Memories stolen by Alzheimer's may be retrievable: study

May 7, 2009
Courtesy MIT and World Science staff

Researchers have pinpointed a gene said to be responsible for a 2007 breakthrough in which mice with Alzheimer's disease symptoms regained long-term memories and the ability to learn.

In the new research, reported in the May 7 issue of the scientific journal Nature, Massachusetts Institute of Technology neuroscientist Li-Huei Tsai and colleagues found that drugs that work on the gene HDAC2 reverse the effects of Alzheimer's and boost cognitive function in mice.

Researchers said the findings serve as evidence that memories lost to Alzheimer's and related conditions aren't gone for good. Rather, they have gotten stuck deep in the brain waiting for the proper medicines to dislodge them.

The HDAC2 gene, and a molecule it produces, "are promising targets for treating memory impairment," Tsai said. The gene controls the activity of many other genes "implicated in plasticity — the brain's ability to change in response to experience — and memory formation."

The gene causes lasting changes in how other genes behave, which is probably necessary to increase numbers of connections between brain cells, she added. The researchers treated mice with Alzheimer's-like symptoms using so-called histone deacetylase, or HDAC, inhibitors, a family of 11 enzymes that seem to act as master regulators of gene activity. The drugs are in experimental stages and are not available for patients' use.

"Harnessing the therapeutic potential of HDAC inhibitors requires knowledge of the specific HDAC family member or members linked to cognitive enhancement," Tsai said. "We have now identified HDAC2 as the most likely target of the HDAC inhibitors that facilitate synaptic plasticity and memory formation.

A person's DNA is packaged as part of a material called chromatin, and certain genes control arrays of other genes simply by restructuring the chromatin. The new research helps clarify how this process works in regulating memory, Tsai said.

Several HDAC inhibitors are currently in clinical trials as novel anticancer agents and may enter the pipeline for other diseases in the coming two to four years. Researchers have had promising results with HDAC inhibitors in mouse models of Huntington's disease.

In the chromatin, molecules called histones act as spools around which DNA winds. Histones are modified in various ways, including through a process called acetylation, which in turn modifies chromatin shape and structure. HDAC inhibitors promote this process. Certain HDAC inhibitors open up chromatin. This allows genes to become active which had been too tightly packaged to go into operation.

The researchers conducted learning and memory tasks using genetically engineered mice that were induced to lose many brain cells. Following Alzheimer's-like brain shrinkage, the mice acted as though they had forgotten tasks they had previously learned. But after taking HDAC inhibitors, the mice regained their long-term memories and ability to learn new tasks, according to Tsai. In addition, mice genetically engineered to produce no HDAC2 at all exhibited enhanced memory formation.

The fact that long-term memories can be recovered by elevated histone acetylation supports the idea that apparent memory "loss" is really a reflection of inaccessible memories, Tsai said. "These

findings are in line with a phenomenon known as ‘fluctuating memories,’ in which demented patients experience temporary periods of apparent clarity,” she added.