T-TYPE Ca\(^{2+}\) CHANNELS IN NORMAL AND ABNORMAL BRAIN FUNCTIONS

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I. INTRODUCTION

Intracellular Ca\(^{2+}\) plays important roles in neuronal functions, including control of neuronal excitability, release of neurotransmitters, and synaptic plasticity. Although many channels and pumps are involved in controlling intracellular Ca\(^{2+}\) levels, voltage-gated Ca\(^{2+}\) channels play a key role in this process (50). Their activity is essential in coupling electrical signals on the cell surface to physiological events in the cells. Once Ca\(^{2+}\) enters into the cell, it works as an important intracellular second messenger. Ca\(^{2+}\) entry into the cell can further depolarize the membrane potential and subsequently activates other ion channels.

At least two distinct classes of Ca\(^{2+}\) channels, low-voltage activated (LVA) and high-voltage activated (HVA), are recognized depending on their electrophysiological characteristics (33, 87). T-type Ca\(^{2+}\) channels are considered to be LVA Ca\(^{2+}\) channels and differ from members of the HVA Ca\(^{2+}\) channel family in several respects. Compared with HVA channels, T-type Ca\(^{2+}\) channels exhibit more rapid voltage-dependent inactivation with smaller single-channel amplitudes, which produces a transient current at the whole cell level. Furthermore, T-type channels require a much smaller depolarization for opening, and a majority of them are tonically inactivated, leaving only a small fraction available for “window” currents at typical neuronal resting membrane potentials (43, 64, 93, 130, 182). A larger fraction of T-type channels are not inactivated in neurons with a relatively hyperpolarized resting membrane potential (98). The current properties, distribution, and pharmacology of T-type Ca\(^{2+}\) channels have been well described in a previous review (182).

The distinctive voltage sensitivity of T-type Ca\(^{2+}\) channels is well suited to regulating cellular excitability and oscillatory behavior near the resting membrane potential. In neurons, a transient membrane hyperpolarization arising from inhibitory postsynaptic potentials (IPSPs) or activation of certain types of potassium channels deinactivates T-type Ca\(^{2+}\) channels; the subsequent rebound of the membrane potential triggers the opening of T-type Ca\(^{2+}\) channels. The resulting Ca\(^{2+}\) entry further depolarizes the membrane potential to reach the threshold for voltage-gated sodium channels, thus initiating a train of action potentials. This phenomenon, termed rebound burst firing, represents a paradoxical enhancement of neuronal firing after inhibitory inputs and is often observed under normal physiological conditions, such as sleep (19, 70, 124, 216), and in patho-
physiological conditions, such as absence epilepsy (113, 166). These properties highlight the physiological significance of T-type channels in regulating neuronal firing patterns (160).

Voltage-activated Ca\(^{2+}\) channels, including T-type Ca\(^{2+}\) channels, are complex proteins consisting of four or five distinct subunits, which are encoded by multiple genes (33). The α1 subunit contains the conduction pore and most of the known sites of channel regulation such as voltage-sensitive sites and ligand binding sites (33). The auxiliary α2δ, β, and γ subunits are known to have crucial roles in modulating the function of voltage-gated Ca\(^{2+}\) channels (6). Three subtypes of T-type channels, Ca\(_{\text{v}}\)3.1, Ca\(_{\text{v}}\)3.2, and Ca\(_{\text{v}}\)3.3, corresponding to complexes containing the pore-forming α1 subunits, α1G, α1H, and α1I, respectively, have been identified (34, 125, 182). These three subtypes are both differentially expressed and colocalized throughout the body, resulting in a substantial degree of biophysical heterogeneity and functional diversity of T-type Ca\(^{2+}\) currents (231).

Since the initial description of low-threshold Ca\(^{2+}\) spikes mediated by T-type Ca\(^{2+}\) channels (31, 169), these events have been studied in isolated neurons and slices obtained from diverse brain regions, including the inferior olivary nucleus (139, 140), thalamus (69, 103), association cortex (79), lateral habenula (252), dorsal raphe (28), CA1-CA3 of the hippocampus (88, 170), medial pontine reticular formation (84), septum (2), deep cerebellar nuclei (137), paraventricular (234) and preoptic nuclei of the hypothalamus (230), globus pallidus (162), and subthalamic nucleus (22) in the central nervous system (CNS). They have also been studied in the peripheral nervous system including sensory neurons (29, 121) and dorsal root ganglion (DRG) neurons (47, 171). The differential distribution of the subtypes in different types of neurons has not been fully defined. A study on the subcellular distribution of the Ca\(_{\text{v}}\)3 subtypes in cortical neurons of the rat brain has shown that Ca\(_{\text{v}}\)3.1 T-type channels are prominent in the soma and the proximal dendritic regions, Ca\(_{\text{v}}\)3.2 channels are expressed in the soma and the proximal-mid dendrites, and Ca\(_{\text{v}}\)3.3 channels exhibit a distinctive localization to the soma and the dendritic arbors in specific cell types (155). These distribution patterns suggest a possibility that T-type channels contribute to multiple neuronal activities. T-type Ca\(^{2+}\) channels are widely expressed in diverse cell types throughout the body, including smooth muscle, heart, sperm, and kidney (59, 135, 164, 196, 206, 249), which suggests that they play a role in diverse physiological functions.

The prominent expression of T-type channels in the CNS indicates a role in a variety of central neuronal functions. In fact, T-type channel dysfunction has been strongly implicated in neurological disorders, including sleep disorders, absence epilepsy, neuropathic pain, Parkinson’s disease-associated tremor, and neuropsychiatric disorders (138). The role of T-type channels in thalamic sensory gating has been a matter of controversy, with different studies reporting different findings (141, 202, 203, 217). Recent studies reveal a potential role of T-type channels in cognitive functions. In this review, we seek to provide a comprehensive overview of the role of T-type Ca\(^{2+}\) channels in epilepsy, sleep, and pain. In addition, we will briefly discuss the role of T-type channels in cognition.

II. ELECTROPHYSIOLOGY

A. Low-Threshold Ca\(^{2+}\) Spikes and Burst Firing

The identification of low-threshold spikes (LTS) in neurons suggested the existence of LVA channels, an inference confirmed by the work of many groups (7, 17, 165, 169). Ca\(^{2+}\) influx through LVA Ca\(^{2+}\) channels engenders low-threshold spikes, which in turn trigger a burst of action potentials mediated by voltage-gated Na\(^{+}\) channels. Adding tetrodotoxin, a blocker of Na\(^{+}\) channels, eliminates only the fast spikes, leaving the slow component of LTS intact. Innumerable studies have demonstrated that the slow component of LTS is mediated by Ca\(^{2+}\) conductance based on the observations that they are not generated either in Ca\(^{2+}\)-free external solutions or in the presence of divalent cations such as Co\(^{2+}\) and Ni\(^{2+}\) which block Ca\(^{2+}\) channel conductance (136). These channels, first described as LVA Ca\(^{2+}\) channels, are distinguished from HVA Ca\(^{2+}\) channels in several respects: they have smaller currents at the single-channel level, slower deactivating tail currents, and equivalent conductance for Ca\(^{2+}\) and Ba\(^{2+}\); they also exhibit whole cell currents with fast inactivation kinetics (17, 165). The most distinctive feature of T-type currents is their transient nature: as soon as the currents reach a peak, they decay. Tsien and colleagues (169) subsequently proposed that they be named T-type for “transient” and also tiny because of the small size of the currents that they generate.

LTS cannot be triggered by depolarization of neurons whose resting membrane potentials are in a range from −60 to −65 mV, whereas they can be triggered by depolarization of neurons with the resting membrane potentials hyperpolarized to −70 mV or greater. In neurons with relatively depolarized resting membrane potentials, LTS can be induced shortly after delivery of a hyperpolarizing pulse which let the T-type channels recover from inactivation, so-called “deinactivation.” T-type channels are deinactivated relatively quickly, with the half recovery within ~100 ms and full recovery after ~200 ms.

B. Window Current of T-Type Channels

At ordinary resting membrane potentials near −60 to −65 mV, a major portion of the T-type Ca\(^{2+}\) channel population...
is tonically inactivated, with a very small fraction remaining available for activation. The small current mediated by these available T-type channels is called the “window current,” defined as the overlap region between activation and steady-state inactivation curves. IPSPs elicit transitory membrane hyperpolarizations, which release T-type channels from inactivation. Then, a larger number of channels are ready for opening upon subsequent membrane depolarizations, thus generating low-threshold Ca\(^{2+}\) spikes which trigger action potential bursts.

Although the window current occupies a very small fraction of total T-type Ca\(^{2+}\) currents in neurons, much attention has been attracted to the potential role of this component near the resting membrane potential. It has been suggested to be essential for the slow (<1 Hz) sleep oscillations of thalamic neurons (92) and be involved in signal amplification (145, 148, 241) and synaptic plasticity (172). A study using the selective blocker for T-type channels, 3,5-di-chloro-N-[1-(2,2-dimethyl-tetrahydro-pyran-4-ylmethyl)-4-fluoro-piperidin-4-ylmethyl]-benzamide (TTA-P2), demonstrated the presence of a small but obvious window component of Ca\(^{2+}\) currents and that activation of only a small fraction of the T-type channel population was enough to generate a robust low-threshold Ca\(^{2+}\) spike, which suggested that LTS can be driven at a membrane potential where only a small fraction of T-type channels are available to generate currents (73).

A recent study utilizing the dynamic clamping techniques assessed the spike probability driven by EPSPs at different membrane potentials (−68, −63, and −58 mV) in TC neurons with and without the T-channel blocker TTA-P2 (67). This study displayed no difference in the spike probability among different membrane potential in the absence of T-channel blocker. However, in the presence of TTA-P2, the spike probability gets significantly reduced at relatively hyperpolarized membrane potentials (−63 and −68 mV) compared with −58 mV, which indicates a role of T-currents in facilitating the spike generation near the resting membrane potential (67). These results together suggest that the window current conveys a physiological role near the resting membrane potential.

**C. Electrophysiological Properties of the Three T-Type Channel Subtypes**

The electrophysiological properties of the three subtypes of T-type channels have been examined after expressing cloned \(\alpha1\) subunits in a variety of heterologous expression systems (119, 125). Currents mediated by \(\alpha1\) subunits expressed in heterologous systems were reported to display \(I-V\) curves and activation-inactivation properties substantially similar to those of T-type currents observed in neurons (118, 119, 125, 156). T-type currents recorded from the three recombinant Ca\(_{v}\)3 channels share typical T-type channel characteristics: low voltage activation, negative steady-state inactivation, strongly voltage-dependent activation and inactivation, and slow deactivation (156), but exhibited characteristic voltage dependencies and the kinetics of activation and inactivation depending on the subtypes (37). They differ in their kinetics of inactivation, recovery from steady-state inactivation, and pharmacology (118, 126, 181). The kinetics of recovery from inactivation is critical to the ability of T-type channels to trigger rebound LTS because the fast deinactivation of T-type channels during IPSP is followed by channel openings as the membrane rebounds to its resting potential. The time course for recovery is highly variable, ranging from 100 to 3,300 ms, depending on the pulse duration of both the inactivating pulse and the test pulse and the membrane potential. Differences in the recovery kinetics of T-type currents among various neurons might also reflect the expression of specific subtypes (118). (118). Of the three subtypes, Ca\(_{v}\)3.1 and Ca\(_{v}\)3.2 channels recover the fastest (~120 ms), Ca\(_{v}\)3.2 channels are the slowest (showing a recovery rate more than 3-fold slower than Ca\(_{v}\)3.1 channels), and Ca\(_{v}\)3.3 channels show an intermediate recovery rate (118, 119, 125). Although most T-type currents display rapid inactivation (<30 ms) compared with HVA Ca\(^{2+}\) currents, subtype-specific variability has been noted, with Ca\(_{v}\)3.1 and Ca\(_{v}\)3.2 exhibiting fast inactivation while Ca\(_{v}\)3.3 displays relatively slow inactivation (118).

The differences in electrophysiological properties of T-type channels suggest that the firing patterns of neurons depend on which subtypes of T-type channels they mainly express. Thus the biophysical heterogeneity and functional diversity of T-type Ca\(^{2+}\) currents (118, 125) arising from the differential expression and colocalization of the channel subtypes (231) highlight the importance of understanding the expression patterns in given brain regions or neurons and the differences in electrophysiological properties of the three subtypes as a prerequisite for understanding their associated neuronal activities.

**III. T-TYPE Ca\(^{2+}\) CHANNELS IN ABSENCE SEIZURES**

Absence seizures are observed with a brief loss of consciousness accompanied by the characteristic 3-Hz spike-wave discharges (SWDs) on electroencephalograms (EEGs) (63). It has long been suggested that generalized seizures accompany hyperexcitable oscillatory activities in the thalamocortical network. The observation that succinimide and related anticonvulsants block thalamic T-type channels (54, 55) gave rise to the proposition that T-type Ca\(^{2+}\) channels might be related to the pathogenesis of SWDs with generalized absence seizures (95).

Some antiepileptic drugs, ethosuximide and valproate, used to treat generalized absence epilepsy were reported to block...
T-type Ca\(^{2+}\) channels in TC neurons at therapeutically relevant concentrations (26, 27, 53). Other anticonvulsant drugs have also been shown to substantially suppress thalamic burst spikes (83, 262, 263). 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. T-type channel antagonists were shown to dampen SWDs in human absence seizure patients and in rodent models of absence seizures (244). However, some studies have found that neither valproic acid (55) nor ethosuximide (133) 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 (205). One such compound, TTA-A2, potently blocked T-type currents in HEK293 cells expressing human Cav3.1, Cav3.2, or Cav3.3 T-channels, and suppressed the active wake state and promoted slow-wave sleep in mice (120), whereas it suppressed the absence epilepsy in WAG/Rij rat models (242). 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 (73) and the contribution of T-currents on EPSP-driven spike probability in TC neurons (67). In addition, the piperidine-based compounds Z941 and Z944 blocked T-type channels, attenuating thalamic burst firing and suppressing absence seizures (239).

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 (38, 115, 124), analysis of T-type channels in animal models of absence epilepsy (213, 240, 260), and analysis of putative candidate genes in human patients (39, 40, 134, 248). The following section summarizes recent achievements in genetic studies to investigate the role of T-type Ca\(^{2+}\) channels in absence epilepsy.

### A. Expression Pattern of T-Type Channels in the Thalamocortical Circuit

The three subtypes of T-type Ca\(^{2+}\) channel, Cav3.1, Cav3.2, and Cav3.3, are highly expressed in the thalamocortical circuit, suggesting a potential role for these channels in this circuit (231). Notably, the three subtypes display a largely complementary expression pattern in the thalamus: Cav3.1 is exclusively expressed in TC regions, whereas Cav3.2 and Cav3.3 channels are abundant in GABAergic neurons in the TRN (26). The slow decay and depolarized membrane potential range for activation of low-threshold Ca\(^{2+}\) currents in the TRN (98) reflect the predominant contribution of Cav3.3 over Cav3.2 channels to the total T-type current in TRN neurons, an interpretation supported by the greater levels of Cav3.3 mRNA compared with Cav3.2 mRNA in these neurons (26, 107, 108). Indeed, T-type current is drastically reduced in TRN neurons following deletion of Cav3.3 T-type channels, strongly supporting the conclusion that the Cav3.3 channel is the predominant contributor to T-type currents in TRN neurons (8).

In situ hybridization experiments have demonstrated the substantial and widespread expression of mRNA signals for the three subtypes in the cortex, Cav3.1 and Cav3.3 throughout all layers of the cortex and Cav3.2 predominantly in layer V (231). The differential distribution of subtypes among cortical layers or in different types of neurons has not been fully established.

### B. Cav3.1 Channels in Absence Seizures

#### 1. TC neurons in absence seizures

Paroxysmal oscillations of the TC network during SWDs are frequently observed with a switch in the firing pattern of TC neurons from tonic to burst firing (141). It has been proposed that low-threshold burst firing driven by Cav3.1 T-type channels in TC neurons is a crucial element in sustained oscillations during SWDs (19, 96, 115), although controversies remain (63, 219).

It was proposed that an excess of hyperpolarizing inputs to TC neurons that leads to the deinactivation of Cav3.1 T-type channels might precede the appearance of absence seizures. In this context, it is noteworthy that TC neurons deficient for HCN2 (hyperpolarization-activated cyclic nucleotide-gated potassium channel 2) display a hyperpolarized resting membrane potential with increased burst firing and are prone to oscillations (144). The β4\(^{lh/lh}\) mice, a mutant mouse model of absence seizures, display a deficiency in the P/Q-type channel activity. The spontaneous absence seizure in β4\(^{lh/lh}\) mice was suppressed by GABA\(_B\) receptor antagonists and exacerbated by GABA\(_B\) agonists (89), which suggested the enhanced GABA\(_B\) receptor-mediated synaptic responses underlie the seizures and GABA\(_B\) antagonists hold promise as anticonvulsants for absence seizures. However, a subsequent study by the same authors reported that β4\(^{lh/lh}\) or a1A\(^{tg/tg}\) mice with mutations in the genes encoding β4 or α1A subunits, respectively, reveals a significant decrease in glutamatergic synaptic transmission, but no significant decrease in GABAergic transmission, suggesting that the independent mutations in the two strains each affected P/Q channel function, causing defective neurotransmitter release specific to glutamatergic synapses in TC neurons (30). These two studies, although they are somewhat inconsistent, imply that an increased ratio between inhibitory and excitatory signals, either by increased inhibitory synaptic inputs or by decreased excitatory synaptic inputs, can lead
to the genesis of absence seizures. Thus these data together suggest that a propensity for membrane hyperpolarization (thus greater deactivation of T-type channels) could effectively escalate the opening probability of T-type Ca\(^{2+}\) channels thus reinforcing SWDs, even without an increase in T-type channel densities. It remains to be elucidated how malfunction of P/Q-type channels leads to the membrane hyperpolarization of TC neurons.

2. Ca\(_{\text{v}}\)3.1 knockout mice are resistant to GABA\(_B\)-mediated absence seizures

An analysis of knockout mice lacking the Ca\(_{\text{v}}\)3.1 subunit of the a1G subtype revealed its essential role in absence epilepsy (115). In the thalamus, Ca\(_{\text{v}}\)3.1 is predominantly expressed in TC neurons, whereas Ca\(_{\text{v}}\)3.2 and Ca\(_{\text{v}}\)3.3 are predominantly expressed in thalamic reticular nucleus (TRN) neurons (231). Therefore, the Ca\(_{\text{v}}\)3.1-knockout (Ca\(_{\text{v}}\)3.1\(^{-/-}\)) 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\(_{\text{v}}\)3.1 in TC neurons (231), deletion of Ca\(_{\text{v}}\)3.1 abolished low-threshold T-type Ca\(^{2+}\) currents and burst firing in TC neurons, as shown in FIGURE 1 (115). In accord with the absence of burst firing in TC neurons of Ca\(_{\text{v}}\)3.1\(^{-/-}\) mice in vivo (115), intracellular current-clamp recordings from thalamic neurons in brain slice preparations in vitro have shown that a rebound low-threshold calcium spike and thus burst firing is also absent in these mice (FIGURE 1A). When progressively more current was injected, a number of spikes with characteristics of tonic firing patterns were eventually evoked (FIGURE 1B). Tonic firing was elicited by depolarizing current inputs in Ca\(_{\text{v}}\)3.1\(^{-/-}\) TC neurons at −60 mV (FIGURE 1C). A quantitative comparison (FIGURE 1D) revealed a significant difference in the number of spikes between wild-type and Ca\(_{\text{v}}\)3.1\(^{-/-}\) TC neurons in burst mode (FIGURE 1D, right) but not in tonic mode (FIGURE 1D, left), indicating that LTS, but not regular action potential, are selectively missing in TC neurons of Ca\(_{\text{v}}\)3.1\(^{-/-}\) mice. Moreover, Ca\(_{\text{v}}\)3.1\(^{-/-}\) mice are resistant to SWD seizures specifically induced by GABA\(_B\)-R agonists. Baclofen or γ-hydroxybutyrate, GABA\(_B\)-R agonists, has been shown to reliably induce absence seizure symptoms in animals accompanied by characteristic behavioral arrest synchronized with SWDs on EEGs (209). These GABA\(_B\)-R agonists evoked distinct emergence of paroxysmal 3–4 Hz SWDs on EEG recordings accompanied by behavioral arrests in wild-type mice, whereas the agonists with the same dose induced only very weak and intermittent SWDs in Ca\(_{\text{v}}\)3.1\(^{-/-}\) mice (FIGURE 2).

In contrast to this phenotype of Ca\(_{\text{v}}\)3.1\(^{-/-}\) mice, studies on rats utilized as animal models of absence seizures have proposed that the cortex, not the thalamus, leads the genesis of SWDs (146, 157, 186, 233). In one such study using rat models of absence epilepsy, GAERS and WAG/Rij strains, the generation of SWDs was suggested to originate from the cortex, not the thalamus (146, 200). Cortical infusion of ethosuximide substantially blocked SWDs in the GAERS model (146). On the other hand, it was reported that the Ca\(_{\text{v}}\)3.1 T-type channel in the mediodorsal thalamus (MD) plays a crucial role in frontal lobe-specific seizures (116).

Many studies corroborate the hypothesis that recurrent oscillatory activity in the network between the TRN and the TC relay nucleus generates the thalamic synchrony, which is further propagated throughout the thalamocortical circuit (11, 19, 96, 100, 152). Whereas SWDs induced by baclofen, a GABA\(_B\)-R agonist, rely on the thalamus, bicuculline, a GABA\(_A\)-R antagonist, is shown to initially induce the cortex-organized seizure spikes that evolve to highly synchronous SWDs throughout the thalamocortical circuit (209, 220). Interestingly, Ca\(_{\text{v}}\)3.1\(^{-/-}\) mice remain vulnerable to bicuculline-induced seizures (115). After systemic injection of bicuculline, both mutant and wild-type mice exhibited a variety of epileptic symptoms with behavioral changes, accompanied by characteristic EEG patterns, comprising SWDs, single spikes with high amplitude, and a variety of epileptic patterns. 4-Aminopyridine, a potassium channel antagonist which would increase the neuronal excitability, also induced tonic-clonic seizures to a similar degree in both wild-type and Ca\(_{\text{v}}\)3.1\(^{-/-}\) mice (115).

The studies utilizing various animal models and drugs suggest that there might be multiple mechanisms to develop absence seizures. The rat models may have a common mechanism with the bicuculline-induced model displaying the cortical-driven seizures. On the other hand, baclofen-induced models and spontaneous mutant mice models with malfunction of P/Q-type channels may share a mechanism where TC burst firing is crucial. In other words, burst activities of TC neurons mediated by T-type channels may not be a prerequisite for SWD generation in the pathogenesis of certain types of absence seizures. This explanation agrees with the finding that rhythmic sequences of GABA\(_B\)-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 (184). Therefore, Ca\(_{\text{v}}\)3.1\(^{-/-}\) mice are resistant to baclofen-induced, thalamus-dependent absence seizures, but not to either bicuculline-induced or aminopyridine-induced absence seizures. Therefore, burst firing of TC neurons mediated by Ca\(_{\text{v}}\)3.1 T-type channels may be an indispensable constituent of only a certain type of absence seizures.
3. Absence epilepsy in P/Q-type channel-deficient (CaV2.1+/−) mice requires CaV3.1

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 mouse models include "tottering (α1A\textsuperscript{Tgr/tgr})" (167, 190) and "leaner (α1A\textsuperscript{Tdl/tdl})" (78), each containing a distinct mutation of the gene encoding the P/Q-type channel Ca\(_{V}2.1\) α1A subunit stargazer.
(stg/stg) (190), containing a mutation in the P/Q-type γ2 subunit, lethargic (B4/h × h) (90), containing a mutation in the P/Q-type β4 subunit, and CaV2.1⁻/⁻ null mutant mice (90, 213). In general, these mice exhibit 5- to 7-Hz SWDs associated with behavioral phenotypes, whereas human patients generally show 3-Hz SWDs on EEG, a diagnostic hallmark. In this latter context, it is interesting that CaV2.1⁻/⁻ null mice, which lack P/Q-type channels, display 3-Hz SWDs, comparable to that observed in human patients (FIGURE 3B). The importance of this characteristic feature of human absence epilepsy is not known. A mutation of the CaV2.1 gene has also been identified as the cause of absence epilepsy associated with episodic ataxia in children (102, 109). The identified mutation of CaV2.1 gene also causes a hypo-function of P/Q channels. Therefore, the CaV2.1⁻/⁻ mice might provide an animal model relevant for studying this specific type of human absence epilepsy.

Whether the CaV3.1 T-type channel is also essential for SWD generation in these genetic mice models of absence seizures would be an intriguing question. This was addressed by generating double-mutant mice through crossing each mutant strain with CaV3.1⁻/⁻ mice (13). The results of these maneuvers were unambiguous: in all cases the generation of SWDs was substantially diminished by deleting the CaV3.1 gene. Representative EEG traces and results of a power spectrum analysis of the EEGs of CaV2.1 and CaV3.1 double-mutant mice are shown in FIGURE 3B, and the effects of CaV3.1 gene doses in those absence mouse models with spontaneous mutations are shown in a bar graph in FIGURE 3C. These results provide firm evidence that CaV3.1 T-type Ca²⁺ channels are necessary for the occurrence of absence epilepsy phenotypes in these mutant mice, just as they are for GABA₁R agonist-induced absence epilepsy.

4. Other opinions on the role of CaV3.1 channels in absence seizures

It has been suggested that it may be premature to conclude that low-threshold Ca²⁺ current-mediated firing plays an essential role in thalamocortical neurons during SWDs (63). For example, researchers have claimed that the inability of CaV3.1 knockout mice to show GBL-induced SWDs might reveal a lack of LTS in cortical neurons (218), or the inability of the window current of the T-type Ca²⁺ current to exert a depolarizing influence in cortical and thalamocortical neurons (92).

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 GABABR-mediated IPSPs and subsequent low-threshold Ca\(^{2+}\)/H\(^{1+}\) potentials were not observed in TC neurons during spontaneous SWDs in GAERS rats, as examined by in vivo extracellular and intracellular recordings (184). In contrast, CaV3.1\(/\)/ 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 CaV3.1 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 (21). 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 (21). The excitation of TRN neurons would generate IPSC in TC neurons, in turn generating the postinhibitory 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 (18, 51, 132). It is also noteworthy that the propensity for low-threshold burst firing in TC neurons increases with these inhibitory inputs.

C. Propensity for TC Bursts in Absence Seizures

T-type Ca\(^{2+}\) conductance is particularly increased in TRN neurons of the GAERS rat (240). A previous study

![Figure 3](http://physrev.physiology.org/)

**FIGURE 3.** Suppression of absence seizures by CaV3.1 deletion in a P/Q channel-deficient (CaV2.1\(^{-/-}\)) genetic background. A: representative traces of total Ca\(^{2+}\) currents of the four genotypes: CaV2.1\(^{-/-}\); CaV3.1\(^{-/-}\) (wild-type), CaV2.1\(^{-/-}\); CaV3.1\(^{-/-}\), CaV2.1\(^{-/-}\); CaV3.1\(^{-/-}\) and CaV2.1\(^{-/-}\); CaV3.1\(^{-/-}\). The bar graph shows a quantitative comparison of the currents among the four genotypes. *Bottom:* power spectrum analysis of the EEG patterns of the two genotypes: CaV2.1\(^{-/-}\); CaV3.1\(^{-/-}\) and CaV2.1\(^{-/-}\); CaV3.1\(^{-/-}\). C: comparison of the frequency of SWD events among mice with different genetic compositions. The effects of the CaV3.1 gene dose on the expression of SWDs in different absence model mice are compared. [Modified from Song et al. (213).]
demonstrated small, but significant, increases in both \( \text{CaV}3.1 \) and \( \text{CaV}3.2 \) mRNA in the relay and reticular thalamic nuclei, respectively, of GAERS rats using the quantitative in situ hybridization technique (232). The increase in T-type \( \text{Ca}^{2+} \) currents in TRN neurons was observed (240), and gain-of-function mutation in \( \text{CaV}3.2 \) channel was reported (189) in this genetic model of absence epilepsy. In addition, larger T-type currents in TC neurons have also been observed in various mutant mice with absence seizure phenotypes (213, 260, 261). These studies suggest that the increase in T-type currents may contribute to the onset of absence epilepsy. The increased T-type currents would strengthen the burst firing of thalamic neurons, and thus reinforce network oscillations in TC circuits.

Another issue is regarding the question as to whether the increased T-type currents are the key factor to generate SWDs in these absence seizure models, or are epiphenomena, byproducts of overall changes in the excitability of thalamic neurons. This point was addressed by a genetic study using double mutants for \( \text{CaV}3.1 \) and \( \text{CaV}2.1 \) (213). As in other absence seizure mice with channel malfunctions (213, 260, 261), the amplitude of T-type \( \text{Ca}^{2+} \) currents was increased in the TC neurons of \( \text{CaV}2.1^{-/−} \) mice (FIGURE 2A). Crossing this mutant with \( \text{CaV}3.1^{-/−} \) mice yields three different groups of \( \text{CaV}2.1^{-/−} \) mice, each with a different dose of \( \text{CaV}3.1 \), i.e., \( \text{CaV}2.1^{-/−} \) with \( \text{CaV}3.1^{+/−} \), \( \text{CaV}3.1^{+/+} \), or \( \text{CaV}3.1^{-/−} \). The TC neurons of \( \text{CaV}2.1^{-/−} \text{CaV}3.1^{+/−} \) mice exhibited increased T-type currents (~160%) compared with wild-type mice, whereas T-type currents were absent in \( \text{CaV}2.1^{-/−} \text{CaV}3.1^{-/−} \) mice, reflecting the deletion of both copies of the \( \text{CaV}3.1 \) gene (FIGURE 3A). The level of T-type currents in \( \text{CaV}2.1^{-/−} \text{CaV}3.1^{+/−} \) mice, containing a single copy of the \( \text{CaV}3.1 \), was below that in wild-type mice (~75%), although the expression level per copy of the gene was increased due to developmental compensation in the \( \text{CaV}2.1^{-/−} \) background (FIGURE 3A). These \( \text{CaV}2.1^{-/−} \text{CaV}3.1^{+/−} \) mice provided the core implement to test the role of increased T-type currents in the generation of SWDs. EEGs revealed that \( \text{CaV}2.1^{-/−} \text{CaV}3.1^{+/−} \) mice generated SWDs to the same degree as did \( \text{CaV}2.1^{-/−} \text{CaV}3.1^{+/+} \) mice, even though their TC neurons had decreased rather than increased T-type currents compared with wild-type TC neurons. Therefore, these results demonstrate that although T-type currents in TC neurons are necessary for the generation of SWDs, their increase is not the core element to the pathogenesis of SWDs in those absence-seizure model mice investigated. However, some studies argue against the function of T-type currents in TC in absence seizures based on the finding that burst firings mediated by T-type currents in TC neurons have rarely been observed synchronously with SWDs on EEG in in vivo recordings from rat and cat absence seizure models (36, 184, 219).

It has been reported that augmented T-type \( \text{Ca}^{2+} \) currents by overexpressing \( \text{CaV}3.1 \) channels throughout the brain was sufficient to engender spontaneous SWDs in transgenic mice (74). However, the enhancement of T-type currents in these mice overexpressing \( \text{CaV}3.1 \) channels was not limited to the TC relay regions but was general throughout the whole brain, which weakens the support for the idea that the augmentation of T-type \( \text{Ca}^{2+} \) currents in TC neurons was the key to the genesis of SWDs in these transgenic mice (63).

One study has suggested that absence seizures may be generated by an increase in the propensity for burst firing of TC neurons, rather than by increasing the magnitude of T-type currents or expression of T-type channels in these cells (44). The phospholipase C\( \beta 4 \) (PLC\( \beta 4 \)) 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 \( \text{Ca}^{2+} \) currents in TC neurons (FIGURE 4, A–D; Ref. 43). TC neurons from PLC\( \beta 4^{-/−} \) mice display a depolarizing shift in the steady-state inactivation of T-type \( \text{Ca}^{2+} \) channels, resulting in significantly increased window currents (FIGURE 4, E AND F), which drastically increases their propensity for burst firing. Therefore, PLC\( \beta 4^{-/−} \)-deficient TC neurons are readily switched to an oscillatory burst firing mode following a weak membrane hyperpolarization (FIGURE 4, I AND J), and display frequent burst firings after slight hyperpolarizations that never induce burst firing in wild-type TC neurons (FIGURE 4, K–M). In addition to the whole-animal knock-out, a TC-restricted knockdown of PLC\( \beta 4 \) using shRNA in mice induces spontaneous SWDs accompanying coincident characteristic behavioral phenotypes. These mice also exhibited the increased susceptibility to GBL- or baclofen-induced SWDs, revealing a leading contribution of TC neurons to initiate the paroxysmal SWDs and thus in the pathogenesis of absence seizures (FIGURE 5). In this study, an abnormally prompt shift from the tonic to burst firing mode in TC neurons appeared to readily switch the thalamocortical circuit into pathological oscillatory modes, signified as SWDs. Taken together, these results propose that the propensity for burst firing of TC neurons is a crucial factor in determining the vulnerability to the pathogenesis of absence seizures in mice.

D. \( \text{CaV}3.3 \) Channel in Absence Seizures

1. TRN neurons in absence seizures

Observations of trains of rhythmic spike-bursts riding the spontaneously recurrent membrane oscillations in TRN neurons (117, 247) have pointed to TRN neurons as the origin of SWDs in absence epilepsy. The inhibitory input from TRN to TC nuclei was considered to be critical to the generation of thalamic synchrony (96, 152).
FIGURE 4. Firing pattern is easily shifted to burst firing mode because of enhanced low-voltage-activated (LVA) and high-voltage-activated (HVA) Ca\(^{2+}\) currents in PLC\(^{−/−}\) TC neurons. LVA (A) and HVA (C) Ca\(^{2+}\) currents were measured from wild-type and PLC\(^{−/−}\) TC neurons. I-V relationships of LVA (B) and HVA (D) Ca\(^{2+}\) current density in wild-type (●) and PLC\(^{−/−}\) (○) TC neurons revealed increased LVA and HVA Ca\(^{2+}\) currents in PLC\(^{−/−}\) TC neurons. E: LVA Ca\(^{2+}\) currents from wild-type [left panel] and PLC\(^{−/−}\) [right panel] TC neurons activated by voltage steps to −40 mV from −100 mV (top panels) and from −60 mV (bottom panels). F: steady-state inactivation and activation curves for LVA Ca\(^{2+}\) currents in wild-type (●, black lines) and PLC\(^{−/−}\) (○, gray lines) show that less steady-state inactivation of LVA Ca\(^{2+}\) currents increased the window currents in PLC\(^{−/−}\) TC neurons. Ca\(^{2+}\) currents were measured with activation steps to −40 mV from a given prepulse potential, ranging from −100 to −50 mV. The degree of inactivation was measured as the ratio of current density at a given prepulse potential to maximum current density, measured at a −100 mV prepulse. Activation curves were obtained from Ca\(^{2+}\) currents measured upon hyperpolarization of the membrane potential to −100 mV followed by activation steps ranging from −90 to −40 mV. Smooth curves represent fits to the data with a Boltzmann equation. G: HVA Ca\(^{2+}\) current was measured in voltage steps from −60 to 0 mV before and after treatment with 10 μM nifedipine in wild-type [left panel] and PLC\(^{−/−}\) [right panel] TC neurons. H: current density of total, nifedipine-sensitive, and nifedipine-insensitive HVA Ca\(^{2+}\) currents. Representative traces showing the firing patterns of wild-type (I) and PLC\(^{−/−}\) (J) TC neurons from whole cell patch-clamp recordings. Tonic firing was induced with 400-pA depolarizing currents. PLC\(^{−/−}\) TC neurons were often shifted from tonic to low-threshold burst firing (J), whereas wild-type TC neurons never showed such a transition in firing mode (I). The bottom panel displays the applied current steps. Injection of prepulses, which slightly hyperpolarized the membrane potentials, elicited low-threshold burst firing in PLC\(^{−/−}\) TC neurons (L), but not in wild-type TC neurons (K). M: spike numbers in aburst induced by various prepulses that hyperpolarized the membrane potentials to between −73 and −63 mV in wild-type (●) and PLC\(^{−/−}\) (○) TC neurons. [Modified from Cheong et al. (43) and Cheong et al. (44)].]
It has been proposed that recurrent inhibitions mediated by GABAARs within the TRN dampens synchrony of the thalamic circuit and thus inhibits seizures (100, 197, 212). An examination of the occurrence of IPSCs and the degree of synchrony in slices from mice lacking GABAAR β3 subunits, which are largely restricted in expression to the TRN in the rodent thalamus, showed that GABAAR-mediated inhibition was substantially eliminated in the TRN of these mice, but was unaffected in TC cells. Furthermore, overall oscillatory synchrony in the thalamocortical circuit was dramatically escalated. In contrast, it was reported that a gain in GABAAR receptor synaptic strength within thalamic subcircuits are involved in the two types of thalamocortical oscillations (158). Consistently, recent studies suggested that the contribution of T-type channels in TRN neurons may not be the same as those in TC neurons in the genesis of sleep spindles and SWDs (8, 128). Deleting CaV3.3 T-type channels in mice leads to a dramatic decrease in burst discharges and a complete loss of rhythmic oscillatory burst discharges in TRN neurons. CaV3.3−/− mice display an increased susceptibility to GBL-induced absence seizures showing enhanced SWDs responses (128), whereas mutant mice showed a selective reduction in power density of sleep spindles as discussed above (8). Interestingly, TRN neurons projecting onto TC neurons in CaV3.3−/− mice display increased tonic firing, which induces larger evoked monosynaptic IPSCs in TC neurons. This reveals the existence of a correlation between the tonic firing rate in TRN neurons and the generation of SWDs. Low-threshold burst firing mediated by T-type channels has been shown to generate these recurrent oscillations via cross-talk with Ca2+-activated after-hyperpolarizing currents (65).

Inhibitory input from TRN to TC nuclei deactivates T-type channels, which is followed by rebound low-threshold burst firings in TC neurons. Thus the deficit of rebound burst firing of TC neurons in CaV3.1−/− mice would interrupt the circuitry to generate SWDs. The function of T-type channels in TRN neurons in the genesis of absence epilepsy can be elucidated through analysis of CaV3.2 and CaV3.3 T-type Ca2+ channels, which are expressed in TRN, but not TC neurons.

2. CaV3.3 channels in TRN neurons in absence seizures

The most direct demonstration for the role of T-type channels and burst firing of TRN neurons in the generation of absence seizures can be provided by a selective deletion of T-type channels in the TRN. It has been shown that TRN neurons predominantly express CaV3.3 and in a lesser degree CaV3.2, but not CaV3.1 (232). On the other hand, one study proposed that CaV3.2 channels mediate the substantial portion of T-type currents in TRN neurons by showing that oxidizing agents such as 5,5′-dithio-bis(2-nitrobenzoic acid) (DTNB), which inhibits CaV3.3, but not either of CaV3.1 or CaV3.3 channels, inhibit T-currents in TRN neurons.
Deletion of CaV3.3 in mice led to a drastic decrease in burst discharges and a complete loss of rhythmic oscillatory burst discharges in TRN neurons (8), demonstrating that the CaV3.3 channel is critical for generation of low-threshold burst and rhythmic oscillations in TRN neurons. According to the long-held theory about the generation of SWD in TRN neurons (19), such mutant mice should show resistance to absence seizures. Contrary to such an expectation, however, CaV3.3\(^{-/-}\) mice displayed an increased susceptibility to \(\gamma\)-butyrolactone (GBL)-induced absence seizures with enhanced SWDs (128). These results are at odds with the generally accepted model and bring up the controversy over the role of the TRN burst in the generation of SWDs.

This unexpected observation may be explained by the presence of a correlation between the tonic firing rate in TRN neurons and the degree of SWD, that are observed in the CaV3.3\(^{-/-}\) mice. TRN neurons projecting onto TC neurons in CaV3.3\(^{-/-}\) mice display increased tonic firing, which might be responsible for enhanced SWDs by increasing the inhibitory synaptic drive to TC neurons. Indeed, evoked monosynaptic inhibitory postsynaptic currents (IPSCs) in TC neurons representing GABA release are significantly larger in CaV3.3\(^{-/-}\) mice than in wild-type mice. Taken together, these recent studies suggest that burst firing in the TRN is not essential for the initiation and maintenance of SWD. Instead, at least in the CaV3.3\(^{-/-}\) mice, tonic firing in the TRN and resulting IPSCs in TC neurons positively modulate SWDs, the hallmark of absence seizures. Therefore, a discrepancy remains in the studies on the role of T-type channels in TRN neurons in the generation of absence. Additional studies in animals with a complete loss of burst firing in TRN neurons induced by deletion of both CaV3.3 and CaV3.2 will further clarify the function of T-type channels, and thus burst discharges in TRN neurons, in the genesis of absence epilepsy.

### E. T-Type Channel Mutations Identified in Human Absence Epilepsy

Genetic studies have not yet pinpointed the precise molecular mechanism or genetic basis of childhood absence epilepsy. However, mutations in a few genes, including those for the GABA\(_A\)R2 subunit (110), the CaV2.1 subunit of P/Q-type channels (102, 109), and the CaV3.2 subunit of T-type channels (39, 40, 134), have been shown to be related with childhood absence epilepsy. On the other hand, no associations have been found between childhood absence epilepsy and mutations in the CaV3.1 subunit. On the other hand, no associations have been found between childhood absence epilepsy and mutations in the CaV3.1 subunit (48 patients) (40) or the CaV3.3 subunit of T-type channels (50 patients) (248). This absence of a link between CaV3.1 and CaV3.3 subtypes and human absence epilepsy may be due to the relatively small patient populations tested or the complex molecular mechanisms controlling neuronal excitability that contribute to the pathogenesis of absence epilepsy. Ultimately, diverse gene mutations may cause absence epilepsy phenotypes in different patient groups.

Mutations in the CaV3.2 gene have been linked to human childhood absence epilepsy. Examination on 118 childhood absence epilepsy patients (39) identified 12 different nonsense mutations, whereas no such mutations were detected in 230 controls. Only 14 of the 118 patients carried one of these mutations, all of which were found in a heterozygous state. They inherited the mutation from their parents who never reported any medical history of absence epilepsy. If the CaV3.2 mutations caused the absence epilepsy in those children, it may speak to the importance of genetic backgrounds and environmental factors in the pathogenesis of absence epilepsy in the mutation carriers.

Functional analyses of cDNA clones corresponding to CaV3.2 mutants identified in patients revealed that some mutations alter channel gating (111, 112, 246), and neuronal modeling predicted that some of these mutations would change the neuronal firing properties to favor burst firings (246). Many of the polymorphisms found in the childhood absence epilepsy patients are clustered in the intracellular loop I–II of CaV3.2 channel. This part of the channel is involved in regulating the channel expression on plasma membrane and gating properties of the CaV3.2 T-type channel (245). Although these results implicate CaV3.2 mutations in patients in clinical absence epilepsy, the functional significance of these mutations in the pathogenesis of absence epilepsy in the mutation carriers.

### IV. T-TYPE Ca\(^{2+}\) CHANNELS IN SLEEP

During sleep, brain activity generally displays slow rhythmic oscillations synchronized among synaptically connected neurons in the thalamocortical network. The thalamus, a subcortical structure, is a major gateway for the flow of sensory signals from the external environment to the cerebral cortex. Incoming sensory signals are prevented from being perceived during sleep. The transition from wakefulness to the sleep state is connected with inhibitory mechanisms leading to the membrane hyperpolarization of thalamic neurons (223). Many in vitro studies displayed that T-type Ca\(^{2+}\) channels provide the ionic basis for the oscillatory properties and voltage-dependent firing of thalamic neurons (52, 104, 105, 151). The observation that an intrinsic slow oscillation with predominance of LTS in TRN neurons in vitro was qualitatively equivalent to that observed in vivo proposes a role of T-type Ca\(^{2+}\) channels in shaping slow oscillations during the deep sleep stage (23).

T-type channels make an intricate contribution to membrane potential oscillations underlying sleep spindles and...
delta waves. A pacemaker activity mediated by T-type channels, presumably CaV3.1 subtype, has been found in single TC neurons exhibiting rhythmic burst firing, which underlies the generation of delta waves in vitro (153) and in vivo (226). TRN neurons also exhibit LTS driven by T-type channels during spindle waves in vitro (247) and in vivo (226), and also show a propensity to generate intrinsic rhythmic oscillations related to LTS (14). Membrane potential oscillations that participate in the manifestation of the brain rhythms of NREM sleep can arise from such intrinsic properties of a single neuron or small neuronal network, although the brain rhythms of NREM sleep result from ensemble activities in the thalamo-cortico-thalamic loop (61, 215). Thus the intrinsic properties of thalamic neurons corroborate an essential role of T-type Ca2+ channels in the generation of sleep rhythms.

In this section, we will concentrate on the contribution of T-type Ca2+ channels in the control of sleep rhythms and sleep quality. Therefore, this section will mostly describe the TC, and mice lacking the gene for CaV3.3 encoding the T-type Ca2+ channels during NREM sleep rhythms. A pacemaker activity mediated by T-type channels in the thalamus during NREM sleep and is predicted to result in maintenance of the sleep state. The absence of low-threshold spike in TC neurons could lower the threshold for the change of vigilance because LTS participate in inhibiting sensory transmission of TC neurons during sleep and anesthesia (114, 225). During the transition from NREM sleep to the awake states, cholinergic innervations from brain stem neurons depolarize TC neurons (66) and thus decrease the probability for the generation of LTS, whereas weakened cholinergic inputs from the brain stem hyperpolarizes the membrane potential of TC neurons and disinhibits TRN neurons (214). Therefore, the absence of LTS in TC neurons would increase the propensity for the shift from NREM sleep to wake states in CaV3.1 T-channel mutants.

Real-time polymerase chain reaction analyses have revealed that gene expression for all T-type channel transcripts isolated from the mouse thalamus exhibited a diurnal fluctuation (168). Peak expression level of the CaV3.1 transcript occurs in the early inactive phase corresponding to the normal sleep state of mice, whereas expression of both CaV3.2 and CaV3.3 peaks near the transition from inactive to active phase. Such diurnal regulation of gene expression is consistent with the inhibitory function of T-type channels in the thalamus, which is predicted to result in maintenance of the sleep state.

On the other hand, a patent application has asserted that an antagonist for T-type Ca2+ channel enhances rather than suppresses the sleep in rats (192). This preclinical study showed that the compound in question blocked T-type currents in HEK293 cells expressing the human CaV3.2 T-channel gene and significantly decreased the duration of wakefulness in rats relative to vehicle controls when administered intravenously 60 min prior to lights on. Moreover, the compound reduced the number of entries into wake state.
states, significantly reducing sleep fragmentation. The same group recently reported that another compound, TTA-A2 [2-(4-cyclopropylphenyl)-N-((1R)-1-[5-[(2,2,2-trifluoroethyl)oxy]-pyridin-2-yl]ethyl) acetamide], also demonstrated as a T-channel antagonist, blocked T-type currents in HEK293 cells expressing human CaV3.1, CaV3.2, or CaV3.3 T-channels (120). Kraus et al. (120) showed that TTA-A2 blocks T-type channels in a voltage-dependent manner with a relatively high potency. To estimate the effect of the T-type Ca\(^{2+}\) channel antagonist on sleep, these authors administered the compound intravenously to mice 1 h prior to lights on, and recorded EEGs and EMGs immediately after drug injection. Efficacy and reversibility were assessed using a crossover design by administering the drug daily for the first 5 days, followed by 2 days of washout and a subsequent reversal of vehicle and compound. The results showed that the T-channel antagonist substantially decreased the duration of wake states compared with the vehicle control, and this effect was maintained for about 2 hours after the drug injection. Furthermore, the T-type antagonist decreased the number of entries into wake states and thus significantly reduced sleep fragmentation. These results were interpreted to indicate that the T-type antagonist is a potential sleep enhancer. Recently, TTA-A2 was also reported to display antipsychotic-like effects on rats (243).

It is hard to explain inconsistencies between the results of studies in CaV3.1 mutant mice, described above, and those from these latter pharmacological studies without more detailed information about the T-type Ca\(^{2+}\) channel antagonists used in these studies. Notably, however, the differential expression pattern of the three T-type channels throughout the brain was not taken into consideration in these studies. In addition, the T-type antagonist described in the patent was tested only on CaV3.2 channels (192), whereas the compound tested in a more recent study was shown to block all three subtypes almost equally (120). These findings, together with the observations of different patterns of diurnal T-channel gene expressions (168), could indicate different roles of the three subtypes of T-type Ca\(^{2+}\) channels in sleep regulation. One possibility is that CaV3.1 in TC neurons promotes sleep, whereas CaV3.2 and CaV3.3 in TRN neurons suppress sleep. Although these compounds were claimed to have a very good selectivity to T-type channels, one cannot completely exclude a possibility that these compounds might work on other target molecules. Studies using CaV3.2 and CaV3.3 T-type channel knockout mice (38, 45) will be needed to clarify such issues.

### B. Slow Rhythms and Delta and Spindle Waves

The shift from wake to sleep states is defined by a pattern of typical sleep EEG characterized by large-amplitude, slow oscillations. These EEG waves are often linked to the intrinsic properties of TC neurons with low-threshold burst firing followed by long refractory periods, with the functional consequence that sensory signal transmission through the thalamus to the cerebral cortex is inhibited (223). There are three characteristic EEG waves observed during NREM sleep. In the early stage of NREM sleep, spindle oscillations, composed of 7- to 14-Hz rhythms with a distinct waxing-and-waning pattern lasting for 1–3 s recur rhythmically every 3–10 s (152). Spindle oscillations often co-occur with slow oscillations (<1 Hz). These slow oscillations are associated with all stages of natural NREM sleep in humans (1, 32, 207). Thus the sleep K-complex, which occurs with spindle oscillations in the early stage of NREM sleep, is the EEG manifestation of a single cycle of the slow oscillation. As sleep progresses to a deeper stage, the occurrence of the slow oscillation and K-complexes increases, and these slow frequency oscillations occupy larger component of the EEG signal (3, 4). At deeper sleep states, the slow oscillation co-occurs with delta waves, and the appearance of delta waves grows more frequent and longer. These EEG waves are essentially generated by synchronized oscillations in the TC network, known to be critically dependent on the rebound properties of T-type Ca\(^{2+}\) channels in thalamic cells, and thereafter on the interactions of neurons within TC circuits (48, 61). Many studies have reported that TC or TRN neurons display oscillatory burst firing that is synchronized with cortical slow rhythms in vivo and in vitro (49, 226, 229, 247).

Spindle oscillations have been proposed to arise from GABAergic TRN neurons with rhythmic burst activity. This activity then induces IPSPs in synaptically connected TC neurons, and therefore relies on the LTS generated within the reciprocally connected TRN and TC networks (50, 222, 247). It was suggested that the delta waves are generated within the thalamus by the interplay of two intrinsic inward currents in TC neurons: I\(_{\text{f}}\), a hyperpolarization-activated cation current and I\(_{\text{TH}}\), mediated by T-type channels (72, 173–175). Another study reported that the generation of delta waves could be within the cortex by demonstrating the delta waves in thalamectomized cats (227). On the other hand, the slow oscillation has been suggested to arise from cortical neurons going through slow up-and-down states composed of a long depolarizing phase and subsequent long-lasting hyperpolarization, as occurs during natural sleep and anesthesia (222, 227, 228, 247). Thus the slow oscillation also survives in the cortex after a thalamectomy (227) and can be generated in cortical slices without the thalamus performed in in vitro preparation (195). However, it has also been proposed that the dynamic interplay of three key oscillators in a corticothalamic circuit is required for the full development of the profound slow sleep oscillation: one cortical oscillator and two intrinsic, conditional thalamic oscillators (62, 142). Despite the diversity of opinions, there is a consensus surrounding the
idea that all sleep-related brain rhythms accompany T-type Ca$^{2+}$ channel-mediated burst firing in thalamic neurons.

Based on the observation that the activity of the thalamocortical network influences the genesis of the sleep rhythms, it could be predicted that T-type Ca$^{2+}$ channel mutations affect these sleep-related rhythms. Indeed, two reports utilizing CaV3.1 mutant mice reported that sleep-related oscillations are changed in the mutant animals (5, 124), as described below.

C. CaV3.1 Channels in Sleep Rhythms

1. Lack of delta oscillations in CaV3.1$^{-/-}$ mice

An analysis of the power spectral density of EEGs has shown that delta wave power is dramatically diminished in CaV3.1$^{-/-}$ mice in a natural NREM sleep state and under urethane anesthesia (124). Systemic injection of urethane elicited delta waves (1–4 Hz) in wild-type mice but not in CaV3.1$^{-/-}$ mice. EEG patterns in NREM sleep states were found to be similar EEG patterns under urethane anesthesia (FIGURE 6). CaV3.1$^{-/-}$ mice displayed a significant reduction in the power of delta waves compared with wild-type mice, which propose that CaV3.1 T-type Ca$^{2+}$ channels contribute to generate delta waves recorded in cortical EEGs.

Delta waves are known to rely on the electrophysiological properties of TC neurons, built by the interplay between the two currents, $I_h$ and $I_T$. Delta oscillations are observed in the TC regions even after being disconnected from related cortical areas (72) and are also evoked in in vitro thalamic slices isolated from cortical connections (131, 235). Therefore, the absence of $I_T$ which eliminates LTS in TC neurons of CaV3.1$^{-/-}$ mice could cause the impairment in the generation of delta oscillations. The results from general knockout mice lacking CaV3.1 channels support the con-

![FIGURE 6](http://physrev.physiology.org/)

EEG power density at delta waves was decreased in CaV3.1$^{-/-}$ mice compared with wild-type mice during NREM sleep. Sample traces show EEG and EMG signals recorded from REM (A) and NREM (B) sleep states in wild-type (CaV3.1$^{+/+}$) mice (top) and CaV3.1$^{-/-}$ mice (bottom). Data include 36 consecutive artifact-free epochs for each state during a 24-h period. Power spectral densities of EEGs from REM (C) and NREM (D) sleep states are expressed as means ± SE (mV$^2$/Hz), averaged for wild-type mice (n = 7) and mutant mice (n = 7) in 0.25-Hz bins. Error bars are plotted for every fourth bin. Asterisks and horizontal black bars in the graph of the NREM power spectrum (D) indicate frequencies with significant differences (2–6.5 and 9.5–10 Hz, respectively) between genotypes ($P < 0.05$ by Student’s t-test). [Modified from Lee et al. (124).]
ventional idea that T-type Ca\(^{2+}\) channels are crucial for the genesis of delta oscillations.

Another report described sleep phenotypes caused by both global and thalamus-specific Ca\(_v\)3.1 knockout (5). Interestingly, the authors of this report noted that delta wave power during NREM sleep in states was increased in both global and thalamus-specific Ca\(_v\)3.1 knockout mice, although they did not present the supporting data in the report. It is difficult to reconcile the opposite effects on delta wave power in these two kinds of Ca\(_v\)3.1 knockout mice based on the conflicting results.

2. Intact slow oscillations in Ca\(_v\)3.1\(^{-/-}\) mice

Unlike delta waves, which are impaired in Ca\(_v\)3.1\(^{-/-}\) mice, slow waves (<1 Hz) are intact in these mice (124). Power spectral density in the slow-frequency range (<1 Hz) are similar under high-dose urethane treatment or during a NREM sleep state in both Ca\(_v\)3.1\(^{-/-}\) and wild-type mice (FIGURE 6). These results suggest that Ca\(_v\)3.1 T-type Ca\(^{2+}\) channels do not play a crucial role in the generation of slow waves. Whereas the initiation and propagation of delta and spindle waves are noted to rely more on the properties of thalamic neurons, slow waves are known to arise from the cortex during NREM sleep (222, 227, 228, 247). They can also be evoked in isolated cortical slices in vitro by repeating synaptic barrages of membrane depolarizations and hyperpolarizations (195, 228).

Interestingly, in addition to the effects of Ca\(_v\)3.1 knockout on the three major sleep rhythms, Ca\(_v\)3.1\(^{-/-}\) mice are differentially susceptible to drug-induced absence seizures, as described above. Thus Ca\(_v\)3.1\(^{-/-}\) mice are resistant to GABA\(_A\)R agonist-induced SWD seizures and remain vulnerable to cortical-driven, GABA\(_A\)R antagonist-induced SWD seizures (115, 220). Likewise, the effect of Ca\(_v\)3.1 deletion on some of sleep rhythms is attributed to ablation of T-channels in TC neurons. Results obtained from thalamus-specific Ca\(_v\)3.1 gene knockout mice are consistent with this interpretation (5).

3. Spindle oscillations in Ca\(_v\)3.1\(^{-/-}\) mice

A classical view on the genesis of spindles was that they arise from TRN neurons. Rhythmic burst activities of GABAergic TRN neurons produce volleys of IPSPs in synaptically connected TC neurons. The IPSPs then promote deinactivation of T-type Ca\(^{2+}\) channels and thus was followed by low-threshold burst firings in TC neurons, which are then transmitted to cortical neurons. Corticothalamic projections complete the cortico-thalamo-cortical loops wherein spindle waves are generated and maintained (15, 16, 225, 226). Spindle oscillations can be engendered in deafferented TRN neurons in vivo (222) and are induced in isolated thalamic slices in vitro (117, 247). Once spindle waves are generated in TRN neurons, they are propagated via TC neurons (117). According to this theory, the prediction is that spindle oscillations should be diminished in the cortical EEGs of Ca\(_v\)3.1\(^{-/-}\) mice, which lack LTS in TC neurons, insofar as the absence of LTS in TC neurons should prevent the transmission of spindle waves from the thalamus to the cortex. Testing the prediction that deletion of T-type Ca\(^{2+}\) currents from TC neurons would lead to an impairment in the genesis of sleep spindle oscillations will require a method better suited for clearly identifying mouse spindle waves (193).

Contrary to expectations, neither the duration nor amplitude of each spindle episode is reduced in Ca\(_v\)3.1\(^{-/-}\) mice (42). An analysis of EEG signals filtered using a 6- to 15-Hz band filter to exclude the slower components, including delta and slow waves, showed that the spindle power density (8–10 Hz) during the natural NREM sleep state was not decreased in Ca\(_v\)3.1\(^{-/-}\) mice. Spindle waves in the cortical EEGs of the Ca\(_v\)3.1\(^{-/-}\) mice were reduced under high-dose urethane anesthesia (2 mg/kg) compared with those in wild-type mice (124). The mean duration and amplitude of spindles induced by a barbiturate injection were also substantially reduced in Ca\(_v\)3.1\(^{-/-}\) mice (42). These findings suggest that the lack of Ca\(_v\)3.1 alters, but does not abolish, spindle waves during natural NREM sleep.

Taken together, these data suggest that T-type Ca\(^{2+}\) channels encoded by Ca\(_v\)3.1 and the resulting low-threshold burst firing in TC neurons are not required to generate and propagate spindle oscillations in thalamocortical circuits, but are necessary for maintaining the strength of the spindle waves. This is quite different from the classical view that the generation of sleep oscillations, including spindles, requires low-threshold burst firing of TC neurons.

D. Ca\(_v\)3.3 Channels in Sleep Rhythms

The TRN has been proposed as the critical oscillatory burst generator in the initiation of thalamocortical oscillatory activity related to sleep rhythms in the brain. The slow decay and lower level of inactivation near the resting membrane potential, distinctive properties of low-threshold Ca\(^{2+}\) currents mediated by the Ca\(_v\)3.3 channel, have been implicated in the vigorous bursting properties of TRN neurons. A recent study reported that Ca\(_v\)3.3 channels are essential for TRN function and sleep spindles (8). This study showed that deletion of Ca\(_v\)3.3 channels in TRN neurons abolished oscillatory burst discharge but spared tonic discharge. The generation of synchronized oscillations within thalamic network underlying sleep-spindle waves was also shown to be markedly weakened in this mutant (8). In addition, Ca\(_v\)3.3\(^{-/-}\) mice exhibited a significant reduction in the power density of spindle oscillations (10–12 Hz) specifically at transitions from NREM to REM sleep, whereas other components of EEG waves being un-
altered. Therefore, this study proposed that CaV3.3 channels in TRN neurons play a pivotal role as a pacemaker in sleep-spindle generation (8).

V. T-TYPE Ca2+ CHANNELS IN THALAMOCORTICAL OSCILLATIONS

T-type Ca2+ channels have been implicated as a pacemaker in thalamocortical oscillations (96, 141, 226, 247) and also as a tremor-rhythm pacemaker of the inferior olivary nucleus in the brain stem (177). Here, we discuss their role in the thalamocortical circuit. Both sleep-related brain rhythms and pathological SWDs observed in absence seizures have been attributed to synchronized and oscillatory neuronal activities in the thalamocortical circuit (19, 152). The classical idea was that recurrent oscillations are generated within the intrathalamic circuit and then propagate throughout the thalamocortical network, composed of the thalamus and the cortex. The activity of T-type Ca2+ channels is especially prominent in the thalamus, where large T-type currents have been found in association with high level, but differential, expression of T-type channel subtypes (see below). In addition to the abundant expression of T-type channels, the distinct firing patterns of thalamic neurons between awake and sleep/absence-seizure states suggest a role for these channels in thalamocortical oscillations. Thalamic neurons have been frequently observed to generate low-threshold burst firing during thalamocortical oscillations.

A. Thalamocortical Oscillatory Circuits

Oscillatory activity of neurons synchronized in the thalamocortical circuit has been observed during normal sleep-related oscillations; pathological paroxysmal oscillations have also been observed (96, 152, 226, 247). Extensive feedback and forward connections between the thalamus and the cortex make a major contribution to strengthen the synchronization of oscillatory activity of the thalamocortical circuit, generating and maintaining both physiological and pathological oscillations (11, 19, 96, 221).

Although it has been generally agreed that the synchronized activity among neurons in the thalamus and cortex is critical to the generation of oscillations within the thalamocortical circuit, there has been a debate about which nucleus leads the generation of oscillations. Some studies have shown that cortical GABAergic interneurons constitute complex functional networks that generate cortical oscillations related with several behavioral functions (12, 13, 210, 255). On the other hand, it has been suggested that reciprocal connections between the thalamic reticular and relay nucleus within the thalamus establish a core oscillatory unit (96). Thalamocortical and corticothalamic innervations between the cortex and the thalamus engage these intrathalamic oscillations into larger thalamocortical networks to produce sleep spindles and the SWDs of absence epilepsy representative of normal and pathological oscillations, respectively (19, 56, 96, 133, 152).

B. TRN and TC neurons in Thalamic Synchrony

The degree of synchrony within the thalamus has been thought to play a critical role in determining whether physiological or pathological oscillations occur. The thalamic circuit is composed of excitatory TC neurons and inhibitory neurons of the TRN. There are extensive synaptic connections linking TC and TRN neurons, which together create a recurrent intrathalamic circuit. It has been shown that inhibitory inputs from the TRN (226, 247) or other brain regions (180) to TC neurons are followed by a postinhibitory response, the rebound of membrane potential which induces burst firing of TC neurons. Activation of TC neurons would in turn activate TRN neurons. Therefore, burst firing of thalamic neurons mediated by T-type Ca2+ currents is important for recurrent intrathalamic oscillatory activities (188).

1. Burst firing and T-type channels in TRN neurons

Reticular nuclei form a shell-like structure encompassing anterior and lateral parts of the dorsal thalamus (183). TRN neurons display rhythmic burst activities generating spontaneous oscillations within TRN nuclei (117, 247), which in turn provide inhibitory inputs to TC neurons to exhibit postinhibitory burst firing. Therefore, TRN neurons have long been hypothesized as pacemakers of thalamocortical oscillations, including spindles and SWDs (70, 82, 222).

It has been proposed that an important component of thalamic synchrony is intrareticular inhibition. TRN neurons inhibit other TRN neurons in addition to inhibiting TC neurons (15, 68, 194). It has been suggested that recurrent inhibition within the TRN (i.e., intrareticular inhibition) serves to reduce synchrony during spindle rhythms or SWDs of generalized absence seizures (100, 211), whereas electrical coupling via gap junctions synchronizes activity among TRN neurons (19, 122). GABA_A antagonists were shown to abolish intrareticular inhibition and convert spindle-like oscillations into slower, more synchronized epileptiform discharges in vitro (97, 247). A similar transformation was generated by knockout of the β3 subunit of the GABA_A, which selectively disrupts intrareticular inhibition (100). It was recently shown 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 in thalamocortical oscillations (179). This result may reveal a previ-
ously unknown mode of cortico-thalamo-cortical transmission. However, 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 burst versus tonic firing mode of TRN neurons controls the overall inhibitory output from the TRN neurons to TC neurons, are not yet understood.

The TRN is composed entirely of inhibitory neurons (91) that express CaV3.2 and CaV3.3 channels (231). CaV3.3 channels, which are the major T-type channels in TRN neurons (8), exhibit the properties slightly different from CaV3.1 expressed in TC neurons (98, 118, 119, 238). In TRN neurons, the inactivation curve of CaV3.3 is shifted to the right, leaving window currents around the resting membrane potential that are the largest among the three subtypes and allowing burst firing from resting conditions (182). A computational analysis has also suggested that the T-type channels in TRN neurons are mainly localized in dendrites that receive incoming excitatory synaptic inputs (71) and thus can enhance afferent signals to these cells (58), including those from TC or cortical neurons.

In TRN neurons, burst firings driven by T-type channels are typically followed by an afterhyperpolarization generated by Ca2+-activated, small conductance (SK)-type K+ currents, and it has been suggested that the interplay between T-type and SK channels is critical for sustaining rhythmic burst firings in TRN neurons (10, 14, 23, 65). One study reported that Ca2+ influx through T-type channels activates the SK2 channel and sarco/endoplasmic reticulum Ca2+-ATPases (SERCA) in TRN dendrites to generate and regulate the strength of TRN oscillations related to sleep (65). More recently, CaV3.3 T-type channel deletion was shown to impair rebound burst firing in TRN neurons. In these CaV3.3−/− mice, the power density of spindle oscillations (10−12 Hz) at transitions from NREM to REM sleep was selectively reduced, whereas other EEG waves remain unaltered. Therefore, these studies suggest that CaV3.3 channels and T-type current-activated SK channels act as a major pacemaker module in sleep-spindle generation.

However, the same mechanism does not seem to apply to the generation of SWDs in absence seizures. Although deleting CaV3.3 T-type channels in mice leads to a dramatic decrease in burst discharges and a complete loss of rhythmic oscillatory burst discharges in TRN neurons, CaV3.3−/− mice display enhanced SWD responses and susceptibility to γ-butyrolactone (GBL)-induced absence seizure (128). Interestingly, TRN neurons projecting onto TC neurons in CaV3.3−/− mice display increased tonic firing, which induces larger evoked monosynaptic IPSCs in TC neurons. This reveals the existence of a correlation between the tonic firing rate in TRN neurons and the generation of SWDs. Another study using CaV2.3−/− mice also revealed a correlation between the level of tonic firing and the degree of SWD, showing that decreased tonic firing in TRN was associated with reduced susceptibility to absence seizures in mice (259). Taken together, these recent studies suggest that burst firing in the TRN is not a prerequisite for the initiation and maintenance of SWD, but rather that stronger tonic firing in the TRN and the resulting stronger evoked IPSCs in TC neurons positively modulate SWDs, which are the hallmark of absence seizures. The implication is that T-type channel-mediated, low-threshold burst firing in TRN neurons plays different roles in sleep spindles and SWDs. Accordingly, rhythmic burst firing in TRN neurons is essential for pacing TC oscillations during sleep spindle oscillations, but not in hypersynchronizing the TC circuit during SWDs. Therefore, the traditional view that rhythmic burst firings in TRN neurons are critical in both types of TC oscillations needs to be reconsidered.

2. Burst firing and T-type channels in TC neurons

Thalamic oscillatory activity accompanies low-threshold burst firing of TC neurons (226, 247). Since Linas and Jahnsen (136) first identified a Ca2+-dependent LTS whose activation could be induced only after membrane hyperpolarization in TC neurons, it has been shown that an LTS generates a long-lasting depolarized membrane potential that triggers a burst of action potentials that ride the crest of the plateau (94). This property of T-type Ca2+ channels in TC neurons is responsible for the unique ability of TC neurons to promote network oscillations in which neural inhibition leads to a paradoxical rebound spiking. Although the major driving force for the burst firing of TC neurons is input from inhibitory neurons in the TRN, a recent study proposed that inhibitory inputs from the substantia nigra pars reticulata (SNR) to the ventral medial (VM) nucleus in TC region also play a crucial role for the control of absence seizures by basal ganglia (180).

CaV3.1−/− mice fail to show low-threshold burst firing, confirming that LTS in TC neurons, which uniformly express high levels of CaV3.1 (231), critically depend on this subtype (115). As noted above, CaV3.1 channels remain inactive around the resting membrane potential of TC neurons, but recover rapidly from inactivation (time constant, ~100 ms), allowing TC neurons to participate in postinhibitory rebound burst firing. It has long been presumed that burst firing in TC neurons is crucial for the generation of oscillations in the TC circuit. Results obtained to date propose that T-type currents and the resulting LTS in TC neurons may not be critical for initiating the oscillations, but rather are necessary for the genesis of generalized SWDs (75, 115). A majority of studies have offered a leading role for TRN neurons in the generation of thalamic oscillations. Thalamocortical oscillations are often observed with a transition from tonic to burst firing of TC neurons (141). Therefore, burst firing mediated by low-threshold T-type Ca2+ currents in TC neurons has been implicated in generalizing...
and sustaining these oscillations in thalamocortical circuit (19, 96, 115), although this view is not without controversy (63, 219).

The role of T-type channels and the resulting burst firing in TC oscillations during either sleep or SWDs has been revealed through studies of mutant mice. CaV3.1−/− mice exhibit a dramatic decrease in delta oscillations during sleep states (124), but show little change in spindle oscillations (42). On the other hand, an overall upregulation of CaV3.1 in mice enhances their vulnerability to SWDs and thus absence seizures (75). Moreover, mice with decreased steady-state inactivation of CaV3.1 T-type channels in TC neurons, and thus an increased propensity for burst firing mode, display a high occurrence of spontaneous SWDs (44). Collectively, these studies suggest that CaV3.1 T-type channels and low-threshold burst firing in TC neurons are crucial for delta oscillations (1–4 Hz) and the thalamocortical oscillations in slower brain rhythms during sleep. The activities of these latter oscillations, which generally occur in the generation of SWDs (3–7 Hz), are highly synchronized in the thalamocortical circuit. However, CaV3.1 T-type channels are not critical for pacing higher frequency (7–12 Hz) sleep spindles in the thalamocortical circuit. This type of faster oscillation in TC neurons may be attributable to the burst firing of TRN neurons, mostly mediated by CaV3.3 channels, as described in the previous section. Therefore, our current view that rhythmic burst firings in TRN and TC neurons are equally critical to both types of thalamocortical oscillations needs to be revised.

VI. T-TYPE Ca2+ CHANNELS IN PAIN PERCEPTION

A. T-Type Channel Expression in Pain Pathways

Since the first reports on the expression of LVA Ca2+ channels in sensory neurons in chicks and rats (31, 76, 199), T-type channels in many central and peripheral neurons have been involved in pain sensory signal transmission (106, 237). Although the three T-type Ca2+ channel subtypes, CaV3.1, CaV3.2, and CaV3.3, display unique as well as overlapping distributions, as noted above, their expression is largely complementary in CNS regions involved in the transmission of pain sensory information (57, 231). Many brain regions show a predominant expression of one subtype, supporting the hypothesis that the pharmacological and physiological heterogeneity of T-type channels comes from differential gene expression of each subtype. Yet some brain regions show mixed expression of these subtypes, complicating efforts to identify which one of these subtypes acts in a given pain-signaling pathway. The participation of T-type currents in controlling neuronal output has also been suggested to indicate specific localization of channels to somatic and dendritic compartments in a given neuronal cell (155).

The activation of low-threshold T-type channels around the resting membrane potential and its major contribution to generate action potentials in sensory neurons efficiently also make this channel a prominent player in pain pathways (31, 76, 80). Many studies utilizing pharmacological and electrophysiological approaches have demonstrated the role of T-type channels in the processing of diverse pain signals, at the peripheral level including acute pain, peripheral sensitization by reducing agents and at the central level including neuropathic pain and central sensitization in the spinal cord (237). It was not previously possible to identify the role of a specific subtype in a given pain signaling pathways in the absence of subtype-specific T-type channel blockers. Recently the significant progresses in genetic technologies have allowed us to investigate specific roles of each T-type channel subtype in diverse pain pathways. The putative role of T-type channels in various pain pathways inferred from the results of pharmacological studies has been addressed in a previous review (237).

B. CaV3.1 Channels in Pain Pathways

1. Acute pain

Since LVA Ca2+ currents were first described in peripheral neurons, which are mostly primary afferent sensory neurons (31, 76), T-type Ca2+ channels have been accused of boosting pain transmission, although their role in normal sensory transmission has not been well described (106). Many studies have assessed the potential of peripheral T-type channels as cellular targets for the development of analgesic agents (24, 77, 178).

The CaV3.1−/− mouse was the first genetic model used to test the role of T-type channels in pain-response behavior. Somewhat surprisingly, CaV3.1−/− mice did not show any impairment in acute pain responses to mechanical, thermal, or sensitized thermal stimuli (114), which exclude a possibility that CaV3.1 T-type Ca2+ channels are a principal constituent which mediates acute pain responses dominantly under the control of peripheral neurons and the spinal reflex circuit. Therefore, the other two subtypes of T-type Ca2+ channels might be responsible for these acute pain responses.

2. Inflammatory and visceral pain

Unlike acute pain responses, visceral and inflammatory pain responses are noted to be governed by both spinal and supraspinal mechanisms (253). In animal studies, visceral pain responses, induced by acetic acid or MgSO4 injection into the peritoneal cavity in the mouse, manifest as writhing responses including abdominal stretching or constriction of the animal.
The thalamus has long been crucially implicated in processing the sensory information because sensory inputs from the periphery are integrated with inputs from other brain regions to the thalamus and then the incorporated information is transmitted from the thalamus to the cortex. The divergent states of sensory signal transmission from the thalamus to the cortex can be represented by distinct firing modes, tonic and burst firing, of TC neurons (154). There has been a controversy over the role of the firing mode of TC neurons in thalamic sensory gating. Tonic firing mode occurring with the membrane depolarization is generally considered as a relay mode for sending afferent sensory signals to the cortex (154). In contrast, low-threshold burst firing mediated by CaV3.1, the prominent T-type Ca\(^{2+}\) channel in TC neurons, has been related to drowsy/sleep states or loss of consciousness in several studies (63, 247). However, a controversy remains concerning the function of T-type channels and resulting burst firing in processing the sensory information in the thalamus (203). This issue will be discussed later in the section on T-type channels in sensory gating.

Interestingly, the behavioral response to visceral pain induced by intraperitoneal injection of chemicals is enhanced in CaV3.1\(^{-/-}\) mice (114). This result was interpreted to suggest that loss of burst firing in TC neurons resulting from deletion of CaV3.1 T-type channels might cause the enhanced pain responses by impairing the pain sensory-gating function of the thalamus. However, a recent examination of pain responses in CaV3.1\(^{-/-}\) mice suggested that the increased visceral pain responses observed in CaV3.1\(^{-/-}\) mice might be related to a decrease in stress-induced analgesia (176). This study indicated that CaV3.1 T-type Ca\(^{2+}\) channels expressed in GABAergic neurons in the periaqueductal gray are important in the stress-induced descending analgesia system (FIGURE 7) (176). Thus both CaV3.1\(^{-/-}\) mice and periaqueductal gray-specific CaV3.1-knockdown mice exhibited impaired opioid-dependent and stress-induced analgesia. Therefore, the enhanced visceral pain response observed in CaV3.1\(^{-/-}\) mice itself does not provide conclusive evidence for the role of thalamic CaV3.1 T-type channels in thalamic pain-sensory gating. Single unit recording in vivo from the VPL/VPM region of mice under urethane anesthesia showed that CaV3.1\(^{-/-}\) TC neurons exhibited a drastic increase in tonic firing rate upon induction of visceral pain compared with the wild-type TC cells, and the increase in firing activity persisted longer (114). This result is in agreement with a recent study showing that TC neurons recorded from behaviorally active mice also display a robust increase in tonic firing upon Formalin-induced pain (99), as discussed below. This increased tonic firing might reflect the enhanced visceral pain responses related to impaired stress-induced analgesia in CaV3.1\(^{-/-}\) mice.

![FIGURE 7](image-url)
A contribution of thalamic firing pattern to thalamic pain-sensory gating was supported by studies showing a correlation between the firing pattern of TC neurons and pain responses (41, 43). Mice lacking PLCβ4 exhibited an increase in bursting and a decrease in tonic firing of TC neurons through concomitant upregulation of T- and L-type Ca2+ currents (43). The thalamic PLCβ4-PKC pathway was shown to concomitantly regulate T- and L-type Ca2+ currents and thus was suggested as a “molecular switch” for the firing modes of TC neurons. PLCβ4−/− mice, with increased bursting and decreased tonic firing of TC neurons, displayed a reduction in visceral pain responses (43). In this study, increasing the tonic firing rate of TC neurons by blocking L-type Ca2+ channels or SK channels in vivo significantly increased the visceral pain responses of the animals, highlighting the importance of tonic firing in thalamic pain sensory transmission. The increased pain response induced by blocking L-type Ca2+ channels may explain the increased visceral pain responses caused by thalamic infusion of mibefradil in the previous study (114). Although mibefradil is often used as a blocker of T-type channels, it has a poor selectivity for Ca2+ channels and blocks L-type and T-type Ca2+ channels almost equally well, even at quite low concentrations. Therefore, the increased visceral responses observed in mice intrathalamically infused with mibefradil could have been caused by the block of L-type Ca2+ channels, which would, in turn, increase the tonic firing rate in TC neurons. A critical role for tonic firing in TC neurons in thalamic pain processing is further supported by another study showing that the selective control of tonic firing is closely correlated with the magnitude of the second phase of Formalin-induced inflammatory pain responses and acetic acid-induced visceral pain responses (both known to have a supraspinal component), but not with any type of acute pain responses, such as mechanical or thermal pain (41).

A very recent study indicated that the burst firing in TC neurons plays a pivotal role in processing long-lasting inflammatory pain in awake and behaviorally active mice (99). Single-unit recordings of the thalamic firing from active mice in response to pain stimuli induced by inflammation revealed that pain responses were positively correlated with tonic firing and negatively correlated with burst firing of TC neurons (FIGURE 8). Furthermore, deep brain stimulation experiments in vivo revealed that electrical stimulation of TC neurons with specific bursting patterns (with 3 ms intra-burst interspike intervals), but not with tonic patterns, significantly decreased the behavioral noiceptive responses of the animal (90). These results support the idea that burst firings in TC neurons are correlated with the pain-sensory gating of the thalamus (FIGURE 8A).

These data together support the notion that the tonic firing of TC neurons reflects pain sensory transmission to the cortex, whereas burst firings mediated by CaV3.1 T-type channels are correlated with reduced pain sensory transmission. However, the exact role of low-threshold burst firing mediated by CaV3.1 T-type channels needs to be further examined using an experimental paradigm that allows deletion of T-type currents without affecting tonic firing.

The distinct roles of CaV3.1 and CaV3.2 T-type channels in inflammatory pain signal processing were also studied by employing injection of formaldehyde into the footpad of a mouse. This treatment causes typical pain behaviors, licking and biting the injected paw, that are composed of two phases. The immediate pain responses arising right after injection and lasting ~5 min are regarded as the first phase and are controlled by the spinal reflex circuit sharing the underlying mechanism with other acute pain responses. Then the pain responses are diminished temporarily, and the second phase of pain responses resumes ~15 min after the injection. The pain responses are progressively intensified reaching a peak around 30 min, and then gradually decaying. The second phase pain response is known to be under a supraspinal control similar to visceral pain.

In the inflammatory pain assay, CaV3.1−/− mice displayed no alteration in the first phase response, but an enhanced pain response in the second phase compared with wild-type mice (204). These results fully agree with studies on acute and visceral pain (114), supporting the absence of a requirement for the CaV3.1 subtype in acute pain responses and impaired thalamic pain sensory gating in CaV3.1−/− mice. It should be noted, however, that there is a high probability that stress-induced analgesia is involved in the second phase of Formalin-induced inflammatory pain responses. Therefore, further study is required to distinguish the contribution of the descending analgesic system from that of thalamic pain sensory gating in this pain behavior of CaV3.1−/− mice.

C. CaV3.2 Channels in Pain Pathways

1. Acute pain

The prediction that T-type Ca2+ channels are involved in pain transmission was confirmed by the observation on the pain behavior of CaV3.2−/− mice (45) and those using antisense oligonucleotides (25). Local injection or intrathecal administration of antisense oligonucleotides specific to CaV3.2, but not to CaV3.1 or CaV3.3, was shown to suppress the pain response in rat models when tested for both acute thermal and mechanical pain. In addition, CaV3.2−/− mice display decreased pain responses in other kinds of acute pain assays, including chemical, thermal, and mechanical pain (45). Other studies also support the idea that the CaV3.2 channel plays a major role in transmitting nociception in peripheral neurons (25, 45). In addition, local
inhibition of CaV3.2 T-type channels in sensory neurons by lipoic acid injection reduces sensitivity to noxious thermal and mechanical stimuli in mice (129).

Collectively, these observations agree with the results that no low-threshold Ca\(^{2+}\)/H11001 currents remain in small DRG neurons of CaV3.2/H11001/H11001/H11001 mice (38), cells known to be peripheral nociceptors (237). Thus these results provide explicit evidence for the role of CaV3.2 T-type channels in pain perception and propose that CaV3.2 may be a good candidate to target for treatment of pain at the peripheral level.

2. Inflammatory and visceral pain

CaV3.2\(^{-/-}\) mice also show a decreased pain response to visceral pain, an observation that agrees with a previous report that no low-threshold Ca\(^{2+}\) currents remained in small dorsal root ganglion (DRG) neurons in these mice (38). This result proposes that small DRG neurons play a substantial role in carrying visceral pain signals. Recently, it was reported that T-type Ca\(^{2+}\)/H11001 channels in primary sensory neurons in colonic and DRG cells are involved in mediating colonic pain transmission (147, 149). In this context, it is notable that CaV3.2 T-type channels are expressed in colonic nociceptive neurons and are suggested to be involved in colonic pain associated with irritable bowel syndrome (147). Colonic luminal hydrogen sulfide, a gastrotransmitter, was shown to promote colonic pain via the redox modulation of T-type Ca\(^{2+}\)/H11001 channels in DRG neurons (150). A recent study demonstrated that the CaV3.2 isoform is expressed in colonic nociceptive primary afferent neurons and contributes to the exaggerated pain percep-

![Figure 8](http://physrev.physiology.org/)

**FIGURE 8.** Behavioral nociceptive responses and temporal changes in ventrobasal neuronal firing patterns induced by Formalin in behaviorally active mice. A: behavioral pain responses to Formalin analyzed in 5-min segments. All data points are means ± SE (F = 14.42, P < 0.01; n = 9 mice). Repeated-measures ANOVAs were used for statistical analysis over time. B: spike sorting sample from a tetrode. C: changes in normalized overall ventrobasal neuronal firing rate, analyzed in 5-min segments, in response to Formalin over time. D: changes in normalized tonic firing and burst firing rate to Formalin over time, analyzed in 5-min segments. All data points in C and D are means ± SE (*P < 0.05 vs. baseline; n = 48 neurons, 7 mice; Student’s t-test). Superimposed dotted line is the behavioral nociceptive response for comparison with the ventrobasal neuronal firing responses. [Modified from Huh et al. (99).]
tion in a butyrate-mediated rodent model of irritable bowel syndrome (147).

The distinct roles played by CaV3.1 and CaV3.2 T-type channels in pain signal processing have been confirmed in inflammatory pain assays. Unlike CaV3.1−/− mice, CaV3.2−/− mice showed attenuated pain responses in both pain response phases. Taken together, these findings are consistent with results obtained for both acute and visceral pain in CaV3.2−/− mice (45), supporting the idea that the CaV3.2 subtype is required for all of these pain signals to be transmitted to the CNS through the peripheral nociceptors, DRG neurons. Monocyte chemoattractant protein-1 (MCP-1), which activates the chemokine receptor 2 (CCR2) implicated in inflammatory pain responses, was shown to inhibit CaV3.2 Ca2+ channels in DRG neurons (258), an observation that also supports the critical role of CaV3.2 Ca2+ channels in the peripheral pain system.

D. The Three Subtypes of T-Type Channels in Neuropathic Pain

T-type Ca2+ channels have been implicated in both peripheral and central neuropathy (161, 204, 236). It has been reported that chemotherapeutics used in cancer treatments might cause sensory abnormalities and peripheral neuropathies, including mechanical allodynia and hyperalgesia (77, 187). Ethosuximide, an antiepileptic and relatively selective T-type Ca2+ channel blocker, elicits a near-complete reversal of chemotherapeutic-induced mechanical allodynia/hyperalgesia, suggesting that T-type Ca2+ channels may play a role in chemotherapy-induced neuropathy (77). However, it could not be excluded that other molecules are also involved in this process because of the limited selectivity of ethosuximide. Diabetic neuropathy is another type of peripheral neuropathic pain whose mechanism is poorly understood. Morbid obesity may be associated with diabetes and painful diabetic neuropathy, manifested as mechanical or thermal allodynia and hyperalgesia. A study using leptin-deficient mice showed that these mice develop a painful diabetic neuropathy associated with substantial changes of T-type channels in DRG neurons, measured as a large increase in the amplitude of T-type currents and the expression of T-type channel mRNA (123). The predominant subtype, CaV3.2, was most strongly affected, and pharmacological antagonism of T-type channels was suggested as a potentially important novel therapeutic approach for the management of painful diabetic neuropathy (123). Silencing the CaV3.2 isoform using antisense oligonucleotides in vivo was shown to have an intense and selective anti-hyperalgesic effect in diabetic rats that was accompanied by a significant downregulation of T-type currents in DRG neurons, indicating a critical role for CaV3.2 in peripheral neuropathy (159).

Similarly, involvement of the CaV3.2 subtype in the neuropathic pain induced by chronic constriction injury of the sciatic nerve was suggested by the use of antisense oligonucleotides (25). In this study, intrathecal administration or local injection of CaV3.2-specific, but not CaV3.1- or CaV3.3-specific, antisense oligonucleotides resulted in a significant reduction in neuropathic pain. However, CaV3.2−/− mice show no significant difference in responses to neuropathic pain induced by spinal-nerve ligation compared with wild-type mice (45). In this well-established model, the resulting pain is known to be caused by central sensitization in the spinal dorsal horn (254). Therefore, barring developmental compensation by other subtypes in CaV3.2−/− mice, this result tends to rule out the involvement of CaV3.2 in the central sensitization to neuropathic pain. Reconciling conflicting results from oligonucleotide experiments and those using CaV3.2−/− mice will require additional studies in other models of neuropathic pain (25, 250).

In dramatic contrast to CaV3.2−/− mice, CaV3.1−/− mice show significantly attenuated responses compared with wild-type mice in a spinal-nerve ligation model of neuropathic pain (161). These results may be related to the known role of the CaV3.1 channel in the synaptic plasticity of spinal lamina I projection neurons that mediate hyperalgesia (101). Thus CaV3.1 may play a role in the central sensitization in the spinal dorsal horn to develop neuropathic pain. A study exhibited that intrathecal administration of CaV3.3 antisense oligonucleotides significantly relieve thermal hyperalgesia and tactile allodynia caused by chronic compression of the DRG of rats (250), raising the possibility that the CaV3.3 subtype in the spinal cord may also be involved in the pathogenesis of neuropathic pain.

1. Subtype-specific and region-specific roles of T-type channels

T-type channels show subtype-specific and region-specific roles in pain pathways. At the spinal level, the CaV3.1 subtype is implicated in developing neuropathic pain, possibly through central sensitization. CaV3.2 in the periphery is necessary for the transmission of various types of pains, including acute, visceral, and inflammatory pains, to the CNS. Moreover, Nelson et al. (163) recently demonstrated that CaV3.2 T-type channels play a part in the sensitization of peripheral pain-sensing nociceptive neurons. These results provide two windows of opportunity for T-type channel blockers to exert analgesic effects. First, T-type blockers capable of passing through the blood-brain barrier might blunt neuropathic pain by blocking CaV3.1-mediated sensitization at the spinal level. However, since the CaV3.1 T-type channel is involved in the descending pain inhibition system, the clinical usefulness of such drugs would be limited. Second, T-type channel blockers in the periphery...
should antagonize all other pain signals that pass through the DRG to the CNS.

VII. T-TYPE Ca\textsuperscript{2+} CHANNELS IN COGNITIVE FUNCTIONS

There is limited evidence for the role of T-type Ca\textsuperscript{2+} channels in cognitive functions, despite the abundant expression of these channels throughout brain regions involved in cognitive functions, including memory processing (57, 231). In this section, we trace the studies suggesting that T-type channels are involved in normal cognitive functions.

A. Ca\textsubscript{V}3.1 T-Type Ca\textsuperscript{2+} Channels in Visual Sensory Processing

The two distinct firing modes of TC neurons (tonic and burst) have been hypothesized to represent nonequivalent functions in thalamic information processing. The role of burst firing of TC neurons in normal behaviors has been a controversial subject, whereas it is generally accepted that the tonic-firing mode provides faithful transmission of information to the cortex (202, 203). As discussed in previous sections, TC burst firing has been correlated with reduced pain sensory transmission (43, 99, 114) and loss of consciousness, such as in sleep states or absence seizures (44, 75, 96, 124).

On the other hand, on the basis of responses of the lateral geniculate nucleus (LGN) to visual stimuli, both tonic and burst firing have also been suggested as a relay mode (86, 202). Because both firing modes are observed in awake animals, it was suggested that both serve as effective relay modes in the awake state (201). The tonic-firing mode of LGN neurons was shown to exhibit better linear summation, but reduced sensitivity for the detection of visual stimuli compared with the burst-firing mode. When LGN neurons fire in burst mode, they fire arrhythmically and respond vigorously to visual stimuli (85, 143). It was reported that the extent of bursting in LGN neurons during wakefulness is low, but is relatively higher with visual stimulation (191). The observation that thalamic bursting potently activates cortical neurons was interpreted to further suggest a role for burst firing in perception (257). This study demonstrated that burst firing in TC neurons elicited larger EPSPs in cortical neurons than did tonic firing, an observation that gave rise to the hypothesis that burst firing in TC neurons might work as a “wake-up call” from the thalamus to the cortex (203). However, this hypothesis faced the immediate argument that it did not fit with existing data (217). Indeed, an alternative interpretation does appear to be possible. Swadlow and Gustave (257) showed that thalamic burst firing evoked larger EPSPs in suspected inhibitory interneurons, judged by their fast-spiking properties. These fast-spiking, inhibitory interneurons in the neocortex were shown to trigger powerful feedforward inhibition onto excitatory neurons (60). Axons from the thalamus to the cortex made stronger and more frequent excitatory inputs onto inhibitory neurons than onto excitatory neurons. Even the circuit dynamics involving TC projections activated inhibitory neurons faster than excitatory neurons, facilitating feedforward inhibition to suppress excitatory neurons (60). Therefore, greater excitement of these inhibitory neurons in the cortex by thalamic burst firings would lead to greater feedforward inhibition of excitatory neurons, potentially resulting in an effect opposite to a wake-up call.

Moreover, another study by the Swadlow group showed that burst firing in TC neurons in awake animals mostly occurs when animals are in an inattentive rather than an alert state (256). Therefore, the role of burst firing and T-type channels in TC neurons in cognitive functions, especially visual sensory processing, needs to be carefully examined.

B. Ca\textsubscript{V}3.1 T-Type Ca\textsuperscript{2+} Channels in Fear Memory

A recent report provided evidence that the firing pattern in TC neurons is affected by the fear-conditioning process (256). In this study, rabbits received a Pavlovian discriminative fear conditioning procedure in which one tone conditioned stimulus (CS+) was always paired with an aversive unconditioned stimulus, and another tone (CS−) was never paired with this aversive unconditioned stimulus. Fear-conditioned, acoustic stimuli were shown to elicit significantly greater firing in dorsal lateral geniculate nucleus (dLGN) neurons in the CS+ versus the CS− group. The dLGN neurons displayed tonic firing during increased cortical arousal and burst firing during decreased cortical arousal, suggesting that dLGN neurons show associative responses to fear-conditioned, acoustic stimuli. This study proposed a model for investigating the neural circuits by which such stimuli affect sensory processing at the thalamic level.

Recently, it was reported that T-type Ca\textsuperscript{2+} channels in the medio-dorsal thalamus are involved in the fear memory process (127). The medio-dorsal thalamic nucleus (MD) is a part of the TC region and has been proposed to participate in the control of memory processing. However, to date, the underlying neural mechanisms, in general, and the involvement of T-type channels, in particular, have remained unclear. Recently, fear extinction was shown to be closely correlated with the firing pattern of MD neurons (127), suggesting the involvement of the MD in the fear-memory process. In this study, PLC-β4−/− mice and mice with MD-specific knockdown of PLC-β4 exhibited impaired fear extinction. MD neurons in PLC-β4-deficient mice displayed increased burst firing accompanied by increased T-type Ca\textsuperscript{2+} currents; moreover, blocking T-type channels in vivo rescued fear extinction in these animals (FIGURE 9). Tonic-
evoking microstimulation of the MD, contemporaneous with the extinction tones, also rescued fear extinction in PLC-β4-deficient mice and facilitated it in wild-type mice. In contrast, burst-evoking microstimulation suppressed extinction in the wild-type, mimicking the PLC-β4 deficiency. These results suggest that the MD firing mode is critical in the modulation of fear extinction. These data further indicate that firing mode in the MD, controlled by the mGluR1-PLCβ4 signaling pathway, can modulate fear extinction bidirectionally: tonic firing facilitates fear extinction in physiological conditions, whereas burst firing suppresses extinction under pathological conditions, such as in PLCβ4 deficiency. This study provided new insight into the role of T-type channels in fear extinction, and suggests a possible role of T-type channels in higher cognitive functions. This experimental system affords a unique opportunity for examining important questions related to how the two different firing modes of the thalamic neurons exert two opposing behavioral controls in the mouse brain. Furthermore, this study opens a new avenue for the treatment of human patients with posttraumatic stress disorder.
VIII. CONCLUSIONS

T-type channels are expressed throughout a wide range of central and peripheral nervous system regions and are involved in various neurological functions. T-type channels and low-threshold burst firing in the thalamocortical oscillations are involved in sleep and absence seizures. The three subtypes of T-type channels have distinct expression patterns within the thalamus: abundant expression of CaV3.1 in the TC relay nucleus and differential expression of CaV3.2 and CaV3.3 in the TRN nucleus. Over the past few decades, T-type channels in both thalamic regions have been implicated as major players in the generation of thalamocortical oscillations during both sleep rhythms and SWDs. However, recent studies indicate that T-type channels in TC regions contribute more to slow-frequency oscillations such as delta rhythms during sleep and to SWDs during absence seizures, whereas T-type channels in TRN regions are involved in spindle oscillations. Therefore, the conventional view that rhythmic burst firing in both TRN and TC neurons are equally critical for both types of thalamocortical oscillations needs to be modified. These data also shed new light on strategies for developing sleep and seizure medicines in that subtype-specific drugs may preferentially control pathological oscillations without affecting physiological oscillations. This principle can also be applied to developing pain killers based on subtype-selective targeting of T-type channels. Further studies should reveal the definitive contributions of each T-type channel in these brain circuits and the detailed molecular mechanism by which they interact with other channels or molecules. The comprehensive understanding of the functional consequences of modulation of each subtype of T-type channels in vivo could guide the development of therapeutic tools for absence seizures, sleep, pain, and even fear disorders. In addition, we expect that the study of T-type channels in the neurobiology of cognition will continue to evolve.

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