NRF2 activation improves mitochondrial function, synaptic plasticity, and ameliorates oxidative stress in A53T α-synuclein hippocampal neurons

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Background
- Cognitive impairment is a common symptom of Parkinson’s Disease (PD), yet it is often overlooked as a target for therapeutic intervention.
- Increased oxidative stress and diminished mitochondrial function contribute to both motor and cognitive symptoms.1
- Activation of the transcription factor nuclear factor erythroid 2-related factor 2 (NRF2) has been shown to induce antioxidant response, improve mitochondrial health and be neuroprotective models PD.2
- There is a functional haplotype in the human NRF2 promoter that is associated with decreased risk and delayed onset of PD.3

Methods
- The A53T Syn mouse overexpresses human A53T α-synuclein and develops profound α-synuclein pathology around 6-9 months of age and cognitive deficits at 11-12 months of age. Mitochondrial dysfunction occurs between 11-14 months of age.4
- Embryonic hippocampal neurons were isolated from A53T Syn mice and their wild type (WT) litter mates. Neurons were in culture for 12, 19, and 26 days for analysis.
- A53T Syn neurons have impaired dendritic arborization relative to WT that worsened over time.
- NRF2 activity alters dendritic arborization in A53T Syn neurons 26 days in culture to the same levels as WT neurons. DMF treatment also increased arborization in WT neurons.
- NRF2 inhibition also impaired arborization in WT neurons.
- NRF2 activity through treatment with DMF attenuated deficits in dendritic arborization in A53T Syn neurons 26 days in culture to the same levels as WT neurons. DMF treatment also increased arborization in WT neurons.
- NRF2 inhibition by treatment with the inhibitor ML385 exhibited exacerbated the deficit in arborization in A53T Syn neurons at 19 days in culture. NRF2 inhibition also impaired arborization in WT neurons.

Results
- NRF2 activation by DMF restored deficits in mitochondrial respiration and attenuated increases in ROS while NRF2 inhibition with ML385 exacerbated these endpoints.

Conclusions and future directions
- Modulating NRF2 activity significantly affects mitochondrial function, oxidative stress, and synaptic plasticity.
- Future studies are needed to confirm these effects in vivo.
- Improving mitochondrial function, reducing oxidative stress and increasing synaptic density are all associated with improved cognitive function suggesting that NRF2 activation may be a viable therapeutic strategy for improving cognitive function in PD.
- DMF is already FDA approved for use in multiple sclerosis making it an attractive candidate for repurposing for use in PD patients.

References
Gureev, et al. (2019). Neurochemical research, 44(10), 2273–2279.

Conclusion
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