Abstract

Project Code: RMU5180010

Project Title: Induction of cellular defense system in drug abused-induced neuronal cell degeneration: A functional study of the molecular mechanism

Investigator: Associate Professor Banthit Chetsawang

Research Center for Neuroscience, Institute of Molecular Biosciences, Mahidol University, Salaya, Nakhonpathom 73170

E-mail Address: grbcs@mahidol.ac.th

Project Period: 3 years (15 May 2008 - 14 May 2011)

Parkinson's disease is a progressive neurodegenerative disorder, associated with the selective loss of dopaminergic neurons in the substantia nigra pars compacta. Methamphetamine (METH) is a potent psychostimulant drug that may cause neuronal cell degeneration. In this study, we investigated an important role of calpain-dependent cascades in methamphetamine-induced toxicity in human dopaminergic neuroblastoma SH-SY5Y cultured cell lines. In addition, the protective effect of melatonin against METH-induced calpain-dependent death pathway was also investigated. The results of the present study show that METH significantly decreased cell viability and tyrosine hydroxylase phosphorylation in SH-SY5Y cultured cells. Melatonin reversed the toxic effect of METH by inducing cell viability. In addition, melatonin was able to restore the reduction in mitochondrial function and phosphorylation of tyrosine hydroxylase in SH-SY5Y treated cells. An induction of calpain expression and activity but a reduction of calpain inhibitor (calpastatin) protein levels were observed in SH-SY5Y cells-treated with METH but these effects were diminished by melatonin. Taken together, increase in phosphorylation of c-Jun and Bax/Bcl-2 ratio was observed in METH-treated cells. Calpastatin can reverse the toxic effect of METH by increasing cell viability, reducing phosphorylation of c-Jun and Bax/Bcl-2 ratio in METH-treated cells. These results implicated calpain-dependent death pathways in the processes of METH-induced toxicity and also indicated that melatonin and calpastatin have the capacity to reverse this toxic effect in SH-SY5Y cultured cells.

Keywords: methamphetamine, calpain, calpastatin, melatonin, neuroprotection, dopamine cells, cell death