Bioactive Sphingolipids in Experimental Model of Oxidative Stress Evoked by 1-methyl-4-phenylpyridinium (MPP+).

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Sphingolipid signaling pathways have been implicated in many critical cellular events, including neurotransmission, synaptic function, cells survival, proliferation and death. Sphingosine kinases (SK1/2) are conserved enzymes, crucial for sphingolipids metabolism. They phosphorylate sphingosine to sphingosine-1-phosphate (S1P), an bioactive molecule, which acts as a primary and secondary messenger. S1P binds to 5 receptors and plays essential role in neural signal transduction under physiological and various pathological conditions. This bioactive sphingolipid is critical for neurogenesis during embryonic development, its regulates neurite shape and several neuronal function, including neurotransmitter release. Although growing evidence suggests important role of SK1/2 and S1P in neurodegenerative disorders including ischemia, inflammation and Alzheimer's Disease, till now disturbances of sphingolipids homeostasis in Parkinson Disease (PD) remain unknown. Our study try to explain the role of SK1/2 and S1P in molecular mechanism of cell survival and death in model of oxidative stress evoked by neurotoxin 1-methyl-4-phenylpyridinium (MPP+), compound widely used in experimental model of PD.

Our data presented that MPP+ evokes death of human neuroblastoma cells SH-SY5Y in time and concentration dependent manner. Reduced level of SK1 protein was detected in SH-SY5Y cells after 24h exposure to MPP+ comparing to control. However S1P pretreatment enhanced survival of these cells and protein level of SK1 comparing to MPP+ treated cells. Also inhibitor of ERK1/2 kinase - U0126 increased by 20% SH-SY5Y cell viability after 24h of MPP+ incubation. Our data indicated that MPP+ evoked neuronal death is mediated by SK1/2 inhibition and altered sphingolipids signaling. These molecular events lead to caspase dependent apoptotic cells death and PARP-1 degradation. Summarizing our results presented the alteration of sphingolipid biostat in experimental model of PD and suggested that stimulation of S1P receptor can offer novel protective strategy in this disorder.

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