Molecular Pharmacological Studies on Dopaminergic Neuroprotection and Regeneration

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Parkinson's disease (PD) is an age-related neurodegenerative disorders and is characterized by bradykinesia, resting tremor, muscular rigidity, and postural instability. Neuropathological hallmarks in PD brains are massive and selective loss of dopamine (DA) neurons and the formation of Lewy bodies in the substantia nigra (SN) pars compacta. L-Dihydroxyphenylamine (L-DOPA, levodopa) substitution is still considered the gold standard of antiparkinsonian drug therapy. However, there is little information that has been available on neuroprotective and regenerative therapies.

Recently, we have found that pramipexole and talipexole (D_2/D_3-dopaminergic agonists) inhibit DA neurotoxin-induced production of reactive oxygen species (ROS), cytosolic release of cytochrome *c* and apoptotic cell death. In addition, treatment with these drugs induces enhancement of anti-apoptotic Bcl-2 expression and inhibition of aggregation of α-synuclein and cytochrome *c*. Interestingly, recent study suggests that pramipexole treatment delays the progression of early PD symptom.

Chronic oral administration of rotenone (30 mg/kg, over 28 days) induced specific nigrostriatal DA neurodegeneration, motor deficits and increase of α-synuclein expression in the surviving DA neurons. Administration of 4-phenylbutyrate, a chemical chaperone, inhibited rotenone-induced neural death and decreased the protein aggregation.

On the other hand, we investigated the transplantation strategy for PD by assessing whether double-transplants of mouse embryonic stem (ES) cell-derived neurons in the striatum (ST) and SN, or ST and subthalamic nucleus (STN) induce functional recovery in rat hemi-parkinsonian models. The study indicates that both the involvement of ST as a place of transplantation and the number of ES cell-derived neurons are essential factors for efficacy on PD animal model.