NEWS RELEASE 18-APR-2019

Two studies explore whether time of day can affect the body's response to exercise

CELL PRESS

Two papers appearing April 18 in the journal *Cell Metabolism* confirm that the circadian clock is an important factor in how the body responds to physical exertion. The studies focused on different components of exercise, thereby complementing each other. Based on this work alone, it's too early to say when the best time is for you to go for a jog. But at least in the lab, exercise in the evening seems to be more productive, although human lifestyles are much more complicated and so this area of research is only just beginning.

"It's quite well known that almost every aspect of our physiology and metabolism is dictated by the circadian clock," says Gad Asher of the Department of Biomolecular Sciences at the Weizmann Institute of Science, who is senior author of one of the studies. "This is true not only in humans but in every organism that is sensitive to light. We decided to ask whether there is a connection between the time of day and exercise performance."

"Circadian rhythms dominate everything we do," adds Paolo Sassone-Corsi of the Center for Epigenetics and Metabolism at the University of California, Irvine, who is senior author of the other paper. "Previous studies from our lab have suggested that at least 50% of our metabolism is circadian, and 50% of the metabolites in our body oscillate based on the circadian cycle. It makes sense that exercise would be one of the things that's impacted."

Both research teams looked at the association between time of day and exercise performance primarily in mice. Because mice are nocturnal, one thing they had to do was translate mouse timing to human timing, by distinguishing between the active phase and resting phase of the mice rather than using numbers on the clock.

Asher's group started by putting mice in treadmills at different times of day within their active phase. They examined the exercise capacity of mice upon different exercise intensities and regimens and found that overall exercise performance is substantially better (about 50% on average and more in some protocols) in the "mouse evening" (toward the end of their active time) compared to the morning hours. These daily differences were diminished in mice that had mutant clocks--supporting a potential role of the clock in the observed variance in exercise performance.

To identify a potential determinant of daily variance in exercise performance, they applied high-throughput transcriptomics and metabolomics on muscle tissue. The researchers found that in response to exercise in the "mouse evening," there were higher levels of a metabolite called ZMP (5-aminoimidazole-4-carboxamide ribonucleotide). ZMP is known to activate metabolic pathways that are related to glycolysis and fatty acid oxidation through activation of AMPK, which is a master cellular metabolic regulator. Therefore, it is likely to contribute to the increased exercise capacity in the evening. "Interestingly, ZMP is an endogenous analog of AICAR [aminoimidazole carboxamide riboside], a compound that some athletes use for doping," Asher says.

The researchers also studied 12 humans and found similar effects. Overall, the people in the study had lower oxygen consumption while exercising in the evening compared with the morning; this translated to better exercise efficiency.

Sassone-Corsi's team also put mice on treadmills, but they had a different approach. Using high-throughput transcriptomics and metabolomics to look at a wide range of possible factors, they characterized the changes in the mice's muscle tissue that occur in response to exercise. This allowed them to look at processes like glycolysis (which contributes to sugar metabolism and energy production) and lipid oxidation (fat burning).

They found that a protein called hypoxia-inducible factor 1-alpha (HIF-1α) plays an important role and that it is activated by exercise in different ways depending on the time of day. HIF-1α is a transcription factor that is known to stimulate certain genes based on oxygen levels in tissue. "It makes sense that HIF-1α would be important here, but until now we didn't know that its levels fluctuate based on the time of day," Sassone-Corsi says. "This is a new finding."

Based on the work from the UC Irvine team, exercise seemed to have the most beneficial impact on the metabolism at the beginning of the active phase phase (equivalent to late morning in humans) compared with the resting phase (evening).

The researchers note that even though circadian clocks have been conserved throughout evolution, translating the findings to humans is not so straightforward. One reason is that humans have more variation in their chronotypes than mice living in a lab. "You may be a morning person, or you may be a night person, and those things have to be taken into account," Sassone-Corsi says.

###

Cell Metabolism, Ezagouri, Zwighaft, and Sobel *et al*.: "Physiological and Molecular Dissection of Daily Variance in Exercise Capacity" https://www.cell.com/cell-metabolism/fulltext/S1550-4131(19)30141-X DOI: 10.1016/j.cmet.2019.03.012

This study was supported by the European Research Council and an EMBO Young Investigator Award. It was also supported by Fonds de Dotation AGIR pour les Maladies Chroniques and a fellowship from the Placid Nicod Foundation.

Cell Metabolism, Sato *et al*.: "Time of Exercise Specifies the Impact on Muscle Metabolic Pathways and Systemic Energy Homeostasis" https://www.cell.com/cell-metabolism/fulltext/S1550-4131(19)30183-4 DOI: 10.1016/j.cmet.2019.03.013

This study was supported by the Novo Nordisk Foundation, the Swedish Diabetes Foundation, the Swedish Research Council, the National Institutes of Health, INSERM, and the Della Martin Foundation.