentials were maintained by DC current input. The amount of current injected is indicated below each trace; pA, picoampere. Scale bars: 100 ms (horizontal) and 50 mV (vertical). (B) Burst firing patterns elicited by positive step-current inputs at −80 mV. Note the increased firing frequency of lower-frequency spikes in wild-type TC neurons with positive input currents greater than 700 pA. Only high-frequency spikes are missing in $Ca_V3.1^{-/-}$ TC neurons. (C) Tonic firing patterns elicited by positive step-current inputs at −60 mV. Low-frequency spikes are elicited equally in wild-type and $Ca_V3.1^{-/-}$ TC neurons. (D) The relationship between the number of spikes and the amount of current injected. The number of spikes during 100-ms positive step-current inputs when membrane potentials are held at −60 mV (left) or −80 mV (right).
Modified from reference [41].

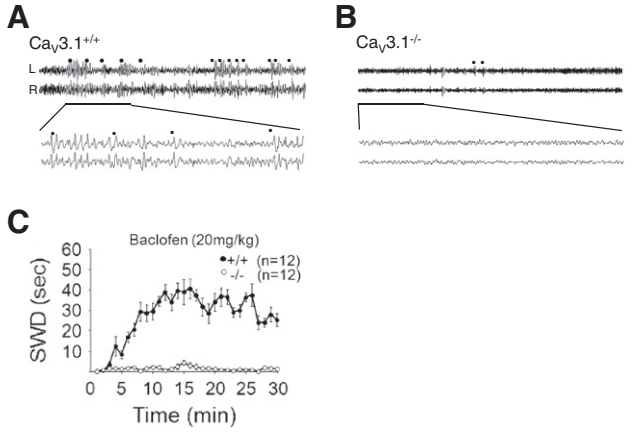

Fig. 3. Baclofen-induced SWDs in wild-type and $Ca_V3.1^{-/-}$ mice. *Top*: Representative EEG traces show that injection of baclofen induces abundant SWD activity in wild-type mice and negligible SWD activity in $Ca_V3.1^{-/-}$ mice. *Bottom*: The frequency of SWD events is plotted against time for $Ca_V3.1^{-/-}$ and wild-type mice.
Modified from reference [104].

mouse models include: *tottering* ($\alpha1A^{tg/tg}$) [111,112] and *leaner* ($\alpha1A^{tgla/tgla}$) [113], each of which contains a distinct mutation of the gene encoding the $Ca_V2.1$ α1A subunit; *stargazer* (*stg/stg*) [112], which has a mutation in the γ2 subunit; *lethargic* ($\beta4^{lh/lh}$) [104], which harbors a mutation in the β4 subunit; and $Ca_V2.1^{-/-}$ null mutant mice [97,104]. In general, these mice exhibit 5–7-Hz SWDs associated with behavioral phenotypes, whereas human patients generally show 3-Hz SWDs on EEG (in fact, this is a diagnostic hallmark). In the latter context, it is interesting that $Ca_V2.1^{-/-}$ null mice, which lack P/Q type channels, display 3-Hz SWDs that are comparable to those observed in human patients (Fig. 4B). The importance of this characteristic feature of human absence epilepsy is not yet known. A mutation in the $Ca_V2.1$-encoding gene has been identified as causing absence epilepsy associated with episodic ataxia in children [114,115], and is known to cause hypo-functioning of P/Q-channels [29]. Therefore, $Ca_V2.1^{-/-}$ mice might provide a relevant animal model for studying this specific type of human absence epilepsy.

It is intriguing to speculate on whether the $Ca_V3.1$ T-type channel is also essential for SWD generation in these genetic mouse models of absence seizures. This question was addressed by crossing each mutant strain with $Ca_V3.1^{-/-}$ mice to generate double mutants [97]. The results were unambiguous: in all cases, the generation of SWDs was substantially diminished by deleting the $Ca_V3.1$ gene. Representative EEG traces and the results from a power spectrum analysis of the EEGs from $Ca_V2.1$ and $Ca_V3.1$ double-mutant mice are shown in Fig. 4B (modified from [97]), and the effects of $Ca_V3.1$ gene doses in absence mouse models with spontaneous mutations are graphed in Fig. 4C. These results provide firm evidence that $Ca_V3.1$ T-type Ca^{2+} channels are necessary for the occurrence of absence epilepsy phenotypes in these mutant mice, just as they are for $GABA_BR$ agonist-induced absence epilepsy.

4.2. Propensity for burst firing of TC neuron is relevant to absence epilepsy

A study using quantitative in situ hybridization demonstrated small but significant increases in both $Ca_V3.1$ and $Ca_V3.2$ mRNA levels in the relay and reticular thalamic nuclei, respectively, of GAERS rats [116]. In the same strain, increased T-type Ca^{2+} currents were observed in TRN neurons [96] and a gain-of-function mutation was identified in the $Ca_V3.2$ channel [117]. Larger T-type currents in TC neurons have also been observed in various mutant mice with absence seizure phenotypes [97,98,118]. These findings collectively suggest that increased T-type currents in the thalamocortical circuit may contribute to the genesis of absence epilepsy.

This raised the question of whether the increased T-type currents are the key to generating SWDs in these absence seizure models versus being epiphenomena (i.e., byproducts of overall changes in the excitability of thalamic neurons). As in other absence seizure mouse models with channel malfunctions [97,98,118], the amplitude of T-type Ca^{2+} currents is increased in the TC neurons of $Ca_V2.1^{-/-}$ mice (Fig. 4A). Crossing this mutant with $Ca_V3.1^{-/-}$ mice yielded three different groups of $Ca_V2.1^{-/-}$ mice with different doses of $Ca_V3.1$ ($Ca_V2.1^{-/-}$ with $Ca_V3.1^{+/+}$, $Ca_V3.1^{+/-}$, or $Ca_V3.1^{-/-}$). The TC neurons of $Ca_V2.1^{-/-}$ $Ca_V3.1^{+/+}$ mice exhibited increased T-type currents (~160%) compared to wild-type mice, while T-type currents were absent in $Ca_V2.1^{-/-}$ $Ca_V3.1^{-/-}$ mice, reflecting the deletion of both copies of the $Ca_V3.1$ gene (Fig. 4A). The level of T-type currents in $Ca_V2.1^{-/-}$ $Ca_V3.1^{+/-}$ mice containing a single copy of $Ca_V3.1$ was below that in wild-type mice (~75%), even though the expression level per gene copy was increased via developmental compensation in the $Ca_V2.1^{-/-}$ background (Fig. 4A). These $Ca_V2.1^{-/-}$ $Ca_V3.1^{+/-}$ mice provided a core tool for testing the role of increased T-type currents in the generation of SWDs. EEGs revealed that $Ca_V2.1^{-/-}$ $Ca_V3.1^{+/-}$ mice generated SWDs to the same degree as $Ca_V2.1^{-/-}$ $Ca_V3.1^{+/+}$ mice, even though their TC neurons showed decreased (rather than increased) T-type currents compared to wild-type TC neurons. These results demonstrate that although T-type currents in TC neurons are necessary for the generation of

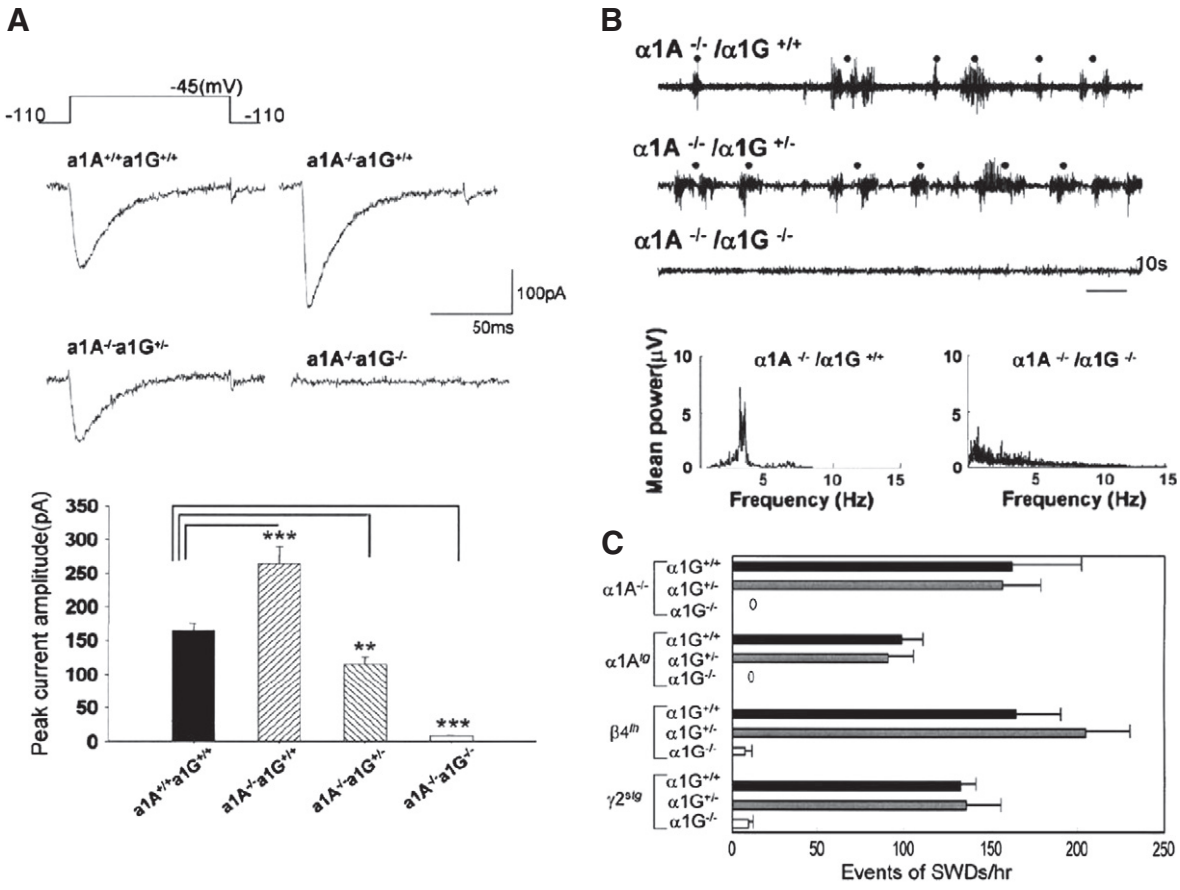

Fig. 4. Suppression of absence seizures by $Ca_V3.1$ deletion in a P/Q channel-deficient ($Ca_V2.1^{-/-}$) genetic background. (A) Representative traces of total Ca^{2+} currents in the four genotypes: $Ca_V2.1^{+/+}$; $Ca_V3.1^{+/+}$ (wild-type), $Ca_V2.1^{-/-}$; $Ca_V3.1^{+/+}$, $Ca_V2.1^{-/-}$; $Ca_V3.1^{+/-}$ and $Ca_V2.1^{-/-}$; $Ca_V3.1^{-/-}$. The bar graph shows a quantitative comparison of the currents among the four genotypes. (B) *Top*: EEG traces of the relevant genotypes. *Bottom*: Power spectrum analysis of the EEG patterns of the two genotypes, $Ca_V2.1^{-/-}$; $Ca_V3.1^{+/+}$ and $Ca_V2.1^{-/-}$; $Ca_V3.1^{-/-}$. (C) Comparison of the frequency of SWD events among mice with different genetic compositions. The effects of $Ca_V3.1$ gene dose on the expression of SWDs in different absence model mice are compared.
Modified from reference [97].

SWDs, their increase is not crucial to the pathogenesis of SWDs in the tested absence seizure mouse models. However, some researchers have argued against the function of T-type currents in TC neurons in absence seizures because burst firings in TC neurons have rarely been observed synchronously with SWDs on EEG in in vivo recordings from rat and cat absence seizure models [42,119,120].

The augmentation of T-type Ca^{2+} currents by overexpressing $Ca_V3.1$ channels throughout the brain is reportedly sufficient to engender spontaneous SWDs in transgenic mice [121]. However, the enhancement of T-type currents in these mice was seen generally throughout the brain rather than being limited to the TC relay regions, weakening the idea that augmentation of T-type Ca^{2+} currents in TC neurons is the key to the genesis of SWDs in these transgenic mice [29]. The augmentation of T-type Ca^{2+} currents in TC neurons would increase the window current near the resting membrane potential, which would enhance the bursting probability of TC neurons.

Another recent study has suggested that spontaneous absence seizures might be generated by an increase in the propensity for bursting (i.e., by a depolarizing shift of the steady-state inactivation curve) among TC neurons, rather than by increasing the magnitude of T-type currents or expression of T-type channels per se in these cells [122]. The phospholipase Cβ4 (PLCβ4) signaling pathway, which lies downstream of the metabotropic glutamate receptor, mGluR1, has been shown to tune the TC firing mode via concomitant regulation of T- and L-type Ca^{2+} currents in TC neurons [12]. TC neurons from PLCβ4$^{-/-}$ mice display a depolarizing shift in the steady state inactivation of T-type Ca^{2+} channels near the resting membrane potential (Fig. 5C–D, modified from [12]). This change in the inactivation curve is predicted to enlarge the window currents, and may drastically increase the propensity of TC neurons for burst firing. PLCβ4-deficient TC neurons displayed burst firings after slight hyperpolarizations that would never induce burst firing in wild-type TC neurons (Fig. 5E–F, modified from [122]), and switched to the oscillatory burst firing mode (Fig. 5G, modified from [122]). Furthermore, a TC-restricted shRNA-mediated knockdown of PLCβ4 induced spontaneous SWDs accompanied by characteristic behavioral phenotypes. These mice also exhibited increased susceptibility to γ-butyrolactone (GBL)- or baclofen-induced SWDs, revealing that TC neurons critically contribute to initiating paroxysmal SWDs and thus the pathogenesis of absence seizures (Fig. 6, modified from [122]). In this study, an abnormal shift from the tonic firing mode to the burst firing mode in TC neurons appeared to readily switch the thalamocortical circuit to the pathological oscillatory mode (signified by SWDs).

It has been proposed that an enhanced $GABA_BR$-mediated hyperpolarization of TC neurons, leading to the de-inactivation of $Ca_V3.1$ T-type channels, might precede the appearance of absence seizures [33,120,123]. In this context, it is noteworthy that thalamic relay neurons deficient for HCN2 (hyperpolarization-activated cyclic nucleotide-gated potassium channel 2) display a hyperpolarized resting membrane potential with an increased propensity for

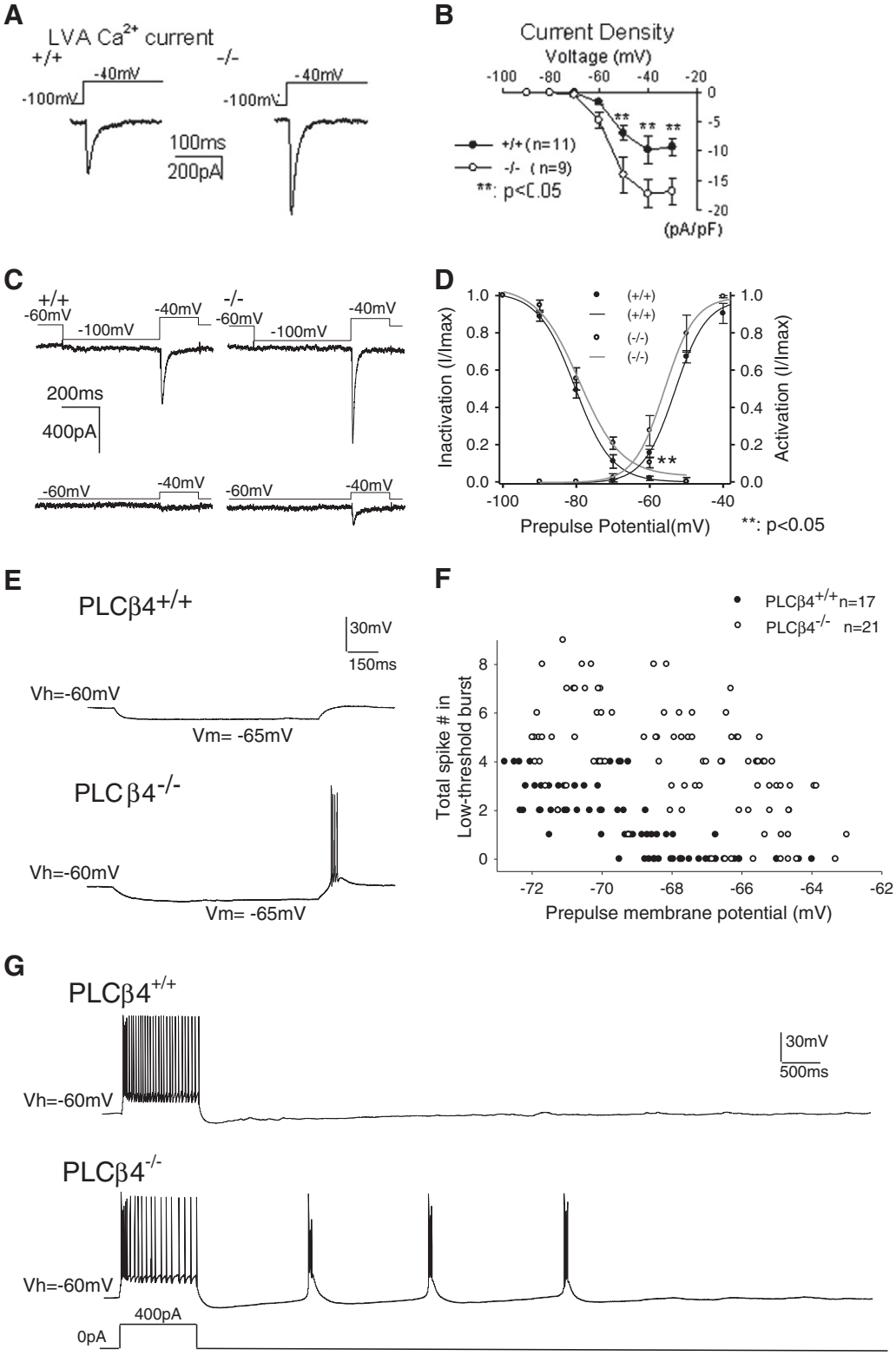

Fig. 5. The firing pattern is easily shifted to the burst firing mode in PLCβ4$^{-/-}$ TC neurons. (A) LVA Ca^{2+} currents were measured from wild-type and PLCβ4$^{-/-}$ TC neurons. (B) Current–voltage (I–V) relationships of LVA Ca^{2+} current density in wild-type (closed circle) and PLCβ4$^{-/-}$ (open circle) TC neurons revealed that LVA Ca^{2+} currents in PLCβ4$^{-/-}$ TC neurons were larger than those in wild-type TC neurons. (C) LVA Ca^{2+} currents from wild-type (left panel) and PLCβ4$^{-/-}$ (right panel) TC neurons activated by voltage steps to −40 mV from −100 mV (upper panels) and from −60 mV (lower panels). (D) Steady-state inactivation and activation curves for LVA Ca^{2+} currents in wild-type (solid circle and black lines) and PLCβ4$^{-/-}$ TC neurons (open circles and gray lines) show that a smaller degree of steady-state inactivation of LVA Ca^{2+} currents increased the window currents in PLCβ4$^{-/-}$ TC neurons. (E) Injection of prepulses (slightly hyperpolarizing the membrane potentials) elicited low-threshold burst firing in PLCβ4$^{-/-}$ TC neurons but not wild-type TC neurons. (F) Spike numbers in bursts induced by various prepulses that hyperpolarized the membrane potentials to between −73 and −63 mV in wild-type (closed circle) and PLCβ4$^{-/-}$ (open circle) TC neurons. (G) Tonic firing was induced with 400-pA depolarizing currents. PLCβ4$^{-/-}$ TC neurons were often shifted from tonic to low-threshold burst firing, whereas wild-type TC neurons never showed such a transition in firing mode.
Modified from references [12,122].

burst firing, and are prone to SWD oscillations [124]. Taken together, these findings suggest that the propensity of TC neurons for burst firing is a crucial factor in determining the vulnerability to absence seizures in mice.

4.2.1. Other opinions on the role of $Ca_V3.1$ channels in absence seizures

It has been suggested that it may be premature to conclude that low-threshold Ca^{2+} current-mediated firing plays an essential role in thalamocortical neurons during SWDs [29]. For example, researchers have claimed that the inability of $Ca_V3.1$ knockout mice to show GBL-induced SWDs might reveal a lack of LTS in cortical neurons [125], or the inability of the window current of the T-type Ca^{2+} current to exert a depolarizing influence in cortical and thalamocortical neurons [126].

The results from studies utilizing various animal models and drugs have suggested that there might be multiple mechanisms underpinning the development of absence seizures. The rat models may reflect a mechanism common with that of the bicuculline-induced model, which displays cortical-driven seizures. In contrast, baclofen-induced models and spontaneous mutant mouse models with malfunctions of P/Q type channels may share a mechanism in which TC burst firing is crucial. In other words, the T-type channel-mediated burst activities of TC neurons may not be a prerequisite for SWD generation in certain types of absence seizures. Consistent with this hypothesis, rhythmic sequences of $GABA_B$R-mediated IPSPs and subsequent low-threshold Ca^{2+} potentials were not observed in TC neurons during spontaneous SWDs in GAERS rats, as examined by in vivo extracellular and intracellular recordings [120]. In contrast, $Ca_V3.1^{-/-}$ mice are resistant to baclofen-induced, thalamus-dependent absence seizures, but not to either bicuculline-induced or aminopyridine-induced absence seizures. Thus, burst firing of TC neurons mediated by $Ca_V3.1$ T-type channels may be an indispensable constituent of only a certain type of absence seizure.

A recent study showed that feedback transcranial electrical stimulation (TES) could dramatically reduce SWDs in rat seizure models, presumably supporting the role of cortical neurons in SWDs [127]. This study also showed that optogenetic stimulation of parvalbumin-expressing (PV) neurons in the TRN induced thalamocortical oscillations resulting in SWDs, whereas the same stimulation of PV neurons on the cortex reduced SWDs [127]. The excitation of TRN neurons would generate IPSC in TC neurons, in turn generating the post-inhibitory low-threshold burst firing mediated by T-type channels in TC neurons. These results are consistent with the idea that T-type channels in TC neurons are important for the genesis of SWDs. However, we do not yet know the detailed mechanism by which the cortical stimulation of PV neurons triggers the reduction of SWDs.

Many studies have emphasized the role of tonic GABA inhibition (mediated by $GABA_A$R or $GABA_B$R) of TC neurons in the generation of absence seizure [128–130]. It is also noteworthy that the propensity for low-threshold burst firing in TC neurons increases with these inhibitory inputs.

5. TRN neurons in absence seizures

5.1. TRN neurons as the origin of thalamocortical oscillations

Observations of trains of rhythmic spike-bursts riding the spontaneously recurrent membrane oscillations in TRN neurons [20,69] have indicated that these neurons are likely to be the origin of SWDs in absence epilepsy. The inhibitory input from TRN to TC nuclei is considered to be critical to the generation of thalamic synchrony [33,35].

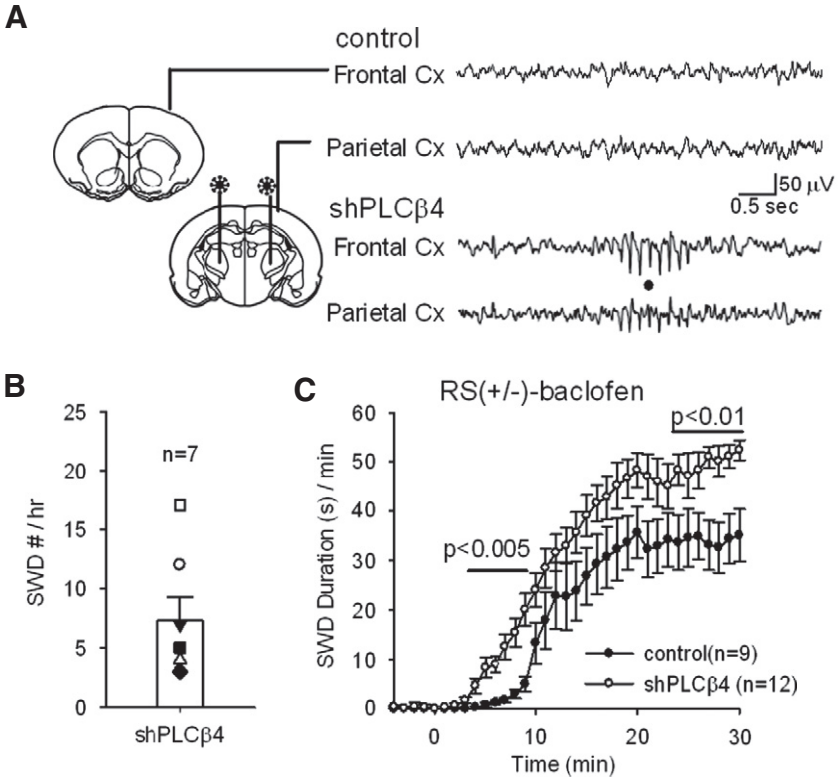

Fig. 6. Deletion of thalamic PLCβ4 leads to absence seizures. (A) Lentiviral vectors containing control shRNA or shPLCβ4 were injected bilaterally into wild-type mice, and EEGs were recorded from frontal and parietal lobes. *Lower panel*: mice injected with LV-shPLCβ4 showed sporadic SWDs. *Upper panel*: mice injected with pLKO-control never showed this high-amplitude paroxysmal EEG pattern. (B) Seven of 12 mice injected with LV-shPLCβ4 showed spontaneous SWDs. The number of SWDs varied from 3 to 17 per hour. (C) The total duration of SWDs per minute induced by 20 mg/kg RS(+/−)-baclofen was greater in mice injected with LV-shPLCβ4 than in mice injected with pLKO-control. Modified from reference [122].

It has been proposed that recurrent inhibitions mediated by $GABA_A$Rs within the TRN dampen the synchrony of the thalamic circuit, thereby inhibiting seizures [34,131,132]. An examination of the occurrence of IPSCs and the degree of synchrony in brain slices from mice lacking $GABA_A$R β3 subunits (largely restricted to the TRN in the rodent thalamus) showed that $GABA_A$R-mediated inhibition was substantially eliminated in the TRN of these mice but was unaffected in TC cells [34]. $GABA_A$R antagonists were shown to abolish intra-reticular inhibition and convert spindle-like oscillations into slower, more synchronized epileptiform discharges in vitro [20,133]. Furthermore, a recent study in the above-described mutant mouse showed that pathological oscillations could still be initiated by cortical inputs via the cortico-TC–TRN–TC pathway, bypassing the direct cortico-TRN excitation generally described for thalamocortical oscillations [134]. This may reveal a previously unknown mode of cortico-thalamo-cortical transmission. In contrast, it was reported that a gain in $GABA_A$ receptor synaptic strength within thalamic reticular nuclei strongly dampened thalamic oscillatory activity and suppressed pharmacologically induced absence seizures [135]. Thus, recurrent inhibitory inputs within the TRN appear to serve as a "desynchronizer" [34,135], reducing the degree of synchronized inhibitory output to TC nuclei. However, future work will be required to examine how reciprocal connections between TRN and TC neurons generate the various types of oscillations (encompassing physiological sleep oscillations and pathological SWDs) within the thalamus, and how the shift between the burst and tonic firing modes of TRN neurons controls the overall inhibitory output from the TRN neurons to TC neurons.

TRN neurons have long been considered to be the origin of thalamocortical oscillations (such as absence seizures) because of their intrinsic rhythmic oscillatory activities. A large body of evidence supports the pivotal role of TRN neurons in pacing the thalamocortical oscillations that serve to generate SWDs [120,136–139]. Some studies have emphasized the role of T-channels in TRN neurons, based on the observation of burst firing among TRN neurons during SWDs [136,138]. A lesion study exhibited that TRN lesion in the WAG/Rij rat model of absence epilepsy decreased the number and duration of SWDs as well as the spectral changes on EEG [137]. However, the same mechanism does not always seem to apply to the generation of SWDs in absence seizures. Another lesion study showed that extensive ibotenic acid-induced lesions of TRN and TC nuclei resulted in the suppression of SWDs and sleep spindles, confirming the critical role of thalamic neurons in both types of thalamocortical oscillations [140]. However, a lesion that spared the rostral pole of the TRN and some TC nuclei resulted in suppression of sleep spindles but a large increase in bilateral SWDs, suggesting that different intrathalamic subcircuits are involved in the two types of thalamocortical oscillations [140].

Inhibitory inputs from TRN to TC nuclei trigger de-inactivation of T-type channels, which is followed by rebound low-threshold burst firings in TC neurons. Thus, the deficit of rebound burst firing in TC neurons of $Ca_V3.1^{-/-}$ mice would interrupt the circuitry needed to generate SWDs. The function of T-type channels in TRN neurons in the genesis of absence epilepsy can be elucidated through the analysis of $Ca_V3.2$ and $Ca_V3.3$ T-type Ca^{2+} channels, which are expressed in TRN neurons but not in TC neurons. The most direct demonstration for the role of T-type channels and burst firing among TRN neurons in the generation of absence seizures can be provided by selective deletion of T-type channels in the TRN.

5.2. T-type channels in TRN neurons

In TRN neurons, burst firing driven by T-type channels is typically followed by an afterhyperpolarization generated by Ca^{2+}-activated small conductance (SK)-type K^+ currents. It has been suggested that the interplay between T-type and SK channels is critical for sustaining rhythmic burst firings in TRN neurons [141–144]. One study reported that the influx of Ca^{2+} through T-type channels activates SK2 channels and sarco/endoplasmic reticulum Ca^{2+}-ATPases (SERCAs) in TRN dendrites to generate and regulate the strength of TRN oscillations related to sleep [144]. Recently, it was shown that $Ca_V3.3$ T-type channel deletion in mice led to a drastic decrease in burst discharges and a complete loss of rhythmic oscillatory burst discharges in TRN neurons [57], demonstrating that the $Ca_V3.3$ channel is critical for generation of low-threshold burst and rhythmic oscillations in TRN neurons. In these $Ca_V3.3^{-/-}$ mice, the power density of spindle oscillations (10–12 Hz) at the transition from NREM to REM sleep was selectively reduced, whereas the other EEG waves remained unaltered. Therefore, these studies suggest that $Ca_V3.3$ channels and T-type current-activated SK channels act as a major pacemaker module in sleep-spindle generation.

According to the long-held theory about the generation of SWD in TRN neurons [17], $Ca_V3.3$ T-type channel-deficient mice should be resistant to absence seizures. As noted above, deletion of $Ca_V3.3$ T-type channels in mice leads to a substantial decrease in burst discharges and a complete loss of rhythmic oscillatory burst discharges in TRN neurons [57]. However, $Ca_V3.3^{-/-}$ mice display increased susceptibility to GBL-induced absence seizures and show enhanced SWD responses [145], contradicting the expectation based on the previous study showing a selective reduction in power density of sleep spindles in these mice [57]. Interestingly, TRN neurons projecting onto TC neurons display increased tonic firing in $Ca_V3.3^{-/-}$ mice, and this induces larger evoked monosynaptic IPSCs in TC neurons. Thus, there appears to be a correlation between the tonic firing rate in TRN neurons and the generation of GBL-induced SWDs. Taken together, these recent studies suggest that burst firing in the TRN is not a prerequisite for the initiation and maintenance of SWDs in the GBL model of absence seizures. Instead, stronger tonic firing in the TRN and the resulting stronger evoked IPSCs in TC neurons appear to positively modulate SWDs. This implies that T-type channel-mediated low-threshold burst firing in TRN neurons plays different roles in sleep spindles and SWDs. For example, rhythmic burst firing in TRN neurons is essential for pacing TC oscillations during sleep spindle oscillations, but not for hypersynchronizing the TC circuit during GBL-induced SWDs. The above-described results [57,145] may be consistent with studies suggesting that different intrathalamic subcircuits are involved in the two types of thalamocortical oscillations [140].

Additional experiments in animals with complete loss of burst firing in TRN neurons induced by deletion of both $Ca_V3.3$ and $Ca_V3.2$ will further clarify the function of T-type channels and burst discharges of TRN neurons in the genesis of absence epilepsy.

5.3. T-type channel mutations identified in human absence epilepsy

Mutations in the $GABA_A$R γ2 subunit [146], the $Ca_V2.1$ subunit of P/Q-type channels [114,115] and the $Ca_V3.2$ subunit of T-type channels [99,100,102] have all been related to childhood absence epilepsy. However, no association has been found between human absence epilepsy and mutations in the $Ca_V3.1$ subunit (n = 48 patients) [99] or the $Ca_V3.3$ subunit of T-type channels (n = 50 patients) [101]. This absence of a link between the $Ca_V3.1$ or $Ca_V3.3$ subtypes and human absence epilepsy may be due to the relatively small patient populations tested or the complex molecular mechanisms of neuronal excitability that contribute to the pathogenesis of absence epilepsy. Ultimately, diverse gene mutations may cause absence epilepsy phenotypes in different patient groups.

Examination of 118 childhood absence epilepsy patients [100] identified 12 different missense mutations in the $Ca_V3.2$ gene, whereas no such mutations were detected in 230 controls. Only 14 out of the 118 patients carried one of these mutations, all of which were found in the heterozygous state. These individuals had all inherited the mutation from a parent, yet no parent reported any medical history of absence epilepsy. If the identified $Ca_V3.2$ mutations cause absence epilepsy in these children, it may speak to the importance of

genetic backgrounds and environmental factors in the pathogenesis of absence epilepsy among mutation carriers.

Functional analyses of cDNA clones corresponding to the $Ca_V3.2$ mutants identified in patients revealed that some of the mutations alter channel gating [147–149], and neuronal modeling predicted that some would change the neuronal firing properties to favor burst firings [149]. Many of the polymorphisms found in the childhood absence epilepsy patients are clustered in the intracellular loop I–II of $Ca_V3.2$ channel, which is involved in regulating the plasma membrane localization and gating properties of the $Ca_V3.2$ T-type channel [150]. Although these results suggest that the $Ca_V3.2$ mutations identified in patients may be clinically relevant to their absence epilepsy, their pathogenic significance remains to be elucidated by additional studies utilizing genetic tools.

6. Summary

T-type channels and low-threshold burst firing in the thalamocortical circuit are involved in the generation of thalamocortical oscillations during absence epilepsy. The three subtypes of T-type channels have distinct expression patterns within the thalamus: $Ca_V3.1$ is expressed in the TC relay nucleus, while $Ca_V3.2$ and $Ca_V3.3$ are expressed in the TRN nucleus. Over the past few decades, the conventional view held that rhythmic burst firings mediated by T-type channels in TRN and TC neurons are critical for the generation of thalamocortical oscillations during both sleep rhythms and SWDs.

In this review, a broad investigation of recent studies suggests that T-type channels in TC regions (more precisely their propensity for low-threshold burst firing in TC neurons) are the most critical component of SWD generation during absence seizures, whereas T-type channels in TRN regions are crucially involved in spindle oscillations but remains controversial for SWD generation (at least in the GBL model of absence seizures). This interpretation sheds new light on potential strategies for developing absence seizure medicines, in that channel subtype-specific drugs may preferentially control pathological oscillations without affecting physiological oscillations. Therefore, understanding the functional consequences of modulating each T-type channel subtype in vivo could guide the development of therapeutic tools for absence epilepsy.

Acknowledgements

We thank our current and former colleagues for their contributions to what was discussed in this article.

References

[1] J.R. Huguenard, Low-threshold calcium currents in central nervous system neurons, Annu. Rev. Physiol. 58 (1996) 329–348.
[2] M. Steriade, R.R. Llinas, The functional states of the thalamus and the associated neuronal interplay, Physiol. Rev. 68 (1988) 649–742.
[3] R. Llinas, Y. Yarom, Properties and distribution of ionic conductances generating electroresponsiveness of mammalian inferior olivary neurones in vitro, J. Physiol. 315 (1981) 569–584.
[4] M.C. Nowycky, A.P. Fox, R.W. Tsien, Three types of neuronal calcium channel with different calcium agonist sensitivity, Nature 316 (1985) 440–443.
[5] B.P. Bean, Two kinds of calcium channels in canine atrial cells. Differences in kinetics, selectivity, and pharmacology, J. Gen. Physiol. 86 (1985) 1–30.
[6] B. Nilius, P. Hess, J.B. Lansman, R.W. Tsien, A novel type of cardiac calcium channel in ventricular cells, Nature 316 (1985) 443–446.
[7] J.R. Serrano, S.R. Dashti, E. Perez-Reyes, S.W. Jones, Mg(2+) block unmasks Ca(2+)/Ba(2+) selectivity of alpha1G T-type calcium channels, Biophys. J. 79 (2000) 3052–3062.
[8] E. Perez-Reyes, Molecular physiology of low-voltage-activated t-type calcium channels, Physiol. Rev. 83 (2003) 117–161.
[9] N. Leresche, J. Hering, R.C. Lambert, Paradoxical potentiation of neuronal T-type Ca2+ current by ATP at resting membrane potential, J. Neurosci. 24 (2004) 5592–5602.
[10] V. Crunelli, T.I. Toth, D.W. Cope, K. Blethyn, S.W. Hughes, The 'window' T-type calcium current in brain dynamics of different behavioural states, J. Physiol. 562 (2005) 121–129.
[11] S.W. Hughes, D.W. Cope, T.I. Toth, S.R. Williams, V. Crunelli, All thalamocortical neurones possess a T-type Ca^{2+} 'window' current that enables the expression of bistability-mediated activities, J. Physiol. 517 (Pt 3) (1999) 805–815.
[12] 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 Ca^{2+} channels controls pain sensory gating in the thalamus, J. Neurosci. 28 (2008) 13331–13340.
[13] J.R. Huguenard, D.A. Prince, A novel T-type current underlies prolonged Ca(2+)-dependent burst firing in GABAergic neurons of rat thalamic reticular nucleus, J. Neurosci. 12 (1992) 3804–3817.
[14] A. Destexhe, D. Contreras, T.J. Sejnowski, M. Steriade, A model of spindle rhythmicity in the isolated thalamic reticular nucleus, J. Neurophysiol. 72 (1994) 803–818.
[15] M. Steriade, Sleep, epilepsy and thalamic reticular inhibitory neurons, Trends Neurosci. 28 (2005) 317–324.
[16] J. Lee, D. Kim, H.S. Shin, Lack of delta waves and sleep disturbances during non-rapid eye movement sleep in mice lacking alpha1G-subunit of T-type calcium channels, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 18195–18199.
[17] M.P. Beenhakker, J.R. Huguenard, Neurons that fire together also conspire together: is normal sleep circuitry hijacked to generate epilepsy? Neuron 62 (2009) 612–632.
[18] H. Khosravani, G.W. Zamponi, Voltage-gated calcium channels and idiopathic generalized epilepsies, Physiol. Rev. 86 (2006) 941–966.
[19] J.L. Noebels, Calcium channel "gaiting" and absence epilepsy, Epilepsy Curr. 5 (2005) 95–97.
[20] M. von Krosigk, T. Bal, D.A. McCormick, Cellular mechanisms of a synchronized oscillation in the thalamus, Science 261 (1993) 361–364.
[21] M.L. Molineux, J.E. McRory, B.E. McKay, J. Hamid, W.H. Mehaffey, R. Rehak, T.P. Snutch, G.W. Zamponi, R.W. Turner, Specific T-type calcium channel isoforms are associated with distinct burst phenotypes in deep cerebellar nuclear neurons, Proc. Natl. Acad. Sci. U. S. A. 103 (2006) 5555–5560.
[22] E. Carbone, H.D. Lux, A low voltage-activated, fully inactivating Ca channel in vertebrate sensory neurones, Nature 310 (1984) 501–502.
[23] R. Llinas, Y. Yarom, Electrophysiology of mammalian inferior olivary neurones in vitro. Different types of voltage-dependent ionic conductances, J. Physiol. 315 (1981) 549–567.
[24] M. Deschenes, M. Paradis, J.P. Roy, M. Steriade, Electrophysiology of neurons of lateral thalamic nuclei in cat: resting properties and burst discharges, J. Neurophysiol. 51 (1984) 1196–1219.
[25] H. Jahnsen, R. Llinas, Electrophysiological properties of guinea-pig thalamic neurones: an in vitro study, J. Physiol. 349 (1984) 205–226.
[26] R. Llinas, U. Ribary, Consciousness and the brain. The thalamocortical dialogue in health and disease, Ann. N. Y. Acad. Sci. 929 (2001) 166–175.
[27] D.A. McCormick, D. Contreras, On the cellular and network bases of epileptic seizures, Annu. Rev. Physiol. 63 (2001) 815–846.
[28] O.C. Snead III, Basic mechanisms of generalized absence seizures, Ann. Neurol. 37 (1995) 146–157.
[29] V. Crunelli, N. Leresche, Childhood absence epilepsy: genes, channels, neurons and networks, Nat. Rev. 3 (2002) 371–382.
[30] D. Williams, A study of thalamic and cortical rhythms in petit mal, Brain 76 (1953) 50–69.
[31] 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.
[32] I. Timofeev, M. Steriade, Neocortical seizures: initiation, development and cessation, Neuroscience 123 (2004) 299–336.
[33] J.R. Huguenard, D.A. McCormick, Thalamic synchrony and dynamic regulation of global forebrain oscillations, Trends Neurosci. 30 (2007) 350–356.
[34] M.M. Huntsman, D.M. Porcello, G.E. Homanics, T.M. DeLorey, J.R. Huguenard, Reciprocal inhibitory connections and network synchrony in the mammalian thalamus, Science 283 (1999) 541–543.
[35] D.A. McCormick, T. Bal, Sleep and arousal: thalamocortical mechanisms, Annu. Rev. Neurosci. 20 (1997) 185–215.
[36] G. Avanzini, F. Panzica, M. de Curtis, The role of the thalamus in vigilance and epileptogenic mechanisms, Clin. Neurophysiol. 111 (Suppl. 2) (2000) S19–S26.
[37] H.K. Meeren, J.P. Pijn, E.L. Van Luijtelaar, A.M. Coenen, F.H. Lopes da Silva, Cortical focus drives widespread corticothalamic networks during spontaneous absence seizures in rats, J. Neurosci. 22 (2002) 1480–1495.
[38] H.O. Tan, C.A. Reid, F.N. Single, P.J. Davies, C. Chiu, S. Murphy, A.L. Clarke, L. Dibbens, H. Krestel, J.C. Mulley, M.V. Jones, P.H. Seeburg, B. Sakmann, S.F. Berkovic, R. Sprengel, S. Petrou, Reduced cortical inhibition in a mouse model of familial childhood absence epilepsy, Proc. Natl. Acad. Sci. U. S. A. 104 (2007) 17536–17541.
[39] P.O. Polack, I. Guillemain, E. Hu, C. Deransart, A. Depaulis, S. Charpier, Deep layer somatosensory cortical neurons initiate spike-and-wave discharges in a genetic model of absence seizures, J. Neurosci. 27 (2007) 6590–6599.
[40] 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.
[41] 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 Ca(2+) channels, Neuron 31 (2001) 35–45.
[42] M. Steriade, D. Contreras, Relations between cortical and thalamic cellular events during transition from sleep patterns to paroxysmal activity, J. Neurosci. 15 (1995) 623–642.
[43] J.H. Lee, A.N. Daud, L.L. Cribbs, A.E. Lacerda, A. Pereverzev, U. Klockner, T. Schneider, E. Perez-Reyes, Cloning and expression of a novel member of the low voltage-activated T-type calcium channel family, J. Neurosci. 19 (1999) 1912–1921.

[44] 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.
[45] 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 Ca^{2+} channels lead to differential Ca^{2+} entry and frequency-dependence during mock action potentials, Eur. J. Neurosci. 11 (1999) 4149–4158.
[46] U. Klockner, J.H. Lee, L.L. Cribbs, A. Daud, J. Hescheler, A. Pereverzev, E. Perez-Reyes, T. Schneider, Comparison of the Ca^{2+} currents induced by expression of three cloned alpha1 subunits, alpha1G, alpha1H and alpha1I, of low-voltage-activated T-type Ca^{2+} channels, Eur. J. Neurosci. 11 (1999) 4171–4178.
[47] J.E. McRory, C.M. Santi, K.S. Hamming, J. Mezeyova, K.G. Sutton, D.L. Baillie, A. Stea, T.P. Snutch, Molecular and functional characterization of a family of rat brain T-type calcium channels, J. Biol. Chem. 276 (2001) 3999–4011.
[48] 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.
[49] E. Perez-Reyes, G protein-mediated inhibition of Cav3.2 T-type channels revisited, Mol. Pharmacol. 77 (2010) 136–138.
[50] J.H. Lee, J.C. Gomora, L.L. Cribbs, E. Perez-Reyes, Nickel block of three cloned T-type calcium channels: low concentrations selectively block alpha1H, Biophys. J. 77 (1999) 3034–3042.
[51] 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.
[52] R. Llinas, H. Jahnsen, Electrophysiology of mammalian thalamic neurones in vitro, Nature 297 (1982) 406–408.
[53] M. Steriade, D.A. McCormick, T.J. Sejnowski, Thalamocortical oscillations in the sleeping and aroused brain, Science 262 (1993) 679–685.
[54] 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.
[55] P.M. Joksovic, D.A. Bayliss, S.M. Todorovic, Different kinetic properties of two T-type Ca2+ currents of rat reticular thalamic neurones and their modulation by enflurane, J. Physiol. 566 (2005) 125–142.
[56] P.M. Joksovic, M.T. Nelson, V. Jevtovic-Todorovic, M.K. Patel, E. Perez-Reyes, K.P. Campbell, C.C. Chen, S.M. Todorovic, CaV3.2 is the major molecular substrate for redox regulation of T-type Ca2+ channels in the rat and mouse thalamus, J. Physiol. 574 (2006) 415–430.
[57] S. Astori, R.D. Wimmer, H.M. Prosser, C. Corti, M. Corsi, N. Liaudet, A. Volterra, P. Franken, J.P. Adelman, A. Luthi, The CaV3.3 calcium channel is the major sleep spindle pacemaker in thalamus, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 13823–13828.
[58] B.E. McKay, J.E. McRory, M.L. Molineux, J. Hamid, T.P. Snutch, G.W. Zamponi, R.W. Turner, Ca(V)3 T-type calcium channel isoforms differentially distribute to somatic and dendritic compartments in rat central neurons, Eur. J. Neurosci. 24 (2006) 2581–2594.
[59] M. Steriade, D. Contreras, R. Curro Dossi, A. Nunez, The slow (<1 Hz) oscillation in reticular thalamic and thalamocortical neurons: scenario of sleep rhythm generation in interacting thalamic and neocortical networks, J. Neurosci. 13 (1993) 3284–3299.
[60] A. Bacci, J.R. Huguenard, Enhancement of spike-timing precision by autaptic transmission in neocortical inhibitory interneurons, Neuron 49 (2006) 119–130.
[61] A. Bacci, J.R. Huguenard, D.A. Prince, Modulation of neocortical interneurons: extrinsic influences and exercises in self-control, Trends Neurosci. 28 (2005) 602–610.
[62] V.S. Sohal, J.R. Huguenard, Inhibitory coupling specifically generates emergent gamma oscillations in diverse cell types, Proc. Natl. Acad. Sci. U. S. A. 102 (2005) 18638–18643.
[63] Z. Xiang, J.R. Huguenard, D.A. Prince, Cholinergic switching within neocortical inhibitory networks, Science 281 (1998) 985–988.
[64] C.L. Cox, J.R. Huguenard, D.A. Prince, Nucleus reticularis neurons mediate diverse inhibitory effects in thalamus, Proc. Natl. Acad. Sci. U. S. A. 94 (1997) 8854–8859.
[65] N. Leresche, H.R. Parri, G. Erdemli, A. Guyon, J.P. Turner, S.R. Williams, E. Asprodini, V. Crunelli, On the action of the anti-absence drug ethosuximide in the rat and cat thalamus, J. Neurosci. 18 (1998) 4842–4853.
[66] 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.
[67] D.M. Porcello, S.D. Smith, J.R. Huguenard, Actions of U-92032, a T-type Ca2+ channel antagonist, support a functional linkage between I(T) and slow intrathalamic rhythms, J. Neurophysiol. 89 (2003) 177–185.
[68] D. Pinault, The thalamic reticular nucleus: structure, function and concept, Brain Res. Brain Res. Rev. 46 (2004) 1–31.
[69] U. Kim, T. Bal, D.A. McCormick, Spindle waves are propagating synchronized oscillations in the ferret LGNd in vitro, J. Neurophysiol. 74 (1995) 1301–1323.
[70] P. Fuentealba, I. Timofeev, M. Steriade, Prolonged hyperpolarizing potentials precede spindle oscillations in the thalamic reticular nucleus, Proc. Natl. Acad. Sci. U. S. A. 101 (2004) 9816–9821.
[71] M. Steriade, L. Domich, G. Oakson, M. Deschenes, The deafferented reticular thalamic nucleus generates spindle rhythmicity, J. Neurophysiol. 57 (1987) 260–273.
[72] T. Bal, M. von Krosigk, D.A. McCormick, Role of the ferret perigeniculate nucleus in the generation of synchronized oscillations in vitro, J. Physiol. 483 (Pt 3) (1995) 665–685.
[73] C. Deleuze, J.R. Huguenard, Distinct electrical and chemical connectivity maps in the thalamic reticular nucleus: potential roles in synchronization and sensation, J. Neurosci. 26 (2006) 8633–8645.
[74] M.V. Sanchez-Vives, T. Bal, D.A. McCormick, Inhibitory interactions between perigeniculate GABAergic neurons, J. Neurosci. 17 (1997) 8894–8908.
[75] V.S. Sohal, J.R. Huguenard, Inhibitory interconnections control burst pattern and emergent network synchrony in reticular thalamus, J. Neurosci. 23 (2003) 8978–8988.
[76] C.E. Landisman, M.A. Long, M. Beierlein, M.R. Deans, D.L. Paul, B.W. Connors, Electrical synapses in the thalamic reticular nucleus, J. Neurosci. 22 (2002) 1002–1009.
[77] J.R. Huguenard, Low-voltage-activated (T-type) calcium-channel genes identified, Trends Neurosci. 21 (1998) 451–452.
[78] H.S. Shin, E.J. Cheong, S. Choi, J. Lee, H.S. Na, T-type Ca2+ channels as therapeutic targets in the nervous system, Curr. Opin. Pharmacol. 8 (2008) 33–41.
[79] D.A. Coulter, J.R. Huguenard, D.A. Prince, Specific petit mal anticonvulsants reduce calcium currents in thalamic neurons, Neurosci. Lett. 98 (1989) 74–78.
[80] D.A. Coulter, J.R. Huguenard, D.A. Prince, Differential effects of petit mal anticonvulsants and convulsants on thalamic neurones: GABA current blockade, Br. J. Pharmacol. 100 (1990) 807–813.
[81] J.R. Huguenard, Neuronal circuitry of thalamocortical epilepsy and mechanisms of antiabsence drug action, Adv. Neurol. 79 (1999) 991–999.
[82] T.A. Glauser, A. Cnaan, S. Shinnar, D.G. Hirtz, D. Dlugos, D. Masur, P.O. Clark, E.V. Capparelli, P.C. Adamson, Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy, N. Engl. J. Med. 362 (2010) 790–799.
[83] T. Broicher, T. Seidenbecher, P. Meuth, T. Munsch, S.G. Meuth, T. Kanyshkova, H.C. Pape, T. Budde, T-current related effects of antiepileptic drugs and a Ca2+ channel antagonist on thalamic relay and local circuit interneurons in a rat model of absence epilepsy, Neuropharmacology 53 (2007) 431–446.
[84] M.A. Rogawski, R.J. Porter, Antiepileptic drugs: pharmacological mechanisms and clinical efficacy with consideration of promising developmental stage compounds, Pharmacol. Rev. 42 (1990) 223–286.
[85] Y.F. Zhang, J.W. Gibbs III, D.A. Coulter, Anticonvulsant drug effects on spontaneous thalamocortical rhythms in vitro: valproic acid, clonazepam, and alpha-methyl-alpha-phenylsuccinimide, Epilepsy Res. 23 (1996) 37–53.
[86] Y.F. Zhang, J.W. Gibbs III, D.A. Coulter, Anticonvulsant drug effects on spontaneous thalamocortical rhythms in vitro: ethosuximide, trimethadione, and dimethadione, Epilepsy Res. 23 (1996) 15–36.
[87] J.W. Gibbs III, Y.F. Zhang, H.S. Ahmed, D.A. Coulter, Anticonvulsant actions of lamotrigine on spontaneous thalamocortical rhythms, Epilepsia 43 (2002) 342–349.
[88] G. van Luijtelaar, D. Wiaderna, C. Elants, W. Scheenen, Opposite effects of T- and L-type Ca(2+) channels blockers in generalized absence epilepsy, Eur. J. Pharmacol. 406 (2000) 381–389.
[89] 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 Ca^{2+} channel antagonist, J. Med. Chem. 51 (2008) 3692–3695.
[90] 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.
[91] 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.
[92] F.M. Dreyfus, A. Tscherter, A.C. Errington, J.J. Renger, H.S. Shin, V.N. Uebele, V. Crunelli, R.C. Lambert, N. Leresche, Selective T-type calcium channel block in thalamic neurons reveals channel redundancy and physiological impact of I(T) window, J. Neurosci. 30 (2010) 99–109.
[93] C. Deleuze, F. David, S. Behuret, G. Sadoc, H.S. Shin, V.N. Uebele, J.J. Renger, R.C. Lambert, N. Leresche, T. Bal, T-type calcium channels consolidate tonic action potential output of thalamic neurons to neocortex, J. Neurosci. 32 (2012) 12228–12236.
[94] 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), (121ra119).
[95] C.C. Chen, K.G. Lamping, D.W. Nuno, R. Barresi, S.J. Prouty, J.L. Lavoie, L.L. Cribbs, S.K. England, C.D. Sigmund, R.M. Weiss, R.A. Williamson, J.A. Hill, K.P. Campbell, Abnormal coronary function in mice deficient in alpha1H T-type Ca^{2+} channels, Science 302 (2003) 1416–1418.
[96] 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.
[97] I. Song, D. Kim, S. Choi, M. Sun, Y. Kim, H.S. Shin, Role of the alpha1G T-type calcium channel in spontaneous absence seizures in mutant mice, J. Neurosci. 24 (2004) 5249–5257.
[98] 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.

[99] Y. Chen, J. Lu, Y. Zhang, H. Pan, H. Wu, K. Xu, X. Liu, Y. Jiang, X. Bao, J. Zhou, W. Liu, G. Shi, Y. Shen, X. Wu, T-type calcium channel gene alpha (1G) is not associated with childhood absence epilepsy in the Chinese Han population, Neurosci. Lett. 341 (2003) 29–32.
[100] 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.
[101] J. Wang, Y. Zhang, J. Liang, H. Pan, H. Wu, K. Xu, X. Liu, Y. Jiang, Y. Shen, X. Wu, CACNA1I is not associated with childhood absence epilepsy in the Chinese Han population, Pediatr. Neurol. 35 (2006) 187–190.
[102] J. Liang, Y. Zhang, J. Wang, H. Pan, H. Wu, K. Xu, X. Liu, Y. Jiang, Y. Shen, X. Wu, New variants in the CACNA1H gene identified in childhood absence epilepsy, Neurosci. Lett. 406 (2006) 27–32.
[103] R.R. Llinas, M. Steriade, Bursting of thalamic neurons and states of vigilance, J. Neurophysiol. 95 (2006) 3297–3308.
[104] D.A. Hosford, S. Clark, Z. Cao, W.A. Wilson Jr., F.H. Lin, R.A. Morrisett, A. Huin, The role of GABAB receptor activation in absence seizures of lethargic (lh/lh) mice, Science 257 (1992) 398–401.
[105] S.J. Caddick, C. Wang, C.F. Fletcher, N.A. Jenkins, N.G. Copeland, D.A. Hosford, Excitatory but not inhibitory synaptic transmission is reduced in lethargic (Cacnb4(lh)) and tottering (Cacna1atg) mouse thalami, J. Neurophysiol. 81 (1999) 2066–2074.
[106] 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.
[107] O.C. Snead III, P.K. Banerjee, M. Burnham, D. Hampson, Modulation of absence seizures by the GABA(A) receptor: a critical rolefor metabotropic glutamate receptor 4 (mGluR4), J. Neurosci. 20 (2000) 6218–6224.
[108] T. Seidenbecher, R. Staak, H.C. Pape, Relations between cortical and thalamic cellular activities during absence seizures in rats, Eur. J. Neurosci. 10 (1998) 1103–1112.
[109] J. Kim, J. Woo, Y.G. Park, S. Chae, S. Jo, J.W. Choi, H.Y. Jun, Y.I. Yeom, S.H. Park, K.H. Kim, H.S. Shin, D. Kim, Thalamic T-type Ca^{2+} channels mediate frontal lobe dysfunctions caused by a hypoxia-like damage in the prefrontal cortex, J. Neurosci. 31 (2011) 4063–4073.
[110] M. Steriade, D. Contreras, Spike-wave complexes and fast components of cortically generated seizures. I. Role of neocortex and thalamus, J. Neurophysiol. 80 (1998) 1439–1455.
[111] J.L. Noebels, R.L. Sidman, Inherited epilepsy: spike-wave and focal motor seizures in the mutant mouse tottering, Science 204 (1979) 1334–1336.
[112] X. Qiao, J.L. Noebels, Developmental analysis of hippocampal mossy fiber outgrowth in a mutant mouse with inherited spike-wave seizures, J. Neurosci. 13 (1993) 4622–4635.
[113] C.F. Fletcher, C.M. Lutz, T.N. O'Sullivan, J.D. Shaughnessy Jr., R. Hawkes, W.N. Frankel, N.G. Copeland, N.A. Jenkins, Absence epilepsy in tottering mutant mice is associated with calcium channel defects, Cell 87 (1996) 607–617.
[114] A. Jouvenceau, L.H. Eunson, A. Spauschus, V. Ramesh, S.M. Zuberi, D.M. Kullmann, M.G. Hanna, Human epilepsy associated with dysfunction of the brain P/Q-type calcium channel, Lancet 358 (2001) 801–807.
[115] P. Imbrici, S.L. Jaffe, L.H. Eunson, N.P. Davies, C. Herd, R. Robertson, D.M. Kullmann, M.G. Hanna, Dysfunction of the brain calcium channel CaV2.1 in absence epilepsy and episodic ataxia, Brain 127 (2004) 2682–2692.
[116] 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.
[117] 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 Cav3.2 T-type calcium channel point mutation has splice-variant-specific effects on function and segregates with seizure expression in a polygenic rat model of absence epilepsy, J. Neurosci. 29 (2009) 371–380.
[118] Y. Zhang, A.P. Vilaythong, D. Yoshor, J.L. Noebels, Elevated thalamic low-voltage-activated currents precede the onset of absence epilepsy in the SNAP25-deficient mouse mutant coloboma, J. Neurosci. 24 (2004) 5239–5248.
[119] 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.
[120] 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.
[121] W.L. Ernst, Y. Zhang, J.W. Yoo, S.J. Ernst, J.L. Noebels, Genetic enhancement of thalamocortical network activity by elevating alpha1g-mediated low-voltage-activated calcium current induces pure absence epilepsy, J. Neurosci. 29 (2009) 1615–1625.
[122] 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.
[123] U. Kim, M.V. Sanchez-Vives, D.A. McCormick, Functional dynamics of GABAergic inhibition in the thalamus, Science 278 (1997) 130–134.
[124] A. Ludwig, T. Budde, J. Stieber, S. Moosmang, C. Wahl, K. Holthoff, A. Langebartels, C. Wotjak, T. Munsch, X. Zong, S. Feil, R. Feil, M. Lancel, K.R. Chien, A. Konnerth, H.C. Pape, M. Biel, F. Hofmann, Absence epilepsy and sinus dysrhythmia in mice lacking the pacemaker channel HCN2, EMBO J. 22 (2003) 216–224.
[125] M. Steriade, F. Amzica, D. Contreras, Cortical and thalamic cellular correlates of electroencephalographic burst-suppression, Electroencephalogr. Clin. Neurophysiol. 90 (1994) 1–16.
[126] S.W. Hughes, D.W. Cope, K.L. Blethyn, V. Crunelli, Cellular mechanisms of the slow (<1 Hz) oscillation in thalamocortical neurons in vitro, Neuron 33 (2002) 947–958.
[127] A. Berenyi, M. Belluscio, D. Mao, G. Buzsaki, Closed-loop control of epilepsy by transcranial electrical stimulation, Science 337 (2012) 735–737.
[128] D.W. Cope, S.W. Hughes, V. Crunelli, GABAA receptor-mediated tonic inhibition in thalamic neurons, J. Neurosci. 25 (2005) 11553–11563.
[129] N. Leresche, R.C. Lambert, A.C. Errington, V. Crunelli, From sleep spindles of natural sleep to spike and wave discharges of typical absence seizures: is the hypothesis still valid? Pflugers Arch. 463 (2012) 201–212.
[130] M.P. Beenhakker, J.R. Huguenard, Astrocytes as gatekeepers of GABAB receptor function, J. Neurosci. 30 (2010) 15262–15276.
[131] V.S. Sohal, M.M. Huntsman, J.R. Huguenard, Reciprocal inhibitory connections regulate the spatiotemporal properties of intrathalamic oscillations, J. Neurosci. 20 (2000) 1735–1745.
[132] C.M. Schofield, J.R. Huguenard, GABA affinity shapes IPSCs in thalamic nuclei, J. Neurosci. 27 (2007) 7954–7962.
[133] J.R. Huguenard, D.A. Prince, Clonazepam suppresses GABAB-mediated inhibition in thalamic relay neurons through effects in nucleus reticularis, J. Neurophysiol. 71 (1994) 2576–2581.
[134] J.T. Paz, A.S. Bryant, K. Peng, L. Fenno, O. Yizhar, W.N. Frankel, K. Deisseroth, J.R. Huguenard, A new mode of corticothalamic transmission revealed in the Gria4(−/−) model of absence epilepsy, Nat. Neurosci. 14 (2011) 1167–1173.
[135] C.M. Schofield, M. Kleiman-Weiner, U. Rudolph, J.R. Huguenard, A gain in GABAA receptor synaptic strength in thalamus reduces oscillatory activity and absence seizures, Proc. Natl. Acad. Sci. U. S. A. 106 (2009) 7630–7635.
[136] G. Avanzini, M. de Curtis, C. Marescaux, F. Panzica, R. Spreafico, M. Vergnes, Role of the thalamic reticular nucleus in the generation of rhythmic thalamo-cortical activities subserving spike and waves, J. Neural Transm. Suppl. 35 (1992) 85–95.
[137] R.K. Berdiev, S.A. Chepurnov, J.G. Veening, N.E. Chepurnova, G. van Luijtelaar, The role of the nucleus basalis of Meynert and reticular thalamic nucleus in pathogenesis of genetically determined absence epilepsy in rats: a lesion study, Brain Res. 1185 (2007) 266–274.
[138] 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.
[139] D. Pinault, M. Vergnes, C. Marescaux, Medium-voltage 5–9-Hz oscillations give rise to spike-and-wave discharges in a genetic model of absence epilepsy: in vivo dual extracellular recording of thalamic relay and reticular neurons, Neuroscience 105 (2001) 181–201.
[140] H.K. Meeren, J.G. Veening, T.A. Moderscheim, A.M. Coenen, G. van Luijtelaar, Thalamic lesions in a genetic rat model of absence epilepsy: dissociation between spike-wave discharges and sleep spindles, Exp. Neurol. 217 (2009) 25–37.
[141] G. Avanzini, M. de Curtis, F. Panzica, R. Spreafico, Intrinsic properties of nucleus reticularis thalami neurones of the rat studied in vitro, J. Physiol. 416 (1989) 111–122.
[142] T. Bal, D.A. McCormick, Mechanisms of oscillatory activity in guinea-pig nucleus reticularis thalami in vitro: a mammalian pacemaker, J. Physiol. 468 (1993) 669–691.
[143] K.L. Blethyn, S.W. Hughes, T.I. Toth, D.W. Cope, V. Crunelli, Neuronal basis of the slow (<1 Hz) oscillation in neurons of the nucleus reticularis thalami in vitro, J. Neurosci. 26 (2006) 2474–2486.
[144] L. Cueni, M. Canepari, R. Lujan, Y. Emmenegger, M. Watanabe, C.T. Bond, P. Franken, J.P. Adelman, A. Luthi, T-type Ca^{2+} channels, SK2 channels and SERCAs gate sleep-related oscillations in thalamic dendrites, Nat. Neurosci. 11 (2008) 683–692.
[145] S. Lee, T. Zaman, J. Lee, C.F. Latchoumane, B. Lee, Z. Saud, M. Kim, E. Cheong, C. Lee, H.S. Shin, Elimination of rebound burst firing in the reticular thalamus leads to an increased sensitivity to drug-induced absence seizures in mice, SFN annual meeting, Poster #: 248.19/S5, 2011.
[146] J.Q. Kang, R.L. Macdonald, The GABAA receptor gamma2 subunit R43Q mutation linked to childhood absence epilepsy and febrile seizures causes retention of alpha1beta2gamma2S receptors in the endoplasmic reticulum, J. Neurosci. 24 (2004) 8672–8677.
[147] H. Khosravani, C. Bladen, D.B. Parker, T.P. Snutch, J.E. McRory, G.W. Zamponi, Effects of Cav3.2 channel mutations linked to idiopathic generalized epilepsy, Ann. Neurol. 57 (2005) 745–749.
[148] 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 Cav3.2 T-type calcium channel associated with childhood absence epilepsy, J. Biol. Chem. 279 (2004) 9681–9684.
[149] 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.
[150] 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 Ca(v)3.2 T-type Ca^{2+} channels: a paradigm for childhood absence epilepsy mutations, J. Neurosci. 27 (2007) 322–330.