Role of Mitochondria-Targeted CYP2D6 in Chemical Toxicity

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USA

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Role of Mitochondria-Targeted CYP2D6 in Chemical Toxicity

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05/09/1985

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3

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

CYP2D6 gene, Isoquinolines, Cytochromes, Mitochondria, Toxic effect

Research Abstract

? DESCRIPTION (provided by applicant): In addition to its well established microsomal (mc), human CYP2D6 is also targeted to mitochondria (mt). The main objective of this application is to investigate the roles of mt-targeted CYP2D6 in the metabolism of environmental, and/or, dietary

neurotoxins N-methyl-Isoquinolines (n-me-IQs) and N-methyl-ß-carbolines (N- me-BCs) in inducing neurotoxicity using state of the art iPSC derived neurons and novel transgenic mouse models. Results with stable expression cell lines show that mt-CYP2D6 actively metabolizes MPTP, a known neurotoxin to toxic MPP+ which is implicated in Parkinson's disease. Primary neurons from WT mice and cultured neuro-2 neurons expressing mt-CYP2D6 are sensitive to MPTP toxicity while neurons from CYP2D6 locus knockout (KO) mice and mock transfected neuro-2 neurons are resistant to MPTP. Human CYP2D6 plays critical roles in the metabolism and activation of large number of drugs used in human therapy. Furthermore, the hepatic mitochondrial contents of these CYPs in some cases exceed the mc- contents. This competing renewal application is based on the hypothesis that mt-CYP2D6 plays distinctive adverse roles in drug metabolism, ROS production, neuronal toxicity. We propose to use novel experimental models to further investigate the paradigm-setting observation on the possible role of mt-CYP2D6 in inducing neuronal dysfunction and Parkinson-like syndrome in humanized mice using the following three aims: Aim 1 proposes to define the role of mtCYP2D6 in N-me-BCs-, and N-me-IQ-mediated neuronal damage using dopaminergic neurons generated by iPSC from genetically modified fibroblasts. Metabolism of neurotoxins in reconstituted CYP2D6 and MAO-B enzyme systems and also iPSc neurons expressing mt- and mc-CYP2D6 and metabolite characterization by LC-MS method will be pursued. Co-culturing of neurons with astrocytes from control and MAO-B (null) mice will also be used to assess the contribution of the two enzyme systems. Neuronal function will be tested by C2+ pulses and action potential. Aim 2 is designed to establish the in vivo role of mitochondria-targeted CYP2D6 in neurotoxin-induced Parkinson syndrome. We will use mouse models expressing mt- and mc-CYP2D6 in CYP2D cluster KO mice, which mimic the human brain CYP2D6 expression pattern, for investigating the in vivo effects of N-me-BCs-, and N-me-IQ in inducing idiopathic Parkinson syndrome. Behavioral, cognitive and locomotor function will be studied in treated animals and correlated with biochemical lesions in mid brain (mesencephalon, substantia nigra) and with the levels of cationic metabolites. Aim 3 proposes translational studies with brain tissues from patients with sporadic PD and familial LRRK2 PD and age matched controls. The brain contents of neurotoxins will be analyzed by LC-MS method and correlated with mt-CYP2D6 levels, neuronal pathology (lewy body) and a-synuclein levels in substantia nigra (pars compacta), amygdala and posterior putamen to correlate with severity and disease staging. Both biochemical analysis of brain tissue fractions and immunohistochemical analysis of marker proteins will be carried out. This study is likely to identify mt-CYP2D6 level as a marker for sporadic PD.

Lay Summary
PUBLIC HEALTH RELEVANCE: CYP2D6 is involved in the metabolism of multitude of drugs used in human medicine. The objective of this proposal to establish its role in dietary and environmental neurotoxins (Isoquinolines and ß-carbolines) induced Parkinson's disease would be a paradigm shift in our understanding of human PD and likely to identify novel therapeutic targets.

Further information available at:

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Investments > €500k

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United States of America

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Parkinson's disease & PD-related disorders

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2016

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N/A

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