Researchers catch ion channels in their opening act

July 10 2008

Each thought or action sends a million electrical signals pulsing through your body. At the heart of the process of generating these electrical impulses is the ion channel.

A new study by researchers from the University of Illinois measures movements smaller than one-billionth of a meter in ion channels. This movement is critical to how these tiny pores in the cell membrane open and close in response to changes in voltage across the membrane. The findings appear this week in the journal *Neuron*.

Ion channels belong to a special class of proteins embedded in the oily membranes of the cell. They regulate the movement of charged particles, called ions, into and out of the cell. Much like water faucets that can be controlled by turning a knob, channels open or close in response to specific signals. For instance, ion channels that open in response to pressure on the skin regulate our sense of touch.

Voltage is an important switch that controls how some channels open. The voltage across the cell membrane depends on the balance of ions inside and outside the cell and also on the type of ions. Voltage-gated channels are critical for transmitting messages from the brain to different parts of the body by means of nerve cells.

"There has been a large controversy in the field with regards to how these channels respond to voltage," said University of Illinois physics professor Paul Selvin, who led the study. The controversy centers on a

key segment of the ion channel called the voltage sensor.

The voltage sensor gauges the voltage across the membrane and instructs the channel to open or close.

One model for the movement of the voltage sensor suggests that it moves up and down by only a small amount, tugging on the pore of the ion channel and opening it just enough for ions to get through. In 2003, Roderick MacKinnon, who won a Nobel Prize in chemistry for his work on the X-ray crystal structures of ion channels, proposed a competing idea, the "paddle model." This idea involved a large movement of the voltage sensor across the membrane. X-ray crystal structures provide snapshots of proteins in exquisite detail, allowing researchers to look at the positions of every atom.

According to Selvin, a problem with the crystal structure is that it only offers a static snapshot of what the protein looks like and provides only limited information about how different parts of the protein move. Another concern is that the conditions used to obtain protein crystals sometimes alter the original structure of the protein.

In the new study, postdoctoral researcher David Posson worked with Selvin to put the models of voltage sensor movement to the test.

They studied the voltage sensor segment in a specific ion channel called the Shaker potassium channel. This protein was first discovered in fruit flies after researchers observed that a mutation in the channel caused the flies to vigorously shake.

To preserve channels in their original state, Posson studied ion channels inserted into the membranes of frog eggs. He tested the two models using a fluorescence technique called Lanthanide resonance energy transfer (LRET) which allowed him to measure small movements in

proteins. The technique involves the use of a special pair of molecular bulbs that glow either brightly or dimly depending on how far apart they are. The measurement is sensitive to movements as small as one-billionth of a meter. Posson also needed a way to control the voltage across the membrane.

He used an approach called electrophysiology that involves inserting electrodes into the frog egg. This gave him the ability to change the voltage across the membrane and regulate channel opening.

"Our approach brings together two distinct biophysical techniques, electrophysiology and fluorescence, which have been independently useful for the study of proteins," Posson said.

To map the movement of the voltage sensor during channel opening, Posson measured distances from several different vantage points on the protein.

"It's a lot like dispatching a team of molecular surveyors that stand at specific positions on the surface of a protein and collect distances from point A to point B," Posson said. "With enough measurements, the surveyors can build a map of the three dimensional shape of the protein." Posson discovered that the largest distances traversed by the sensor were about two to three times smaller than what was predicted by the paddle model. It showed that the sensor moves by only a small amount to allow the flow of ions.

"We are seeing a clear result that the movement of the sensor isn't super teeny, and isn't super huge," Posson said. The measurements challenge models that predicted large movements of the protein segments, such as the paddle model. The findings also refute models that have a near zero movement of the sensor region. "It's a small piece to the puzzle of how the voltage sensor moves" Selvin said.

Source: University of Illinois at Urbana-Champaign