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T-Type Channel Druggability at a Crossroads

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ABSTRACT: Low-voltage activated T-type calcium channels mediate essential functions in the nervous system, and alteration of channel activity is causally linked to a number of neurological conditions. Therefore, T-type channels hold great promise as pharmacological targets for new medicines. In this Viewpoint, we discuss the potential of T-type channels as druggable targets and reevaluate the strategies available for developing therapeutically efficient and specific modulators of this channel.

KEYWORDS: *Calcium channels, T-type channels, Ca_v3 channels, pharmacology, drug discovery, neuron, epilepsy, neuropathic pain*

Through their ability to pass calcium ions across the plasma membrane of cells, voltage-gated calcium channels are essential regulators of a wide range of calcium-dependent cellular processes and physiological functions in electrically excitable cells. These include neurons, myocytes, and pancreatic β-cells, and also in many nonexcitable cells such as endocrine cells, endothelial cells, osteoblasts, and lymphocytes. The T-type calcium channel subfamily comprises three distinct isoforms: $Ca_v3.1$, $Ca_v3.2$, and $Ca_v3.3$.[1] T-type channels are unique among voltage-gated calcium channels in the sense that they operate at negative voltages near the resting membrane potential of nerve cells. This aspect is exemplified by their ability to generate low-threshold calcium spikes and bursts of action potentials that underlie rhythmic activities in a number of neuronal circuits. Although T-type channels inactivate rapidly within tens of milliseconds, their slow deactivation supports a large tail current that allows significant calcium influx following an action potential. In addition, because of the overlap between their voltage-dependences of activation and inactivation, a small fraction of T-type channels remain open at rest, providing a permeation route for calcium entry. This so-called "window" current is important even in relatively depolarized conditions such as in vascular smooth muscle cells.

Ethosuximide (Zarontin) is one of the earliest known clinically used T-type calcium channel blockers and was approved in 1960 for the treatment of absence epilepsy, even though at this time, T-type calcium channels had not yet been discovered. After the discovery of T-type calcium channels in the mid 1970s, the T-type calcium channel blocker mibefradil (Posicor) with vasodilatator activity was developed in the early 1990s and prescribed for the treatment of hypertension and chronic angina pectoris before it was withdrawn due to life-threatening interactions with cytochrome P450. The molecular cloning of T-type calcium channel genes not only provided new and important insights into the roles of these channels in pathophysiology, but also facilitated the development of drug molecules acting on these channels. For example, in the early 2000s, the first evidence that genetic variation of *CACNA1H* encoding for $Ca_v3.2$ channels is associated with generalized epilepsy opened up a new era. Over 30 potentially pathogenic variants have since been identified with a subset causing a gain-of-function of the channel. In parallel, it has emerged that increased expression of $Ca_v3.2$ channels in primary afferent nociceptive fibers is one of the mechanisms underlying chronic pain conditions. With this growing body of evidence linking $Ca_v3.2$ channels to neurological conditions, T-type channels have emerged as one of the most highly regarded druggable targets of the past decade, as evidenced by 43 patents published between 2012 and 2018 that describe new small organic molecules blocker of T-type channels.[2] However, despite of the growing arsenal of molecules with T-type channel blocking activity, the last approval of a drug molecule with T-type channel activity was zonizamide (Excegran) that was introduced in Japan in 1989 for the treatment of epilepsy. There are at least two reasons for this lack of progress: (i) the exofacial side of T-type channels exhibits a high degree of homology with other voltage-gated calcium channel members, and even with voltage-gated sodium channels, thus rendering the design of selective T-type channel blockers problematic; and (ii) T-type channels, in addition to being widely expressed in the nervous system, are found in a number of other tissues including cardiovascular cells, endocrine cells, spermatogenic cells, and immune cells.[3] Therefore, not only is it a considerable challenge to design specific T-type channel blockers, but the task is rendered even more demanding when these molecules also need to be tissue specific. Indeed, there have been several recent failures of T-type calcium channel blockers in preclinical and clinical studies for neurological disorders. For example, ML218, a drug candidate for Parkinson's disease, failed to pass preclinical tests in MPTP-treated parkinsonian monkeys. Ethosuximide, despite to be approved for the treatment of epilepsy, failed a clinical trial for the treatment of neuropathic pain because of many adverse effects. Similarly, ABT-639, despite acceptable tolerance, failed clinical trials for the treatment of pain due to lack of effectiveness. And finally, MK-8998 proposed for the treatment of acute psychosis in patients with schizophrenia was

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rejected for lack of efficacy. In spite of these failures, two compounds, Z944 and ACT-709478, are currently pursued in phase II clinical trials for the treatment of pain and generalized epilepsy, respectively[4] (Figure 1).

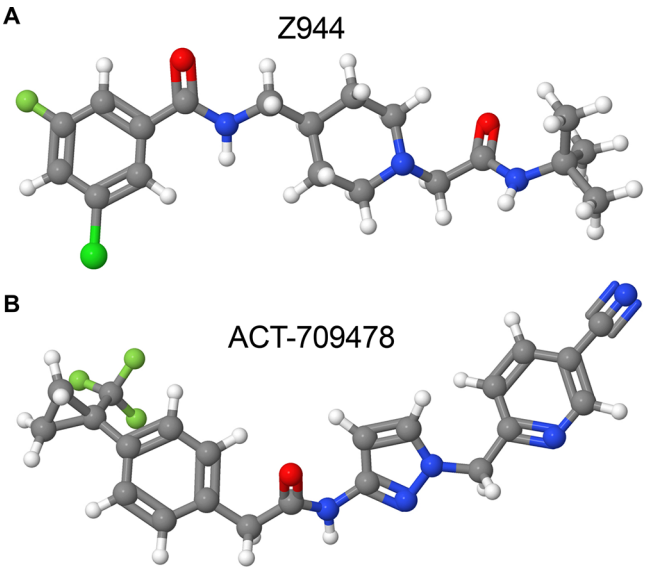

Figure 1. Two pan-T-type channel blockers currently evaluated in clinical trial. (A) Z944 (Taro Pharmaceutical Inc.) is a piperazine derivative evaluated (phase II) for the treatment of pain including peripheral and central neuropathic pain, musculoskeletal pain, inflammatory pain, visceral pain, and acute pain. (B) ACT-709478 (Idorsia Pharmaceuticals Ltd.) is a heteroaromatic amide evaluated (phase II) for the treatment of generalized epilepsy.

Since most studies linking T-type channels to epilepsy and neuropathic pain have advanced the idea of a gain-of-function of the channel as the underlying disease mechanism, much effort has been devoted to the development of molecules with T-type channel blocking activity. However, this notion was recently challenged by a number of reports suggesting that loss-of-channel function may be equally pathogenic. For instance, mutations in *CACNA1H* consistent with a loss-of-function of $Ca_v3.2$ were reported in individuals with autism spectrum disorders, schizophrenia, and amyotrophic lateral sclerosis. In addition, it was suggested that an age-dependent decrease of $Ca_v3.1$ expression in a mouse model of Alzheimer's disease might be a trigger of amyloid-β production. Along these lines, the T-type channel enhancer SAK3 that promotes T-type channel activity via a calcium/calmodulin-dependent protein kinase II pathway improves cognitive impairment and inhibits amyloid-β deposition.[5] Finally, a recent study reported a role for T-type channels in the maintenance of neuronal progenitor cell viability suggesting that alteration of T-type channels could possibly contribute to neurodevelopmental disorders. The question then arises as to whether chronic long-term use of drug molecules with T-type channel blocking activity could place patients at increased risk for neurodegenerative conditions. This aspect will require particular attention in future clinical evaluations of these molecules.

Are there additional ways to target T-type channels in a more specific and safe manner? At least three avenues may deserve consideration (Figure 2). First, numerous T-type channel splice variants, especially the $Ca_v3.2$ channel isoform, have been documented. Although these splice variants require further investigation in terms of their functional characteristics, it is a possibility that some variants may present a more restricted tissue distribution, raising the possibility that a splice isoform selective T-type calcium channel modulator might exhibit a wider safety profile. Second, several disorders such as epilepsy and pain are characterized by aberrantly increased neuronal excitability. Hence, the development of state-

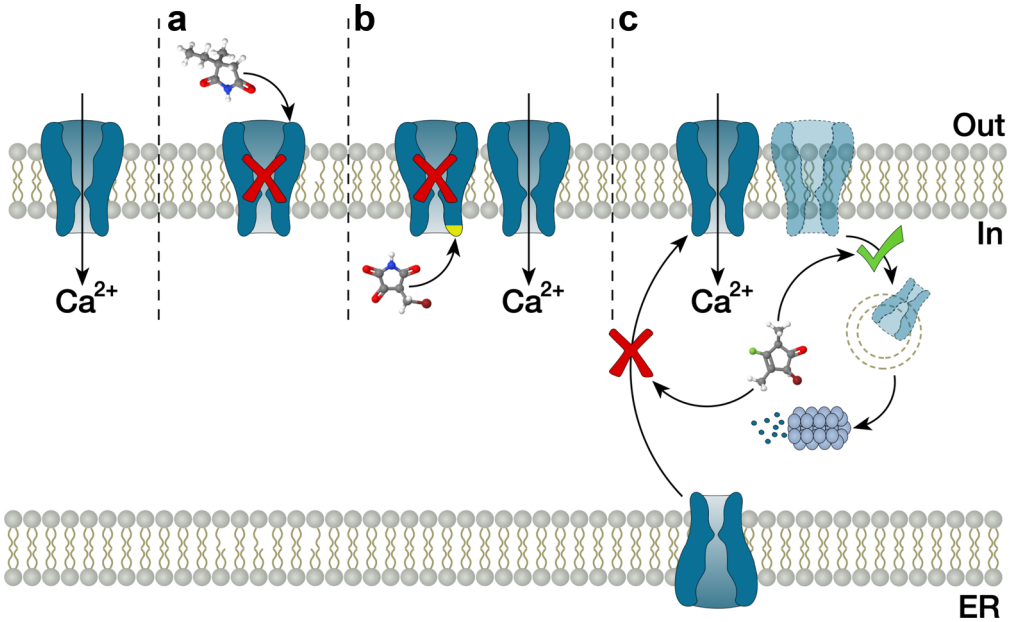

Figure 2. Targeting strategies for T-type channels. As an alternative to exofacial targeting of T-type channels by small molecules (a), T-type channel activity may be disrupted using molecules targeting endofacial molecular structures involved in the gating and/or regulation of channel activity (b). Additionally, small molecule disruptor of channel trafficking by preventing the sorting of the channel to the plasma membrane and/or enhancing its internalization from the plasma membrane represent a promising strategy to modulate the density of the channel at the cell surface (c).

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dependent channel modulators may provide for an opportunity to selectively target such dysregulated brain circuits. For instance, a state dependent blocker might be able to preferentially inhibit T-type calcium channels in the thalamocortical circuitry compared to electrically nonexcitable cells such as immune cells where calcium entry may be governed mostly by the window current. Third, in contrast to the exofacial side of T-type channels, the endofacial structures are much more variable between other channel isoforms and therefore may allow for a more specific targeting of the channel, directly or indirectly via signaling pathways modulating T-type channel expression and/or activity. This approach has already shown promising outcomes where inhibition of T-type channel surface expression by targeting of $Ca_v3.2$/USP5 interactions produced analgesia in various animal pain models.[4]

Altogether, T-type calcium channels hold great promise as pharmacological targets for new generation antiepileptic and analgesic drugs, and possibly for other neurological conditions. The rational design of pharmacological modulators combined with our growing understanding of the cellular pathways and molecular actors controlling the expression of T-type channels will determine the best approach for targeting these channels in a safe and effective manner.

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Notes

The authors declare no competing financial interest.

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