GDE and Neurodegenerative Diseases

https://neurodegenerationresearch.eu/survey/gde-and-neurodegenerative-diseases/

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Country

USA

Title of project or programme

GDE and Neurodegenerative Diseases

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,180,073.39

Start date of award

30/09/2014

Total duration of award in years

3

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... Rare Diseases... Transmissible Spongiform Encephalopathy (TSE)

Research Abstract

? DESCRIPTION (provided by applicant): This proposal imagines a paradigm shift for understanding human Alzheimer’s disease that is based on a newly discovered, druggable

enzyme. Our current understanding of AD proposes a central role for the accumulation of amyloid A? (1), but there is great need for advances in understanding mechanisms that cause increases of A? in sporadic AD. Moreover, there are many aspects of the pathology of AD that cannot be simply understood as a consequence of A? accumulation, and suggest other molecular mechanisms contribute to pathogenesis. There is also a great need for diagnostics that can be rationally linked to pathogenesis. Most of all there is a need for effective therapeutics. These challenges are well known to the field. We see a unique opportunity to advance AD research that builds on the discovery of a novel enzyme family that controls several of the most important signalling pathways in brain development. GDEs catalyze cleavage of the phosphodiester bond that links a class of extracellular proteins to the cell surface (2). These GPI-linked proteins act as activators or inhibitors of Notch, sonic hedgehog, fibroblast growth factor, Wnt, ephrin (EphA5), ciliary neurotrophic factor receptor (CNTF), glial derived neurotrophic factor, and contactins. The role of GDEs in neurodegeneration was made serendipitously with the discovery that conditional deletion of GDE in adult brain results in profound, age-dependent neurodegenerative changes that include many of the hallmarks of human neurodegenerative disease. We hypothesize that loss of GDE function contributes to human neurodegenerative disease. The approach exploits the fortunate consequence of GDE activity, which is to shed substrate proteins into the extracellular compartment and CSF. This creates “”biomarkers”” of GDE activity. As proof of concept, we have determined that prion protein is a substrate of GDE. Prion protein is present in the CSF at levels that are reduced in human AD subjects in parallel with cognitive decline(3), and recent studies implicate prion protein in pathological reduction of synaptic strength and enhanced A? generation in AD(4, 5). We will expand this precedent using non-biased methods to identify GDE substrates in CSF and brain of normal and diseased humans. These biomarkers will identify specific signalling pathways consequent to GDE function that are consistently disrupted in AD. Where successful, this approach will provide mechanism-linked biomarkers of disease that can be combined with modulators of the GDE pathway as new mechanism-based diagnostics and therapeutics for AD.

Lay Summary

PUBLIC HEALTH RELEVANCE: GDEs are signaling enzymes implicated in neurodegeneration in mouse models. We will test the hypothesis that GDEs are important for human neurodegenerative diseases by developing and examining biomarkers of GDE activity in human CSF and brain tissue. Studies hold the promise to establish new, mechanism-based diagnostics for therapeutic targets for human neurodegenerative 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

Database Tags:
N/A