The S4 domain is directly involved in determining the voltage sensitivity of Kv11.1 channel inactivation

M.D. Perry, S. Wong, C.A. Ng and J.I. Vandenberg, Victor Chang Cardiac Research Institute, 405 Liverpool Street, Darlinghurst, NSW 2010, Australia.

Perturbation to cardiac ion channel function, whether caused by mutations or drug block, significantly increases the risk of cardiac arrhythmias. Kv11.1 channels, one of the major contributors to cardiac repolarization, undergo rapid and voltage dependent inactivation, which is critical for maintenance of the plateau phase of the action potential. Drug block of Kv11.1 channels is also facilitated by channel inactivation. Despite the clear importance of inactivation gating to Kv11.1 channel physiology and pathophysiology, there is scant information about the dynamic changes in the protein that underlie the intrinsic voltage dependence of this gating process. Here, using the protein engineering technique of phi-value analysis, we show that hydrophobic residues, but not the charged residues, within the voltage sensor domain play a critical role in regulating the voltage dependence of channel inactivation. Furthermore, our data suggest that hydrophobic inter-subunit interactions involving the fourth and fifth transmembrane domains are critical for the allosteric communication between the voltage sensor and pore domains that results in the selectivity filter collapse that underlies inactivation. These results provide a specific mechanism to explain the intrinsic voltage dependence of Kv11.1 channel inactivation. More generally, in addition to the role played by charged residues within the voltage sensor, our results highlight an important role for hydrophobic interactions between adjacent transmembrane domains in the regulation of channel gating.