New target identified for Alzheimer's disease

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Neurological researchers at Rush University Medical Center have found a new therapeutic target that can potentially lead to a new way to prevent the progression of Alzheimer's disease. The target called neutral sphingomyelinase (N-SMase) is a protein that when activated, can cause a chain of reactions in the cell leading to neuronal death and memory loss.

Results from the study funded by the National Institutes of Health and the Alzheimer's Association will be published in the September 22 issue of the Journal of Neuroscience.

"There are multiple, neurotoxic, disease-causing pathways that converge on the neutral sphingomyelinase that can cause neuronal loss in the brain of an Alzheimer's patient," said Kalipada Pahan, PhD, neurological researcher and lead investigator at Rush. "If we can stop the activation of the neutral sphingomyelinase, we may be able to stop memory loss and the progression of Alzheimer's disease."

In the brain of a patient with Alzheimer's disease, two abnormal structures called plaques and tangles are prime suspects in damaging and killing nerve cells. While neurons die, other brain cells like astroglia and microglia do not die. These brain cells become activated, and the glial cell activation plays a key role in the destruction of neurons. However, the molecular mechanisms by which activated glial cells can kill neurons have been poorly understood until now.

Beta-amyloid, which is a protein fragment deposited in the brains of

patients who have Alzheimer's disease, causes the activation of glial cells. Neuritic plaques are mainly composed of aggregates of beta-amyloid. When healthy nerve cells in the brain are exposed to beta-amyloid, they exhibit a number of pathological changes that are characteristic of Alzheimer's pathology.

Researchers at Rush were able to determine that the neutral sphingomyelinase is triggered by the activated brain cells and beta-amyloid. However, when the neutral sphingomyelinase was inhibited by using a small molecule inhibitor and a chemical inhibitor, the activated brain cells and beta amyloid were unable to kill neurons.

Experts tested the two inhibitors using human brain cells in a mouse model and a cell culture model.

"Understanding how the disease process works is important in identifying effective approaches to protect the brain and stop the progression of Alzheimer's disease," said Pahan. "The results of this study are very promising and our next step is to translate these findings to the clinic."

"If we can develop and test a clinical medication that can target the neutral sphingomyelinase, we may be able to halt memory loss in Alzheimer's disease patients," said Pahan.

Alzheimer's disease is an irreversible, progressive brain disease that slowly destroys memory and thinking skills, and eventually even the ability to carry out the simplest tasks. In most people with Alzheimer's, symptoms first appear after age 60. Alzheimer's disease is the most common cause of dementia among older people. Alzheimer's disease affects as many as 5.3 million Americans.

Provided by Rush University Medical Center