Gene-Environment Interactions in Neurodegeneration: Role of Efflux Transporters

https://neurodegenerationresearch.eu/survey/gene-environment-interactions-in-neurodegeneration-role-of-efflux-transporters/

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Country

USA

Title of project or programme

Gene-Environment Interactions in Neurodegeneration: Role of Efflux Transporters

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 1,724,085.32

Start date of award

01/09/2014

Total duration of award in years

3

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

ABCB1 gene, Paraquat, gene environment interaction, Nerve Degeneration, Pesticides

Research Abstract

DESCRIPTION (provided by applicant): Parkinson’s disease (PD) is a chronic, degenerative neurological disorder that is estimated to affect at least 1 million individuals in the U.S. and ovr 10 million worldwide. PD is a complex disorder, and no single gene has been linked to a significant percentage of cases, suggesting that environmental factors or gene-environment interactions may contribute to the etiology or clinical manifestation. A polymorphism in the xenobiotic transporter Multidrug resistance protein 1 (MDR1, also known as P-glycoprotein) that reduces its function has been observed more frequently in PD patients who were exposed to pesticides. This finding raises the possibility that altered MDR1 function increases the risk for PD in people exposed to pesticides. Since MDR1 is critically important in expelling chemicals from the brain, we have hypothesized that MDR1 actively effluxes pesticides from the brain and genetic or acquired deficiency in this transporter may contribute to neurodegeneration. Our main research aim is to identify MDR1 as a primary efflux transporter responsible for removing pesticides, including the herbicide paraquat that has been linked to dopaminergic neurodgeneration, from the brain and protecting against neurodegeneration. This is significant because 1) MDR1 is prominently expressed in human brain capillary endothelial cells and other neuronal cells, 2) a polymorphism in MDR1 has been associated with increased risk of PD in patients exposed to pesticides, and 3) neuroinflammation, which is associated with multiple degenerative diseases including PD, has been found to down-regulate MDR1. Therefore, it is expected that these data will provide a better understanding of the genetic and inflammatory regulation of MDR1 as well as the potential role of MDR1 in the retention of pesticides in the brain, and will allow us to determine the mechanism of gene-environment interactions between MDR1, pesticides, and neurodegeneration.

Lay Summary

PUBLIC HEALTH RELEVANCE: This project will provide a mechanistic insight into the associations between pesticide exposure, MDR1 genetic variation, and neurodegeneration. By studying the interaction of genetic variation, inflammation, and environmental exposure, we will likely demonstrate the convergence of multiple pathways previously implicated in the pathogenesis of Parkinson’s disease. This, in turn, could lead to new avenues in identifying individuals most susceptible to pesticides-induced neurotoxicity and potentially lead to therapeutic interventions to increase clearance of pesticides from the brain.

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

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