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Chemical Messenger Lets Synapses Communicate as Neurons Learn

Each neuron in the brain communicates with thousands of its neighbors. This constant chatter demands coordination not only between neurons, but also between different sites on individual nerve cells. Researchers have now used sophisticated new imaging technology to identify a chemical messenger that helps neurons manage this task, enabling them to adjust their sensitivity to incoming signals to facilitate learning and memory.

Karel Svoboda, a group leader at the Howard Hughes Medical Institute's Janelia Farm Research Campus, and his colleagues, Christopher Harvey, Ryohei Yasuda, and Haining Zhong, published their findings in the June 13, 2008, issue of the journal *Science*. Harvey and Yasuda, who is now at Duke University, were lead authors of the paper.

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— Karel Svoboda

Most of the cognitive functions in mammals — ranging from perception to memory formation — are performed in the cortex, a massive network of neurons. Neurons are linked into circuits by synapses, which pass information between neurons. Svoboda's research group is interested in understanding how the circuits and synaptic mechanisms underlying this awesome neural network produce our perception of the world. How plastic are these neural circuits — that is, how do the physical properties of the neural network change in response to experience? he asks. The answers to these questions will profoundly change our understanding of the function and diseases of the brain.

Synapses are supported on tiny mushroom-shaped spines that sprout from dendrites, the branches of neurons that receive incoming signals. Each spine acts as a receiving station for chemical signals—neurotransmitters—from neighboring neurons.

As synapses are repeatedly triggered to transmit an impulse, the strength of those connections can change through a process called long-term potentiation (LTP). LTP enables the brain to modify circuits during learning.

Last year, Harvey and Svoboda found that after a synapse undergoes LTP, weaker stimuli can cause LTP at neighboring synapses. They showed that there must be a message that travels within neurons from one spine to another to coordinate the strengthening of synaptic connections, but the nature of the chemical signal was unknown.

In their latest experiments, Svoboda and his colleagues studied a signaling molecule called Ras, which they thought might be one of the molecules that spread from a stimulated spine to neighboring spines. This molecule was a candidate because it was known to be a critical part of the cellular signaling machinery activated during LTP.

The researchers engineered rat neurons so that they would express a fluorescent protein that changes its properties when Ras was activated. They then combined two new technologies to stimulate the synapses in single tiny spines and observe the migration of activated Ras.

To make such precise measurements in intact tissue, Svoboda's team built a sensitive microscope that combines two-photon excitation with fluorescence lifetime imaging microscopy. Svoboda's team used the new technology, called two-photon lifetime imaging microscopy, to dissect the role of Ras in synaptic plasticity at the level of single synapses. Two-photon laser scanning microscopy can capture clear images of individual dendritic spines.

We found that Ras activity increased very rapidly in the stimulated spine and persisted for about five minutes, said Svoboda. And over that time active Ras escaped the stimulated spine and spread into the dendrite and invaded neighboring spines, he said. The result was that the threshold of stimulation in the neighboring spines was lowered.

Importantly, said Svoboda, their experiments showed that the diffusion of Ras from the stimulated spine was necessary for inducing LTP — not activation of Ras that was already present in the neighboring spines. Thus, he said, Ras carries functionally important signals among spines.

We think that Ras is one of the factors involved in the crosstalk between synapses, and it is a necessary factor, but likely not the only factor, said Svoboda. This is the opening salvo in uncovering a rich vocabulary for intersynaptic communication.