

Sensing pressure with K_{2P} channels

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The K_{2P} channels are highly conserved from *C. elegans* to humans. They are structurally distinct from other K^+ channel family members, with four transmembrane segments and 2P domains in tandem. K_{2P} channels are homo- or hetero-dimers that play a dominant role in cell electrogenesis, controlling the resting membrane potential and the action potential duration.

The K_{2P} channel TREK-1 is predominantly expressed in the central and peripheral nervous system, with a particularly strong expression during early development. TREK-1 is activated by membrane stretch as well as cell swelling. Mechanical force is transmitted directly to the channel via the lipid bilayer. Moreover, intracellular acidosis strongly sensitizes TREK-1 to membrane stretch, leading to channel opening at atmospheric pressure.

TREK-1 is reversibly opened by polyunsaturated fatty acids, including arachidonic acid (AA). Activation of TREK-1 by AA in the excised patch configuration indicates that the effect is direct by interacting either with the channel protein or by partitioning into the lipid bilayer. Additionally, TREK-1 channel activity is reversibly stimulated by volatile general anaesthetics including halothane.

The recent invalidation of TREK-1 in a mouse model demonstrates that this K^+ channel is important for neuroprotection against epilepsy and ischemia. Furthermore, TREK-1 $-/-$ mice are also more resistant to volatile general anaesthetics, indicating a key role for TREK-1 in the mechanism of general anaesthesia.

Mutagenesis studies have demonstrated that the cytosolic carboxy terminal domain of TREK-1 plays a key role in TREK-1 gating. Protonation of a key residue in this region, E306, leads to channel activation. Interaction of the carboxy terminal domain of TREK-1 with the inner leaflet phospholipids including PIP_2 is critical for channel activity and is controlled by a cluster of cationic residues. Conversely, down-modulation of TREK-1 is achieved by receptor-coupled protein kinase A phosphorylation of residue S333.

In conclusion, the TREK channels are polymodal K^+ channels that integrate multiple physical and chemical stimuli.