Metformin Ameliorates 3-Nitropropionic Acid-Induced Huntington Disease-Like Symptoms in Rats: Modulation of Oxidative Stress and Motor Dysfunction

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Abstract

Huntington's disease (HD) is a hereditary neurodegenerative disorder characterized by motor dysfunction and progressive cognitive impairment. To experimentally model HD-related neurodegeneration, the neurotoxin 3-nitropropionic acid (3-NP) is widely used. 3-NP irreversibly inhibits succinate dehydrogenase (SDH) in the mitochondrial respiratory chain, inducing selective striatal degeneration, energy failure, oxidative stress, and motor deficits, thereby closely replicating the clinical and neuropathological features of human HD. This investigation assessed the neuroprotective potential of metformin against 3-NP-induced HD-like pathology in rats. Forty rats were allocated into four groups (n = 10/group): control, metformin, 3-NP, and 3-NP plus metformin. 3-NP was administered at 10 mg/kg/day for 30 days, while metformin was given at 150 mg/kg/day from day 10 for three weeks. Behavioral, neurochemical, molecular, and histopathological assessments were performed. 3-NP administration induced marked locomotor and coordination deficits, excitotoxic glutamate elevation, and dopamine depletion. At the molecular level, 3-NP depleted glutathione (GSH), glutathione peroxidase 4 (GPX4), nuclear factor erythroid 2-related factor 2 (Nrf2), and markedly elevates malondialdehyde (MDA), lipid peroxidation products. Metformin co-administration significantly reversed all of these alterations, restoring Nrf2 signalling which led to enhanced antioxidant defences by increasing GPX4, GSH, and reducing MDA. The present study investigated the potential neuroprotective effects of metformin against 3-NP-induced Huntington-like neurodegeneration, with particular emphasis on its modulation of oxidative stress-related pathways, including the Nrf2/GSH/GPX4 signalling axis, lipid peroxidation, and antioxidant associated mediators.

Keywords

Huntington disease, Metformin, 3-NP, Nrf2, Oxidative stress.