# Modulating a protein in the brain could help control Alzheimer's disease

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A protein known to exist in the brain for more than 30 years, called 5-lipoxygenase, has been found to play a regulatory role in the formation of the amyloid beta in the brain, the major component of plaques implicated in the development of Alzheimer's disease, according to researchers at Temple University's School of Medicine.

The researchers also found that inhibitors of this protein currently used to control asthma could possibly be used to prevent or treat Alzheimer's disease.

The researchers published their findings, "5-Lipoxygenase as Endogenous Modulator of Amyloid Beta Formation in Vivo," in the Annals of Neurology.

According to Domenico Praticò, an associate professor of pharmacology in Temple's School of Medicine and the study's lead researcher, the 5-Lipoxygenase enzyme is found in abundance mainly in the region of the brain, the hippocampus, involved in memory.

Praticò and his team discovered that 5-lipoxygenase, which unlike most proteins in the brain increases its levels during the aging process. It also controls the activation state of another protein, called gamma secretase, a complex of four elements which are necessary and responsible for the final production of the amyloid beta, a peptide that when produced in excess deposits and forms plaques in the brain. Today the amount of these amyloid plaques in the brain is used as a measurement of the severity of Alzheimer's.

"What we found was 5-lipoxygenase regulates and controls the amount of total amyloid beta produced in the brain," said Praticò. "With aging, the more 5-lipoxygenase you have the more amyloid beta you're going to produce. This will translate into a higher risk to develop full Alzheimer's"

A previous study by Praticò, in which researchers crossed a mouse model of Alzheimer's with a mouse that did not genetically feature 5-lipoxygenase, demonstrated that a lack of this enzyme protein alone can reduce the amount of disease in the brain by up to half.

"It has been known for years that the 5-lipoxygenase is an important protein in other areas of the body, such as the lung, but nobody really cared about its role in the brain," he said. "Based on some previously know information, we questioned whether this enzyme was a primary or secondary player in the development of Alzheimer's. What we found was a new primary role for an old enzyme."

Praticò said that the key in the process was 5-lipoxygenase's direct control over the gamma secretase, the only source of amyloid beta in the brain. "If you can modulate this enzyme easily, then you can control the amount of total amyloid beta that is produced by the gamma secretase in the brain, thus controlling the amount of Alzheimer's disease."

Praticò said that armed with new information, new therapies could be developed to block the increase of 5-lipoxygenase levels in the aging brain, which would in turn prevent the formation of amyloid beta.

He said that there are several FDA-approved 5-lipoxygenase inhibitors currently being used for the treatment of asthma, and that the Temple researchers tested some of these inhibitors in the lab against the production of amyloid beat with initial positive results.

"These drugs are already on the market, they're inexpensive and, most importantly, they are already FDA-approved, so you wouldn't need to go through an intense drug discovery process," said Praticò. "So you could quickly begin a clinical trial to determine if there is a new application for an old

drug against a disease where there is currently nothing."

Provided by Temple University