Early life brain inflammation and vulnerability to neurodegeneration in late life

https://www.neurodegenerationresearch.eu/survey/early-life-brain-inflammation-and-vulnerability-to-neurodegeneration-in-late-life/

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Country

USA

Title of project or programme

Early life brain inflammation and vulnerability to neurodegeneration in late life

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,424,636.70

Start date of award

15/07/2013

Total duration of award in years

2

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

Encephalitis, Lipopolysaccharides, dopaminergic neuron, Perinatal, Rotenone

Research Abstract

DESCRIPTION (provided by applicant): Recent studies indicate that perinatal brain infection/inflammation may contribute to not only brain damage and subsequent neurological

dysfunction in the neonatal and juvenile stages, but also neurodegenerative diseases that occur in late life. It has been reported in rats that prenatal exposure to lipopolysaccharide (LPS) is linked to loss of dopaminergic (DA) neurons in the offspring brain at adult stages, a hallmark feature of Parkinson’s disease (PD) which is a neurodegenerative disease typically seen in aged people. Interestingly, our previously data suggested that perinatal LPS exposure through intraperitoneal (i.p.) injection, an exposure route more likely to be encountered in newborn infants with infections, results in decreased expression of tyrosine hydroxylase in DA neurons, but not the actual death of DA neurons in the substantial nigra (SN). The rationale is that perinatal LPS exposure enhances susceptibility of DA neurons in the SN in the adult brain to an ordinarily non-toxic or sub-toxic dose of rotenone, thus, resulting in actual loss of DA neurons and PD-like symptoms. Based on these observations, we hypothesize that: 1) perinatal systemic LPS exposure may result in chronic brain inflammation and prolonged exposure to such an environment may enhance vulnerability of DA neurons in the SN of adult brain to an ordinarily non-toxic or sub-toxic dose of neurotoxin to develop PD-like symptoms; and 2) the long-term effect of perinatal LPS exposure is mediated, at least partially, by a sustained elevation in IL-1¿ levels, accumulation of ¿ -synuclein (¿- SYN) aggregation, activation of microglia, and induction of cyclooxygenases-2 (COX-2) in the SN. The following specific aims will be addressed: Aim 1: to investigate the effects of environmental toxin, paraquat, at an ordinarily non-toxic or sub-toxic dose, in order to characterize the chronic inflammatory conditions in the SN following perinatal systemic LPS exposure and correlate the enhanced vulnerability of the DA neurons with the chronic inflammatory conditions. Aim 2: to determine the role of sustained elevations in IL-1¿ and accumulation of ¿-SYN aggregation following perinatal LPS exposure on the enhanced vulnerability of DA neurons to rotenone at adult stages through i.c. injection of IL-1 ¿, or treatments with IL-1ra or ¿ SYN siRNA in LPS-exposed animals, and then compare the impairment of DA neurons and motor dysfunctions induced by a sub-toxic dose of rotenone in late life. Aim 3: to determine the role of sustained activation of microglia an induction of COX-2 following perinatal LPS exposure on enhancement of DA neuron vulnerability to rotenone toxicity, using minocycline, an inhibitor of microglia activation, or celecoxib, a selective COX-2 inhibitor, in both animal and microglia-mesencephalic DA neuron co-cultures. The proposed studies will not only greatly enhance our understanding of mechanisms involved in long-term adverse effects of perinatal brain inflammation on late-onset neurodegenerative diseases, but may also lead to identification of key targets/pathways for developing preventive/therapeutic strategies against these adverse effects.

Lay Summary
PUBLIC HEALTH RELEVANCE: There is increasing evidence that perinatal infection is not only one of the major contributors to infant mortality and morbidity, but also an important risk factor for development of late-onset neurodegenerative diseases such as Parkinson’s disease. This proposed project will explore mechanisms involved in the link between perinatal brain inflammation and the enhanced risk for triggering neurodegenerative diseases in a late life stage, and it is highly relevant to public health.

Further information available at:

Types:
Investments > €500k

Member States:
United States of America

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Parkinson's disease & PD-related disorders

Years:
2016

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