

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

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

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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)

## Total sum awarded (Euro)

€ 1,646,050.46

## Start date of award

01/02/2013

## Total duration of award in years

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- $\beta$  (A $\beta$ ). Approximately 30% of all fatal TBI cases present with A $\beta$  plaques, however the deposition of A $\beta$  is dependent on the APOE genotype of the patient. Only 10% of non-APOE4 brains have A $\beta$  plaques after injury, while 35% of heterozygous APOE4 brains, and 100% of homozygous APOE4 brains, develop A $\beta$  plaques. The APOE gene encodes for the apolipoprotein E (apoE) protein, which was recently shown to facilitate the enzymatic degradation of A $\beta$ . These data suggest that individuals carrying the APOE4 genotype are unable to clear the excess A $\beta$  that is produced as a result of TBI. Accumulation of excess A $\beta$  is known to cause neuronal apoptosis and trigger neuroinflammation. We have recently shown that preventing A $\beta$  production, or enhancing A $\beta$  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 A $\beta$  clearance after TBI. We are testing the hypothesis that apoE is instrumental in A $\beta$  degradation after TBI, but the apoE4 isoform is dysfunctional at this process. We believe that the accumulation of A $\beta$  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 A $\beta$  clearance after TBI Aim 2) Determine the effect of APOE genotype on A $\beta$  clearance after TBI Aim 3) Test if the poorer prognosis after TBI in APOE4 carriers is due to prolonged A $\beta$  accumulation These data will allow us to determine the mechanism by which A $\beta$  accumulates aggressively in APOE4 patients after TBI, and the functional consequences of that A $\beta$  accumulation.

### **Lay Summary**

**PUBLIC HEALTH RELEVANCE:** After traumatic brain injury (TBI) the human APOE- $\epsilon$ 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 A $\beta$  peptide after TBI is responsible for these detrimental effects, and tests pharmacological treatments to reverse these deficits.

### **Further information available at:**

#### **Types:**

Investments > €500k

#### **Member States:**

United States of America

#### **Diseases:**

Alzheimer's disease & other dementias

#### **Years:**

2016

#### **Database Categories:**

N/A

**Database Tags:**

N/A