Proteomic reconstructive microscopy of healthy and diseased dendrites

https://neurodegenerationresearch.eu/survey/proteomic-reconstructive-microscopy-of-healthy-and-diseased-dendrites/

Principal Investigators

NICHOLSON, DANIEL A

Institution

RUSH UNIVERSITY MEDICAL CENTER

Contact information of lead PI
Country

USA

Title of project or programme

Proteomic reconstructive microscopy of healthy and diseased dendrites

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,203,508.26

Start date of award

30/09/2013

Total duration of award in years

4

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)... Biotechnology... Brain Disorders... Dementia... Neurodegenerative... Neurosciences

Research Abstract

DESCRIPTION (provided by applicant): Over the last several decades, our understanding of the diversity of ion channels and their role in electrical signaling in neurons has increased exponentially. Such advances have helped understand and treat some brain disorders, but the mechanisms underlying many other common brain disorders remain to be discovered. In- deed, to the extent examined, many of these conditions are associated with synaptic or channelopathic abnormalities, including ones that emerge in adolescence, with aging, or as a result of experience (e.g., drug expo- sure, post-traumatic stress disorder). Deepening our understanding of the links among ion channels, synapses, dendrites, and brain disease is therefore a fundamental goal of both basic and clinical neuroscience research. One critical bottleneck to such an endeavor is that thin dendrites remain inaccessible to patch-clamp physiology, the technique responsible for much of our understanding with regard to dendritic and neuronal integration. Consequently, our understanding of neuronal and dendritic function is based primarily on a combination of inferences from large-diameter dendritic recordings and computational models. To circumvent such limitations and fill crucial knowledge gaps, this project will determine the expression patterns of several key ligand- and voltage-gated ion channels for entire, complete dendrites from hippocampal CA1 pyramidal neurons using at or near ultrastructural resolution techniques. To accomplish this, the proposed experiments will combine field emission scanning electron microscopy (FESEM) and array tomography (AT) with immunogold or immunoflourescence channel detection, respectively. Such an approach will fill limiting gaps in our knowledge of the single-dendrite proteome in both mice and humans. And, if successful, the proposed approach has the poten- tial to revolutionize our understanding of the role of ion channels in dendritic/neuronal function because trafficking networks and expression levels are likely to differ intradendritically in single neurons throughout the brain. Finally, to validate the potential clinical/translational relevance of such an approach, a channelopathy that emerges with age in two different mouse models of Alzheimer’s disease will be acutely reversed pharmacologically, and then probed with FESEM and AT to determine whether expression is indeed rendered normal again, or whether such a treatment induces a functional, but not a restorative, reversal of the channelopathy.

Lay Summary

PUBLIC HEALTH RELEVANCE: The thin dendrites of most neurons are the major sites of synapses and ion channel expression, but remain inaccessible to patch-clamp recordings. Such inaccessibility severely limits our understanding of the role of synaptic and dendritic ion channels in neuronal integration and the pathogenesis of brain diseases. The experiments in this proposal will overcome this critical limitation using large-scale microscopic reconstructions of dendrites and synapses from healthy neurons and other neurons affected by Alzheimer’s disease-linked molecular processing, probed proteomically for several important ligand- and voltage-gated ion channels with immunogold particles and fluorescence markers.

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