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T-type calcium channels: From molecule to therapeutic opportunities

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ABSTRACT

T-type calcium channels serve an essential role in the functioning of the nervous system. They exhibit unique properties among voltage-gated calcium channels, and mediate specific roles in brain function. Over the recent years, it has come to light that a number of chronic neurological disorders arise from defects in T-type channel function. The question then arises as to whether T-type channels could represent a relevant druggable target. In this review, we introduce the diversity, molecular structure, and principal electrophysiological properties of T-type channels. Then, we highlight their role in neuronal development, and their pathophysiological role in the nervous system. Finally, we discuss the potential of T-type channels as therapeutic targets in light of recent advances in their pharmacopoeia.

1. Introduction

T-type calcium channels are low-voltage-activated channels that belong to the family of voltage-gated calcium channels (VGCCs) (Ertel et al., 2000). To our knowledge, the very first observation of the existence of a low-threshold voltage-activated calcium conductance, later named as T-type current, dates back to 1975 with the work of Hagiwara et al., in invertebrate starfish eggs (Hagiwara et al., 1975), followed by a long period where T-type currents were documented in a number of neuronal tissues (Carbone and Lux, 1984; Nowycky et al., 1985). By the end the 1990s, T-type channels were cloned (Perez-Reyes, 2003), allowing for their detailed biophysical characterization and examination of their expression patterns in the central and peripheral nervous system, while landmark studies have revealed the essential role of T-type channels in of neuronal network activities. Additionally, genetic studies have identified numerous pathological T-type channel variants, thus linking T-type channels to a number of chronic neuronal disorders including congenital forms of seizure disorders. Although the existence of T-type current blockers such as mibefradil (Ro 40–5967) was known long before the molecular cloning of T-type channels, much effort has been made over the last decade towards identification of novel classes of molecules that act as modulators of T-type channels with potential therapeutic use. In this minireview, we provide an overview of these multiple facets and discuss future directions in light of recent advances in the neuronal pathophysiology of T-type channels.

2. Diversity, structure, and function

In humans, three genes, *CACNA1 G*, *CACNA1H*, and *CACNA1I*, located on chromosomes 17, 16, and 22, respectively, encode for the three T-type channel isoforms $Ca_v3.1$, $Ca_v3.2$, and $Ca_v3.3$ (Fig. 1A). In addition, a number of splice variants have been identified and contribute to the molecular and functional diversity of T-type channels (Powell et al., 2009). Although the three T-type channel isoforms operate at hyperpolarized potentials, their rapid inactivation kinetics ($Ca_v3.1 > Ca_v3.2 > Ca_v3.3$) represent a specific signature of their molecular identity (Fig. 1A). In contrast to other VGCC members that form macromolecular complexes with additional ancillary subunits, T-type channels are exclusively formed by the main Ca_v3 pore-forming subunit. Although the high-resolution structure of T-type channels has not been resolved yet, and only a three-dimensional structure at 23 Å exists for $Ca_v3.1$ (Walsh et al., 2009), it is expected that their three dimensional folding resembles that of other $Ca_v\alpha_1$ subunits. Indeed, the Ca_v3 subunit putatively consists of four homologous domains, each of them made up of six transmembrane helices (S1 to S6) (Fig. 1B). The four domains (DI to DIV) are linked together with intracellular loops (I-II, II-III, and III-IV) between the S6 segment of the preceding domain and the S1 segment of the following domain. The pore of the channel is formed by the re-entrant extracellular regions (p-loops), connecting segments S5 and S6 of each domain, which contain four key acidic residues (glutamate or aspartate) that are responsible for the calcium selectivity. The voltage sensor is formed by the positively-charged arginine / lysine-rich S4 segments (Jurkovicova-Tarabova et al., 2018).

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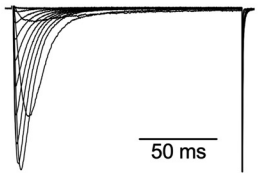
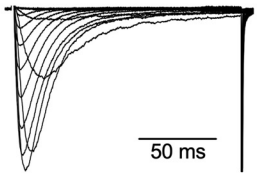
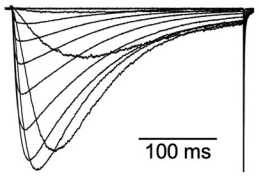
A

Channel	$Ca_v3.1$	$Ca_v3.2$	$Ca_v3.3$
Gene	*CACNA1G*	*CACNA1H*	*CACNA1I*
Chromosome	17	16	22
Current	T-type 	T-type 	T-type 

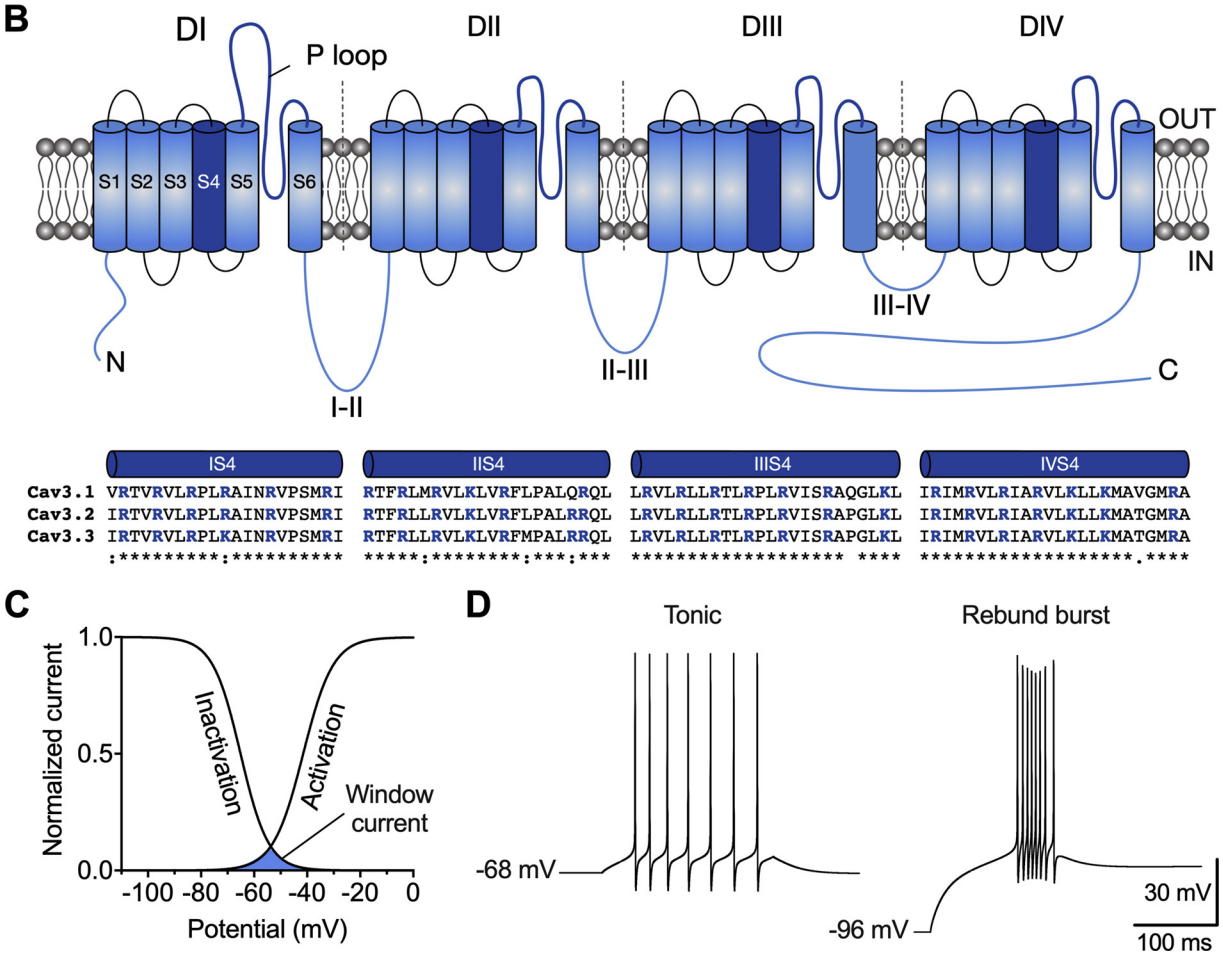


Fig. 1. Diversity, molecular structure, and electrophysiological properties of T-type channels. A. Diversity of T-type channel family comprising $Ca_v3.1$, $Ca_v3.2$ and $Ca_v3.3$. Chromosomal location of the genes is indicated in humans. B. Membrane topology of the Ca_v3-pore forming subunit. It consists of four repeats (DI to DIV) made up of six transmembrane helices (S1 to S6) and connected by cytosolic linkers (I-II, II-III, and III-IV). The arginine (R) / lysine (K)-rich S4 segments form the voltage sensor, whereas the re-entrant P-loops form the pore of the channel and provide calcium selectivity. C. Voltage dependence of activation and inactivation of T-type channels. The overlap (blue) represents the window current. D. Computational simulation of reticular thalamic neuron activity in response to 200 ms current injection of 100 pA (left panel, tonic firing), and −200 pA (right panel, burst firing) (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

At the functional level, T-type channels display unique properties. First openings of T-type channels occur at hyperpolarized membrane potentials near the foot of an action potential, which alter the electrogenic properties of the plasma membrane and therefore directly impact neuronal excitability. For instance, T-type channels are highly abundant in dendrites of thalamic and hippocampal neurons where they enhance subthreshold excitatory postsynaptic potentials, and sustain the propagation of the electrical signal to the cell body (Crandall et al., 2010). Additionally, expression of T-type channels in the axon initial segment influence the generation and timing of action potentials

(Bender and Trussell, 2009). The role of T-type channels in the control of neuronal excitability is further exemplified by their ability to modulate the activity of a number of calcium-activated potassium channels. For instance, T-type channels form a signaling complex with K_v4 (A-type) potassium channels that ensure K_v4 channels to function in a subthreshold membrane potential range to regulate neuronal firing (Anderson et al., 2010). A remarkable feature that arises from the voltage properties of T-type channels is the overlap between their voltage dependence of activation and inactivation where a tiny fraction of channels (not more than a few percent of the total population) remain open and create a "window" for calcium influx at rest (Fig. 1C). Although a window current is also observed with other voltage-gated calcium channel isoforms including L-type channels, T-type-dependent window current is unique in the sense that it occurs near to the resting membrane potential of nerve cells. The physiological role of the window current is not fully understood, it may support membrane potential bistability (Williams et al., 1997), *i.e.* the existence of two resting membrane potentials, a key cellular mechanism underlying the generation of slow (< 1 Hz) neuronal oscillations that occur for instance during sleep (Hughes et al., 2002). Another remarkable feature is the ability of T-type channels to generate calcium spikes upon membrane hyperpolarization, which directly lead to rebound burst firing of action potentials (Fig. 1D). This feature is particularly relevant in the function of the thalamocortical circuitry where the burst-firing mode of action potentials is involved in the genesis of spike-and-wave discharges that occur in absence epilepsy (Kim et al., 2001). Finally, T-type channels are also localized at presynaptic nerve terminals (Huang et al., 2011) and the observation that some neurons can release significant amounts of neurotransmitters near their resting membrane potential has uncovered a new role for T-type channels in the control of vesicular exocytosis (Weiss and Zamponi, 2013), possibly by virtue of their coupling to some of the molecular components of the vesicular release machinery (Weiss et al., 2012).

3. Trafficking of T-type channels

The trafficking of T-type channels to and from the plasma membrane represents an essential control mechanism of neuronal excitability, and a number of signaling pathways and molecules that govern this process have been identified (Weiss and Zamponi, 2017). For example, the actin binding protein kelch-like 1 (KLHL1) binds to and enhances surface expression of T-type channels (Aromolaran et al., 2010). Additionally, binding of Stac adaptor protein 1 (Stac1) to the amino-terminal region of $Ca_v3.2$ enhances surface expression of the channel (Rzhepetskyy et al., 2016b). Recently, it was reported that calnexin, an endoplasmic reticulum integral membrane protein, interacts with $Ca_v3.2$ to modulate the sorting of the channel to the plasma membrane (Proft et al., 2017). Importantly, this process was regulated by alternative splicing of the channel and was disrupted by a mutation that underlies absence seizures in Genetic Absence Epilepsy Rats of Strasbourg (GAERS) (Proft et al., 2017). Additionally, a role for post-translational modification was recently documented (Lazniewska and Weiss, 2017). For instance, asparagine (*N*)-linked glycosylation of $Ca_v3.2$ is essential for proper surface expression, stability, and gating of the channel (Weiss et al., 2013; Ondacova et al., 2016). In addition, N-glycosylation supports glucose-dependent potentiation of $Ca_v3.2$ surface expression (Lazniewska et al., 2016), a process that may potentially be relevant in the development of painful diabetic neuropathy. Consistent with this notion, *in vivo* pharmacological disruption of N-glycosylation reduced T-type currents and neuropathic pain in a rodent model of diabetes (Orestes et al., 2013). Surface expression of T-type channels is also regulated by the ubiquitin proteasome system (UPS). The ubiquitin ligase WWP1 and the counterpart ubiquitin protease USP5 were found to play an essential role in the control of $Ca_v3.2$ density in the plasma membrane of primary nociceptive fibers and spinal cord neurons, where *in vivo* disruption of $Ca_v3.2$/USP5 complex produced marked analgesia in various rodent models of inflammatory and neuropathic pain (García-Caballero et al., 2014).

4. T-type channels control neuronal growth and differentiation

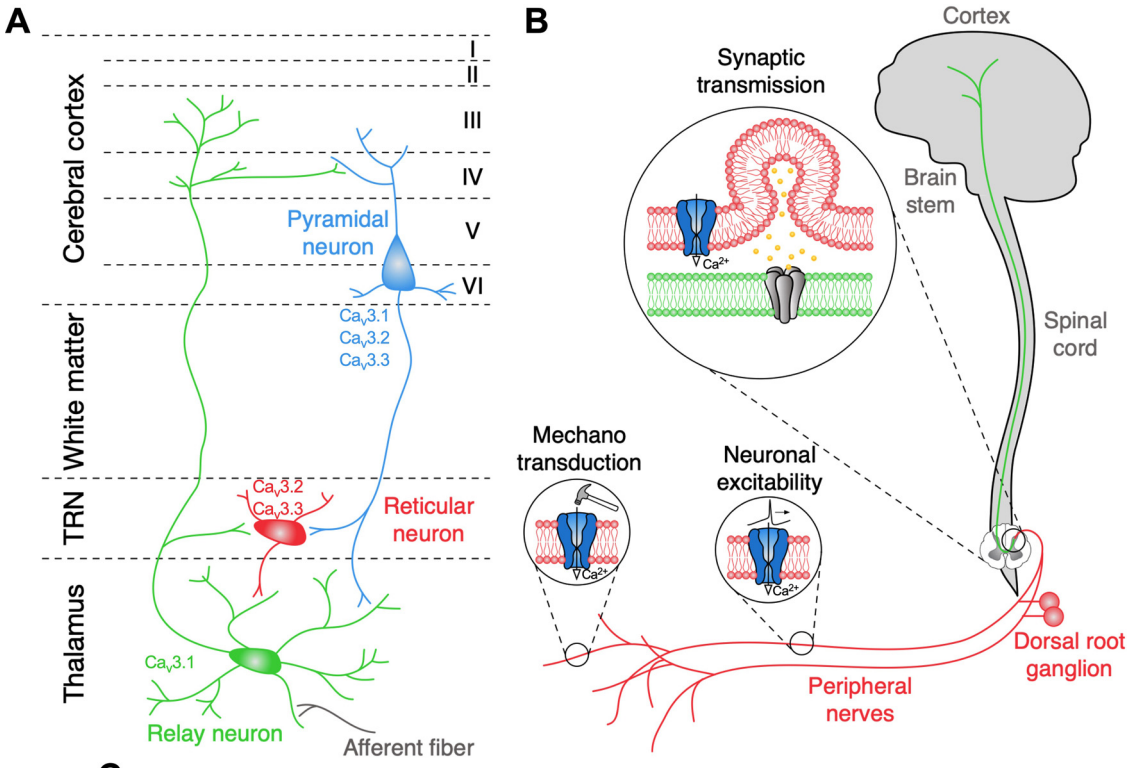
T-type channels are implicated in a number of neurodevelopmental processes including axonal and dendritic outgrowth, and also neuronal migration. For instance, they initiate highly localized Ca^{2+} oscillations that are essential for the expression of guidance molecules in migrating axons of chick embryonic motor neurons (Wang et al., 2009). More recently, it was reported that T-type channels mediate TNFα reverse signaling-induced axonal growth of sympathetic neurons (Kisiswa et al., 2017). Interestingly, T-type channels not only contribute to the morphological maturation of nerve cells, but also support the reshuffling of ion conductances during neuronal development. For instance, pharmacological or oligonucleotide-based knockdown of $Ca_v3.2$ in differentiating neuroblastoma NG108-15 cells alters development-dependent expression of high-voltage-activated (HVA) calcium channels (Chemin et al., 2002). This notion is further supported by the observation that hydrogen sulfite-evoked neurite outgrowth and expression of HVA channels in NG108-15 cells requires the activation of T-type channels (Nagasawa et al., 2009), presumably *via* an Src kinase-dependent signaling pathway (Tarui et al., 2010). Recently, an important role of T-type channels in the maintenance of neuronal progenitor cell viability was reported, suggesting a new paradigm for a role of T-type channels in neurodevelopmental or neurodegenerative disorders (Kim et al., 2018).

5. T-type channels in neurological disorders

Considering the essential role of T-type channels in the function of the nervous system, it is not surprising that alteration of T-type channel activity is linked to a number of neurological disorders. To date, the best-documented pathological implication of T-type channels is in absence epilepsy. T-type channels are present in thalamic relay neurons ($Ca_v3.1$), reticular thalamic neurons ($Ca_v3.2$ and $Ca_v3.3$), and cortical pyramidal neurons ($Ca_v3.1$, $Ca_v3.2$, and $Ca_v3.3$) (McKay et al., 2006) that together form a circuitry where T-type channels sustain oscillatory burst firing that is regarded as the underlying mechanism of spike-and-wave discharges that occur during absence seizures (Cain et al., 2018) (Fig. 2A). In addition, several genetic alterations in $Ca_v3.2$ have been identified in patients with absence epilepsy. Consistent with the notion that T-type channel activity underlies spike-and-wave discharges, these mutations generally cause a gain-of-function of the channel that in principle is expected to drive seizures.

A pathological role for T-type channel was also documented in peripheral neuropathic pain. It is well established that $Ca_v3.2$ channels are present within neurons of the dorsal root ganglia, where axonal $Ca_v3.2$ contribute to the excitability of afferent fibers. Expression of $Ca_v3.2$ was reported in nerve endings in skin hair follicles where they support the transmission of low-threshold mechanical signaling (François et al., 2015). Additionally, $Ca_v3.2$ channels are found in presynaptic terminal endings where they are implicated in excitatory synaptic transmission in the dorsal horn of the spinal cord (Jacus et al., 2012) (Fig. 2B). Interestingly, expression of $Ca_v3.2$ channels in primary afferent fibers appears to be highly plastic, and increased surface expression of $Ca_v3.2$ is associated with a number of chronic pain conditions arising from nerve injury, diabetes, and chemotherapy agents (Bourinet et al., 2014).

In contrast to the implication of T-type channels in absence epilepsy and neuropathic pain that appears to be related to an increased activity of the channels, loss-of-function mutations have been identified in several other neuronal disorders. For instance, loss-of-function mutations in $Ca_v3.2$ have been reported in patients with autism spectrum disorder (Splawski et al., 2006) and amyotrophic lateral sclerosis (Rzhepetskyy et al., 2016a). Similarly, a loss-of-function mutation in



C

Compound	Structure	Target	Main indications	Status
Ethosuximide (Zarontin®)		T-type	Epilepsy	Approved
Valproic acid (Depakene®)		T-type	Epilepsy, bipolar disorder	Approved
Zonizamide (Zonegrans®)		T-type	Epilepsy	Approved
Nimodipine (Nimotop®)		T-type L-type	Hypertension	Approved
Z944		T-type	Pain	Phase II
ACT-709478		T-type	Generalized epilepsy	Phase II

Fig. 2. Pathological aspects of T-type channels and pharmacology. A. Schematic representation of the thalamocortical circuitry comprised of thalamic relay neurons (green, expressing $Ca_v3.1$), thalamic reticular neurons (red, expressing $Ca_v3.2$ and $Ca_v3.3$), and cortical pyramidal neurons (blue, $Ca_v3.1$, $Ca_v3.2$, and $Ca_v3.3$), and involved in the generation of spike-and-wave discharges during epilepsy seizures. TRN, thalamic reticular nucleus. B. Schematic representation of the ascending pain neuraxis. Primary nociceptive fibers have their soma in the dorsal root ganglia and project onto the first relay neuron in the dorsal root of the spinal cord. $Ca_v3.2$ channels present in nerve endings contribute to the detection of mechanical stimuli, while axonal channels contribute to neuronal excitability and action potential propagation triggered by various kinds of nociceptive stimuli. Presynaptic $Ca_v3.2$ are implicated in synaptic transmission in the spinal cord. C. T-type channel modulators currently approved or in clinical trials. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this

$Ca_v3.1$ is linked to cerebellar ataxia (Coutelier et al., 2015), and loss-of-function mutations in $Ca_v3.3$ are associated with schizophrenia (Andrade et al., 2016). Although the underlying mechanisms linking T-type channels to these neuronal disorders remains largely hypothetical and remain to be explored in detail, these data highlight the large spectrum of disorders in which T-type channels may play a pathogenic role. Finally, a role for T-type channels in Parkinson's disease has recently emerged, where T-type channels appeared to contribute to rotenone-induced mitochondrial stress and apoptosis of dopaminergic neurons derived from patient iPSC cells (Tabata et al., 2018).

6. Are T-type channels druggable?

Considering the growing body of evidence linking T-type channels to various neurological disorders, the question has arisen as to whether T-type channels constitute suitable drug targets. *In vivo* studies have shown that direct pharmacological inhibition of T-type channels in rodent models of epilepsy and neuropathic pain may indeed represent an avenue for therapeutic intervention into neurological disorders involving altered T-type channel activity (Zamponi, 2016). However, expression of T-type channels is not restricted to the nervous system, raising the question as to whether systemic T-type channel modulators will affect biological functions outside of the nervous system. In that respect, $Ca_v3.3$ whose expression is much more restricted to the central nervous system compared to $Ca_v3.1$ and $Ca_v3.2$, may represent a more attractive target. Additionally, the existence of multiple T-type channel splice variants, whose expression patterns may possibly be limited to specific neuronal structures, may represent an additional opportunity for drug targeting, however, as most of these splice variations occur outside of the channel molecular determinants that are responsible for the binding of currently known channel modulators, this may prove challenging. Moreover, because of the high degree of homology among the Ca_v3 calcium channel family members, the development of Ca_v3 subtype specific inhibitors is not trivial. Alternatively, targeting the trafficking of the channel, which is more likely to differ between channel isoforms and their splice variants may represent an attractive opportunity. Indeed, such an approach is being pursued towards identifying disruptors of $Ca_v3.2$-USP5 interactions for the purpose of treating chronic pain (García-Caballero et al., 2014; Gadotti et al., 2015; Garcia-Caballero et al., 2016; Gadotti and Zamponi, 2018).

Currently, four T-type channel blockers have been approved for clinical use (Fig. 2C): Ethosuximide (Zarontin®) is a non-specific T-type channel blocker with additional blocking activity on sodium and calcium-dependent potassium channels indicated for the symptomatic treatment of epilepsy; Valproic acid (Depakene®) and Zonizamide (Zonegrans®) are non-specific T-type channel blockers also indicated for epilepsy; and Nimodipine (Nimotop®) is a dual T-type and L-type channel blocker indicated for hypertension with possible indication in febrile seizures. Finally, two T-type channel blockers, Z944 and ACT-709478, for which the specificity remains to be further investigated in native tissues, are currently in phase II clinical trials for pain and generalized epilepsy, respectively. Many additional T-type channel inhibitors have been identified and tested in preclinical studies for pain (Snutch and Zamponi, 2018), and it remains to be seen whether any of these compounds will enter and pass clinical studies. ABT-639, a peripherally acting T-type channel inhibitor has failed multiple clinical trials for pain (Serra et al., 2015; Wallace et al., 2016), thus underscoring the difficulties in bringing new T-type channel blocking analgesics to market.

7. Concluding remarks

In this review, we presented the key functional aspects of T-type channels and their inherent implication in specific activities of the nervous system. It is also apparent that T-type channels are causally linked to a number of neurological conditions that derive from increased activity of T-type channels, and this has led to the pursuit of selective blockers for the treatment of epilepsy and neuropathic pain. However, over the recent years, it has also emerged that loss of T-type channel activity may equally contribute to conditions such as schizophrenia, autism spectrum disorders, and amyotrophic lateral sclerosis. Although the detailed mechanisms by which T-type channels contribute to these disorders remain to be exposed, the question arises as to whether T-type channel blockers that have shown promising outcomes for the symptomatic treatment of epilepsy may perhaps present additional risks when used chronically.

Author contributions

N.W. and G.W.Z. contributed to literature review analysis and preparation of the manuscript.

Competing interests

The authors have declared that no conflict of interest exists.

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