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Modulation of cell viability by L-DOPA *via* the ERK and JNK-c-Jun systems in dopaminergic neuronal cells

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Parkinson's disease (PD) is caused by the degeneration of dopaminergic neurons in the substantia nigra-striatal region. L-3,4-dihydroxyphenylalanine (L-DOPA) is the most frequently prescribed drug for controlling the symptoms of PD. However, the high levels of L-DOPA lead to cell death by generating reactive oxygen species in dopaminergic neuronal and PC12 cells. Recently, it has been reported that the intracellular cyclic AMP levels increased in response to cytotoxic levels of L-DOPA and multiple treatments with non-toxic L-DOPA (MT-LD) reduced dopamine biosynthesis in PC12 cells. In this study, the effects of L-DOPA on dopaminergic neuronal cell death *via* the ERK1/2 and JNK1/2-c-Jun systems were investigated. In PC12 cells, MT-LD (20 μM) induced cell survival *via* PKA-transient ERK1/2 activation, and then it induced differentiation *via* the Epac-sustained ERK1/2 system. MT-LD initially enhanced c-Jun phosphorylation (Ser73), but later induced c-Jun phosphorylation (Ser63) and c-Jun expression, which subsequently led to the cell death process. In the 6-hydroxydopamine-lesioned rat model of PD (6-OHDA lesion), L-DOPA administration (10 mg/kg) protected against neurotoxicity through c-Jun phosphorylation (Ser73) for 1–2 weeks. However, L-DOPA administration (10 or 30 mg/kg) showed neurotoxicity through c-Jun phosphorylation (Ser63) and c-Jun expression *via* ERK1/2 phosphorylation for 3–4 weeks. In addition, gynosaponin TN-2 from ethanol extract of *G. pentaphyllum* (GP-EX) protected against L-DOPA-induced neurotoxicity in PC12 cells. Gypenosides and GP-EX also showed the protective effects on long-term L-DOPA administration in 6-OHDA lesion. Our data indicate that chronic treatment of L-DOPA causes neurotoxicity *via* the cyclic AMP-ERK1/2-c-Jun system in dopaminergic neuronal cells and GP-EX might serve as an adjuvant agent for PD.

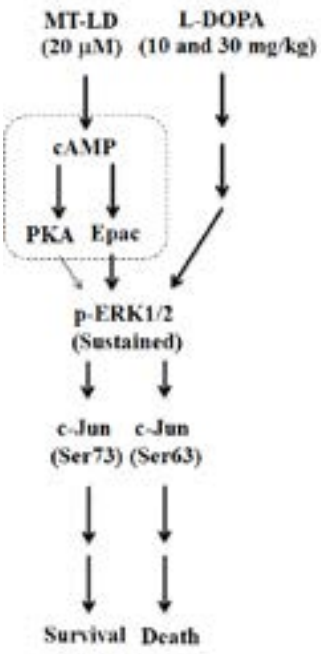

Figure1: Multiple L–DOPA treatment (20 μM) induced c–Jun phosphorylation at Ser63 via Epac–dependent sustained ERK1/2 in PC 12 cells, which led to cell death. These results were validated by long term L-DOPA administration in a rat model of Parkinson's disease.

Recent Publications

1. Shin K S, Park H J, Park K H, Lee K S, Jeong S W, Hwang B Y, Lee C K and Lee M K (2018) Effects of gynosaponin TN-2 on L-DOPA-induced cytotoxicity in PC12 cells. Neuro Report 29(1):1-5.
2. Zhao T T, kim K S, Shin K S, Park H J, Kim H J, Lee K E and Lee MK (2017) Gypenosides ameliorate memory deficits in MPTP-lesioned mouse model of Parkinson's disease treated with L-DOPA. BMC Complementary and Alternative Medicine 17(1):449.
3. Park K H, Shin K S, Zhao T T, Park H J, Lee K E and Lee M K (2016) L-DOPA modulates cell viability through the ERK-c-Jun system in PC12 and dopaminergic neuronal cells. Neuropharmacology 101:87-97.
4. Shin K S, Zhao T T, Park K H, Park H J, Hwang B Y, Lee C K and Lee M K (2015) Gypenosides attenuate the development of L-DOPA-induced dyskinesia in 6-hydroxydopamine-lesioned rat model of Parkinson's disease. BMC Neuroscience 16:23.
5. Shin K S, Zhao T T, Choi H S, Hwang B Y, Lee C K and Lee M K (2014) Effects of gypenosides on anxiety disorders in MPTP-lesioned mouse model of Parkinson's disease. Brain Res 1567:57-65.

Biography

Myung Koo Lee, Professor of College of Pharmacy, Chungbuk National University (CNU), Korea, has completed his Ph.D. from the Faculty of Pharmaceutical Sciences, Kyushu University (Japan) in 1988 and postdoctoral studies from Cornell University Medical School in 1991-1992. He has served as a dean at the College of Pharmacy, CNU in 2002-2004, and as a president at the Society of Korean College of Clinical Pharmacy in 2010-2012. He has also served as the director at the Research Center for Bioresource and Health, CNU in 2001-present. He has published more than 210 papers in journals.

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