Contributions of T-type calcium channels to the pathophysiology of pain signaling

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Among the family of voltage-gated calcium channels, low threshold T-type channels have only recently joined their high threshold N-type channel brother in being generally accepted as molecular players within pain signaling. The ability of T-type channels to modulate neuronal excitability at low thresholds has implications concerning their participation in pain neurotransmission at multiple levels including peripheral nociceptors, the spinal cord and the brain. Consensus is rapidly developing that in the periphery and spinal cord the Cav3.2 T-type calcium channel isoform selectively plays a pronociceptive role and therefore represents an attractive target for future therapeutic strategies.

Introduction

The unpleasant sensory and emotional experiences known as pain are caused by electrical signals that are relayed through well-defined neuronal pathways to specific areas of the brain (for reviews, see [1,2]). The encoding and processing of these potential or actual tissue-damaging (noxious) events in the nervous system is referred to as nociception. Noxious stimuli activate sensor receptors (e.g. sensitive to heat, pressure, acid, inflammation) to generate sensor potentials in peripheral pain-sensing free nerve endings of the nociceptors. Upon reaching sufficient amplitude, the potentials trigger action potentials (APs) at the soma of nociceptors (dorsal root ganglion, DRG), which then conduct down axons to the superficial laminae located in the dorsal horn of the spinal cord. Subsequent activation of dorsal horn spinal neurons by neurotransmitter release (primarily glutamate) from the nociceptors causes the generation of APs that propagate to the thalamus, mainly through the spinothalamic tract (STT) pathway (Fig. 1). Specific thalamic nuclei innervated by the STT relay the nociceptive signals to areas of the brain responsible for the sensory discriminatory (lateral thalamocortical system) and affective (medial thalamocortical system) aspects of the painful stimuli. Generally, both tissue inflammation (inflammatory pain) and damage to neurons (neuropathic pain) can result in pathophysiological pain wherein nociceptors fire spontaneously or are hyper-responsive to either innocuous (alldynic) or noxious (hyperalgesic) stimuli. Although low voltage-activated (LVA) T-type voltage-gated calcium (Ca) channels are well known to be expressed in pain pathway components [3,4], a lack of specific antagonists and molecular genetic tools delayed the elucidation of their specific contributions in pain signaling. Most recently, the defining of three distinct genes encoding for T-type Ca channels has lead to new tools utilized to uncover their involvement in nociceptive processes.
A brief history of T-type calcium channels

Twenty-five years ago, Llinas and Yarom used current clamp intracellular recordings on inferior olive brain slices to identify low-threshold Ca spikes linked to both a prolonged depolarization after the initial Na⁺ spike of the AP (called the after-depolarizing potential, ADP) and to rebound burst firing after membrane hyperpolarization [5,6]. Shortly thereafter, Carbone and Lux used whole-cell and single channel patch-clamp recordings in an in vitro preparation of chick and rat sensory neurons to define the biophysical properties of LVA Ca channels [4]. Subsequent studies in isolated DRGs demonstrated that LVA Ca currents (now called T-type) could be distinguished from high voltage-activated (HVA) Ca currents by their faster kinetics of activation and inactivation, slower deactivation kinetics, more hyperpolarized voltage-dependence of activation and inactivation, and smaller single-channel conductance [7–9]. Overall, these distinct biophysical properties enable T-type Ca channels to regulate subthreshold excitability including mediating bursting behaviors and firing rates (reviewed in [3]). The observed heterogeneity in the biophysical properties of native T-type Ca currents found in various types of neurons can largely be explained by the existence of three distinct genes that encode for Ca channel α₁ subunit proteins with LVA biophysical properties: Cav3.1 (α₁G), Cav3.2 (α₁H) and Cav3.3 (α₁I) (reviewed in [10]). The three T-type α₁ subunits are differentially expressed at the cellular and subcellular levels throughout the nervous system and there also exist several alternatively spliced variants that generate further T-type biophysical diversity [11–15]. While high affinity, subtype specific pharmacological agents that can distinguish between the Cav T-type isoforms have yet to be developed, the channels exhibit several unique properties (e.g., Cav3.2 has an ~tenfold higher sensitivity to Ni²⁺ blockade; Cav3.3 has proportionally slower activation and inactivation kinetics and faster deactivation kinetics, Cav3.1 has a greater permeability to Ca²⁺ than Ba²⁺ [10,16]) that permit at least partial distinctions to be made.

T-type calcium channels in peripheral nociceptors

Cav3.2 is the major T-type channel isoform expressed in peripheral nociceptors

Peripheral sensory neurons are classically divided into functional groups based on axonal conduction velocity, which itself is positively correlated with cell soma size [17]. Approximate classifications based upon DRG diameter can be made: small diameter DRGs (15–30 μm) are slowly conducting unmyelinated C sensory fibers, medium diameter DRGs
(31–40 μm) are thin, myelinated Aδ fibers, and large diameter DRGs (45–51 μm) are large myelinated Aα and Aβ sensory fibers. Peripheral nociceptors are known to be composed of C- and Aδ-sensory fibers [18]. Most small-size DRGs are sensitive to capsaicin and exhibit long duration APs, both hallmarks of nociceptors, whereas a majority of medium-sized DRG neurons do not respond to capsaicin, raising the question of which medium-sized DRGs are in fact nociceptors [19]. Although somewhat variable from cell to cell, small DRGs generally express lower levels of whole-cell T-type currents (up to 250 pA) compared to some medium-sized DRGs with very large T-type currents (>4000 pA; and often designated as D-hair mechanoreceptors) and little to no observable T-type conductances in large DRGs [19–21]. Todorovic and co-workers [22] have recently identified a novel subset of small DRGs (26–31 μm) named ‘T-Rich’ that express both capsaicin receptors and the isolectin β-4 (IB4) nociceptor marker and possess a high density of T-type currents (up to 3000 pA) with virtually no HVA Ca currents. Several lines of evidence demonstrate that Cav3.2 is the predominant T-type Ca channel isoform expressed in peripheral nociceptors. In situ hybridization and quantitative RT-PCR for all three T-type channel isoforms reveals that Cav3.2 is transcribed at significantly higher levels (five to tenfold) compared to Cav3.1 and Cav3.3 in small and medium DRGs [15,23]. Electrophysiologically, T-type currents in small and medium DRGs also exhibit fast inactivation kinetics and potent block by Ni2+, properties that are characteristic of Cav3.2 channels [8,23]. Finally, conclusive evidence arises from experiments examining Cav3.2 gene knock-out (KO) mice, wherein T-type whole-cell currents are functionally absent in the small DRGs [24].

**T-type channels are linked to excitability in peripheral nociceptors**

Through a combination of biophysical, pharmacological and ion substitution experiments, White et al. [25] have shown a role for T-type currents in switching from tonic to phasic firing in sensory neurons. The authors find that in 30–50 μm medium to large DRGs, T-type currents contribute to the ADP which is occasionally crowned with repetitive bursts. Recent studies with action potential command waveforms suggest that in small DRGs T-type Ca channels have a minor role in directly contributing to Ca ion entry during the ADP, whereas tetrodotoxin-resistant Na channels and HVA Ca channels carry most of the inward current during the ADP shoulder [26]. By contrast, the T-Rich subset of nociceptors (26–31 μm DRGs) have a high density of T-type current that when robustly enhanced by the endogenous amino acid, γ-cysteine, results in a lower depolarization threshold for excitability and a concomitant increase in the probability of burst firings containing APs and ADPs. Computer simulations demonstrate that the increase in nociceptor excitability is due to a hyperpolarizing shift in the voltage-dependence of T-type activation, whereas loss-of-function experiments with 100 μM Ni2+ (blocking Cav3.2) show that loss of T-type current causes a significant decrease in the amplitude of the ADP and an increase in the threshold for AP firing [22].

Hepperstall and Lewin [27] have recently argued that it is unclear in vivo whether T-rich sensory cells are nociceptors or rather are low-threshold mechanoreceptors: (1) the T-rich DRGs have short-duration APs which are ‘in vivo’ invariably a unique property of low-threshold mechanoreceptors’ and (2) the T-rich experiments examined the cell bodies of sensory neurons grown in culture, where some ionic properties can be lost or altered. We would counter that in a detailed characterization by Cardenas et al., a prevalent group of small DRGs (25 μm mean diameter) had both short duration APs and were highly capsaicin sensitive and thus, were most likely nociceptors and distinct from mechanoreceptors [19]. Additionally, Nelson et al. [22] have identified small diameter DRGs with similar T-Rich biophysical and pharmacological properties in whole-cell recordings of an intact DRG preparation. Overall, combining the aspects of DRG size, positive nociceptive markers, and a hyperpolarizing response to serotonin application (which is characteristic of C- and Aδ-sensory fibers; [22]) makes it more likely that T-Rich DRGs are in fact a subset of nociceptors rather than low-threshold mechanoreceptors.

**T-type currents contribute to both acute peripheral nociception and neuropathic pain**

Physiologically, T-type Ca channels have been linked to peripheral nociception in studies showing that the endogenous reducing agent γ-cysteine both enhances T-type currents in small DRGs in vitro and also causes thermal and mechanical hyperalgesia in vivo. Conversely, an endogenous inhibitor of T-type currents, allopregnanolone, promotes thermal and mechanical analgesia in vivo [28,29]. This evidence for the pronociceptive role of T-type currents in peripheral nociceptors is strengthened by observations that the amounts of γ-cysteine that increase T-type currents in vitro and that are hyperalgesic in vivo are within physiologically-relevant concentration ranges [29]. A variety of other pharmacological agents block T-type Ca channels with varying degrees of affinity and specificity including clinical antiepileptics (ethosuximide, phenytoin, zonisamide), antipsychotics (penfluridol, pimozide) and antiarrhythmics (bepridil, mibefradil, efundipine), as well as dietary agents (ω-fatty acids) and endogenous messengers (endocannabinoids). Extensive studies examining these weakly-selective agents in acute and neuropathic pain animal models as well as human pain conditions are highly suggestive that modulation of T-type Ca channel activity is a valid approach to the broad treatment of pain conditions (reviewed in [30]).

A recent study by Bourinet et al. was the first to move past pharmacological correlations and to directly demonstrate a
role for the Cav3.2 T-type channel isoform in peripheral nociceptors [23]. Intrathecal administration of Cav3.2-specific, but not Cav3.1- or Cav3.3-specific, antisense oligonucleotides results in antinociceptive and analgesic effects in rat models of both acute thermal and mechanical pain. The local injection of Cav3.2 antisense oligonucleotides also results in the significant and long-term attenuation of surgically-induced neuropathic hypersensitivity [23]. The robust antinociceptive effects mediated by reducing Cav3.2 T-type channel expression are similar or greater in amplitude but have greater duration of action than reference analgesics such as morphine and clomipramine. Control experiments show that Cav3.2 antisense injection results in a dramatic reduction in expression of both Cav3.2 mRNA and protein in DRGs of the targeted SC regions, as well as a 75% and 92% decrease in T-type whole-cell currents in small and medium DRGs, respectively [23].

Most recently, Choi et al. have characterized the pain susceptibility of Cav3.2 gene KO mice that exhibit normal locomotion, motor coordination and anxiety levels [31]. The authors find attenuated responses to mechanical, thermal, and chemical cutaneous pain stimuli as well as chemical visceral pain stimuli in the Cav3.2 gene KO mice thus providing further direct evidence for a pronociceptive role of Cav3.2 in the periphery. In contrast to Cav3.2 antisense studies examining the rat chronic constrictive injury (CCI) model of neuropathic pain [23], Cav3.2 gene KO mice that had spinal-nerve ligation (SNL)-induced neuropathic pain showed no significant differences in behavioral responses when compared to wild-type mice with the same treatment.

In the CCI rat model of neuropathic pain, local injection of inhibitors of T-type channels, including mibebradil, oxidizing agents, neuroactive steroids and ethosuximide all result in a reduction of CCI-induced hyperalgesia, and in some cases abolish the progression of neuropathic pain [32–34]. The reduction in the ability of reducing agents such as l-cysteine to induce hyperalgesia and the robust analgesia induced by oxidizing agents such as S,S'-dithio-bis-(2-nitrobenzoic acid) in CCI rats has lead to the hypothesis that the metabolic stress induced by neuronal injury causes a reduced peripheral cellular environment wherein T-type channels are in a more sensitized state, contributing to hypersensitivity of nociception [33,35]. In support of this notion, local and intrathecal administration, but not intrathecal administration, of mibebradil relieves CCI-induced tactile and thermal hypersensitivity, suggesting a peripheral site of action [34].

There have been conflicting reports that the levels of T-type channel expression in DRGs either does not change [36] or decreases [37] in neuropathic animal models compared to wild-type animals. These studies examined acutely dissociated medium-sized DRGs (between 33 and 50 μm), the majority of which are likely not nociceptors, thus additional studies are required examining T-type current density in intact peripheral nociceptors (mostly small DRGs) in animal models of neuropathic pain. This highlights one of the biggest limitations of most studies of T-type channels in peripheral nociceptors: almost all electrophysiological recordings are from acutely dissociated or cultured DRGs that contain only the nociceptor soma. T-type channels are well known to be highly expressed in dendrites throughout the nervous system [38–41] and in peripheral nociceptors they may play significant roles defining the excitability of nerve endings, although this has largely been unexplored. It is likely that high resolution Ca imaging combined with subtype specific T-type channel antagonists and antibodies will be required to investigate these issues.

T-type calcium channels in the spinal cord

Under conditions of severe or persistent nociceptive signaling, C-fibers can fire repetitively and induce a progressive increase in the response of the dorsal horn spinal projection neurons (PNs) that express neurokinin-1 receptors (NK1) and that have ascending connections to the brain. This frequency-dependent form of synaptic potentiation between C-fibers and superficial laminae spinal neurons is known as wind-up and shares many properties with both central sensitization and the spinal cord-mediated hyperalgesia observed after peripheral nerve damage [42]. Similar to that for peripheral nociceptors, in situ hybridization reveals that Cav3.2 is the primary T-type channel isoform expressed in the superficial layers of the dorsal horn of the spinal cord [15]. Application of 100 μM Ni²⁺ blocks a significant portion of voltage-gated Ca transients in lamina I neurons of the dorsal horn, suggestive of functional T-type currents in these cells being most likely encoded by the Cav3.2 channel [43].

In work directly demonstrating a nociceptive role for spinal T-type channels, Ikeda et al. have shown that high frequency stimulation of C-fibers causes release of substance P that activates NK1 receptors on the lamina I PNs, leading to a signal transduction pathway that facilitates NMDA receptors and increases cytosolic Ca levels (Fig. 2). The synergistic activation of NMDA receptors and T-type currents increases intracellular Ca levels and potentiates postsynaptic responses [44]. This Ca-dependent wind-up phenomenon appears to only occur in PNs wherein the presence of T-type currents allows for both broadening of the action potential and a more negative threshold for firing.

Further support for a role of T-type channels in spinal pain signaling comes from in vivo electrophysiological recording experiments in sham-operated and CCI rats in which intrathecal injection of a weakly selective T-type antagonist, ethosuximide, dose-dependently reduces the responses of dorsal horn neurons to innocuous and noxious electrical, mechanical, and thermal stimuli [45]. Also, μ-opioid receptors that morphine acts upon are located in lamina I/II of the
dorsal horn and intrathecal injection of the T-type antagonist, mibefradil, potentiates both morphine- and [D-Ala(2), NMePhe(4), Gly-ol(5)] enkephalin (DAMGO)-induced antinociception [46].

T-Type calcium channels in the thalamus

Differential expression and function of T-type channel isoforms in thalamic neurons

Two of the main cell types in the thalamus are relay thalamocortical (TC) neurons, which relay signals from the periphery to various regions of the cortex, and the GABAergic reticular thalamic neurons (nRT), which hyperpolarize TC neurons to induce rebound burst firing. In situ hybridization reveals that Cav3.1 is the most abundant T-type isoform in TCs whereas Cav3.2 and Cav3.3 mRNAs are more highly expressed in nRT cells [15]. Consistent with these findings, whole-cell T-type currents in TC cells are completely abolished in Cav3.1 gene KO mice, suggesting that Cav3.1 underlies functional T-type currents in these cells [47]. Electrophysiological recordings of nRT cells reveal two distinct populations of T-type currents with properties similar to that for the Cav3.2 and Cav3.3 isoforms [39,48]. The observation that there remains a significant T-type current in the nRT cells of Cav3.2 gene KO mice is also suggestive that both isoforms are normally present in these cells [49].

T-type currents appear to play an essential role in the reciprocal firing interactions between TC and nRT cells that both initiate oscillating rebound bursting patterns and the spindle waves that underlie slow-wave sleep [50]. Indeed, altering T-type currents in these cells abolishes rebound-burst firing and the proper timing of AP firing and disrupts sleep gating [47,51]. Over-activity of T-type currents in TC and nRT cells is also associated with pathophysiological spike-and-wave discharges that underlie absence epilepsy [47,52]. A linkage between the thalamus and higher level pain signaling is demonstrated in findings that lesions in the lateral spinothalamic system can result in neurogenic pain, whereas medial thalamotomies can relieve neurogenic pain [53]. Of particular relevance, electrophysiological recordings can be made from the lateral thalamic nuclei in awake patients with chronic neurogenic pain. TC cells from these patients display abnormal low-threshold spikes and burst firing in frequency ranges (3–5 Hz) which are normally associated with slow wave sleep and not wakefulness, potentially implicating involvement of T-type Ca channels [50,53].
Thalamic Cav3.1 currents are antinociceptive in visceral pain responses
As described above, in both the spinal cord and periphery, T-type Ca channels (mainly the Cav3.2 subtype) are implicated in pronociceptive mechanisms of somatic pain. By contrast, a recent study has implicated a novel antinociceptive role of thalamic Cav3.1 T-type channels in visceral pain mechanisms. Of note, Cav3.1 gene KO mice exhibit normal responses to thermal and mechanical somatic pain, as well as hyperalgesia to cutaneous pain similar to that for wild-type mice, providing supporting evidence that Cav3.2 is the major T-type isoform involved in SC and peripheral pain pathways [54]. However, in Cav3.1 KO animals the induction of visceral pain by the intraperitoneal injection of either acetic acid or MgSO4 results in significantly enhanced writhing responses. In phenocopy experiments with wild-type mice, intraperitoneal injection of mibebradil (which does not effectively cross the blood-brain-barrier) reduces visceral pain (likely through neural injection of mibebradil [54]). This suggests that the Cav3.1 T-type channel in visceral pain is restricted to the thalamus.

In vivo membrane potential recordings of VPL neurons comparing Cav3.1 gene KO and wild type mice shows that while the firing rate of single AP spikes is similar to that for wild-type mice, the VPL neurons of the Cav3.1 gene KO mice have a significantly lower total firing frequency owing to a lack of burst firing. Although the onset of visceral pain in wild-type mice results in an initial surge of single spike APs followed by a gradual increase in burst spikes correlated with a decay in the elevated single spike firing rate, in Cav3.1 gene KO mice the initial increase of single AP spikes in response to visceral pain is sustained because burst-spike activity is not possible [54]. This suggests that the Cav3.1 T-type channels of the VPL are normally involved in sensory gating by inhibiting high frequency single spike visceral pain signals through the initiation of rebound burst firing. As intraperitoneal injections of acetic acid or MgSO4 are an artificial model of visceral pain, it will be interesting to determine whether a similar mechanism occurs under more physiological models of visceral luminal pain, such as colorectal distention or intracolonic perfusion of irritant substances [55]. Additionally, as noxious visceral pain signals reach the VPL through the dorsal column of the SC [56], the role of thalamic T-type Ca channels in pain signaling via classical nociceptive STT pathways remains to be explored.

Conclusions
The differential expression of a biophysically diverse family of LVA T-type Ca channels contributes to the diversification of physiological functions in the nervous system, including that of the nociceptive pathways. Centrally expressed Cav3.1 T-type Ca channels appear to have an antinociceptive role in thalamic visceral pain responses and thus blockade of this channel by pharmacological agents that penetrate the CNS may prove to be pronociceptive. Contrastingly, evidence has emerged to support a pronociceptive role for Cav3.2 T-type Ca channels in modulating excitability and contributing to pain signaling within both peripheral nociceptors and spinal cord dorsal horn neurons. Together with the potential contributions of peripheral and spinal T-type Ca channels towards the central sensitization implicated in neuropathic pain mechanisms, the development of Cav3.2 selective blockers may provide a new avenue of clinical treatment concerning both acute and neuropathic conditions. Interestingly, the high voltage-activated N-type Ca channel (Cav2.2/α1B) localized to nociceptor presynaptic terminals in the spinal cord dorsal horn is the target of a marketed peptide for severe intractable pain (PrialtTM), as well for several small organic molecules currently in development (reviewed in [57]). It is tempting to speculate that there might be an opportunity for novel pharmacological agents targeting both peripheral Cav3.2 T-type and spinal Cav2.2 N-type channels. Such mixed N- and T-type Ca channel blockers might provide a new and powerful strategy aimed at treating a broad spectrum of human pain conditions.

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References
et al.
19 Cardenas, C.G.
et al.
22 Nelson, M.T.
et al.
25 White, G.
et al.
23 Bourinet, E.
et al.
28 Pathirathna, S.
et al.
29 Todorovic, S.M.
et al.
32 Pathirathna, S.
et al.
35 Jevtovic-Todorovic, V. and Todorovic, S.M. (2006) The role of peripheral
T-type calcium channels in pain transmission. Cell Calcium 40, 197–203
Bacei, M.L. and Kocsis, J.D. (2000) Voltage-gated calcium currents in
axotomized adult rat cutaneous afferent neurons. J. Neurophysiol. 83,
2227–2238
37 McCallum, J.B. et al. (2003) Loss of T-type calcium current in
sensory neurons of rats with neuropathic pain. Anesthesiology 98,
209–216
38 Magee, J. et al. (1998) Electrical and calcium signaling in dendrites of
hippocampal pyramidai neurons. J. Physiol. 60, 327–346
39 Joksovic, P.M. et al. (2005) Different kinetic properties of two T-type Ca2+
currents of rat reticular thalamic neurons and their modulation by
enflurane. J. Physiol. 566 (Pt 1), 125–142
34 Dogrul, A. et al. (2003) Reversal of experimental neuropathic pain by T-
type calcium channel blockers. Pain 105, 159–168
35 Jevtovic-Todorovic, V. and Todorovic, S.M. (2006) The role of peripheral
T-type calcium channels in pain transmission. Cell Calcium 40, 197–203
Bacei, M.L. and Kocsis, J.D. (2000) Voltage-gated calcium currents in
axotomized adult rat cutaneous afferent neurons. J. Neurophysiol. 83,
2227–2238
37 McCallum, J.B. et al. (2003) Loss of T-type calcium current in
sensory neurons of rats with neuropathic pain. Anesthesiology 98,
209–216
38 Magee, J. et al. (1998) Electrical and calcium signaling in dendrites of
hippocampal pyramidai neurons. J. Physiol. 60, 327–346
39 Joksovic, P.M. et al. (2005) Different kinetic properties of two T-type Ca2+
currents of rat reticular thalamic neurons and their modulation by
enflurane. J. Physiol. 566 (Pt 1), 125–142
34 Dogrul, A. et al. (2003) Reversal of experimental neuropathic pain by T-
type calcium channel blockers. Pain 105, 159–168
35 Jevtovic-Todorovic, V. and Todorovic, S.M. (2006) The role of peripheral
T-type calcium channels in pain transmission. Cell Calcium 40, 197–203
Bacei, M.L. and Kocsis, J.D. (2000) Voltage-gated calcium currents in
axotomized adult rat cutaneous afferent neurons. J. Neurophysiol. 83,
2227–2238
37 McCallum, J.B. et al. (2003) Loss of T-type calcium current in
sensory neurons of rats with neuropathic pain. Anesthesiology 98,
209–216
38 Magee, J. et al. (1998) Electrical and calcium signaling in dendrites of
hippocampal pyramidai neurons. J. Physiol. 60, 327–346
39 Joksovic, P.M. et al. (2005) Different kinetic properties of two T-type Ca2+
currents of rat reticular thalamic neurons and their modulation by
enflurane. J. Physiol. 566 (Pt 1), 125–142
34 Dogrul, A. et al. (2003) Reversal of experimental neuropathic pain by T-
type calcium channel blockers. Pain 105, 159–168
35 Jevtovic-Todorovic, V. and Todorovic, S.M. (2006) The role of peripheral
T-type calcium channels in pain transmission. Cell Calcium 40, 197–203
Bacei, M.L. and Kocsis, J.D. (2000) Voltage-gated calcium currents in
axotomized adult rat cutaneous afferent neurons. J. Neurophysiol. 83,
2227–2238
37 McCallum, J.B. et al. (2003) Loss of T-type calcium current in
sensory neurons of rats with neuropathic pain. Anesthesiology 98,
209–216
38 Magee, J. et al. (1998) Electrical and calcium signaling in dendrites of
hippocampal pyramidai neurons. J. Physiol. 60, 327–346
39 Joksovic, P.M. et al. (2005) Different kinetic properties of two T-type Ca2+
currents of rat reticular thalamic neurons and their modulation by
enflurane. J. Physiol. 566 (Pt 1), 125–142
34 Dogrul, A. et al. (2003) Reversal of experimental neuropathic pain by T-
type calcium channel blockers. Pain 105, 159–168
35 Jevtovic-Todorovic, V. and Todorovic, S.M. (2006) The role of peripheral
T-type calcium channels in pain transmission. Cell Calcium 40, 197–203
Bacei, M.L. and Kocsis, J.D. (2000) Voltage-gated calcium currents in
axotomized adult rat cutaneous afferent neurons. J. Neurophysiol. 83,
2227–2238
37 McCallum, J.B. et al. (2003) Loss of T-type calcium current in
sensory neurons of rats with neuropathic pain. Anesthesiology 98,
209–216
38 Magee, J. et al. (1998) Electrical and calcium signaling in dendrites of
hippocampal pyramidai neurons. J. Physiol. 60, 327–346
39 Joksovic, P.M. et al. (2005) Different kinetic properties of two T-type Ca2+
currents of rat reticular thalamic neurons and their modulation by
enflurane. J. Physiol. 566 (Pt 1), 125–142
34 Dogrul, A. et al. (2003) Reversal of experimental neuropathic pain by T-
type calcium channel blockers. Pain 105, 159–168
35 Jevtovic-Todorovic, V. and Todorovic, S.M. (2006) The role of peripheral
T-type calcium channels in pain transmission. Cell Calcium 40, 197–203
Bacei, M.L. and Kocsis, J.D. (2000) Voltage-gated calcium currents in
axotomized adult rat cutaneous afferent neurons. J. Neurophysiol. 83,
2227–2238
37 McCallum, J.B. et al. (2003) Loss of T-type calcium current in
sensory neurons of rats with neuropathic pain. Anesthesiology 98,
209–216
38 Magee, J. et al. (1998) Electrical and calcium signaling in dendrites of
hippocampal pyramidai neurons. J. Physiol. 60, 327–346
39 Joksovic, P.M. et al. (2005) Different kinetic properties of two T-type Ca2+
currents of rat reticular thalamic neurons and their modulation by
enflurane. J. Physiol. 566 (Pt 1), 125–142
34 Dogrul, A. et al. (2003) Reversal of experimental neuropathic pain by T-
type calcium channel blockers. Pain 105, 159–168
35 Jevtovic-Todorovic, V. and Todorovic, S.M. (2006) The role of peripheral
T-type calcium channels in pain transmission. Cell Calcium 40, 197–203
Bacei, M.L. and Kocsis, J.D. (2000) Voltage-gated calcium currents in
axotomized adult rat cutaneous afferent neurons. J. Neurophysiol. 83,
2227–2238
37 McCallum, J.B. et al. (2003) Loss of T-type calcium current in
sensory neurons of rats with neuropathic pain. Anesthesiology 98,
209–216
38 Magee, J. et al. (1998) Electrical and calcium signaling in dendrites of
hippocampal pyramidai neurons. J. Physiol. 60, 327–346
39 Joksovic, P.M. et al. (2005) Different kinetic properties of two T-type Ca2+
currents of rat reticular thalamic neurons and their modulation by
enflurane. J. Physiol. 566 (Pt 1), 125–142
34 Dogrul, A. et al. (2003) Reversal of experimental neuropathic pain by T-
type calcium channel blockers. Pain 105, 159–168
35 Jevtovic-Todorovic, V. and Todorovic, S.M. (2006) The role of peripheral
T-type calcium channels in pain transmission. Cell Calcium 40, 197–203
Bacei, M.L. and Kocsis, J.D. (2000) Voltage-gated calcium currents in
axotomized adult rat cutaneous afferent neurons. J. Neurophysiol. 83,