Jefferson scientists uncover new clues to how crucial molecular gatekeepers work

October 11 2005

One of the biggest mysteries in molecular biology is exactly how ion channels – tiny protein pores through which molecules such as calcium and potassium flow in and out of cells – operate. Such channels can be extremely important; members of the voltage-gated ion channel family are crucial to generating electrical pulses in the brain and heart, carrying signals in nerves and muscles.

When channel function goes awry, the resulting diseases – known as channelopathies, including epilepsy, a number of cardiomyopathies and cystic fibrosis – can be devastating.

Ion channels are also controversial, with two competing theories of how they open and close. Now, scientists at Jefferson Medical College, reporting October 6, 2005 in the journal Neuron, have detailed a part of this intricate process, providing evidence to support one of the theories. A better understanding of how these channels work is key to developing new drugs to treat ion channel-based disorders.

According to Richard Horn, Ph.D., professor of physiology at Jefferson Medical College of Thomas Jefferson University in Philadelphia, voltage-gated ion channels are large proteins with a pore that pierces the cell membrane. They open and close in response to voltage changes across the cell membrane, and the channels determine when and which ions are permitted to cross a cell membrane.

In the conventional theory, when an electrical impulse called an action

potential travels along a nerve, the cell membrane charge changes. The inside of the cell (normally electrically negative), becomes more positive. In turn, the voltage sensor, a positively charged transmembrane segment called S4, moves towards the outside of the cell through a small molecular gasket called a gating pore. This movement somehow causes the ion channel to open, releasing positively charged ions to flow across the cell membrane. After the action potential is over, the cell's inside becomes negative again, and the membrane returns to its normal resting state.

The more recent and controversial theory proposed by Nobel laureate Roderick MacKinnon of Rockefeller University holds that a kind of molecular paddle comprised of the S4 segment and part of the S3 segment moves through the cell membrane, carrying S4's positive charges with it across the lipid. As in the conventional theory, the S4 movement controls the channel's opening and closing. The two theories differ in part because the paddle must move its positive charges all the way across the cell membrane. The conventional theory says that charges move a short distance through the gating pore.

In the current work, Dr. Horn and colleague Christopher Ahern, Ph.D., a research assistant in the Department of Physiology at Jefferson Medical College, showed that the field through which the voltage sensor's charges moved is very short, lending support to the conventional model.

"Using a molecular tape measure with a very fine resolution – 1.24 Angstroms – we tethered charges to the voltage sensor," Dr. Horn explains. "When the tether is too long, the voltage sensor can't pull it through the electric field," meaning the electric field is highly focused.

"This is another nail in the coffin of the paddle model," he says, "because the thickness of the electric field is much smaller than predicted by that model. The measurement is unambiguous in terms of

the relationship between length of the tether and how much charge gets pulled through the electric field.

Next, the researchers are tackling the relationship between S4's movement and the gates that open and close the channels.

Source: Thomas Jefferson University