Endogenous GABAergic Activity in the Mammalian Brain

https://neurodegenerationresearch.eu/survey/endogenous-gabaergic-activity-in-the-mammalian-brain/

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Country

USA

Title of project or programme

Endogenous GABAergic Activity in the Mammalian Brain

Source of funding information

NIH (NIA)

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01/05/1992

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2

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Parvalbumins, Interneurons, Amyloid beta-Protein Precursor, SCN1A protein, beta-site APP cleaving enzyme 1

Research Abstract

DESCRIPTION (provided by applicant): As the world’s population gradually ages, Alzheimer’s disease (AD) is becoming a public health emergency. Preventing the progression of this

devastating disease requires the understanding of key alterations in the brain that take place during its beginnings. AD patients and mouse models of the disease exhibit anomalous neuronal network activity characterized by disturbances in neuronal synchrony. An early hallmark of the disorder in mouse models of AD is a characteristic state of neuronal unrest that may promote disease progression. Using a revolutionary new mouse model of AD, the present proposal will maintain the theme of this grant for the past 20 years by focusing on the altered GABAergic inhibition and the resulting aberrant brain network function during the inception of AD. Our previous studies in hAPPJ20 AD mice have identified parvalbumin interneurons (PV INs), one of the most critical players controlling cortical network activity, as having diminished excitability due to reduced voltage-gated Na+ channel (Nav1.1) expression during the initiation phase of AD. The APP-NL/F-KI mice, newly generated by a knock-in gene targeting approach, most closely replicate the pathologies found in human AD compared to all other existing mouse AD models. One of the most critical factors in AD pathology is the ?ite amyloid precursor protein (APP)-cleaving enzyme (?secretase; BACE1). BACE1 has many known cleavage targets of which three specific proteins converge in the GABAergic PV INs, and may eventually interact to cause the initial neuronal dysfunction in AD. These are: APP, neuregulin 1 (NRG1), and the auxiliary subunit of Nav1.1 channels, Nav?that promotes their trafficking to the membrane. We will examine the hypothesis that during the onset of AD, a cascade of events consisting of increased BACE1 activity, elevated amyloid ?A?production altered NRG1 signaling through ErbB4 receptors, and a decreased surface expression of Nav1.1 channels converge in PV INs thus leading to enhanced network excitability that acts as a positive feedback to advance disease progression. In APP-NL/F-KI mice, we will use a variety of state-of-the art approaches including continuous high-bandwidth in vivo intracortical EEG monitoring, super-resolution fluorescent imaging with STORM microscopy, in vitro recordings for detecting cellular and synaptic alterations, and optogenetics. Through carefully planned animal husbandry we will create Cre recombinase expressing PV INs in APP-NL/F-KI mice. Breeding these latter mice with other strains carrying floxed constructs will allow us to perform proof of principle experiments aimed at restoring PV IN excitability during the early stages of the disease through channelrhodopsin-2 (ChR2) stimulation or reduced tonic GABAergic inhibition. Our studies will uncover the fundamental mechanisms underlying the disturbances in neuronal network function during the onset of AD, and will highlight potential approaches for intervention to prevent the progressive deterioration of brain function during the later stages of this devastating disorder.

Lay Summary

PUBLIC HEALTH RELEVANCE: Alzheimer’s disease (AD) is a progressive neurodegenerative disorder resulting in severe dementia responsible for >70% of dementia cases in individuals aged >70 years. With the gradual aging of the US population, in another decade and a half, 7.7 million people will be affected by AD. Transgenic mouse models of AD have provided many insights into the mechanisms of the disease, but none of the models fully replicate the pathologies found in humans with AD. The shortcomings of previous models have now been circumvented in a new mouse model where a mutated human amyloid precursor protein (APP) replaces that of the mouse, and thus replicates most, if not all, pathologies of human AD. In this model we will investigate the dysfunction of neuronal synchrony, also found in AD patients, that occurs early on in the disease. Understanding the causes of this early pathology could uncover potential new therapies to prevent the progression of AD.

Further information available at:

Types:

Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

Database Categories:
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