The role of apoE and APOE genotype in amyloid-beta clearance after TBI

https://neurodegenerationresearch.eu/survey/the-role-of-apoe-and-apoe-genotype-in-amyloid-beta-clearance-after-tbi/

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Country

USA

Title of project or programme

The role of apoE and APOE genotype in amyloid-beta clearance after TBI

Source of funding information

NIH (NIA)

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01/02/2013

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2

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Abeta clearance, Apolipoprotein E, Traumatic Brain Injury, Amyloid, Genotype

Research Abstract

DESCRIPTION (provided by applicant): After traumatic brain injury (TBI) the human APOE-?4 (APOE4) gene polymorphism is associated with increased mortality, increased coma time, poor

prognosis, and an increased risk of late-onset Alzheimer’s disease (AD). The APOE4 gene is found in 27% of the US population, and as such affects an estimated 459,000 TBI cases each year. It is not known how APOE4 genotype negatively impacts outcome after TBI, or if genotype-specific treatments are required to improve prognosis. TBI causes the accumulation and deposition of a neurotoxic peptide called amyloid-ß (Aß). Approximately 30% of all fatal TBI cases present with Aß plaques, however the deposition of Aß is dependent on the APOE genotype of the patient. Only 10% of non-APOE4 brains have Aß plaques after injury, while 35% of heterozygous APOE4 brains, and 100% of homozygous APOE4 brains, develop Aß plaques. The APOE gene encodes for the apolipoprotein E (apoE) protein, which was recently shown to facilitate the enzymatic degradation of Aß. These data suggest that individuals carrying the APOE4 genotype are unable to clear the excess Aß that is produced as a result of TBI. Accumulation of excess Aß is known to cause neuronal apoptosis and trigger neuroinflammation. We have recently shown that preventing Aß production, or enhancing Aß clearance, can ameliorate secondary injury and prevent cognitive and motor deficits caused by experimental TBI in mice. Here we will study the role of apoE isoforms in Aß clearance after TBI. We are testing the hypothesis that apoE is instrumental in Aß degradation after TBI, but the apoE4 isoform is dysfunctional at this process. We believe that the accumulation of Aß in APOE4 mice leads to increased cell death and poorer functional and cognitive outcome after injury. We will test this hypothesis in our Specific Aims: Aim 1) Determine the role of apoE in Aß clearance after TBI Aim 2) Determine the effect of APOE genotype on Aß clearance after TBI Aim 3) Test if the poorer prognosis after TBI in APOE4 carriers is due to prolonged Aß accumulation These data will allow us to determine the mechanism by which Aß accumulates aggressively in APOE4 patients after TBI, and the functional consequences of that Aß accumulation.

Lay Summary

PUBLIC HEALTH RELEVANCE: After traumatic brain injury (TBI) the human APOE-?4 (APOE4) gene polymorphism is associated with increased mortality, increased coma time, poor prognosis, and an increased risk of late-onset Alzheimer’s disease (AD). The APOE4 gene is found in 27% of the US population, and as such affects an estimated 459,000 TBI cases each year. It is not known how APOE4 genotype negatively impacts outcome after TBI, or if genotype-specific treatments are required to improve prognosis. This R01 proposal proposes that impaired clearance of the neurotoxic Aß peptide after TBI is responsible for these detrimental effects, and tests pharmacological treatments to reverse these deficits.

Further information available at:

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United States of America

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Alzheimer's disease & other dementias

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