

How does the membrane electric field gate an ion channel open and close?

Francisco Bezanilla, Departments of Physiology and Anesthesiology. University of California at Los Angeles, Los Angeles, CA, U.S.A.

Voltage dependent sodium and potassium channels are responsible for the generation and propagation of the nerve impulse. Voltage dependence is achieved by the translocation of about 12 e across the membrane field. The movement of this charge generates a transient current called gating current that precedes channel opening. Most of the gating charge is located in the first most extracellular arginines of the fourth transmembrane helix (S4 segment) found in voltage-gated channels. Accessibility studies with protons in mutants that replace the arginines by histidine, reveal that those residues are alternatively exposed to the inside at hyperpolarized potentials and outside at depolarized potentials because the histidine-replaced voltage sensor can act as a proton transporter. The most extracellular site generates a proton pore in the closed state, indicating that the electric field becomes very intense in a narrow region of the channel. A voltage sensing probe attached in this region confirms that the field is at least three times as large as the field in the bilayer. Resonance energy transfer experiments to several sites in S4 using the pore or the bilayer as a reference show that the S4 does not translocate across the membrane. The large number of charges (12 e) must then move in a small region where all the electric field is concentrated. In the hyperpolarized state, a water crevice penetrates from the intracellular medium all the way to the most extracellular charge exposing all the gating charges to the inside. We propose that, when the membrane is depolarized, the S4 changes its tilt and the charges change their exposure to an extracellular water-filled crevice while the intracellular crevice is obliterated. Thus in the process, the charges have been translocated without a significant translocation of the S4 segment in much the same way that a transporter operates. The change in tilt of the S4 segment induced by depolarization couples its motion to the S5 segment that allows the conformational change of S6 that opens the conduction pathway. A molecular model of the open and closed states based on multiple experimental results and the crystal structure of KvaP is able to reproduce quantitatively the movement of 12 e with less than 2 Å of S4 translocation.

Supported by NIH grant GM30376.