Optogenetic dissection of hippocampal circuitry underlying Alzheimers disease

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Country

USA

Title of project or programme

Optogenetic dissection of hippocampal circuitry underlying Alzheimers disease

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,839,103.67

Start date of award

01/09/2014

Total duration of award in years

2

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

optogenetics, Dissection, memory retrieval, Hippocampus , Alzheimer's Disease

Research Abstract

DESCRIPTION (provided by applicant): It is of utmost importance to identify the circuits underlying learning and memory in order to understand not only the mechanisms of memory but

also the how these mechanisms become dysregulated in memory disorders, such as Alzheimer’s disease (AD). Human and rodent lesion studies have suggested a role for the hippocampus (HPC) in long-term memory, specifically the subregion CA1. CA1 is preferentially activated when a memory must be retained over a long period of time, and studies have shown that a large proportion of CA1 neurons are reactivated in repeated exposures to the same environment. However, no previous studies have been able to assess the long-term (> 1 month) involvement of individual CA1 neurons in learning and memory, or in AD, since all previous transgenic lines have lacked an indelible label. In this application, the contribution of individua CA1 neurons to the encoding of an experience and to the retrieval of a corresponding memory will be investigated by utilizing a transgenic line, the ArcCreERT2 mice. This mouse line allows for the indelible labeling of cells expressing the immediate early gene Arc/Arg3.1 and allows for a comparison between the cells that are activated during the encoding of an experience and those that are activated during the retrieval of the corresponding memory. In combination with optogenetic reporter lines, these studies will assess the long- term involvement of CA1 neurons in memory encoding and retrieval. To fully characterize the role of CA1 neurons in memory, we will selectively express the blue light activated cation channel channelrhodopsin-2 (ChR2) or the yellow light activated outward proton pump archaerhodopsin (Arch) in populations of CA1 neurons during encoding. Using optogenetics, we will then test the hypothesis that a subpopulation of CA1 neurons is sufficient and necessary for the retrieval of a corresponding long-term memory. Next, the role of CA1 in memory encoding and retrieval will be delineated in AD mice by utilizing a triple transgenic design in which CA1 neurons, initially labeled during encoding, can be optogenetically modulated in control and AD mice. In vivo, we will test the hypothesis that optogenetic stimulation or inhibition of CA1 pyramidal neurons during memory retrieval will improve expression of a memory in AD mice. Finally, optogenetic manipulations will be used in order to mimic a deep brain stimulation-like protocol in control and AD mice in order to improve overall cellular function, cell survival, and memory retrieval in AD mice.

Lay Summary

PUBLIC HEALTH RELEVANCE: This application is the first to examine how hippocampal neural ensembles contribute to learning and memory, and how these neural ensembles are altered in Alzheimer’s disease (AD). Optogenetic modulation of these ensembles will be utilized to improve memory retrieval in control and AD mice. Identifying the circuits underlying the memory dysfunction in AD will provide new avenues for developing novel therapies and treatments that would be beneficial for the treatment of AD.

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