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Crystallographic studies of voltage-gated sodium and calcium channels

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Voltage-gated ion channels (VGICs) mediate electrical signaling within the nervous system and regulate a wide range of physiological processes. Voltage-gated sodium (Nav) channels are responsible for initiating action potentials and their rapid activation, sodium selectivity, and drug sensitivity are unique among VGICs. Nav channels are the molecular targets of drugs used in local anaesthesia and in the treatment of genetic and sporadic Nav channelopathies including inherited epilepsy, migraine, periodic paralysis, cardiac arrhythmia, and chronic pain syndromes. Recent crystal structures of a Nav channel from the bacterium Arcobacter butzleri (NavAb) have revealed surprising insights into the structural basis for voltage-dependent activation, sodium selectivity, drug block, and slow inactivation (1,2). The available structures of NavAb will be described alongside complementary functional and molecular dynamic studies. Distinct from Nav channels, the closely related voltage-gated calcium (Cav) channels initiate processes such as synaptic transmission, muscle contraction, and hormone secretion in response to membrane depolarization. Cav channels catalyze the rapid and highly selective influx of calcium ions into cells despite a 70-fold higher extracellular concentration of sodium. By grafting a Cav channel selectivity filter onto NavAb, crystallographic and functional analyses of the resulting CavAb channel will be described that have revealed a multi-ion selectivity filter which establishes a structural framework for understanding the mechanisms of ion selectivity and conductance in vertebrate Cav channels (3).

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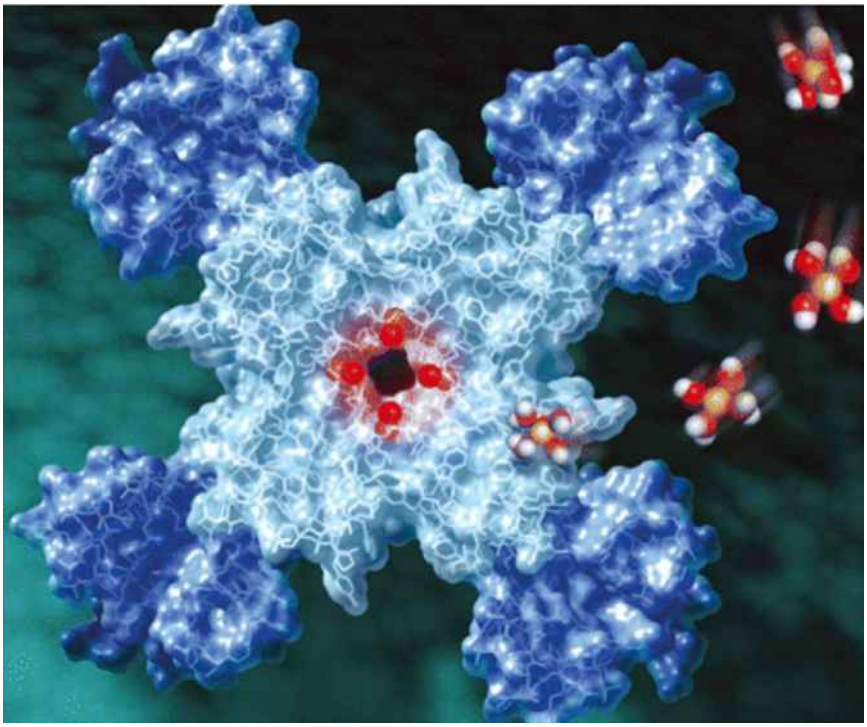

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