Developmental Factors for Reducing Dopamine Loss in Primate Models of PD & Aging

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Principal Investigators

ELSWORTH, JOHN D

Institution

YALE UNIVERSITY

Contact information of lead PI
Country

USA

Title of project or programme

Developmental Factors for Reducing Dopamine Loss in Primate Models of PD & Aging

Source of funding information

NIH (NINDS)

Total sum awarded (Euro)

€ 2,134,641.28

Start date of award

01/06/2016

Total duration of award in years

5

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

Paraoxonase-2, UCP2 protein, dopaminergic neuron, Primates, Dopamine

Research Abstract

? DESCRIPTION (provided by applicant): In normal human brain the population of midbrain dopaminergic neurons falls by about 3-5% every decade, while in Parkinson's disease (PD) this decline is much greater. This inexorable loss of dopamine (DA) innervation to forebrain regions has been firmly linked with declines in both motor and cognitive functions. Despite knowing that oxidative stress is a key conspirator in the loss of DA neuron function in PD and aging, there are no treatments to halt the attrition of DA neurons. Part of this problem is due to the inadequacy of animal models. Adult DA neurons are very susceptible to the parkinsonian-like oxidative stress exerted by either MPTP or methamphetamine (METH), but our group has demonstrated that for a restricted period early in life, the primate brain is remarkably resistant to such damage. This provides a new neuroprotection model for DA neurons, possessing ""built-in"" resilience to oxidative damage. The existence of this window of protection against MPTP or METH cannot be explained by altered drug levels, or by immaturity of key transporters or enzymes necessary for the toxic effect of the drugs. The goal of this project is to understand the factors and mechanisms shielding young primate DA neurons from oxidative stress and use this knowledge to provide protection to DA neurons at the later vulnerable stages of life. This approach promises to be successful as it relies on reinstating extant anti-oxidant mechanisms, rather than attempting to protect DA neurons using drugs that may manipulate biochemical signaling non-physiologically. We have identified 2 potential ""juvenile protection factors"" that are preferentialy expressed in the young primate brain and have strong anti-oxidant properties; uncoupling protein-2 (UCP2) and paraoxonase-2 (PON2). One aim tests the hypothesis that UCP2 plays a major role in mitigating the level of mitochondrial reactive oxygen species and subsequent damage to young DA neurons, and that 5? adenosine monophosphate-activated protein kinase (AMPK) activity regulates UCP2. Another aim examines the protection against induced oxidative stress in adult DA neurons that is achieved by using novel agents to activate UCP2 expression in vivo. Less is known about PON2 than UCP2, and the final aim will test hypotheses about its regulation and its role in protecting young primate DA neurons against oxidative stress damage, and will also examine to what extent up-regulation of PON2 expression in the adult affords protection against in vivo oxidative stress in DA neurons. In addition, we will pursue our data on male-female differences in expression of these juvenile protection factors in primate brain, as this may relate to the lower incidence of PD in female subjects and also provide new ways to induce protection in DA neurons. This proposal will pursue these novel directions using biochemical, histochemical, and pharmacological studies in vervet monkeys. The timing of critical milestones in developing DA neurons display important species differences, so these primate studies have particular translational relevance. This research is expected to stimulate new approaches to prevent the occurrence or progression of DA-dependent age-related disorders.

Lay Summary

PUBLIC HEALTH RELEVANCE: Dopamine neurons in brain are known to be particularly susceptible to damage from oxidative stress, and the ensuing deficiency in dopamine neuron function has been implicated in a number of brain disorders. However, early in life, primate dopamine neurons are naturally protected from oxidative stress; the proposed research will increase understanding of the factors responsible for this resistance and use this knowledge to test novel approaches for preventing the loss of dopamine neurons that occurs with aging and in conditions such as Parkinson’s disease. Thus, the proposed research is relevant to the missions of NIA and NICHD as it is expected to lead to novel treatment strategies and so reduce the burden of neurological and psychiatric disorders.

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