Imaging Innate Immune Responsiveness of Microglia in Alzheimers Disease Brain

https://neurodegenerationresearch.eu/survey/imaging-innate-immune-responsiveness-of-microglia-in-alzheimers-disease-brain/

Principal Investigators

SALARDINI, ARASH

Institution

YALE UNIVERSITY

Contact information of lead PI
Country

USA

Title of project or programme

Imaging Innate Immune Responsiveness of Microglia in Alzheimers Disease Brain

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

422591.7431

Start date of award

01/09/2016

Total duration of award in years

1

Keywords

Acquired Cognitive Impairment... Aging... Alzheimer's Disease... Alzheimer's Disease including Alzheimer's Disease Related Dementias (AD/ADRD)... Brain Disorders... Clinical Research... Clinical Research - Extramural... Dementia... Immune System... Neurodegenerative... Neurosciences

Research Abstract

Project Summary Histopathological studies of Alzheimer’s disease have consistently demonstrated the presence of inflammation in Alzheimer’s disease (AD). Inflammation was previously thought to be a bystander in the pathogenesis of disease however several lines of

evidence, most importantly from genetic studies of susceptibility loci have demonstrated a number of genes, most of which are implicated in the function of microglia. Microglia, the main protagonist in the innate immunity of the brain, interacts with constituents of the amyloid plaque and appears to be activated by this interaction. However it is not clear whether this activation is protective, destructive or protective in one setting of disease and destructive in another. Contradictory evidence comes from animal models, epidemiological data and clinical trials. Part of the problem has been the difficulty of in vivo study of central nervous system immunity. The discovery of the transporter protein (TSPO) may represent a breakthrough in the in vivo study of neuroinflammation. TSPO is located in the outer mitochondrial membrane and is upregulated during activation of microglia. Several PET ligands exist which image this molecule and, in particular, 11C-PBR28 is well suited to the study of neuroinflammation in AD. One study using this ligand was able to show increased binding in AD but not mild cognitive impairment, leaving a number of tantalizing questions unanswered. Firstly it is not clear whether the increased baseline activation of microglia in AD is simply due to the presence of amyloid or represents a dysregulation of microglial response to stimulation. Secondly, if this dysregulation is demonstrated, are the inflammatory increases in AD subjects simply due to microglial senescence or represents a disease-specific jump in microglial reactivity. For this reason, we propose to apply a technique to measure inflammatory reactivity using TSPO imaging of the brain at baseline and 180 minutes after the intravenous administration of lipopolysaccharide. We define microglia activation reserve index as the percentage change in TSPO binding (measured as volume of distribution) at baseline and after LPS. We also aim to compare microglia activation reserve index between young healthy individuals, cognitively normal elderly and subjects with AD. We expect to find an increase in the reactivity in the innate immune systems of subjects with AD which exceed that which may be expected from simply the effect of aging. These results, if demonstrated, will have profound diagnostic and therapeutic implication in the management of Alzheimer’s disease. Increased MARI with AD may be used as a diagnostic biomarker and point the way to anti-inflmmatory therapies for disease course modification.

Further information available at:

Types:
Investments < €500k

Member States:
United States of America

Diseases:
N/A

Years:
2016

Database Categories:
N/A

Database Tags:
N/A