CNS and Plasma Amyloid–Beta Kinetics in Alzheimers Disease

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Country

USA

Title of project or programme

CNS and Plasma Amyloid--Beta Kinetics in Alzheimers Disease

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 2,630,059.63

Start date of award

01/08/2012

Total duration of award in years

3

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Amyloid beta-Protein, Neuraxis, Alzheimer's Disease, Kinetics, Cerebrospinal Fluid

Research Abstract

DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) is the most common cause of dementia and currently has no disease modifying treatments or simple accurate diagnostic tests. Several targets have been identified as contributors to AD pathophysiology (e.g. A?, tau,

inflammation), with most current therapeutic approaches targeting amyloid- beta (A?). However, A? pathophysiology is not fully understood. The amyloid hypothesis proposes that amyloid-beta over-production or under-clearance leads to a common pathophysiology resulting in a cascade of events which culminate in neuronal death and manifest as progressive clinical dementia of the Alzheimer's type. Therefore, treatment of AD during the mild to moderate stage of dementia in therapeutic trials may be too late as 50% of AD specific neurons are already dead. Thus, a better understanding of the pathophysiology of A? and biomarkers based on A? pathophysiology are necessary to offer anti-A? therapeutic strategies their best chance of success. The overall goal of this project is to determine the changes that occur in A? metabolism in AD and model the production, transport, metabolism and clearance of A? in the human central nervous system (CNS) and periphery to improve clinical trial designs. In order to understand A? kinetics in the pathophysiology of AD, the applicant will use Stable Isotope Labeling Kinetics (SILK) to metabolically label and quantify proteins in the human CNS. The specific aims are 1) to determine A? isoform production and clearance rates in steady state infusion labeled blood, and 2) to measure blood and CSF A? SILK from a pulse oral labeled SILK protocol in AD and control participants. In SA1, blood A? kinetics will be compared to CSF A? kinetics and combined utilizing multi-compartment and structural models to determine the direction and magnitude of transport and breakdown. The oral labeling protocol in SA2 will provide additional information on A? kinetics and potentially better distinguish AD from controls. Results from SA2 will be incorporated into complimentary models with results from SA1 and ongoing studies to provide measures of A? production, transport, and breakdown within and between the brain, CSF and blood compartments. The proposed work builds on the prior pioneering approach that has influenced the understanding of A?'s role in the amyloid hypothesis and pathophysiological causes of AD. The approach has been extended with significantly improved techniques, novel labeling protocols, and cutting-edge modeling approaches. In summary, these studies will provide the first human measurements of A? kinetics in blood, develop comprehensive models of A? metabolism, and determine changes of A? metabolism in AD that will lead to better clinical trial designs and potentially a blood biomarker for AD.

Lay Summary
PROJECT NARRATIVE Alzheimer's disease (AD) is the most common cause of dementia and currently has no disease modifying treatments or simple accurate diagnostic tests. The goal of this project is to study how amyloid-beta (a protein thought to cause AD) is made, transported and cleared in the human body. Findings from this study may lead to better treatments for AD.

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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