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Popular Target of Experimental Drugs Boosts Memory, Too

A protein that is already the target of experimental drugs that aim to extend life is now known to play a key role in learning and memory. The discovery, which comes from mouse experiments led by Howard Hughes Medical Institute investigator Li-Huei Tsai, suggests that boosting this linchpin protein, called SIRT1, in the brain may help prevent or reverse cognitive decline in Alzheimer's disease and other cognitive disorders.

The findings are published in the July 11, 2010, issue of the journal *Nature*. "Our research strongly suggests that SIRT1 is a very good target for therapeutic interventions in neurological disorders that include cognitive impairments," says Tsai, who is also the Picower Professor of Neuroscience in the Department of Brain and Cognitive Sciences at the Massachusetts Institute of Technology.

Scientific interest in SIRT1 exploded about a decade ago after various researchers discovered that the protein could prevent obesity, maintain healthy metabolism, and extend the life of laboratory animals. An intense effort to develop drugs that boost SIRT1 activity is now underway, with several drugs in human trials.

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Three years ago, a team led by Tsai first investigated the SIRT1 protein's activity in the brain. Although the protein was known to have restorative effects in the body, activity in the brain was unknown until Tsai and her team found that SIRT1 in the brain helped protect neurons that otherwise degenerate in a mouse model of Alzheimer's disease. The finding was published in the *EMBO Journal* in 2007.

Following up, Tsai and colleagues developed a transgenic mouse that cannot make functioning SIRT1 in the brain. In a battery of learning and memory tests, these SIRT1-deficient mice displayed severe impairments in navigating water mazes, recognizing new objects, and learning to respond to small shocks to the feet. “The deficiencies were so striking that we immediately thought that SIRT1 plays an important role in cognition,” says Tsai. “It looked like it was necessary for normal learning and memory.”

Further, the brains of mice lacking SIRT1 displayed many fewer neurons and neuronal connections than normal mice, especially in the hippocampus, the mid-brain horseshoe-shaped structure known to be a pivotal center of memory formation.

The *SIRT1* gene is considered a master gene, because it controls the activity of many other genes. So Tsai suspected that in the brain, *SIRT1* was regulating genes that are important for forming neuronal connections, or synapses, and by extension, for learning and memory. She homed in on *CREB*, a gene known to be critical for healthy synapse development. Tsai calls CREB “one of the most studied molecules in all of neuroscience.”

As she examined CREB RNA and protein levels in the brains of the SIRT1-deficient mice, Tsai discovered something curious. CREB protein levels were much lower than in normal mice. And yet, these mice still had a normal number of messenger RNA molecules for CREB – a copy of the gene that serves as the blueprint for CREB protein production. The finding suggested that low SIRT1 concentrations somehow interfered with the translation of CREB RNA into CREB protein.

A class of tiny snippets of RNA called microRNAs is known to interfere with translation of messenger RNA into protein, so Tsai decided to survey the brains of her mice for microRNAs. Using a commercial chip that measures hundreds of known microRNAs, Tsai discovered elevated concentrations of several microRNAs in the hippocampuses of the SIRT1-deficient mice. While studying these microRNAs, one popped out as particularly interesting, called mir134. Another research group had previously found this microRNA to be important in synapse formation. More critically, Tsai’s team discovered that DNA near the *CREB* gene held sites that mir134 could bind to. That finding suggested that upregulation of mir134 might be the cause of the diminished CREB protein levels.

To assess this, Tsai engineered mice with too much mir134 in their brains, but normal amounts of SIRT1. Sure enough, these mice displayed the same memory, learning, and synapse deficits as the SIRT1-deficient mice. Further, in SIRT1-deficient mice, chemically removing mir134 reversed the cognitive deficits. The mice could learn a maze as well as their SIRT1-normal cagemates.

Tsai says that the experiments show that SIRT1 plays a central role in synapse formation in the hippocampus. Unfortunately, none of the SIRT1-boosting drugs in clinical trials get into the brain very well, so they are not good candidates for treating cognitive decline. However, Tsai says that it might be possible to find an RNA-based drug that depletes mir134 in the brain – another way to boost the positive neuronal effects of SIRT1.

“If we could find a way to upregulate SIRT1 activity, it might have multiple beneficial effects on the brain,” she says.