Roles of reticulon proteins in neurodegenerative disorders

https://neurodegenerationresearch.eu/survey/roles-of-reticulon-proteins-in-neurodegenerative-disorders/

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Country

USA

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Roles of reticulon proteins in neurodegenerative disorders

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NIH (NIA)

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15/01/2005

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12

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

Research Abstract

? DESCRIPTION (provided by applicant): With the lifespan of humans increasing, preserving

the quality of life among elderly people becomes increasingly important. Aging is a risk factor for Alzheimer's disease (AD), which is characterized by two typical pathological features in the brain: extracellular neuritic plaques and intraneuronal neurofibrillary tangles. Neuritic plaques are deposits of aggregated ß-amyloid peptides (Aß), which are often surrounded by dystrophic neurites and reactive glial cells in AD brains. In this application, we aim to investigate the roleof reticulon 3 (RTN3) in regulating the formation of these pathological features. RTN3 is a neuronal protein belonging to the reticulon family, which is highly conserved through evolution. Genetic studies using a S. cerevisiae model suggest that the prototypical function of RTN is to shape tubular endoplasmic reticulum (ER) structure. Mice deficient in RTN3 show the following features: 1) protein levels of BACE1, an enzyme critical for Aß generation, are significantly elevated; and 2) phosphorylation of tau is significantly increased, and the hyper- phosphorylated tau is linked to form helically wound filaments and intraneuronal tangles. On the other hand, overexpression of RTN3 results in RTN3 aggregation, particularly in the hippocampus, which correlates with the formation of RTN3-immunoreactive dystrophic neurites (RIDNs). RIDNs are commonly present surrounding amyloid deposits in AD or aging brains. The presence of RIDNs, which we have demonstrated is not readily reversible, impairs learning and memory as shown by various assays, including electrophysiological recordings, behavioral tests and morphological confirmations. In searching for RTN3-interacting proteins, we discovered that the ER tubular protein REEP2 specifically interacted with RTN3 and co-existed with RTN3 in RIDNs, suggesting a potential dysfunction of tubular ER in aging and AD brains. Thus, a shift from RTN3 monomeric protein to RTN3 aggregation results in negative effects associated with both under- and overexpression of RTN3. In light of this knowledge, we propose to further extend our study by testing our novel hypothesis in this renewal application that aging induces tubular ER dysfunction via shifting the balance between RTN3 monomer and aggregated forms, leading to changes in BACE1 expression, tau hyper- phosphorylation, and the accumulation of RIDNs. Biochemical and mouse genetic approaches will be employed to test the following three Specific Aims. Our first two aims focus on the novel results seen in RTN3-null mice. Aim 1 is designed to investigate the effects of RTN3 deficiency on BACE1 expression. Aim 2 is designed to determine how RTN3 deficiency increases tau phosphorylation. Since we postulate that aging induces RTN3 expression and tubular ER dysfunction, Aim 3 is designed to explore how the potential contribution of the dysfunctional tubular ER structure leads to the formation of RTN3 aggregation and RIDNs. The knowledge gained from this application will be useful for the development of therapeutic agents that will inhibit dystrophic neurite formation and cognitive decline and/or prevent tubular ER dysfunction in AD.

Lay Summary

PUBLIC HEALTH RELEVANCE: In today's world, improved living and health conditions have significantly extended human life expectancy. The percentage of people living in their post-retirement life is steadily increasing. While people deserve to enjoy their happy elderly lives, more and more people suffer reduced quality of life due to Alzheimer's disease (AD) or other aging-related cognitive dysfunction. In the U.S. alone, over 5.4 million senior citizens are diagnosed with AD and more elderly people show age-dependent cognitive impairments. Extracellular neuritic (senile) plaques and intraneuronal neurofibrillary tangles are two known pathological hallmarks in brains of patients with AD. Our study aims to explore how a protein named reticulon 3 (RTN3) plays a role in AD pathogenesis. Our prior study using both in vitro and in vivo models shows that RTN3 impacts formation of amyloid deposition and dystrophic neurites, two pathological features in neuritic plaques. We will extend our study to further

investigate the molecular mechanisms associated with changes in these features in AD and aging people. Our study will also explore how to target RTN3 for therapeutic application for improving cognitive functions in AD patients.

Further information available at:

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