Medical Xpress

This is your brain on fatty acids

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Saturated fats have a deservedly bad reputation, but Johns Hopkins scientists have discovered that a sticky lipid occurring naturally at high levels in the brain may help us memorize grandma's recipe for cinnamon buns, as well as recall how, decades ago, she served them up steaming from the oven.

The Hopkins team, reporting Oct. 29 in *Neuron,* reveals how palmitate, a fatty acid, marks certain brain proteins - NMDA receptors - that need to be activated for long-term memory and learning to take place. The fatty substance directs the receptors to specific locations in the outer membrane of brain cells, which continually strengthen and weaken their connections with each other, sculpting and resculpting new memory circuits.

Moreover, the researchers report, this fatty modification is a reversible process, with some sort of on-off switch, offering possibilities for manipulating it to enhance or even, perhaps, erase memory.

"Before now, no one knew that NMDA receptors change in response to the addition of palmitate," says Richard Huganir, Ph.D., professor and director of the Solomon H. Snyder Department of Neuroscience at Johns Hopkins.

Scientists have known that a brain signaling chemical called glutamate normally activates NMDA receptors, allowing two neurons to communicate with one another. However, they were less certain what allowed this receptor to assemble properly, or what caused it to make its way to the synapse, the specialized part of nerve cells where communication takes place.

The discovery emerged from work with live neurons in a dish, to which the scientists first fed radioactive palmitate, then separated out the NMDA receptors. By tracking radioactivity on X-ray film, they were able to determine that the fat had attached to the NMDA receptors.

Next, the scientists put both normal and altered NMDA receptors into non-brain cells that don't normally manufacture their own NMDA receptors. By tracking the radioactive fat, they were able to determine where on the NMDA receptor the fat had attached.

Results showed that the NMDA receptor undergoes "dual palmitoylation," in two different regions, each of which plays a distinct role in controlling the fate of the receptor in neurons. When the fat attaches to the first region, it stabilizes the receptor on the surface of neurons. When the fat attaches to the second region, the receptors accumulate inside neurons, perhaps awaiting a signal to send them to synapses. The researchers suspect that this could be part of a quality control measure, assuring that all the Lego-like protein subunits of the receptor are put together properly.

"It is rapidly becoming clear that palmitate regulates not only NMDA receptors, but also other brain proteins at work during signaling across synapses," says Gareth Thomas, Ph.D., a Howard Hughes Medical Institute postdoctoral fellow at Hopkins.

The researchers suspect that if palmitoylation fails, the result would be learning and memory impairment because if NMDA receptors don't make their way to the synapses - the specialized contact points between cells across which chemical messages flow - then communication between neurons is compromised.

"This new modification of the NMDA receptor deepens our molecular understanding of how synapses are regulated and how memories might be formed. It also reveals new potential drug targets, such as the enzymes that add or remove the palmitate," Huganir says. "If we could shift the balance of the palmitoylation, then perhaps we could affect and enhance learning and memory."

Source: Johns Hopkins Medical Institutions