Voltage-sensing domain mode shift is coupled to the activation gate by the N-terminal tail of hERG channels

P.S. Tan,[1] M.D. Perry,[1] C.A. Ng,[1,2] J.I. Vandenberg[1,2] and A.P. Hill,[1,2] [1]Molecular Cardiology and Biophysics Division, Victor Chang Cardiac Research Institute, 405 Liverpool Street, Darlinghurst, NSW 2010, Australia and [2]St Vincent's Clinical School, University of New South Wales, NSW 2052, Australia.

The cytoplasmic N-terminal domain of human-ether-a-go-go related gene (hERG) K^+ channel is responsible for regulation of slow deactivation kinetics of the channel. However, the mechanism of how this occurs, and the connection between voltage sensor domain (VSD) return and closing of the gate are unclear. To examine this relationship we have used voltage clamp fluorometry to simultaneously measure VSD motion and gate closure in N-terminally truncated constructs. On prolonged depolarization, VSD movement is shifted to more hyperpolarized potentials and this behaviour is referred to as a 'mode shift'. We report that mode shifting of the hERG channel's VSD results in a corresponding shift in the voltage-dependent equilibrium of channel closing and that at negative potentials, coupling of the mode shifted VSD to the gate defines the rate of channel closure. Deletion of the first 25 amino acids from the N-terminus of hERG channel does not alter mode shifting of the VSD, but uncouples the shift from closure of the cytoplasmic gate. Based on these observations we propose the N-terminal tail as an adapter that couples voltage sensor return to gate closure to define slow deactivation gating in hERG channels. Furthermore, since the mode shift occurs on a timescale relevant to the cardiac action potential, we suggest a physiological role for this phenomenon in maximizing current flow through hERG channels during repolarization.