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Exercise timing and circadian rhythms

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Circadian rhythms and exercise physiology are intimately linked, but the symbiosis of this relationship has yet to be fully unraveled. Exercise exerts numerous health benefits from the organelle to the organism. Proper circadian function is also emerging as a prerequisite for maintaining health. The positive effects of exercise on health may be partially mediated by an exercise-induced change in tissue molecular clocks and/or the outcomes of exercise may be modified depending on when exercise is performed. This review provides a brief overview of circadian biology and the influence of exercise on the molecular clock, with an emphasis on skeletal muscle. Additionally, we provide considerations for future investigations seeking to unravel the mechanistic interactions of exercise and the molecular clock.

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Introduction

The positive health effects of acute and chronic exercise on tissue-specific and organism-wide function have been a primary interest for nearly a century. Overall health improvements from exercise include reduced risk for cardiometabolic, neurodegenerative, and metastatic diseases, thereby reducing mortality risk [1]. The mechanisms through which exercise training confers health benefits are well-studied with selected tissues but incompletely understood at the system level [2,3]. To further address the relationship between exercise and health, the Molecular Transducers of Physical Activity Consortium (<https://www.motrpc.org/>) will provide data-rich resources to expand the breadth of existing knowledge in exercise physiology and health. While it is well-understood that the physiological responses to

exercise are complex, the emergence of circadian rhythm biology as a parameter of human physiology has added another fundamental layer of complexity into understanding exercise responses.

The purpose of this review is to integrate the concepts of circadian biology and the molecular clock mechanism with growing research implementing different circadian concepts with exercise. We will briefly overview the molecular clock and its role in maintaining homeostasis. We will then highlight recent work integrating circadian concepts into exercise physiology two main themes. The first theme will review studies on how the timing of exercise impacts exercise outcomes and the second theme will review research that has contributed to our understanding of exercise as a time cue for skeletal muscle. Lastly, we will provide considerations for experimental design, and suggest intriguing future directions for the nascent field of exercise chronophysiology.

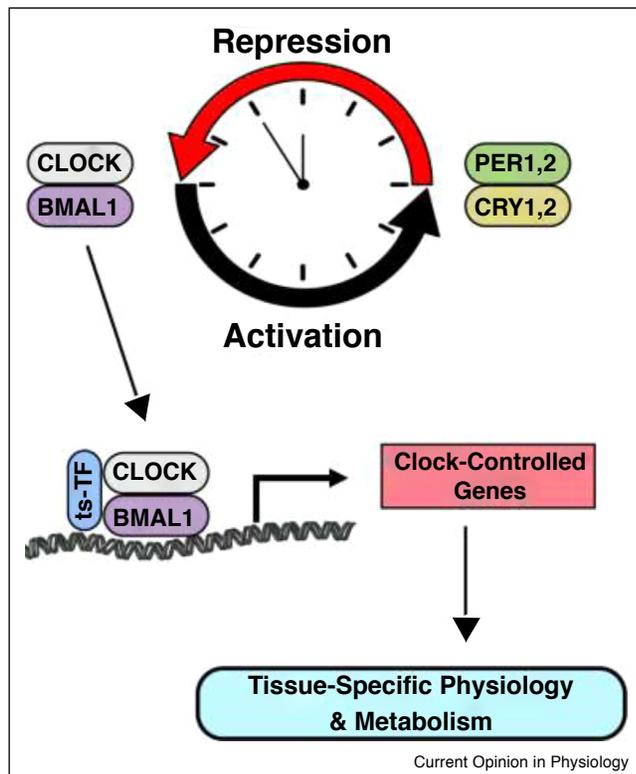
The mammalian molecular clock

Core molecular clock and the clock-controlled transcriptional program

It is now well established that the primary mechanism underlying circadian rhythms is the molecular clock. The elucidation of this mechanism was recently recognized with a Nobel Prize in Physiology or Medicine in 2017. The molecular clock is a self-sustaining transcriptional–translational feedback loop (TTFL) that exists in virtually every cell of the body and functions to direct a daily program of gene transcription and a more in-depth review of the molecular clock can be found here [4]. The primary genes that comprise the molecular clock are ubiquitous in all cells and include *Clock* and *Bmal1* which comprise the positive limb and induce the expression of *Period1* (*Per1*), *Per2* and Cryptochrome (*Cry1*, *Cry2*). The PERs and CRYs are part of the negative limb that function to repress the transcriptional activity of CLOCK and BMAL1, closing the approximate 24 hour loop. A simplified cartoon of the molecular clock is provided in [Figure 1](#).

In addition to its timekeeping function, the molecular clock regulates a daily transcriptional program. It is estimated that BMAL1 and CLOCK directly modulate expression of over 4000 genes and these genes are called clock-controlled genes (CCGs) [5]. In contrast to the core molecular clock factors, CCGs are expressed in a tissue-specific manner with very limited overlap in expression across all the tissues in the body [6]. Lineage-specific transcriptional regulators (e.g. MYOD1 in skeletal muscle) are likely key factors linking the ubiquitous clock with the tissue-specific CCG

Figure 1



Conceptual cartoon depicting links between the molecular clock and tissue-specific clock controlled gene expression.

Bmal1 and Clock direct the transcription of clock-controlled genes including Periods and Cryptochromes, which in turn form a heterodimer to repress activity of BMAL1 and CLOCK and maintain an approximate 24 hour rhythm of gene expression. In coordination with tissue-specific transcription factor(s) (ts-TF), BMAL1 and CLOCK direct the transcription of clock-controlled genes. This oscillating gene expression output from the molecular clock directs a daily program of transcription that impacts cellular physiology and metabolism.

transcriptional profile [7^{*},8^{**}]. The importance of this daily transcriptional program is highlighted by the recognition that CCGs include transcriptional regulators and rate-limiting enzymes important for cell-specific homeostasis [9,10]. Thus, the core molecular clock machinery through the tissue-specific CCG program play an important role in maintaining cell and tissue health.

Phase setting of the molecular clock

As noted above the molecular clock within each cell is defined as a self-sustaining 24 hour TTFL that functions in the absence of signals from the environment. However, the phase of clock mechanism, as defined by the time of the peak, is sensitive to cues from the environment and can shift in response to the timing of the cues [11]. The most well-established environmental time cue is light. Light exposure during the dark phase modifies the phase of the molecular clock mechanism in the suprachiasmatic

nuclei (SCN) in the brain, known as the central clock [12]. Historically, the respective phases of the molecular clocks across all the peripheral tissues were believed to be under direct control of the SCN through neurohumoral factors. However, studies in the last 10 years have demonstrated that time of feeding and time of physical activity/exercise are bone fide time cues that can modify the phase of the clock mechanisms in many peripheral tissues, and these changes occur independent of any phase change in the central clock [13–15]. These results are exciting as they have opened new concepts for using circadian or time of day principles when considering application of exercise interventions for the purpose of health or performance outcomes.

Circadian rhythms in rodents and humans

One of the common questions within the circadian field is the translation of research findings from nocturnal mice to diurnal human beings. There has been significant work at the behavioral, physiological, and molecular levels to establish the commonality of the circadian system between these mammalian species [12,16,17]. Comparative analysis has demonstrated that many daily physiological rhythms in nocturnal species are at an opposite phase to humans [12,16,17]. For example, daily core body temperature, heart rate, and blood pressure peak in the light or active phase and is lowest at dark or rest phase in humans. In contrast, these physiological variables peak in the dark or active phase and are lowest during the light or rest periods in rodents. The common principle here is that temperature, heart rate and blood pressure peak in the active phase of the mammal independent of lighting. This principle holds true with the molecular clock expression in rodents versus humans [11,18]. Taking data from a time series of muscle biopsies from humans and comparing clock gene expression to muscle from rats and mice confirm that the core clock factors are commonly regulated across the active and inactive phases [11,18].

Exercise and the molecular clock: outcomes and time cue

Circadian timing affects exercise outcomes

Because exercise is a major physiological perturbation, the circadian oscillation of basal physiological rhythms has a direct effect on exercise responses. Several studies in humans and rodents have revealed that variables such as skeletal muscle strength and oxidative capacity demonstrate significant differences over time of day [19–22]. For example, studies have consistently demonstrated increased strength in the later afternoon versus morning [19] while oxidative capacity peaks in the late evening [22]. In addition, basal systemic hormone and metabolite concentrations oscillate over a 24 hour period, although the impact of these oscillation on exercise are unclear [20,22,23^{**},24,25]. It is clear, however, that exercise at different times of day leads to different outcomes

[19,25–27]. One recent example was provided by Dalbram *et al.* who reported that exercise in the late active phase of mice reduced the accumulation of body mass during high-fat diet compared to exercise in the early active phase [28]. The effect of circadian timing on an integrative outcome, such as weight gain, is exciting and will provide important considerations for future interventions. Additionally, future studies in both human and rodent interventions must take care to provide transparent reporting of circadian conditions (e.g. light/dark cycles, feeding status), as well as robust time of day sampling rates. Attention to these details are critical to help distinguish intrinsic circadian related changes versus environmental/behavior effects [29*]. We also suggest cautious assessments of experimental circadian controls before sweeping conclusions regarding the outcomes of an intervention.

Circadian timing has also been reported to affect exercise outcomes at the molecular level. The molecular responses of muscle to exercise are well-characterized. In particular, the mechanistic target of rapamycin complex 1 (mTORC1) and peroxisome proliferator activated receptor gamma coactivator 1 (PGC1) pathways are widely studied exercise-responsive pathways. Recently, these exercise-stimulated pathways were identified as being downstream of the molecular clock, providing a molecular mechanism through which circadian timing can influence exercise responses [30,31]. For instance, Wu *et al.* reported that PER2 lowers mTORC1 activity [32], and PER2 expression oscillates (peaking at the end of the inactive phase [33]), linking time-of-day to the exercise response. Additionally, morning resistance exercise, but not afternoon exercise in trained individuals lead to the activation of the mTORC1 signaling pathway, as assessed by p70^{S6K} phosphorylation [34]. Despite the influence of circadian timing on hypertrophic signaling following acute resistance exercise, circadian timing of resistance exercise training does not influence skeletal muscle hypertrophy [27,34]. Endurance exercise increases PGC1 α , which is a clock-controlled gene in skeletal muscle [35]. Thus, circadian timing may influence the endurance exercise response by modulating the activation PGC1 in skeletal muscle. To our knowledge, no investigations have assessed the impact of circadian timing as a modifier of endurance exercise training responses. However, it is unclear if any human investigation has performed exercise at the onset of the inactive phase (dark), which would closely mirror previous interventions using rodent models [15,36,37].

One approach to test the influence of the circadian clock on exercise outcomes is with genetic models of circadian disruption. In one model of circadian disruption (Clock Δ 19), where mice have a 27–28 hour endogenous period length, mutant mice had a 49% reduction in treadmill exercise duration compared to wild type [38] suggesting that animals with internal clocks out of sync

with environmental cues (i.e. misalignment) have reduced exercise capacity. Additionally, in a model of complete circadian disruption, activity levels in mice lacking *Bmal1* were severely reduced (~2 fold) compared to wild type animals [39]. Together, these findings suggest that circadian disruption reduces exercise capacity. However, despite reduced exercise capacity in mice with circadian disruption, the animals retain plasticity. Specifically, exercise training restored the exercise capacity of the Clock Δ 19 mice, although no studies have examined exercise training in *Bmal1* knockout animals. Together, these findings have major therapeutic implications, as circadian disruption has been linked to numerous diseases [24,40,41]. Thus, exercise may reduce mortality through restoring the function of disrupted molecular clocks. Below we highlight the mechanisms through which exercise modulates the molecular clock.

Exercise as a circadian time cue

Several studies have shown that exercise can impact circadian behavior (see Refs. [36,42]). For the purpose of this review, we will focus on exercise and its role on the molecular clock mechanism. Data from the PER2::LUC [43] circadian reporter mouse, and *in vitro* assays [44] have revealed that exercise acts as a circadian time cue [15,37,45]. Specifically, four weeks of exercise on a treadmill or running wheel significantly shifted the phase of both the skeletal muscle and lung, but did not influence the phase of the central clock [15]. Exercise restored circadian patterns of activity, heart rate, and body temperature in mice with central circadian disruption [37]. Additionally, studies in humans have revealed that resistance [46,47], and endurance exercise [47] stimulate the expression of core clock genes. These data suggest that exercise serves as a circadian time cue, and changes the phase of the molecular clock, specifically in peripheral tissues. However, the specific mechanisms through which exercise serve as a circadian time cue have not been completely resolved. Below we highlight how the effects of exercise, or exercise-induced signaling on the molecular clock may serve as a circadian time cue.

In addition to core factors that directly repress the core molecular clock (e.g. Pers and Crys), factors external to the clock can regulate the stability, phase, or function of core molecular clock proteins. Emerging evidence suggests that exercise-responsive genes, including AMPK [31,48,49], HIF-1 α [50], and PGC1 α [51] influence the expression of core molecular clock genes, revealing a potential mechanism through which exercise serves as a circadian time cue. For instance, AMPK activity increases in response to exercise and increased AMPK activity alters the stability of PER and CRY proteins to affects the expression of core molecular clock genes [31,52]. Specifically, AMPK activation results in reduced stability of CRY1, allowing derepression of *Bmal1*:Clock targets [52]. Additionally, CRY1/2 proteins reduce

exercise capacity through PPAR δ repression [53^{••}], suggesting that AMPK activity directly influences the molecular clock, revealing a mechanism through which exercise acts as a circadian time cue. Exercise also induces HIF-1 α expression, which influences the output of the molecular clock through direct binding to core clock gene promoters [50]. Thus, HIF-1 α may partially mediate the effects of exercise as a circadian time cue. Another potential mechanism through which exercise may act as a time cue is through mechanical input, as cellular compression has been reported to influence molecular clock oscillation in mammary cells [54]. Considering the mechanical effect of exercise on skeletal muscle [55], mechanical changes may contribute to the effect of exercise on the molecular clock, although the exercise-related regulation of CCG expression is likely multifactorial.

Concluding remarks and future directions

Exercise imparts numerous health benefits, and the mechanisms through which exercise improves health continue to be revealed [1, [29[•]]]. With this review, we suggest two new considerations: (1) Applying circadian or time of day principles to exercise interventions hold promise for improving the outcomes for exercise for healthy subjects, patient populations as well as elite athletes. (2) The molecular clock with its impact through clock controlled genes maybe one of the mechanisms through which exercise improves cell/tissue health. This is still a new field and there is much to be learned about fundamental molecular clock function across all cell types as well as how these clocks in peripheral tissues sense and respond to exercise. Further, it is our sincere hope that future investigations aimed to examine the interplay between exercise physiology and circadian biology implement rigorous study designs [29[•]] to allow for an in-depth understanding of the interaction of these two exciting fields. While our review highlights the unknowns of circadian exercise biology from the perspective of the skeletal muscle, the intricate system-wide effects of exercise and the global physiological enhancements on health that are associated with exercise timing and training remain unexplored.

Conflict of interest statement

Nothing declared.

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