Naturally occurring protein fragment found in brain inhibits key enzyme implicated in Alzheimer's

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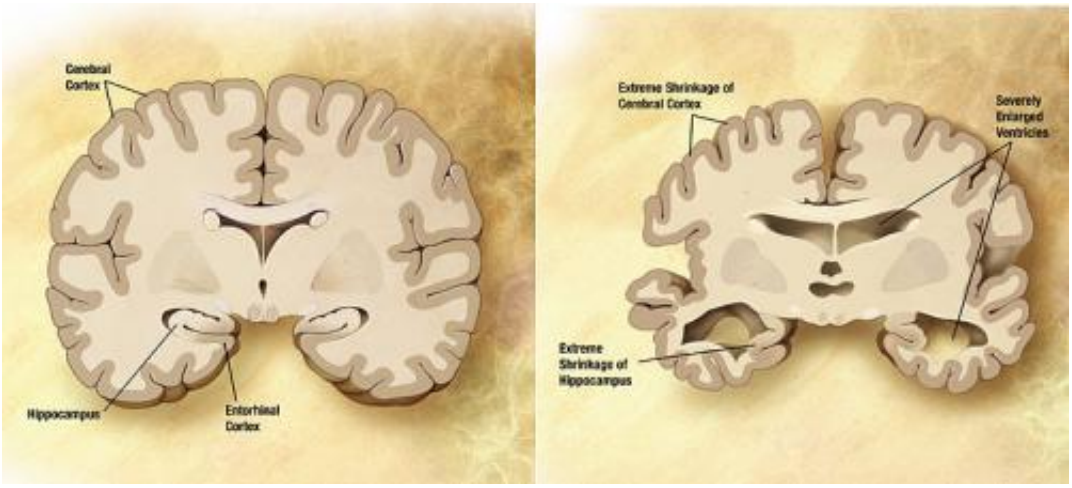

Diagram of the brain of a person with Alzheimer's Disease. Credit: Wikipedia/public domain.

For the first time, UCLA researchers have shown that a natural protein fragment produced in the brain can act as an inhibitor of a key enzyme implicated in the onset of Alzheimer's disease, a finding that could lead to the development of new drugs to treat the disease.

The study found that the protein fragment, sAPPα, inhibits the proteolytic enzyme BACE1. Increased BACE1 activity contributes to production of the amyloid beta aggregates and plaques that are the

hallmark of Alzheimer's.

"Because sAPPα inhibits the BACE1 enzyme, it may be possible that it can be used to help prevent potentially dangerous increases in BACE1 activity, and thus prevent the onset of Alzheimer's disease," said senior study author Varghese John associate professor of neurology and principle investigator of the Drug Discovery Lab in the Mary S. Easton Center for Alzheimer's Disease Research at UCLA.

The findings appear July 28, 2015 in the peer-reviewed *Journal of Alzheimer's Disease*.

The protein fragment sAPPis normally produced by neurons and is involved in maintenance of memory. UCLA researchers have shown that this normal brain fragment is also a potent inhibitor of the proteolytic enzyme BACE1. The new finding sheds light on brain regulation of amyloid beta production and could lead to development of new therapeutics.

The need for a new approach to treatment of Alzheimer's disease is urgent. Alzheimer's is the most common age-related dementia and the number of cases in the United States is expected to increase from the current number of about five to six million to 15 million by 2050. The costs to family life and on the health care system are enormous. Alzheimer's and other dementias are projected to cost the United States $226 billion in 2015 alone, with that number rising to as high as $1.1 trillion in 2050.

There currently are no truly effective treatment or prevention strategies for Alzheimer's, and the available drugs only reduce symptoms temporarily.

John and his team employed a technique called small-angle X-ray

scattering, or SAXS, and found that the sAPPα inhibition of BACE1 activity is likely due to the unique, three-dimensional structure of the protein fragment itself. Going forward, John and his team are determining the binding site of sAPP to BACE1 using X-ray crystallography and other techniques.

"Our study suggests that developing sAPPα itself as a biologic, finding a smaller protein or peptide fragment that has similar effects, or identifying a chemical compound that increases levels of this beneficial protein fragment could be new and effective therapeutic strategies for mild cognitive impairment and Alzheimer's patients," John said. "These strategies could help normalize brain function and either restore memory and cognitive function, or prevent its decline."

The protein fragment is critical to normal brain function, and creation of a new class of CNS therapeutics that enhance sAPPα may be of benefit beyond Alzheimer's. The potential drug could also help those who have suffered stroke or traumatic brain injury. Increasing levels of sAPPα may also be beneficial in treatment of ALS (Lou Gehrig's disease).

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