Targeting the kynurenine pathway in Alzheimers disease

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Country

USA

Title of project or programme

Targeting the kynurenine pathway in Alzheimers disease

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 2,207,847.71

Start date of award

01/09/2014

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... Dementia... Neurodegenerative... Neurosciences... Prevention

Research Abstract

DESCRIPTION (provided by applicant): The preclinical development of Alzheimer’s disease

(AD) begins decades prior to onset of cognitive decline. Epidemiologic studies demonstrate that in cognitively normal aging populations, non-steroidal anti-inflammatory drugs (NSAIDs), which block cyclooxygenase (COX-1/COX-2) activity and PGE2 production, prevent development of AD. Given that the prevalence of AD doubles every 5 years in persons above the age of 65, a fundamental challenge in the AD field will be to stem the projected exponential increase in new AD diagnoses and the significant societal and economic costs that this will cause. A compelling clue to a mechanism underlying NSAID prevention has emerged from our recent studies modeling the preventive effects of NSAIDs in wild type and mutant APP mice, wherein we identified suppressive effects of ibuprofen on expression of enzymes involved in tryptophan metabolism. The enzymes TDO2 and IDO1 metabolize the essential amino acid tryptophan to kynurenine, itself a substrate of the neuroactive molecules quinolinic acid and kynurenic acid; moreover, in metabolizing tryptophan, the substrate for serotonin synthesis, TDO2 and IDO1 will negatively influence levels of serotonin. Importantly, recent biomarker studies in human serum report a significant increase of tryptophan metabolism in AD patients. Thus, in this proposal, we will test whether the enzymes TDO2 and IDO1 contribute to early and late development of AD pathology and cognitive decline using genetic and pharmacologic strategies in AD model mice. We will also test whether levels of tryptophan metabolites in cerebrospinal fluid and serum will correlate with measures of cognition, A?42/tau ratios, and/or diagnosis in control, mild cognitive impairment (MCI), and AD subjects from the ADRC at the University of Washington. Our proposed studies will determine whether increased tryptophan metabolism is mechanistically linked to development of AD and whether TDO2/IDO1 tryptophan metabolism can be targeted in prevention and treatment of AD.

Lay Summary
PUBLIC HEALTH RELEVANCE: The proposed work will determine whether generation of kynurenine from tryptophan by the enzymes TDO2 and IDO1 functions in development of AD pathology. We will use genetic and pharmacologic approaches in murine models of AD to identify mechanisms of action of these enzymes in early and late stages of AD development and we will also test whether tryptophan metabolism changes in de-identified human subjects with progression from normal to MCI to AD states. Successful completion of these studies may lead to a novel preventive strategy to delay onset of AD in at-risk aging populations.

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

Database Tags:
N/A