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## Understanding the Neuron's Green Architecture

Being green is a lifestyle. Turns out, each of your neurons is deeply committed to that green lifestyle - and you didn't even know it. In just a thousandth of a second, a neuron can dump up to 5,000 molecules of its chemical messenger - a neurotransmitter - into the synapse, where it will trigger an impulse in a neighboring nerve cell.

The neuron is a recycler *par excellence* when it comes to these neurotransmitters. Neurons must not only ready neurotransmitter receptors to receive the signals coming fast and furious, but they must also recycle receptors that have been used. And you thought you had recycling problems?

Researchers have now determined the identity of one of the more significant features of a neuron's green architecture. They identified a cellular anchor that keeps the recycling machinery in place in the cell membrane so that it can recycle spent neurotransmitter receptors. The anchor is critical; without it, neurons would not be able to remove used receptors and install new ones in the cell membrane. And beyond being a mere anchor, the protein is part of a larger ensemble of proteins that help neurons adjust and maintain the strength of their signaling connections.

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- Michael D. Ehlers

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Howard Hughes Medical Institute investigator Michael Ehlers and his colleagues published their discovery in the September 20, 2007, issue of the journal *Neuron*. Ehlers and his research team at Duke University Medical Center collaborated on the study with scientists from the University of North Carolina at Chapel Hill.

In their experiments, the researchers were looking for a molecule that keeps endocytic zones anchored in the neuronal membrane. These endocytic zones house the machinery for recycling neurotransmitter receptors. Neurons use neurotransmitters to communicate with one another across synapses, the junctions between them. They release neurotransmitters into a synapse to trigger or inhibit a nerve impulse in a neighboring neuron.

Ehlers said neuroscientists have been searching for a better understanding of how the recycling areas (endocytic zones) are connected to a region of the membrane called the postsynaptic density, where receptors cluster to receive neurotransmitter signals.

In previous studies, Ehlers and his colleagues established that endocytic zones are the sites where neurotransmitter receptors are recycled. “We found these hot spots of endocytosis right next to each postsynaptic density, but we wondered what molecular mechanism could couple these two membrane domains,” said Ehlers. “Understanding this coupling mechanism is crucial for beginning to understand how neurons solve the problem of modifying the strength of a single synapse.”

The coupling mechanism is also critical in permitting neurons to adjust the number of receptors on their surface—and then preserving that modification for a long period of time. “The challenge for the neuron,” said Ehlers, “is to precisely regulate the number of receptors, even as they are constantly escaping the postsynaptic density. There had to be a mechanism to capture escaped receptors for recycling.”

In searching for the anchor molecule for endocytic zones, the researchers concentrated on a protein called dynamin-3. They chose dynamin-3 because, although its function was unknown, it is well concentrated in the brain and is a member of a family of proteins that chain together to form molecular nooses that pinch off vesicles in the receptor recycling process.

The researchers employed fluorescent imaging studies that revealed that dynamin-3 concentrates at the endocytic zone and couples itself to another protein, called Homer. Homer was known to attach to the postsynaptic density. Molecular studies revealed dynamin-3 can latch onto Homer by forming chains of dynamin proteins that bridge the distance between the endocytic zone and the postsynaptic density.

Ehlers noted that one of his group's key experiments showed that the endocytic machinery uncoupled from the postsynaptic density when dynamin-3 was knocked out in the neurons. “Even though our molecular analysis showed quite clearly that dynamin-3 functions as a connector, it was really surprising that disrupting dynamin-3 so completely caused this uncoupling,” said Ehlers. “This gives a tool to do experiments nobody has done before—exploring what happens when you no longer have recycling going on right next to the postsynaptic density.”

“There are still a lot of molecular details of the dynamin-3 mechanism we don't understand,” said Ehlers. “But we now have the tools to disrupt it selectively, to further explore its function. Furthermore, we can now manipulate the pools of receptors and ask interesting questions about how availability of receptors affects the ability of the synapse to undergo critical plastic change in its strength,” he said. “This process is fundamental for normal brain development and likely goes awry in disorders of cognition and memory.”