Guanosine Protects human Neuroblastoma SH-SY5Y cells Against Mitochondrial Oxidative Stress by Inducing Heme Oxigenase-1 via PI3K/Akt/GSK-3β pathway.

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Oxidative stress is implicated in cell death induced by distinct neurotoxic situations such as glutamate-, β-amyloid-, or hydrogen peroxide-induced cytotoxicity. Guanosine exerts neuroprotective effect in the central nervous system by stimulation of the phosphatidylinositol-3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) cell survival pathways. Heme-oxygenase (HO-) is an antioxidant enzyme. HO-1 is induced in response to a variety of stress-inducing pathological conditions. In this study, we investigated the possible neuroprotective effect of guanosine against oxidative stress induced by mitochondrial activity disruption, due to the blockade of mitochondrial complexes I and V with the combination of rotenone plus oligomycin-A (rot/oligo) and the putative signaling pathway involved in guanosine-evoked neuroprotection. SHSY-5Y cells exposure to rot/oligo for 24 hours decreased cell viability (62%) and increased reactive oxygen species (ROS) production. Guanosine incubated concomitantly with rot/oligo abolished rot/oligo-induced cell death and ROS production in a concentration dependent manner. The neuroprotection afforded by guanosine was not abolished by a MEK inhibitor (PD98059) or by a PKC inhibitor (cheleritrine). Otherwise, when the PI3K pathway was inhibited by LY294002, neuroprotection as well as guanosine ability to reduce rot/oligo-induced ROS production were abolished. Additionally, guanosine increased p-AKT and p-GSK3-β levels. Guanosine is able to promote an increase in the amount of HO-1 in SHSY-5Y cells. Up-regulation of HO-1 was prevented by LY294002, indicating that the PI3K pathway is participating in the induction of this antioxidant enzyme. These results point out to guanosine as an effective pharmacological intervention in neurological diseases which involves oxidative stress-induced cell death.

**Key words:** Guanosine, Neuroprotection, Reactive oxygen species, Akt phosphorylation, Heme oxygenase-1.

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