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Loss of cellular energy leads to neuronal dysfunction in neurodegenerative disease model

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A new study from the Gladstone Institutes shows for the first time that impairments in mitochondria—the brain's cellular power plants—can deplete cellular energy levels and cause neuronal dysfunction in a model of neurodegenerative disease.

A link between mitochondria, energy failure, and neurodegeneration has long been hypothesized. However, no previous studies were able to comprehensively investigate the connection because sufficiently sensitive tests, or assays, were not available to measure ATP (the energy unit of the cell that is generated by mitochondria) in individual neurons.

In the current study, which was chosen as the Paper of the Week in the *Journal of Biological Chemistry*, the scientists created novel assays to more accurately measure the brain's energy production. Using a model of Leigh's disease, a genetically inherited neurodegenerative disorder that affects mitochondria, the researchers tested energy levels in neurons using the new assays. They found that the genetic mutation associated with Leigh's disease compromised ATP levels, and this reduction of ATP was enough to cause significant cellular dysfunction.

"It was always assumed that defects in mitochondria would result in a depletion of energy levels, which would be toxic to neurons," says first author Divya Pathak, PhD, a postdoctoral fellow in the Gladstone Institute of Neurological Disease. "But no one had been able to prove

this because the necessary assays were not available. Now that we've demonstrated the link between impaired mitochondria, a loss of ATP, and neuronal dysfunction, the next step is to see if this connection holds true in conditions like Parkinson's disease and Alzheimer's disease."

Applying their new assay in healthy neurons, the researchers also determined the energy threshold needed to support synaptic vesicle cycling—the process by which brain cells release neurotransmitters to communicate with each other. The scientists blocked glycolysis, another way that cells make ATP, so that the cells had to rely solely on their mitochondria for energy. This allowed the researchers to more accurately assess the contribution of mitochondrial ATP to different steps in the cycle, and how this process goes awry when mitochondria malfunction.

From this exploration, the scientists revealed that bringing the vesicles back up into the cell after they have released their neurotransmitters is the most energy-demanding process. Indeed, in the model of Leigh's disease, the cells did not have enough ATP to complete this step.

The researchers also compared energy levels in boutons—the docks from which neurotransmitters are shipped—with and without mitochondria. Remarkably, there was no difference in energy levels between the two, and both types of boutons had sufficient ATP to support synaptic vesicle cycling. From this, the scientists concluded that under normal conditions, ATP diffuses rapidly from boutons with mitochondria to those without, so that even those boutons lacking mitochondria have sufficient energy to function under normal conditions. They note it will be important to determine if boutons lacking mitochondria will still be able to function properly in diseases that disrupt the distribution of mitochondria.

Senior author Ken Nakamura, MD, PhD, an assistant investigator at the

Gladstone Institute of Neurological Disease, says that conducting this research in both healthy and diseased cells is essential for interpreting the findings. "We really need to understand the basics of cell biology in a normal setting in order to comprehend changes in disease," he explains. "It's worth taking the time to study these underlying biological processes so that we can identify the best therapeutic targets for neurodegenerative disorders."

More information: *Journal of Biological Chemistry*, www.jbc.org/content/290/37/22325

Provided by Gladstone Institutes

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