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# Voltage-gated calcium channels in epilepsy

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## Summary

**Voltage-gated calcium channels contribute to the control of excitability at both the cellular and neural network levels. Alterations in the expression or biophysical properties of specific subtypes of calcium channels can have pathophysiologic effects on the frequency and patterns of action potential firing and causally contribute to epileptic seizures. For an expanded treatment of this topic see *Jasper's Basic Mechanisms of the Epilepsies, Fourth Edition* (Noebels JL, Avoli M, Rogawski MA, Olsen RW, Delgado-Escueta AV, eds), published by Oxford University Press (available on the National Library of Medicine Bookshelf [NCBI] at www.ncbi.nlm.nih.gov/books).**

**KEY WORDS: Absence, Burst firing, Electrical excitability, Gain of function mutations, Intracellular signaling, Seizures, Thalamocortical circuitry, T-type calcium channels.**

Voltage-gated calcium channels are integral membrane proteins that mediate calcium influx that both controls electrical excitability and regulates calcium-sensitive intracellular signaling pathways. Although the substrates underlying the genesis and maintenance of seizures remain to be fully understood, burst-firing in the thalamocortical circuitry is known to be evoked by activation of low-voltage–activated (T-type) calcium channels (Contreras, 2006) and is thought to give rise to spike-wave discharges associated with absence epilepsy (Zamponi et al., 2010). The altered expression of T-type as well as P/Q-type and R-type calcium channels has been associated with several animal models of seizure. Many of the prescribed antiepileptic drugs have been shown to inhibit calcium channel activity, although these agents typically interact with multiple molecular targets (Weiergraber et al., 2010). Consequently, it is has been difficult to define the exact contributions of individual calcium channel subtypes using pharmacologic tools alone. More recently, gain-of-function mutations have been identified in a subset of calcium channel genes from both epilepsy patients and animal models of epilepsy, providing useful tools for elucidating the underlying involvement of calcium channel isoforms in disease pathophysiology (Adams & Snutch, 2007).

The mammalian genome contains genes for three distinct T-type calcium channels, $Ca_V3.1$, $Ca_V3.2$, and $Ca_V3.3$, and naturally occurring rodent genetic models of absence epilepsy have revealed that at least the $Ca_V3.1$ and $Ca_V3.2$ subtypes play critical roles in disease etiology. Elevated T-type channel activity within the thalamocortical network is sufficient to trigger spike-wave discharges causally related to absence seizures. Upregulation of T-type channels is also observed in the hippocampus of rodents in the pilocarpine pharmacologic model of temporal lobe epilepsy. Given the unique distributions of T-type calcium channel subtypes and their contributions to higher brain functions, the selective pharmacologic blockade of T-type calcium channel subtypes may provide attractive targets for the development of future therapeutic treatments.

## Disclosure

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