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Neuroscientists boost memory using genetics and a new memory-enhancing drug

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When the activity of a molecule that is normally elevated during viral infections is inhibited in the brain, mice learn and remember better, researchers at Baylor College of Medicine reported in a recent article in the journal *Cell*.

"The molecule PKR (the double-stranded RNA-activated protein kinase) was originally described as a sensor of viral infections, but its function in the brain was totally unknown," said Dr. Mauro Costa-Mattioli, assistant professor of neuroscience at BCM and senior author of the paper. Since the activity of PKR is altered in a variety of cognitive disorders, Costa-Mattioli and colleagues decided to take a closer look at its role in the mammalian brain.

The authors discovered that mice lacking PKR in the brain have a kind of "super" memory. "We found that when we genetically inhibit PKR, we increased the excitability of brain cells and enhanced learning and memory, in a variety of behavioral tests," he said. For instance, when the authors assessed spatial memory (the memory for people, places and events) through a test in which mice use visual cues for finding a hidden platform in a circular pool, they found that normal mice had to repeat the task multiple times over many days in order to remember the platform's location. By contrast, mice lacking PKR learned the task after only one training session.

Costa-Mattioli and colleagues wanted to know how this molecular process actually works. They found that when PKR is inhibited, the

increased synaptic activity (that is, the enhanced communication between neurons) is caused by gamma interferon, another molecule involved in immunity.

"These data are totally unexpected, and show that two molecules classically known to play a role in viral infection and the immune response regulate the kind of brain activity that leads to the formation of long-term memory in the adult brain," said Costa-Mattioli.

Another key finding made by Costa-Mattioli and his team of researchers was the fact that this process could be mimicked by a PKR inhibitor - a small molecule that blocks PKR activity and thus acts as a "memory-enhancing drug."

"It is indeed quite amazing that we can also enhance both memory and brain activity with a drug that specifically targets PKR". Definitely then, the next step is to use what we have learned in mice and to try to improve brain function in people suffering from memory loss, said Costa-Mattioli.

Although Costa-Mattioli's memory pill may be years away from approval by the U.S. Food and Drug Administration, its impact on society and medicine could be very profound. There are roughly 6 million Americans and 35 million people world-wide with Alzheimer's disease and more than 70 million Americans over the age of 60 who may suffer from aged-associated impairment of memory.

Costa-Mattioli said, "More investigation is undoubtedly necessary to translate these findings to effective therapies but we would be delighted if our scientific studies were to contribute in some way to this ultimate goal."

"Our identity and uniqueness is made up of our memories," Costa-

Mattioli said. "This molecule could hold the key to how we can keep our memories longer, but also how we create new ones."

Provided by Baylor College of Medicine