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Timing tweaks exercise

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Abstract

Exercise is the elixir of health. However, timing can boost or blunt exercise performance and health benefits. Two complementary studies used transcriptomic and metabolomic tools to dissect how time of day affects the impact of exercise. The findings open new avenues for optimizing timing of physical activity to boost its benefits further.

Any exercise is better than none. However, quality, quantity and frequency of structured exercise are known to have an effect on exercise outcomes[1,2]. With the arrival of circadian science, which suggests that every aspect of physiology shows daily rhythms, the timing of exercise is emerging as a factor that could modulate the outcomes of exercise. Whether it is to maximize athletes' performances or to mitigate cardiometabolic disease, defining the best time of the day to exercise holds great translational potential.

Exercise has several benefits, including improving glucose tolerance and insulin sensitivity and maintaining whole-body circadian rhythms. Many aspects of exercise show time-dependent effects; for example, at low or moderate intensity, exercise performance in humans is higher in late afternoon than in early morning, while intense exercise does not show any time-dependent effects[1]. Exercise performance results from several factors, some of which might be intrinsic to skeletal muscle, while several factors are extrinsic, such as heart rate and body temperature. Therefore, factors contributing to time-dependent effects of exercise probably originate from different tissues. However, circadian clocks are cell autonomous, and the clock components primarily regulate tissue function through modulation of expression of hundreds or thousands of genes in different organs. This characteristic has inspired circadian transcriptome studies to assess the baseline rhythm in gene expression and related circadian rhythms in cellular functions. Two recent studies have gone further in examining both the baseline difference in skeletal muscle at different times and the effect of exercise on muscle gene expression and the metabolome[3,4]. The results indicate that exercise at different times has distinct implications; some might even last beyond 24 h.

When young untrained nocturnal mice were exercised on treadmills at low (45% aerobic capacity) or moderate (55%) levels, the mice completed longer durations when late in their active phase (2 h before morning) than when early in their active phase (2 h after evening).

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Competing interests

S.P. authored "The Circadian Code" for which he collects author royalty. A.C. declares no competing interests.

When mice exercised at high intensities (100% capacity), no difference in exercise performance between early evening or late night was observed[4]. This finding is a mirror image of what is found in humans (described in the previous paragraph)[1]. Interestingly, the difference in exercise capacity is dependent on their circadian clock, as the mice that lack *Per1* and *Per2* (essential components of circadian clocks) do not show time-of-day differences in physical performance in a moderate-intensity exercise protocol. Gene expression and metabolomics analyses of sedentary mice at these two time points confirmed the presence of daily rhythms in pathways known to contribute to exercise performance, including peroxisome proliferator-activator receptor (PPAR), AMPK and hypoxia-inducible factor (HIF)[4].

Similarly, pathways that modulate fuel source metabolism, FoxO, insulin signalling and lipid metabolism rapidly responded to moderate exercise[4]. However, a deeper examination of metabolites and gene expression revealed time-dependent differences in the molecular effect of exercise. Exercise in early evening resulted in incomplete β-oxidation and mitochondria stress. Conversely, activity late at night led to increased levels of phosphorylated AMPK, which activates catabolic pathways and β-oxidation to boost ATP production. This effect is probably mediated through increased levels of 5-aminoimidazole-4-carboxamide ribonucleotide (ZMP), a metabolite from purine histidine biosynthesis and an allosteric activator of AMPK[5]. Although the basal ZMP level does not change between early and late time-active phases, exercise elevates ZMP level >60% more in the late exercise group than in the early exercise group. Exogenous application of the corresponding ribonucleoside analogue (AICAR) improves exercise performance[6]. These molecular changes probably contribute to time-dependent changes in exercise performance.

A complementary study suggested similar changes in gene expression and metabolites in exercising mice[3]. This study compared mice exercising at times when they would naturally sleep, in early morning, or when they would be active, in early evening. In addition to the acute response to exercise, they also monitored metabolites and gene expression changes for up to 24 h after exercise and wholebody energy expenditure for >2 days after exercise. As expected, exercise in the early evening led to increased activation of HIF1α and utilization of glycolysis and lipid oxidation as a fuel source. Even an hour of exercise improved the amplitude of circadian expression of many genes. Therefore, moderate exercise could be a method to sustain a robust circadian rhythm.

Several metabolic changes in response to exercise also modulate the expression or protein levels of circadian clock components[3,4] and hence exercise should act as a time-cue (Zeitgeber) to reset the phase of the circadian clock in sedentary mice. Light is the best known Zeitgeber. One hour of light pulses at night affects the hypothalamic clock and can delay or advance the phase of the activity–rest cycle in a time-dependent manner[7]. Accordingly, an hour of exercise should affect the muscle circadian clock in a time-dependent manner. Skeletal muscle, being the largest metabolic organ, makes an important contribution to daily rhythms in energy expenditure and related rhythms in respiratory exchange ratio (RER). Exercise in early evening or early morning had opposite effects on these rhythms in the subsequent days. Exercise in the morning led to a slight decrease in RER, while evening exercise led to a slight increase in RER during the following daytime.

Opposite changes to RER were found in the subsequent nights. Surprisingly, early morning exercise led to a net increase in energy expenditure in the ensuing days.

Human volunteers doing moderate exercise (50% maximum power output) in the morning versus evening also showed differences in exercise capacity and metabolic parameters[4]; however, the differences are much smaller in magnitude than those found in rodents. Exercise reduces blood levels of glucose; however, evening exercise lowered blood levels of glucose to slightly lower levels than morning exercise. This paradigm might contribute to understanding why evening exercise is more effective in reducing blood levels of glucose in patients with type 2 diabetes mellitus[8].

How representative and generalizable are these results? Like a majority of studies in circadian rhythm or exercise, both studies used young male mice or young men who habitually exercise. So, it is difficult to extrapolate the effect of time on exercise performance of female mice or female athletes. Furthermore, as mice and humans age, our overt rhythm in activity, rest and various other physiological circadian rhythms dampen. Whether exercise in older adults will show similar time-of-day effects remains unknown. If the *Per*-deficient mice that lack circadian rhythms are a model of dampened rhythms in old age, one should not expect any time-of-day difference. However, consolidating caloric intake to a consistent time window of 8–12 h can restore some physiological rhythms and impart health benefits even in mice lacking a functional clock[9]. Hence, whether a combination of time-restricted feeding and timed exercise can restore daily rhythms in exercise performance remains to be examined.

In addition, whether the observed difference in acute response to morning or afternoon exercise will persist under chronic and repeated exercise training is unknown. For example, the HIF1 response blunts over repeated exercise owing to the induction of counter-regulatory mechanisms to ensure improved oxygen consumption in skeletal muscle. Similarly, the effect of acute exercise on PPARγ co-activator 1α decays with repeated exercise[10]. Therefore, the current studies offer a foundation and potential pathways for further examination of repeated exercise or exercise adaptation.

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References

1. Gabriel BM & Zierath JR Circadian rhythms and exercise — re-setting the clock in metabolic disease. Nat. Rev. Endocrinol 15, 197–206 (2019). [PubMed: 30655625]
2. Burke LM & Hawley JA Swifter, higher, stronger: what's on the menu? Science 362, 781–787 (2018). [PubMed: 30442803]
3. Sato S et al. Time of exercise specifies the impact on muscle metabolic pathways and systemic energy homeostasis. Cell Metab 10.1016/j.cmet.2019.03.013 (2019).
4. Ezagouri S et al. Physiological and molecular dissection of daily variance in exercise capacity. Cell Metab 10.1016/j.cmet.2019.03.012 (2019).
5. Sullivan JE et al. Characterisation of 5′-AMP-activated protein kinase in human liver using specific peptide substrates and the effects of 5′-AMP analogues on enzyme activity. Biochem. Biophys. Res. Commun 200, 1551–1556 (1994). [PubMed: 8185610]
6. Narkar VA et al. AMPK and PPARdelta agonists are exercise mimetics. Cell 134, 405–415 (2008). [PubMed: 18674809]
7. Hatori M & Panda S The emerging roles of melanopsin in behavioral adaptation to light. Trends Mol. Med 16, 435–446 (2010). [PubMed: 20810319]
8. Savikj M et al. Afternoon exercise is more efficacious than morning exercise at improving blood glucose levels in individuals with type 2 diabetes: a randomised crossover trial. Diabetologia 62, 233–237 (2019). [PubMed: 30426166]
9. Chaix A et al. Time-restricted feeding prevents obesity and metabolic syndrome in mice lacking a circadian clock. Cell Metab 29, 303–319 (2019). [PubMed: 30174302]
10. Hawley JA et al. Maximizing cellular adaptation to endurance exercise in skeletal muscle. Cell Metab 27, 962–976 (2018). [PubMed: 29719234]