Mechanisms of PhIP-induced dopaminergic neurotoxicity

https://neurodegenerationresearch.eu/survey/mechanisms-of-phip-induced-dopaminergic-neurotoxicity/

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Country

USA

Title of project or programme

Mechanisms of PhIP-induced dopaminergic neurotoxicity

Source of funding information

NIH (NINDS)

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01/06/2016

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5

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

2-Amino-1-Methyl-6-Phenylimidazo[4,5-b]pyridine, neurotoxicity, heterocyclic aromatic amines, N hydroxylation, LRRK2 gene

Research Abstract
? DESCRIPTION (provided by applicant): The causes of most Parkinson’s disease (PD) cases are unknown, ~90% are ‘sporadic’, ~10% are attributed to inheritance. Environmental factors,

including pesticides and solvents, have long been suspected, but no toxicant has been convincingly identified. Most cases are thought to arise from gene -environment interactions. A specific example is leucine-rich repeated kinase 2 (LRRK2), a large multi-domain protein with an unknown endogenous function. Numerous LRRK2 mutations cause PD. However, incomplete penetrance in humans and heightened sensitivity to dopaminergic (DA) neuron toxicants in animals expressing mutations suggest the importance of gene-environment interactions. Mounting data from the Cannon laboratory and others suggests that heterocyclic aromatic amines (HAAs) are neurotoxic and associated with neurodegenerative diseases, including PD. HAAs have been primarily investigated as carcinogens in laboratory animals and as potential human carcinogens. HAAs are formed during high temperature meat and poultry cooking. Thus, chronic HAA exposure through diet may be much more common and occur at higher levels than for many environmental toxicants. This proposal tests the hypothesis that: 2-Amino-1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP), the most mass abundant HAA in cooked meats and poultry, exhibits selective dopaminergic neurotoxicity by a newly proposed mechanism of neurotoxic action through N-hydroxylation, a metabolite in common with PhIP's mediated genotoxicity. Our data suggests that mechanistic studies on PhIP neurotoxicity are critical to understanding a potential role in PD. The major goals of this proposal are to: 1) Characterize PhIP-mediated neurotoxicity in vivo; 2) Determine if PhIP exposure potentiates pathology in animals expressing mutated (G2019S) LRRK2 (the most common genetic cause of PD); 3) Identify key mechanism(s) of PhIP-mediated DA-selective neurotoxicity through examination of whether N-hydroxylation is a key pathogenic event, and by assessing the propensity of N-oxidized PhIP metabolites to broadly form adducts with major biomolecules. Modifications and adduct formation in specific PD-implicated proteins will also be examined. Success of this project will lead to several major advances. 1) Identification of a possible causative factor: PhIP is a common toxicant produced in cooked meats and may be consumed in higher doses than rarely encountered known DA toxicants; 2) Creation of a new gene-environment interaction model utilizing the most common PD causing-mutation and a compound to which humans are widely exposed; 3) New PD mechanisms: mechanistic studies would likely identify novel pathogenic pathways that may be therapeutic targets; 4) Prompt follow-up epidemiological and biomarker studies. In summary, using both in vivo and in vitro systems, we will carefully characterize PhIP-induced neurodegeneration and identify mechanisms of DA neurotoxicity. If PhIP exposure is proven to have a causative role in PD, then recommendations can be provided to the public because PhIP exposure can be mitigated by changes in cooking methods.

Lay Summary

PUBLIC HEALTH RELEVANCE: Parkinson's disease (PD) is a debilitating neurological disease, with most cases caused by unknown factors. This proposal investigates a ubiquitous genotoxicant, 2-amino–1-methyl-6-phenylimidazo[4,5-b]pyridine (PhIP) that is formed during the cooking of meats, poultry, and fish as a possible PD-relevant toxicant. Investigating mechanisms of how PhIP can induce neurotoxicity and pathology relevant to PD may increase our understanding of the disease process and lead to new lines of research on prevention and therapeutic approaches.

Further information available at:

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Investments > €500k

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United States of America

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