SOUTHWESTERN NEWS

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BRAIN PROTEINS COULD HOLD KEY TO SEIZURES, MEMORY, LEARNING

DALLAS — June 22, 1995 — Treating neurological and psychiatric disorders without a fundamental understanding of how the brain functions is a little like playing the lottery. Sometimes you may win, but your ability to do it consistently doesn't improve.

Researchers in molecular genetics and at the Howard Hughes Medical Institute (HHMI) at UT Southwestern Medical Center at Dallas are working to improve those odds by studying synapsins and other proteins that play a key role in the way brain cells communicate with each other.

Dr. Thomas Südhof, professor of molecular genetics and an HHMI investigator, reported on this research in two separate issues of *Nature* this month. In the June 8 issue of the international scientific research journal, he and colleagues described studies that showed the significance of synapsins, a family of proteins that appear to be key players in brain function.

In the June 22 *Nature*, Südhof reviewed what he and others have learned so far about the chemical transmission of signals from one brain cell to another across the microscopic gap between them known as a synapse.

"Synaptic transmission is the currency of information exchange in the brain," he said.

All cells communicate with each other via complex biochemical pathways, but communication from neuron to neuron — between cells of the central nervous system — is by far the fastest and most tightly regulated.

Südhof describes nine steps in this biochemical communication process, called the synaptic vesicle cycle. Synaptic vesicles are tiny bubbles on a neuron's surface that fuse with the cell membrane, releasing a cascade of proteins that perform different parts of the task of relaying messages from one cell to the next. Synapsins, the focus of Südhof's June 8 journal article, are by far the most abundant of these proteins.

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The studies detailed in that article examined the effects of a lack of synapsins on knock-out mice. The mice are called "knock-outs" because one or both pairs of genes for synapsins have been removed or "knocked out."

The knock-outs missing one type of synapsin had more seizures than normal. Mice lacking genes for both synapsins experienced an even higher incidence of seizures.

This is one of the first times genes have been identified as playing a direct role in seizures, Südhof said. The finding could make the knock-out mice a useful model for epilepsy research. His experiments with synapsin knock-outs also pinpointed the role these proteins play. Synapsins are not essential for development of the synaptic vesicles, nor are they a component of the basic mechanism of synaptic signal transmission. What they do is accelerate or slow transmission of signals, he said, thus regulating the flow of information. You might call them the traffic signals of the brain.

Despite all that has been discovered about the process by which brain cells communicate with one another and the proteins involved, there is a long way yet to go. "At this point the molecular description of the synaptic vesicle pathway has reached the sophistication of cartography in the 16th century," Südhof said. "We can delineate contours of continents, but the interiors are largely blank."

For Südhof and his colleagues, the next steps are to investigate how synapsins affect synaptic plasticity — the brain's ability to process varying amounts of information at varying speeds — and to uncover what else affects this vital capacity of the brain to possess, process and store information.

"Since a major component of brain function consists of synaptic function and synaptic changes, an understanding of synaptic plasticity could give us important insights into the underlying mechanisms of learning and memory," Südhof said.

Südhof's research was supported by HHMI and the Perot Foundation.

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