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Atomistic insight into function and dysfunction of inward-rectifier potassium channels.

Abstract

Inwardly rectifying potassium (Kir) channels play a vital role for many physiological processes, such as repolarization of the cardiac action potential, control of neuronal excitation, and modulation of the secretion of hormones like insulin. Alteration of these functions can have a serious impact on health. Gene sequencing allowed the identification of mutations in different inward-rectifier potassium channels that lead to very rare and often also severe diseases, as for example Keppen-Lubinsky syndrome, Cantú syndrome, or DEND syndrome. Therefore, it is important to understand the mechanism of how Kir channels exert their function in terms of gating and ion selectivity. Additionally, it is crucial to learn how mutations impair the function of Kir channels as a basis for future developments of possible drug treatments.

Various Kir channels have been extensively studied by different experimental methods. The elucidation of X-ray and Cryo-EM structures increased our understanding about potassium channels by revealing regions that are responsible for gating and ion selectivity. Unfortunately, published structures of wild type Kir channels show very similar states, even under different experimental conditions (addition of modulators etc.).

We performed numerous microsecond-scale molecular dynamics (MD) simulations with Kir3.2 and Kir2.2 channels and their bound main modulator Phosphatidylinositol-4,5-bisphosphate (PIP2) to study atomistic details of K+ ion movement through these channels under an applied electric field. Our work suggests that PIP2 alone is enough to open the channel gate of Kir3.2 and reveals unique gating motions. Further, we described a stop-and-go mechanism of ion conduction through the selectivity filter of Kir3.2, which might represent known "flickering" behavior of this ion channel. In both channels, ion permeation occurred via a direct knock-on mechanism, similar as recently proposed for Kv channels. Additionally, we studied two different mutations. Introduction of a G178D mutation in Kir2.2 led to the first available open structure of this channel. The disease mutation G154S (Kir3.2) was reported in a case of Keppen-Lubinsky syndrome. This mutation causes loss of ion selectivity in mice. Our study shows how an introduced serine alters the conformation of the selectivity filter and describes the mechanism how sodium is conducted by the mutant potassium channel. Summarizing, our simulations provide details about ion permeation through two different Kir channels. Further, microsecond-scale simulations led to open state structures that allow future investigations on pore blockers or the mechanism of inward rectification caused by polyamines.