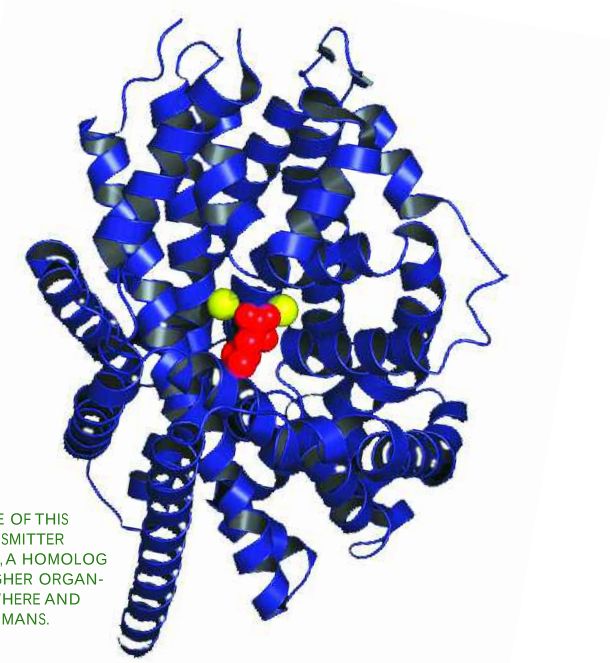
Synaptic Shape Shifters

Three HHMI laboratories chart the landscape of nerve connections.



THE ATOMIC STRUCTURE OF THIS BACTERIAL NEUROTRANSMITTER TRANSPORTER (LEUTAA), A HOMOLOG OF ONES FOUND IN HIGHER ORGANISMS, MAY ILLUMINATE WHERE AND HOW DRUGS ACT IN HUMANS.

HHMI INVESTIGATOR ERIC GOUAUX ONCE JOKED THAT HIS lab studies "how the garbage is taken out" of the synapse, the junction between two nerve cells. But it's really no joke: Excess chemicals can lead to chaos in the nervous system.

Gouaux and colleagues published new work on synapses in July 2005, around the same time that two other HHMI laboratories also announced discoveries about how synapses work. The three labs took different approaches, as if viewing the synapse junction through various photographic lenses.

Gouaux's group (then at Columbia University, he has since moved his lab to the Vollum Institute at Oregon Health & Science University in Portland) took a high-resolution close-up of a transporter molecule. Robert B. Darnell's laboratory at the Rockefeller University in New York shot a panoramic view of a whole genome's worth of synapse proteins. And Terrence J. Sejnowski's team at the Salk Institute for Biological Studies in La Jolla, California, modeled synaptic function using a computer simulation. Their collective results may change how researchers define the synapse and its role in the brain cells controlling motor movement, mood, and memory.

First, the close-up. The transporters that move the neurotransmitter serotonin back into nerve cells are a target for antidepression drugs. How those transporters work, though, is still a mystery, which means the drug action also remains unknown. Gouaux's group solved the atomic structure of a bacterial transporter that is structurally similar to the human transporters. Its symmetry and shape suggest which portions of the molecule are involved in binding to the neurotransmitters, which may give clues to where and how drugs will act.

Zooming out from the atomic to the genomic level, Darnell's group searched for nerve cell proteins whose production is regulated by one RNA splicing molecule, called Nova. To do that, they used a gene microarray tool that would show which RNAs were present in a nerve cell when Nova was present but not when Nova was absent. They found 49 such RNAs and, surprisingly, found that some 80 percent of the corresponding proteins function at the synapse. (The other 20 percent are involved in axon guidance.) In addition, 75 percent interact with each other.

"There's an aspect of gene regulation going on here that wasn't clear before," says Darnell. "Nova is acting in a complex way to change the nature of the synapse." And by changing the quality of synapse proteins, Nova may also modify synaptic plasticity—the mechanism used by repeatedly activated synapses to form memories.

Both Gouaux's and Darnell's work details synapse proteins at a specific point in time. But synapses are dynamic, releasing and recycling neurotransmitters and firing nerve impulses. In the past, neuroscientists charted these dynamics by measuring electrical activity but without visualizing individual synapses.

Now, through computer simulation, Sejnowski's group has designed an animated prediction of what happens in one particular type of synapse in the chick ciliary ganglion. They used data from three-dimensional tomography imaging—a type of electron microscopy in which a thick tissue slice is imaged at different angles to show its 3-D structure—to generate a topographic map of the synapse's crinkled surfaces. To this map, they added electrical and chemical measurements taken from wet lab experiments to simulate neurotransmission.

"It's as if we had a simulated microscope that could zoom into the synapse," says Sejnowski. The simulation program, called MCell, surprised him when it showed that most of the nerve cell transmission was occurring outside the "active zone," the area in the synapse where researchers thought most nerve transmission occurs. (For more about MCell, see this issue's Tool Box column on page 52.) "We suspect that a similar thing is happening at other synapses in the brain," says Sejnowski. He says this type of ectopic transmission may serve to increase the background activity level of neurons, sensitizing them during times of rest to be fire-ready when needed. MCell could also help drug developers "watch" the effects of candidate drugs.

Each of these three groups has added new ways to envision synapse functions. Their work shines a searchlight on new pathways to treating disorders of the central nervous system like depression, epilepsy, and movement disorders. ■

~Kendall Powell~

SYNAPSE INVESTIGATORS

Eric Gouaux

Gouaux studies the molecular mechanisms of communication between nerve cells by studying the receptors and transporters that detect and remove neurotransmitters from synapses.

Robert B. Darnell

Darnell's research seeks a basic understanding of a group of rare brain diseases. These studies are producing insights into tumor immunology, autoimmunity, and neuronal cell biology.

Terrence J. Sejnowski

Sejnowski's goal is to discover principles linking brain mechanisms and behavior. His laboratory uses both experimental and modeling techniques to study biophysical properties of neurons.

ILLUSTRATION: ERIC GOUAUX; *GOUAUX:* PAUL FETTERS; *DARNELL:* ROCKEFELLER UNIVERSITY/DIRK WESTPHAL; *SEJNOWSKI:* MARK HARMEL