Regulation of Mitochondrial Quality Through Mitophagy in Alzheimers Disease

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Country

USA

Title of project or programme

Regulation of Mitochondrial Quality Through Mitophagy in Alzheimers Disease

Source of funding information

NIH (NIA)

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€ 1,555,334.86

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01/09/2014

Total duration of award in years

3

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

SNAPIN gene, retrograde transport, Mitochondria, Alzheimer's Disease, late endosome

Research Abstract

DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) is an age-related progressive neurodegenerative disease that affects a staggering percentage of the aging population and

causes memory loss and cognitive decline. Currently, 5.4 million Americans suffer from AD, which is a major health concern in our society. Mitochondria are cellular energy power plants that supply ATP to power various biological activities essential for neuronal function and survival. Imaging studies in living AD patients reveal mitochondrial deficits at early disease stage. Mitochondrial dysfunction and oxidative stress occur early in animal models of AD. Accumulation of defective mitochondria is a feature of both familial and sporadic AD and plays an early important role in AD pathophysiology. Dysfunction of synaptic mitochondria has been proposed as a key factor involved in early synaptic alterations in AD. Mitophagy, a cargo-specific autophagy-lysosomal pathway for removal of damaged mitochondria, constitutes a key cellular pathway in mitochondrial quality control. Recent studies indicate that PINK1/Parkin-mediated pathways ensure mitochondrial integrity and function, thus preventing from the accumulation of dysfunctional mitochondria. However, a long-standing question is whether the mitophagy process itself is targeted by AD initiation mechanisms to impair routine elimination of synaptic mitochondria, and thereby make critical contributions to initiating synaptic pathology. We recently revealed unique features of Parkin-mediated mitophagy to eliminate damaged mitochondria via the autophagy-lysosomal pathway in live mature cortical neurons. We previously established that Snapin, a dynein motor adaptor, up-regulates lysosomal function by coordinating retrograde transport of late endosomes and late endosome-lysosomal trafficking in neurons. Our recent study uncovered an altered cellular pathway in AD neurons: an impaired substrate proteolysis due to the defects in Snapin-mediated and dynein-driven retrograde transport. In the current proposal, we are applying multidisciplinary approaches of molecular, cell biology, and long time-lapse with multi-channel live imaging in mature neurons derived from an AD model combined with gene rescue experiments. With these approaches, we will elucidate the mechanisms underlying mitophagy and lysosomal deficits in AD neurons, and their impact on quality control of axonal mitochondria. This is a key dynamic cellular process directly linked to early pathophysiology of AD. Three specific aims are proposed: Aim 1 is to establish a causative linkage between mitophagy deficit and mitochondrial pathology in a physiological AD model; Aim 2 is to determine whether lysosomal deficits constitute a core aspect of mitochondrial quality control deficiency in AD neurons; and Aim 3 is to elucidate operative mechanisms rescuing mitochondrial pathology and synapse loss in AD mouse brains. The identified mechanisms are expected to provide the basis for the development of novel protective and therapeutic strategies to overcome AD and other major neurodegenerative diseases associated with mitochondrial dysfunction and autophagy-lysosomal pathology.

Lay Summary

PUBLIC HEALTH RELEVANCE: The identified mechanisms are expected to provide new concepts leading to preventive and therapeutic strategies that will benefit the growing number of Alzheimer’s disease (AD) patients who have either mitochondrial dysfunction or autophagy-lysosomal pathology. It is expected that the findings from the proposed study will be applicable to preventing and treating other major aging-related neurodegenerative diseases.

Further information available at:

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Investments > €500k

Member States:

United States of America

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Alzheimer's disease & other dementias

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