Medical Xpress

# Scientists zero in on the cellular machinery that enables neurons to fire

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If you ever had a set of Micronauts – toy robots with removable body parts – you probably had fun swapping their heads, imagining how it would affect their behavior. Scientists supported by the National Institutes of Health have been performing similar experiments on ion channels – pores in our nerve cells – to sort out the channels' key functional parts.

In the November 15 issue of *Nature*, one group of researchers shows that a part of ion channels called the paddle is uniquely transplantable between different channels. Writing in the same issue, another group exploited this property to probe the three-dimensional structure of ion channels on an atomic scale.

"The effects of many toxins and therapeutic drugs, as well as some diseases, can be wholly explained by changes in ion channel function," says Story Landis, Ph.D., director of the National Institute of Neurological Disorders and Stroke (NINDS), part of the NIH. "We also know that ion channels are at least a contributing player in epilepsy, chronic pain, Parkinson's disease and other disorders. As we learn more about how channels work, we're able to pursue more approaches to treatment."

Ion channels are proteins that control the flow of electrically charged salt particles (ions) across the nerve cell membrane. It's the opening and closing of these channels that enables nerve cells to fire off bursts of electrical activity. A built-in voltmeter, called a voltage sensor, pops the channel open when the nerve cell is ready to fire. The papers in Nature hone in on a part of the voltage sensor called the paddle, named for its shape.

In the first study, a team led by NINDS senior investigator Kenton Swartz, Ph.D., shows that the paddle works as a modular unit. Using recombinant DNA technology, they swapped the paddle from an ion channel found in an ancient, volcano-dwelling bacterium to a channel found in rat brain. As long as the paddle was intact, the hybrid channel still worked. This portability could one day be exploited to test potential drugs. For example, researchers who want to target a paddle from a poorly characterized ion channel could stick it into a well-studied channel where the effects of drugs are easier to measure.

Other results in the paper suggest that the paddle itself will be a useful target for new therapeutic drugs. Dr. Swartz's group found that the paddle is the docking site for certain toxins in tarantula venom, which are known to interfere with ion channel opening. There are hints that scorpions, sea anemones and cone snails make similar toxins, Dr. Swartz said. If nature has found ways to manipulate ion channel function, medicinal chemists might be able to do the same, he said.

In the second study, supported by the National Institute of General Medical Sciences (NIGMS), researchers took advantage of the paddle's unique transplantability to create a hybrid ion channel ideal for structural studies. Led by Roderick MacKinnon, M.D. – a Nobel Laureate, an investigator of the Howard Hughes Medical Institute and a biophysicist at Rockefeller University in New York – the team produced data that explain how the voltage sensor is positioned within the membrane and how it triggers channel opening.

"The determination of the three-dimensional structures of ion channels has yielded a framework to understand their fascinating functional properties," says NIGMS director Jeremy M. Berg, Ph.D. "These new results show how clever experimental designs can focus on key questions and steer the direction of additional studies."

Source: National Institute of Neurological Disorders and Stroke