Reverse apoE4 effects by apoE2 expression in Alzheimers disease

https://neurodegenerationresearch.eu/survey/reverse-apoe4-effects-by-apoe2-expression-in-alzheimers-disease/

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Research Abstract

PROJECT SUMMARY/ABSTRACT MAYO CLINIC JACKSONVILLE Alzheimer’s disease (AD) is the leading cause of dementia in the elderly, currently with no disease-altering therapy available. The accumulation, aggregation, and deposition of amyloid-? (A?) peptides in the brain are central events in the pathogenesis of AD. Increasing evidence has shown that the ?4 allele

of the apolipoprotein E (APOE) gene is the strongest genetic risk factor for AD among its three polymorphic alleles (?2, ?3 and ?4), whereas the ?2 allele is protective. ApoE is abundantly produced in both astrocytes and in vascular mural cells. While apoE4 exacerbated A? deposition by suppressing A? clearance, apoE2 is more protective against A? accumulation than other isoforms. Furthermore, apoE4 is less efficient than apoE3 in mediating cholesterol transport, protecting synaptic integrity/repair, controlling neuroinflammation and supporting cerebrovascular function. In fact, APOE4 carriers account for about 60% of all AD patients. Interestingly, although pharmacological approaches increasing lipidated apoE levels improve memory and reduce A? levels in amyloid model mice, the upregulation of apoE4 in astrocytes exacerbates its harmful effects on amyloid pathology without repairing synaptic functions. Therefore, better understanding of apoE isoform-dependent effects on cognition and other AD-related pathways should allow us to address why apoE2 reduces but apoE4 increases the risk for AD, and how we can target this pathway for therapy. In this proposal, we aim to investigate the potential therapeutic effects of apoE2 in different brain cell types on cognition and amyloid pathology in amyloid model APP/PS1 mice carrying human APOE4. We hypothesize that forced expression of apoE2 reverses apoE4-related phenotypes and reduces brain A? accumulation in AD. Our specific aims are as follows: Aim 1. Determine the effects of Adeno-Associated Virus (AAV)- mediated APOE2 gene delivery in astrocytes or vascular mural cells carrying APOE4 on A? metabolism, neuroinflammation and cerebrovascular functions; Aim 2. Examine how expression of apoE2 alters apoE4- related amyloid pathology and cognitive decline using cell-type specific apoE2 inducible mice. Collectively, these studies explore both mechanism and therapeutic value of apoE2 in AD.

Further information available at:

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