T-type calcium channels in health and disease

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T-type or low voltage-activated calcium channels are ubiquitously expressed in mammalian excitable cells. They are distinguished from high voltage-activated channels by low voltage threshold for activation. Therefore, these channels are able to initiate so-called low voltage calcium spikes and to contribute to specific types of excitability in neurons or in sinoatrial nodus cells. In health these channels regulate cardiac pacemaking or thalamocortical sleep rhythm. Their mutations underlie certain channelopathies, e.g., various types of epilepsy or bradycardia. The knowledge of the precise mechanisms that control the gating of LVA channels will potentially open new possibilities for the treatment of frequent disorders.

Voltage-gated calcium channels (VGCC) including LVA channels are composed of four homologous domains, each containing six transmembrane segments S1-S6 and a pore loop (P) between segments S5 and S6. Four voltage-sensing domains each composed of the transmembrane segments S1 - S4 are placed peripheral to a central pore domain formed by four sets of S5-P-S6. Most important role in Ca_v3 channel activation and inactivation has the voltage sensor in the domain III while than in the domain IV lacks a crucial role. The voltage sensors in domains I and II contributed intermediately to channel gating.

In addition to the low voltage activation threshold of Ca_v3 channels, the nonlinear charge movement reflecting conformational changes of the S4 segment in the putative voltage sensor of the channel i) precedes the ion current reflecting pore opening by less than 10 mV; and ii) only about 20% of the total charge is moved when inward current activation is already saturated. These peculiar features lead to a hypothesis that the pore of T-type calcium channel may be partly open before its voltage sensor is fully transferred into an activated state. Such interpretation is supported by recent discovery of the gating brake in the I-II loop of the $Ca_v3.2$ channel. This putative gating brake may prevent Ca_v3 channels from opening at membrane voltages close to cell resting potential as minimal movements of voltage sensor are sufficient for full opening of the conductive pore.

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