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Gating mechanisms of a mechanosensitive ion channel: experiments and molecular simulations

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Summary

Mechanosensing is ubiquitous in our body. Not only specialized mechanoreceptors like inner ear hair cells and visceral baroreceptors, but also ordinary cells can respond to mechanical stimuli, by which cells can regulate their volume, shape and motility properly. The major biophysical issue in this field is to understand the physicochemical mechanisms of mechanotransduction based on the molecular structure of mechanosensors. To date the mechanosesnitive (MS) ion channel is the only identified molecular class of mechanosensors. Among them the bacterial MS channel MscL is the best studied one owing to the resolved 3D structure of its closed state. MscL forms a homopentamer of a subunit having two(inner and outer) transmembrane alfa-helices and neighboring inner helices cross each other near the cytoplasmic surface, thus forming the most constricted part (gate) of the channel pore. The issue is to understand the underlying mechanism during the gating (opening) process driven by tension in the membrane; more concretely where and how the channel protein receives forces and how the forces lead to gate opening. To identify the tension-sensing site, we performed molecular dynamics (MD) simulations and site-directed mutagenesis at each hydrophobic residue in the outer helix facing lipid moiety and found that the hydrophobic interaction between Phe78 and lipids near the periplasmic surface is essential to tension sensing. Upon tension increase, the tension sensor (Phe78)s were dragged radially by lipids followed by a tilting of the helices and an outward sliding of the cross points (gate) between inner helices, leading to the gate opening. Calculated changes in the interaction energy at the crossings (gate) during gate opening were comparable to those experimentally obtained. Our MD system also reproduced successfully the behaviors of several mutants, indicating that our model depicts the essential physical process of the real MscL gating.

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