Study details how aerobic exercise reverses degenerative process that leads to metabolic diseases

December 7 2020, by Karina Toledo

Experiments with mice and humans showed that exercise training increased the expression in adipose tissue of a key enzyme for the organism's metabolic health, combating the harmful effects of aging and obesity. Credit: Danilo Ferrucci and Bruna B. Brandão

Adipose tissue is not just a simple reservoir of energy for periods of

food scarcity. It contributes significantly to regulation of the metabolism, releasing various molecules into the bloodstream, including microRNAs that modulate the expression of key genes in different parts of the organism, including the liver, pancreas, and muscles.

Research has shown that both aging and obesity can impair the production of these regulatory microRNAs by adipose tissue and favor the development of diseases such as diabetes and dyslipidemia. The good news is that this degenerative process can be reversed by practicing regular aerobic exercise, according to a study published in *Proceedings of the National Academy of Sciences (PNAS)*.

"Experiments with mice and humans have shown that aerobic exercise stimulates expression of an enzyme called DICER, which is essential to the processing of these microRNAs. We, therefore, observed an increase in production of these regulatory molecules by adipose cells, with several benefits for the metabolism," said Marcelo Mori, a professor at the University of Campinas's Institute of Biology (IB-UNICAMP) in the state of São Paulo, Brazil, and one of the principal investigators for the project, which was supported by FAPESP (São Paulo Research Foundation) and conducted in partnership with groups at the University of Copenhagen in Denmark and Harvard University in the United States.

The experiments were performed during the postdoctoral research of Bruna Brasil Brandão, formerly Mori's Ph.D. student and now at Harvard Medical School working as a research fellow in the laboratory of Professor C. Ronald Kahn.

The results showed the occurrence of communication between muscle and adipose tissue during aerobic exercise via signaling molecules secreted into the bloodstream. This exchange of information makes energy consumption by adipose cells more efficient, enabling the metabolism to adapt to exercise and enhancing the performance of the

muscles.

The mice were subjected to a 60-minute treadmill running protocol for eight weeks. As they became fitter, treadmill speed and inclination were increased. At the end, in addition to the improvement in performance, the scientists found a significant elevation in adipocyte levels of DICER expression, which was accompanied by a reduction in body weight and visceral fat.

When they repeated the experiment with mice that were genetically modified not to express DICER in adipose cells, the researchers found that the beneficial effects of aerobic exercise were far smaller. "The animals didn't lose weight or visceral fat, and their overall fitness didn't improve," Mori said. "We also observed that adipose cells used the energy substrate differently in these GM mice than in wild mice, leaving less glucose available for muscles."

In humans, six weeks of high-intensity interval training (HIIT) were sufficient to yield a fivefold increase in the amount of DICER in adipose tissue on average. The effect was observed in both younger volunteers, aged about 36, and older subjects, aged about 63. The response varied considerably between individuals, however, with DICER increasing as much as 25 times in some, and very little in others.

Detailed mechanism

The role of DICER and microRNA processing in adipose tissue was first described in 2012 in an article published in *Cell Metabolism*, reporting a study led by Mori and Khan in collaboration with an international group of researchers. The main finding here was that expression of DICER in the adipose tissue of mice declined as the animals gained weight and that this reduced their lifespan. The study also showed that caloric restriction could reverse the deleterious effects of obesity.

In another study, published in 2016 in the journal *Aging*, Mori and his group showed that caloric restriction in mice prevented the aging-related decline in microRNA production by adipose tissue and the development of type 2 diabetes. In a study reported in 2017 in *Nature*, they proved that the microRNAs produced by adipose tissue entered the bloodstream and acted on distant tissues, regulating gene expression.

"In this latest study we found that aerobic exercise, like caloric restriction, can reverse the drop in DICER expression and microRNA production thanks to the activation of a very important metabolic sensor, the enzyme AMPK [adenosine monophosphate-activated protein kinase]," Mori said.

The sensor is activated, he explained, when the cell consumes ATP (adenosine triphosphate, the molecule that acts as an energy substrate for cells) and creates an energy deficit. In experiments with mice, the researchers found that aerobic exercise activated AMPK in muscle cells and that this somehow induced DICER expression in adipose cells.

"The obvious conclusion is that the effect on gene expression occurs in the same cell in which the energy deficit occurs, which is indeed the case, but here the sensor is also activated in muscles and controls the response that occurs in adipose tissue," he said.

To confirm communication between tissues, the scientists collected blood serum from a trained animal and injected it into a sedentary animal. This "treatment" increased DICER expression in adipose tissue. In another experiment, they incubated cultured adipocytes with serum from trained mice and observed the same effect.

"This finding suggests trained individuals have one or more molecules in their bloodstream that directly induce a metabolic improvement in adipose tissue," Mori said. "If we can identify these molecules, we can

investigate whether they also induce other benefits of aerobic exercise, such as cardioprotection. Moreover, we may think about converting this knowledge into a drug at some stage."

To obtain an even more detailed understanding of the metabolic regulation mechanism, the researchers analyzed all of the thousands of microRNAs expressed in the organism of the trained mice and compared them with those found in sedentary mice.

"We identified a molecule called miR-203-3p, whose expression increases with both training and caloric restriction," Mori said. "We showed that this microRNA is responsible for promoting metabolic adjustment in adipocytes. When muscles use up all their glycogen during prolonged exercise, molecular signals are sent to adipose tissue and miR-203-3p fine-tunes the adipocyte metabolism. We found this metabolic flexibility to be essential to good health as well as performance enhancement."

Absent this modulation, adipocyte consumption of glucose during exercise increases, leaving less energy substrate available to muscles, he added. This can lead to hypoglycemia, one of the main performance limitations for athletes.

"In GM mice that don't express DICER in adipocytes, this conversation between adipose tissue and muscles doesn't happen. It's a model that mimics aging and obesity. So when DICER declines, metabolic health is poor and degenerative processes accelerate" Mori said.

More information: Bruna B. Brandão et al, Dynamic changes in DICER levels in adipose tissue control metabolic adaptations to exercise, *Proceedings of the National Academy of Sciences* (2020). DOI: 10.1073/pnas.2011243117

Provided by FAPESP