

# Potential Alzheimer's disease drug target identified

March 14 2008

---

In findings with the potential to provide a therapy for Alzheimer's disease patients where none now exist, a researcher at the University of California, San Diego and colleagues have demonstrated in mice a way to reduce the overproduction of a peptide associated with the disease. The study, which showed substantial improvement in memory in an animal model of Alzheimer's disease, was led by Vivian Y. H. Hook, Ph.D., professor of the Skaggs School of Pharmacy and Pharmaceutical Sciences and professor of neurosciences, pharmacology and medicine at the UCSD School of Medicine, together with American Life Science Pharmaceuticals of San Diego.

The study will be published in the March 21 edition of the *Journal of Biological Chemistry*, online March 14.

A hallmark sign of Alzheimer's disease, seen during autopsy of a patient's brain, is the accumulation of amyloid plaque deposits composed primarily of the neurotoxic beta-amyloid (A $\beta$ ) peptide which is believed to be a major factor in the cause of the disease. The A $\beta$  peptides are "cut" out from a larger protein called the amyloid precursor protein (APP) and bind together to form plaques in brain regions responsible for memory. One drug strategy to fight Alzheimer's disease is to reduce production of A $\beta$ .

"We discovered two chemical compounds that inhibit a new enzyme target, leading to reduced production of beta-amyloid and improved memory in a mouse model of Alzheimer's disease," said Hook.

Accumulation of A $\beta$  and plaque build-up are initiated when the large precursor protein, APP, a long string of amino acids, is “cut” into the smaller, neurotoxic A $\beta$  peptides that generate amyloid plaques. Protease enzymes, a type of protein, are the “scissors” that cut the large APP to generate A $\beta$  peptides. The protease must cut the APP amino acid sequence in two places: at the beta-secretase and the gamma-secretase sites. In this study, by inhibiting and therefore preventing the enzymatic “scissors” from “cutting” the APP chain into smaller peptides, the research team observed improved memory, as well as reduced levels of beta-amyloid protein in the brain, in mice bred to exhibit Alzheimer’s disease symptoms.

In the past, many scientists have focused on a mutant beta-secretase sequence only seen in one extended family of patients in Sweden with Alzheimer’s disease, Hook explained. This mutation, the so-called Swedish mutation, was known to result in an overproduction of A $\beta$ . Past research has shown that this Swedish mutant sequence is cut by a protease called BACE1.

Hook and colleagues found that a different protease, called Cathepsin B (CatB) works to cut the normal beta-secretase site – which is the site present in more than 99 percent of patients with Alzheimer’s disease – but not the Swedish mutant site. They also tested compounds that inhibit CatB – E64d and CA074Me – in a mouse model of Alzheimer’s disease with the normal beta-secretase site.

“After drug treatment, using water maze memory tests, we found that the mice exhibited great improvement in their memory, as well as reduced brain levels of beta amyloid,” said Hook. “These results are consistent with previous research indicating that CatB is elevated in brains of patients with Alzheimer’s disease.”

She added that a drug that duplicates this reduction by targeting CatB in

humans could be an effective treatment for Alzheimer's disease in the more than 99 percent of individuals with the normal beta-secretase site. "By disabling the enzyme's ability to cut the 'beta' end of the amino acid sequence, researchers may discover a way to limit production of neurotoxic A $\beta$  and reduce amyloid plaques in the brain."

Source: University of California - San Diego

Citation: Potential Alzheimer's disease drug target identified (2008, March 14) retrieved 3 May 2024 from <https://phys.org/news/2008-03-potential-alzheimer-disease-drug.html>

<p>This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.</p>
--