Antioxidant and neuroprotective actions of IGF-II against glucocorticoid-induced toxicity in dopaminergic neurons

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The neurodegenerative Parkinson's disease (PD) affects 1–3% of the population aged over 65. A wide range of pathways and mechanisms are involved in its pathogenesis, such as oxidative stress, mitochondrial dysfunction, inflammation and neuronal glucocorticoid-induced toxicity, which ultimately produce a progressive loss of nigral dopamine neurons. Insulin-like growth factor II (IGF-II) has shown antioxidant and neuroprotective effects in some neurodegenerative disorders. Therefore, our aim was to study IGF-II protective effects against oxidative damage on a cellular combined model of PD and mild to moderate stress, based on corticosterone (CORT), an endocrine response marker to stress, and the dopaminergic neurotoxin 1-methyl-4-phenylpyridinium (MPP+).

The dopaminergic neuronal cell line SN4741 (RRID:CVCL_S466) derived from mouse substantia nigra were exposed to 200 μM MPP+, 0.5 μM CORT or both, with or without 25 ng/mL IGF-II, for 2.5 or 6 h. Cell viability, oxidative stress parameters, mitochondrial and dopamine markers and intracellular signaling pathways were evaluated.

The administration of MPP+ or CORT individually led to cell damage compared to control situations, whereas the combination of both drugs produced very considerable toxic synergistic effect. IGF-II counteracts the mitochondrial-oxidative damage, protecting dopaminergic neurons from death and neurodegeneration. IGF-II maintained the tyrosine hydroxylase expression and promotes PKC activation and nuclear factor (erythroid-derived 2)-like 2 antioxidant response in a glucocorticoid receptor-dependent pathway, preventing oxidative cell damage and maintaining mitochondrial function.

This work revealed the potential neuroprotective role of the hormone IGF-II in a cell model of PD aggravated by mild to moderate hormonal stress. IGF-II capacity to protect nigral dopamine neurons against mitochondrial-oxidative damage induced by CORT and MPP+ was demonstrated. Thus, IGF-II is a potential therapeutic tool for prevention and treatment of PD patients suffering mild to moderate emotional stress.

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