Dissecting the role of 5LO in neurodegeneration associated with homocysteine

https://neurodegenerationresearch.eu/survey/dissecting-the-role-of-5lo-in-neurodegeneration-associated-with-homocysteine/

Principal Investigators

PRATICO, DOMENICO

Institution

TEMPLE UNIV OF THE COMMONWEALTH

Contact information of lead PI
Country

USA

Title of project or programme

Dissecting the role of 5LO in neurodegeneration associated with homocysteine

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,788,990.83

Start date of award

01/08/2016

Total duration of award in years

1

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... Genetics... Neurodegenerative... Neurosciences... Prevention

Research Abstract
? DESCRIPTION (provided by applicant): Alzheimer’s disease (AD) is the most common chronic neurodegenerative disorder associated with dementia in the elderly, affecting approximately 6-8% all person aged >65 years. Although an effective treatment for the disease is unavailable, intervention to control risk factors implicated in the disease onset can still redue the number of cases and the associated enormous economic cost. This fact has stimulated a large effort to identify those factors and to develop treatments to reduce and/or prevent them. Abnormal elevation of homocysteine (Hcy) levels is considered a risk factor that significantly increases the probability to develop AD. However, the mechanism(s) involved in this biologic effect remain to be fully investigated. Our preliminary data demonstrate that Hcy specifically up-regulates 5Lipoxygenase (5LO), a protein widely expressed in the brain where it modulates A? formation and tau metabolism, and that 5LO is required for the changes in the AD-like phenotype secondary to Hcy. Taken together, these findings provide the rationale and biologic basis of our working hypothesis: Hcy activates the 5LO pathway, which then results in an abnormal formation of A? peptides, an excessive tau phosphorylation and cognitive deficits. We will test this hypothesis by studying the essential role of 5LO in the development of the A? and tau neuropathologies, and behavior deficits in transgenic mouse models of AD during a chronic condition of elevated Hcy. We will next investigate the mechanisms whereby Hcy via the 5LO modulates A?/APP processing and tau metabolism in neuronal cells. Finally, we will ascertain these mechanisms in vivo by using a pharmacologic and a genetic approach. Our studies are novel and significant because they will establish a biological link between Hcy and 5LO in the context of the AD pathogenesis. They also will provide new mechanistic knowledge into the neurobiology of Hcy, and useful clues for new therapeutic approaches in individuals carrying this risk factor for developing the disease.

Lay Summary
PUBLIC HEALTH RELEVANCE: Alzheimer’s disease (AD) is characterized by a progressive and irreversible impairment of memory. Currently in the USA there are more than 5 million individuals with this disease for which we still do not have a cure. Numerous studies have indicated that people with high levels in the blood of an aminoacid called homocysteine are at higher risk to develop AD. However, how this aminoacid increases the risk is not known. Recently, we have discovered that when the amount of homocysteine is elevated in the brain a protein called 5-Lipoxygenase becomes more active. As a result of this activation, different new compounds are produced and they stimulate the formation of abnormal amount of amyloid beta and altered tau protein, which will form the amyloid plaques and tangles, the two major brain lesions responsible for the clinical manifestation and symptoms of AD. This observation suggests that the 5-Lipoxgenase is involved and may be required in the homocysteine-dependent development of AD. Our proposed studies by testing this hypothesis will provide us with important information for future clinical trials targeting individuals with this risk factor fr preventing or delaying AD.

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