Trafficking and Endosomal Sorting of APP and BACE-1

https://www.neurodegenerationresearch.eu/survey/trafficking-and-endosomal-sorting-of-app-and-bace-1-2/

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Country

USA

Title of project or programme

Trafficking and Endosomal Sorting of APP and BACE-1

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,437,538.53

Start date of award

11/08/2016

Total duration of award in years

4

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

Research Abstract
DESCRIPTION (provided by applicant): The amyloid precursor protein (APP) is sequentially

cleaved by ß- and ?-secretases to generate amyloid ß-peptide (Aß) in the brain – a central player in Alzheimer's disease. APP cleavage by ß-secretase-1 (BACE-1) is the rate-limiting step for production of Aß. Aß is believed to exert its toxicity on neurons while in a soluble and oligomeric state, prior to deposition as insoluble fibrils in brain. Thus, for reasons related to bth pathophysiology and therapeutics, understanding mechanisms and pathways of Aß generation from APP is a major focus of many laboratories. An intriguing aspect of Aß production is that its release is dependent upon neuronal activity – enhanced synaptic activity results in more Aß release. Though pathways involved in trafficking and cleavage of APP in neurons are of obvious importance, the vast majority of previous studies on APP/BACE-1 trafficking have been carried out in non-neuronal cells. These findings may not always be applicable to neurons, which are highly polarized and are known to have very different trafficking mechanisms. Furthermore, inferences on how neuronal activity modulates APP processing by BACE-1 require work in neurons. The prevailing view is that at presynaptic terminals, heightened synaptic vesicle recycling that accompanies high synaptic activity results in increased internalization into endosomes of APP where proteolysis by secretases take place. However, our recent studies using live neuronal imaging showed rather surprising results in that APP and BACE-1 normally traffic in distinct vesicles – perhaps preventing unabated cleavage – but converge in dendrites upon activity-induction. This led us to propose a new model whereby neuronal activity brings together APP and BACE-1 in dendrites where the two molecules interact. Only subsequently are these two molecules sorted into axons to distal terminals. Experiments in this proposal will examine a number of predictions that emanate from this working model and dissect the trafficking pathways of APP and BACE-1; revealing their relationship to amyloidogenesis and neuronal activity. Four Aims are proposed: 1) Test the hypothesis that APP and BACE-1 are first conveyed into dendrites in distinct carriers after biogenesis. 2) Determine specific neuronal subcellular site(s) of APP/BACE-1 interaction and Aß release. 3) Determine the biogenesis and molecular composition of the axonal APP/BACE-1-carrying organelle. 4) Visualize APP/BACE-1 associations in brains and in human induced pluripotent stem cells (iPSCs). Collectively, results from these studies will provide new insights into the trafficking pathways of APP and BACE-1 and demonstrate how neuronal activity modulates these pathways to enhance APP cleavage and Aß release.

Lay Summary

PUBLIC HEALTH RELEVANCE: Alzheimer's disease (AD) is the epidemic of our time, with tremendous social and economic consequences; however despite this urgency, currently there are no disease-modifying drugs on the market. Amyloid-beta (Aß) is widely considered to play a central role AD – initiating the toxic cascade of events – and though the mechanisms by which Aß is generated has been a topic of interest for many years, means by which Aß is generated in neurons is still unclear. Coupling novel tools and experimental paradigms with cultured neurons, in-vivo brain imaging, and human induced pluripotent stem cells, our studies propose to pinpoint the pathways initiating – and ultimately generating – Aß fragments in neurons.

Further information available at:

Types:

Investments > €500k

Member States:

United States of America

Diseases:

Alzheimer's disease & other dementias

Years:
2016

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