Circadian dysfunction and GSK3 in neurodegenerative disease

https://neurodegenerationresearch.eu/survey/circadian-dysfunction-and-gsk3-in-neurodegenerative-disease/

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Contact information of lead PI
Country

USA

Title of project or programme

Circadian dysfunction and GSK3 in neurodegenerative disease

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,461,653.21

Start date of award

15/03/2013

Total duration of award in years

3

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Glycogen Synthase Kinase 3, Circadian Rhythms, Neurodegenerative Disorders, Alzheimer's Disease, Circadian Dysregulation

Research Abstract

DESCRIPTION (provided by applicant): Behavioral disturbance and day-night rhythm disruption of dementia patients are top reasons for institutionalization and cause of caregiver burden.

Patients with dementia or Alzheimer’s disease often exhibit “”sundowning syndrome,”” a constellation of symptoms including late afternoon/evening hyperactivity, restlessness, confusion, and aggression, along with misaligned core body temperature and activity rhythms. These symptoms suggest a dysregulated circadian network, which normally allows anticipation of and preparation for daily recurring environmental events, including time-of-day-specific variability in cognitive function. Identification of the molecular abnormalities underlying circadin dysregulation would allow for the development of targeted strategies for reinstating rhythmicity and associated behaviors. This project will test the hypothesis that glycogen synthase kinase 3 provides a time-of-day-specific gating mechanism for intrinsic excitability, and that disruptions i daily changes in the phosphorylation state balance of this enzyme within specific brain regions contribute to circadian and cognitive abnormalities of neurodegenerative disease. Specifically, this project will determine whether day-night changes in phosphorylation of glycogen synthase kinase 3 regulate oscillations of clock gene expression and physiology and that cognition and circadian behavioral abnormalities in neurodegenerative disease are mediated by loss of daily glycogen synthase kinase 3 phosphorylation cycles and dysregulated neural activity rhythms. Proposed studies will examine this hypothesis in the suprachiasmatic nucleus and hippocampus under normal physiologic conditions (Aim 1) as well as under pathological conditions (Aim 2) utilizing animal models of neurodegenerative disease. Successful completion of these experiments will establish glycogen synthase kinase 3 as a key player in day-night variation of membrane properties and synaptic physiology, which are critical for appropriately timed cognitive function and rest/activity patterns. They will also lay the groundwork for translational studies designed to target this mechanism for proper therapeutic timing in dementia and neurological disease.

Lay Summary
PUBLIC HEALTH RELEVANCE: Behavioral disturbance and day-night rhythm disruption of dementia patients are top reasons for institutionalization and cause of caregiver burden. The proposed research will investigate whether disruptions in daily changes in the phosphorylation state balance of an enzyme implicated in neurological disease contribute to circadian and cognitive abnormalities. Successful completion of these experiments will lay the groundwork for translational studies designed to target this mechanism for proper therapeutic timing for patients with dementia and/or Alzheimer’s disease.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

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N/A

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