

Scientists decipher the formation of lasting memories

November 10 2009

Researchers at the Swedish medical university Karolinska Institutet have discovered a mechanism that controls the brain's ability to create lasting memories. In experiments on genetically manipulated mice, they were able to switch on and off the animals' ability to form lasting memories by adding a substance to their drinking water. The findings, which are published in the scientific journal *PNAS*, are of potential significance to the future treatment of Alzheimer's and stroke.

"We are constantly being swamped with sensory impression," says Professor Lars Olson, who led the study. "After a while, the brain must decide what's to be stored long term. It's this mechanism for how the connections between nerve fibers are altered so as to store selected memories that we've been able to describe."

The ability to convert new sensory impressions into lasting memories in the brain is the basis for all learning. Much is known about the first steps of this process, those that lead to memories lasting a few hours, whereby altered signalling between neurons causes a series of chemical changes in the connections between nerve fibers, called synapses. However, less is understood about how the chemical changes in the synapses are converted into lasting memories stored in the cerebral cortex.

A research group team at Karolinska Institutet has now discovered that signalling via a receptor molecule called nogo receptor 1 (NgR1) in the nerve membrane plays a key part in this process. When nerve cells are activated, the gene for NgR1 is switched off, and the team suspected that

this inactivation might be important in the creation of long-term memories. To test this hypothesis they created mice with an extra NgR1 gene that could remain active even when the normal NgR1 was switched off.

"Doing this, we found that the ability to retain something in the memory for the first 24 hours was normal in the genetically modified mice," says Professor Olson. "However, two different memory tests showed that the mice had serious difficulties converting their normal short-term memories to long-term ones, the kind that last for months."

In order to be able to switch the extra NgR1 gene on and off, the group attached a regulatory mechanism to the gene that reacted to a harmless additive in their [drinking water](#). When the extra gene was then switched off, the mice retained their normal ability to form long-term memories. By subsequently switching it off at different times after a memory-forming event, they were able to pinpoint the effect of the NgR1 gene to the first week after such an event.

"We know that concussion can cause someone to forget events that occurred in the week before the injury, what we call retrograde amnesia, even though they can remember events that occurred earlier than about a week before. This we believe tallies with our findings," says Alexandra Karlén, one of the scientists involved in the study.

The scientists hope that their findings will eventually be of use in the development of new treatments for memory impairments, such as those related to Alzheimer's and stroke. Medicines designed to target the NgR1 receptor system would be able to improve the brain's ability to form long-term memories. The studies were conducted in collaboration with American researchers at the National Institute on Drug Abuse (NIDA), NIH.

More information: "Nogo receptor 1 regulates formation of lasting memories", A. Karlén, T. E. Karlsson, A. Mattsson, K. Lundströmer, S. Codeluppi, T. M. Pham, C. M. Bäckman, S. O. Ögren, E. Åberg, A. F. Hoffman, M. A. Sherling, C. R. Lupica, B. J. Hoffer, C. Spenger, A. Josephson, S. Brené, & L. Olson, *PNAS*, Online Early Publication Edition, 9-13 November 2009.

Source: Karolinska Institutet ([news](#) : [web](#))

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