Metabolic Networks and Pathways in Alzheimers Disease

https://neurodegenerationresearch.eu/survey/metabolic-networks-and-pathways-in-alzheimers-disease/

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Country

USA

Title of project or programme

Metabolic Networks and Pathways in Alzheimers Disease

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 3,867,739.45

Start date of award

15/09/2014

Total duration of award in years

3

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... Clinical Research... Clinical Research - Extramural... Dementia... Genetics... Neurodegenerative... Neurosciences... Translational Research

Research Abstract

DESCRIPTION (provided by applicant): Alzheimer's disease (AD) is a major national public health priority. Despite advances, clinical trials have not yielded therapies to prevent or slow disease progression with recent failures highlighting our incomplete knowledge of mechanisms. Accumulating evidence suggests the synaptic failure in AD is associated with dysregulation in multiple metabolic networks and that AD is not a singular condition but may be a combination of altered networks. Recent advances in analytical chemistry led to the emergence of a new field called metabolomics. Metabolomics allows simultaneous measurement of 100's to 1000's of metabolites for mapping perturbations in interconnected pathways and in metabolic networks enabling a systems approach to the study of AD. Over the past 4 years we assembled an interdisciplinary research team that includes experts in metabolomics, AD clinical and basic research, genetics, biochemistry and bioinformatics, and have started to define perturbations in metabolic networks across the trajectory of disease. We identified novel changes in methionine, norepinephrine, tryptophan and purine pathways, and networks in both MCI and AD subjects. We also found links between metabolic perturbations and core AD pathology markers (total tau and amyloid-beta 42) suggesting changes in these biochemical pathways might parallel or even precede formation of plaques and tangles and provide new insights into pathophysiology. Our overall goal is to leverage large investments made by the NIH in the AD Neuroimaging Initiative (ADNI) and Pharmacometabolomics Research Network taking an integrated metabolomics-genetics-imaging systems approach to define network failures in AD. In Specific Aim 1 we propose to study three cohorts (two clinic based and one population based) to further define alterations in interconnected metabolic pathways and networks in four diagnostic groups (asymptomatic but at-risk for developing AD (APOE ?4 carriers), individuals with cognitive complaints but normal objective memory, MCI, and AD) and controls to define network alterations that track both progression of cognitive decline as well as pathology (CSF amyloid-beta and tau). In Specific Aim 2 we will relate metabolomics data to genetic variation (GWAS) bi-directionally to determine whether novel genetic markers identified in earlier studies (e.g. ADNI) have metabolic correlates and whether metabolic phenotypes identified in this study yield novel genetic insights. We will assess models of imaging and other biomarker data with metabolomics and genetics in a systems framework. In Specific Aim 3 we propose to use stable isotope tracers and NMR spectroscopy in ApoE4 TR and APP/PSI/ApoE4 mouse models, at three different ages, to probe these metabolic networks in both blood and spinal fluid in greater detail to determine the relative validity of the targets identified in aims 1 and 2. This innovativ, well-integrated and targeted approach is likely to transform our understanding of the heterogeneity underlying AD pathogenesis and will provide novel insights highly relevant for novel drug discovery and development.

Lay Summary

PUBLIC HEALTH RELEVANCE: As metabolic processes are at the core of physiology, metabolomics is ideally positioned to characterize an integrated view of metabolic failures in AD across the trajectory of disease. Such information could provide totally novel insights about disease mechanisms, disease heterogeneity, and help bridge knowledge from genetics to metabolism by providing insights about functions of genes implicated in AD pathogenesis and can lay a new path for drug discovery.

Further information available at:

Types:

Investments > €500k

Member States:
United States of America

Diseases:
Alzheimer's disease & other dementias

Years:
2016

Database Categories:
N/A

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N/A