

Orphan nuclear receptors in drug discovery for Parkinson's disease

M. Jodeiri^{1,*}, K. Ghaedi¹, A. Ghoochani², M. Peymani², A. Kiani Esfahani², S. Rahgozar³, M. Nourbakhshnia³, M. Nasre Esfahani²

¹*Department of Biology, School of Science, University of Isfahan and Department of Reproduction and Development Reproductive Biomedicine Center. Royan Institute for Animal Biotechnology, ACECR, Isfahan, I.R. Iran.*

²*Department of Reproduction and Development Reproductive Biomedicine Center. Royan Institute for Animal Biotechnology, ACECR, Isfahan, I.R. Iran.*

³*Department of Biology, School of Science, University of Isfahan, Isfahan, I.R. Iran.*

Background and Aims: Parkinson's disease (PD) is a progressive neurodegenerative movement disorder that results primarily from the death of dopaminergic neurons in the substantia nigra. The present study was designed to explore the orphan nuclear receptors role as therapeutic agents in this disease. Peroxisome Proliferator Activated Receptor γ (PPAR γ) and Nur Related Protein 1 (Nurr1) agonists were used because they have therapeutic roles and can be act as novel drug discovery for improvement Parkinson's disease treatment.

Methods: In this study we used Pheochromocytoma Cells (PC12) as an in vitro model of Parkinson's disease. These cells were treated with various concentration of MPP+ (50-500 μ M), MPP+ caused the death of PC12 cells in a time- and dose-dependent manner. GW1929 (PPAR γ agonist) and 6-mercaptopurine (Nurr1 agonist) were acted as neuroprotective agents in in this experiment. At the next step several functional characteristics of these cells such as IL-6, VMAT2, TH, ROS generation, mitochondrial outer membrane potential and NF-kB were evaluated.

Results: In Parkinson's disease model cells, several genes expressions like TH, DAT, NF-kB, and other markers such as ROS production and mitochondrial outer membrane potentials were changed. However, in combination of GW1929 and 6-mercaptopurine applications, we improved these markers expressions and generations compare with untreated cells. These agonists combination exerted synergetic effects and improved better than before strategies when these agonists were used alone.

Conclusions: The search for ligands of orphan nuclear receptors has led to the discovery of many signaling pathways and has revealed a direct link of nuclear receptors to human conditions such as neurodegenerative diseases. Identification of compounds with selective activities for specific orphan receptors is of clinical and pharmacological importance and promises a bountiful harvest in the near future.

Keywords: Parkinson's disease; PPAR γ ; Nurr1; PC12 Cells