Function of ceramide in neurodegenerative disease

https://neurodegenerationresearch.eu/survey/function-of-ceramide-in-neurodegenerative-disease/

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Country

USA

Title of project or programme

Function of ceramide in neurodegenerative disease

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,872,600.92

Start date of award

01/09/2010

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

? DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) is characterized by

progressive neurodegeneration and build-up of A? peptides, amyloid plaques, and neurofibrillary tau tangles. Current strategies to prevent A? formation or secretion are not successful. Preventing A? build-up while enhancing A? uptake and clearance is an alternative approach to minimize the effect of A? peptides. A critical barrier to progress in the development of novel drugs that prevent A? build-up and improve clearance is the lack of a thorough understanding of how A? amyloid plaques are nucleated and proliferate instead of A? being taken up and cleared by glial cells. Our goal is to interrupt amyloid plaque nucleation and propagation to enhance A? clearance and delay the onset and reduce neurodegeneration in AD. Our central hypothesis is that ceramide-enriched exosomes secreted by astrocytes form complexes with A? (A?/Exos) that function as “”seeds”” to catalyze nucleation and propagation of neurotoxic plaques instead of facilitating A? transport and clearance by microglia. Secretion, aggregation, and neurotoxicity of A?/Exos is enhanced by elevation of ceramide levels, in particular by neutral sphingomyelinase 2 (nSMase2), an enzyme generating ceramide when activated by A?. Drug (e.g., nSMase2 inhibitor)-induced reduction of ceramide will prevent A?/Exo build-up/spreading and protect neurons, which is a novel treatment option for AD. Our objectives are to 1) test key regulatory factors that control secretion of exosomes and their association with A?; 2) test a novel molecular mechanism by which A?/Exos induce plaque formation, tau hyperphosphorylation, and neuronal cell death; 3) test pharmacological drugs that prevent exosome secretion, A?/Exo-induced plaque formation, tau hyperphosphorylation, and neuronal cell death in vitro and in vivo; and 4) test if A?/Exos in serum and cerebrospinal fluid from AD model mice and AD patients can be used as a novel diagnostic tool for monitoring plaque and tangle build-up, and treatment success. Our expected outcomes include 1) determining an exosome composition that induces association with A?, plaque nucleation and propagation, tau hyperphosphorylation, and neuronal cell death; 2) identifying ceramide-modulating drugs that prevent A?/Exo-induced plaque formation, tau hyperphosphorylation, and neuronal cell death; and 3) defining a level of A?/Exos in serum that indicates severity of AD and success of treatment. The impact of this project on public health will include knowledge needed for the development of new strategies and treatments that could delay and reduce the onset of progressive neurodegeneration in AD. We will test by which mechanism ceramide promotes association and aggregation of A?42 (Aim 1), how A?42/Exos induce plaque formation and neurodegeneration (Aim 2), and which treatment prevents exosome-induced amyloid aggregation, plaque formation, and AD pathology (Aim 3).

Lay Summary
PUBLIC HEALTH RELEVANCE: Development of novel drugs to treat Alzheimer’s disease (AD) by preventing amyloid plaque formation and neurodegeneration is being impeded by lack of knowledge of how neurotoxic plaques are nucleated and propagated. Our goal is to interrupt amyloid plaque nucleation and propagation to enhance amyloid peptide clearance and delay the onset and reduce neurodegeneration in AD. The impact of this project on public health will include knowledge needed for the development of new strategies and treatments that could delay and/or reduce the onset of progressive neurodegeneration in Alzheimer’s disease.

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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