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Mechanism explains link between apolipoprotein E and Alzheimer's disease

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Scientists have discovered a previously unknown mechanism by which apolipoprotein E, a molecule whose mutation is linked to Alzheimer's disease (AD), stimulates degradation of sticky amyloid beta (A-beta) protein within the brain. The research, published by Cell Press in the June 12 issue of the journal *Neuron*, may lead to a powerful new therapy for this devastating disease.

One of the primary characteristics of AD is the accumulation and deposition of neuron-damaging clumps of A-beta protein. Apolipoprotein E (ApoE), a cholesterol transport protein, is known to be a key regulator of brain A-beta levels, and it is likely that processes that regulate ApoE activity will influence A-beta deposition and clearance. "An isoform of ApoE, ApoE4, has been shown to confer dramatically increased risk for late-onset AD; however, the basis for this remains one of the major unanswered questions of disease pathogenesis," writes study author Dr. Gary E. Landreth from the Alzheimer Research Laboratory at Case Western Reserve University School of Medicine in Cleveland, Ohio.

Dr. Landreth and colleagues sought to unravel the link between ApoE, A-beta clearance in the brain, and an enhanced risk for AD. The researchers found that ApoE profoundly enhanced the intracellular and extracellular degradation of A-beta. This enhancement varied for different isoforms of ApoE with the ApoE4 isoform exhibiting an impaired ability to promote A-beta degradation when compared to other ApoE isoforms. The number of lipid molecules associated with ApoE

was also critical to its ability to stimulate A-beta degradation. Activation of liver X receptors (LXRs) to enhance expression of lipidated ApoE significantly facilitated A-beta degradation. Importantly, use of an LXR agonist to increase lipidated forms of ApoE in a mouse model of AD resulted in reduced A-beta plaque levels and an improvement in contextual memory.

The results of this study document a major role for ApoE in the stimulation of A-beta degradation within the brain and highlight the importance of lipidation to the function of ApoE. This work also explains the previous observation that inactivation of a gene which helps the brain to process lipids (called Abca1) resulted in decreased levels of ApoE along with a seemingly paradoxical elevation of A-beta levels and plaque formation in mice. "Our data suggest that therapeutic agents that increase the levels of lipidated forms of ApoE, including LXR agonists, represent a potentially efficacious therapy for AD," concludes Dr. Landreth.

Source: Cell Press