Short Sleep: Locus Coeruleus Metabolics and the Temporal Progression of Alzheimers

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Country

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Short Sleep: Locus Coeruleus Metabolics and the Temporal Progression of Alzheimers

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NIH (NIA)

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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... Dementia... Neurodegenerative... Neurosciences... Sleep Research

Research Abstract

ABSTRACT The age at onset of symptomatology and the temporal progression of sporadic Alzheimer’s disease (AD) can vary by decades. Earlier cognitive decline carries tremendous personal and societal impact, yet little is known of mechanisms influencing the onset and progression of AD. Locus coeruleus (LC) neurons evidence early deposition of tau protein and early degeneration in AD and may contribute to the spreading of tau within the forebrain. Intermittent short sleep (ISS), common in modern societies, disturbs metabolic homeostasis in LC neurons, resulting in mitochondrial hyperacetylation, oxidative neural injury and degeneration. In Preliminary Studies, we find that the amyloid precursor protein (APP) single knock-in mouse (APPki) evidences heightened susceptibility to ISS-induced mitochondrial hyperacetylation and oxidative stress and that ISS produces a robust increase in LC neuronal A?1-42 and tau, marked degeneration of LC neurons and earlier cognitive impairment. Remarkably, two months after ISS, LC neuronal tau acetylation and A?1-42 remain elevated, and spatial object recognition is impaired. The overall hypothesis for our work is that early life metabolic stress in specific groups of neurons activates amyloid and tau responses within affected neurons that, in turn, promote feed forward intraneuronal metabolic injury that hastens AD onset and/or progression. To gain insight into the relevance of LC injury from ISS and its influence on AD progression, we propose to implement novel murine models of targeted viral vectors, STOP-LoxP/cre mice and CRISPR/Cas9 LoxP/cre mice to modify LC levels of tau, mitochondrial sirtuin 3 activity, and A?1-x, respectively. We will test the following hypotheses: (1) that ISS is sufficient a metabolic stressor for LC neurons to result in a sustained tau acetylation accumulation in LC neurons and that tau propagation from LC neurons with cell to cell spread of pathological tau is modified by ISS; (2) that improving mitochondrial deacetylase activity improves LC neuron clearance of toxic amyloid and tau, lessens ISS-induced degeneration and delays cognitive decline in the APPki mouse; and (3) that LC intraneuronal A? is essential for ISS-increased LC tau acetylation and accumulation, LC degeneration, cortical ISS tau propagation and hastening the progression of cognitive decline. These studies will inform the significance of young adulthood chronic sleep loss in AD progression and advance our understanding of LC intraneuronal A?? tau accumulation and metabolic homeostasis interactions in mechanisms of AD progression that in turn will unveil the promise of potential therapeutic targets.

Lay Summary

PROJECT NARRATIVE The proposed studies are designed to determine how chronic short sleep times influence the progression of Alzheimer’s disease (AD). We will test the hypothesis that chronic sleep loss early in life advances the progression of AD and that these effects occur, in part, through mitochondrial dyshomeostasis in neurons activated by wakefulness, including the locus coeruleus neurons. Understanding the molecular mechanisms underlying sleep loss hastening of AD should unveil novel therapeutic avenues to slow or prevent the disorder.

Further information available at:

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Investments > €500k

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United States of America

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Alzheimer's disease & other dementias

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