Plasticity circuits in Alzheimers disease

https://neurodegenerationresearch.eu/survey/plasticity-circuits-in-alzheimers-disease-2/

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Country

USA

Title of project or programme

Plasticity circuits in Alzheimers disease

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 2,481,600.00

Start date of award

15/03/2009

Total duration of award in years

7

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... Stem Cell Research... Stem Cell Research - Induced Pluripotent Stem Cell... Stem Cell Research - Induced Pluripotent Stem Cell - Human... Stem Cell Research - Nonembryonic - Non-Human

Research Abstract

? DESCRIPTION (provided by applicant): Hippocampal neurogenesis is implicated in regulation

of plasticity, learning and memory and experience in novel environments. However, the role of neurogenesis in learning and memory deficits and in Alzheimer’s disease (AD), a neurodegenerative disease characterized by loss of memory and cognitive decline, is not fully elucidated. We have shown that hippocampal neurogenesis is impaired early in life in animal models of Familial Alzheimer’s disease (FAD). Deficits in neurogenesis precede onset of hallmarks and onset of learning and memory impairments, suggesting that defective neurogenesis may play a role in the development of cognitive decline. In addition, we have shown that experience of mice in environmental enrichment rescues impaired neurogenesis and attenuate neuropathology. However, it is not clear whether impairments in neurogenesis in AD are causative and whether up regulation of neurogenesis would rescue cognitive deficits. To address that, we generated mouse models, in which neurogenesis is regulatable. Specifically, ablation of neurogenesis in APPswe/PS1?E9 was achieved by ganciclovir-induced depletion of neural progenitor cells expressing a modified version of the herpes simplex virus thymidine kinase (APPswePS1?E9/nestin-?-HSV-TK mice). Enhancement of neurogenesis in APPswe/PS1?E9 mice was achieved by tamoxifen-induced ablation of Bax in neural progenitor cells (APPswePS1?E9/nestin-CreERT2/Baxlox/lox mice). In a preliminary study we show that ganciclovir-treated APPswePS1?E9/nestin-?-HSV-TK mice exhibit significantly reduced extent of neurogenesis accompanied by deficits in contextual encoding, pattern separation and novel object recognition, as early as three months of age. Intriguingly, we observed more amyloid deposition in the hippocampus of these mice compared to vehicle-treated APPswePS1?E9/nestin-?-HSV-TK or APPswePS1?E9 mice. Taken together, these observations suggest the hypothesis that impaired hippocampal neurogenesis plays a key role in the development of cognitive deficits and neuropathology in AD, and that enhancement of neurogenesis would restore these deficits. Experiments will determine the effect of loss or gain of neurogenesis in FAD mice on extent of proliferation, survival and cell fate determination of hippocampal neural progenitor cells and new neurons (Specific Aim 1), progression of neuropathology (Specific Aim 2) and learning and memory (Specific Aim 3). In Specific Aim 4 we will examine the association between extent of neurogenesis, level of cognitive function and neuropathology in human brain tissue of Mild Cognitive Impairment (MCI) and AD patients. These experiments will determine the role of neurogenesis in AD and lead to the development of neurogenesis-based treatment of cognitive deficits in the disease.

Lay Summary

PUBLIC HEALTH RELEVANCE: This project will establish the role of adult hippocampal neurogenesis in cognitive decline and neuropathology in Alzheimer’s disease in mouse models of modulated neurogenesis in Alzheimer’s disease as well as in human brain tissue of Alzheimer’s patients.

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

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