Scientists develop a new way to target Alzheimer's disease

December 4 2006

The pathological embrace between two proteins plays a key role in the development of Alzheimer's disease by triggering the formation of neuron-killing plaques of amyloid beta protein. Now a group of scientists at NYU School of Medicine have devised a way to reduce amyloid beta deposition by interfering with the deadly embrace of these proteins.

Researchers hope to slow or even prevent the development of Alzheimer's by reducing or preventing the aggregation of amyloid beta. These deposits are one of the defining characteristics of Alzheimer's disease. Although scientists still aren't sure whether plaques are the initial trigger for the disease or are a consequence of it, the clumps can appear years before the onset of clinical symptoms. By the time dementia emerges, the plaques litter the brain.

In a new animal study, the NYU School of Medicine researchers report that they have reduced by around 50 percent the aggregation of toxic amyloid protein in the brains of mice by blocking the interaction between a protein called apolipoprotein E (apo E) and amyloid. Apo E acts as a sort of biological chaperone, ferrying cholesterol and fats around the brain.

The researchers, led by Martin Sadowski, M.D., Ph.D., Assistant Professor of Neurology and Psychiatry and Dr. Thomas Wisniewski, M.D., Professor of Neurology, Pathology and Psychiatry, created a nontoxic, synthetic protein fragment or peptide that binds to apo E, preventing it from latching onto amyloid. Deprived of its biochemical

chaperone, amyloid won't form deadly plaques.

In a series of studies in transgenic mice, the peptide reduced the amount of plaque in the brain and the amount of amyloid in the brain's blood vessels. It did not cause any apparent inflammation or leaks in blood vessels in the animals' brains, according to the study. Finally, in another set of experiments, the treated mice did not exhibit any memory decline when they were put into a radial arm maze, which evaluates working memory based on the animals' behavior. The peptide, which crosses the blood-brain barrier, was injected into the animals' abdomens.

It is the first time apo E has been manipulated in this way, according to Dr. Wisniewski. The study is published in the December 5, 2006, issue of the Proceedings of the National Academy of Sciences.

"Our approach opens up a completely new avenue for therapy," says Dr. Wisniewski. "There is a lot of data showing that apo E is important in sporadic Alzheimer's disease. But until now no one has really addressed how you can manipulate its interaction with amyloid beta." Alzheimer's affects some 4.6 million people in the United States, and the devastating neurodegenerative disease occurs most commonly as "sporadic," meaning it affects individuals who do not have rare genetic mutations.

Amyloid beta is a shape-changing chameleon. It normally exists as a nontoxic linear chain of amino acids. But the protein becomes a killer of neurons when it transforms itself into a spiral-like form that aggregates into plaques in the brain.

Apo E is a key player in the deadly transformation of amyloid. Dr. Wisniewski, who is among the scientists who first described the role of apo E in amyloid deposition, describes the lipoprotein as a "pathological chaperone." A string of amino acids on amyloid beta binds to apo E, and this deadly embrace triggers the transformation of amyloid. The NYU

researchers stitched together the string of amino acids on amyloid beta to create their synthetic peptide "mimic."

In a recent review article in the journal Science, scientists enumerated several approaches that are being pursued to reduce amyloid in the brain. One of the most promising is to inhibit an enzyme that shears off amyloid beta from a larger protein. However, this enzyme plays a variety of roles in the body, and concerns have arisen about the deleterious systemic affects of inhibiting it. Concerns also have emerged about vaccines to amyloid beta, and a clinical trial of one vaccine had to be halted because 6 percent of patients developed brain inflammation. In addition, studies in Alzheimer animal models and in the few vaccinated individuals who have had autopsies have suggested that vaccination can produce bleeding in the brain.

The NYU researchers said they were encouraged that their synthetic peptide did not appear to cause inflammation or bleeding in the brains of the animals tested. "In order for a peptide like this to be used in humans it would have to be taken for many years, much like statin medications for cholesterol," said Dr. Sadowski, whose research has been supported by a Paul B. Beeson Career Development in Aging a grant jointly funded by the American Federation of Aging Research and the National Institute on Aging. "Our ongoing research is now focusing on transforming the peptide used in the study into an agent that could be used clinically. It would have to be taken for a very long period of time without causing toxicity."

Source: New York University Medical Center and School of Medicine