Interactions between testosterone and oxidative stress in dopamine neurons

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Country

USA

Title of project or programme

Interactions between testosterone and oxidative stress in dopamine neurons

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NIH (NINDS)

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01/07/2015

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4

The project/programme is most relevant to:

Parkinson's disease & PD-related disorders

Keywords

Testosterone, dopaminergic neuron, Oxidative Stress, Parkinson Disease, gender difference

Research Abstract

? DESCRIPTION (provided by applicant): Two common risk factors for the development of Parkinson’s disease (PD) are oxidative stress and male gender. It is unclear how these

conditions increase the risk for PD in men. Our data suggests that the major male sex hormone, testosterone (T), is involved in mediating this gender difference. This is of concern as T therapy use has increased 3-fold in aging men just this past decade, yet we know little about how T impacts brain vulnerability to age-related disorders. In this proposal, we will investigate the rol of T on oxidative stress generation in substantia nigral dopamine neurons, which are lost during PD progression. T and oxidative stress are hypothesized to cooperatively increase PD progression. Both T and oxidative stress affect key features of PD pathology, including NADPH oxidases and ?-synuclein accumulation. We postulate that an interaction between T and oxidative stress increases PD pathogenesis through cell signaling pathways that regulate these aspects of PD pathology. To investigate these hypotheses, we propose three aims. In Aim 1, we will determine whether a G-protein coupled receptor mediates T induced oxidative stress generation in a dopaminergic cell line and an early stage PD animal model. In Aim 2, we will investigate if T increases oxidative stress by activating NADPH oxidases, key enzymes involved in oxidative stress generation, in a dopaminergic cell line and early stage PD animal model. Finally, in Aim 3 we will characterize the effects of T on oxidative stress generation in an advanced stage PD animal model. These three aims will allow us to examine the effects of T and oxidative stress on dopaminergic neuronal function from early stage to advanced stage PD. Completion of our studies will mechanistically define interactions between T and oxidative stress and how they promote PD progression in men. Further, our studies will address the NIH Institute of Medicine’s recommendation for more research on T therapy in aging men.

Lay Summary
PUBLIC HEALTH RELEVANCE: The proposed research is relevant to public health because it will contribute to understanding the clinical risk factor of male gender in oxidative stress-associated pathologies, such as Parkinson’s disease. The proposed research is relevant to NIH’s mission, since it may lead to the development of therapeutic strategies aimed at decreasing the neurotoxic effects of androgens, such as testosterone, in oxidative stress-associated diseases. Further, this project addresses the NIH Institute of Medicine’s recommendation for more research on testosterone therapy in aging men.

Further information available at:

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Investments > €500k

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