Synaptic substrates of age-dependent memory deficits

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Principal Investigators

DISTERHOFT, JOHN F

Institution

NORTHWESTERN UNIVERSITY AT CHICAGO

Contact information of lead PI
Country

USA

Title of project or programme

Synaptic substrates of age-dependent memory deficits

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NIH (NIA)

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15

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)... Basic Behavioral and Social Science... Behavioral and Social Science... Biotechnology... Brain Disorders... Dementia... Neurodegenerative... Neurosciences

Research Abstract

? DESCRIPTION (provided by applicant): Though aging itself is the biggest risk factor for Alzheimer's disease (AD), many aged persons with memory problems do not ultimately suffer from AD. In such persons, pathology that would merit AD diagnosis is absent, despite the overlapping cognitive symptomatology. The principal goal of this research program is to model such ""normal"" age-related cognitive heterogeneity in rats and then use high-resolution techniques to reveal the synaptic and dendritic substrates of age-associated decline in forms of memory that require the hippocampus. As the primary output of the hippocampus, region CA1 has been a primary target of such investigation by us and others. Indeed, past studies have revealed that while major age-related synapse and neuron loss are absent in CA1, more subtle aging-linked changes collude to modify neuronal activity patterns and behavioral plasticity. Importantly, such alterations are present in only a subset of aged rats, with others the same chronological age showing young adult-like acquisition on Morris Water Maze (MWM) learning and trace eyeblink conditioning (TEBC). Such cognitive heterogeneity among aged rats, then, provides an important opportunity to reveal both the substrates of age-related memory decline as well as the substrates of memory preservation. The experiments proposed in this renewal application will continue to reveal the synaptic and dendritic substrates of age-related cognitive heterogeneity, but do so by building on our past findings with conceptual and technical complexity. Specifically, in Aim 1, we will behaviorally characterize young adult and aged F344xBN F1 hybrid rats with MWM learning and TEBC and then probe synaptic Ca2+ signaling with 2-photon laser scanning (2PLSM) Ca2+ imaging and 2-photon glutamate (2Pglutamate) uncaging onto spines in discrete microdomains of individual basal, oblique, and tuft dendrites. Following this high-resolution functional probing, Aims 2 and 3 will use immunogold field emission scanning electron microscopy for backscattered electrons (iFESEM) and immunofluorescence array tomography (iAT) to morphologically reconstruct the imaged dendrites and then proteomically reconstruct the dendrites' signaling networks. Aim 2 will focus on an interactome of ion channels involved in synaptic and dendritic voltage signaling and integration. Aim 3 will probe the imaged dendrites for ion channels involved in an interactome that governs synaptic and dendritic Ca2+ signaling. Using the information provided by these Aims, Aim 4 will rescue age-related memory impairments and signaling abnormalities with viral transfection to up or down-regulate expression of ion channels linked to cognitive impairment or preservation. Such ""rescue"" will be probed with behavioral testing, 2PLSM Ca2+ imaging, 2Pglutamate uncaging, and reconstructive proteomic microscopy with iFESEM and iAT. Together, the experiments in the proposed Aims will identify the key regulators of dendritic signaling and memory function in aged rats with molecular precision, reveal deep insight into both ""successful"" and ""unsuccessful"" cognitive aging, and provide critical information about viable drug targets that could slow or prevent aging-linked cognitive decline.

Lay Summary

PUBLIC HEALTH RELEVANCE: Many parameters of an ion channel determine how it contributes to neuronal integration, including its abundance and its location. The experiments in this proposal will probe the function of thin dendrites of hippocampal CA1 pyramidal neurons from behaviorally characterized young adult and aged rats, and then locate and quantify expression levels of ion channels involved in dendritic Ca2+ and voltage signaling with ultrastructural resolution. Such information will sophisticate our understanding of the effects of age on neuronal computation, as well as help design treatments to maintain cognition in the face of chronological aging.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

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Alzheimer's disease & other dementias

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