

Scientists find excess mitochondrial iron, Huntington's disease link

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University of Wyoming Professor Jonathan Fox, in the Department of Veterinary Sciences, leads research that has found a link between excess mitochondrial iron and Huntington's disease. Credit: University of Wyoming

Scientists at the University of Wyoming have found that mice engineered to have Huntington's disease (HD) have an over-accumulation of iron in their mitochondria.

The research identifying a pathway for the neurodegenerative disease also has relevance to understanding related disorders such as Parkinson's disease, Alzheimer's and Lou Gehrig's disease, says Jonathan Fox, a professor in UW's Department of Veterinary Sciences.

The article, "Brain mitochondrial iron accumulates in Huntington's disease, mediates mitochondrial dysfunction, and can be removed pharmacologically," was published online in the journal *Free Radical Biology and Medicine*.

Others involved in the research were postdoctoral scientist Sonal Agrawal, in the Fox laboratory in the UW College of Agriculture and Natural Resources, and Baskaran Thyagarajan, an associate professor in the School of Pharmacy.

HD is an inherited genetic disorder that causes neurons to die in brain areas important for movement and cognition. Symptoms become progressively worse and include involuntary movements, changes in behaviors and cognitive decline, Fox says. There are no treatments that delay disease progression.

The Fox team experimented with a drug that crossed the mitochondrial membrane and removed [excess iron](#), or it may bind with the iron and make it nontoxic.

Mitochondria are the key site of energy production and also have many other functions critical for cell health and survival, says Fox, who participates in the Neuroscience Program at UW.

Mitochondria are a main site of oxygen use in cells. The Fox lab members collaborated with Thyagarajan, who has expertise in evaluating mitochondrial functions, to measure oxygen consumption in mouse HD mitochondria. They found oxygen deficits in HD mitochondria with

unusual amounts of iron. The research suggests iron accumulation in mitochondria interferes with respiration and oxygen uptake, and that this may contribute to neuronal malfunction and death.

Excess iron in cells can be detrimental, but adequate iron supplies also are essential to many cell functions.

"A wide variety of different proteins require iron," says Fox, who also teaches in UW's Wyoming, Washington, Alaska, Montana and Idaho (WWAMI) medical program. "Probably the best known is hemoglobin. The protein requires iron to transport oxygen properly. Iron metabolism is central for normal cell function."

The flip side is that too much can be toxic. Cells are challenged to provide iron for functions that require it but also prevent toxic accumulations.

"In HD, we think that normal iron metabolism is disrupted, and these adverse effects of iron are allowed to continue," Fox says.

He says, however, that this pathway is not the only factor that drives HD.

"There are many other pathways that have been shown to be important," he says. "We're saying this is an important part of the picture."

Fox says the research helps lay the foundation for developing drug therapies.

Fox's research involves studying mainly mouse models of HD; however, the researchers also obtain human brain tissue collected at autopsies and supplied by a National Institutes of Health-supported brain bank.

"Mouse HD models are great for studying the human disease but are not

perfect," he says. "Whenever possible, we try to verify the findings in animal models are actually present in the human condition. We were fortunate enough to obtain human brain tissue and show similar changes to the HD mice in the current study."

The scientists also are interested in environmental factors that can affect HD. Their latest paper adds to previous work showing high iron intake by HD mice early in life promotes the disease in adulthood.

Still, he says the researchers in his lab are interested in pursuing two areas.

They want to further understand the mechanisms by which iron causes mitochondria dysfunction in HD. The other, broader aspect is that HD is part of a group of related diseases, and "while they don't have identical mechanisms, they do have some important features in common," he says.

"So, we are interested in determining if mitochondrial [iron](#) accumulation occurs in models of Parkinson's, Alzheimer's and brain aging. We are interested in expanding beyond HD mouse models," he says.

More information: Sonal Agrawal et al, Brain mitochondrial iron accumulates in Huntington's disease, mediates mitochondrial dysfunction, and can be removed pharmacologically, *Free Radical Biology and Medicine* (2018). [DOI: 10.1016/j.freeradbiomed.2018.04.002](#)

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