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Evaluation of rotenone mediated α-synuclein spreading and neurotoxicity in α-synuclein PFF induced animal model of Parkinson's disease.

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Background. Parkinson's disease (PD) is the second most prevalent progressive neurodegenerative disorders after Alzheimer's disease. It affects more than 10 million people worldwide, with cases rising rapidly within UAE as well. It is characterized by a variety of motor symptoms like tremors, bradykinesia (slowness in movement), postural instability etc. which occur because of the selective loss of dopaminergic neurons in a region of the brain called substantia nigra (SNc), affecting the patient's quality of life (QoL). While the exact cause of neuronal loss remains unknown, the histopathological signature of PD is the presence of intraneuronal aggregates of α-synuclein protein known as Lewy bodies. Mounting evidence indicate the propagation of α-synuclein via cell-to-cell transfer in a prion-like fashion. We are investigating whether rotenone, an environmental mitochondrial toxin (pesticide) has any role in enhancing the propagation of α-synuclein and produce Lewy body like pathology and neurotoxicity.

Methods. Human α-synuclein PFF seeds are injected into mouse (C57BL6) striatum by stereotaxic surgery, after which rotenone (2.5mg/kg.body-weight) is administered intraperitoneal once daily for four consecutive weeks. Animals are sacrificed twenty-four hours after the last injection for immunohistochemical analysis.

Results. Our preliminary immunofluorescence analysis suggests that rotenone (2.5mg/kg.body weight) enhances the spreading of endogenous synuclein in the cortex and SNc area. We observed a decrease in the staining intensity for Dopamine transporter in striatal brain sections and a decrease in the number of TH immuno-positive neurons in the SNc of the experimental group (PFF + Rotenone) as opposed to the control (PFF + Vehicle). It is noteworthy to point that delivery of the same dose of rotenone alone does not cause TH neuronal loss or synuclein spreading.

Conclusions. Our results indicate that administration of above-mentioned dose of rotenone causes enhancement of α-synuclein spreading and neurotoxicity, and provides a foundation for the development of a robust PD animal model replicating the pathological processes underlying PD. The PFF+Rotenone mouse is expected to reflect the etiology of sporadic PD such as the underlying interaction between genetic and environmental factors involved. Such

a model system would be beneficial in identifying therapeutic targets that respond to α-syn pathology, thereby aiding in the development of effective treatment strategies for PD patients and improving their QoL.

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