

## **SULFORAPHANE INHIBITS 6-HYDROXYDOPAMINE-INDUCED APOPTOSIS BY UPREGULATION OF MEK/ERK AND PI3K/AKT IN HUMAN NEURONAL CELLS**

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Natural sources can provide candidate compounds with potential therapeutic effects in neurodegenerative disorders including Parkinson's and Alzheimer's diseases. Isothiocyanates (ITCs), present in cruciferous vegetables, are known as cancer chemopreventive agents and strong inducers of phase II detoxification enzymes. Among the various ITCs, sulforaphane shows interesting ability to decrease aging-related CNS inflammation in rats. In this study, we investigated the mechanism basis of the neuroprotective potential of sulforaphane in a neuronal cell model of Parkinson. An experimental approach using a pulse/chase treatment of SH-SY5Y cells with 6-OHDA (100  $\mu$ M), a Parkinson specific neurotoxin to determine neuronal apoptosis, has been applied. Pre-treatment of SH-SY5Y cells with sulforaphane (0.6-2.5  $\mu$ M) showed a significant dose-dependent inhibition of apoptotic events, such as mitochondrial activity loss, translocation of phosphatidylserine and DNA fragmentation increase. These highlights resulted from a increase of glutathione levels (3-fold) and other phase II detoxication and antioxidant enzymes, such as glutathione-S-transferase (2.6-fold), glutathione reductase (1.4-fold) and NADPH-quinone reductase (1.5-fold). Interestingly, our results also demonstrated that treatment of neurons with sulforaphane after 6-OHDA treatment showed a significant decrease of apoptotic events. These neuroprotective effects were abolished by PI3K (LY294002) and MEK1 (PD98059) inhibitors. In particular, the treatment of SH-SY5Y with sulforaphane induced an increase of phospho-ERK1/2 (1.6-fold) and -Akt (1.8-fold) levels. Taken together, these results demonstrate that sulforaphane inhibitory effect on 6-hydroxydopamine-induced apoptosis appears to be, at least partly, due to the activation of PI3K/AKT and MEK/ERK pathways. In conclusion, these results encourage further research in Parkinson animal models to explore the potential profile of sulforaphane as novel neuroprotective agent.