Activation and Inhibition of Potassium Channels

Impact of the C-terminus on the Activation and Inhibition of Homomeric TREK K_2P Channels

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In Short

- Two-pore domain (K2P) K_+ channels play important role in diverse physiological processes and are related with different diseases.
- We revealed in previous studies that the selectivity filter as the primary gate in the K2P channels.
- We aim to understand the role of C-terminus of the TREK channels in gating and how the stimuli are transferred from C-terminus to the primary gate at the selectivity filter.

Two-pore domain (K2P) K^+ channels represent a structurally unique family of channels involved in diverse physiological functions such as cell regulation, apoptosis, vasodilation, central chemosensitivity, neuronal excitability and the perception of pain. They also act as a major target for volatile anesthetics and represent attractive therapeutic targets for the treatment of a wide variety of cardiovascular and neurological disorders [1–3].

Different from many other classes of K^+ channels, we revealed in our previous work that the selectivity filter acts as the primary gate in the K2P channels. From the molecular dynamics (MD) simulations and electrophysiological recordings we could show that the selectivity filter gate in many K2P channels is tightly controlled by the ion occupancy enabling a so-called "ion-flux-coupled" voltage activation mechanism [4]. Strong activation can be also achieved by different permeant ion species, which are Rb^+ and Cs^+. Moreover, the "ion-flux" mode can be converted into "leak mode" by many physiological stimuli activating these channels (e.g. mechanical stretch, temperature or cellular lipids like PIP_2 or arachidonic acid) [2]. We showed in a recent study that a series of negatively charged small molecules ligands can also induce the "leak mode" [5]. The activation by mechanical stretch is thought to involve the transition of TREK-1/-2 and TRAAK K_2P channels from a less active down state (with the TM4 more pointing to the cytoplasm) to a highly active up state (with TM4 moved up more into the membrane) [6].

Within this project, we will use theoretical approaches to investigate the role of the C- terminus of different TREK channels in gating. From our preliminary results we could show that the conformational

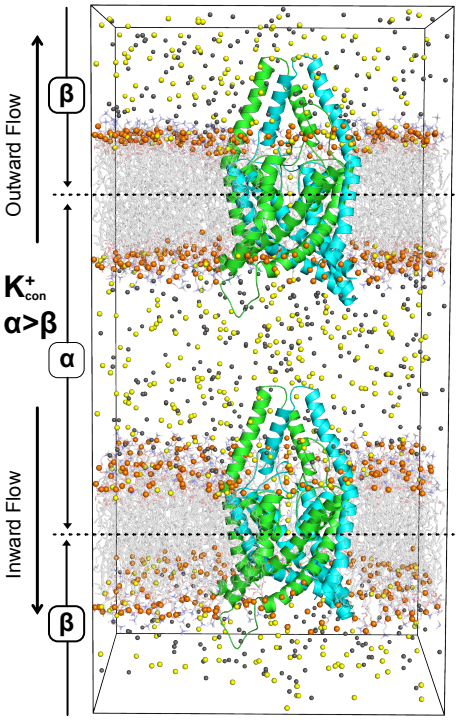

Figure 1: *Computational Electrophysiology of human TREK-1 channel: The system used in the computational electrophysiology simulations, consisting of two membranes (lipids in grey), each including one TREK-1 channel (green cartoon: PDB ID: 6CQ6), surrounded by water (red lines), K^+ ions (purple balls) and Cl^- ions (cyan balls). Periodic boundary conditions create two compartments, a and b, with distinct ion concentrations. Thus, a transmembrane voltage gradient is established across each membrane. In case of a>b, outward and inward permeation can be observed in the upper and lower channel, respectively.*

state of the C-terminus is indeed coupled with the primary gate at the SF using MD based computational electrophysiology simulations [7] (Fig1). Furthermore, we attached different methanethiosulfonate (MTS) molecules to the C-terminal of the TREK-2 channel, which can activate or inhibit the channel depending on their chemical structures and molecular charges. For the MTS molecule that is able to activate the channel, we observed an insertion of the hydrophobic ligand in the lipid membrane. By extending and systematic comparison of these simulations with the ones of apo-TREK channels, we are now trying to understand stimulus transduction mechanism from the C-terminus to the SF gate. Finally, we will investigate how diverse drug molecules such as fluoxetine inhibit the channel.

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More Information

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