Brain enzyme treatment relieves memory lapse in Alzheimer's mice

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An enzyme that helps neurons rid themselves of excess or aberrant proteins is required for normal brain function, according to a new report in the August 25, 2006 issue of the journal *Cell*. What's more, by increasing brain levels of the enzyme in mice with Alzheimer's symptoms, the researchers found they could reverse lapses of memory characteristic of the debilitating disease.

Treatments that elevate the protein, known as ubiquitin C-terminal hydrolase L1 (Uch-L1), might therefore have potential as a new therapy for Alzheimer's disease, according to the researchers. Currently available therapies have almost exclusively targeted amyloid beta (Aß), the protein responsible for the "amyloid plaques" that riddle the brains of patients with Alzheimer's disease, they added.

"By injecting what is essentially a Uch-L1 drug to raise its levels in the brain, we were able to restore a great deal of brain activity in a transgenic mouse model of Alzheimer's disease," said Michael Shelanski of Columbia University.

"While amyloid beta is certainly a key player in Alzheimer's disease--and efforts to reduce it remain a worthy goal--our results show that, even in the presence of the plaque, damage to memory can be reversed."

The findings suggest that neurons' protein-ridding machinery, the so-called ubiquitin/proteasomal pathway, may play an important early role

in the pathogenesis of Alzheimer's disease, he added.

Ubiquitin is a "tag" that marks proteins for destruction by the cellular "garbage disposal" known as the proteasome, Shelanski explained. Uch-L1 acts as the proteasome's "gatekeeper," he added. Before proteins can be eliminated by the proteasome, Uch-L1 must remove their ubiquitin tag.

Earlier studies found that the brains of Alzheimer's disease patients show an accumulation of ubiquitin-tagged proteins, suggesting some defect of the protein degradation machinery, the researchers noted. Studies of the brains of humans with Alzheimer's after death found evidence that the proteasome remained intact but largely unable to degrade proteins.

Interestingly, Uch-L1--a protein found almost exclusively in nerve cells--was also found at reduced levels in the Alzheimer's brain. Unpublished studies by Shelanski's group found that cells treated with Aß exhibited a rapid drop in Uch-L1, he said.

To further investigate in the current study, the researchers treated brain slices with a chemical that blocks Uch-L1 function. The treated brain tissue displayed a decline in "long-term potentiation" (LTP), a process whereby nerve connections are strengthened. LTP is regarded as the cellular basis for learning and memory.

Treatments that restored Uch-L1 levels corrected deficits in nerve transmission both in brain slices treated with Aß and in slices taken from transgenic mice with mutations that lead to elevated Aß and associated cognitive decline.

The researchers next asked whether Uch-L1 played an important role in fear conditioning, a form of learning known to be impaired in several mouse models of Alzheimer's disease.

For fear conditioning, mice treated with the Uch-L1 inhibitor and control mice were placed in a novel context (a fear-conditioning box) and exposed to a tone paired with a mild foot shock. Their ability to learn fear was tested 24 hr later by measuring "freezing" behavior in response to the box or the auditory cue. Contextual versus cued responses represent different forms of learning that depend on different parts of the brain.

A day after their exposure to the shock, mice with reduced levels of Uch-L1 showed a decrease in freezing behavior to 65% that of normal mice when placed in the box. The differences between treated and untreated mice persisted 7, 14, and 21 days after exposure to the electric shock, they reported.

On the other hand, the mice showed no differences in response to the auditory tone, suggesting variation among brain regions in the role of Uch-L1.

In mice with symptoms that mimic those found in patients with Alzheimer's disease, treatments that raised Uch-L1 greatly increased their freezing time compared to their transgenic littermates when contextual learning was assessed over time, the researchers found. Improvements in the treated animals' ability to establish a memory for fear did not depend on changes in Aß levels.

The findings provide a new window into the Alzheimer's brain that could lead to new therapies, the researchers said.

"The rapid fall in Uch-L1 activity in response to Aß raises the possibility that, in the Alzheimer's brain, Aß initiates a signaling cascade that results in the partial inhibition of proteasome activity more rapidly than is likely as the result of the accumulation of misfolded or undigestable proteins."

"Our data suggest that Uch-L1 could be an attractive target for the development of new therapeutic approaches to Alzheimer's disease, either alone or in combination with therapies that alter Aß levels."

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