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Neuron's "Hardware Store" Discovered

Neurobiologists have discovered the neuron's Home Depot - a rich source of building materials that nerve cells use to construct new connections during learning. The scientists said their discovery offers a new place to search for the factors that cause neurons to sprout connections called dendritic spines.

The research team, led by Howard Hughes Medical Institute investigator Michael Ehlers, found that sac-like organelles called endosomes are the neuronal hardware stores that contribute the membrane material—and likely a multitude of other molecules—necessary for constructing new connections between neurons. Ehlers, who is at Duke University Medical Center, and his colleagues, reported their findings in the December 7, 2006, issue of the journal *Neuron*.

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— **Michael D. Ehlers**

Neurons propagate nerve signals throughout the brain and spinal cord, communicating with one another across junctions called synapses. Neuronal branches called dendrites support the connections between neurons. Each dendrite sprouts large numbers of tiny mushroom-shaped spines, which act as receiving stations for signals from neighboring neurons. The spines contain receptors for neurotransmitters, which are released from nearby nerve cells to communicate with neighboring neurons. Spines cover the surface of most neurons and are responsible for mediating close to two thirds of all neuronal connections in the brain.

According to Ehlers, researchers have long known that dendritic spines play a role in the strengthening of synaptic connections that occurs during learning - a process known as long-term potentiation (LTP). And they knew that growth of these spines depends on the remodeling and growth of the cellular scaffolding, or cytoskeleton. But an unanswered question has been where does the membrane for this growth come from, said Ehlers. We had shown

before that compartments called recycling endosomes are the source of new receptors that enable the functional strengthening of synapses in LTP. So, it was an attractive idea that these endosomes are also the source of the membrane and other materials that enable structural changes such as spine growth.

To determine whether endosomes contribute these materials, the researchers tagged endosomes with various fluorescent tracers in cultures of neurons and used light microscopy and electron microscopy to visualize the activity of endosome. They first observed that the endosomes nestle near the base of dendritic spines, where they would be well positioned to contribute materials for spine growth.

They also found that the spines were profoundly affected by chemically or genetically blocking transport of material from the endosomes. Normally there is ongoing movement of molecules and membrane from these recycling endosomes to the cell surface and back, said Ehlers. But when we disrupted that movement, the spines shrunk and collapsed. The researchers also found that blocking recycling endosome transport rendered the cultured neurons unable to respond to chemical signals that would otherwise stimulate neurons to trigger LTP and spine growth.

The scientists also used microscopy and fluorescent tags to see the detailed action of the endosome machinery during LTP. We could see that stimulating receptors would cause these endosomes to move into the spine and send a shower of small vesicles toward the spine plasma membrane, where they would fuse and release their contents at the spine, said Ehlers.

One intriguing finding, said Ehlers, was that the amount of membrane material lost from endosomes during the process was equivalent to the amount gained by the spines. It is just a correlation, but it is a strong one that suggests that the endosome membrane is sufficient to account for growth of the spine, he said. Ehlers said the endosome is quite likely the source of many other materials for spine growth, as well. Our working theory is that recycling endosomes provide a plasticity module that can supply all at once protein, lipids, and other molecular components for spine growth, he said. It's an attractive possibility that one simple transport step could provide all the needed material in one shot.

Discovery of this neuronal hardware store means that we now have a place where we can look in unprecedented detail for the critical molecular mediators of brain plasticity, said Ehlers. And we also have a potentially valuable new way to monitor functional changes in synapses. We can use these optical probes to look into the brain and ask which synapses are active; which ones are undergoing plasticity.

Ehlers's co-authors of the *Neuron* paper included Mikyoung Park, Thomas Helton and Carmenzind Robinson of Duke, Kristen Harris of the University of Texas at Austin, and Jennifer Salgado and Linnaea Ostroff of the Medical College of Georgia.