Major clue in long-term memory making discovered

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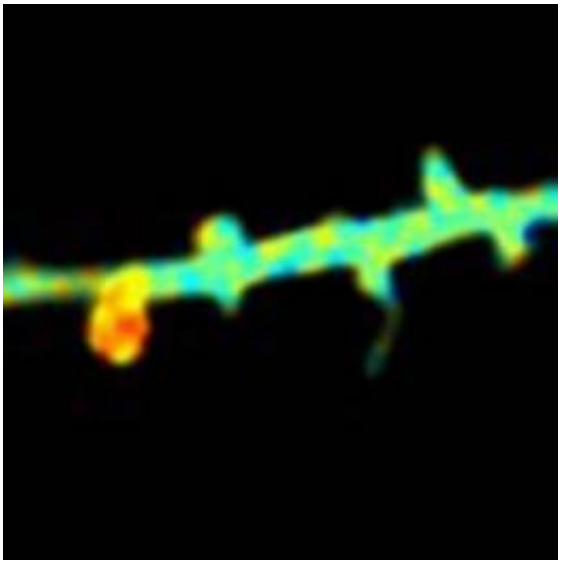

Image shows the formation of dendritic spines during long-term potentiation in a single synapse. Signaling activity is color coded (red = high activity of Cdc42, blue = low activity). Activity is high only in the growing spine, and this shows Cdc42 helps to strengthen a synapse for long-term memory storage. Credit: Ryohei Yasuda, Duke University Medical Center

You may remember the color of your loved one's eyes for years. But how?

Scientists believe that long-term potentiation (LTP) – the long-lasting increase of signals across a connection between brain cells -- underlies our ability to remember over time and to learn, but how that happens is a

central question in neuroscience.

Researchers at Duke University Medical Center have found a cascade of signaling molecules that allows a usually very brief signal to last for tens of minutes, providing the brain framework for stronger connections (synapses) that can summon a memory for a period of months or even years.

Their findings about how the synapses change the strength of connections could have a bearing on Alzheimer's disease, autism and mental retardation, said Ryohei Yasuda, Ph.D., assistant professor of neurobiology and senior author.

"We found that a biochemical process that lasts a long time is what causes memory storage," said Yasuda, who is a Howard Hughes Medical Institute Early Career Scientist.

This work was published in the March 20 issue of *Nature*.

The researchers were investigating the signaling molecules that regulate the actin cytoskeleton, which serves as the structural framework of synapses.

"The signaling molecules could help to rearrange the framework, and give more volume and strength to the synapses," Yasuda said. "We reasoned that a long-lasting memory could possibly come from changes in the building block assemblies."

The Duke researchers knew that long-term potentiation, a long-lasting set of electrical impulses in nerve cells, is triggered by a transient increase of calcium (Ca^{2+}) ions in a synapse. They devised experiments to learn exactly how the short Ca^{2+} signal, which lasts only for ~0.1s, is translated into long-lasting (more than an hour) change in synaptic

transmission.

The team used a 2-photon microscopy technique to visualize molecular signaling within single synapses undergoing LTP, a method developed in the Yasuda lab. This microscopy method allowed the team to monitor molecular activity in single synapses while measuring the synapses for increase in their volume and strength of the connections.

They found that signaling molecules Rho and Cdc42, regulators of the actin cytoskeleton, are activated by CaMKII, and relay a CaMKII signal into signals lasting many minutes. These long-lasting signals are important for maintaining long-lasting plasticity of synapses, the ability of the brain to change during learning or memorization.

Many mental diseases such as mental retardation and Alzheimer's disease are associated with abnormal Rho and Cdc42 signals, Yasuda said. "Thus, our finding will provide many insights into these diseases."

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