A limited 4 a radial displacement of the s4-s5 linker is sufficient for internal gate closing in kv channels

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Voltage-gated ion channels are responsible for the generation of action potentials in our nervous system. Conformational rearrangements in their voltage sensor domains in response to changes of the membrane potential control pore opening and thus ion conduction. Crystal structures of the open channel in combination with a wealth of biophysical data and molecular dynamics simulations led to a consensus on the voltage sensor movement. However, the coupling between voltage sensor movement and pore opening, the electromechanical coupling, occurs at the cytosolic face of the channel, from where no structural information is available yet. In particular, the question how far the cytosolic pore gate has to close to prevent ion conduction remains controversial. In cells, spectroscopic methods are hindered because labeling of internal sites remains difficult, whereas liposomes or detergent solutions containing purified ion channels lack voltage control. Here, to overcome these problems, we controlled the state of the channel by varying the lipid environment. This way, we directly measured the position of the S4-S5 linker in both the open and the closed state of a prokaryotic Kv channel (KvAP) in a lipid environment using Lanthanide-based resonance energy transfer. We were able to reconstruct the movement of the covalent link between the voltage sensor and the pore domain and used this information as restraints for molecular dynamics simulations of the closed state structure. We found that a small decrease of the pore radius of about 3-4 Å is sufficient to prevent ion permeation through the pore.

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