Characterization of a caspase-cleavage resistant tau knock-in mouse

https://neurodegenerationresearch.eu/survey/characterization-of-a-caspase-cleavage-resistant-tau-knock-in-mouse/

Principal Investigators

D'ADAMIO, LUCIANO

Institution

ALBERT EINSTEIN COLLEGE OF MEDICINE, INC

Contact information of lead PI
Country

USA

Title of project or programme

Characterization of a caspase-cleavage resistant tau knock-in mouse

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

421330.2752

Start date of award

15/04/2015

Total duration of award in years

3

Keywords

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

Research Abstract

DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) is the most common cause of ageing-dependent dementia in the world and is associated with cerebral amyloid plaques and neurofibrillary tangles (NFTs). Amyloid plaques are mostly composed of Aß peptides while NFTs are composed of abnormal aggregates of hyperphosphorylated forms of the cytoskeletal

protein tau. Aß peptides are produced by a double cleavage of the amyloid precursor protein (APP). BACE1 cleavage produces the C-terminal fragment, ß-CTF, which is then processed into several Aß isoforms by ?-secretase. Genetic data suggest that regulation of APP processing contributes to AD. Current drug discovery approaches in AD have focused on preventing Aß formation or removing existing amyloid deposits. The repeated failures of compounds/biologics targeting amyloid in clinical trials can either be attributed to the inclusion of AD patients who were too advanced in their disease progression to benefit from therapeutic intervention, or to the fact that Aß is not the main cause of AD patho-physiology. The most advanced alternative hypothesis of AD is that of tau toxicity. Consistent with this hypothesis, reducing endogenous tau expression prevents behavioral deficits in transgenic mice expressing human APP with familial AD mutations, without altering Aß levels. Our preliminary data indicate that tau also mediates behavioral deficits in Familial Danish Dementia (FDDKI mice), an AD-like dementia associated with mutations in the regulator of APP processing BRI2/ITM2B, also characterized by tauopathy. Some evidence suggests that caspases are activated early in the progression of AD and may play a role in neuronal loss and NFT pathology. Tau is cleaved at D421 (?Tau) by executioner caspases. Following caspase-cleavage, ?Tau facilitates nucleation-dependent filament formation and adopts a conformational change recognized by MC1, an early pathological tau marker. ?Tau can be phosphorylated and recognized by the NFT antibody PHF-1. In AD brains, ?Tau associates with markers of NFTs and correlates with cognitive decline. Furthermore, ?Tau initiates NFT formation and can exert toxic effects. These findings have led to the hypothesis that ?Tau is a critical toxic moiety underlying neurodegeneration. To directly test this theory, we have generated knock-in mice in which the endogenous tau codon GAC in exon 12, encoding for D421, has been mutated into AAC, which now encodes for an asparagine (N). These knock-in mice, called TauD421N, express a tau mutant, taucas/res that cannot be cleaved by caspases and therefore cannot generate ?Tau. TauD421N mice will be used to determine whether ?Tau mediates synaptic plasticity and memory deficits in animal models of AD and FDD, two neurodegenerative disorders in which tau plays a pathogenic role. Our studies will speak to whether modulation of ?Tau formation is a potential strategy for the treatment of AD and other neurodegenerative disorders mediated by neuro-toxic tau forms.

Further information available at:

Types:
Investments < €500k

Member States:
United States of America

Diseases:
N/A

Years:
2016

Database Categories:
N/A

Database Tags:
N/A