Neuroprotective Immunity and HIV Dementia

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Contact information of lead PI
Country

USA

Title of project or programme

Neuroprotective Immunity and HIV Dementia

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,687,654.13

Start date of award

01/04/1995

Total duration of award in years

1

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

HIV-associated neurocognitive disorder, alpha synuclein, Nitrates, Dementia, Parkinson Disease

Research Abstract
DESCRIPTION (provided by applicant): The numbers of human immunodeficiency virus (HIV) infected peoples over the age of 50 have grown in the past decade as has changing disease biology for the nervous system. Indeed, HIV-associated neurocognitive disorders (HAND) in the aged is a clinical diagnosis but is associated, in measure, with atrophy of the nigrostriatum and frontostriatal circuits and early signs of beta-amyloidosis, microtubule-associated tau

aggregation, and alpha synuclein inclusions. Such findings are seen in Alzheimer's and Parkinson's diseases (AD and PD). For PD and HAND, in particular, common anatomical, immunologic and neurochemical axes exist within the nigrostriatum. In recent years our laboratories uncovered a bridge between both diseases through linked adaptive immune activities serving to halt neuronal loss seen in models of HAND, PD, AD and amyotrophic lateral sclerosis. These findings suggest that multicellular regulatory responses exist for both virus and brain-specific proteins. To test this notion we will profile, the principal target cell(s) for viru in the nervous system, the mononuclear phagocyte in a laboratory setting reflective of PD and HAND. This will be done through proteomic, bioinformatic and functional immune tests following chronic HIV and/or misfolded and aggregated nitrated alpha synuclein (N-a-syn) exposures. Based on the cellular profiles seen we will investigate neural and immune responses observed in brains of HIV-1 infected humanized mice exposed to 1- methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) or to N-a-syn. Here we will assess how neuronal and glial responses affected by each pathobiologic event alone and together in disease-effected specific brain subregions and performed in the setting of combination antiretroviral therapy (cART). Neuropathologic evaluations will be linked to T cell subsets and viral load tests to provide correlation between neurodegeneration with immune profiling. Coordinate magnetic resonance imaging and behavioral testing for screening of brain impairments and stable isotope labeling of amino acids in mammals for mechanistic study will anchor protein chemistry, histology, cognition and immunology to neurodegenerative processes. To substantiate the links of adaptive immunity to neurodegeneration we will perform immune-based therapeutic interventions to halt neurodegeneration. In this manner the mechanism of and the means to correct such functional neuronal deficit(s) will be sought. These studies will uncover the role of chronic HIV infection on the onset of progression of parallel neurodegenerative processes and means to intervene. Such studies tackle changing patterns of neuroAIDS in the era of cART with an eye towards changes in behavioral impairments. An interdisciplinary team of investigators with a strong track record of working together successfully was assembled for these studies.

Lay Summary
PUBLIC HEALTH RELEVANCE: Both human immunodeficiency virus (HIV) infection of the nervous system and Parkinson's disease (PD) (driven by misfolded, nitrated and aggregated alpha synuclein) lead to robust immune responses that drive neuronal injury and cognitive impairments. How the two influence one another is not known; but as HIV- infected people age, the influences of the two on one another will be more significant. To this end we will investigate, in laboratory and animal models of HIV and PD, the means to better understand how the two diseases affect one another with an eye towards bench to bedside translation.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

Diseases:
Parkinson's disease & PD-related disorders

Years:
2016

Database Categories:
N/A

Database Tags:
N/A