Protein in the brain could be a key target in controlling Alzheimer's

25 January 2012

A protein recently discovered in the brain could play a key role in regulating the creation of amyloid beta, the major component of plaques implicated in the development of Alzheimer's disease, according to researchers at Temple University's School of Medicine.

A group led by Domenico Pratico, professor of pharmacology and microbiology and immunology at Temple, discovered the presence of the protein, called 12/15-Lipoxygenase, in the brain three years ago.

"We found this protein to be very active in the brains of people who have Alzheimer's disease," said Pratico. "But three years ago, we didn't know the role it played in the development of the disease."

Following two years of study, the Temple researchers have found that the protein is at the top of a pathway and controls a biochemical chain reaction that begins the development of Alzheimer's. They have published their findings, "Transcriptional Regulation of ßsecretase-1 by 12/15 Lipoxygenase Results in Enhanced Amyloidogenesis and Cognitive Impairments," in the journal *Annals of Neurology*.

Pratico said that their research has shown that 12/15-Lipoxygenase controls Beta secretase (BACE-1), an enzyme that is key to the development of amyloid plaques in Alzheimer's patients.

"For reasons we don't yet know, in some people, 12/15-Lipoxygenase starts to work too much," he said. "By working too much, it sends the wrong message to the Beta secretase, which in turn starts to produce more amyloid Beta. This initially results in cognitive impairment, memory impairment and, later, an increase of amyloid plaque."

BACE-1 has long been a biological target for researchers seeking to create a drug against Alzheimer's disease, said Pratico. But because little has been known about how it functions, they have been unsuccessful developing a molecule that could reach the brain and block it.

"We now know much better how Beta secretase works because we have found that the 12/15-Lipoxygenase protein is a controller of BACE functions," he said. "You don't need to target the Beta secretase directly because the 12/15-Lipoxygenase is really the system in the brain that tells BACE to work more or work less."

Pratico said that they have validated 12/15-Lipoxygenase as a target for a potential Alzheimer drug or therapy.

"By modulating BACE levels and activity through controlling the 12/15-Lipoxygenase, we can potentially improve the cognitive part of the phenotype of the disease, and prevent the accumulation of amyloid beta inside the neurons, which will eventually translate into less of those plaques," he said. "This is a totally new mechanism for controlling BACE."

Pratico said his group has looked at an experimental compound that blocks 12/15-Lipoxygenase function as a potential therapy to inhibit BACE function in the brain. In their lab, using animal models, they saw the drug's ability to restore some cognitive function, as well as improve learning and memory ability.

"There is an opportunity here to study this molecule and develop an even stronger molecule to target 12/15-Lipoxygenase function in the brain," he said.

Provided by Temple University