Researchers use spider venom compound to treat paralysis

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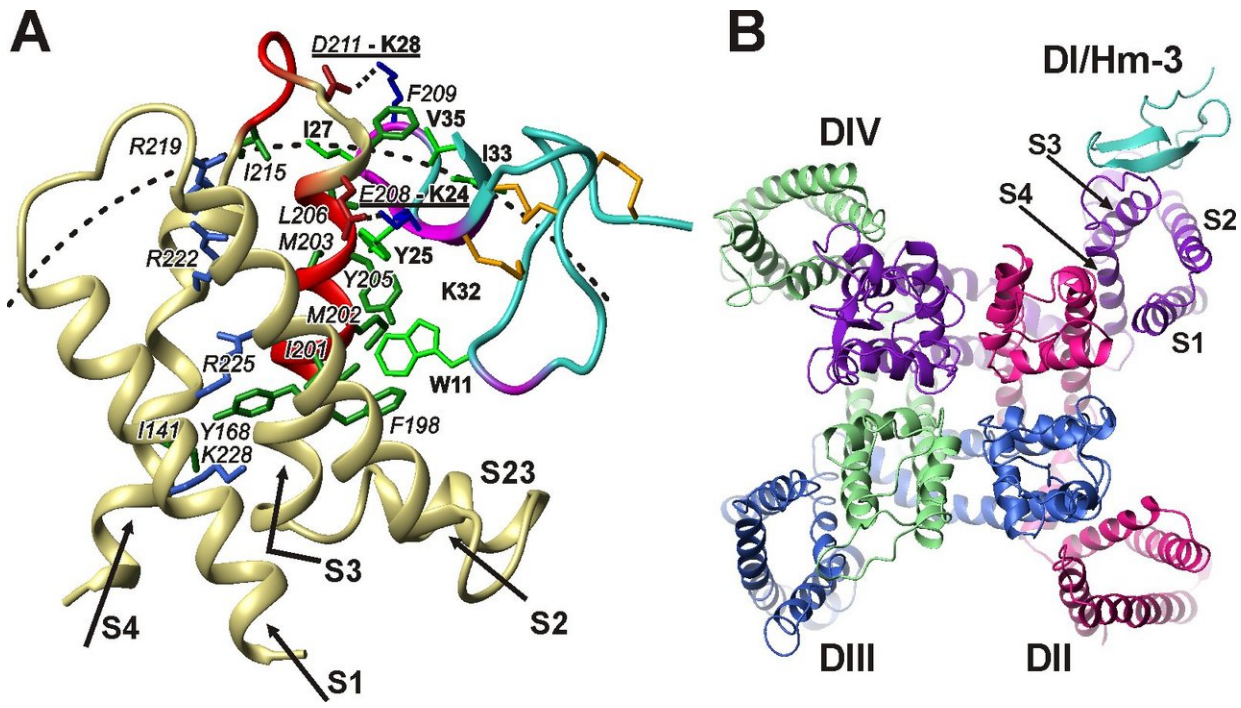

The complex of the Nav1.4 channel from human muscle cells with the Hm-3 toxin extracted from the venom of the Heriaeus melloteei spider. (A) The interaction of Hm-3 (blue/purple) with the first voltage-sensing domain (D1) of the channel (sandy/red) revealed by NMR data. Lateral view from the lipid bilayer. (B) The toxin-channel complex. View of the membrane plane from the extracellular space. Credit: Alexander Vasilevskiy

A team of Russian scientists together with foreign colleagues, reports

that the venom of the crab spider Heriaeus melloteei may be used as a basis for a treatment against hypokalemic periodic paralysis. This disease is caused by genetic mutation that leads to the occurrence of the so-called ω-currents, or leakage currents, via voltage-gated ion channels Nav1.4 in skeletal muscles. As a result of such "leakages," the muscles are unable to respond to signals from the nervous system and a patient suffers symptoms ranging from muscle weakness to total paralysis. There is still no reliable medicinal drug to cure all cases of this disease. The results were published in *Proceedings of the National Academy of Sciences (PNAS)* journal.

Each cell membrane has ion channels—protein pores that selectively conduct ions in and out of the cell. As they function, the cell membranes become electrically charged and develop transmembrane potential. Under the influence of certain signals, ion channels may open or close, changing the flow of ions in and out of the cell and the charge of the membrane. As a result, certain cells (neurons, muscle cells, and gland cells) are activated and respond to a signal.

However, sometimes channel-coding genes get damaged and degrade the response to signaling. For example, defects in certain domains of voltage-gated sodium channels Nav1.4 in muscle cells cause the membrane to "leak out" even when the channels are closed. Sodium ions penetrate the membrane and change the electric potential. In this case, signals of the nervous system cannot activate the muscle cells, and paralysis results. . Unfortunately, existing drugs against this condition are often inefficient.

"In our work, we studied human voltage-gated ion channels, in particular the mutated forms of Nav1.4 channel from skeletal muscle. These mutations lead to a severe disease, type 2 hypokalemic periodic paralysis. We are the first to prove that there are natural chemical compounds able to block the leakage currents through mutated channels," said biologist Mikhail Petrovich Kirpichnikov of the Russian

Academy of Sciences and dean of the Faculty of Biology, MSU.

Using a range of genetic methods, protein engineering, electrophysiology, NMR spectroscopy, and computer modeling, the scientists studied the causes of abnormal activities in the channels damaged by mutation. For the first time, they suggested a blocking agent for leakage currents—the toxin Hm-3, extracted from the venom of the Heriaeus melloteei spider. According to the data obtained using site-directed mutagenesis, electrophysiology, NMR spectroscopy, and computer modeling, the toxin fixes the voltage-sensing domain of the channel in the position that prevents leakage of ions.

"The discovery of this toxin property gives us hope of developing efficient medicinal drugs for the treatment of patients with hypokalemic paralysis and other similar diseases. The model of interaction between the channel and the toxin offers prospects for the development of new drugs," concludes Alexander Vasilevskiy of the Russian Academy of Sciences.

Zakhar Shenkarev of the Russian Academy of Sciences, said, "Studying the structure of ion channel complexes in the membrane is a difficult task. The main issue of our work was the instability of samples in the course of the NMR experiment. To solve it we had to come up with a range of new experimental methods that speeded up the process of structural data collection from several days to hours."

More information: Roope Männikkö et al, Spider toxin inhibits gating pore currents underlying periodic paralysis, *Proceedings of the National Academy of Sciences* (2018). DOI: 10.1073/pnas.1720185115

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