The Role of KCa3.1 in Neuroinflammation in Alzheimer Disease

https://neurodegenerationresearch.eu/survey/the-role-of-kca3-1-in-neuroinflammation-in-alzheimer-disease/

Principal Investigators

MAEZAWA, IZUMI

Institution

UNIVERSITY OF CALIFORNIA AT DAVIS

Contact information of lead PI
Country

USA

Title of project or programme

The Role of KCa3.1 in Neuroinflammation in Alzheimer Disease

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,423,827.52

Start date of award

30/09/2013

Total duration of award in years

4

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

Research Abstract

DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) is the most common cause of

dementia in the elderly. To meet the public health challenge posed by AD, a goal set by the National Alzheimer's Project Act is to prevent or treat AD by 2025. Therefore currently there is an urgent need for new therapeutic target discovery and corresponding compound development. A protein deposited in AD brains called amyloid-beta (Abeta) has been hypothesized to play a critical role in AD pathogenesis. Abeta can activate microglia to clear Abeta but at the same time also stimulate microglia to release cytotoxic substances that cause neuronal damage. Using the small molecule TRAM-34, which was synthesized by our group, as a pharmacological tool we recently demonstrated that the calcium-activated potassium channel KCa3.1 plays an important role in microglia activation and microglial neurotoxicity. In vivo evidence indicates that blockade of KCa3.1 by TRAM-34 can inhibit microglia-mediated neuronal killing without affecting their migration and phagocytotic activities. Relevant to AD, our results suggest that TRAM-34 blocks the neurotoxicity induced by Abeta-activated microglia, but does not inhibit their beneficial function of phagocytosing Abeta. KCa3.1 blockade, therefore, is a potential new approach for the treatment of AD. With the help of this grant we wish to perform proof-of-principle studies to validate KCa3.1 as a novel therapeutic target for reducing microglia-mediated neurotoxicity and microglial dysfunction in Alzheimer's disease (AD), through the following three Specific Aims: Aim-1: Determine the effect of KCa3.1 blockade on Ab-induced microglial activation. We will treat cultured microglia with Abeta aggregates (oligomer and fibril) and evaluate the effect of KCa3.1 blockade by TRAM-34 treatment (Aim-1a) or genetic knockout (Aim-1b) on chemotactic and phagocytotic activities, signaling pathways, and the production of chemokines, cytokines, reactive oxygen species, and nitric oxide. Aim-2: Assess the contribution of KCa3.1 to AD-like pathology and cognitive deficits seen in the APPswe/PS1dE9 (APP-PS1) model using the genetic knockout approach. We will cross-breed APP-PS1 mice with KCa3.1-/- mice and evaluate whether KCa3.1 reduction affects neuropathological and behavioral abnormalities in APP-PS1 mice. We will further determine if KCa3.1 reduction can alleviate microglial dysfunction seen in APP-PS1 mice. Aim-3: Validate KCa3.1 as a therapeutic target for AD by performing preclinical studies with TRAM-34. We will determine if a 2-month course of TRAM-34, a selective inhibitor of KCa3.1, administered to APP-PS1 mice will reduce neuroinflammation, alleviate microglial dysfunction, and improve the neuropathological and behavioral outcomes of APP-PS1 mice. Because KCa3.1 blockade is relatively safe, our preclinical studies will have translational significance for future developmen of drugs for treating individuals with mild cognitive impairment or AD through inhibition of detrimental microglia functions.

Lay Summary
PUBLIC HEALTH RELEVANCE: Microglia, a type of white blood cells found in the brain, play an important role in the pathogenesis of Alzheimer's disease. The aims of our proposal are to establish that the calcium-activated potassium channel KCa3.1 is a therapeutic target for reducing microglia mediated brain damage in Alzheimer's disease.

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