2003 Nobel Prize in Chemistry Awarded to NSLS User Roderick MacKinnon

Roderick MacKinnon, M.D., a professor at Rockefeller University, investigator at the Howard Hughes Medical Institute, and frequent NSLS user, shared this year's Nobel Prize in Chemistry for work explaining how a class of proteins helps to generate nerve impulses – the electrical activity that underlies all movement, sensation, and perhaps even thought. The work leading to the prize was done primarily at the Cornell High Energy Synchrotron Source (CHESS) and the NSLS.

Rod MacKinnon

"Without the synchrotrons, none of the work I do would be possible," MacKinnon told *Newsday.*

The proteins, called ion channels, are tiny pores that stud the surface of nearly all living cells. These channels allow the passage of potassium, calcium, sodium, and chloride molecules called ions. Rapid-fire opening and closing of these channels releases ions, moving electrical impulses from the brain in a wave to their destination in the body. The entire sequence of events takes only a few milliseconds, and occurs tens of thousands of times every day in human beings and organisms of all varieties.

Starting in 1998, after 10 years spent studying the biophysics of ion channels, MacKinnon and his research team surprised the entire research community when they published the very first potassium channel structure, which revealed the way that positively charged potassium ions flow easily through a pore formed by a protein that spans the cell membrane. Thanks to this contribution we can now "see" ions flowing through channels that open and close in response to different cellular signals.

In the five years following, the Rockefeller scientists have continued their research, revealing the inner workings of sodium and potassium channels, or the whys and hows of ion movement through a cell's membrane. This series of structural solutions, determined by x-ray crystallography, offers high resolution molecular-level "snapshots" of ion channels that literally showed the scientific community how electrical signaling occurs.

These structures not only portray an elusive ion channel structurally and mechanically, but also bring history full circle by showing, for the first time, the natural molecular mechanism that underlies the "action potential" theory. In 1952, the theory was demonstrated in a mathematical formulation by English physiologists Alan Hodgkin and Andrew Huxley, who identified a loop relationship between cell membrane permeability (the ability of a cell to open up via ion channels) and the voltage between the inside and outside of the cell.

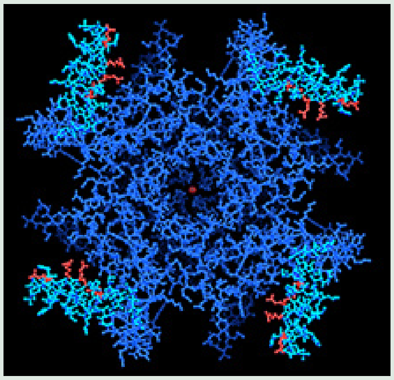
In this theory, the "action potential" of nerve cells is generated when an ion channel on the surface of a nerve cell is opened by a chemical signal – a neurotransmitter called glutamate – which is sent from an adjacent nerve cell. As a result, positively charged sodium ions enter the cell's negatively charged interior. But this single event triggers an electrical pulse that propagates, like a chain reaction, along the surface of the nerve cell, causing sodium-conducting channels on the cell's surface to open up. More sodium enters the cell, and the normal negative inside/positive outside voltage common to all living cells is upset. The whole process occurs in a matter of milliseconds.

The overall effect is an explosive, and then restorative, burst of energy to the otherwise placid cell membrane. As soon as the cascade of sodium channeling begins, hyper-sensitive voltage-dependent potassium channels along the same cell's surface sense the catastrophic switching of the charge value inside the cell. In their own domino effect, they open up to allow positively charged potassium ions to quickly flow out of the cell, restoring the negative inside/positive outside charge balance.

Until the research of MacKinnon and his group, however, no group of researchers had ever completed the loop by solving the riddle of how the membrane voltage determines the permeability. Their work widens a foot trail into an avenue for an entire new area of medical study on the hundreds of ion channel-related diseases and disorders, such as epilepsy, cystic fibrosis, and osteoporosis.

MacKinnon, a biophysicist and self-taught X-ray crystallographer, shares the 2003 Nobel Prize in Chemistry with Peter Agre, M.D., of Johns Hopkins University School of Medicine, who received his award for studies of another type of membrane channel protein.

—Karen McNulty Walsh, Laura Mgrdichian, and Lynn Love



An overhead view of a voltage-dependent potassium ion channel shows four red-tipped "paddles" that open and close in response to positive and negative charges. This structure, discovered by Rockefeller scientists, shows for the first time the molecular mechanism by which potassium ions are allowed in and out of living cells during a nerve or muscle impulse.