Low-density lipoprotein receptor reduces damage in Alzheimer's brain

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The low-density lipoprotein receptor (LDLR) has received a lot of attention because of its connection with coronary heart disease and atherosclerosis, but now it appears as if it may have a beneficial influence in degenerative brain diseases. New research, published by Cell Press in the December 10th issue of the journal *Neuron*, links LDLR with a reduction in brain changes associated with Alzheimer's disease (AD) and suggests a new therapeutic strategy for this incurable disease.

Amyloid beta-protein (Aβ) plays a major pathogenic role in AD, a devastating neurodegenerative disorder characterized by progressive cognitive impairment and memory loss. Accumulation of sticky extracellular Aβ plaques damages neurons and is thought to play a central role in disease pathogenesis. Apolipoprotein E (apoE), an established genetic risk factor for late-onset AD, is involved in the metabolism and transport of fats, and previous work has implicated apoE in Aβ accumulation.

"Modulating the function of proteins that control apoE metabolism in the brain will likely alter the extent of amyloid deposition and ultimately affect the disease process," explains senior study author, Dr. David M. Holtzman from the Washington University School of Medicine. "We know that low-density lipoprotein (LDL) receptor binds to apoE, yet its potential role in AD pathogenesis remains unclear."

Dr. Holtzman and colleagues created transgenic mice that overexpressed

LDLR in the brain and bred them with transgenic mice that were engineered to exhibit key pathological changes associated with AD, such as Aβ accumulation. Brain apoE levels were decreased by 50% to 90% in the LDLR transgenic mice and increased expression of LDLR-facilitated elimination of extracellular Aβ. Importantly, LDLR overexpression led to dramatic reductions in Aβ aggregation, amyloid plaque formation, and neuroinflammatory responses.

"Our study clearly demonstrates the beneficial effects of LDLR overexpression in the brain on pathogenic Aβ aggregation and subsequent neuroinflammatory responses," concludes Dr. Holtzman. "Given the results from these studies, the therapeutic potential of previously identified compounds, and potential new agents, which regulate LDLR in peripheral tissues merit additional testing in animal models of Aβ amyloidosis."

Source: Cell Press (news : web)