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Title: Gating of potassium channels

Abstract in English

Ion channels enable selective passive ion flow across otherwise impermeable cell membranes. They are essential for membrane excitability, cell proliferation and neuronal communication. Their importance is further emphasized by the existence of mutations associated with severe diseases. Several crystal structures have been published, leading to a better understanding of these proteins; however, all channels undergo poorly understood conformational changes during gating. Thus, my thesis focuses on gating dynamics. In particular, I investigated strong inward rectifier K^+ channels. An intriguing feature of this family is the strong lipid dependence of the gating process. Recent studies indicate that PIP_2 as well as other anionic lipids are essential for conductance. Under experimental conditions, these channels are in the open state, when PIP_2 is bound. Unfortunately, available $K_{IR}2.X$ crystal structures are in closed conformations, despite some being co-crystallized with PIP_2. There is no consensus how PIP_2 leads to channel opening. Thus, the aim of this thesis was to investigate how PIP_2 regulates the dynamics of K_{IR} channels, using molecular dynamics simulations. Several different setups including wild type $K_{IR}2.2$ and selected mutations were tested. In wild type simulations with different PIP_2 concentrations, gating changes could not be observed within 4.8 μs sampling time. Thus, single-point mutations, identified in experiments, were introduced. In two mutant molecular dynamics simulations the open state was reached. Stable open state conformations could be maintained upon re-mutation to wild type. Free energy calculations support that these states are conductive. Summarizing, simulations provide detailed insights into gating dynamics of $K_{IR}2.2$. The obtained open state models will be useful to investigate the mechanism by which ligands, such as polyamines regulate ion flux.