Activation of the Nrf2 Pathway Prevents Mitochondrial Dysfunction Induced by Caspase-3 Cleaved Tau: Implications for Alzheimer's Disease

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Abstract

Alzheimer's disease (AD) is characterized by memory and cognitive impairment, accom-panied by the accumulation of extracellular deposits of amyloid β-peptide (Aβ) and the presence of neurofibrillary tangles (NFTs) composed of pathological forms of tau protein. Mitochondrial dysfunction and oxidative stress are also critical elements for AD development. We previously showed that the presence of caspase-3 cleaved tau, a relevant pathological form of tau in AD, induced mitochondrial dysfunction and oxidative damage in different neuronal models. Recent studies demonstrated that the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) plays a significant role in the antioxidant response promoting neuroprotection. Here, we studied the effects of Nrf2 activation using sulforaphane (SFN) against mitochondrial injury induced by caspase-3 cleaved tau. We used immortalized cortical neurons to evaluate mitochondrial bioenergetics and ROS levels in control and SFN-treated cells. Expression of caspase-3 cleaved tau induced mitochondrial fragmentation, depo-larization, ATP loss, and increased ROS levels. Treatment with SFN for 24 h significantly prevented these mitochondrial abnormalities, and reduced ROS levels. Analysis of Western blots and rt-PCR studies showed that SFN treatment increased the expression of several Nrf2-related antioxidants genes in caspase-3 cleaved tau cells. These results indicate a potential role of the Nrf2 pathway in preventing mitochondrial dysfunction induced by pathological forms of tau in AD.

Author keywords

Alzheimer's disease; Antioxi-dant; Mitochondrial dysfunction; Neuroprotection; Nrf2; Sulforaphane; Tau