

Mechanisms of regulation of amyloid-beta metabolism by CALHM1

<https://www.neurodegenerationresearch.eu/survey/mechanisms-of-regulation-of-amyloid-beta-metabolism-by-calhm1/>

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USA

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NIH (NIA)

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Alzheimer's disease & other dementias

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Research Abstract

DESCRIPTION (provided by applicant): Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by A β peptide deposition into cerebral senile plaques. CALHM1 is a recently identified neuronal calcium channel controlling AD age-at-onset and A β levels both in vitro in cell culture systems and in vivo in human cerebrospinal fluid (Dreses-Werringloer et al, Cell 2008; Koppel et al., Mol Med 2011). These results strongly support the notion that CALHM1, via an unknown mechanism, controls A β metabolism and AD pathogenesis. In order to gain insight into the mechanism by which CALHM1 controls A β metabolism, we recently generated a CALHM1 knockout (KO) mouse model. In these KO mice, we found that CALHM1 was required for the expression of insulin-degrading enzyme (IDE), a protease controlling A β clearance in vivo. Preliminary results also showed that CALHM1 KO mice have elevated levels of brain A β and develop significant deficits in memory formation. The long-term goal of this application is to test the working model that CALHM1 influences A β levels by controlling cerebral IDE expression, a mechanism that, when impaired, leads to A β -dependent cognitive deficits in mice. In CALHM1 KO mice, we will first determine whether CALHM1 deficiency affects neuronal integrity and leads to amyloid deposition in the mouse brain. We will also determine the extent to which CALHM1 deficiency leads to A β -dependent cognitive deficits in mice. Finally using cell and molecular biology methods, we will elucidate the molecular mechanism by which CALHM1 controls IDE expression.

Lay Summary

Alzheimer's disease is an incurable disorder of the brain characterized by the presence in the brain of protein aggregates called amyloid plaques. Recently, our group identified CALHM1 as a gene potentially involved in the pathological processes of the disease. The goal of this proposal is to elucidate the exact role played by CALHM1 in amyloid plaque formation and in the progression of Alzheimer's disease.

Further information available at:

Types:

Investments > €500k

Member States:

United States of America

Diseases:

Alzheimer's disease & other dementias

Years:

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