K2P channel gating mechanisms revealed by structures of TREK-2 and a complex with Prozac

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Keywords: *TREK, K2P channel, gating, Prozac*

Abstract

The mechanisms behind potassium 2-pore domain (K2P) channel gating have been a mystery ever since their discovery in the mid-90s. Classical potassium channels such as voltage gated potassium channels are gated by an intracellular bundle crossing, which K2P channels lack. TREK-2 is a K2P channel that is regulated by a diverse array of stimuli including physical factors such as mechanical stretch, voltage and temperature, natural ligands such as polyunsaturated acids arachidonic acid, as well as both intra- and extracellular pH. Its activity can also be modulated by a variety of pharmacological agents such as volatile anesthetics, neuroprotective drugs, and antidepressants such as fluoxetine (Prozac). We solved structures of TREK-2 in multiple conformations, and in complex with a state dependent inhibitor norfluoxetine. Norfluoxetine binds within intramembrane fenestrations found only in one of these two conformations. Channel activation by arachidonic acid and mechanical stretch reduced norfluoxetine inhibition, suggesting that this mechanism involves conversion between these states via movement of the pore-lining helices. These results therefore not only provide a structural explanation for TREK channel mechanosensitivity, but also their regulation by other diverse stimuli and explain how Prozac inhibits TREK channels.