Researchers solve membrane protein mystery

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A University of Wisconsin-Madison research team has solved a 25-year mystery that may lead to better treatments for people with learning deficits and mental retardation.

Synaptophysin is the first protein and most abundant ever found on the membranes surrounding the tiny sacs that carry chemical messengers to synapses, the gaps where communication between nerve cells occurs. But even though the loss of synaptophysin has recently been linked to learning deficits and mental retardation, scientists have been unable for more than a quarter-century to explain what it actually does.

Now UW-Madison researchers have shown that synaptophysin controls the replacement of the constantly needed sacs, also known as vesicles. The study, appearing in the current issue of the journal *Neuron*, may lead to future drugs that could restore normalcy when vesicles are not utilized efficiently.

"Vesicles are at the heart of fusion, the fundamental process by which information is exchanged between and inside all cells in the body," says Edwin Chapman, a Howard Hughes Medical Institute professor at the UW-Madison School of Medicine and Public Health.

In the nervous system Chapman's team studied, the process begins when an impulse triggers exocytosis — that is, when a vesicle releases neurotransmitter at the synapse. Then a receiving neuron on the other side of the synapse binds to the neurotransmitter and activates a signal. To wrap up the first phase, the spent vesicle is incorporated into the

donor cell membrane.

In the recovery phase of the process, called endocytosis, a new vesicle is pinched off from the donor cell surface and reloaded with neurotransmitter.

"This is a tightly coupled recycling process involving trillions of vesicles throughout the brain," says Chapman, based in the Department of Neuroscience. "As vesicles are consumed, if they are not immediately replaced, then you have a synapse that is not active anymore, and this is a problem."

The synaptophysin mystery had stayed in the back of Chapman's mind since he had been a graduate student in the late 1980s. When his current graduate student Sung E. Kwon said he wanted to apply some of the newest techniques to analyzing the problem, Chapman encouraged him to do it, despite the fact that other scientists had failed for years to find what synaptophysin does.

Using a mouse that had been genetically engineered to have no synaptophysin, Kwon attached a fluorescent tag to a vesicle protein so he could study the exocytosis-endocytosis cycle optically. He also used electrophysiological methods to analyze signaling in normal versus synaptophysin-free vesicles.

The experiments showed that the lack of synaptophysin had no effect on exocytosis, but produced a clear-cut deficit in the recycling of vesicles during endocytosis. Kwon was able to confirm the effect when he inserted synaptophysin and regained normal endocytosis.

"We found that synaptophysin regulates two distinct phases of endocytosis in synaptic vesicles, both during and after sustained neuronal activity," Kwon says. "Lack of synaptophysin delayed the replenishment

of usable vesicles."

The defect may help explain why people with synaptophysin mutations may have mental retardation, he says.

"It will take more studies to directly link how this cycling defect leads to mental retardation, but we now have a good starting point," Kwon says.

Scientists could also now begin to screen for molecules that could override the defect and restore normal rates of endocytosis, adds Chapman.

"You can't do anything like that until you know what the protein does," he says. "And now we do."

Provided by University of Wisconsin-Madison