

The Role of BDNF/PI3K/AKT/Nrf2 Signaling in Nicotine's Protective Effects Against MPTP-Induced Parkinson's Disease

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Parkinson's disease (PD) is characterized by progressive loss of dopaminergic neurons in the substantia nigra, where oxidative stress and apoptosis play central roles. Epidemiological evidence suggests that nicotine may exert neuroprotective effects, but the molecular mechanisms remain incompletely understood. This study investigated whether nicotine mitigates MPTP-induced neurotoxicity in mice through modulation of the BDNF/PI3K/AKT/Nrf2 signaling pathway.

Male BALB/c mice were divided into control, nicotine, MPTP, and MPTP+nicotine groups. Histological analysis revealed that nicotine significantly reduced MPTP-induced neuronal pyknosis and preserved tyrosine hydroxylase-positive dopaminergic neurons. Biochemical assays showed that nicotine attenuated MPTP-induced increases in malondialdehyde, lactate dehydrogenase, and lactate/pyruvate ratio, while restoring complex I activity and antioxidant enzyme activities (SOD, CAT, GPx, GR). Western blotting demonstrated that nicotine reversed MPTP-induced suppression of phosphorylated PI3K, AKT, and Nrf2, and shifted apoptotic signaling toward survival by increasing Bcl-2 and reducing Bax and Bad.

Importantly, nicotine restored BDNF levels in the substantia nigra, and ex vivo experiments confirmed that nicotine upregulated BDNF via $\alpha 7$ nicotinic acetylcholine receptor activation. These findings suggest that nicotine confers neuroprotection by enhancing BDNF-mediated activation of the PI3K/AKT/Nrf2 axis, leading to improved antioxidant defenses and anti-apoptotic signaling.

In conclusion, nicotine mitigates MPTP-induced dopaminergic neurodegeneration via BDNF/PI3K/AKT/Nrf2 signaling. While nicotine's addictive properties limit its therapeutic use, selective targeting of nicotinic pathways may represent a promising strategy for disease-modifying interventions in PD.