ATTENUATION OF LPS-INDUCED APOPTOSIS IN NGF-DIFFERENTIATED PC12 CELLS VIA NF-ΚB PATHWAY AND REGULATION OF CELLULAR REDOX STATUS BY AN OXAZINE DERIVATIVE

N. Ansari¹, F. Khodagholi¹, M. Amini², F. Shaerzadeh¹

¹Neuroscience Research Center, Shahid Beheshti University of Medical Sciences, ²Department of Medicinal Chemistry, Faculty of Pharmacy, and Drug Design & Development Research Center, Tehran University of Medical Sciences, Tehran, Iran

Introduction: Neuronal cell death due to apoptosis is a common characteristic of neurodegenerative diseases. This pathway can be triggered by a variety of cytotoxic stressors, such as lipopolysaccharide (LPS), which induce activation of executioner caspases and other signaling cascades that ultimately lead to apoptotic destruction of the cells. LPS also induces activation of nuclear factor-κB (NF-κB), a redox-sensitive transcription factor.

Aims: In the present study, we evaluated neuroprotective and anti-apoptotic effects of 2-ethoxy-4,5-diphenyl-1,3-oxazine-6-one, EDPOO, against LPS-induced oxidative stress in PC12 cells and also determined its mechanism of action.

Methods: Cells were treated with 10 nM, 100 nM and 1 µM of EDPOO, followed by adding LPS (1 mg/ml). The extent of apoptosis was assessed by MTT test, acridine orange/ethidium bromide staining, and determination of Bax, Bcl-2 and caspase-3 levels. Nuclear levels of transcription factors, Nrf2 and NF-κB, were determined by western blot analysis.

Results: We found that EDPOO exerts its neuroprotective effect through the upregulation of heat shock proteins Hsp-70 and Hsp-32. EDPOO also modulates nuclear levels of Nrf2 and NF-κB, transcription factors that are activated by intracellular reactive oxygen species and/or mediators generated due to chemical exposure of cells. Pretreatment of cells with this oxazine derivative also increases γ-GCS level, as well as antioxidant enzyme activities (SOD and CAT), in a dose-dependent manner.

Conclusions: We provided documentation of neuroprotective effect of a synthetic 1,2-diaryl oxazine, EDPOO, against LPS-induced oxidative stress in PC12 cells. Neuroprotective effect of this compound could represent a promising approach for treatment of neurodegenerative diseases.