The Nrf2 Pathway as a Novel Target for Neuroprotective Strategies

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Neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease, are defined by the progressive loss of specific neuronal cell populations and are associated with protein aggregates. A common feature of these diseases is extensive evidence of oxidative stress (OS), which might be responsible for the dysfunction or death of neuronal cells that contributes to disease pathogenesis. OS manifests its toxic effects through a variety of different pathways, which provide a number of potential therapeutic strategies. Induction of Nuclear factor E2-related factor 2 (Nrf2) by drugs has become a potential therapeutic target for neurodegenerative diseases that are known to involve oxidative damage (Calkins et al., 2009; Joshi et al., 2012). Nrf2 is a transcription factor known to induce expression of a multitude of redox status, detoxification, cytoprotective and anti-inflammation genes. Many new Nrf2 inducers have been found from a variety of sources, including natural products and derivates, clinical drugs and endogenous compounds. Among the inducers, the isothiocyanates (ITCs), present in cruciferous vegetables, have gained attention as potential neuroprotective compounds with indirect antioxidant properties involved in the activation of Nrf2. In this context, we studied the ability of ITCs to prevent and/or counteract the redox status impairment and cell death induced by different neurotoxins, including amyloid-beta peptide and 6-hydroxidopamine, in various models of neurons and glial cells. Based on experimental approaches, we found that the pre-treatment of various cells with ITCs showed inhibitory effects of neurotoxin-induced reactive oxygen and nitrogen species formation, inflammation processes and neuronal death through the translocation of Nrf2 into the nucleus and subsequent antioxidant endogenous molecule and enzyme induction. Interestingly, the ability of ITCs to exert neuroprotective and anti-inflammatory effects through the induction of Nrf2 was also recorded during or after the treatment with neurotoxin, suggesting that Nrf2-controlled target genes are involved in neuronal and glial cell survival. Taken together, these findings show that the pleiotropic neuroprotective effects of ITCs could be ascribed to its peculiar ability to active the Nrf2 pathway. Further, these studies suggest that Nrf2 pathway inducers may be a promising class of drug for new neuroprotective strategies. *Supported by MIUR-FIRB project RBAP11HSZS (2011) and Fondazione del Monte di Bologna e Ravenna (Italy)*

Calkins et al. (2009). *Antioxid Redox Signal.* 11, 497-508.
Joshi et al. (2012). *Recent Pat CNS Drug Discov.* 7, 218-229.