Research Highlight #2003

Dr. Steven M. Graves
University of Minnesota

Monoamine oxidase enzymes contribute to mitochondrial oxidant stress and methamphetamine-induced neurodegeneration

Dr. Steven Graves is interested in investigating the pathogenesis of neurodegenerative diseases and drug-induced neurotoxicity. More specifically, he explores methamphetamine-induced neurodegeneration and the implications this has for developing neurodegenerative diseases such as Parkinson's Disease. Methamphetamine increases cytosolic dopamine, which is metabolized by monoamine oxidase (MAO) enzymes. Historically, it was believed that cytosolic dopamine would auto-oxidize into a reactive quinone or be deaminated by MAO enzymes resulting in the generation of free electrons that were thought to contribute to cytosolic hydrogen peroxide production. However, during Dr. Graves' work with Dr. D. James Surmeier at Northwestern University using multiphoton microscopy, they discovered that the electrons generated by MAO metabolism of dopamine were not released into the cytosol; rather, these electrons were transferred to the mitochondrial intermembrane space, thereby supporting the electron transport chain but also increasing oxidant stress.

> "Using a genetically encoded biosensor, we saw that this increase was not causing cytosolic stress that we could see. What was happening was the cytosolic dopamine did get metabolized by monoamine oxidase enzymes, but those enzymes are tethered to the mitochondria. And what actually happened is that the electrons that were generated, were getting transferred into the intermembrane space of the mitochondria. This means there's a reason for the monoamine oxidase to be tethered to the mitochondria—it's basically an on-demand fuel source for the electron transport chain. When the cytosolic dopamine gets metabolized, electrons are provided to the electron transport chain to provide bioenergetic support. However, this process also increased mitochondrial stress."

This novel discovery provided a fresh insight on the impact of dopamine metabolism in brain cells. Using the Ultima multiphoton microscope, Graves was also able to see where exactly within the neuron that this process was occurring.

> "One of the interesting things is that we saw this occurring out in axons, but not in the soma. Without the resolution of multiphoton imaging and incorporation of genetically encoded biosensors, we would have been limited in our ability to interrogate subcellular compartments, such as axons in live ex vivo brain slices."

The localization of MAO within the mitochondria, has a clear biological purpose—providing bioenergetic support. However, Graves also commented on the potential drawbacks of causing mitochondrial oxidant stress in neuronal populations that are vulnerable to neurodegeneration, such as substantia nigra pars compacta dopamine neurons. Dr. Graves found that chronic administration of methamphetamine to mice resulted in degeneration of substantia nigra pars compacta dopamine neurons and that monoamine

ABOUT THE RESEARCHER

Dr. Steven M. Graves is an Assistant Professor in the Department of Pharmacology and part of the Medical Discovery Team on Addiction at the University of Minnesota. Dr. Graves received his Bachelor of Science degree from the University of Michigan in Biopsychology and Cognitive Sciences and Ph.D. degree from Rush University Medical Center in the Department of Pharmacology. Before joining the University of Minnesota in 2018, Dr. Graves completed his postdoctoral training with Dr. D. James Surmeier and held a position as a Research Assistant Professor at Northwestern University in the Department of Physiology, now the Department of Neuroscience.

Website: Visit Dr. Graves Lab website

Recent Publications

Graves, S. M., et al. (2019). Dopamine metabolism by a monoamine oxidase mitochondrial shuttle activates the electron transport chain. *Nature Neuroscience*, 23(1), 15–20. https://doi.org/10.1038/s41593-019-0556-3

Du, Y., Lee, Y. B., & Graves, S. M. (2021). Chronic methamphetamine-induced neurodegeneration: Differential vulnerability of ventral tegmental area and substantia nigra pars compacta dopamine neurons. *Neuropharmacology*, 200, 108817. *Neuropharmacology*, 200, 108817. https://doi.org/10.1016/j.neuropharm.2021.108817

oxidase inhibition, which attenuates methamphetamine-induced mitochondrial stress, was neuroprotective.

> "It provides electrons to the electron transport chain, so you'd have bioenergetic support. But at the same time, there's no such thing as a free lunch, right? The consequence of that is mitochondrial stress, so it's a double-edged sword. With methamphetamine, cytosolic dopamine concentrations are substantially elevated and therefore flood this MAO-mitochondrial system. When you administer meth for protracted periods of time, or basically when you start chronically bullying the mitochondria, then it seems to be a key driver of degeneration."

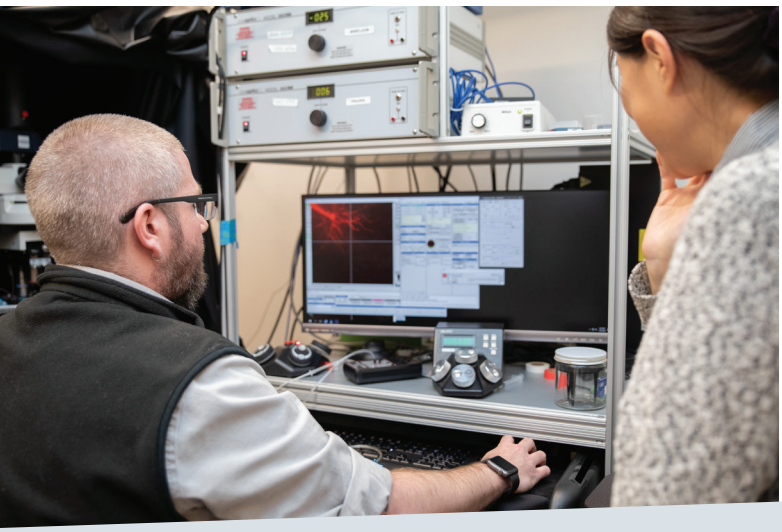
Dr. Graves then shared a metaphor for the relationship between overwhelming the mitochondria and subsequent neurodegeneration.

> "If you think of it as if you rev an engine, that's not bad for an engine. But if you redline it for too long, the engine is going to fail. And that's kind of how I see this monoamine oxidase electron shuttle, it's a good thing in moderation. But if you run that engine too much, then you're just going to push it overboard."

This new understanding of the impact of MAO metabolism on mitochondrial oxidant stress has been transformative to the direction of his research. As a recently minted independent investigator at the University of Minnesota, he is continuing to advance this line of research to investigate other monoaminargic systems. His group recently published their findings in *Neuropharmacology* showing that unlike substantia nigra pars compacta dopamine neurons, ventral tegmental area dopamine neurons are resistant to chronic methamphetamine-induced degeneration despite having the same methamphetamine-induced MAO-dependent mitochondrial stress in axons. Using multiphoton microscopy to again interrogate axonal compartments they attributed this differential vulnerability to the presence of L-type calcium channel-dependent mitochondrial oxidant stress in substantia nigra pars compacta but not ventral tegmental area neurons. Similar to his work centering on MAO inhibition, L-type calcium channel inhibition was also neuroprotective and prevented chronic methamphetamine induced degeneration of substantia nigra pars compacta dopamine neurons. Most recently he has extended this work to locus coeruleus neurons — his group presented data at the 2021 Society for Neuroscience virtual meeting showing that locus coeruleus norepinephrine neurons, like substantia nigra pars compacta dopamine neurons, have methamphetamine-induced MAO-dependent and L-type calcium channel-dependent mitochondrial oxidant stress in axons. As they predicted, they found that locus coeruleus neurons were also vulnerable to chronic methamphetamine-induced neurodegeneration, painting a very similar picture to the vulnerability of catecholaminergic neurons in Parkinson's disease.

> "Right now we have two projects focused on exploring mechanisms of degeneration. One is focusing on methamphetamine-induced neurodegeneration; this was inspired by our findings relating to methamphetamine-induced monoamine oxidase-dependent mitochondrial oxidant stress. We're also investigating the intersection between alcohol abuse and Alzheimer's disease. In both projects we are investigating the role of mitochondria in the degenerative process and how drugs of abuse such as methamphetamine or alcohol might impact the mitochondria, particularly in axonal compartments. Basically, the question is what role is the mitochondria playing in degeneration and how do extrinsic factors such as methamphetamine or alcohol impact the mitochondria? By answering these questions we hope to not just uncover mechanisms that allow us to better understand the process of neurodegeneration and the deleterious consequences of substance abuse but to identify druggable targets that could be advanced to develop efficacious neuroprotective treatments."

By using multiphoton microscopy, Dr. Graves showed that dopamine metabolism by mitochondrially tethered MAO enzymes transfer electrons to the mitochondria, rather than the cytosol, and that this can support electron transport chain activity but at the cost of mitochondrial stress. In vulnerable neuronal populations it seems that engaging this stress mechanism via methamphetamine administration is the tipping point that drives degeneration. A refined understanding of the mechanisms driving drug-induced neurotoxicity and neurodegeneration is important for the development of potential treatments and therapeutics.



"We've been using the two-photon system to examine mitochondrial oxidative stress in different neuronal populations, and different cellular compartments like axonal versus somatic to try and determine mechanisms underlying differential vulnerability of neurons to degeneration from a drug-induced insult."

– Steven M. Graves, Ph.D."

Learn more

To learn more about multiphoton microscopy and Bruker's Ultima multiphoton microscopes, visit www.bruker.com/multiphoton.

Author

Savana Lipps
Bruker, Life Science Writer
Savana.lipps@bruker.com

Bruker Fluorescence Microscopy

Madison, WI • USA
Phone +1.608.662.022

productinfo@bruker.com

Multiphoton Microscopy | See Deeper into Brain Activity

www.bruker.com/Ultima