Targeting the apoE/A-beta Interaction as a Therapeutic Approach for AD

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Country

USA

Title of project or programme

Targeting the apoE/A-beta Interaction as a Therapeutic Approach for AD

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NIH (NIA)

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15/03/2008

Total duration of award in years

6

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Dementia... Neurodegenerative... Neurosciences... Prevention

Research Abstract

Alleles of the apolipoprotein (apo) E gene are by far the strongest identified genetic risk factor modulating susceptibility to sporadic Alzheimer's disease (AD) and the burden of ?-amyloid (A?) deposition in the brain following the rank order of ?4>>?3>?2. Encoded by these alleles, apoE isoforms differ structurally and functionally but all bind in vitro synthetic A? peptide promoting its ?-sheet folding and fibrillar assembly. Knockout (KO) of the Apoe gene in APP transgenic (Tg) mice prevents formation of fibrillar A? plaques and vascular deposits, confirming a critical role for apoE as a catalyst of A? deposition in vivo. In the current period of this award we developed APPSW/PS1dE9/apoE-TR mice (APP/E-TR) with targeted replacement (TR) of the mouse Apoe gene with various human APOE alleles, which faithfully reproduce the differential effect of apoE isoforms on the magnitude of A? deposition. We showed that systemic treatment of APP/E2 and APP/E4 mice with A?12-28P, which is a brain permeable synthetic peptide that binds apoE and prevents apoE/A? interaction, lowers A? deposition and level of toxic A? oligomers and attenuates neuritic degeneration in both lines of mice. This observation suggests a notion that targeting the apoE/A? interaction could reduce A? deposition in carriers of all types of APOE alleles. Development of apoE/A? antagonists for possible clinical application remains however problematic since neither the A? binding domain on apoE nor the structure of A? "super epitope" within its 12-28 sequence responsible for apoE interaction are presently known. In addition to catalyzing deposition of fibrillar A?, apoE isoforms also show differential effect on the clearance of soluble A? from the brain interstitial space, modulate microglia response and synaptic plasticity. Modus operandi of apoE on the clearance of A? from the interstitial fluid (ISF) remains elusive. Our preliminary microdialysis work indicates substantial interaction between apoE and soluble A? in the brain ISF, and suggests that apoE/A? antagonists may enhance soluble A? clearance and prevent A? oligomerization. This indicates potential for targeting the apoE/A? interaction as a disease preventive measure. In addition, systemic treatment of APP and APP/E-TR mice with A?12-28P reduces amyloid angiopathy and perivascular microhemorrhages and attenuates microglia activation, which suggests that combining an apoE/A? antagonist with anti-A? passive immunization could temper chronic inflammation and vasculotropic complications produced by the latter, while having synergistic outcome on A? reduction. The specific aims are: 1) To identify the A? binding domain on apoE and characterize its variability across apoE isoforms and to determine the structure of A? super epitope for apoE interaction. 2) To investigate how apoE isoforms differentially modulate soluble A? metabolism in the ISF and to study how targeting apoE/A? interaction improves A? clearance and attenuates its oligomerization. 3) To investigate whether combining apoE/A? targeting with anti-A? passive immunization would provide amplified therapeutic response and reduce the rate of adverse vascular events in APP/E-TR mice.

Lay Summary

Project narrative This project investigates how interaction between A? and isoforms of human apoE differentially modulates A? metabolism and affects susceptibility to Alzheimer's disease. It also studies targeting the apoE/A? interaction as a therapeutic approach for Alzheimer's prevention and treatment.

Further information available at:

Types:

Investments > €500k

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United States of America

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Alzheimer's disease & other dementias

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