SYNAPTIC REGULATION OF ERK-MEDIATED AMYLOID-BETA METABOLISM

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Country

USA

Title of project or programme

SYNAPTIC REGULATION OF ERK-MEDIATED AMYLOID-BETA METABOLISM

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NIH (NIA)

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5

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... Neurodegenerative... Neurosciences

Research Abstract

DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) is initiated by the progressive

accumulation of amyloid-ß (Aß) peptide in the brain as toxic structures such as amyloid plaques and soluble oligomers. Conversion of Aß into these toxic species appears to be concentration-dependent; therefore identifying mechanisms that regulate or lower Aß levels will provide a fundamental understanding of the underlying causes of AD and may lead to new therapeutic strategies. Recent work by our group demonstrates that activation of serotonin receptors (5HT-Rs) cause an acute reduction in brain Aß levels in mouse models of AD (Cirrito et al., 2011). Systemic administration of SSRI antidepressants or direct infusion of serotonin into the hippocampus of a mouse model of AD causes brain interstitial fluid (ISF) Aß levels to decline by 25-30% within a few hours and with Aß levels remaining low for over 24 hours after a single administration. This reduction in Aß is completely blocked if mice are pretreated with inhibitors of the extracellular regulated kinase (ERK), the prototypical MAP kinase. ERK activation appears to increase ?-secretase cleavage of APP, thus reducing Aß generation as well as may reduce mRNA levels of several components of the ?-secretase complex. Chronic administration of a SSRI for 4 months dramatically reduces plaque load and CSF Aß levels in a mouse model of AD. The objective of this proposal is to define the ERK signaling pathways and related molecules that regulate Aß generation, in particular the pathways that lead from serotonin receptor to activation of ERK and then ERK to changes in APP processing. While many molecules can activate ERK and ERK can have many downstream substrates, its activity is remarkably regulated so that each extracellular receptor can very specific effects within a cell This specificity is partially controlled via scaffold proteins that link receptors with appropriate signaling complexes. Not all molecules that activate ERK suppress Aß generation; therefore we will determine the role that scaffold and localization proteins, such as ß-arrestin and Self, play n providing target specificity for this signaling pathway. Using a combination of genetics, biochemistry, and pharmacology, as well as an in vivo microdialysis technique we developed to assess brain ISF Aß levels over time; we will assess the cellular pathways linking 5HT-Rs, ERK, and Aß generation in living mice. SSRIs are one of the safest neuroactive drugs approved by the FDA. A demonstration not only of their effectiveness in lowering Aß levels, but also the cellular mechanisms by which they act, may provide a strong impetus for testing this class of compounds for their ability to attenuate, and possibly prevent, AD in human subjects.

Lay Summary
Reducing levels of amyloid-ß, the peptide that accumulates and initiates Alzheimer’s disease (AD), is the most likely method to treat or prevent this disease. Our preliminary data from humans and mouse models of AD strongly suggest the serotonin signaling suppresses Aß generation by activating the extracellular regulated kinase (ERK) signaling pathway. Chronic treatment with selective serotonin reuptake inhibitor (SSRI) antidepressants reduces brain Aß levels and plaques in mouse models of AD and is associated with less plaques humans. This proposal will determine the cellular pathways and molecules that link serotonin receptors, ERK, and Aß suppression in living mice.

Further information available at:

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Investments > €500k

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United States of America

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