

Contributions of T-type calcium channel isoforms to neuronal firing

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Abbreviations: Ca_v , voltage-gated calcium channel; HVA, high voltage-activated; LVA, low voltage-activated; DRG, dorsal root ganglion; LTS, low threshold spike; CICR, calcium-induced calcium release; RTN, reticular thalamic nucleus

Low voltage-activated (LVA) T-type calcium channels play critical roles in the excitability of many cell types and are a focus of research aimed both at understanding the physiological basis of calcium channel-dependent signaling and the underlying pathophysiology associated with hyperexcitability disorders such as epilepsy. These channels play a critical role towards neuronal firing in both conducting calcium ions during action potentials and also in switching neurons between distinct modes of firing. In this review the properties of the $Ca_v3.1$, $Ca_v3.2$ and $Ca_v3.3$ T-type channel isoforms are discussed in relation to their individual contributions to action potentials during burst and tonic firing states as well their roles in switching between firing states.

Introduction

T-type calcium channels are uniquely both “first responders” to depolarization and also contribute to regulating intracellular calcium levels near the resting potential of many cells.^{1,2} The low voltage threshold for activation of T-type channels drives their opening in response to relatively small positive changes in membrane potential. Further, an overlap in the membrane potentials at which T-type channels open, close and inactivate endows them with a particular property known as a “window current” whereby a basal inward flux of calcium ions can occur near the resting potential (Fig. 1).^{3,4} Window currents are thought to contribute to distinct neuronal firing patterns, resulting in varied network rhythms.^{5,6} In some neurons, the rapid activation of T-type channels at low voltages is also essential for the generation of low-threshold spikes (LTS) which underlie both pro-epileptic and sleep-related “burst-firing” patterns (Fig. 1).⁷ In native systems difficulties occur in determination of the individual roles of T-type channel subtypes ($Ca_v3.1$, $Ca_v3.2$ and $Ca_v3.3$) largely due to a combination of their distinct subcellular localizations, the lack of subtype specific pharmacological tools and contamination by other calcium currents such as those carried by high voltage-activated (HVA) calcium channels and TRP channels.⁸ More

recently, the individual contributions of specific T-type calcium channel isoforms to neuronal excitability has been investigated using a variety of electrophysiological and computer modeling approaches combined with subtypes-specific molecular biological manipulations. These studies have revealed complex roles for T-type channels in modulating neuronal firing, with individual subtypes displaying unique contributions.

Biophysical Properties of T-type Calcium Channels

The unique biophysical properties of T-type calcium channels determine how they respond during particular types of neuronal firing. The rates and voltage-dependencies of channel activation, inactivation, deactivation and recovery from inactivation are the primary properties that determine how the individual T-type isoforms conduct calcium (Fig. 2). In exogenous systems the $Ca_v3.1$ and $Ca_v3.2$ T-types generally open and close at approximately similar membrane potentials, while $Ca_v3.3$ channels open and close at about +10 mV more depolarized potentials.⁹ Similarly, $Ca_v3.1$ and $Ca_v3.2$ channels inactivate (as determined at steady-state) around 5 mV more hyperpolarized than $Ca_v3.3$ channels and, therefore, require more hyperpolarized potentials to become available for subsequent opening via de-inactivation. $Ca_v3.1$ channels display the fastest activation and inactivation kinetics, marginally faster than $Ca_v3.2$, and both of which are significantly faster than for $Ca_v3.3$ channels.^{9,10} Therefore, $Ca_v3.1$ and $Ca_v3.2$ channels open fastest in response to depolarization when compared to $Ca_v3.3$, but are also quickest to inactivate during depolarization. Conversely, $Ca_v3.3$ channels display the fastest deactivation kinetics, far faster than $Ca_v3.1$, which is marginally faster than $Ca_v3.2$ and, therefore, upon repolarization $Ca_v3.3$ channels are the quickest to close when the membrane potential begins to repolarize. With respect to the rate at which the T-subtypes recover from inactivation, $Ca_v3.1$ channels display the fastest rate of recovery, followed by $Ca_v3.3$ and with $Ca_v3.2$ being the slowest. Following depolarization $Ca_v3.1$ channels tend to de-inactivate quickly upon repolarization and are therefore likely to conduct more calcium on subsequent depolarizations than the other T-subtypes. Overall, it is the combination of these biophysical factors, each distinctly sensitive to membrane potentials achieved during physiological firing processes that likely determines how each T-type calcium channel subtype conducts

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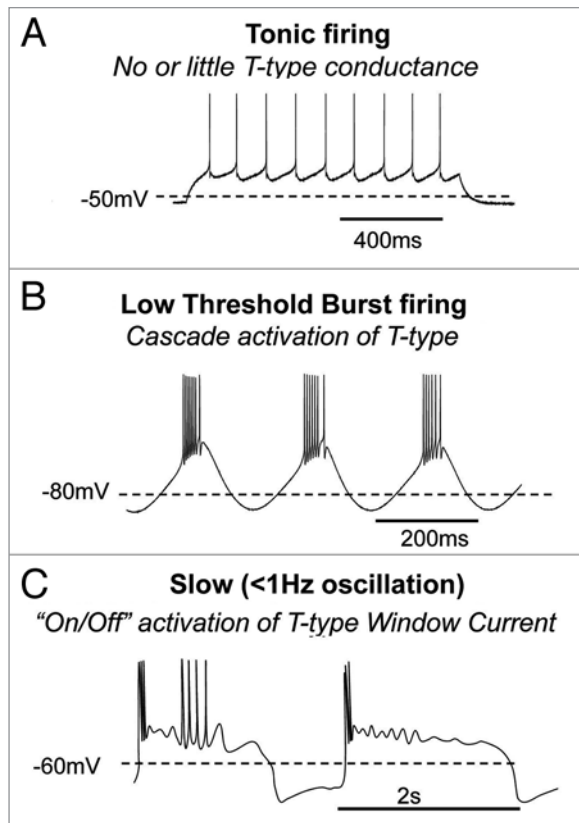


Figure 1. T-type activity control over neuronal firing patterns. Recordings from reticular thalamic (A and B) and thalamic lateral geniculate (C) neurons displaying altered firing properties depending on the level of contribution from T-type currents. (A) Neurons with a depolarized membrane potential (and therefore inactivated T-type channels) or neurons that have a low level of expression of T-type channels are more likely to fire single or tonic action potentials. T-type channels will conduct calcium during single or tonic action potentials if the firing occurs from a sufficiently hyperpolarized membrane potential and if the expression density is too low to induce burst firing. (B) Burst firing will occur if a high density of T-type channels are present and the neuron is held at a hyperpolarized membrane potential to ensure T-type channels are not inactivated. (C) Slow oscillations occur as a result of bistability of particular neurons depending on whether the window current is "on" or "off", however this is also highly dependent on leak potassium and the non-specific cationic conductances I_h and I_{CAN} . (C) Redrawn with permission: Hughes et al. *Neuron* 2004; 42:253–68.

calcium passively and during tonic or burst action potential firing. Many experiments examining the biophysical properties of T-type channels and their activity during different firing modes in vitro have been undertaken at room temperature. Of note, at more physiological temperatures some of the described kinetic and voltage-dependent parameters can be affected to varying degrees depending upon the nature of the T-type isoform.¹¹

T-type Channel Activity during Action Potential Firing

During a prototypical neuronal action potential the activation of T-type channels occurs during the initial depolarization phase (should the initial membrane potential have been hyperpolarized

sufficiently for T-type channels to be in the closed but not inactivated state). However, the majority of calcium conductance through T-type channels occurs during the repolarization phase as the cell rapidly hyperpolarizes back to its resting membrane potential through the activation of voltage-gated potassium channels.^{12,13} This likely results from the fact that T-type channel activation, inactivation and deactivation kinetics are relatively slow compared to the action potential itself and thus many T-type channels remain open as the action potential transitions through its repolarization phase (Fig. 3). During repolarization the driving force on calcium increases as the cell moves further away from the equilibrium potential for calcium ($\sim +10$ to $+40$ mV in general, but varying with specific conditions) thereby increasing calcium conductance during what is known as a "tail current", which then deactivates. An early study examining the responses of T-type (primarily $Ca_v3.2$) and HVA channels expressed in dorsal root ganglion (DRG) neurons found that a square pulse resulted in a relatively small T-type current in comparison to that generated by HVA channels.¹³ Contrastingly, upon exposure to an action potential waveform T-type channels generated a disproportionately large calcium current when compared to HVA channels.¹³ This is due in part to the lower threshold of activation of T-type channels, which will open earlier in the action potential (where the driving force is stronger) and therefore stay above their opening threshold for longer, but primarily because T-type channels deactivate more slowly than HVA channels promoting more prominent tail currents. Calcium entry during action potential repolarization is sensitive to the repolarization rate, with a slower repolarization allowing longer for channels to activate (although these also then inactivate) and faster repolarization inducing a rapid increase in driving force and strong tail current (although this quickly deactivates). Overall, the authors found that for the DRG $Ca_v3.2$ -like current the calcium entry increases with longer repolarization rates, although this eventually plateaus, whereas with HVA channels this continues to increase exponentially with repolarization rate.

The different biophysical properties of the individual T-subtypes also appear to generate specific responses to action potentials (Fig. 3). Experiments utilizing mock action potentials demonstrated that the $Ca_v3.1$ and $Ca_v3.2$ channels display similar amplitude currents in response to a single action potential, while due to the slower activation kinetics of $Ca_v3.3$ channels the resulting currents are significantly smaller.¹⁰ Of note however, the amplitude of $Ca_v3.3$ currents increases with slowed rate of repolarization whereas the amplitudes of $Ca_v3.1$ and $Ca_v3.2$ currents generally decrease in response to a slower repolarization phase. This is likely the result of a longer repolarization phase providing the slower activating $Ca_v3.3$ channels with more time to open, whereas $Ca_v3.1$ and $Ca_v3.2$ channels quickly activate and inactivate. Despite these differences, with a slowed repolarization rate the calcium charge transference increases for all three T-subtypes albeit with $Ca_v3.1$ and $Ca_v3.2$ channels reaching a plateau and $Ca_v3.3$ channels increasing linearly.¹⁰

The individual characteristics of the T-type isoforms become even more apparent in response to a series of multiple action potentials, as might be observed in neurons firing in a tonic pattern

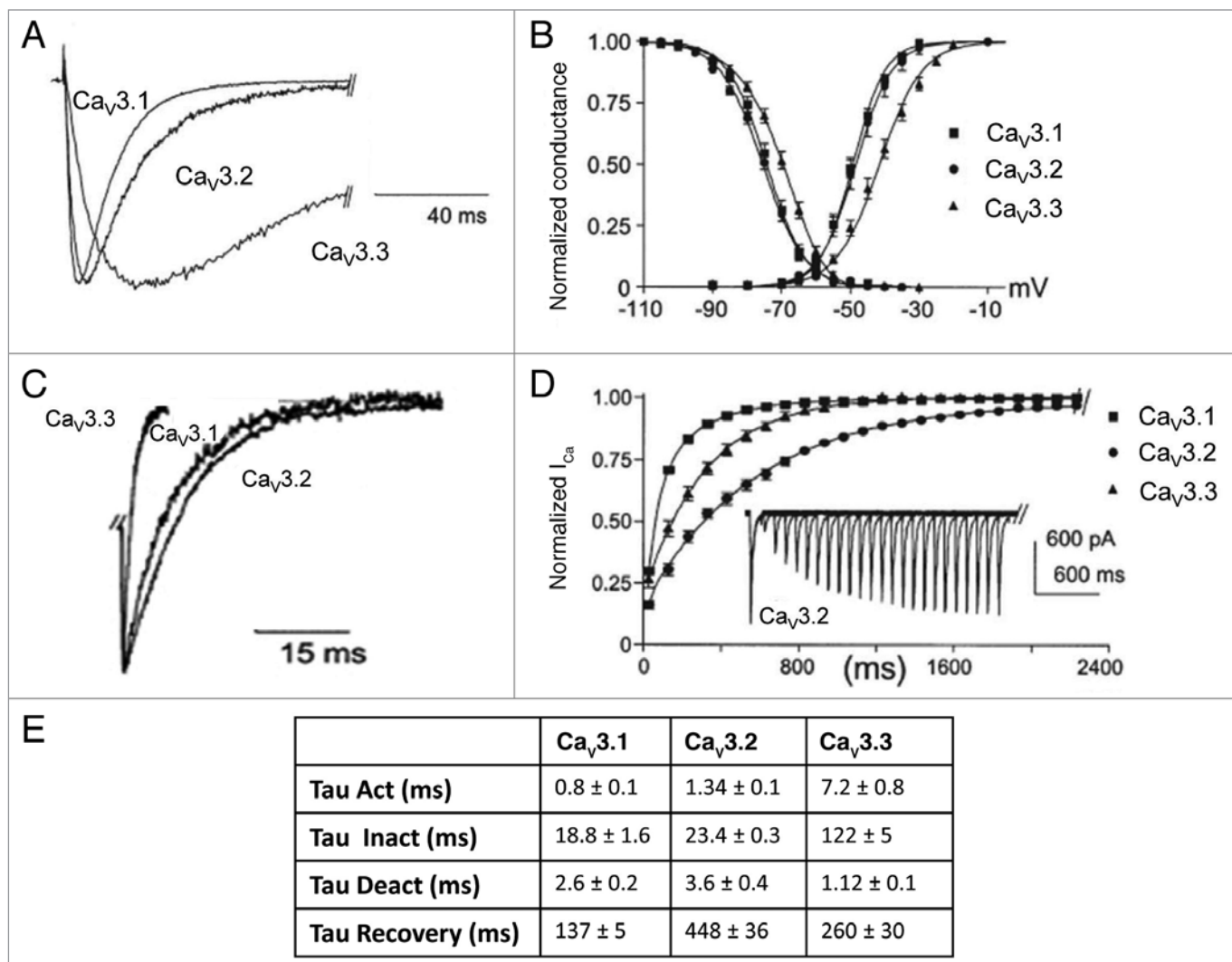


Figure 2. Basic biophysical properties of T-type calcium channels. (A) Representative currents, (B) conductance and inactivation profiles, (C) representative deactivating currents and (D) recovery from inactivation properties of cloned Ca_v3.1, Ca_v3.2 and Ca_v3.3 T-type channels exogenously expressed in HEK293 cells. (E) Table summarizing mean kinetic properties of the three T-subtypes at representative voltages. Redrawn with permission: Chemin et al. *J Physiol* 2002; 540:3–14.

(Fig. 3). At low frequency firing (~1 Hz) the three T-subtypes display biophysical responses similar to those described for single action potentials, since all seem to be fairly resistant to accumulating inactivation at this frequency. Contrastingly, at higher frequencies (e.g., at or above 10 Hz) the differing accumulated inactivation the T-type isoforms results in altered attenuation of calcium influx as the series of action potentials progresses. Ca_v3.1-mediated currents attenuate fastest, whereas Ca_v3.2 currents attenuate at a slower rate and Ca_v3.3 channels require high frequencies (>50 Hz) to exhibit any significant attenuation.^{9,10,14} Furthermore, at high frequencies (50–100 Hz) Ca_v3.3-mediated currents appear to show a facilitation of current amplitude over the first few action potentials, likely due to their slower activation and inactivation kinetics which results in greater current responses to action potentials that are further into the series. It should be noted that Ca_v3.2-mediated currents also display facilitation at very high frequencies (250 Hz).

The relative rates of repolarization also play an important role during repetitive action potential firing, wherein faster repolarization appears to induce an increased attenuation across a series of action potentials for Ca_v3.2 channels compared to the Ca_v3.1 and Ca_v3.3 isoforms.¹⁰ A further interesting facet concerning the activity of T-type channels during repetitive action potential firing concerns their relative sensitivity to rate of recovery from inactivation. It is well established that T-type channels display sensitivity to both membrane potential and the amount of time that conditioning pre-pulses are applied for prior to a test pulse. Of note, the different T-subtypes also display individual characteristics in response to whether the pre-pulse is accompanied by action potential firing. For example, Ca_v3.1 channels exhibit sensitivity to the duration of a series of action potentials applied on the crest of a mild (-55 mV) conditioning depolarizing step, with longer periods of firing inducing a slower rate of recovery from inactivation.¹⁴ Contrastingly, both the Ca_v3.2 and Ca_v3.3

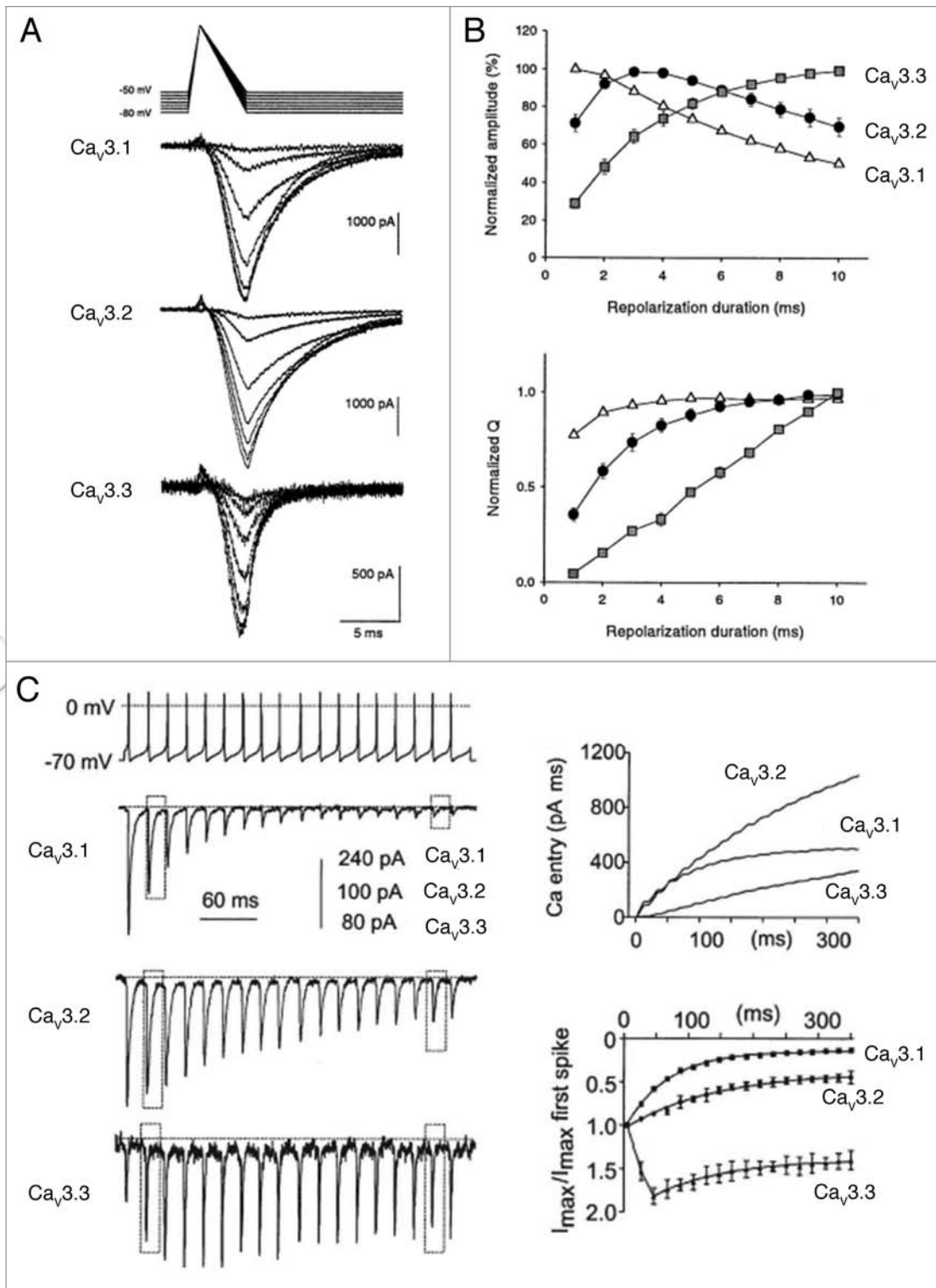


Figure 3. T-type calcium channel conductance during action potentials. (A) Response of $Ca_v3.1$, $Ca_v3.2$ and $Ca_v3.3$ T-type channels to mock action potentials at varying holding potentials. (B) Response of T-subtypes to mock action potentials with altered repolarization rates summarized with respect to current amplitude and charge transference. (C, left parts) Response of T-subtypes to action potential waveforms recorded from Purkinje neurons during repetitive tonic firing. (C, right parts) Summarized mean data from (C, left part) with respect calcium entry and maximum amplitude of T-current during tonic action potential firing. All figures display results from cloned T-type channels expressed in HEK293 cells. (A and B) Redrawn with permission: Kozlov et al. *Eur J Neurosci* 1999; 11:4149–58. (C) Redrawn with permission: Chemin et al. *J Physiol* 2002; 540:3–14.

isoforms appear insensitive to similar pre-conditioning stimuli, yet still display sensitivity to a continuous mild depolarization in the absence of action potentials.

T-type Channel Activity during Bursting

The involvement of T-type calcium channels in burst firing has been extensively investigated in a number of neuronal cell types and disease models, and their importance in this firing mode is well established.^{5,7,15-23} In short, depolarization activates T-type channels, which further depolarizes the membrane potential. If the density of T-type calcium channels is sufficient the depolarization will occur in a cascade manner producing a sharp positive shift in the membrane potential to approximately -40 mV.^{4,24-26} This in turn can activate sodium channels and action potentials are then able to fire at high frequency on the crest of the depolarization in a “burst” until small conductance calcium-activated potassium (sK) channels repolarize the neuron. The non-action potential portion of this process is known as a “low threshold spike” (LTS) and is critical for low threshold burst firing and wherein the longer magnitude and duration of the LTS correlates with action potential number.^{27,28} Each of the individual T-type isoforms are capable of generating an LTS,^{17,20,29} although a combination of T-type channels is likely often responsible (Fig. 4). For example, in thalamocortical neurons the majority of the LTS is generated by Ca_v3.1 channels,^{15,22,29,30} whereas in hippocampal CA1 neurons subjected to pilocarpine treatment to induce status epilepticus the majority of the LTS is generated by Ca_v3.2 channels.^{16,20,31} In neurons of the reticular thalamic nucleus (RTN), the LTS appears to be generated by a combination of Ca_v3.2 and Ca_v3.3 channels,^{21,32-34} and in centromedial thalamic neurons is thought to be carried by both Ca_v3.1 and Ca_v3.3 channels.¹⁵ Overall, the individual biophysical properties of T-type calcium channels likely determines the rate of depolarization and the duration of the LTS and the specific combinations of T-type isoforms is predicted to be crucial to burst physiology *in vivo*.

An elegant study combining cloned T-type channels expressed exogenously in HEK293 cells and action potential waveforms recorded from cerebellar Purkinje and thalamocortical and RTN neurons with dynamic clamp and computer modeling, examined the contribution of individual T-type isoforms to different types of bursts and correlated this with the predicted expression of T-type channels in each type of neuron.⁹ It was found that similar to tonic firing, Ca_v3.1-mediated currents attenuated quickest over the duration of a burst, closely followed by Ca_v3.2 currents, whereas Ca_v3.3 currents display very slow attenuation. Also similar to the responses recorded for tonic firing, Ca_v3.3 currents displayed a marked facilitation in the first few action potentials of a burst, reflecting the high frequency nature of burst firing. The burst firing in modeled Purkinje neurons and thalamocortical neurons closely followed the calcium conductance generated from Ca_v3.1 channels where these channels are predicted to generate the majority of the LTS. Computer modeling was also used to remove the contribution of native T-type channels from model thalamocortical and RTN neuronal bursts and to replace these with properties recorded from exogenously expressed T-type

channels (Fig. 4). With this approach the thalamocortical burst closely resembled that generated by Ca_v3.1 channels, producing a short and fast burst as seen in thalamocortical neurons. Contrastingly, the Ca_v3.2 and Ca_v3.3 subtype properties produced bursts of much longer duration, with the longest duration burst produced by Ca_v3.3 channels. Using the same method to examine RTN properties, it was shown that Ca_v3.3-mediated currents generated bursts that most closely correlated with the typical RTN burst. However, Ca_v3.2 channels are also expressed in the RTN and Ca_v3.2-like currents are observed in these neurons. In this regard, the fast activation kinetics and lower threshold for activation Ca_v3.2 channels may play a critical role in the initiation of bursts as well as make important physiological contributions that become apparent during a series of multiple bursts. A number of studies have examined the involvement of calcium-induced calcium-release (CICR) from the sarcoplasmic reticulum in shaping multiple burst firing.³⁵⁻³⁷ CICR-mediated inhibition of burst firing has been proposed to occur via inhibition of T-type channels in RTN neurons.³⁵ However, it is alternately suggested that this occurs due to CICR-mediated inhibition of the SK₂ channels necessary for after-hyperpolarization, as opposed to direct inhibition of T-type channels.^{36,37} Thus, under a series of multiple bursts, such as during neuronal oscillations, a progressive inhibition of SK₂ channels may prevent adequate hyperpolarization required for T-type channel de-inactivation. Overall, this topic remains to be fully explained and highlights the necessity to assess burst firing patterns as a multiple series and at different frequencies in order to truly elucidate the contributions of T-type channels to burst firing. Furthermore, how these bursts contribute to calcium influx in dendrites is a topic of intense research at present, with synaptic induction of burst firing seen as a potential encoder of spatial neuronal function.³⁷⁻³⁹

T-type Channel Window Currents and Neuronal Firing

The overlap between the activation, inactivation and deactivation voltage thresholds of T-type channels at certain membrane potentials results in a fraction of channels that are open at the resting potential, although the entire population constantly transitions between the open, closed and inactivated states (Fig. 4). The physiological roles of window currents has been difficult to ascertain since these are quite small (by calculation rarely more than 5% of the peak T-type current), however, a steady influx of calcium has been long predicted to make important contributions towards neuronal physiology.^{1,3,4,7,40,41} In particular, the window current has been implicated in the generation of slow (<1 Hz) sleep oscillations as a result of intrinsic “bistability” of thalamic neurons.^{3,5,42-45} In thalamic neurons, brief injections of positive or negative current have been shown to induce lasting depolarization or hyperpolarization of the steady resting membrane potential (~15–20 mV), respectively, although only when the “hyperpolarization-activated mixed sodium/potassium conductance” (I_h) is blocked to prevent switching between the two states.^{3,42} This is believed to arise from the complex interplay of the T-type window and leak potassium conductances, which can

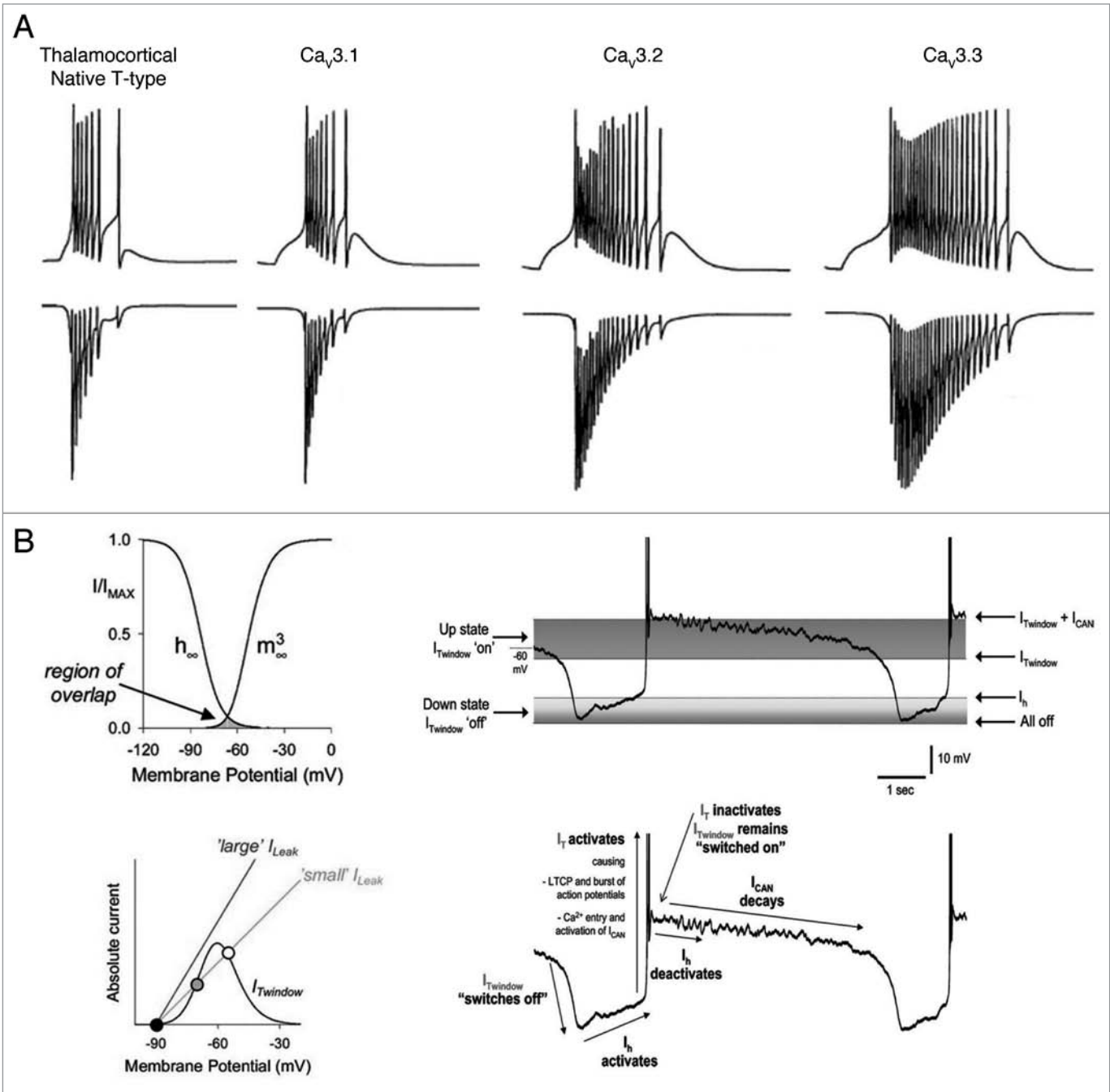


Figure 4. T-type calcium channel conductance during burst firing and slow oscillations. (A) In a computer generated model of a thalamocortical neuron the native T-type current was replaced with biophysical parameters of each of the cloned $Ca_v3.1$, $Ca_v3.2$ and $Ca_v3.3$ T-type currents determined from experiments in HEK293 cells. $Ca_v3.1$ generated short bursts, $Ca_v3.2$ slightly longer bursts and $Ca_v3.3$ very long sustained bursts (A, upper parts), each correlating with the current generated by the particular subtypes (A, bottom parts). (B, top left part) Schematic of typical T-type activation and inactivation graphs with window current highlighted in grey. (B, bottom left part) Diagram representing the bistable neuronal membrane potential as a result of the interplay between leak potassium conductances and the T-type window calcium conductance. (B, right parts) Schematics describing the activity of the hyperpolarization-activated sodium/potassium conductances (I_h), the calcium-activated non-specific cation conductance (I_{CAN}) and T-type window calcium conductance during slow oscillations. (A) Redrawn with permission: Chemin et al. *J Physiol* 2002; 540:3–14. (B) Redrawn with permission: Crunelli et al. *J Physiol* 2005; 62:121–9.

be balanced at distinct membrane potentials to create two stable voltages where the neuron rests (Fig. 4). If the leak conductance is too large or the T-type conductance too small then only a single point of balance is created and therefore only one resting

stable membrane potential exists. During slow oscillations in thalamocortical neurons additional depolarizing influences are provided by I_h and the “calcium-activated non-selective cation conductance” (I_{CAN}). I_h depolarizes the membrane from

a hyperpolarized voltage or “down state” where the window current is “off”, to a point where the T-type channels activate, generating a burst of action potentials (discussed above). While the majority of T-type channels then inactivate, the T-type window conductance remains on and together with I_{CAN} prolongs the low-threshold depolarization (“up state”) upon which tonic action potential firing can occur. This process continues until the repolarizing leak potassium conductances in combination with the decaying I_{CAN} result in hyperpolarization to a level outside the T-type channel window range and the window current fully inactivates (reviewed in ref. 42). Taken together, even the relatively small calcium conductance generated by the T-type channel window current can significantly influence neuronal firing patterns. High-threshold bursting has also been proposed to occur in thalamic neurons leading to generation of alpha and theta rhythms, although the true nature of this particular firing pattern is still somewhat unclear.^{5,46,47} These bursts occur at membrane potentials that are too depolarized to be generated by typical T-type currents, however it is predicted that high threshold bursting may in part result from calcium conductance through a small population of non-inactivated (i.e., window current) T-type channels. This may also occur via activation of mid-threshold (such as R-type) or HVA calcium channels, or may arise simply from poor space clamp wherein burst-firing in dendrites might relay a false reading of membrane potential at the location of recording.

Conclusions

The unique biophysical properties of T-type calcium channels bestow particularly important attributes with respect to neuronal firing rates and patterns. Their response to brief depolarization

and the calcium they conduct during action potentials not only provides a distinct charge transference compared to HVA calcium channels, but also allows for the fine tuning of conductance depending upon the nature of the T-type channel isoforms. The specific responses to action potentials can be extended to activity of the T-type channels during burst firing, wherein the expression of individual or multiple T-subtypes can result in a variety of differing burst patterns. This becomes more complicated when variable amounts of T-subtypes are co-expressed and even more so when T-type channel splice variants are considered. Indeed, T-type channel splice variants with distinct biophysical properties are known to be expressed temporally and spatially.⁴⁸⁻⁵¹ To perhaps further complicate matters, splice variation also appears to play an important role in disease pathology and it is becoming apparent that mutations associated with certain pathophysiological disorders have different functional effects in distinct variants.⁵²⁻⁵⁴ Taken together, the variety of responses that T-type calcium channels may contribute to particular firing patterns will likely vary considerably depending upon a combination of splice variant, developmental stage and disease state. Finally, the “passive” role played by T-type channel window currents in slow oscillations reveals another significant factor to be considered in the involvement of these channels in neuronal firing and their importance in physiological and pathophysiological processes.

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