# Effect of APOE on CNS Neurons: Role of LRP

https://www.neurodegenerationresearch.eu/survey/effect-of-apoe-on-cns-neurons-role-of-lrp/

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**Country**

USA

**Title of project or programme**

Effect of APOE on CNS Neurons: Role of LRP

**Source of funding information**

NIH (NIA)

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**Start date of award**

01/09/1996

**Total duration of award in years**

3

**The project/programme is most relevant to:**

Alzheimer's disease & other dementias

**Keywords**

tau Proteins, Apolipoprotein E, tau aggregation, Intercellular Fluid, Amyloid

**Research Abstract**

DESCRIPTION (provided by applicant): APOE genotype is the strongest genetic risk factor for Alzheimer’s disease (AD); the ?4 allele increases risk in a dose-dependent fashion and the ?2 allele decreases risk. APOE appears to influence AD at least in part via isoform-specific effects of apoE on Aß clearance and aggregation; however, there are likely additional mechanisms by which apoE influences AD. Interactions between apoE and tau, whose aggregation is linked

with neurodegeneration, may be an important mechanism as to how apoE influences AD. Certain forms of apoE can bind to tau in an isoform-specific fashion and tau pathology is increased in the brain of ?4 carriers with AD. We have preliminary data validating a recent paper which shows that a mouse model of tauopathy, (P301S), develops significantly more tauopathy in the absence of apoE. Data from many labs including our own strongly suggests that an important mechanism in tau pathogenesis in tauopathies including AD is that aggregated forms of tau escape the cytoplasm and spread to both adjacent and synaptically connected cells to induce transcellular seeding of tau and disease progression. Tau is present in the interstitial fluid space of the brain normally and this is likely also the case for tau aggregates. Since apoE is an abundantly secreted protein from glial cells, can bind to tau, and both apoE and tau aggregates strongly bind to HSPGs, we hypothesize that apoE interacts with tau in the brain extracellular space to influence its metabolism, aggregation, and effects on neurodegeneration. Our primary hypothesis is that human APOE isoforms dose-dependently influences tau pathology both directly as well as via effects on Aß. Our secondary hypothesis is that human apoE-containing lipoproteins bind to extracellular tau aggregates and influence their ability to induce tau seeding/spreading. The specific aims are: 1) To determine the effect of human APOE isoforms on tau pathology in the presence and absence of human Aß. 2) To determine the effects of human APOE isoforms on the mouse models in Aim 1 on brain interstitial fluid (ISF) tau by microdialysis as well as tau seeding activity in ISF, CSF, and brain lysates. 3) To assess the binding of apoE-containing lipoproteins to both monomeric and aggregated tau and assess their effect on cellular binding, uptake, and tau seeding activity

**Lay Summary**
PUBLIC HEALTH RELEVANCE: Alzheimer’s disease is a major public health problem with no treatments that delay, slow, or prevent the disease. We are trying to better understand mechanisms underlying how the most important genetic risk factor for Alzheimer’s disease, APOE, is causing its effects. This could lead to novel insights into new treatments.

**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

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