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**Multiscale simulations of ion channel opening and closing provide insights into the molecular mechanisms of gating**

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We develop and implement a multiscale molecular simulation approach to study the opening and closing of a ligand-gated ion channel at atomic resolution. Ligand-gated channels are essential in biological signaling pathways that range from chemical sensing in bacteria to the firing of neurons in humans. On the basis of recently determined crystal structures and with the help of multiscale molecular simulations we study the conformational changes associated with GLIC ion channel gating transition. Starting from a coarse-grained transition pathway constructed on the basis of a multistate elastic network model, we perform string-method molecular dynamics simulations to refine the pathway at full atomic resolution. We find that the channel closes in an iris-like fashion as a result of a two-stage tilting of the pore lining helices. Water plays a central role in the gating transition. We find that the hydrophobic gate of the pore undergoes highly cooperative transitions between a densely filled and an empty state. The subtle tilting of the helices shifts the balance to the dry state, in which a 1.5 nm long hydrophobic stretch of the pore completely empties. By calculating the ionic conductance and the underlying free energy surface, we quantitatively demonstrate that this drying of the hydrophobic constriction, not sterics, is the major determinant of ion conductivity in the GLIC pentameric ion channel.

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