Cytosolic Phospholipase A2 in Amyloid-beta Peptide-stimulated Cerebral Endothelial cells

https://www.neurodegenerationresearch.eu/survey/cytosolic-phospholipase-a2-in-amyloid-beta-peptide-stimulated-cerebral-endothelial-cells/

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Country

USA

Title of project or programme

Cytosolic Phospholipase A2 in Amyloid-beta Peptide-stimulated Cerebral Endothelial cells

Source of funding information

NIH (NIA)

Total sum awarded (Euro)

€ 1,402,814.68

Start date of award

01/01/2016

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)... Bioengineering... Brain Disorders... Cerebrovascular... Dementia... Neurodegenerative... Neurosciences

Research Abstract

DESCRIPTION (provided by applicant): The overall goal of this project is to investigate the role of cytosolic phospholipase A2 (cPLA2) in the cellular pathways associated with alterations of membrane molecular order and membrane tethering adhesion mechanics in amyloid-beta peptide (Abeta)-stimulated cerebral endothelial cells (CECs). Membrane tethering adhesion is the first mechanical step governing the transmigration of monocytes across the endothelial layer; thus, increased microglial cells in brains differentiated from peripheral monocytes exacerbate the progression of Alzheimer’s disease (AD). In this project, we will test the hypothesis that Ab stimulates CECs and results in activation of cPLA2 and its upstream mitogen-activated protein kinases (MAPKs) which play a critical role in the increase in adhesion molecules, p-selectin, through the nuclear factor-kB (NFkB) pathway, and subsequently enhanced actin polymerization, and alteration of the molecular order of cell membranes, and membrane tether adhesion mechanics.. This project will be accomplished by biochemical, biophysical, and biomechanical approaches. Biochemical approaches include cell reporter assay to measure NFkB, Western blot analysis to characterize activation of MAPKs and cPLA2 and quantitative immunofluorescence microscopy (QIM) to quantify reactive oxygen species, adhesion molecules (p-selectin), and actin polymerization in Abeta-stimulated CECs. For the biophysical approach, fluorescence microscopy of LAURDAN will be applied to examine the role of MAPKs and cPLA2 on membrane molecular order in Abeta-stimulated CECs. For the biomechanical approach, atomic force microscopy will be used to determine the role of MAPKs, cPLA2, and NFkB in alterations of cell membrane adhesion in Abeta-stimulated CECs. Results derived from this project will fill the gap in the field by providing the mechanism for involvement of cPLA2 activation and the relationship between Abeta-induced cPLA2-related pathway and membrane tether adhesion mechanics in CECs. Since membrane tether adhesion is a determining mechanical step for transmigration of monocytes, and monocytes can further differentiate into microglial cells which exacerbate oxidation and neuro-inflammation conditions in AD brains, this project is expected to contribute to our understanding of the oxidation and inflammation in AD brains. Ultimately, information derived from this project will provide new insights into therapeutic strategies for AD treatment and progression of the disease.

Lay Summary

PUBLIC HEALTH RELEVANCE: The overall goal of this project is to investigate the role of cytosolic phospholipase A2 (cPLA2) in the cellular pathways associated with alterations of membrane tethering adhesion mechanics in Abeta-stimulated endothelial cells, the first mechanical step governing the transmigration of monocytes across the endothelial layer. This transmigration process is one of the main factors leading to neuro-inflammation and oxidation in Alzheimer’s disease (AD) brains. Ultimately, information derived from this project will provide new insights into therapeutic strategies for AD treatment and progression of the disease.

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