Activation and Inhibition of Potassium Channels

Investigation of Activation and Inhibition Mechanism in TREK-1 Potassium Channel

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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-1 channel 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-volume 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][2][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 K2P 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].

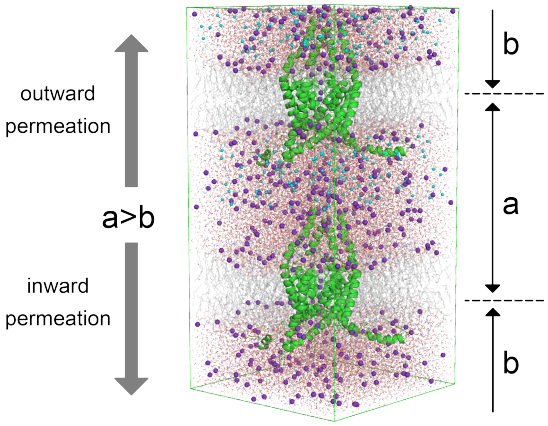

***Figure 1:** Computational Electrophysiology of human TREK-1 channel: The system used in the computational electrophysiology simulations, consisting of two membranes (lipids in grey), each including one TREK-1 channel (green cartoon: PDB ID: 6CQ6), surrounded by water (red lines), K^+ ions (purple balls) and Cl^- ions (cyana 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.*

Within this project, our aim is to obtain a comprehensive understanding on the coupling between the lower helix gate involving the movement of the TM4 helix and the primary gate at the selectivity filter. To this end, we will perform computational simulations [7] on the TREK-1 channel by attaching two small molecule ligands on the C-terminus (Figure 1), which is known to activate or inhibit the channel experimentally. By comparing the simulations with the apo-TREK-1 channel, we expect to understand the role of the proximal C-terminus and elucidate the unknown stimulus transduction mechanism from the C-terminus to the selectivity filter.

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http://www.leibniz-fmp.de/de/lange.html

More Information

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Project Partners

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