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Mutation improves memory, may lead to memory-enhancing pill

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A mind-altering mutation in mice results in an enhanced long-term memory, researchers report in the April 6, 2007 issue of the journal *Cell*, published by Cell Press. These findings point to a potential target for the development of a drug to treat memory loss, according to the researchers.

The researchers studied a gene that normally increases levels of a natural memory-blocking protein. Animals that carry a defective version of this gene showed improved performance in classical behavioral memory tests, they show. Moreover, animals treated with a small molecule that had the opposite effect—leading ultimately to an increase in the memory-blocker's concentration—showed signs of memory impairment.

"There are very few examples where you can increase memory, especially by deleting genes," said study author Nahum Sonenberg of McGill University in Montreal, Canada. "It's a small, but important part of the big puzzle of how memory works."

"The next step, which is inevitable, is to look for small molecules that mimic this memory-enhancing effect," he continued.

"If such a pill could be generated, it might provide a new method for treating people with memory-related diseases such as Alzheimer's," said Mauro Costa-Mattioli, a senior postdoctoral fellow in Sonenberg's laboratory. "While a drug that worked in this way wouldn't cure the disease itself, it might rescue the symptoms of memory loss."

Memories are formed when the repeated activation of brain cells leads to a strengthening of neural connections, or synapses. This process, considered the cellular basis of learning and memory, is known as synaptic plasticity.

Both memory and synaptic plasticity have two components, the researchers explained. One, which is evoked by weak training protocols, yields only transient phenomena—including short-term memory, lasting for minutes to hours, or the beginning stages of longer-term memory storage, lasting for one to three hours. The second component, which follows strong or repetitive training, activates mechanisms that stabilize the memory and nerve connections, resulting in long-term memory, lasting days, weeks, or years.

"Quite different molecular machineries, widely conserved from sea slugs to rodents, are thought to underlie these two components. While modifications of pre-existing proteins are sufficient for the transient changes, new gene expression is required for those that are sustained," the researchers said, emphasizing that a gene's expression depends on both its transcription into messenger RNA and the translation of that messenger RNA into functional proteins.

Sonenberg and Costa-Mattioli earlier found the first genetic evidence that control over protein synthesis plays an important role in the formation of lasting memories.

"Most of the focus on gene control is at the level of transcription," Sonenberg said. "In contrast, here there is control at the level of translation—in making protein from messenger RNA, a less appreciated mode of regulation."

When the regulatory protein eIF2a is chemically modified with the addition of a phosphate to one of its amino acids, it switches on the

protein synthesis of another factor that halts production of genes required for the long-term storage of memories. Sonenberg and his colleagues previously discovered that mice lacking the enzyme that performs the phosphorylation reaction have a superior ability to remember new things under certain training conditions.

“Those results led us to suspect that decreasing the phosphorylation of eIF2a enhanced memory storage,” Costa-Mattioli said.

In an effort to validate their earlier findings, the researchers have now generated mice carrying a version of eIF2a that cannot be phosphorylated. The mutant mice have lower levels of phosphorylated eIF2a and showed an improved talent for spatial learning in a water maze test.

In the test, the mice were trained to swim to a hidden platform. After several days of training, the altered mice were able to find the platform significantly faster than normal mice could, they reported.

"For example, if a person were reading a page of a textbook, it might take several times to memorize it," Costa-Mattioli said. "A human equivalent of these mice would get the information right away."

The mutant mice also performed better than normal mice in a "fear-conditioning" test. In that test, animals are put into a cage followed by a mild foot shock or are exposed to a tone paired with a foot shock. Their memory for the earlier bad experience is determined based on how much they freeze in response to the "scary" place or sound 24 hr later.

Importantly, the researchers also showed that treatment of animals with a small molecule that increases eIF2a's phosphorylation led to poorer performance on the memory tests.

“These data strengthen the idea that eIF2a phosphorylation is a key, bidirectional point of memory control,” with the ability to turn long-term memory formation on and off, Costa-Mattioli said.

"Taken together, these data strongly support the notion that, under physiological conditions, a decrease in eIF2a phosphorylation constitutes a critical step for the activation of gene expression that leads to the long-term synaptic changes required for memory formation," the researchers concluded. "These findings also raise the interesting possibility that regulators of translation could serve as therapeutic targets for the improvement of memory, for instance in human disorders associated with memory loss."

Source: Cell Press