Voltage Gated Calcium Channels: Gating, Conductance, and Pharmacology at Atomic Resolution

William A. Catterall

Department of Pharmacology, University of Washington, Seattle, WA 98195-7280 USA

Voltage-gated sodium channels initiate action potentials, and voltage-gated calcium channels initiate neurotransmission, secretion, contraction, and many other physiological processes. Discovery of their bacterial ancestors, including NavAb, allowed us to determine the structural basis for voltage-dependent activation, selective calcium conductance, and calcium antagonist drug action. Structural studies support a sliding-helix mechanism of voltage-dependent activation, in which gating charges in the S4 transmembrane helix move across the membrane through the protein structure, exchange ion-pair partners, and initiate a conformational change to open the pore. Electromechanical coupling is mediated by the S4-S5 helical linker that connects the voltage-sensing module to the pore-forming module. Pore-opening is mediated by subtle rotation and bending of the pore-lining S6 helices to open the activation gate at their intracellular ends to an orifice of ~10.5 Å. Voltage-dependent inactivation involves partial collapse of the pore, in which two S6 segments move toward the central axis. Rapid and selective ion conductance is mediated by an ion selectivity filter that is ~4.6 Å wide and water-filled. Mutation of three negative charges to give the construct CavAb changes ion selectivity 12,000-fold to Ca:Na=400. Calcium is conducted as a partially hydrated cation. It interacts first with a square of glutamate sidechains, which catalyze inward movement of partially hydrated calcium ions with a dunking motion. Calcium then binds to two additional coordination sites formed by backbone carbonyls. High-resolution structures reveal the mechanism of ion conduction and selectivity through interactions of hydrated calcium ions with sites in the extracellular vestibule and selectivity filter. High-affinity calcium binding prevents monovalent cation permeation, and alternating occupancy of three calcium-binding sites generates a knock-off effect and mediates rapid and selective conductance. Calcium channels are drug targets for arrhythmia, hypertension, and angina pectoris. We imaged CavAb with phenylalkylamine, benzothiazepine, and dihydropyridine calcium-antagonist drugs bound to their receptor sites. Verapamil and diltiazem bind to overlapping sites in the central cavity of ion permeation pathway, just on the intracellular side of the selectivity filter. Dihydropyridines bind to an allosteric site on the lipid-facing surface of the pore, creating an asymmetric pore structure with calcium tightly bound in a blocking position. These two separate binding sites reveal why verapamil and diltiazem mediate frequency-dependent block and are effective in treating

cardiac arrhythmias, whereas dihydropyridines mediate voltage-dependent block and are effective in treatment of hypertension and angina pectoris. Supported by research grants from NINDS and NHLBI, National Institutes of Health, USA.