mGlu Allosteric Modulation in Neurodegenerative Diseases

https://neurodegenerationresearch.eu/survey/mglu-allosteric-modulation-in-neurodegenerative-diseases/

Principal Investigators

ROOK, JERRI MICHELLE

Institution

VANDERBILT UNIVERSITY

Contact information of lead PI
Country

USA

Title of project or programme

mGlu Allosteric Modulation in Neurodegenerative Diseases

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,800,458.72

Start date of award

15/05/2016

Total duration of award in years

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)... Basic Behavioral and Social Science... Behavioral and Social Science... Brain Disorders... Dementia... Neurodegenerative... Neurosciences

Research Abstract

? DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) is the most frequently observed cause of dementia and cognitive decline associated with neurodegeneration. Current therapies provide modest improvement in cognitive function in some patients, while providing no efficacy in others. Glutamate is the primary excitatory neurotransmitter of the central nervous system and glutamatergic transmission is severely disrupted in AD and other neurodegenerative disorders. Among the principle cognitive deficits associated with AD are deficiencies in hippocampal-mediated learning and memory. Glutamatergic neurotransmission is critical in hippocampal synaptic plasticity and hippocampal-dependent cognitive function and accumulating evidence suggests that enhancement of glutamatergic neurotransmission could help to reverse cognitive deficits associated with AD. In recent years, a specific subtype of metabotropic glutamate (mGlu) receptor, termed mGlu5, has emerged as an exciting target for new therapeutic agents that could be used to reduce impaired cognitive function in patients suffering from AD and other neurodegenerative disorders. The mGlu5 receptor is the most highly expressed mGlu receptor subtype in the hippocampus and cortical regions that are impacted in AD patients, and plays a major role in the regulation of forms of synaptic plasticity that are believed to underlie learning and memory and other aspects of cognitive function. Furthermore, activation of mGlu5 can induce non-pathologic processing of amyloid precursor protein (APP) to reduce brain levels of A?. Interestingly, evidence suggests that mGlu5 signaling is impaired in tissue from AD patients. These studies raise the exciting possibility that highly selective activators of mGlu5 could provide a novel approach to reverse the cognitive impairments and reduce some of the pathophysiological changes that are associated with AD. While initial attempts to develop selective orthosteric agonists of individual mGlu receptor subtypes were unsuccessful, we and others have been highly successful in discovery of selective positive allosteric modulators (PAMs) for mGlu5. These PAMs do not activate the mGlu receptors directly but potentiate glutamate-induced activation, thus preserving spatio-temporal signaling of the endogenous ligand. We now propose a series of studies aimed at fully characterizing the in vivo efficacy of mGlu5 PAMs to restore deficits in synaptic and cognitive function in the CK-p25 mouse model of AD. CK- p25 mice provide a preclinical model of AD that displays a number of pathological features that bear a striking similarity to those observed in AD patients, including neurodegeneration, increased tau phosphorylation and neurofibrillary tangles, elevated amyloid-beta protein (A?) and the amyloid precursor protein (APP) processing enzyme, ?-secretase (BACE1), as well as pronounced deficits in synaptic and cognitive function. This provides an excellent model that is well suited for testing the hypothesis that mGlu5 PAM will have efficacy in improving synaptic plasticity, cognitive function, and other pathological changes that are characteristic of human AD and neurodegenerative disorders.

Lay Summary

PUBLIC HEALTH RELEVANCE: In recent years, a specific subtype of metabotropic glutamate (mGlu) receptor, termed mGlu5, has emerged as an exciting new target for therapeutic agents that could be used to reduce impaired cognitive function in patients suffering from AD and other neurodegenerative disorders. Newly developed, highly selective positive allosteric modulators (PAMs) for mGlu5, provide the unprecedented opportunity to test the ability of selective activation of mGlu5 to enhance synaptic and cognitive function in preclinical models of AD and neurodegenerative disorders. We propose a series of studies aimed at fully evaluating the in vivo efficacy of mGlu5 PAMs to restore deficits in synaptic and cognitive function in a preclinical model of AD that best emulates the human condition.

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