

# Study connects mitochondria to psychological stress response and species resilience

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Mitochondria. Credit: Wikipedia commons

(Medical Xpress)—Mitochondria are symbiotic organelles that reside in most of the body's cells and power cellular functions. They contain their own DNA, called mtDNA, and they produce adenosine triphosphate (ATP), which transports energy within cells. Mitochondria have a number of additional biological functions, and there is evidence that the mitochondrion influences an organism's integrated response to psychological stress.

Though no rigorous studies have previously examined whether [mitochondria](#) modulate an organism's [psychological stress](#) response, there are three reasons for the hypothesis that they do: First, requirements for ATP must be increased to face stress-induced cellular perturbations. Second, mitochondria generate reactive metabolic intermediates and reactive oxygen species (ROSs) during electron flow, which leads to [oxidative stress](#) in the absence of sufficient antioxidants.

The generation of these constituents is a signal of adaptation, altering gene expression, which means that the stress-induced epigenetic changes observed in the hippocampus could be a result of mitochondrial activity. And third, stress-induced physiological responses like insulin resistance, inflammation and others can be triggered by mitochondrial dysfunction alone. So mitochondria are a likely hub of [stress response](#) and modulation.

Based on this evidence, a group of researchers from the University of Pennsylvania and Rockefeller University hypothesized that abnormal mitochondrial functions would have different modulation effects on an organism's multi-systemic response to psychological stress. They designed a study of this response in mice, and have published their results in the *Proceedings of the National Academy of Sciences*.

The researchers generated mice with ubiquitously expressed mutations in mtDNA genes that decrease the activity of respiratory chain complexes; they also studied mice with genetic deletions in nDNA that impair the transport of ATP from the mitochondrion to the cytoplasm, and that regulate the intramitochondrial redox balance. They studied the impact of these genetic manipulations on physical parameters linked to the restraint of stress.

The authors write, "All investigated neuroendocrine, metabolic, inflammatory, and transcriptional responses were perturbed by at least one of the mitochondrial defects. Notably, each mitochondrial defect produced a unique stress-response signature. Collectively, our results therefore establish that mitochondria impact the nature and magnitude of physiological and molecular responses to a controlled psychological stressor."

In order to be successfully adaptive, organisms mount integrated stress responses across multiple organ systems. The ability to mount appropriate responses to psychological stress is critical for survival, and is thus considered a driver of species evolution. Maladaptive stress response in humans results in chronic stress characterized by specific symptoms, and which ultimately contributes to disease.

"Stressful experiences, on their own, do not cause damage or disease," the authors write. "Rather, it is the organism's responses to stress that have the potential to result in physiological dysregulation and dysfunction, culminating in allostatic load and disease. Our study demonstrates how mitochondria can shape the major stress-response pathways, thereby recalibrating the multisystemic response to psychological stress."

The authors note further that based on this model, it seems that mitochondria lie at the interface of genetic and environmental factors that shape an organism's evolution. They suggest that future research targeting mitochondria can contribute to biological resilience, psychological health, and response to environmental stressors.

**More information:** Mitochondrial functions modulate neuroendocrine, metabolic, inflammatory, and transcriptional responses to acute psychological stress. *PNAS* 2015 ; published ahead of print November 16, 2015, [DOI: 10.1073/pnas.1515733112](https://doi.org/10.1073/pnas.1515733112)

### Abstract

The experience of psychological stress triggers neuroendocrine, inflammatory, metabolic, and transcriptional perturbations that ultimately predispose to disease. However, the subcellular determinants of this integrated, multisystemic stress response have not been defined. Central to stress adaptation is cellular energetics, involving mitochondrial energy production and oxidative stress. We therefore hypothesized that abnormal mitochondrial functions would differentially modulate the organism's multisystemic response to psychological stress. By mutating or deleting mitochondrial genes encoded in the mtDNA [NADH dehydrogenase 6 (ND6) and cytochrome c oxidase

subunit I (COI)] or nuclear DNA [adenine nucleotide translocator 1 (ANT1) and nicotinamide nucleotide transhydrogenase (NNT)], we selectively impaired mitochondrial respiratory chain function, energy exchange, and mitochondrial redox balance in mice. The resulting impact on physiological reactivity and recovery from restraint stress were then characterized. We show that mitochondrial dysfunctions altered the hypothalamic–pituitary–adrenal axis, sympathetic adrenal–medullary activation and catecholamine levels, the inflammatory cytokine IL-6, circulating metabolites, and hippocampal gene expression responses to stress. Each mitochondrial defect generated a distinct whole-body stress-response signature. These results demonstrate the role of mitochondrial energetics and redox balance as modulators of key pathophysiological perturbations previously linked to disease. This work establishes mitochondria as stress-response modulators, with implications for understanding the mechanisms of stress pathophysiology and mitochondrial diseases.

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