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A hydrophobic barrier deep within the inner pore of the TWIK-1 K2P potassium channel (Article)

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Abstract

Recent X-ray crystal structures of the two-pore domain (K2P) family of potassium channels have revealed a unique structural architecture at the point where the cytoplasmic bundle-crossing gate is found in most other tetrameric K^+ channels. However, despite the apparently open nature of the inner pore in the TWIK-1 (K2P1/KCNK1) crystal structure, the reasons underlying its low levels of functional activity remain unclear. In this study, we use a combination of molecular dynamics simulations and functional validation to demonstrate that TWIK-1 possesses a hydrophobic barrier deep within the inner pore, and that stochastic dewetting of this hydrophobic constriction acts as a major barrier to ion conduction. These results not only provide an important insight into the mechanisms which control TWIK-1 channel activity, but also have important implications for our understanding of how ion permeation may be controlled in similar ion channels and pores.

Indexed keywords

EMTREE drug terms: ion channel, potassium channel, two pore domain potassium channel, unclassified drug, KCNK1 protein, human, lipid bilayer, tandem pore domain potassium channel, water

GEOBASE Subject Index: crystal structure, cytoplasm, hydrophobicity, molecular analysis, stochasticity, X-ray spectroscopy

EMTREE medical terms: article, channel gating, controlled study, crystal structure, hydrophobicity, ion current, ion transport, lipid bilayer, lipid membrane, molecular dynamics, nonhuman, protein expression, stochastic model, Xenopus, animal, chemical phenomena, chemistry, human, metabolism, protein conformation, site directed mutagenesis

MeSH: Animals, Humans, Hydrophobic and Hydrophilic Interactions, Lipid Bilayers, Molecular Dynamics Simulation, Mutagenesis, Site-Directed, Potassium Channels, Tandem Pore Domain, Protein Conformation, Water, Xenopus

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