Novel storage mechanism allows command, control of memory

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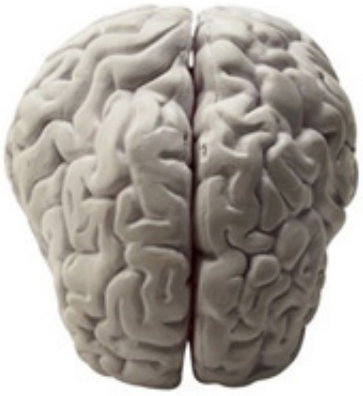

(Medical Xpress)—Introductions at a party seemingly go in one ear and out the other. However, if you meet someone two or three times during the party, you are more likely to remember his or her name. Your brain has taken a short-term memory – the introduction – and converted it into a long-term one. The molecular key to this activity is mTORC2 (mammalian target of rapamycin complex 2), according to researchers at Baylor College of Medicine in an article that appeared online in the journal *Nature Neuroscience*.

"Memory consolidation is a fundamental process," said Dr. Mauro Costa-Mattioli, assistant professor of neuroscience at BCM and corresponding author of the report. "Memories are at the center of our identity. They

allow us to remember people, places and events for a long time, even a lifetime. Understanding the precise mechanism by which memories are stored in the brain will lead to the development of new treatments for conditions associated with memory loss".

For the last five decades, neuroscientists have known that making long-lasting memories is dependent on the ability of brain cells (neurons) to synthesize new proteins. In their studies, Costa-Mattioli and his colleagues found a new mechanism by which memories are stored in the brain. The newly discovered mTORC2 regulates memory formation by modulating actin fibers, an important component of the architectural structure of the neuron.

"These actin fibers allow long-lasting changes in synaptic strength and ultimately long-term memories," said Wei Huang, a BCM graduate student and first author in the study.

Using genetically-engineered mice, the researchers found that turning off mTORC2 in the hippocampus (a crucial region required for memory formation) and surrounding areas allowed the animals to have a normal short-term memory, but prevented them from forming long-term memories. Similar to human patients with injury in the hippocampus, these mutant mice were no longer able to form new long-lasting memories.

According to Costa-Mattioli's findings, mTORC2's role is evolutionarily conserved and likely relevant to humans. Like mTORC2-deficient mice, fruit flies lacking TORC2 show defective long-term memory storage.

"Given that flies and mice last shared a common ancestor 500 million years ago, it is quite remarkable and telling that the function of mTORC2 in the regulation of memory is indeed maintained," said Dr. Gregg Roman, director of the Biology of Behavior Institute at the

University of Houston, who contributed to the fly experiments.

The Holy Grail of memory neuroscience and to a certain extent, of industry efforts to produce a "smart drug," has been the identification of molecules that promote the formation of long-term memory, said Costa-Mattioli. "We therefore wondered whether by turning on mTORC2 or even actin polymerization itself, we could form long-term memories more easily," said Dr. Ping Jun Zhu, assistant professor of neuroscience at BCM, co-first author and senior scientist in Costa-Mattioli's lab.

The team has identified a small molecule (a drug) that by activating mTORC2 and consequently actin polymerization enhances not only the synaptic strength between nerve cells but also long-term memory formation. In addition, the authors found that by directly promoting actin polymerization, with a second drug, long-term memory is generated more easily.

Costa-Mattioli's team has identified two memory-enhancing drugs, but can they enhance memory in people? It is perhaps too early to say.

Huang said, "mTORC2, as far as we know, is really a new potential target for therapeutic treatments of human disorders. In the next few years, I predict we will see a lot of studies focusing on mTORC2 as a target."

Costa-Mattioli's short-term goals are to identify human cognitive disorders in which mTORC2 activity is dysfunctional and to see whether its restoration can return to normal impaired memory function in aging or even Alzheimer's disease. But a small molecule alone might not do the job. Similar to the treatments for HIV or cancer, he believes that a combination of small molecules improving different aspects of memory formation will be required to efficiently treat cognitive disorders.

"We should start thinking about an efficient 'memory cocktail' rather than a single 'memory pill.' One molecule alone might not be enough. We may be years away from a decisive treatment, but I believe we are definitely on the right path," he said.

Others who took part in this work include Hongyi Zhou, Loredana Stoica and Mauricio Galiano, all of BCM, Krešimir Krnjević of McGill University in Montreal, Canada; and Shixing Zhang of the University of Houston.

More information: www.nature.com/neuro/journal/v …nt/full/nn.3351.html

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