Insights into the structural basis of inactivation of HERG K^+ channels

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Potassium channels encoded by the *human ether-a-go-go-related gene* (HERG) have unusual kinetics, most notably slow activation but very rapid inactivation. These kinetic features are critical for the role these channels play in normal cardiac repolarization and suppression of arrhythmias initiated by premature beats. We have used a combination of NMR spectroscopy, CD spectroscopy, site-directed mutagenesis and electrophysiology to probe the molecular and structural basis of inactivation in HERG channels. Our NMR studies of the outer pore domain of HERG have identified two unusual features of HERG channels compared to other K^+ channels. First, the outer pore domain contains an additional amphipathic α-helix; and second, the pore helix domain of HERG extends significantly further into the extracellular space than the homologous domain in the K^+ channels for which the 3-dimensional structures are known. Our electrophysiology studies, in combination with site-directed mutagenesis, have shown that both of these regions are critical for normal inactivation of HERG channels. Our CD studies of the outer pore domain have revealed that the novel amphipathic α-helix is thermally labile; this correlates well with the temperature dependence of inactivation of HERG as well as the temperature dependence of toxin binding to the channels. These studies provide a basis for toxin footprinting and other investigations of the 3-dimensional structure of the outer pore domain of HERG and hence to define its kinetic mechanism of operation.