Research Week 2020

NRF2 activating dimethyl fumarate improves mitochondrial function, reduces oxidative stress and enhances synaptic plasticity a neuronal model of synucleinopathy

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Keywords

alpha-synuclein, antioxidant, NRF2, mitochondrial function, synaptic density

Abstract

Lewy bodies comprised of aggregated alpha synuclein (αSyn) protein are a pathological hallmark of the Parkinson's disease (PD). Increased oxidative stress, mitochondrial dysfunction and synaptic loss are also features of the PD brain. NRF2 regulates the antioxidant response pathway and has been shown to be neuroprotective in many models of neurodegenerative diseases. Dimethyl fumarate (DMF) is a NRF2 activator that is FDA approved for treatment of multiple sclerosis making it an attractive candidate to be repurpose for use in PD. Here we investigate the antioxidant, mitochondrial and synaptic effects of DMF in neurons isolated from the A53T αSyn mouse model of synucleinopathy.

Embryonic hippocampal neurons were isolated from A53T αSyn mice as well as wild-type (WT) littermates. Cells were treated with either DMF or the NRF2 inhibitor ML385 and mitochondrial function was evaluated along with markers of synaptic plasticity and oxidative stress.

Relative to WT neurons, αSyn neurons had impaired dendritic arborization and DMF treatment restored this deficit. Increased reactive oxygen species and impaired mitochondrial function were also seen in the αSyn neurons and DMF treatment likewise improved these endpoints. Inhibition of NRF2 with ML385 resulted in a greater impairment of mitochondrial function, further increases in oxidative stress and a greater reduction in markers of synaptic density in αSyn neurons.

These data show that NRF2 activation can reduce oxidative stress, improve mitochondrial function and restore synaptic plasticity in neurons isolated from A53T αSyn mice whereas NRF2 inhibition exacerbates these endpoints. Taken together these data suggest that NRF2 may be a viable therapeutic target in PD.