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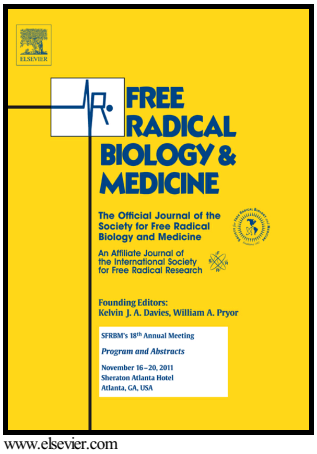

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PII: S0891-5849(18)30165-5
DOI: https://doi.org/10.1016/j.freeradbiomed.2018.04.002
Reference: FRB13702

To appear in: *Free Radical Biology and Medicine*

Received date: 20 February 2018
Revised date: 1 April 2018
Accepted date: 2 April 2018

Cite this article as: Sonal Agrawal, Julia Fox, Baskaran Thyagarajan and Jonathan Fox, Brain mitochondrial iron accumulates in Huntington's disease, mediates mitochondrial dysfunction, and can be removed pharmacologically, *Free Radical Biology and Medicine,* https://doi.org/10.1016/j.freeradbiomed.2018.04.002

Brain mitochondrial iron accumulates in Huntington's disease, mediates mitochondrial dysfunction, and can be removed pharmacologically

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Abstract

Mitochondrial bioenergetic dysfunction is involved in neurodegeneration in Huntington's disease (HD). Iron is critical for normal mitochondrial bioenergetics but can also contribute to pathogenic oxidation. The accumulation of iron in the brain occurs in mouse models and in human HD. Yet the role of mitochondria-related iron dysregulation as a contributor to bioenergetic pathophysiology in HD is unclear. We demonstrate here that human HD and mouse model HD (12-week R6/2 and 12-month YAC128) brains accumulated mitochondrial iron and showed increased expression of iron uptake protein mitoferrin 2 and decreased iron-sulfur cluster synthesis protein frataxin. Mitochondria-enriched fractions from mouse HD brains had deficits in membrane potential and oxygen uptake and increased lipid peroxidation. In addition, the membrane-permeable iron-selective chelator deferiprone (1 μM) rescued these effects *ex-vivo*, whereas hydrophilic iron and copper chelators did not. A 10-day oral deferiprone treatment in 9-week R6/2 HD mice indicated that deferiprone removed mitochondrial iron, restored mitochondrial potentials, decreased lipid peroxidation, and