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Culprit in Alzheimer's Disease May Have a Good Side

Researchers have found evidence that may partially exonerate a protein known to be a culprit in the progression of Alzheimer's disease. Their new studies show that the protein p25, which wreaks havoc in the brains of patients with Alzheimer's disease, also has a good side in promoting the plasticity of the brain.

In studies in mice, the scientists have shown that the enzyme promotes structural changes in the brain associated with learning and memory. The studies indicate that when the concentration of the protein reaches excessive levels, it contributes to the brain cell death associated with Alzheimer's disease (AD). Their discovery of the dual nature of p25 suggests that drugs that partially inhibit p25's target enzyme could protect the neurons of patients with AD.

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The research team, which was led by Howard Hughes Medical Institute investigator Li-Huei Tsai, reported its findings in the December 8, 2005, issue of the journal *Neuron*. Tsai and her colleagues at Harvard Medical School collaborated on the studies with researchers from the National Institute of Mental Health.

In earlier studies, Tsai and her colleagues discovered that an enzyme called cyclin-dependent kinase 5 (Cdk5) plays a central role in AD pathology. Like other kinases, Cdk5 switches on enzymes by attaching a phosphate group to them. Under tight regulation by a protein called p35, Cdk5 controls the construction and maintenance of neuronal connections in the brain.

Tsai and her colleagues showed that in the neurons of people with AD, however, p35 is snipped apart abnormally, which leaves behind a different regulatory protein called p25. The resulting increase in the level of p25 in the

brain hyperactivates Cdk5. Mice with prolonged expression of p25 exhibit pathological hallmarks of AD such as brain atrophy, neuronal loss and neurofibrillary tangles.

In their latest studies, the researchers explored what happened when the brains of mice are exposed to a transient pulse of p25. They used mice that were genetically engineered so that adding the antibiotic doxycycline to their food would suppress production of p25. If doxycycline were removed from the food, p25 would be overproduced in the neurons of the mice.

"In our earlier studies with these mice, we had found that inducing p25 expression for eight to twelve weeks produced severe neurodegeneration," said Tsai. "So in this new study, we wanted to trace the early time-course of the pathology. When we looked at the effects of six weeks of exposure, we saw the first sign of neurodegeneration. But when we induced p25 for only two weeks, we saw absolutely no sign of neurodegeneration."

In fact, said Tsai, when they tested the learning and memory of mice that produced high levels of p25 for only two weeks, they saw enhanced neural function. "We saw significantly higher learning ability in these animals, and that was very surprising," she said. "It took us a while to get used to those observations."

The researchers tested the mice using two widely applied measures of learning and memory. In one of those tests, they measured how well the mice remembered the association between a tone or a particular cage chamber with a harmless but unpleasant electrical shock to their paws. In the other test, the researchers measured how well the mice remembered the location of a submerged platform in a tank of murky water. These tests revealed that p25 enhanced learning and memory during the two-week pulse, and for many weeks beyond — even when p25 is no longer produced in the transgenic mice.

The researchers also studied the effects of p25 on the circuitry and physiology of the hippocampus — the brain's learning and memory center. Their electrophysiological measurements revealed that the two-week pulse of p25 enhanced long-term potentiation, which underlies learning and memory. The hippocampi of these mice also had a higher density of dendritic spines and more synapses. "These findings showed us why the effects of the p25 pulse lasted so long," said Tsai. "They showed actual structural changes in the mouse brains."

Overall, said Tsai, the findings exonerate p25 as a complete villain in AD. "We always associated p25 with pathological conditions, especially since previous studies had found it to be quite toxic," she said. "Now, we think there is a very intriguing possibility that p25 is normally produced at a low level in the brain, perhaps to maintain synaptic plasticity. But if there is a systemic or chronic neurotoxicity, then p25 might be produced in large quantity, perhaps as the brain attempts to compensate for impaired synaptic function." What's more, said Tsai, p25 production might also naturally increase with normal aging, to compensate for normal neuronal loss.

Tsai said that the new findings suggest that a drug that offsets p25 hyperactivation of Cdk5 by partially inhibiting Cdk5 might also protect AD patients against neuronal loss. "Obviously, however, you cannot completely inhibit Cdk5, because that would impair synaptic plasticity," she said. "So, as is the case with many drugs, there would have to be a fine balance in such drug treatment to achieve benefits without being harmful."

In further studies, Tsai and her colleagues plan to trace the machinery Cdk5 uses to regulate synaptic plasticity, for example by increasing the density of dendritic spines. Also, she said, her laboratory is pursuing the critical question of how p25-hyperactivated Cdk5 kills neurons.