Endocannabinoids in Neurodegenerative Diseases

https://neurodegenerationresearch.eu/survey/endocannabinoids-in-neurodegenerative-diseases/

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Country

USA

Title of project or programme

Endocannabinoids in Neurodegenerative Diseases

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,486,451.38

Start date of award

15/06/2012

Total duration of award in years

3

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

2-arachidonylglycerol, Endocannabinoids, beta-site APP cleaving enzyme 1, CNR1 gene, Neurodegenerative Disorders

Research Abstract

DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) is the most common cause of dementia among older people. AD is characterized by accumulation and deposition of amyloid

plaques and neurofibrillary tangles, neuroinflammation, synaptic dysfunction, progressive deterioration of cognitive function and loss of memory in association with widespread degenerated neurons and neuronal death. Currently, there are no effective medications to prevent and treat AD and halt the disease progression. This is largely due to our limited understanding of the mechanisms involved in the development and neuropathology of AD. Endocannabinoids are naturally occurring fatty acids displaying anti-inflammatory and neuroprotective properties. Recently we demonstrated that exogenous and endogenous 2-arachidonoylglycerol (2-AG) protects hippocampal neurons in culture against beta-amyloid-induced neurodegeneration and neuroinflammation. In particular, our ongoing research revealed that strengthening 2-AG signaling by inhibition of monoacylglycerol lipase (MAGL), the enzyme metabolizing 2-AG, robustly reduced protein expression of beta-site APP cleaving enzyme 1 (BACE1), the key enzyme for A-beta synthesis, and decreased deposition of A-beta plaques, neuroinflammation and neurodegeneration, and improved synaptic and cognitive function in an animal model of AD. This means that 2-AG likely plays an important role in counteracting pathogenesis and neuropathology of AD. Previous studies demonstrated that expression of BACE1 at protein levels, but not at mRNA levels, is elevated, both in AD human and animals, suggesting that expression of BACE1 is regulated by an epigenetic mechanism at post-transcriptional levels. Our preliminary studies revealed that expression of the noncoding microRNAs targeting BACE1, was significantly down-regulated both in the brains of AD humans and animals, but the expression was returned to the normal control levels when brain 2-AG levels were elevated in APP transgenic AD animals. Thus, we hypothesize that the actions of brain 2-AG signaling in preventing and reducing pathogenesis and neuropathology of AD are through CB1 receptor-dependent regulation of the expression of the specific miRNAs that repress BACE1, resulting in decreases in A-beta production and accumulation, neuroinflammation and degeneration and improvements in synaptic and cognitive function in AD animals. The proposed project will not only provide molecular mechanisms of strengthening 2-AG signaling in preventing or decreasing pathogenesis and neuropathology of AD, but also will open a new area for the development and discovery of novel drugs aimed at preventing and treating AD, or slowing AD progression.

Lay Summary

The proposed application will tackle a novel and intriguing topic that 2-AG signaling is crucial in maintaining homeostasis of normal brain function and its beneficial effects are likely through CB1 receptor-dependent regulation of miRNAs that target the enzyme synthesizing beta-amyloid. The results generated from this application will not only provide molecular mechanisms of strengthening 2-AG signaling in preventing or decreasing pathogenesis and neuropathology of AD, but also will open a new area for the development and discovery of novel drugs aimed at preventing and treating AD, or slowing AD progression.

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