Altered Amyloid Processing HIV

https://neurodegenerationresearch.eu/survey/altered-amyloid-processing-hiv/

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Country

USA

Title of project or programme

Altered Amyloid Processing HIV

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,869,111.01

Start date of award

19/07/2013

Total duration of award in years

5

The project/programme is most relevant to:

Alzheimer's disease & other dementias

Keywords

Amyloid, Sphingolipids, Amyloid beta-Protein, HIV, amyloid precursor protein processing

Research Abstract

DESCRIPTION (provided by applicant): Neurocognitive impairments in HIV-infected individuals, collectively known as HIV-Associated Neurocognitive Impairments (or HAND) remains a significant problem in the era of Combined Antiretroviral Therapy (CART). In many HIV-infected individuals there is evidence of accelerated aging, including aberrant processing of amyloid precursor protein (APP). These disruptions seem to result in accumulations of pathogenic forms

of amyloid-ß (ß) in brain and are thus likely to also decrease the formation of soluble APP? (sAPP?), an important neurotrophic peptide. Our preliminary data suggest that accumulations of sphingolipids and complex glycolipids in intracellular compartments accelerates Aß formation by enhancing the activity of ß- and ?- secretases (that process APP to Aß), and by perturbing the intracellular trafficking / clearance of Aß. Previously we have documented accumulations of multiple sphingolipid species in HIV-infected individuals. These combined findings prompted us to determine if the accumulations of sphingolipid products in endosomes, lysosomes and/or autophagosomes are associated with aberrant APP processing, increased Aß deposition and decreased sAPP? in the setting of HIV-infection. In this application we propose a comprehensive approach to address this question, using human brain tissues, cellular/molecular approaches, and transgenic model systems to determine if increased brain levels of these lipid metabolites shifts APP processing to a more amyloidogenic (Aß) and less trophic (sAPP?) pheotype and if interventions that target sphingolipid metabolism can reverse these effects.

Lay Summary
PUBLIC HEALTH RELEVANCE: People infected with the Human Immunodeficiency Virus (HIV) are at increased risk for cognitive impairments that are collectively termed HIV-Associated Neurocognitive Impairments (or HAND). Accumulating evidence is beginning to show that a significant number of people infected with HIV are at risk for accelerated brain aging. One manifestation of accelerated brain aging is an increase in the brain deposition of a protein known as amyloid-beta (Aß). This deposition normally increases with age, but appears to be accelerated by 20-30 years in people infected with HIV. These deposits can disrupt brain functions and may contribute to cognitive impairment in people infected with HIV. Additionally, the production of Aß disallows the formation of a protein known a soluble APP alpha, (sAPP?), which protects neurons. This study proposes to determine the extent to which the production of these proteins is modified by HIV-infection, and the HIV-associated mechanisms that may perturb the formation of these proteins. Several pathways are targeted that may have therapeutic potential to slow brain aging in this population.

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