Novel Drug Discovery for AD Targeting Ryanodine Calcium Channels

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Principal Investigators

STUTZMANN, GRACE E.

Institution

ROSALIND FRANKLIN UNIV OF MEDICINE & SCI

Contact information of lead PI
Country

USA

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Novel Drug Discovery for AD Targeting Ryanodine Calcium Channels

Source of funding information

NIH (NIA)

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15/08/2016

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1

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)... Biotechnology... Brain Disorders... Dementia... Neurodegenerative... Neurosciences... Translational Research

Research Abstract

? DESCRIPTION (provided by applicant): Currently, there are no effective strategies or

treatments to preserve cognitive function in AD patients. The recent series of disappointing clinical trials highlight the need to explore alternative pathways. Novel compounds that can preserve cognitive function and prevent disease progression in a manner distinct from previous approaches could provide new therapeutic opportunities. To this end, we are developing and testing small molecule compounds designed as allosteric modulators of the ryanodine receptor (RyR), a large conductance calcium channel found on the ER membrane, as candidates for clinical testing in early AD or MCI patients. In both human AD patients and AD mouse models, increased RyR2 expression precedes the amyloid deposition, tau histopathology, neuronal loss, and cognitive impairments. In AD mouse models, increased RyR-evoked calcium release is greatest in dendritic spines and synaptic compartments, and contributes to synaptic pathology and dysfunction, increased amyloid and tau pathology, disrupted memory function, and other AD-defining features. We and others have recently demonstrated that treating AD mice with dantrolene, a RyR channel stabilizer, resulted in exciting therapeutic effects. Although our treatment regimens differed, the consistent results demonstrate normalized calcium signaling (Chakroborty et al., 2012a; Oule et al., 2012; Stutzmann et al., 2006), normal synaptic transmission and plasticity expression (Chakroborty et al., 2012a), restored synaptic structure and integrity (Briggs et al., 2014), reduced A? levels (Chakroborty et al., 2012a; Oule et al., 2012; Peng et al., 2012), restored RyR isoform levels (Chakroborty et al., 2012a; Oule et al., 2012), and improved performance on memory tests (Oule et al., 2012; Peng et al., 2012; Stutzmann lab, unpublished data). These data support a strong case for stabilizing RyR function, with a focus on RyR2, as a novel therapeutic strategy for AD. The objective of this study is to design, test, and optimize compounds that will function as RyR channel negative allosteric modulators, serving to suppress excessive calcium release while maintaining physiological functions. The central hypothesis is that development and optimization of small molecule RyR stabilizers will generate therapeutic leads for clinical testing in early AD and MCI patients, and through the preservation of calcium homeostasis and synaptic function, will protect cognitive abilities. This will be accomplished with the following Aims: 1. Compound development and medicinal chemistry optimization. This will use iterative medicinal chemistry procedures and bioactivity assays in mice. 2. Rapid screening assay in cell culture systems and neurons from AD mice. Initial screening will use automated fluorometric testing of RyR-evoked calcium signals in cultured N2A cells in 96-well plates, followed by screening in primary neurons from control and AD mice. 3. In vivo verification in mouse models. Sub chronic treatment in AD and control mice, followed by physiological and biochemical assays, will then be used to identify and finalize the optimal compounds. The significance to public health is the availability of an effective and novel treatment for AD.

Lay Summary

PUBLIC HEALTH RELEVANCE: The objective of this study is to design, test, and optimize a series of small molecule compounds for the purpose of stabilizing dysregulated calcium signaling in early AD and MCI patients and people at risk for converting to AD-like dementia. The rationale is based on findings that disruptions in ryanodine-receptor mediated calcium signaling are a central component of AD pathogenesis, and, treatment with compounds that modulate the ryanodine receptor provide broad-spectrum therapeutic effects in AD mouse models. Developing these compounds may lead to a novel and effective treatment option that will preserve cognitive function.

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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