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## A Rewarding Discovery Shows How Dopamine Activates Brain Circuitry

Researchers have discovered how dopamine—a molecule important for communication between neurons in the brain—stimulates the synthesis of proteins in neuronal processes. This local stimulation of protein synthesis may modify synapses in the brain during learning, said the researchers.

The new findings add to the understanding of dopamine's influence on the brain's reward circuitry that appears to be altered by addictive drugs. The research team, led by Erin M. Schuman, a Howard Hughes Medical Institute investigator at the California Institute of Technology, published its findings in the March 3, 2005, issue of the journal *Neuron*. Lead author on the paper was Bryan Smith in Schuman's laboratory.

Neurons trigger nerve impulses in their neighbors by launching bursts of neurotransmitters, such as glutamate and dopamine, across junctions called synapses. The neurotransmitter receiving stations on neurons are tiny spines that festoon the surfaces of dendrites, which are small branches that extend from neurons.

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"Dopamine and regulation of dopamine signaling is important for reward circuits in the brain, including those responsible for our ability to learn about the positive or negative consequences of environmental stimuli including drugs of abuse," said Schuman. Dopamine-triggered neuronal signaling is also involved in regulating motivation, and in such diseases as Parkinson's disease and schizophrenia, she said.

According to Schuman, it was known that dopamine influenced the strengthening of synaptic connections among neurons. It was also known that such strengthening, or plasticity, involved activation of protein synthesis in

the dendrites, which somehow led to enhanced activity of other kinds of neurotransmitter receptors. However, she said, the mechanism by which dopamine influenced such local protein synthesis and triggered plasticity was not known.

In their studies, Schuman and her colleagues introduced the gene for a fluorescent “reporter” molecule into cultured rat neurons, such that when protein synthesis was activated, the neurons would emit a telltale glow. When the researchers activated dopamine receptors on the dendrites, they detected the glow in the dendrites, revealing that dopamine did activate local protein synthesis and, thus, promoted plasticity. In a more targeted experiment, they introduced molecules directly into the dendrites that would tag newly synthesized endogenous proteins fluorescently. Those experiments also revealed local protein synthesis due to activation of dopamine receptors.

The researchers' measurements indicated that dopamine receptor activation triggered immediate enhancement of protein-synthesis-sensitive synaptic transmission among the neurons. “That's a result that people have been seeking for years,” said Schuman. “It's a very rapid effect on synaptic transmission that is protein-synthesis-sensitive.”

Schuman and her colleagues also identified a specific neurotransmitter receptor subunit whose synthesis was switched on by dopamine-triggered plasticity. That subunit, called GluR1, is part of another class of neurotransmitter receptors, called AMPA receptors—which play a key role in normal synaptic transmission and the plasticity associated with learning and memory. The researchers demonstrated that dopamine caused an increase in the GluR1 subunit delivery to the cell membrane, where it would be expected to play a role in enhancing responsiveness to transmitter.

“This evidence is consistent with the concept of the ‘silent synapse,’” said Schuman. “That idea holds that such synapses are functionally silent because they do not possess functional AMPA-type receptors. Rather, these silent synapses possess only receptors known as NMDA-type receptors, which are thought to be inactive. However, when AMPA-type receptors are inserted into the membrane, according to this theory, a silent synapse converts to an active one.”

The researchers also demonstrated a link between dopamine-related plasticity and NMDA receptor activity. They found that when they blocked NMDA receptors, the dopamine-regulated synthesis of GluR1, as well as enhanced synaptic transmission, were blocked. “This experiment showed that there may be some specificity to dopamine's actions, at least in how it stimulated local protein synthesis,” said Schuman. “You may need both dopamine release and functional NMDA receptors to trigger protein synthesis and plasticity.”

According to Schuman, their findings could have implications for understanding drug addiction and its treatment. “Over the past few years, investigators have begun to focus on the dendrite and its spines as potential sites that are altered during reward and addiction,” she said. “This raises the possibility that some of the signaling that goes awry during addiction may have to do with local protein synthesis.”