A multi-scale data-driven model of the Abeta pore function and Ca2+ toxicity in Alzheimers disease

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Country

USA

Title of project or programme

A multi-scale data-driven model of the Abeta pore function and Ca2+ toxicity in Alzheimers disease

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,938,949.54

Start date of award

01/09/2016

Total duration of award in years

1

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... Complementary and

Alternative Medicine... Dementia... Neurodegenerative... Neurosciences

Research Abstract
Alzheimer’s disease (AD) is a chronic neurodegenerative disorder that leads to progressive deterioration in a broad range of cognitive functions and finally death. Three amyloid beta (A?) peptides, A?40, A?42, and A?43 have been implicated as a key factors in the pathogenesis of AD. Recent findings indicate that extra- and intracellular accumulations of oligomeric forms of A? rather than large insoluble aggregates are the likely pathological culprits, and that their toxicity is mediated through uncontrolled elevation of cytosolic Ca2+ by formation of toxic Ca2+-permeable pores in the plasma membrane (PM). Yet, detailed information about the function of different A? pore types and which leaflet of the PM is more susceptible to pore formation are lacking. These pores have shown significant diversity and time dependent changes in their functional properties. Moreover, pharmacological comparisons between pores due to the three types of peptides are lacking. The highly heterogeneous and dynamic nature of A? pores poses extreme challenges in investigating their pathogenic mechanisms through traditional single channel approaches. Our goal is to fill a critical void in the understanding of A?-mediated Ca2+ signaling disruptions in AD using multi-scale data-driven modeling in conjunction with advanced imaging techniques having a resolution down to single channel level. Using our optical patch clamp technique, we will monitor and compare the gating properties and time- dependent evolution of hundreds of A? pores formed by extra- and intracellular A? oligomers. We will measure and compare the conductance properties, gating kinetics, and time-dependent evolution of the three A? pore types. We propose to perform parallel experiments on A?40, A?42, and A?43 pores in identical conditions to: (1) elucidate and compare their function in the presence of various modulators including Zinc, Aluminum, and Copper, (2) compare the effects of A? pore blockers such as NA7 and Bexarotene, (3) how natural phenols including Curcumin, Oleuropein, and Resveratrol affect their formation and evolution, and (4) how changes in membrane components including cholesterol and phosphatidylserine affect the function of A? pores. Driven progressively by experimental data, we will develop specific models for different variants (based on peak permeability) of each pore type, followed by combining these models into a unified model encompassing both the fast (milliseconds) gating kinetics and slow (tens of minutes and hours) evolution of each A? pore type. We will incorporate the effect of modulators and PM components into each model and test how the concurrent presence of different modulators affect A? pores’ behavior in different cell membranes? We will use these models to perform long simulations (many hours or days) to better understand how pores evolve and how they contribute to overall Ca2+ toxicity as a function of time, spatial arrangement, motility, and ratio of A?40, A?42, and A?43 when inserted into PM and membranes of different intracellular organelles including ER, mitochondria, and lysosomes.

Lay Summary
Extra- and intracellular accumulation of A?40, A?42, and A?43 oligomers has been proposed as the trigger events leading to memory loss and cell death in the pathology of Alzheimer’s disease with the formation of Ca2+- permeable A? pores in neuronal plasma membrane as one of the mechanisms that poses as a major potential therapeutic target. Detailed information about the function of different A? pore types and which leaflet of biological membrane is more susceptible to pore formation are lacking, and the highly heterogeneous and dynamic nature of A? pores poses extreme challenges in investigating their pathogenic mechanisms that renders traditional single channel approaches inadequate. We propose to combine novel imaging techniques in conjunction with data-driven computational modeling to pin down the molecular mechanisms

behind the Ca2+ toxicity and mechanisms of action of different A?, and elucidate their functional diversity.

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