Scientists restore memory in mice with neurodegeneration

April 29 2007

Mice whose brains had lost a large number of neurons due to neurodegeneration regained long-term memories and the ability to learn after their surroundings were enriched with toys and other sensory stimuli, according to new studies by Howard Hughes Medical Institute researchers. The scientists were able to achieve the same results when they treated the mice with a specific type of drug that encourages neuronal growth.

The new studies suggest two promising avenues for treatment that might alleviate learning deficits and memory loss in humans with Alzheimer's disease or other neurodegenerative diseases.

The results of the experiments suggest that the term "memory loss" may be an inaccurate description of the kinds of mental deficits associated with neurodegenerative diseases. "The memories are still there, but they are rendered inaccessible by neural degeneration," said the senior author Li-Huei Tsai, a Howard Hughes Medical Institute researcher at the Massachusetts Institute of Technology.

Tsai led the research group that published its findings on April 29, 2007, in an advance online publication in the journal *Nature*.

"I believe that these findings could have particular significance for treatment of people who already have advanced neurodegenerative disease," said Tsai. "Most current treatments seem to be aimed at affecting the early stages of the disease. But our mouse model shows that

even when there has been a significant loss of neurons, it is still possible to improve learning and memory."

Over the last five plus years, Tsai's research team has developed and refined a mouse model of Alzheimer's disease. In earlier studies, Tsai's group had shown that a protein called p25 contributes to neurodegeneration. Over time they developed a genetically engineered mouse in which they are able to turn on p25 gene expression at specific stages in development. In these animals, evidence of neuronal loss is first detected six weeks after the induction of p25. At this age, animals exhibit a profound impairment in learning and memory that is accompanied by synaptic loss and impaired long-term potentiation (LTP), a process involved in the storage of memories.

The researchers engineered mice so that they could switch the p25 transgene on at will. Activation of p25 has been implicated in a variety of neurodegenerative diseases. Once activated in the mice, the p25 transgene produces neural pathology very similar to that of patients with Alzheimer's disease, said Tsai. The animals show brain atrophy and loss of neurons due to the same kind of cellular abnormalities seen in people who have Alzheimer's disease, she said.

Researchers have long known that an environment rich in sensory stimuli can improve learning in mice. So, Tsai and her colleagues decided to explore whether such an environment could improve learning and memory in their mice after a large number of neurons were already lost.

In their experiments, they switched on p25 in older mice. The genetic change induced brain atrophy and neuronal loss. They then used two tests to assess learning and memory in these older mice. In the "fear-conditioning" test, the animals were required to learn to associate a specific chamber with a mild electric shock. The second test required the animals to learn to find a submerged platform in a tank of murky

water.

The researchers placed some of the animals in a large chamber with a variety of stimuli: an exercise treadmill, colorful toys with various shapes and textures that were changed daily, and other mice. Their experiments showed that animals with neurodegeneration due to p25 activation had significant gains in learning and memory when they were exposed to this enriched environment. Those animals fared better on memory tests than the animals that remained in standard cages.

The researchers also tested the effects of an enriched environment on the animals' long-term memory. They knew that the fear-conditioning test established a lasting long-term memory in the mice. So, they tested whether environmental enrichment improved the p25-induced animals' ability to remember that conditioning weeks after training. They found that the enriched animals showed marked recovery of the long-term memory when compared to mice that did not live in a stimuli-rich environment.

"This recovery of long-term memory was really the most remarkable finding," said Tsai. "It suggests that memories are not really erased in such disorders as Alzheimer's, but that they are rendered inaccessible and can be recovered."

When the researchers studied the brains of the animals that had been exposed to the extra stimuli, they found no evidence of increased growth or formation of new neurons when compared to brains of mice that had not experienced the enriched environment. However, they did find anatomical and biochemical evidence for growth of connections among neurons.

Tsai and her colleagues also sought to understand the biological mechanism by which environmental enrichment enhanced learning and

memory in the mice. "Even though the learning-enhancement effects of environmental enrichment have been known for half a century, nobody really knows the mechanism behind it," said Tsai. "However, there has also been a growing body of evidence that chromatin remodeling has a beneficial effect on learning and memory," she said.

Chromatin is found in the nuclei of cells. It is composed of DNA spooled around bundles of histone proteins. The addition of small chemical tags to known as acetyl of methyl groups to the histones can alter the way chromatin is organized, which in turn determines which genes are turned on. Indeed, when Tsai and her colleagues analyzed the histones of enriched mice versus non-enriched animals, they found that environmental enrichment induced histone modification in the enriched mice.

Tsai and her colleagues tested whether a class of drugs that preserves histone acetylation, called histone deacetylases inhibitors, could affect learning and memory in the p25-induced mice. "In those studies, we found that using drugs to increase histone acetylation artificially produced an effect very similar to that observed in environmental enrichment," said Tsai. "This leads us to believe that further studies of ways to target chromatin remodeling could offer a treatment for Alzheimer's and other forms of dementia," she said. Tsai's group is now investigating the molecular mechanism by which such drugs work and which specific drug targets might be most effective at enhancing learning and memory.

Source: Howard Hughes Medical Institute