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A key enzyme helps keep the synapse on track

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At its core, healthy neurological function hinges on the efficient passage of information between brain cells via the synapse.

Figuring out how the synapse traffics this information -- a process called neurotransmission -- is crucial to understanding the function of the healthy and diseased brain.

Now, a team led by researchers at Weill Cornell Medical College in New York City has spotted a crucial new piece to that puzzle.

Their findings, published today in *Neuron*, focus on the role of a cellular enzyme called Synaptojanin 1 (Synj1).

Prior research had suggested the enzyme was key to certain late steps in the synaptic vesicle cycle, a critical aspect of synaptic function. But the new study finds that removing synj1 from the synapse dramatically slows one of the very first steps in the vesicle cycle in a process known as endocytosis.

"By disabling synj1 activity at key points, we effectively slowed endocytosis. That suggests this enzyme is far more important than we had ever assumed before," says study senior author Dr. Timothy A. Ryan, professor of biochemistry at Weill Cornell Medical College.

Here's how endocytosis works: Within brain cells, information is stored as electrical signals. However, before that information can be passed cell-to-cell, it must first be converted at the cell's surface into chemical

signals that flow via the synapse.

Each synaptic transmission involves the carriage of a packet, or "vesicle," of neurotransmitter chemicals. Each synapse has only about 100 of these packets.

"Endocytosis involves the shuttling back and forth of these sac-like objects from the cell surface to the cell interior," Dr. Ryan says. When a vesicle empties, it isn't discarded, however. Instead, it undergoes complex chemical changes that enable it to be recycled and readied for another run.

Chemical signaling is crucial to this recycling process, and typically involves the addition or subtraction of phosphates from key lipid molecules. Synj1 is an unusual type of phosphate-removing enzyme, or phosphatase.

"It's unusual in that it actually contains not one but two distinct enzymes -- each of which clips off phosphate at a different position or domain on the lipid molecule, in this case the '4' and '5' positions," explained lead researcher Meera Mani, an M.D/Ph.D. candidate in Dr. Ryan's lab.

In prior research, researchers led by Dr. Pietro de Camilli, of Yale University School of Medicine and the Howard Hughes Medical Institute, found that synj1 was essential to vesicle recycling. Their work showed that synj1 helped strip vesicles of a clathrin molecule "coat" once it had delivered its cargo to the cell membrane.

Collaborating on the new study, Dr. Ryan and Dr. de Camilli wanted to see if synj1 played an even greater role in the life of the synapse.

"We found that it does," Dr. Ryan says. In fact, endocytosis slows down once synj1 is disabled in any key way, he says.

In their experiments, Drs. Ryan and de Camilli created genetically engineered "knockouts" of the dual-enzyme synj1 to which they could then add back different versions of the protein. One version lacked the functioning enzyme aimed at the 4 position, while another lacked the functioning enzyme aimed at the 5 position. "We also created a third variant that mutated the 'tail' of the synj1 molecule, rendering it unable to 'talk to' certain elements of the endocytic machinery," Dr. Ryan says.

In each case, endocytosis slowed to a crawl, due in part, at least, to a buildup of clathrin coating on vesicles.

Some synj1 mutations were more disruptive than others. "Dysfunction in the dephosphorylating enzyme for position 5 was universally disruptive, but the other two mutants were pretty effective at putting a stop to endocytosis, too," Mani notes.

On the other hand, simply adding normal synj1 to the "knockout" neurons restored healthy endocytosis and cell-to-cell synaptic communication, the researchers found.

"The importance of synj1 to endocyotosis generally came as a surprise," Dr. Ryan says. "This expands yet again our knowledge of this crucial neuronal machinery and gives us new targets for research into the origins of neurological diseases and potential ways to treat them."

He stressed that the cure for brain diseases is not imminent based on these types of findings, but the building blocks are being added, one by one.

"In the future, medicine will be highly personalized, based on an intimate knowledge of key mutations each of us may carry that predispose us to neurological disease," Dr. Ryan explains. "All of that will come to pass over the next few decades. But this is 2007, and right

now we're still busy writing the 'shop manual' for how the brain is made and works. Discoveries like these are adding new pages to the manual every day, and it's that kind of knowledge that will someday save and enhance lives."

Source: New York- Presbyterian Hospital