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.
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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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