Modeling Cell 'Doors' Could Aid Drug Development

January 18 2007

To open the door for better medicines, University of Pittsburgh assistant professor Michael D. Grabe thought he first needed to open the 'doors,' or channels, that allow for passage in and out of cells to see what science is up against when developing new drugs.

A faculty member in the biological sciences department in the School of Arts and Sciences, Grabe created a model of open channels in plant cells to gauge the appearance of closed channels in the human heart and brain, which resemble open plant channels. The results appeared in the online edition of *Nature* last month and will be published later in print.

Scientists already know the shape of open channels in human and animal cells. With more knowledge on the shape of closed channels in animal cells, scientists will be better able to understand how to control channels with medicine and restore cell function to treat such conditions as epilepsy and heart arrhythmia, Grabe said.

“Unless we know how these small devices work, it's really difficult to re-create how they work together in the body,” he explained. “It's hard to fix a door when you don't have any idea what a hinge looks like or what a hinge is.”

Known as ion channels, the passages that Grabe studied are proteins that open and close so that electric-charged atoms, or ions, can pass into cells. The ion's charge then passes from one cell to the next, allowing the cells to communicate over long distances.

For example, ions spark a chain of electric impulses in human nervous system cells that go from a person thinking, “I want to open my hand,” to the hand actually opening, Grabe said.

“We wouldn't have consciousness if it wasn't for our cells' ability to hold and pass ions,” he addedd.

Ion channels cannot always be open or shut. Those in human hearts and brains, for instance, have voltage sensors that respond to certain levels of electric charge to open and close the channel. Without sensors to close the channels, the cell would run out of energy. Some toxins, such as those from puffer fish and tarantulas, work by clogging the cell's channels and killing the signals, he said.

Similarly, research links mutations in voltage sensors with conditions such as epilepsy, heart arrhythmia, and deafness, Grabe said. These mutations hinder normal activity of the channel itself, the cell, and the whole body system.

Modern drug developers target ion channels because of their prominent role in molecular harmony. According to Grabe, his model gives scientists another reference when mapping the mechanics of ion channels.

“When developing a drug, researchers need to know what the target of the drug looks like,” he said. “My research focused on what ion channels look like when they're closed and when they're open.”

Grabe based his model on a voltage-gated potassium channel from a plant cell. The channel acts in getting potassium to a plant's roots. The leap from plant to human is not fantastical: Grabe's model hinges on the widely held assumptions that voltage-gated channels operate similarly across most of nature and that the open voltage sensor of plant channels

looks like the closed voltage sensor of animal cells, he said.

“The real reason we care about these things is not because of the plants but because many people, including myself, believe these ion channels behave and look similarly in different cells,” Grabe said. “They've just been co-opted into different organisms for whatever they need.”

Grabe began working on his model approximately four years ago at the University of California at San Francisco with funding from the National Institutes of Health and Howard Hughes Medical Institute.

The next step is to understand how diseases and mutations manipulate the ion channel and how medicine could counteract that interference, Grabe said. Ultimately, he wants to know why proteins take their shape and how disease alters that process, a distant goal right now.

“These are small pieces in a big puzzle,” Grabe said of his latest research. “But it helps.”

Source: University of Pittsburgh