Relating structure to function in HCN channels

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Hyperpolarization-activated cyclic nucleotide-gated (HCN) channels are the molecular determinants of the If/Ih current, a mixed Na+/K+ current that controls pacemaking in cardiac and neuronal cells. HCN channels are activated by membrane voltage hyperpolarization, and conduct an inwardly directed cation current, which slowly depolarizes pacemaker cells to the threshold for action potential firing. In addition to voltage, HCN channels are modulated by the second messenger cAMP, which enhances channel open probability. How the two signals are integrated by the protein contribute to pore opening is still an open question. We have recently solved the structures of HCN4, the cardiac isoform, with and without cAMP bound by single particle cryoEM. From their comparison we could identified conformational transitions occurring upon cAMP binding and functionally validated them by patch clamp and computational methods. Our data indicate that HCN4 channels undergo a complex mechanism of gating, experiencing multiple closed states before the voltage-operated opening step. Precise structural knowledge of this channel will allow screening for isoform-specific and state-dependent inhibitors.