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RESEARCH NEWS

JULY 01, 1999

Mathematics Reveals Inner Workings of Potassium Pipeline

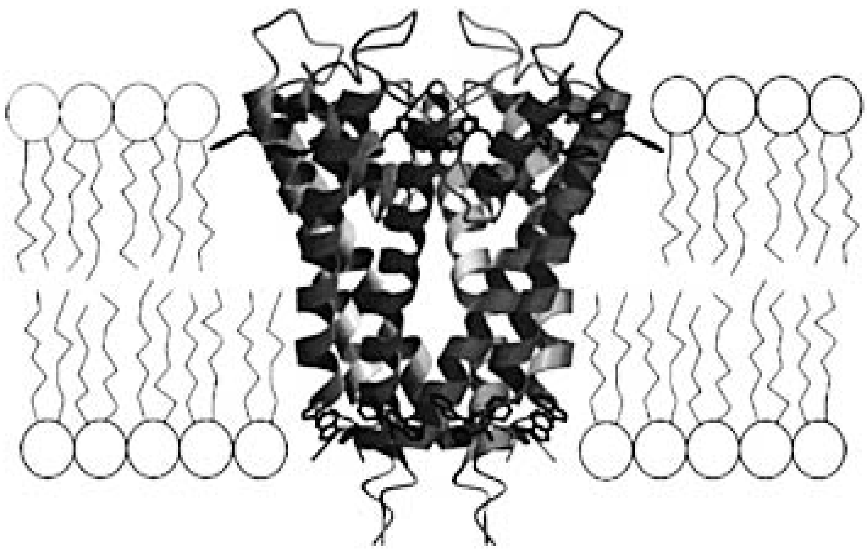

Image Title: Solving the three-dimensional structure of a potassium channel has allowed Roderick MacKinnon and colleagues to gain a better understanding of how the channel functions. - Chris Denney

Many of the body's cells need a reliable flow of potassium to perform their daily tasks. One key to potassium flow, now revealed to researchers, appears to be the energetic effect of a pool of approximately 50 water molecules and four protein spirals that sit in the middle of a narrow channel embedded within cell membranes.

Roderick MacKinnon, a Howard Hughes Medical Institute investigator at The Rockefeller University, and chemist Benoit Roux at the University of Montreal, arrived at this conclusion after calculating the electrical forces operating at the center of the so-called potassium channel. This mathematical analysis follows MacKinnon's team's determination of the three-dimensional structure of a potassium channel last year. The current work appears in the July 2, 1999, issue of the journal *Science*.

The critical problem facing cells is that potassium as well as other small, charged entities known as ions would rather be surrounded by water than by the fatty substances that make up the cell membrane. As MacKinnon explained, "these ions are equally stable in the watery environments found inside or outside of the cell, but getting from one side of the cell membrane to the other is like crossing a large mountain.

"The result is that potassium does not cross the cell membrane easily, no matter which direction it has to travel," he added.

Moving potassium through the cell membrane is critical to numerous life-sustaining functions, including nerve signal generation, heartbeat, and insulin release in response to changes in blood sugar. For example, when a nerve signal travels the length of a neuron, large amounts of potassium must be able to flow quickly from the inside to the outside of a cell.

Last year, MacKinnon and his colleagues showed that the potassium channel is essentially a pore-like structure containing four identical proteins spanning the thickness of the cell membrane. Their studies revealed that each of the four proteins folds together to form the pore and that sections of each protein coil into spiral structures known as a -helices.

One part of the channel, lying close to the outside of the cell membrane, acts as a filter, allowing only potassium ions into the channel. Four of the α -helices meet in the center of the pore and point toward a cavity capable of holding a potassium ion and about 50 water molecules.

In their current study, MacKinnon and Roux's mathematical analysis showed that the local electrical forces associated with the four helices and the water molecules create an environment more like the inside or outside of the cell than the typical center of a cell membrane. This allows potassium to move quickly through the otherwise unfavorable environment of the cell membrane.

"What this organization does is kind of level the energy mountain separating the inside and outside of the cell. This is a very beautiful design that nature has developed," said MacKinnon.

Though this research is "as basic as it gets," MacKinnon noted that understanding the way the potassium channel functions may play an important role in the development of drugs to deal with diseases ranging from diabetes to heart problems. He said that improved understanding of the channel's structure may allow researchers to design medications that can restore the channel's proper functioning should it go awry.

"If we can properly tune potassium channels, we could, for example, develop new ways of affecting airway smooth muscle, which might have implications for asthma," said MacKinnon.