【P-58】

Nitric Oxide induces activation of NF-E2-related transcription factor (Nrf2) through S-nitrosylation of Keap1 in PC12 cells.

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Nitric oxide (NO) exerts bifunctional effects on cell death. While high concentrations of NO induce cell death by various mechanisms, a low concentration of NO exhibits a protective effect against cell death. However, the molecular mechanism underlying protective effect of NO is not clearly understood. One of the transcription factors that confer cellular protection from oxidative stress is NE-E2 related transcription factor2 (Nrf2), which remains sequestered in cytoplasm by forming inactive complex with Klech like protein (Keap1). Previous studies have suggested that various stimuli induces the dissociation of Nrf2 from Keap1 in cytosol by activating several upstream kinases, such as MAPK, PI3K/Akt, and PKC, thereby facilitating nuclear translocation of Nrf2. The modification of cysteine residue of Keap1 hasalso been proposed as a possible mechanism of Nrf2 activation. Since S-nitrosylation that can modify the function or activity of target proteins through NO-mediated modification of cysteine, we attempted to investigate whether the protective effect of NO against cell death is mediated through Nrf2 activation via nitrosylation of cysteine residue of Keap1. Our present study revealed that treatment of PC 12 cells with a NO donor SNAP activated Nrf2 at 1 hr, when none of the above mentioned upstream kinases were activated, and NO could form S-nitrosylation of Keap1 at the same treatment period. We, therefore, suggest that Nrf2 can be activated by S-nitrosylation of Keap1 upon exposure of PC 12 cells to nitric oxide donor.

Keyword : Nrf2, Keap1, S-nitrosylation, PC12 cells