

Cholesterol metabolism links early- and lateonset Alzheimer's disease

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Although the causes of Alzheimer's disease are not completely understood, amyloid-beta (A-beta) is widely considered a likely culprit — the "sticky" protein clumps into plaques thought to harm brain cells.

But now researchers at Washington University School of Medicine in St. Louis have uncovered evidence strengthening the case for another potential cause of Alzheimer's. The finding also represents the first time scientists have found a connection between early- and late-onset Alzheimer's.

In a study published in the Oct. 4, 2007 issue of the journal *Neuron*, the scientists report that when A-beta is made, a small bit of protein is also released that can regulate cholesterol levels in the brain. The discovery adds weight to the less prominent theory that abnormal brain cholesterol metabolism plays a role in the mental decline seen in Alzheimer's patients.

"Our research links two major determinants for early- and late-onset Alzheimer's disease," says senior author Guojun Bu, Ph.D., professor of pediatrics and of cell biology and physiology. "And we've shown that the process that links them is implicated in brain cholesterol metabolism."

The report follows closely on another study reporting that statins, widely prescribed cholesterol-lowering drugs, could prevent certain neural changes that signal the progression of Alzheimer's disease. Additional earlier studies support the idea that statins could benefit Alzheimer's



patients; however, other studies have found no such protective effect from statins.

"The studies of statins and Alzheimer's have generated quite a bit of controversy," Bu says. "Those that show positive effects from statins seem to suggest that high cholesterol could increase the risk of Alzheimer's disease. But other evidence contradicts this idea."

In fact, the brain needs a high level of cholesterol, according to Bu. "The brain represents only about 2 percent of your body weight, but actually has about 20 percent of your body's cholesterol," Bu says. "There is strong evidence that cholesterol is important for synaptic function and is an essential component of cell membranes in the brain, and I believe partial defects in the regulation of cholesterol metabolism in the brain likely contribute to the development of Alzheimer's."

In the current study, Bu and colleagues found an aspect of cholesterol transport and metabolism in the brain was a link between early- and late-onset Alzheimer's disease. Both forms of the disease result in similar brain lesions and have the same symptoms, including difficulties communicating, learning, thinking and reasoning, which suggests they share underlying mechanisms. But until now, no one has been able to identify such a mechanism.

Early-onset Alzheimer's can be traced to mutations in one of three genes, and the gene coding for A-beta's precursor, APP, is one of these. People with mutations in APP nearly always develop Alzheimer's disease, usually at a relatively young age.

The genetic origins of late-onset Alzheimer's, which accounts for 95 percent of cases, have proven harder to pin down. However, studies have shown that people who have a particular mutation in the gene for a cholesterol carrier called apolipoprotein E are far more likely to develop



Alzheimer's in old age than those who don't have the mutation.

Bu and colleagues demonstrated that APP and apolipoprotein E have a molecular connection. When APP is cleaved by a specific enzyme in the brain, it releases A-beta plus a small protein fragment. The fragment then can regulate apolipoprotein E, which moves cholesterol in the brain from support cells to neurons.

Past research by others implies that neural synapses, the junctions that nerves use to send impulses and communicate, are particularly sensitive to cholesterol levels and that interfering with cholesterol transport and metabolism could cause loss of synapses and degeneration of nerves.

"Cholesterol metabolism in the brain is an understudied area, and our findings could inspire Alzheimer's researchers to look further into the role of the cholesterol pathway," Bu says. "Right now, research on Alzheimer's treatment focuses largely on reducing A-beta production or increasing its clearance from the brain. Our study suggests that there could be an alternate way to treat the disease, perhaps by modulating the function of apolipoprotein E and cholesterol in the brain."

Bu and his colleagues plan to screen for compounds that regulate the molecular components that they found to be involved in cholesterol metabolism. They hypothesize that such compounds could work to enhance the brain's cholesterol metabolism and alleviate Alzheimer's symptoms.

Citation: Liu Q, Zerbinatti CV, Zhang J, Hoe H-S, Wang B, Cole SL, Herz J, Muglia L, Bu G. Amyloid precursor protein regulates brain apolipoprotein E and cholesterol metabolism through lipoprotein receptor LRP1. Neuron Oct. 4, 2007.

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