Tackling cognitive deficits in Alzheimer's disease: 1 'STEP' at a time

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Lowering levels of a key protein involved in regulating learning and memory -- STtriatal-Enriched tyrosine Phosphatase (STEP) -- reversed cognitive deficits in mice with Alzheimer's disease, Yale School of Medicine researchers report in the October 18 issue of *Proceedings of the National Academy of Sciences*.

"This finding provides a rationale for drug discovery and for developing therapeutic agents that could inhibit STEP proteins and might improve the outlook for Alzheimer's disease patients," said senior author of the study Paul Lombroso, M.D., professor in the Yale Child Study Center and in the Departments of Neurobiology and Psychiatry at Yale School of Medicine.

To test the idea that lowering STEP levels might reverse cognitive deficit in Alzheimer's disease, Lombroso and a team that included Nobel laureate Paul Greengard of Rockefeller University conducted a study on mice that were genetically engineered to still have the Alzheimer's mutation, but without the STEP protein. They compared these animals to mice with only the Alzheimer's mutation in a series of memory tests including a water maze. Mice without the STEP protein learned the maze after a 10-day training period, but the Alzheimer's mice did not. "This tells us that reducing STEP levels is sufficient to reverse the cognitive defect in these mice," said Lombroso.

Lombroso discovered the STEP protein in earlier studies. Past research has shown that increased STEP levels are caused by the toxic peptide

beta amyloid that blocks an organelle programmed to destroy these proteins. "When that organelle is inhibited, proteins, including STEP won't be degraded and will accumulate," said Lombroso.

Lombroso said that glutamate receptors on the surface of neurons are key to learning and memory. He and his team determined that the excess level of STEP was removing these glutamate receptors and preventing short-term memories from turning into long-term memories.

In addition to Alzheimer's disease, increased levels of STEP in the brain have been implicated in other disorders such as schizophrenia and Fragile X, which is characterized by cognitive deficits and other disabilities. Once again, high levels of STEP proteins remove glutamate receptors from synapses and contribute to the cognitive deficits present in these diseases.

"These new findings need to be replicated, but if genetically reducing STEP levels is improving cognition, we could perhaps discover a drug designed to reduce STEP activity," said Lombroso. "Our current work is focused on looking for STEP inhibitors."

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