Malfunctioning protein a cause of Alzheimer's plaques

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(Medical Xpress) -- In a new study published in *Science Translational Medicine*, scientists from the Washington University School of Medicine in St Louis reveal their discovery of a protein made by an Alzheimer's gene that hinders the brain's ability to remove the key ingredient in the amyloid plaques that are a signature of the disease.

Apolopoprotein E, or APOE, can be found in three forms known as E2, E3 and E4 and previous studies have shown that APOE E4 greatly increased the risk of Alzheimer's as well as lowered the age of onset by 10 to 15 years. Lead researcher Dr. David Holtzman says, "We knew that APOE was linked with amyloid beta accumulation and suspected that APOE E4 might slow amyloid-beta clearance. This study directly shows that this is particularly true for APOE E4."

Researchers began by looking at the APOE genes in almost 300 healthy individuals. They looked at the cerebrospinal fluid and brain scans to evaluate how much amyloid plaque was found in each of the participant's brains. They discovered that those participants who had one or multiple copies of APOE E4 had a higher chance of having plaque deposition.

To determine whether APOE E4 was the cause of increased amyloid beta production or simply slowed its removal, Joseph Castellano examined genetically altered mice that made one of the three forms of APOE. Using in vivo microdialysis to track amyloid levels in the mice brains, he discovered that the mice with APOE E4 showed mush higher

levels of amyloid beta and removed it much slower than the other mice. This presence of APOE E4 in the older mice also revealed much more amyloid plaque disposition.

Next, Castellano wanted to determine if the different forms of APOE played any role in the amyloid beta production rates. Using stable isotope labeling kinetics, he partnered with Dr. Randall Batemann, an assistant professor of neurology from Washington University. The results revealed that neither APOE E2, E3 nor E4 made a difference in the production rates.

The researchers have also discovered a receptor in the brain that removes the amyloid beta and APOE and Holtzman says, "We would like to find out whether that receptor clears amyloid beta and APOE together, or if the two are removed from the brain through distinct mechanisms. Answering these questions could be very important for new therapies."

More information: J. M. Castellano, J. Kim, F. R. Stewart, H. Jiang, R. B. DeMattos, B. W. Patterson, A. M. Fagan, J. C. Morris, K. G. Mawuenyega, C. Cruchaga, A. M. Goate, K. R. Bales, S. M. Paul, R. J. Bateman, D. M. Holtzman, Human apoE Isoforms Differentially Regulate Brain Amyloid-β Peptide Clearance. *Sci. Transl. Med.* 3, 89ra57 (2011). DOI: 10.1126/scitranslmed.3002156

ABSTRACT
The apolipoprotein E (APOE) ε4 allele is the strongest genetic risk factor for late-onset, sporadic Alzheimer's disease (AD). The APOE ε4 allele markedly increases AD risk and decreases age of onset, likely through its strong effect on the accumulation of amyloid-β (Aβ) peptide. In contrast, the APOE ε2 allele appears to decrease AD risk. Most rare, early-onset forms of familial AD are caused by autosomal dominant mutations that often lead to overproduction of Aβ42 peptide. However,

the mechanism by which APOE alleles differentially modulate Aβ accumulation in sporadic, late-onset AD is less clear. In a cohort of cognitively normal individuals, we report that reliable molecular and neuroimaging biomarkers of cerebral Aβ deposition vary in an apoE isoform - dependent manner. We hypothesized that human apoE isoforms differentially affect Aβ clearance or synthesis in vivo, resulting in an apoE isoform - dependent pattern of Aβ accumulation later in life. Performing in vivo microdialysis in a mouse model of Aβ-amyloidosis expressing human apoE isoforms (PDAPP/TRE), we find that the concentration and clearance of soluble Aβ in the brain interstitial fluid depends on the isoform of apoE expressed. This pattern parallels the extent of Aβ deposition observed in aged PDAPP/TRE mice. ApoE isoform - dependent differences in soluble Aβ metabolism are observed not only in aged but also in young PDAPP/TRE mice well before the onset of Aβ deposition in amyloid plaques in the brain. Additionally, amyloidogenic processing of amyloid precursor protein and Aβ synthesis, as assessed by in vivo stable isotopic labeling kinetics, do not vary according to apoE isoform in young PDAPP/TRE mice. Our results suggest that APOE alleles contribute to AD risk by differentially regulating clearance of Aβ from the brain, suggesting that Aβ clearance pathways may be useful therapeutic targets for AD prevention.