

## N-acetyl serotonin protects neuronal cell death induced by oxidative stress via elevation of TrkB/CREB/BDNF and Akt/Nrf2 pathways

Mee Ree Kim

Chungnam National University, South Korea

Recently, N-acyl serotonin, present in the intestine, has been reported to exert neuroprotective action against oxidative stress by inducing antioxidant enzymes. However, the mechanism for neuroprotective action of N-acetyl serotonin (NAS) as a precursor of melatonin is not clarified. In this study we focused on the suppressive effect of N-acetyl serotonin on glutamate-induced apoptosis in HT-22 cells, and then examined the molecular mechanism for its anti-apoptotic action. For this purpose, we performed flow cytometry, immunoblotting analyses and antibody-mediated neutralization. When HT-22 cells were preincubated with NAS prior to glutamate treatment, NAS dose-dependently reduced apoptotic bodies and recovered mitochondrial potential in glutamate-treated HT-22 cells. NAS dose-dependently inhibited oxidative stress-induced cell death in HT-22 cells. Moreover, NAS suppressed glutamate-induced apoptosis by suppressing expression of pro-apoptotic factors such as AIF, Bax, calpain, cytochrome c and cleaved caspase-3, whereas it enhanced expression of Bcl-2, an anti-apoptotic factor. In addition, NAS improved phosphorylation of tropomyosin-

related kinase receptor (TrkB) and cAMP response element-binding protein (CREB) as well as expression of brain-derived neurotrophic factor (BDNF), whereas the inclusion of each inhibitor of JNK, p38 or Akt neutralized the neuroprotective effect of NAS, but not that of ERK. Meanwhile, NAS dose-dependently reduced the level of reactive oxygen species, and enhanced the level of glutathione in glutamate-treated HT-22 cells. Moreover, NAS not only increased expression of heme oxygenase-1, NAD(P)H quinone oxidoreductase-1 and glutamate-cysteine ligase catalytic subunit, but also enhanced nuclear translocation of NF-E2-related factor-2. Separately, NAS at 30 mg/kg suppressed scopolamine-induced memory impairment and cell death in CA1 and CA3 regions in mice. In conclusion, NAS shows actions of antioxidant and anti-apoptosis by activating TrkB/CREB/BDNF pathway and expression of antioxidant enzymes in oxidative stress-induced neurotoxicity. Therefore, such effects of NAS may provide the information for the application of NAS against neurodegenerative diseases.

### Biography

Mee Ree Kim has completed her PhD from Seoul National University and is a Visiting Professor at Wisconsin-Madison University, Department of Toxicology. She is the former President of Korean Food Related Academic Association. She has published more than 120 papers in reputed journals and has been serving as an Editorial Board Member of reputed such as Journal of Medicinal Food.

mrkim@cnu.ac.kr

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