Body and mind: Hormones in the brain may explain how exercise improves metabolism

February 2 2021

Credit: Unsplash/CC0 Public Domain

A mitochondrial hormone expressed by cells deep in the brain appears to play a role in improving metabolism and fighting off obesity, according to a new study in mice.

A collaboration between the USC Leonard Davis School of Gerontology and researchers in South Korea has shown how moderate exercise prompts cells in the hypothalamus, the small region within the brain that controls metabolism, to release a hormone called MOTS-c. MOTS-c is a small protein that is encoded in cells' smaller mitochondrial genome, rather than the larger collection of genes in the nucleus, said Changhan David Lee, assistant professor of gerontology at the USC Leonard Davis School and co-senior author of the new study.

Mitochondria, while more commonly known as the energy-producing parts of cells, have in recent years been found to play much bigger roles in health and aging by providing instructions for cellular processes. Subsequent studies by Lee and his colleagues have shown how mitochondrial-encoded MOTS-c interacts with the nuclear genome and regulates cellular metabolism and stress responses.

Stress as a balancing act

The new study also illustrates how stress in the mitochondria can promote healthy metabolism—when kept in careful balance.

Existing research has shown how low-grade stress in mitochondria can promote health and longevity, a phenomenon termed mitohormesis, Lee said. Essentially, while high levels of a stressor such as a toxin can cause major harm, a small amount of a stressor may actually strengthen healthy mitochondrial function.

"As [philosopher Friedrich] Nietzsche once said, 'That which does not kill us makes us stronger,'" Lee remarked.

To examine the effects of mitochondrial stress on metabolism, Lee and colleagues examined mice that were bred to be either partially or completely deficient in a single gene within a specific type of brain cell,

hypothalamic proopiomelanocortin (POMC) neurons. The missing gene, Crif1, controls how cells use proteins encoded by mitochondria.

The mice that were homodeficient in Crif1—meaning that they had no copies of the Crif1 gene at all—experienced severe mitochondrial stress and showed indicators of metabolic problems when they reached adulthood, including weight gain and reduced energy expenditure. In addition, the mice missing Crif1 entirely also had insulin resistance and high blood sugar, much like type 2 diabetes in humans.

However, the mice that were heterodeficient in the Crif1 gene—they could partially express the gene, but not as much as normal mice—experienced mild mitochondrial stress and protection against obesity or insulin resistance. When fed a high-fat diet, the mice missing part of their Crif1 function gained less weight than normal mice on the same diet, even though the former ate more calories. Further study of the mice revealed that their affected neurons expressed both more MOTS-c as well as more beta-endorphin (β-END), a pain-suppressing molecule typically released during exercise.

The mice with mild mitochondrial stress in POMC neurons may have avoided obesity due to the fat tissues within their bodies changing. The researchers noticed that the Crif1 heterodeficient mice display more thermogenesis—the ability to generate heat—and further examination of the fat cells revealed increased amounts of brown fat cells.

Brown fat appears brown because of the presence of more mitochondria versus white fat. In babies, who don't yet have the ability to shiver to keep their bodies warm, their larger proportion of brown fat consumes sugar and white fat to generate energy and produce heat. Scientists are interested in the effects of "browning" fat, or turning white fat into brown fat, as a possible way to address obesity in adults, who typically retain only small pockets of brown fat.

MOTS-c treatment, exercise each give similar benefits

In later experiments, the researchers were able to mimic these changes, including increases in brown fat and thermogenesis, in normal mice by directly administering MOTS-c to the brain..

Tellingly, the same benefits also arose after mice engaged in moderate exercise. The study's findings indicate that the process of balancing mild mitochondrial stress may be a key part of why exercise improves metabolism. The process appears to be mediated by MOTS-c, adding to the body of research supporting the hormone's metabolic involvement.

"Our brain is a control center for a lot of physiological functions," Lee said. "This is a new mechanism of exercise physiology that may provide new venues for future therapeutic development of exercise-mimetics."

Lee and Pinchas Cohen, professor of gerontology, medicine and biological sciences and dean of the USC Leonard Davis School, first described MOTS-c in 2015, along with its role in restoring insulin sensitivity and counteracting diet-induced and age-dependent insulin resistance—effects commonly associated with exercising. In a separate paper published January 20 in *Nature Communication*, Lee, Cohen, and colleagues demonstrated that MOTS-c levels increase upon exercise in humans and, when given to mice, can double the running capacity of young and old animals. These studies raise the possibility of developing drugs to provide the health benefits of exercise to frail or disabled individuals who cannot safely exercise.

The current study indicates that the mitochondrial hormone is not just acting locally within muscle tissues but arising from the brain's headquarters for metabolism, Lee said.

"The question is, 'upon exercise, do mitochondria communicate to your

command center, or do they bypass that and talk straight to the target (peripheral) organs?'" Lee said of the research surrounding MOTS-c's role in exercise and metabolism. "We're showing that it could be both."

More information: Gil Myoung Kang et al. Mitohormesis in Hypothalamic POMC Neurons Mediates Regular Exercise-Induced High-Turnover Metabolism. *Cell Metabolism*. Volume 33, Issue 2, P334-349.E6, February 02, 2021 DOI: 10.1016/j.cmet.2021.01.003

Provided by University of Southern California