T-type Ca\(^{2+}\) channels as therapeutic targets in the nervous system
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Low-voltage-activated calcium channels, also known as T-type calcium channels, are widely expressed in various types of neurons. In contrast to high-voltage-activated calcium channels which can be activated by a strong depolarization of membrane potential, T-type channels can be activated by a weak depolarization near the resting membrane potential once deinactivated by hyperpolarization, and therefore can regulate the excitability and electroresponsiveness of neurons under physiological conditions near resting states. Recently, the molecular diversity and functional multiplicity of T-type channels have been demonstrated through molecular genetic studies coupled with physiological and behavioral analysis. Understanding the functional consequences of modulation of each subtype of these channels in vivo could point to the right direction for developing therapeutic tools for relevant diseases.

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Introduction
After its first description in the inferior olivary neurons by Llinas and Yarom [1], the biophysical properties of ionic conductance by low-threshold, T-type Ca\(^{2+}\) channels have been defined by numerous subsequent voltage-clamp studies: their faster kinetics of activation and inactivation, slower deactivation kinetics, voltage dependence on stronger hyperpolarization for activation and inactivation, and smaller single-channel conductance, compared with high-voltage-gated Ca\(^{2+}\) channels [2–4]. These properties enable this channel to control neuronal excitability, particularly because it can be activated by a weak depolarization near the resting membrane potential.

The functional significance of the currents carried by T-type Ca\(^{2+}\) channels in sensory neurons has been well demonstrated by White et al. [5]. They suggested that T-type Ca\(^{2+}\) channels are the molecular basis for the afterdepolarizing potentials and repetitive burst firings in dorsal root ganglion (DRG) neurons. T-type Ca\(^{2+}\) channels are known to play an important role in the generation of burst firing in the thalamic relay and reticular neurons that is accompanied by a synchronized oscillatory activity of the thalamocortical or corticothalamic loops [6,7].

There are three genes for the pore-forming \(\alpha_1\) subunit of T-type calcium channels, \(\alpha_{1G}\), \(\alpha_{1H}\), and \(\alpha_{1I}\) for \(\alpha_{1G}\), \(\alpha_{1H}\), and \(\alpha_{1I}\) (reviewed in [8]). These three \(\alpha_{1}\) subunits are expressed differentially as well as concomitantly throughout the peripheral and central nervous system, which results in the biophysical heterogeneity and the functional diversity of low-threshold calcium conductance [9]. Although the presence and the different biophysical properties of the three subtypes of T-type Ca\(^{2+}\) channels have been demonstrated [8], the physiological roles of each subtype in the nervous system were unclear because of the lack of selective or subtype-specific blocker for these channels. Only recently this obstacle was removed with the utilization of genetic approaches, such as gene knock-out by gene targeting or gene knock-down by antisense techniques [10–14]. These genetic tools can delete or block the function of each subtype selectively. In this review, we will focus on the recent advances in functional characterization of T-type Ca\(^{2+}\) channels, in vitro, especially in the generation of absence seizures and sleep modulation that share the same patho-physiological mechanism related to the thalamocortical circuit, and in nociceptive processing, mainly based on the results of experiments using genetic approaches that have complemented the previous limitations of pharmacological studies. A clear possibility emerges that T-type Ca\(^{2+}\) channels can be good targets for drug development, especially for controlling pain and absence seizures, at the least.

T-type Ca\(^{2+}\) channels are required for absence epilepsy
Typical absence epilepsy is characterized by a brief loss of consciousness accompanied with coinciding 3 Hz spike wave discharge (SWD) on the electroencephalogram (EEG). The feedforward and feedback connections between the thalamus and the cortex have been thought to generate and maintain SWDs in generalized absence epilepsy by reinforcing the synchronized oscillatory activity of the circuit. It was shown that activation of this
Ca2+ channels and thalamic bursts in the pathogenesis of SWDs have expanded our understanding of the role of T-type Ca2+ channels and thalamic bursts in the pathogenesis of absence epilepsy. Applications of molecular genetic tools to study this issue have expanded our understanding of the role of T-type Ca2+ channels and thalamic bursts in the pathogenesis of absence epilepsy. We summarize the recent genetic studies related to the involvement of T-type Ca2+ channels in absence epilepsy.

**CaV3.1 T-type channel function is essential as well as spontaneous absence seizures**

There was a controversy on the role of T-type currents in the thalamic relay neurons in the genesis of absence epilepsy. Study using a knock-out (KO) mouse for CaV3.1, the gene coding for the a1G subtype of T-type Ca2+ channels, yielded conclusive evidence for the essential role of T-type Ca2+ channels in absence epilepsy [13]. In this CaV3.1 KO mouse low-threshold, T-type, Ca2+ currents were completely abolished, and burst firing was not inducible in the TC neurons. These results are consistent with the fact that the CaV3.1 is the predominant T-type channel expressed in TC neurons [9]. The CaV3.1 KO mice were resistant to the SWD seizures induced by GABAB receptor agonists, such as baclofen and γ-hydroxybutyrate (GHB). In wild-type mice, these GABAB receptor agonist drugs induced strong paroxysmal SWDs of 3–4 Hz on epidural EEG recordings accompanied with behavioral absence.

There are a few mouse models of absence each with a mutation in various subunits of P/Q-type Ca2+ channels. They include tg (tottering) and tglα (leaner), mutations of the CaV2.1 subunit; sgl (stargazer), a mutation of the CaV3.2; lh (lethargic), a mutation of CaV3.B4; and CaV2.1 KO mice. It has been also shown that thalamic T-type currents are increased in these animal models of absence epilepsy [17,18]. It was interesting to know whether the CaV3.1 T-type channel is required for the SWD generation in those spontaneous absence mice, as was the case with the drug-induced absence. To address this question, double mutant mice were derived by crossing each of the mutant strains to CaV3.1 KO mice and their absence phenotypes were analyzed [19]. The results were very clear: in all the double mutant models, the generation of SWDs was almost completely suppressed by the deletion of the CaV3.1 gene. These results provided with firm evidence that CaV3.1 T-type Ca2+ channels were required for the expression of spontaneous absence epilepsy in those mutant mice, as they were for the GABAB receptor agonist-induced absence epilepsy.

**T-current enhancement in thalamic neurons in absence epilepsy: an epiphenomenon or a causal element?**

T-type Ca2+ current was shown to be selectively increased in the RT neurons of the GAERS rat [17], a genetic model of absence epilepsy. The quantitative in situ hybridization technique was also used to demonstrate significant, but small, elevations of T-type Ca2+ channel mRNA in the thalamus of GAERS [20]. A similar increase of T-type Ca2+ currents was also observed in the mutant mouse models of absence epilepsy [18,19]. These results raised an interesting possibility that the increased T-currents may contribute to the pathogenesis of absence epilepsy by enhancing the bursting activity of thalamic neurons, and thereby increasing the ability to recruit network oscillatory actions in the thalamocortical circuits. Are the increased T-currents the key element in generating SWDs in those absence model animals, or are they just epiphenomena? This issue was addressed genetically by using double mutants for CaV3.1 and CaV2.1 [19]. The CaV2.1 KO mice show strong absence epilepsy accompanied with SWDs on EEG. By crossing CaV2.1 mutant mice to CaV3.1 mutant mice, three different groups of CaV2.1−/−/CaV3.1−/− mice were derived, each with a different dose of the CaV3.1 gene: CaV2.1+/−/CaV3.1−/− with two copies of CaV3.1, CaV2.1−/−/CaV3.1−/− with one copy of CaV3.1, and CaV2.1−/−/CaV3.1−/− with no CaV3.1. The TC neurons of mice with CaV2.1−/−/CaV3.1−/− had T-type Ca2+ currents increased by ~60% over the wild-type mice, and CaV2.1−/−/CaV3.1−/− had no remaining T-currents because of the deletion of both copies of the CaV3.1 gene. The CaV2.1−/−/CaV3.1−/− mice had T-currents at a level below the wild-type mice (~75%) because it has only one copy of the gene, though the level of expression per copy of the gene is increased because of the CaV3.1 homozygote null mutation. These CaV2.1−/−/CaV3.1−/− mice were the key animals in testing the role of increased T-currents in SWD generation. EEG results showed that CaV2.1−/−/CaV3.1−/− mice developed SWDs to the same degree as that of the CaV2.1−/−/CaV3.1−/− mice, even though their TC neurons did have rather decreased currents, compared to wild-type mice. These results indicate that although T-currents are essential for development of SWDs, their increase itself is irrelevant to the pathogenesis of SWD in those absence model mice.

**Cortical versus thalamic origins for SWD genesis**

An interesting observation was that CaV3.1 KO mice are selectively resistant to the thalamicus-dependent, GABAB agonist-induced absence seizures, whereas they show normal susceptibility to the SWD seizures induced by a systemic administration of bicuculline [13], a GABA_A antagonist. This treatment is known to evoke seizure spikes originating from the cortex, which develop into highly synchronous SWDs in both the cortex and thalamus [21].
Studies on the GAERS and WAG/Rij strains, rat models of absence epilepsy, have suggested that the origin of SWD was the cortex [22]. These results may indicate that those rat models of absence epilepsy may share the mechanism with the bicuculline-induced absence epilepsy model, but not with the baclofen-induced seizure which is dependent on the thalamocortical burst activities. Therefore, CaV3.1 T-type channel-mediated burst firings of thalamocortical neurons may not be an essential component in the SWD generation in GAERS or WAG/Rij. This interpretation is consistent with the results obtained by in vivo extracellular and intracellular recordings from TC neurons in GAERS rats during spontaneous SWD [23].

**Gene mutations identified in human absence epilepsy**

A few gene mutations are known to be associated with human absence epilepsy, including mutations on the GABAA receptor γ2 subunit [24] and the CaV2.1 subunit of P/Q-type channels [25]. Moreover, mutations in the CaV3.2 gene have been identified in human childhood absence epilepsy: 12 different missense mutations in about 10% of those patients [26].

Interestingly, some of the mutated cDNA clones for the CaV3.2 gene of the patient revealed some alterations in channel gating [27,28], and computer simulations predicted that some mutations would favor burst firings [28], which is consistent with the interpretation that those mutations may have caused the disease. A recent study showed that the intracellular loops I–II where the most of polymorphisms are found in the childhood absence epilepsy patients controls plasma membrane expression and gating of CaV3.2 subunit of T-type channels [29**]. Although these results suggest that those CaV3.2 gene mutations may be responsible for the clinical absence epilepsy in the patients, further experiments are required for conclusive evidence.

**Imbalance in inhibitory/excitatory inputs to TC neurons: the cause of absence epilepsy?**

Results obtained so far may suggest that T-type currents in TC neurons may not be the initiating element but a necessary step in the pathway to SWD genesis. The event preceding the absence may be an overload of hyperpolarizing inputs to TC neurons. In this regard, it was very interesting to see several abstracts in a recent meeting demonstrating the enhanced extrasynaptic GABA signals in drug-induced as well as genetic models of absence epilepsy (SJ Fyson et al., abstract in Soc Neurosci Abstr 2007, 142.7; AC Errington et al., abstract in Soc Neurosci Abstr 2007, 142.8; GD Giovanni et al., abstract in Soc Neurosci Abstr 2007, 142.9). One of the key experiments in future would be to figure out how the hypo-functioning of P/Q-type channels brings about enhanced inhibitory inputs to TC neurons.

**T-type calcium channels and sleep**

The enhanced excitability of neurons after membrane hyperpolarization is predominantly found in the thalamus during nonrapid eye movement (NREM) or slow-wave sleep, and much less frequent or rare during rapid eye movement (REM) sleep or wakefulness [6,34]. The low-threshold spike (LTS) followed by rhythmic burst firing in the TC neurons has been known to be driven by Ca2+-dependent low-threshold currents (I<sub>LTS</sub>) [35]. The prevalence of LTS during NREM sleep suggests the involvement of T-type calcium channels in slow-wave sleep. Recent studies utilizing gene knock-out mice have demonstrated the involvement of T-channels, and thus of thalamic burst firings, in the regulation of sleep and sleep rhythms; null mutant mice [13,36], or conditional knock-out mice of the gene for CaV3.1 [10].

**Altered sleep rhythms in CaV3.1 KO mice**

In the cortical EEG of the CaV3.1 KO mice, spindle waves were altered under the anesthesia induced by a high dose of urethane (2 mg/kg) anesthesia and during natural NREM sleep states compared to those in the wild-type mice [36]. Power spectral analyses of the cortical EEG in the CaV3.1 KO mice showed a reduction of the power in the frequency range of 8–10 Hz under anesthesia and of 9.5–10 Hz during NREM sleep. These findings suggest
that the deletion of CaV3.1 impaired spindle waves during NREM sleep.

A classical idea is that spindles arise in GABAergic nRT neurons whose rhythmic spike-burst activities induce barrages of IPSPs in target TC neurons. These IPSPs promote burst firings in TC neurons, which, then, are transferred to the cortical neurons, thereby generating the EEG spindle waves [6]. In this model, TC neuronal bursts play a crucial role in the spindle oscillations. It has been shown that the burst firing is absent in TC neurons of CaV3.1 KO mice [11]. Thus, spindles would not be expected to be evident in the cortical EEG of CaV3.1 KO mice lacking LTS in TC neurons, as this lack should have prevented spindle waves from being transmitted to the cortex. Episodes of spindle-like oscillations with reduced amplitudes, however, were remaining in the envelope of slow waves in NREM sleep in CaV3.1 KO mice. Thus, it will be necessary to examine the spindle-like oscillations observed in the mutants more carefully with a better method.

In the analysis of the power spectral density of EEG, the delta wave power was dramatically decreased in the CaV3.1 KO mice under the urethane anesthesia and during natural sleep states [36]. Urethane treatments evoked delta waves (1–4 Hz) in the wild-type animals but not in the CaV3.1 KO mice. During natural sleep states, similar results to those of urethane treatments were found in the EEG recordings. In the CaV3.1 KO mice, the power of the low frequencies (2–6.5 Hz) including delta waves was significantly reduced when compared with that of wild-type littermates. These results suggest that the genesis of delta waves recorded in the cortical EEG is dependent on the α1G T-type calcium channels. However, see Anderson et al. [10] for different results.

Unlike impaired delta and spindle waves, the slow waves (<1 Hz) were intact in the CaV3.1 KO mice under a high dose of urethane anesthesia or during natural sleep states [36]. Both CaV3.1 KO and wild-type mice showed a similar power spectral density in the range of slow frequencies (<1 Hz) under the urethane treatment or during NREM sleep states. These results indicate that the CaV3.1 T-type calcium channels are not required for the cortical mechanisms underlying slow waves. Although the delta and spindle waves are known to depend on thalamic neurons for their generation and propagation, the slow waves originate from the cerebral cortex during anesthesia or natural sleep and can be generated in isolated cortical slices in vitro by recurring sequences of synaptic barrages of depolarizing and hyperpolarizing phases [37]. In addition, it has been proposed that CaV3.3 is involved in the genesis of slow oscillation. Recently, Blethyn et al. suggested that the activation of group I metabotropic glutamate receptors (mGluRs) induce an intrinsic slow oscillation in thalamic reticular (nRT) neurons in vitro [38**]. A slow oscillation could also be evoked by the activation of mGluRs on nRT neurons via the tetanic stimulation of corticothalamic fibers. Based on these results, they suggested that the slow oscillation is predominantly generated by the component of the T-type Ca2+ currents that may be elicited by CaV3.3 in thalamic reticular nucleus, because it is the main subtype in this nucleus [9]. Further experiments would be required to examine the role of this subtype in the generation of slow oscillation at the thalamic reticular level by genetic approaches.

**Sleep patterns of CaV3.1 KO mice; sleep amount and sleep fragmentation during NREM sleep**

The physiological role of T-type calcium channels in sleep regulation has been reported in two studies utilizing CaV3.1 KO mice [10,36]. Both global and thalamus-restricted deletion of CaV3.1 T-type calcium channels did not affect the diurnal preference for sleep under the 12-hour light/dark cycle. The total amount of sleep, however, was significantly reduced in the KO animals compared to the wild-type. The reduction of sleep amount in the mutants resulted from a decreased amount of NREM sleep during the lighted period. Fragmentation of sleep by brief awakenings was also observed both in the global and in the thalamus-specific CaV3.1 KO mice, which indicates that this sleep phenotype was because of the defect in TC neurons in the mutant mice, that is, lack of LTS and thus of burst firings.

Fragmented sleep by brief awakenings with a prolonged duration in the CaV3.1 mutant suggests that CaV3.1 T-type calcium channels play an inhibitory role in the transition from sleep to wake states. The lack of LTS in TC neurons could contribute to a reduction of the threshold for this transition because LTS is involved in reducing sensory responses of thalamic neurons during sleep and anesthesia [39,40]. Therefore, the lack of LTS in TC neurons would result in a reduced threshold for the transition from NREM sleep to wake states in the CaV3.1 KO mice.

**T-channel blockers as potential sleeping pills**

On the contrary to the results from CaV3.1 KO mouse studies, a recent patent application states that a T-type calcium channel antagonist works as a sleep enhancer rather than a suppressor [41]. The compound identified as a T-channel antagonist has been shown to block T-currents in HEK293 cells expressing the human CaV3.2 T-channel gene. In the preclinical study to assess the effect of the T-type calcium channel inhibitor on sleep, the compound was administered intravenously into rats 60 min before light on, and EEG and EMG were recorded immediately after the drug injection. As a result, the T-channel inhibitor significantly reduced the duration of wakefulness relative to the vehicle control, and this effect lasted approximately two hours following
the drug injection. Moreover, the T-type inhibitor reduced the entries into wake states, representing a significant reduction in sleep fragmentation. These results led to the interpretation that the T-type antagonist functioned as an effective sleep enhancer in the patent.

Without further detailed information on the compound such as specificity it is difficult to explain the contradicting results between the studies of CaV3.1 mutant mice and the preclinical study with the drug in the patent. Nonetheless, such results along with the finding of circadian oscillatory patterns of T-channel gene expression [42] may imply a role for the other two subtypes of T-type calcium channels, CaV3.2 and CaV3.3, in sleep regulation. Studying the sleep phenotype of the CaV3.2 KO mice [12,43] will be needed.

**Diverse roles of T-channel subtypes in pain signaling**

T-type channels are expressed in the neural pathways known to be mediating pain sensory signals [9]. The low-threshold activation of T-type channels near the resting membrane potential, and its efficient activation of action potential in sensory neurons also made it a good candidate to play a major role in pain perception [2–4]. Indeed, many pharmacological and electrophysiological studies have implicated T-type channels in the pain signal processing: acute pain, peripheral sensitization by reducing agents, central sensitization in the spinal cord, and neuropathic pain (well reviewed in [44*]). In the absence of subtype-specific T-type channel blockers, however, it was not possible to define which of the three subtypes are involved in the specific pain signaling pathways. Recent studies utilizing gene technologies have now made significant progress in assigning specific roles to different T-type channel subtypes in the pain pathway. These results will be described here. For more information on the pharmacological and physiological studies on the potential role of T-type channels in pain pathways, the readers are referred to recent review [44*].

**T-type channels in acute pain signaling measured by the spinal reflex**

The CaV3.1 KO mouse was the first T-channel mutation that was examined for pain response behavior. A somewhat surprising finding was that the CaV3.1 KO mice did not show any impairment in acute pain responses for mechanical, thermal, or sensitized thermal pain [39]. These results ruled out αT G T-type calcium channel as an essential component in the acute pain pathway, and raised a possibility that other subtypes might be responsible for those pain responses. This prediction was fulfilled by the results of experiments on the pain behavior of the CaV3.2 KO mice [43**], and experiments using antisense oligonucleotides [11**]. Local injection or intrathecal administration of antisense oligonucleotides specific to α11T, but not to α1G or α11L, resulted in suppression of pain response in rat models of both acute thermal and mechanical pain. Similarly, the CaV3.2 KO mice showed reduced pain responses to all the acute pain assays, including mechanical, thermal, and chemical pain [43**]. This observation is consistent with the finding that virtually no low-threshold Ca2+ current was left in the small DRG neurons of the CaV3.2 KO mice [12], the cells known to be peripheral nociceptors [45].

**T-type channels in visceral pain**

Visceral pain response which can be induced in the mouse by injecting acetic acid or MgSO4 solution into the peritoneal cavity is displayed by abdominal stretching or writhing of the mouse. Unlike the acute pain responses which are under the control of the spinal reflex circuit, the visceral pain response is known to be influenced by supraspinal mechanisms [46].

An interesting finding was that the CaV3.1 KO mice showed an enhanced pain response, that is, hyperalgesia, to the visceral pain induced by the chemical injections into the peritoneum [39]. Experiments with single-unit recordings in vivo of the neurons in the VPL/VPM region of the thalamus revealed the existence of a novel antinoceptive mechanism operating in the thalamus. This mechanism appears to rely on the sensory gating function of the thalamus, which is dependent on the burst firing property of TC neurons. The thalamic sensory gating mechanism must be impaired in the mutant mice, resulting in an enhanced pain sensory relay to the somatosensory cortex because the mutant TC neurons are lacking the burst firing activity because of the deletion of CaV3.1. In fact, the mutant TC neurons showed a more robust increase in the frequency of tonic firing upon visceral pain inductions as well as the increased firing activity persisted longer compared to the wild-type TC cells.

In contrast to CaV3.1 KO mice, the CaV3.2 KO mice showed a decreased pain response to the same kind of visceral pain. This result may be explained by the finding that low-threshold Ca2+ currents are totally deleted in the small DRG neurons in the mutant mice [12]. This also suggests that the small DRG neurons are probably the nociceptors for the visceral pain signals. Therefore, the visceral pain signal is suppressed from its initial step of propagation in the CaV3.2 KO mice.

**T-channels in formaldehyde-induced inflammatory pain responses**

The distinct roles that the α1G and the α111 T-type channels play in the pain signal processing was further confirmed in the inflammatory pain assay. The mouse shows typical pain behaviors in response to formaldehyde injections into the footpad: licking and biting the injected paw. Such pain behaviors come in two phases, each revealing different aspects of the pain signaling mechanism. The first phase, starting immediately after injection
and lasting about 5 min, is believed to be controlled by the spinal reflex circuit much the same way as other acute pain modalities. The pain behaviors disappear for a while, and then the second phase of pain behaviors begins at around 15 min after the injection, slowly increases in intensity, peaking at about 30 min, and then slowly decreases. This second phase pain response is known to be controlled by a supraspinal mechanism as is the case with the visceral pain.

In this pain assay, the CaV3.1 KO mice showed no change in the first phase response but showed an enhanced pain response in the second phase (Figure 1a). These results are in full accord with the results on the acute pain and those on the visceral pain [39], confirming no requirement of the α1G subtype in acute pain responses and the impaired thalamic sensory gating in the CaV3.1 KO mice. On the contrary, the CaV3.2 KO mice showed attenuated pain responses in both phases of the pain responses (Figure 1b). Again, these results are consistent with the results on both acute and visceral pain of this mutant mouse [43**], supporting the idea that α1H subtype is needed for all those pain signals to enter the central nervous system through the peripheral nociceptors, DRG neurons.

**T-type channels in neuropathic pain induced by peripheral or central sensitization**

Recent work by Bourinet et al. using antisense oligonucleotides suggests that the T-type channel involved in the neuropathic pain induced by chronic constriction injury of the sciatic nerve is the α1H subtype of T-type calcium channels [11**]. Intrathecal administration as well as local injection of CaV3.2-specific, but not CaV3.1-specific or CaV3.3-specific, antisense oligonucleotides resulted in a significant reduction of neuropathic pain.

On the contrary, the CaV3.2 KO mice showed no significant difference from wild-type mice in neuropathic pain responses induced by spinal-nerve ligation (SNL) treatment (Figure 2, spontaneous pain in the right panel of a and thermal hyperalgesia in the right panel of b) [43**]. The SNL neuropathic pain model has been well established to be caused by central sensitization in the spinal dorsal horn [47]. Therefore, this result may rule out CaV3.2 as being involved in the central sensitization for neuropathic pain, sparing the possibility of development of compensation by other subtype in the mutant mouse. This KO mouse needs to be examined on the other models of neuropathic pain to confirm the results of the antisense oligonucleotide experiments [11**,14**].

In a dramatic contrast to CaV3.2 KO mice, CaV3.1 KO mice that were treated to develop SNL-induced neuropathic pain showed significantly attenuated responses when compared to wild-type mice with the same treatment (Figure 2, left panels of a and b, [48]). These results raise a possibility that α1G is the T-type channel that is known to be involved in the synaptic plasticity in spinal lamina I projection neurons known to mediate hyperalgesia [49]. Thus, α1G may be involved in central sensitization in the spinal dorsal horn for development of neuropathic pain.

Intrathecal administration of CaV3.3 antisense oligonucleotide significantly relieved tactile alldynia and thermal hyperalgesia in chronic compression of dorsal root ganglion (CCD) of rats [14**], raising a possibility that the CaV3.3 subtype calcium channels in the spinal cord may also be involved in the pathogenesis of neuropathic pain.

**T-channel blockers as pain killers**

T-type channels show subtype-specific and region-specific roles in the pain pathway. In the thalamus, the α1G subtype plays an antinociceptive role for persistent inflammatory pain. At the spinal level, this subtype appears to be involved in the development of neuropathic pain presumably by central sensitization. In the periphery, α1H is
required for various pains — acute, visceral, inflammatory — to enter the central nervous system. Moreover, Nelson et al. recently demonstrated that modulation of α1H channel controls the sensitization of nociceptors, the peripheral pain-sensing neurons [50/C15/C15]. These results show two windows of chances for T-type channel blockers to be analgesic (Figure 3). T-type blockers that can pass the BBB may have a good chance to block neuropathic pain by blocking α1G-mediated sensitization at the spinal level. Antagonizing the antinociceptive role of α1G by the same drug at the thalamus may not be a significant problem in this pain control strategy, because the suppression of the neuropathic pain at the origin may make the thalamic problem irrelevant. The other chance is that T-channel blockers in the periphery will block all other pain signals that go through the DRG to the central nervous system.

Conclusion
Deletion of CaV3.1 dramatically altered the properties of thalamocortical neurons of the mouse: loss of low-threshold Ca2+ currents, low-threshold spikes, and burst firings. These mice were resistant to absence seizures, a brief interruption in consciousness accompanied with SWDs on the EEG. Such phenotype of the mutant mice suggests that the ablation of the CaV3.1 gene presumably impaired the sensory gating function of the thalamus, leading to a deficit in controlling the vigilance level to external sensory stimuli. The other phenotypes of the CaV3.1 mutant mice, hyperalgesia to chronic pain [39] and sleep instability [36], can also be attributed to the impairment of the sensory gating function of the thalamus in the CaV3.1 mutant mice. This explanation is consistent with the idea that burst firings of TC neurons play a crucial role in the thalamic sensory gating, and thus for the control of consciousness.

For the translation side of the story, it may be suggested that T-type channel blockers have high potentials to become drugs for controlling absence epilepsy and pain, especially neuropathic pain, at the least.

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References and recommended reading
Papers of particular interest, published within the annual period of review, have been highlighted as:

- of special interest
- of outstanding interest


Here authors described that all the polymorphisms clustered in the intracellular loop connecting repeats I and II (I-II loop) increase the surface expression of extracellularly tagged Ca(v)3.2 channels, showing how CACNA1H polymorphisms may contribute to function and expression of Ca(v)3.2 channel, especially to absence epilepsy.


This demonstrated that mice with a null mutation of the Ca3.2 gene showed attenuated responses to acute noxious mechanical, thermal, and chemical stimuli, as well as in the visceral pain. In contrast to the results of intrathecally administered antisense oligonucleotide in the CCI and CCD, however, mutant didn’t show any altered behavioral responses in the spinal nerve ligation model of neuropathic pains.

44. Todorovic SM, Jevtovic-Todorovic V: The role of T-type calcium channels in peripheral and central pain processing. CNS Neurol Disord Drug Targets 2006, 5:639-653.

This gives an overview of participation of T-type calcium channels in pain processing at multiple levels.


This study suggested the molecular mechanism underlying the roles of T-channels in peripheral sensitization, demonstrating that endogenous modulators of Ca(V)3.2 can control the excitability of C-type dorsal root ganglion nociceptors.