Journal of Molecular Cell Biology (2022), 14(3), mjac018 https://doi.org/10.1093/jmcb/mjac018
Published online March 23, 2022

Highlight

A gating mechanism of K2P channels by their selectivity filter

Fan Yang *

Department of Biophysics, and Kidney Disease Center of the First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310058, China
* Correspondence to: Fan Yang, E-mail: fanyanga@zju.edu.cn

Cellular excitability is determined by the flow of different ions across the cell membrane, which is in turn controlled by the opening and closing of ion-permeable pores, the ion channels (Hille, 2001). For instance, in neurons, the opening of voltage-gated sodium channels allows the outward flow of intracellular sodium ions, so that the membrane potential is increased (depolarization) to fire the action potential, which encodes and delivers neuronal information. Upon membrane depolarization, voltage-gated potassium (Kv) channels are opened, so that the extracellular potassium ions flow into the cell to decrease the membrane potential and terminate one firing of the action potential (Sigworth, 1994). The two-pore potassium (K2P) channels, unlike Kv channels, are not activated by the membrane potential but by mechanical forces when the cell membrane is stretched (Honore, 2007). Such 'leaky' K2P channels control cell excitability by setting the resting potential in cells (Gonzalez et al., 2012). Therefore, understanding how K2P channels are opened or closed (gating) is critical.

The investigation of K2P channel gating mechanisms has been prompted by studies on Kv channels. In Kv channels, after channel opening by depolarization, a part of the N terminus can block the channel pore from the intracellular side,

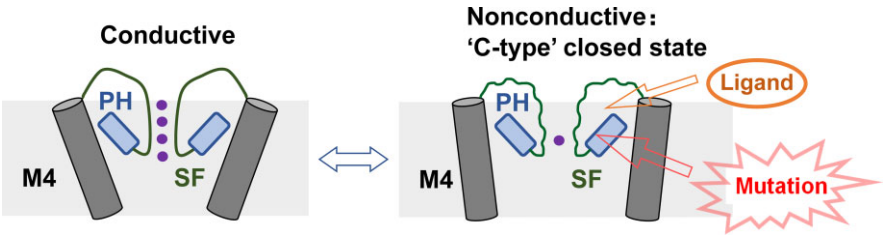

Figure 1 A schematic diagram of a TREK-1 channel pore in the conductive and nonconductive 'C-type' closed states. Dots in purple and the light gray box denote the permeating potassium ions and cell membrane, respectively. SF, selectivity filter; PH, pore helix.

which is known as the 'N-type' inactivation (Hoshi et al., 1990). Another form of Kv channel inactivation, which at first appeared to involve the C terminus, is known as the 'C-type' inactivation (Hoshi et al., 1991). Later studies have demonstrated that the 'C-type' inactivation in Kv channels is actually caused by conformational changes in the selectivity filter and pore helix, where ions can no longer pass (Cordero-Morales et al., 2007; Cuello et al., 2010). K2P channels share similar structures in the pore region, including the selectivity filter, to Kv channels. However, in the currently available structures of K2P channels, the selectivity filter is always in a conformation that allows ions to pass. Therefore, whether the selectivity filter in K2P channels changes its conformation in a manner similar to the 'C-type' inactivation in Kv channels to control ion permeation remains to be explored.

The study by Dr Huaiyu Yang's group has elegantly revealed a non-conducting conformation of the selectivity filter in the TREK-1 channel (Figure 1), which is a prototypic member of the K2P channel family (Zhang et al., 2022). By performing conventional full-atom molecular dynamic (MD) simulation and steered MD simulation, they observed that the movements in the M4 helix of TREK-1 led to conformational rearrangements in the selectivity filter, so the permeating ions were not regularly coordinated by the backbone carbonyl atoms in the residues in the selectivity filter like I143, and thus the channel was in a 'C-type' closed state.

Such a 'C-type' gating mechanism of TREK-1 in its selectivity filter satisfactorily explains the effects of point mutations on TREK-1. In the wild-type TREK-1 channel, M4 movements lead to the interaction between T141 in the selectivity filter and W275 in the M4 to disrupt the hydrogen bonding network around the selectivity filter. In the gain-of-function mutant W275S, its side chain no longer interacts with T141, so the hydrogen bonding network is preserved to stabilize a conductive selectivity filter conformation.

Furthermore, the 'C-type' gating mechanism of TREK-1 underlies the pharmacology of ML335, an agonist of this channel. Based on MD simulations, ML335

binds to the vicinity of the selectivity filter and serves as a wedge between P1 and M4 helix. In this way, ML335 limits the movements of M4 to keep the selectivity filter in the conductive state.

In summary, discoveries from this study not only offer mechanistical insights regarding the gating mechanisms of K2P channels, but also exert profound impact on drug development in the future. Membrane proteins, including ion channels and G protein-coupled receptors, form the largest superfamily of drug targets (Santos et al., 2017). With the rapid advancements in structural biology, high-resolution three-dimensional structures of more and more ion channels have been determined. To take full advantage of protein structures, MD simulation is expected to probe the dynamic transitions in ion channels and unveil cryptic binding sites of ligands. Insights gained from carefully designed and executed MD simulations, like this study by Dr Yang's group (Zhang et al., 2022), will help reveal mechanisms of action in known ligands and facilitate virtual screening campaigns to discover novel hit molecules binding to cryptic pockets.

[This study was supported by the National Natural Science Foundation of China (32122040, 31971040, and 31800990) and Zhejiang Provincial Natural Science Foundation of China (LR20C050002) to F.Y.]

References

Cordero-Morales, J.F., Jogini, V., Lewis, A., et al. (2007). Molecular driving forces determining potassium channel slow inactivation. Nat. Struct. Mol. Biol. *14*, 1062–1069.

Cuello, L.G., Jogini, V., Cortes, D.M., et al. (2010). Structural mechanism of C-type inactivation in K^+ channels. Nature *466*, 203–208.

Gonzalez, C., Baez-Nieto, D., Valencia, I., et al. (2012). K^+ channels: function–structural overview. Compr. Physiol. *2*, 2087–2149.

Hille, B. (2001). Ion Channels of Excitable Membranes (3rd edn). Sunderland, Mass.: Sinauer Associates.

Honore, E. (2007). The neuronal background K2P channels: focus on TREK1. Nat. Rev. Neurosci. *8*, 251–261.

Hoshi, T., Zagotta, W.N., and Aldrich, R.W. (1990). Biophysical and molecular mechanisms of Shaker potassium channel inactivation. Science *250*, 533–538.

Hoshi, T., Zagotta, W.N., and Aldrich, R.W. (1991). Two types of inactivation in Shaker K^+ channels: effects of alterations in the carboxy-terminal region. Neuron *7*, 547–556.

Santos, R., Ursu, O., Gaulton, A., et al. (2017). A comprehensive map of molecular drug targets. Nat. Rev. Drug Discov. *16*, 19–34.

Sigworth, F.J. (1994). Voltage gating of ion channels. Q. Rev. Biophys. *27*, 1–40.

Zhang, Q., Fu, J., Zhang, S., et al. (2022). 'C-type' closed state and gating mechanisms of K2P channels revealed by conformational changes of the TREK-1 channel. J. Mol. Cell Biol. *14*, mjac002.