

Researchers identify new enzyme to fight Alzheimer's disease

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An enzyme that could represent a powerful new tool for combating Alzheimer's disease has been discovered by researchers at Mayo Clinic in Florida. The enzyme—known as BACE2—destroys beta-amyloid, a toxic protein fragment that litters the brains of patients who have the disease. The findings were published online Sept. 17 in the science journal *Molecular Neurodegeneration*.

Alzheimer's disease is the most common [memory disorder](#). It affects more than 5.5 million people in the United States. Despite the disorder's enormous financial and personal toll, effective treatments have not yet been found.

The Mayo research team, led by Malcolm A. Leissring, Ph.D., a neuroscientist at Mayo Clinic in Florida, made the discovery by testing hundreds of enzymes for the ability to lower beta-amyloid levels. BACE2 was found to lower beta-amyloid more effectively than all other enzymes tested. The discovery is interesting because BACE2 is closely related to another enzyme, known as BACE1, involved in producing beta-amyloid.

"Despite their close similarity, the two enzymes have completely opposite effects on beta-amyloid—BACE1 gives, while BACE2 takes away," Dr. Leissring says.

Beta-amyloid is a fragment of a larger protein, known as APP, and is produced by enzymes that cut APP at two places. BACE1 is the enzyme

responsible for making the first cut that generates beta-amyloid. The research showed that BACE2 cuts beta-amyloid into smaller pieces, thereby destroying it, instead. Although other enzymes are known to break down beta-amyloid, BACE2 is particularly efficient at this function, the study found.

Previous work had shown that BACE2 can also lower beta-amyloid levels by a second mechanism: by cutting APP at a different spot from BACE1. BACE2 cuts in the middle of the beta-amyloid portion, which prevents beta-amyloid production.

"The fact that BACE2 can lower beta-amyloid by two distinct mechanisms makes this enzyme an especially attractive candidate for [gene therapy](#) to treat Alzheimer's disease," says first author Samer Abdul-Hay, Ph.D., a neuroscientist at [Mayo Clinic](#) in Florida.

The discovery suggests that impairments in BACE2 might increase the risk of Alzheimer's disease. This is important because certain drugs in clinical use—for example, antiviral drugs used to treat human immunodeficiency virus (HIV)—work by inhibiting enzymes similar to BACE2.

Although BACE2 can lower beta-amyloid by two distinct mechanisms, only the newly discovered mechanism—beta-amyloid destruction—is likely relevant to the disease, the researchers note. This is because the second mechanism, which involves BACE2 cutting APP, does not occur in the brain. The researchers have obtained a grant from the National Institutes of Health to study whether blocking beta-amyloid destruction by BACE2 can increase the risk for Alzheimer's disease in a mouse model of the disease.

Provided by Mayo Clinic

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