Immune-based nutrient deprivation and neurodegenerative disease

https://neurodegenerationresearch.eu/survey/immune-based-nutrient-deprivation-and-neurodegenerative-disease/

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Country

USA

Title of project or programme

Immune-based nutrient deprivation and neurodegenerative disease

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 2,095,746.79

Start date of award

15/08/2013

Total duration of award in years

4

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... Immune System... Infectious Disease and Bioterrorism... Neurodegenerative... Neurosciences

Research Abstract

DESCRIPTION (provided by applicant): The role of the immune system in neuronal death in

chronic neurodegenerative diseases remains a critical unsolved question. One common view is that chronic neurodegeneration represents a form of immune pathology, in which the excessive production of inflammatory mediators such as TNFalpha, IL-1beta, and reactive nitrogen or oxygen species leads to neuronal cell death. There is a strong precedent for such immune pathology in diseases such as acute viral or bacterial infection. However new evidence from multiple sources argues that pro- inflammatory immune pathology is not the cause of neuronal loss in chronic brain disease. Here we propose that a different type of immune pathology, one most commonly associated with immune suppression, is responsible for neuronal cell death in chronic neurodegenerative diseases such as Alzheimer's disease. Immunosuppression is a feature of acquired immune privilege that protects critical cells but reduces the ability of the tissue to mount an effective toxic response that would ""clear"" immunogens including Abeta. Ineffectual clearance leads to ""persistent infection"" and hence to a chronic inflammatory disease. Our data on a mouse model of AD that shows full AD-like pathology (the CVN mouse) strongly suggest that Alzheimer's disease may represent an inappropriate immunosuppressive state, initiated or facilitated by Abeta production. Preliminary data from this mouse show increased expression of anti- inflammatory/repair genes and proteins at the onset of cellular Abeta production and parenchymal deposition. Pro-inflammatory gene expression occurs with age but is accompanied by increased expression of anti-inflammatory and tolerogenic genes and proteins. Thus, we believe that an immunosuppressive environment is maintained throughout the neurodegenerative process. Nutrient deprivation is a principal mechanism by which immune cells induce immune- suppression. By increasing arginine and tryptophan uptake, immune cells reduce the levels of these essential amino acids in the microenvironment. Surrounding cells may undergo amino acid starvation and increased autophagy leading to cell death. Our preliminary data suggest that amino acid starvation occurs in CVN mice brain. Increased activity of two enzymes are featured in immunosuppression; namely arginase (Arg) that uses arginine to make ornithine for polyamine and proline production and Indoleamine dioxygenase (IDO) that uses tryptophan to produce kyneurine. The CVN mouse model of AD demonstrates both decreased brain levels of arginine and increased arginase and IDO expression. This proposal will focus on the role of nutrient deprivation as a key factor in the induction of autophagy and neuronal loss in AD. The aims will establish, 1) the relationship between nutrient deprivation and the progression of AD- like pathology in the CVN mouse 2) if immunosuppressive immune cells contribute directly to disease progression through regional nutrient deprivation and 3) if immune-mediated nutrient deprivation plays a causal role in neuronal death and AD pathology. These proposed studies represent a novel approach to understanding the basic mechanisms of immune mediated disease in chronic neurodegenerative disease.

Lay Summary

PUBLIC HEALTH RELEVANCE: Alzheimer's disease is a chronic neurodegenerative disease that includes a major immune component. This research proposal will investigate a novel mechanism of the immune system's involvement in the production of AD-pathology including neuronal death. Specifically, we will examine how immune-mediated nutrient deprivation will kill neurons by reducing amino acid levels in the brain.

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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