Structural and dynamic differences between selective and non-selective ion channels

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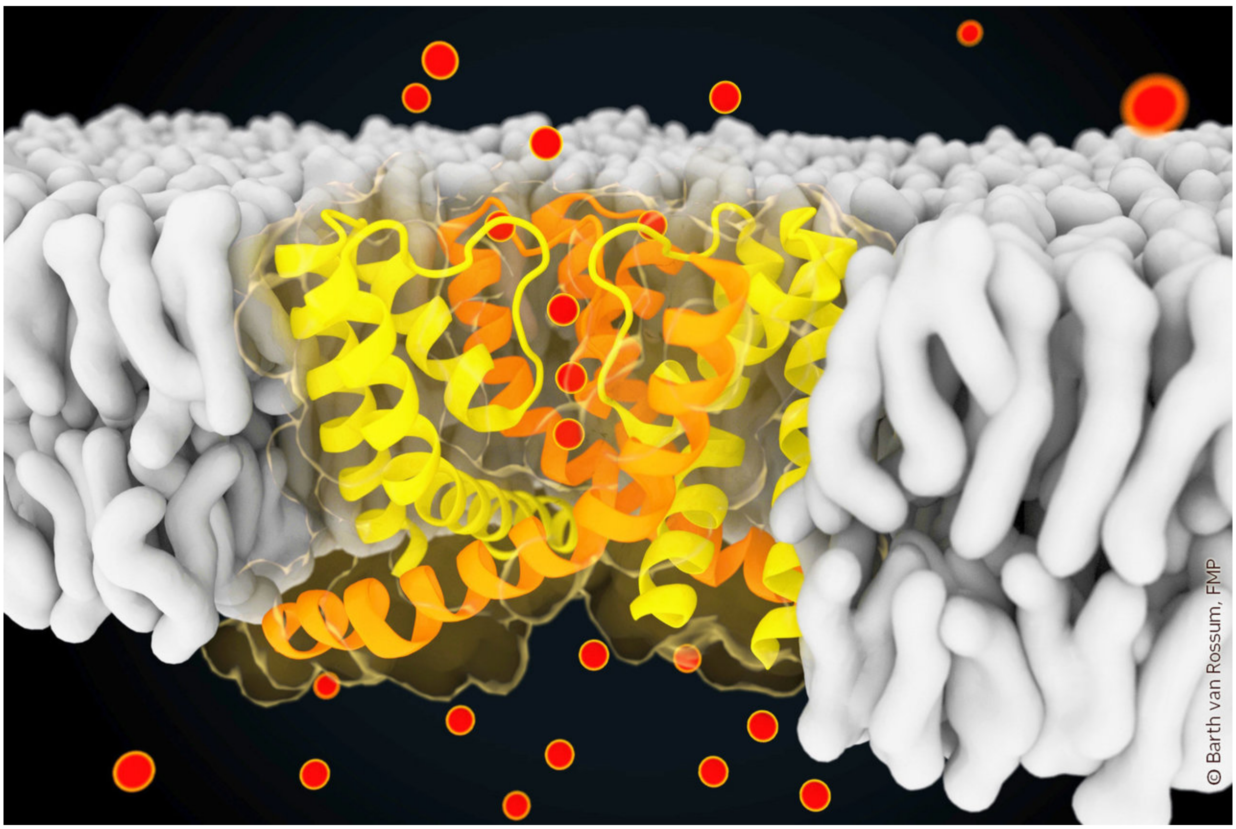

Snapshot taken during the computer simulation of the NaK channel - This channel (shown in yellow and orange) enables the flow of ions (e.g. potassium ions [red spheres]) across the cell membrane. (The membrane lipids are depicted in gray.) Credit: Barth van Rossum / FMP

Most ion channels are very selective about the ions that may or may not pass through them. They may be conductive for potassium ions and non-conductive for sodium ions, or vice versa. However, a number of ion channels allow for the efficient passage of both kinds of ions. How do these channel proteins accomplish this? A team of scientists around Dr. Han Sun and the research group of Professor Adam Lange at the Leibniz-Forschungsinstitut für Molekulare Pharmakologie (FMP) found the answer to this question.

Their study revealed structural and dynamic differences between selective and non-selective ion channels. The scientists described their findings and conclusions in the journal *Nature Communications*. In non-selective channels, the selectivity filter exhibits sizeable dynamics not present in selective channels. The selectivity filter of non-selective ion channels can exist in two different forms. Dependent on the state of the selectivity filter, one or the other ion type may pass.

Ion channels play prominent roles in organisms. For example, ion channels are in action when the organism registers stimuli and passes the information on to the brain in the form of electric signals. During this signal transmission, charged atoms (ions) must enter and leave the involved cells. Ions cannot permeate lipophilic cell membranes. Instead, they pass through protein channels in the cell membranes.

In many cases, the ion channels allow the passage of only one specific ion type, i.e. they may be conductive for potassium but not for sodium ions or vice versa. The selectivity filter that is the narrowest part of the channel is responsible for this ion discrimination. However, the NaK channel allows for the passage of both sodium and potassium ions. It was in the focus of the present study by FMP scientists around Dr. Han Sun and Professor Adam Lange together with colleagues in Göttingen (Germany) and Hefei (China).

Non-selective ion channels are very important in medicine.

Until now, it has remained controversial why NaK channels allow for the passage of both sodium and potassium ions. Professor Adam Lange explains: "While X-ray crystallographic images showed us the three-dimensional structure of the channel, it was difficult to explain why this channel is conductive to two different ion types with similarly high efficiency. This was particularly hard to understand because the sequence and the 3-D structure of the selectivity filter are similar to the ones in potassium selective channels."

Scientist Dr. Han Sun added that this is a model system for several other non-selective ion channels in the human body. In this context, the cyclic nucleotide-gated and hyperpolarization-activated cyclic nucleotide–gated channels (CNG and HCN channels) are medically and physiologically relevant. "We know that CNG channels are important for vision and smell. Dysfunctional HCN channels are implicated in various neurological diseases such as epilepsy or autism."

Specific Ions Prefer Specific Channel Structures

The scientists used a combination of nuclear magnetic resonance (NMR) spectroscopy and computer-assisted molecular dynamics simulations. The results revealed that the selectivity filter of the NaK channel dynamically changes between two structures. Each structure is conductive for one of the two ion types. Dr. Han Sun says, "Surprisingly, the computer simulations showed that potassium ions passing through the NaK channel prefer the structure of a potassium selective channel, while the mechanism of the sodium ion passage is similar to the passage of sodium ions through a sodium selective ion channel." Until now, researchers believed that the structure of the selectivity filter is the same for sodium and potassium ion transport through the NaK channel.

To gather further evidence for the crucial role of the dynamic structure of the NaK selectivity filter, the scientists experimented with a mutated

NaK channel (NaK2K double point mutation). This mutated NaK channel is conductive only for potassium ions. Professor Adam Lange gives an account of the results: "Our NMR investigations clearly revealed that the selectivity filter of this channel forms only a single structure."

More information: Chaowei Shi et al. A single NaK channel conformation is not enough for non-selective ion conduction, *Nature Communications* (2018). DOI: 10.1038/s41467-018-03179-y

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