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Motor Molecule for Memory Identified

Storing memories in the brain is a physical process that requires some demolition and a lot of construction. Ground zero for this makeover is the synapse - a specialized junction that is the site of chemical chatter between neurons. When new memories are stored, synapses are rapidly reconfigured and rebuilt so neurons are equipped to respond more readily in the future.

Researchers are now zeroing in on how single synapses change over time, and one of the key questions facing scientists is how the raw materials are transported to the construction site in a timely manner. Now, Howard Hughes Medical Institute researchers have identified the chief motor protein that hauls the building materials to their destinations in the synapse—just when they are needed. Researchers suspect that breakdowns in this transport process may contribute to deficits in learning and memory that accompany certain disorders, such as Alzheimer's disease and addiction.

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— Michael D. Ehlers

Howard Hughes Medical Institute investigator Michael Ehlers and his colleagues at Duke University Medical Center published their findings in the October 31, 2008, issue of the journal *Cell*. Ehlers's group collaborated on the research with scientists at Brown University, the McLaughlin Research Institute in Montana, and the University of Massachusetts Medical School.

Neurons communicate by releasing chemical neurotransmitters into synapses, the junctions between neighboring neurons. These neurotransmitters are signals that activate receptors on the surface of a nearby neuron that then trigger a nerve impulse. As repeated signaling occurs at a particular synapse, a process called long term potentiation (LTP) rapidly increases certain kinds of receptors on the surfaces of the receiving cell. Once the population of these AMPA receptors is increased, neurons are prepared to respond more

efficiently to the next wave of incoming signals.

Researchers knew that AMPA receptors and other LTP-enhancing molecules are held in reserve at the base of dendritic spines in containers called recycling endosomes. They also knew that LTP is triggered by activation of specific receptors on the spines that in turn launch an influx of calcium into the neuron. But the nagging biological mystery was how this calcium blast causes endosomes to be transported to the dendritic spines where they discharge their cargo. How a calcium signal gets translated into long-lasting changes in the molecular composition and function of the synapse is a central question in synaptic plasticity and in neuroscience in general, said Ehlers.

Researchers had previously established that myosin proteins are the long-haul truckers of the cell—molecular motors that carry cargo along cellular highways made of actin filaments. One particular myosin protein, Myosin Vb (MyoVb), was known to exist in the brain and to be activated by calcium, said Ehlers. So Ehlers and his colleagues decided to explore whether MyoVb might be the learning engine they were seeking. Their experiments showed that MyoVb concentrates in dendritic spines. Furthermore, they found that when neurons receive signals that trigger LTP, the MyoVb protein homes in on the endosomes and attaches itself just as a good transporter protein should.

Finally, using fluorescent tracers and high-resolution imaging, the researchers observed the MyoVb motor proteins actually carrying their endosome cargo to the dendritic spines in neurons that had been stimulated to enable LTP. And they demonstrated that when they shut down MyoVb, LTP was completely blocked.

Understanding MyoVb's function could yield insights into malfunctions of synaptic plasticity, Ehlers said. We know this form of synaptic plasticity is abnormal in a range of neurological and psychiatric disorders, he said. For example, it is one of the early abnormalities in animal models of Alzheimer's disease. And excessive plasticity of the type that involves MyoVb is associated with the aberrations in brain reward circuitry seen in addiction and compulsive behaviors. Also, he said, developmental abnormalities in the machinery of synaptic transmission related to LTP have been linked to autism and epilepsy.

Our hope is that a better understanding of LTP and the molecules that mediate it might yield new ways to target this process to either enhance or inhibit it, depending on the clinical objective, said Ehlers.

Ehlers also emphasized that hauling cargo in neurons is probably not Myosin Vb's only job. We know that Myosin Vb is not just expressed in neurons, but is found throughout the body, he said. So, we think that this transport mechanism may be employed in all kinds of cell types in the body to allow for local signal-dependent changes in the molecular composition of the cell membrane. This requirement for localized transport is a fundamental feature of many aspects of cell biology, including cell migration, cell division and cell differentiation, he said.