MedicalXpress

Gene limits learning and memory in mice

September 17 2010

Deleting a certain gene in mice can make them smarter by unlocking a mysterious region of the brain considered to be relatively inflexible, scientists at Emory University School of Medicine have found.

Mice with a disabled RGS14 gene are able to remember objects they'd explored and learn to navigate mazes better than regular mice, suggesting that RGS14's presence limits some forms of learning and memory.

The results were published online this week in the Early Edition of the Proceedings of the National Academy of Sciences.

Since RGS14 appears to hold mice back mentally, John Hepler, PhD, professor of pharmacology at Emory University School of Medicine, says he and his colleagues have been jokingly calling it the "Homer Simpson gene."

RGS14 is primarily turned on in one particular part -- called CA2 -- of the hippocampus, a region of the brain known for decades to be involved in consolidating new learning and forming new memories. However, the CA2 region lies off the beaten path scientifically and it's not clear what its functions are, Hepler says.

RGS14, which is also found in humans, was identified more than a decade ago. Hepler and his colleagues have previously shown that the RGS14 protein can regulate several molecules involved in processing different types of signals in the brain that are known to be important for learning and memory. They believe RGS14 is a key control protein for

these signals.

To probe RGS14's functions, Sarah Emerson Lee, a graduate student working with Hepler, characterized mice whose RGS14 genes were disabled using gene-targeting technology. In collaboration with Serena Dudek, PhD, at the National Institute of Environmental Health Sciences, they examined how the CA2 region responded to electrical stimulation in the gene-altered mice.

Many researchers have examined how other parts of the hippocampus are involved in long-term potentiation, a strengthening of connections between neurons that can be seen after new memory formation or artificial stimulation in a culture dish. The CA2 region is distinct from other regions for being resistant to long-term potentiation, and neurons within CA2 are able to survive injury by seizures or stroke more than neurons in other parts of the hippocampus.

The researchers were surprised to find that, in mice with a disabled RGS14 gene, the CA2 region was now capable of "robust" long-term potentiation, meaning that in response to electrical stimulation, neurons there had stronger connections. On top of that, the ability of the gene-altered mice to recognize objects previously placed in their cages was enhanced, compared to normal mice. They also learned more quickly to navigate through a water maze to a hidden escape platform by remembering visual cues.

"A big question this research raises is why would we, or mice, have a gene that makes us less smart - a Homer Simpson gene?" Hepler says. "I believe that we are not really seeing the full picture. RGS14 may be a key control gene in a part of the brain that, when missing or disabled, knocks brain signals important for learning and memory out of balance."

The lack of RGS14 doesn't seem to hurt the altered mice, but it is still

possible that they have their brain functions changed in a way that researchers have not yet been able to spot. Besides being resistant to injury by seizure, certain types of CA2 neurons are lost in schizophrenia, and loss of another gene turned on primarily in the CA2 region leads to altered social behaviors, Hepler notes.

"This suggests that these mice may not forget things as easily as other mice, or perhaps they have altered social behavior or sensitivity to seizures," he says. "But not necessarily."

Lee is investigating some of these possibilities now.

"The pipe dream is that maybe you could find a compound that inhibits RGS14 or shuts it down," he adds. "Then, perhaps, you could enhance cognition."

More information: S.E. Lee et al. RGS14 is a natural suppressor of both synaptic plasticity in CA2 neurons and hippocampal-based learning and memory. *PNAS* Early Edition (2010). www.pnas.org/content/early/201 … /1005362107.abstract

Provided by Emory University