Gamma-Secretase and Myelin: A Paradigm Shift in Brain Disorders

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Contact information of lead PI
Country

USA

Title of project or programme

Gamma-Secretase and Myelin: A Paradigm Shift in Brain Disorders

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,592,281.65

Start date of award

15/02/2013

Total duration of award in years

3

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

nicastrin protein, gamma secretase, myelination, Myelin, Brain Diseases

Research Abstract

DESCRIPTION (provided by applicant): ?-secretase is a membrane-bound complex of four proteins – presenilin, nicastrin, Aph-1, and Pen-2 – that cleaves a wide variety of substrates. ?-secretase is a key signal molecule that controls several essential biochemical and cellular

pathways. When defective, it is genetically and causatively linked to Alzheimer’s disease and other human disorders. Cleavage of the amyloid precursor protein by ?-secretase produces the neurotoxic ?-amyloid peptides that comprise the hallmark plaques found in the brains of Alzheimer’s patients. Cleavage of Notch by ?-secretase regulates cell fate, including differentiation, proliferation, and survival, and has thus been implicated in multiple human diseases. Cleavage of ErbB4 regulates the myelination of neurons and ErbB4-mediated signaling pathway is linked to schizophrenia. This proposal asks whether loss of ?-secretase activity in oligodendrocytes contributes to behavioral changes consistent with neural dysfunctions. Only approximately 10 percent of the brain is neurons by mass. Glial cells comprise the remaining 90 percent, of which oligodendrocytes comprise the majority. During development and upon injury, oligodendrocytes surround the axons of neurons to form compact myelin, a fatty membrane that protects and nourishes neurons and facilitates the rapid conductance of nerve potentials from neuron to neuron. Neurobiology has traditionally focused on studying neurons, and on why neurons become defunct and die in neuropsychiatric and neurodegenerative disorders. This project, however, analyzes how ?-secretase contributes to myelination and whether defects in myelination alone contribute to the neural dysfunctions seen in various brain diseases. Specific Aim 1 asks whether mice that lack nicastrin in oligodendrocytes exhibit behaviors consistent with neural dysfunctions. This aim also asks whether loss of presenilin from oligodendrocytes exhibits similar behaviors. Several psychoactive drugs will be tested for their ability to reverse these behavioral changes. Specific Aim 2 asks whether the loss of nicastrin from oligodendrocytes results in changes in the ability of these cells to myelinate their target axons. Changes in myelination will be examined both in vivo (in the brains of animal model) and in vitro (in an oligodendrocyte-neuron co-culture system). Specific Aim 3 asks what cellular signaling pathways are affected by loss of nicastrin in oligodendrocytes. Here, the most important and relevant ?-secretase substrates, Notch, ErbB4, and APP, will be analyzed in the mouse model and the co- culture system. Together, the experiments described herein will elucidate ?-secretase’s role in regulating myelination and answer how oligodendrocyte ?-secretase contributes to the integrity of neural networks crucial for behaviors. As such this work represents a new way of thinking about brain functions and disorders.

Lay Summary

PUBLIC HEALTH RELEVANCE: Myelin is a fatty membrane that surrounds neurons; myelin protects and nourishes neurons and facilitates the rapid conduction of nerve impulses. This project asks how the ?-secretase complex, an enzyme genetically and causatively linked to Alzheimer’s disease, contributes to the myelination of neurons and its implications in neural function and dysfunction. The basic research described herein will provide crucial insights into such brain disorders as demyelinating disease, schizophrenia, attention-deficit hyperactivity disorder, obsessive- compulsive disorder, glioma, and dementia.

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