Structure, Function, and Pharmacology of Na^+ and Ca^{2+} Channels at Atomic Resolution

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All rapid physiological processes are triggered by electrical signals. Voltage-gated sodium channels initiate action potentials and voltage-gated calcium channels initiate contraction, secretion, neurotransmission, and more. Dysfunction of these channels causes epilepsy, autism, migraine, periodic paralysis, cardiac arrhythmia, and chronic pain. Recent discovery of bacterial ancestors of sodium and calcium channels, including NavAb, has allowed us to determine the structural basis for voltage-dependent activation, inactivation, and rapid, highly selective ion conductance at atomic resolution. Rapid and selective ion conductance is mediated by an ion selectivity filter that is short, ~4.6 Å wide, and water-filled, with four negative charges surrounding the ion-conduction pathway. Molecular dynamics studies show that sodium is conducted as a hydrated cation and interacts sequentially with three sites in the ion selectivity filter during conduction. Addition of two more negative charges to give the CavAb construct changes ion selectivity 12,000-fold, from Ca:Na=0.03 to Ca:Na=400. Addition of a single negative charge on the extracellular side of the high field-strength site accounts for a 1000-fold increase in calcium selectivity by itself. The high-resolution structures of CavAb and mutants reveal the mechanism of ion conduction and selectivity through interactions of the hydrated calcium ion with sites in the extracellular vestibule and three ion coordination sites within the selectivity filter. High affinity calcium binding prevents monovalent cation permeation, and alternating occupancy of the three calcium binding sites generates a knock-off effect and mediates rapid and selective calcium conductance. Sodium and calcium channels are targets for drugs used for pain, epilepsy, arrhythmia, hypertension, and angina pectoris. Local anesthetics and calcium antagonist drugs are effective inhibitors of NavAb and CavAb, and we have now imaged CavAb with blocking ions and with phenylalkylamines and dihydropyridine calcium antagonist drugs bound to their separate receptor sites at atomic resolution. Blocking ions lodge at the high field strength in the ion selectivity filter. Verapamil and other phenylalkylamines are also direct pore blockers, which bind in the ion permeation pathway just on the intracellular side of the ion selectivity filter. In contrast, dihydropyridines are allosteric inhibitors and bind to a site on the lipid-facing surface of the pore domain. Their binding induces a conformational change that creates an asymmetric pore structure with a calcium ion tightly bound in a blocking position, thereby revealing a unique allosteric mechanism for inhibition of an ion channel. The binding sites for sodium-channel-blocking local anesthetics and antiarrhythmic drugs are now being elucidated at atomic resolution, with important implications for structure-based drug design.