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International Conference on

Parkinson's, Huntington's & Movement Disorders

April 17-18, 2019 | Frankfurt, Germany

Pharmacological correction of Mitochondrial Dysfunction in rotenone model of Parkinson's disease: potential participation of P53, NF κB and Nrf2

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Mitochondrial dysfunction has been widely implicated in the neuronal degeneration in Parkinson's disease (PD). Mitochondria-targeted protective compounds that prevent or minimize a wide range of mitochondrial defects constitute new therapeutic strategies in the prevention and treatment of such degeneration. The antioxidant mexidol (2-ethyl-6-methyl-3-hydroxypyridine succinate) is used in clinical practice as a neuroprotector due to its positive influence on the brain energetic metabolism and free radical processes. However, its application as mitochondria-targeted agent to prevent or treat of PD had not been studied yet. We have used rotenone long-term administration as a rat model of PD to investigate in brain mitochondrial oxidative stress intensity, protein expression/activity of antioxidant enzymes-manganese superoxide dismutase (MnSOD), glutathione peroxidase (GPx), and antiapoptotic Bcl-2 as well as protein expression of their upstream regulators: P53, Nrf2 and NF-kB. Rotenone intoxication induced an increase in ROS formation, lipid peroxidation, H2O2 production and a decrease in GSH/GSSG ratio, mitochondrial aconitase activity as well as disorders in mitochondrial antioxidant status (reduced MnSOD, GPx activities/protein content and mRNA expression). In parallel with P53 mitochondrial translocation, we found a decrease in Bcl-2 protein level, an enhance in nuclear accumulation of the phosphorylated NF κB p65 protein. Under the action of rotenone with mexidol, there was demonstrated a reduction in oxidative stress biomarkers, elevation of antioxidant capacity by an increase in protein expression of Nrf2 and its targets (MnSOD and GPx). In brain mitochondria Mexidol interrupted apoptotic cascade by lowering of P53 protein accumulation as well as increasing Bcl-2 protein content. Simultaneously we registered some decline in NF κB p65 protein level in nuclear extracts of brain cells. The efficacy of mexidol determined in the rotenone model of PD may be explain by its ability to influence on mitochondrial redox status and in that way modulate many signaling pathways in brain cells.

Speaker Biography

Olga Gonchar is a senior researcher, Department of Hypoxia, Bogomoletz Institute of Physiology National Academy of Sciences of Ukraine, and she studied mechanisms of correction of tissue hypoxia by common use of biomembrane stabilizators and antioxidants; studied the methods of adaptation to hypoxia (high altitude stay and intermittent hypoxia) and their use in medicine and sports; studied the genetic and epigenetic mechanisms of the oxygen-dependent cell processes regulation under adaptation to hypoxia and oxidative stress; experimental and clinical (Parkinson's disease and Diabetes mellitus) investigation of mitochondrial dysfunction development under hypoxia and oxidative stress.

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