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RESEARCH NEWS

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Visualizing a Potassium Channel

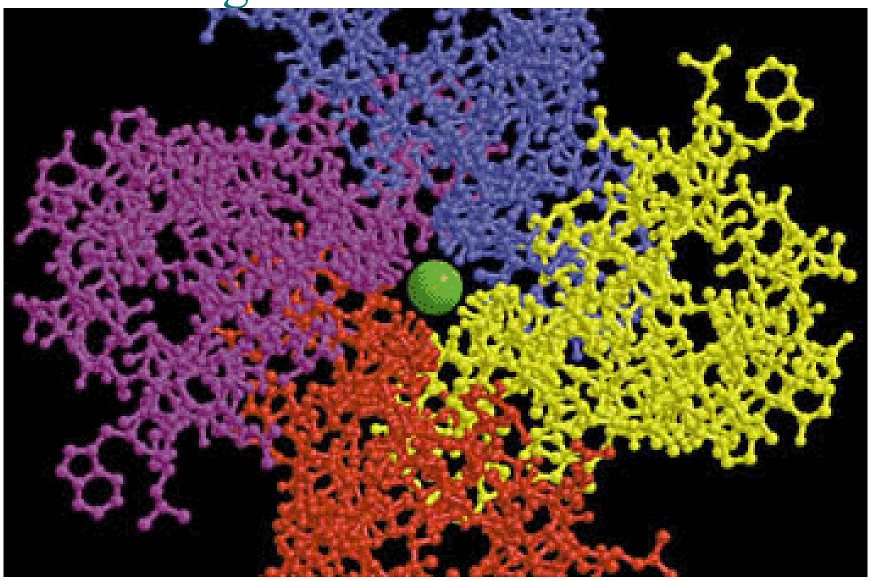

Image Title: This image shows a view of the four-fold axis of the KcsA potassium channel from the bacterium *Streptomyces lividans.* Each of the channel's four identical subunits is shown in a different color. The center of the channel contains a potassium ion (green). - Roderick MacKinnon Laboratory/HHMI at The Rockefeller University

For many years, scientists have dreamed of knowing exactly how potassium channels are constructed, hoping that knowledge would tell them more about how such channels work.

Now, in two reports in the journal *Science,* a research team led by Hughes investigator Roderick MacKinnon at The Rockefeller University unveils the crystal structure that shows the potassium channel's surprising architecture.

"The crystal structure of the potassium ion channel presented by MacKinnon and his laboratory is a dream come true for biophysicists," writes Clay Armstrong of the University of Pennsylvania in an accompanying article in the April 3, 1998, issue of *Science.*

Nearly 50 years ago researchers showed that electrical activity in neurons is produced by subtle changes in the neuron's potassium concentration. "Since then, it's been well established that the flow of potassium ions is central to many different cellular processes," said MacKinnon. Potassium currents in the brain, for example, underlie perception and movement, and the heart's contraction relies upon the steady ebb-and-flow of potassium.

To maintain the correct concentration of potassium, cells are equipped with pore-like proteins that poke through the cell membrane. These proteins, called ion channels or potassium channels, create sieves through which potassium ions flow from inside to outside the cell.

During the last 10 years, molecular biologists have identified many of the genes that produce the protein components of potassium channels in a variety of organisms. Studies of those genes showed researchers that potassium channels from different organisms were likely to be structurally similar. Mutational analysis revealed more: "By mutating those genes and looking at the functional consequences of those mutations, we've been able to identify specific regions of potassium channel proteins that serve crucial functions," MacKinnon said.

MacKinnon's laboratory and others around the world understood that a complete picture of a potassium channel was badly needed. About 18 months ago, his group began trying to crystallize potassium channel proteins from the bacterium *Streptomyces lividans.* After producing suitable crystals, they bombarded the protein crystals with x-rays at the Cornell High Energy Synchrotron Source and collected the data that would reveal the long-awaited structure.

Analysis of the x-ray crystallography data showed that the potassium channel from *S. lividans* is shaped like a cone or "inverted teepee." According to MacKinnon, the structure helps explain one of the great biophysical mysteries - the chemical nature of the pore's main ion conduction pathway. Potassium ions are normally surrounded by water. When they slip into the channel, MacKinnon explains, the potassium ions shed water. In order for this to happen, however, the pore must offer a surrogate for water. "We can now see from the structure how that happens," MacKinnon said.

Ion discrimination takes place in a region of the pore called the selectivity filter. This area is called a filter because it is narrower than the rest of the channel. "When a potassium ion enters the channel, water floats away. Oxygen atoms from the protein then surround the ion, making it more stable," MacKinnon said.

Scientists have also wondered why the sodium ion, which is smaller than the potassium ion, doesn't jump into the potassium channel. Again, the structure may provide insight: "It appears that the selectivity filter - which is held in a very precise conformation - is more tuned for the larger potassium ion," MacKinnon said.

In a second article in *Science,* MacKinnon's team sought confirmation that the bacterial potassium channel they had crystallized was indeed structurally similar to eukaryotic potassium channels found in humans. MacKinnon and

Hughes investigator Christopher Miller at Brandeis University had performed earlier experiments that showed that the deadly scorpion toxin binds tightly to eukaryotic potassium channels. With this information in mind, MacKinnon's group decided to see if the same toxin would bind to the bacterial channel. "Our logic for this experiment was that if the bacterial potassium channel really has the same structure as the human potassium channel, then the bacterial channel should form a binding site for the scorpion toxin," MacKinnon said.

In collaboration with Rockefeller colleagues Steven Cohen and Brian Chait, MacKinnon's team showed that the scorpion toxin binds to a slightly modified bacterial potassium channel, confirming that the two channels are structurally similar.