The molecular mechanism of mechanosensitivity in K_{2P} channels

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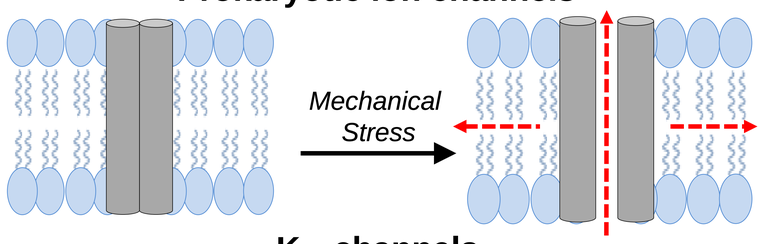
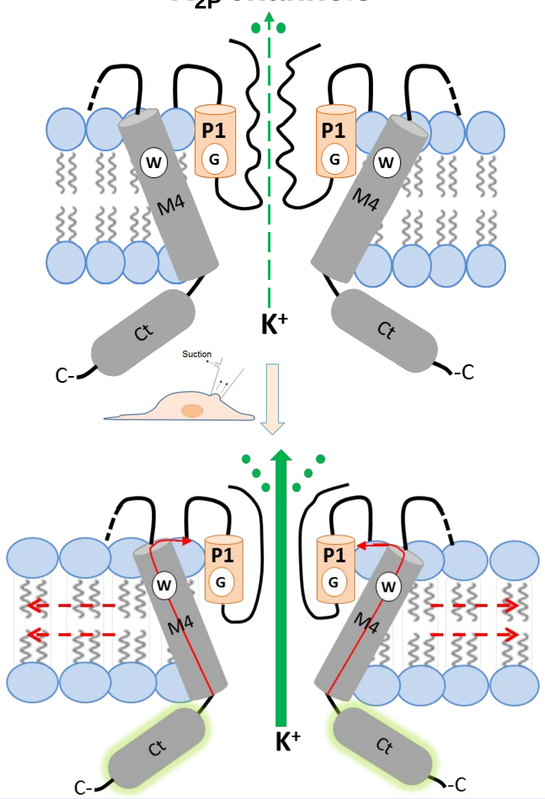
Abstract

The mechanosensitive two-pore (K_{2P}) potassium channels TREK-1, TRAAK and TREK-2 contribute to generation of resting membrane potential in somatosensory neurons and muscle cells though mediating membrane stretch-activated potassium outflow. Here, we show that the extracellular selectivity filter-based gate of TREK-1 is the principal channel element that controls ion flux in response to force application. However, the gate lacks robust intrinsic mechanosensitivity and requires allosteric communication with the intracellular C-terminal tail, which serves as the primary stretch-sensing element of the channel. We found that TREK-2 and TRAAK operate through a similar mechanism, demonstrating that the stretch-sensing apparatus is conserved across the K_{2P} family. These results illuminate a novel mechanism of force perception by MSCs. Instead of expanding channel core, changes in membrane tension act on a modular intracellular sensory domain, which affects channel function through allosteric coupling with a stretch-insensitive extracellular gate.

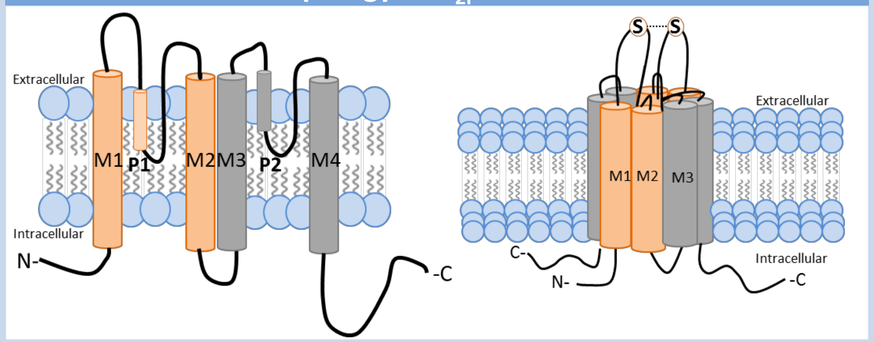
Prokaryotic ion channels



K_{2P} channels

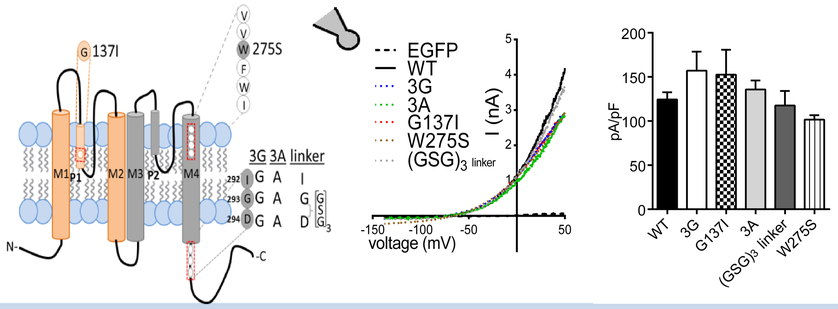


Topology of K_{2P} channels



Approach and Results

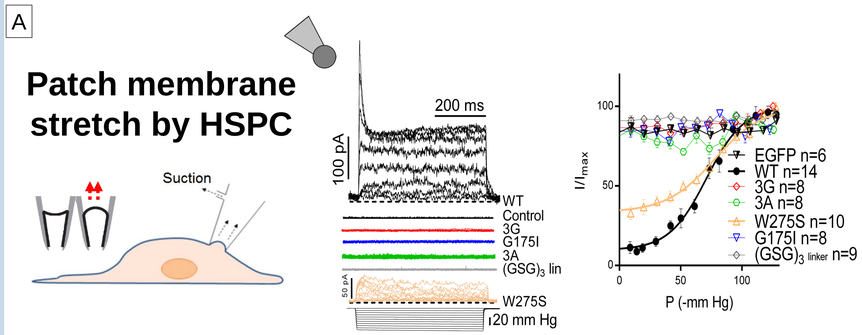
Electrophysiological analysis of TREK-1 bearing mutations in the extracellular C-type gate, and in the intracellular Ct domain.



Ct tail and C-type gate are crucial for TREK-1 mechanosensitivity

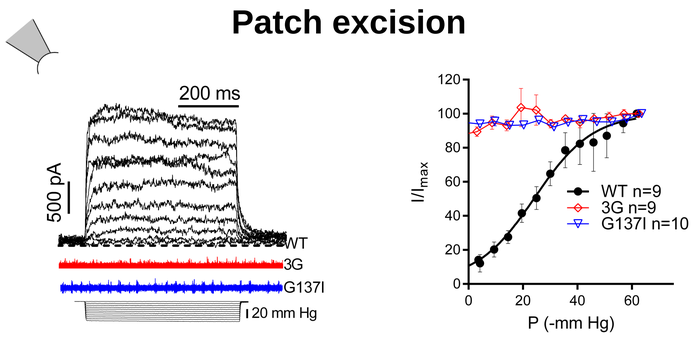
A

Patch membrane stretch by HSPC

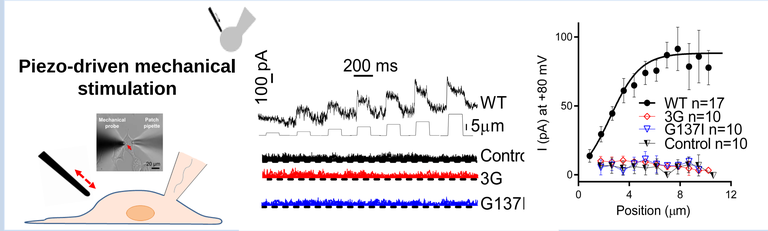


B

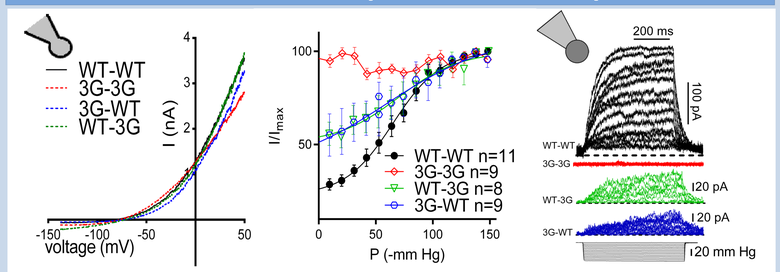
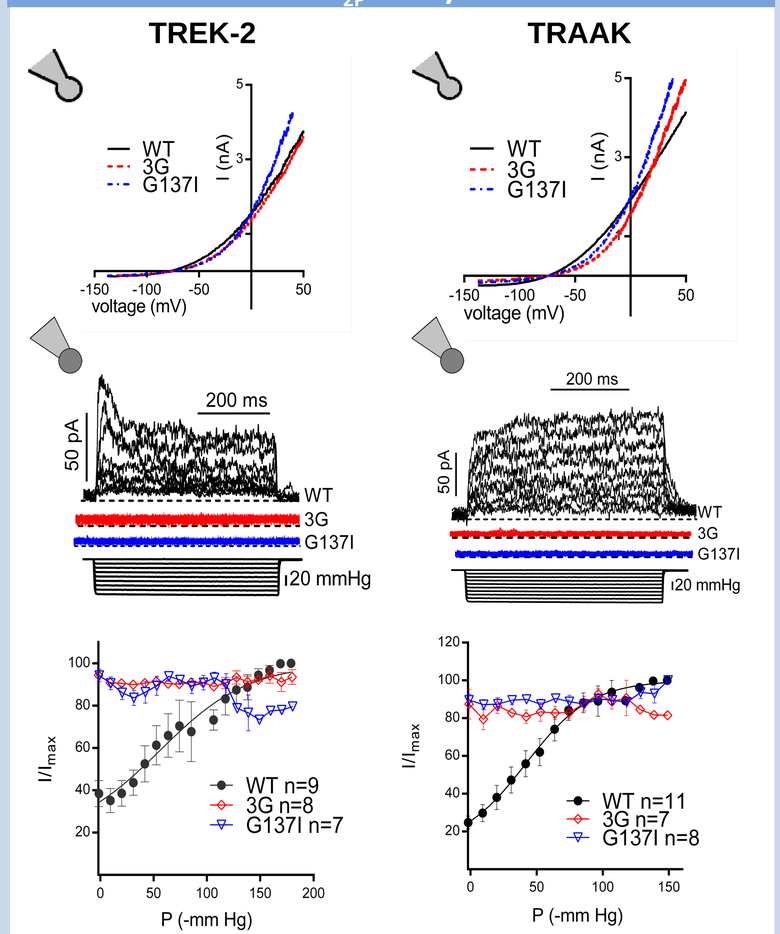
Patch excision



Piezo-driven mechanical stimulation fails to activate mechano-insensitive mutants



Both Ct tails are required for full response



The mechanosensitivity apparatus is conserved across K_{2P} family