Validating novel ryanodine receptor-targeted compounds for AD therapeutics

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Principal Investigators

STUTZMANN, GRACE E.

Institution

ROSALIND FRANKLIN UNIV OF MEDICINE & SCI

Contact information of lead PI
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USA

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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 failed clinical trias

designed to target A? processing or inflammatory pathways highlight the need to explore alternative pathways. Novel compounds that can effectively preserve cognitive function and prevent disease progression in a manner distinct from previous approaches could provide new therapeutic opportunities. To this end, we developed >100 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, neuronal loss, and cognitive impairments. In AD mouse models, increased RyR-evoked calcium release is greatest in dendritic spines and synaptic compartments, and contributes synaptic pathology, 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; Oules et al., 2012; Stutzmann et al., 2006), normal synaptic transmission and plasticity expression (Chakroborty et al., 2012a), restored synaptic integrity (Stutzmann lab), reduced A levels (Chakroborty et al., 2012a; Oules et al., 2012; Peng et al., 2012), restored RyR isoform levels (Chakroborty et al., 2012a; Oules et al., 2012), and improved performance on memory tests (Oule et al., 2012; Peng et al., 2012). These data support a strong case for stabilizing RyR function, with a focus on RyR2, as a therapeutic strategy. The objective of this study is to test and optimize compounds that will function as RyR channel regulators, serving to suppress excessive calcium release while maintaining physiological functions. The central hypothesis is that stabilizing RyR-mediated calcium release with novel small molecule compounds will normalize calcium signaling, preserve synaptic function, and reduce histopathology, thus serving as an effective therapeutic strategy to prevent cognitive decline in AD. This will be accomplished with the following Aims: 1. Identify optimal RyR2 stabilizing compounds in model cells and iPSC from human AD patients using calcium imaging, electrophysiological and immunoassay techniques. 2. Demonstrate broad efficacy of successful novel compounds on calcium signaling, synaptic plasticity and histopathology in chronically treated 3xTg-AD mouse models. The significance to public health is the development of an effective and novel treatment for AD.

Further information available at:

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