

JULY 24, 2005

## Protein Structure Shows How Transporters Tidy Up Synapses

By determining the structure of a protein involved in modulating the electrical signals sent from one nerve cell to another, scientists have resolved, in exquisite detail, a mechanism responsible for helping to move important chemicals around the brain.

The new finding, reported July 24, 2005, in the online edition of the journal *Nature*, has important implications for future treatment of depression, Parkinson's disease, epilepsy and other conditions that are caused when the flow of the brain's chemical neurotransmitters is reduced or otherwise impaired.

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The new work, by a team of scientists led by Howard Hughes Medical Institute investigator Eric Gouaux, reveals the crystal structure of a prokaryotic homolog of neurotransmitter transporters, proteins that clear synapses—critical junctions between brain cells—of the chemicals that facilitate the transmission of the electrical signals the brain routinely sends from cell to cell.

"Transporters are important because they terminate signal transduction at synapses by taking up neurotransmitters," said Gouaux, who is at Columbia University. "They're a little bit like vacuum cleaners for synapses."

In the new study, Gouaux and his team resolved the three-dimensional crystal structure of a neurotransmitter transporter homolog from a bacterium known as *Aquifex aeolicus*, a microbe that thrives in superheated deep-sea vents. The transporter found in the bacterium is, in many important respects, similar to transporters found in the brains of higher organisms, including humans. In humans, these neural cogs are important targets of drugs and their dysfunction is associated with diseases such as depression, epilepsy and

Parkinson's. They are also the targets of illicit drugs, such as cocaine and amphetamines.

“In humans, drugs exert their key activities on these transporters,” said Gouaux.

Gouaux and colleagues Atsuko Yamashita, Satinder K. Singh, Toshimitsu Kawate and Yan Jin resolved the structure of the transporter from the bacterium using x-ray crystallography, a technique capable of revealing the three-dimensional structure of proteins in superb detail. Knowing the arrangement of the atoms that make up the transporter molecule, it is possible to discern the functional features of the protein to see how it goes about its business of tidying up synapses.

“One of the things the structure has told us is where the transporter specifically binds to sodium,” Gouaux noted. That insight, he said, is important because it shows how the transporter hooks up with the sodium ions, charged atoms, found in the proximity of nerve cells.

Nerve cells communicate with one another at breakneck speed, sending electrical impulses that encode information to help cells carry out their everyday functions. Those electrical signals are converted to chemical energy as they leave the transmitting cell and are switched back to electrical energy as they pass through the synapse to the receiving cell. Transporters play a critical role by helping to regulate the electrical signals and cleaning up the chemical neurotransmitters from the synapse in the blink of an eye.

By drilling down to the nuts and bolts of how the bacterial transporter works, Gouaux and his team have established not only the details of a key element in the synaptic flow of information in the brain, but guiding insight into how entire classes of transporters perform their biological functions.

“Until now, there has been essentially no information at the level of the atom of how this activity occurs,” Gouaux explained. “The notion of how coupling occurs and where these sites are is an important general advance.”

The work, he added, may go far in helping scientists determine how neural transporters specify chemical neurotransmitters in humans. “We can extrapolate this work to human proteins.”

For example, transporter dysfunction can amplify and complicate the effects of Parkinson's disease. “Because these transporters move dopamine, they can contribute to the symptoms of Parkinson's,” Gouaux said.

Gouaux believes, however, that the most important potential clinical upshot of the new work will involve the treatment of depression. Depression is associated with low levels of the neurotransmitter serotonin, and drugs that regulate the transport of serotonin have been used to treat depression successfully.

“Currently, there is no understanding of what the human serotonin transporter looks like,” according to Gouaux. “This work provides a template on which a human serotonin transporter could be modeled.”

Such a model would enable the development of new drugs to regulate serotonin levels and alleviate the symptoms of depression, which include altered mood, emotion, sleep and appetite. The disease affects as many as 17 million people in the United States alone.

Because there are only two classes of neural transporters, using the newly solved structure of the *Aquifex aeolicus* transporter to understand the details of other important human transporters is likely, Gouaux said.

“One could not only try to model the human serotonin transporter, but others as well. The motif is used over and over again in the human nervous system.”