Neural Toxicity of Paraquat is Related to Iron Regulation in the Midbrain

https://www.neurodegenerationresearch.eu/survey/neural-toxicity-of-paraquat-is-related-to-iron-regulation-in-the-midbrain/

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Country

USA

Title of project or programme

Neural Toxicity of Paraquat is Related to Iron Regulation in the Midbrain

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 2,536,889.91

Start date of award

24/11/2014

Total duration of award in years

3

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

Paraquat, Midbrain structure, Iron, pars compacta, Substantia nigra structure

Research Abstract

DESCRIPTION (provided by applicant): There are at least two types of Parkinson’s disease (PD), familial and sporadic (sPD). By far, sPD accounts for the majority of cases and is

becoming to be seen as the result of several genes and their interaction with the environment, including widely used pesticides. One such agent is paraquat (PQ), an herbicide used widely in developing countries and also in the USA. The data from epidemiological studies linking PQ exposure with sPD are inconclusive and we will show that PQ exposure alone is likely insufficient to produce sPD. At least one other factor is iron content [Fe] in the substantia nigra pars compacta (SNc). Iron in the SNc is considered to be another risk factor for sPD. Studies conducted in vitro have shown that PQ and Fe act synergistically in killing dopamine neurons in the SNc, the pathological hallmark of PD. In the proposed research, we will show that PQ disrupts iron homeostasis in the SNc and that the increased iron in this tissue is what defines PQ neurotoxicity. The overall goal of this research is to identify genes and gene networks that confer differential susceptibility to PQ-induced increased Fe in the SNc. In order to address the problem, we will study the effect of PQ- increased Fe in 40 recombinant inbred strains derived from C57BL/6 and DBA/2 parental strains. The first experiment will be to show wide, genetic-based variability in paraquat- increased Fe in the SNc. The second experiment will be to show that PQ-based destruction of dopamine neurons is related to the extent of PQ-related disruption of Fe homeostasis in the SNc. We will next investigate the effects of paraquat on gene expression by microarray analysis in the substantia nigra, pars compacta and then by combining QTL analysis for the gene expression with QTL for PQ-increased Fe in the SNc, we will elucidate the biochemical pathways involved in paraquat-iron neurotoxicity as well as elucidating genetic markers that indicate increased (decreased) risk for damage to dopamine neurons in the SNc

Lay Summary
PUBLIC HEALTH RELEVANCE: Sporadic Parkinson’s disease (sPD) is one of the most common neurodegenerative diseases and affects an estimated 1% of individuals aged 65 or over. The herbicide, paraquat (PQ) is suspected of being a risk factor for sPD, but not all of those exposed develop obvious signs of sPD. Iron is also a suspected risk factor for sPD and in this research we will show that PQ disrupts iron regulation in the brain and allows excess iron to accumulate in the PD-vulnerable substantia nigra. Moreover, we will show that individual differences in the effects of PQ on brain iron underlie individual differences in susceptibility to PQ neurotoxicity. This work will yield biomarkers for PQ and perhaps other pesticide sensitivity and will lead to new means to prevent and perhaps treat pesticide-related sPD.

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

Database Tags:

N/A