Potential new drug candidate found for Alzheimer's disease

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Researchers at the University of California, San Diego, the Medical University of South Carolina and American Life Science Pharmaceuticals of San Diego have demonstrated that oral administration of a cysteine protease inhibitor, E64d, not only reduces the build-up of β-amyloid (Aβ) in the brains of animal models for Alzheimer's disease, but also results in a substantial improvement in memory deficit.

A paper detailing the findings has been published as an early online version and is scheduled for publication in the September 6 issue of the *Journal of* Alzheimer's Disease.

According to lead investigator Vivian Y. H. Hook, PhD, professor of the UCSD Skaggs School of Pharmacy and Pharmaceutical Sciences and professor of neurosciences, pharmacology and medicine at the UCSD School of Medicine, this is major news for scientists studying Alzheimer's disease.

"The finding is especially exciting because E64d has previously been shown safe for use in humans, so we believe the compound has strong potential as a new therapy for Alzheimer's disease," said Hook.

Increased Aβ levels in the brain are associated with the development of memory loss and amyloid plaque, the hallmark of Alzheimer's disease. Aβ peptides are "cut" out from a larger protein called the amyloid precursor protein (APP) by an enzymatic "scissor" called β-secretase,

and aggregate to form plaques in the brain regions responsible for memory.

E64d reduces Aβ by inhibiting the β-secretase "scissors" from "cutting" the APP chain into smaller toxic Aβ peptides. But in this study, the researchers found that the compound actually increases the activity of a protease called BACE1 which, to date, has been regarded as the primary β-secretase. Instead, E64d appears to lower brain Aβ by inhibiting the β-secretase activity of another protease, Cathepsin B.

"The study indicates Cathepsin B as a new target for therapeutic inhibition of Aβ production and subsequent improved memory function," said Hook. "This is an important finding because we show that β-secretase inhibition can occur with Cathepsin B inhibition and without BACE1 inhibition."

The researchers studied both old and young transgenic Alzheimer's disease mice, and found that memory loss improved in both. In young mice, feeding E64d prevented development of memory loss; in old mice with memory loss, it improved memory.

The study builds upon work published in March 2008 that first demonstrated that inhibitors of Cathepsin B resulted in improved memory and reduction of Aβ and amyloid plaque; but in that study, the drug was administered directly into the brains of AD mice. In the new study, oral administration of the drug was efficacious and could lead the way to clinical trials in humans.

Provided by University of California - San Diego

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