Combinations between sulforaphane and levodopa for Parkinson's disease treatment: neuroprotective effects in *in vitro* and *in vivo* models

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Parkinson's disease (PD) is a common neurodegenerative movement disorder, caused by dopaminergic neuron death in the substantia nigra. In this regard, dopamine mediated oxidative stress may also contribute to progressive dopaminergic neurodegeneration. Levodopa, a metabolic precursor of dopamine, represents the main treatment route for motor symptoms associated with PD. However, a spectrum of conflicting data suggests that high concentrations of levodopa may damage dopaminergic neurons due to oxidative stress, whilst other data suggest that low concentrations of levodopa itself may induce low levels of oxidative stress, which in turn stimulates endogenous antioxidant mechanisms and neuroprotection. Recent studies demonstrate the ability of various compounds to reduce the neuronal death occurring in neurodenegerative diseases through the activation of the transcriptional factor Nrf2, a master regulator of detoxification, antioxidant, anti-inflammatory and cytoprotective mechanisms. Among Nrf2 inducers, we evaluated the neuroprotective effects of sulforaphane isothiocyanate combined with different concentration levels of levodopa in an in vitro model of dopaminergic neurons. We found that the pre-treatment of neurons with the combination of sulforaphane and low concentrations of levodopa showed synergistic inhibitory effects of H_2O_2-induced neuronal death through the translocation of Nrf2 into the nucleus and subsequent antioxidant endogenous molecule induction, such as glutathione. Further, we recorded the ability of sulforaphane to prevent or counteract the neuronal death elicited by high concentrations of levodopa, suggesting that the Nrf2 pathway is involved in dopaminergic neuron survival. Moreover, sulforaphane also showed the ability to counteract the levodopa-induced dyskinesia in a rat model of PD. Taken together, these findings suggest that the Nrf2 pathway may be a pharmacological target to ameliorate the ratio risk/benefit associated with levodopa therapy.