MedicalXpress

Research finds key molecules involved in forming long-term memories

September 10 2012

How does one's experience of an event get translated into a memory that can be accessed months, even years later? A team led by University of Pennsylvania scientists has come closer to answering that question, identifying key molecules that help convert short-term memories into long-term ones. These proteins may offer a target for drugs that can enhance memory, alleviating some of the cognitive symptoms that characterize conditions including schizophrenia, depression and Parkinson's and Alzheimer's diseases.

Joshua Hawk, now a postdoctoral research fellow at Yale University, led the study, which was conducted as part of his Ph.D. work in the Neuroscience Graduate Group at Penn. He worked with Ted Abel, Penn's Brush Family Professor of Biology. Additional Penn team members were Shane Poplawski, Morgan Bridi, Allison Rao, Michael Sulewski and Brian Kroener. The Penn researchers collaborated with Angie Bookout and David Manglesdorf of the Howard Hughes Medical Institute and the University of Texas Southwestern Medical Center.

"There are many drugs available to treat some of the symptoms of diseases like schizophrenia," Abel said, "but they don't treat the cognitive deficits that patients have, which can include difficulties with memory. This study looks for more specific targets to treat deficits in cognition."

Published in the Journal of Clinical Investigation, the study focused on a group of proteins called nuclear receptors, which have been implicated

in the regulation of a variety of biological functions, including memory formation.

Nuclear receptors are a kind of transcription factor, proteins that can bind to DNA and regulate the activity of other genes. Their regulatory role may be significant in memory formation, as gene transcription is required to turn short-term memories into long-lasting ones by strengthening neuronal synapses in the brain.

To identify how this class of transcription factors figures in memory formation, the research team trained mice using a common method to create memories of a place and event, in which animals learn to associate a particular context or a certain tone with a specific experience. Associations with a place or context are believed to be encoded in the hippocampus, while memories associated with a cue such as a tone are believed to be encoded in the amygdala.

In the 24 hours after exposing mice to the initial training, the researchers examined expression patterns of all 49 nuclear receptor genes. They found 13 that increased in expression in the hippocampus in the first two hours after training. Included in this group were all three members of a class of nuclear receptors called Nr4a. Nr4a genes had previously been found to increase in expression upon use of a memory-enhancing class of drugs called histone deacetylase inhibitors, or HDAC inhibitors.

The scientists next created a transgenic mouse in which they could selectively block the activity of the three Nr4a genes.

"Having the transgenic mouse is very useful," Hawk said. "We can manipulate it so that the Nr4a genes will only function in certain brain regions and then see how the mouse's memory-forming ability is affected."

When the researchers exposed the mice to the training context a second time, they found that the transgenic mice had reduced memory of the location where the training took place—memories that are located in the hippocampus—compared to normal mice. In contrast, the mutant mice's amygdala-associated memories of a cue—the tone played during training—remained intact.

"The mice had impairment for contextual memory, which means something in the hippocampus is affected," Abel said. "That is the type of memory that goes away in Alzheimer's and schizophrenia."

The research team also showed that the mutant mice's short-term memory was not impaired. When trained in short-term memory tasks, their performance ranked similarly to their normal siblings.

In addition, the scientists confirmed that Nr4a genes play a role in long-term memory storage by injecting the Nr4a-deficient mice with HDAC inhibitors, which have been shown to enhance memory in normal mice. The treatment did not enhance the memory-forming ability of the mutant mice, suggesting that the drug acts upon the Nr4a genes to boost long-term-memory storage.

Finally, the researchers screened mice for molecules that act "downstream" of Nr4a and could be part of the signaling cascade by which those nuclear receptors help create long-term memories. They found two genes, Fosl2 and Bdnf1, that appeared to be downstream targets of Nr4a genes and also increased in expression following treatment with an HDAC inhibitor.

"Finding these targets is promising in terms of new drug development," Abel said. "Most drugs for schizophrenia, depression and some other neurological disorders now target neurotransmitter systems and can have affects on many systems. In this case, we would change gene expression

much more specifically."

"The more selective we can get for the pathway that's enhancing memory ," Hawk said, "the more likely we can find effective drugs."

Provided by University of Pennsylvania