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Scientists ID gene key to Alzheimer's-like reversal

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(PhysOrg.com) -- A team led by researchers at MIT's Picower Institute for Learning and Memory has now pinpointed the exact gene responsible for a 2007 breakthrough in which mice with symptoms of Alzheimer's disease regained long-term memories and the ability to learn.

In the latest development, reported in the May 7 issue of *Nature*, Li-Huei Tsai, Picower Professor of Neuroscience, and colleagues found that drugs that work on the gene HDAC2 reverse the effects of Alzheimer's and boost cognitive function in mice.

"This gene and its protein are promising targets for treating memory impairment," Tsai said. "HDAC2 regulates the expression of a plethora of genes implicated in plasticity — the brain's ability to change in response to experience — and memory formation.

"It brings about long-lasting changes in how other genes are expressed, which is probably necessary to increase numbers of synapses and restructure neural circuits, thereby enhancing memory," she said.

The researchers treated mice with Alzheimer's-like symptoms using histone deacetylase (HDAC) inhibitors. HDACs are a family of 11 enzymes that seem to act as master regulators of gene expression. Drugs that inhibit HDACs are in experimental stages and are not available by prescription for use for Alzheimer's.

"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.

"This will help elucidate the mechanisms by which chromatin remodeling regulates memory," she said. It also will shed light on the role of epigenetic regulation, through which gene expression is indirectly influenced, in physiological and pathological conditions in the central nervous system.

"Furthermore, this finding will lead to the development of more selective HDAC inhibitors for memory enhancement," she said. "This is exciting because more potent and safe drugs can be developed to treat Alzheimer's and other cognition diseases by targeting this HDAC specifically," said Tsai, who is also a Howard Hughes Medical Institute investigator. 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.

Remodeling structures

Proteins called histones act as spools around which DNA winds, forming a structure in the cell nucleus known as chromatin. Histones are modified in various ways, including through a process called acetylation, which in turn modifies chromatin shape and structure. (Inhibiting deacetylation with HDAC inhibitors leads to increased acetylation.)

Certain HDAC inhibitors open up chromatin. This allows transcription and expression of genes in what had been a too tightly packaged chromatin structure in which certain genes do not get transcribed.

There has been exponential growth in HDAC research over the past decade. HDAC inhibitors are currently being tested in preclinical studies to treat Huntington's disease. Some HDAC inhibitors are on the market to treat certain forms of cancer. They may help chemotherapy drugs better reach their targets by opening up chromatin and exposing DNA. "To our knowledge, HDAC inhibitors have not been used to treat Alzheimer's disease or dementia," Tsai said. "But now that we know that inhibiting HDAC2 has the potential to boost synaptic plasticity, synapse formation and memory formation, in the next step, we will develop new HDAC2-selective inhibitors and test their function for human diseases associated with memory impairment to treat neurodegenerative diseases."

The researchers conducted learning and memory tasks using transgenic mice that were induced to lose a significant number of brain cells. Following Alzheimer's-like brain atrophy, the mice acted as though they did not remember tasks they had previously learned.

But after taking HDAC inhibitors, the mice regained their long-term memories and ability to learn new tasks. 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 said.

Source: Massachusetts Institute of Technology (news : web)