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Structures of the human two-pore domain potassium channels TREK-1 and TREK-2

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TREK-1/2 are members of the mechano-gated subfamily of two-pore (K2P) domain potassium channels leaking K+ out of the cell and contributing to the resting membrane potential. In contrast to the classical tetrameric potassium channels, K2P channels are dimeric with an atypical architecture and the structural mechanisms underlying their channel gating are poorly understood. Here we present the crystal structures of human TREK-1 and TREK-2 at resolutions of 2.7 and 3.4Å which provide insights into the basis of intracellular and extracellular gating in this unique family of ion channels. We have solved the structure of TREK-2 in two distinct conformations differing in the orientation of the pore-lining transmembrane helices. The C-terminal M4 helix is hinged at a conserved glycine residue so that it adopts one of two distinct orientations. The M4 helix is either kinked towards the membrane, packing against the M2 inner helix of the adjacent subunit ("M4 up") or straightens and interacts with the M2/M3 helices from the same subunit ("M4 down"). In the M4 down state, a hydrophobic lateral opening runs perpendicular to the ion conductance pathway between M2 and M4 and links the inner vestibule to the membrane-exposed face of the channel. Transition between the "M4 down" and "M4 up" conformations may play a role in channel activation and gating. Cocrystallisation with a TREK-1/2 channel inhibitor promotes the "M4 down" state. The structure of TREK-1 exhibits an "M4-up" conformation but is unusual in that the selectivity filter is significantly distorted with only two correctly-formed potassium sites. The structure also reveals a divalent ion binding site between the extracellular cap and the pore domain loop. The TREK-1 structure illustrates how changes at an extracellular site can affect the pore structure. The structures will be described in detail along with their implications for channel gating in response to intracellular and extracellular stimuli.

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