CNS TAU KINETICS IN ALZHEIMERS DISEASE

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Country

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Title of project or programme

CNS TAU KINETICS IN ALZHEIMERS DISEASE

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NIH (NIA)

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15/07/2016

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2

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

tau Proteins, Neuraxis, Alzheimer's Disease, Kinetics, Stable Isotope Labeling

Research Abstract

Project Summary Tauopathies are neurodegenerative diseases with tau pathology, and are the most common pathological manifestation in neurodegenerative diseases, including corticobasal degeneration (CBD), progressive supranuclear palsy (PSP), and frontotemporal dementia (FTD), and Alzheimer’s disease (AD), which is the most common tauopathy and is reaching epidemic proportions. Recently, tau-targeted therapies have gained significant attention in the

AD research field. Levels of cerebrospinal fluid (CSF) total tau and phosphorylated tau (p-tau) are increased with AD and are important biomarkers for AD. However, proper methods to measure tau kinetics in humans have not been established to evaluate the efficacy of tau-targeted therapeutics. Surprisingly, a recent longitudinal biomarker study in dominantly inherited AD patients showed that CSF tau levels decrease after cognitive decline begins. The results suggest that tau concentrations decrease with symptomatic disease progression, or brain sequestration of tau is increased in the AD brain. Interestingly, recent studies of tau positron emission topography (PET) imaging indicate increasing tau deposition only after the time of cognitive decline, coinciding with decreasing CSF tau concentrations. Thus, a more comprehensive study of in vivo tau dynamics in the human central nervous system (CNS) is critical to understanding the pathophysiology of AD and why tau concentration is elevated and later may decrease with increasing tau aggregation. This proposal will utilize the Stable Isotope Labeling Kinetics (SILK) method to elucidate tau kinetics in vivo in the human CNS and its alteration in AD. A total of 100 participants (30 normal controls, 30 AD and 40 age-matched controls) will be recruited and labeled intravenously with a stable isotope to measure tau kinetics using the newly developed tau SILK method. Aim 1 will measure the physiological kinetics of human tau in the CNS and identify age-related changes by stratifying participants by age and comparisons will be made across three different age groups (18-39; 40-64; 65+). Aim 2 will examine CNS tau kinetics and tau aggregation by tau PET in late-onset AD dementia compared to cognitively normal, age-matched controls. Further, to determine the impact of AD pathology on the physiological kinetics of human tau in the CNS, tau SILK data will be correlated to amyloid and tau brain pathology assessed by PET imaging. Results from this tau SILK study with tau PET imaging will help elucidate the dynamic kinetics of human CNS tau in physiology and pathophysiology of tauopathies. The tau SILK method will facilitate future efforts to evaluate the efficacy of tau-targeted therapies and help effectively design future clinical trials which target tau.

Lay Summary
Project Narrative The goal of this proposal is to characterize tau kinetics and tau aggregation in the human central nervous system (CNS) and to test the hypothesis that tau kinetics are altered (i.e. increased production, decreased clearance, and increased aggregation rate) with normal aging and in Alzheimer’s disease (AD). Results from these highly innovative and important studies will inform both scientists and clinicians about how tau protein changes in the human brain over time and to what extent. The information g a r n e r e d from this tau SILK and tau Pet study will be important in effectively designing future clinical studies which aim to treat AD by targeting tau.

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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