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REVIEW

The mammalian circadian clock and its entrainment by stress and exercise

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Abstract The mammalian circadian clock regulates day–night fluctuations in various physiological processes. The circadian clock consists of the central clock in the suprachiasmatic nucleus of the hypothalamus and peripheral clocks in peripheral tissues. External environmental cues, including light/dark cycles, food intake, stress, and exercise, provide important information for adjusting clock phases. This review focuses on stress and exercise as potent entrainment signals for both central and peripheral clocks, especially in regard to the timing of stimuli, types of stressors/exercises, and differences in the responses of rodents and humans. We suggest that the common signaling pathways of clock entrainment by stress and exercise involve sympathetic nervous activation and glucocorticoid release. Furthermore, we demonstrate that physiological responses to stress and exercise depend on time of day. Therefore, using exercise to maintain the circadian clock at an appropriate phase and amplitude might be effective for preventing obesity, diabetes, and cardiovascular disease.

Keywords Mammalian circadian clock · Liver · Muscle · Oxidative stress

Introduction

Numerous physiological phenomena in the human body, such as sleep–wake cycles, hormonal and nervous activity, and body temperature, exhibit rhythmic changes over the course of 24 h (Fig. 1) [1, 2]. These oscillations are regulated by an internal circadian clock system, of which the central pacemaker is located in the suprachiasmatic nucleus (SCN) of the hypothalamus [3, 4]. Peripheral tissues also contain circadian clocks that regulate local physiological functions, and essential core clock genes such as *Clock, Bmal1, Per1/2,* and *Cry1/2* have been shown to cooperate with each other to generate cell-autonomous oscillations with circadian rhythm accuracy [1].

In addition, approximately 8–10 % of all genes exhibit rhythmic mRNA expression, which is produced by several important circadian transcriptional factors, including RORs, PPARs, REV-ERBs, SREBPs, DBP, TEF, and HLF [5, 6]. Recent microarray analysis demonstrated an overlap of these genes in various tissues; however, there are also large disparities in the expression of specific rhythmic genes in each tissue, suggesting that each peripheral clock regulates tissue-specific functions [7]. Moreover, post-transcriptional and post-translational modifications, which have been observed using recently developed sequencing techniques, are also important factors that affect molecular clocks and clock-regulated functions [8, 9].

Circadian clocks are invariably either fixed or are adjusted by external stimuli, including sunlight for "photic entrainment", and food/nutrition, temperature, arousal, stress, and exercise for "non-photic entrainment" (Fig. 1)

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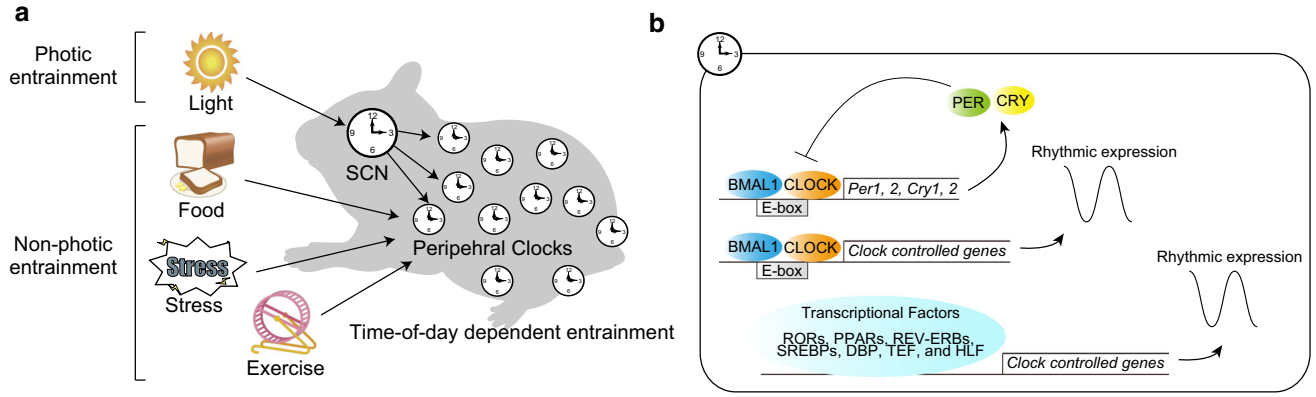

Fig. 1 Schematic diagram of the mammalian circadian clock. **a** External cues, such as light, food, stress, and exercise, entrain the central (suprachiasmatic nucleus; SCN) and peripheral (peripheral tissues) clocks. Light directly entrains the SCN, whereas other stimuli reset the peripheral clocks, and entrainment depends on the timing of stimulation. **b** The molecular clock is regulated by transcriptional feedback loops of core clock genes, and oscillations of clock-regulated genes in each tissue are controlled by various transcriptional factors, including CLOCK/BMAL1, RORs, PPARs, REV-ERBs, SREBPs, DBP, TEF, and HLF

[1, 2]. In the case of photic entrainment, light stimuli are conveyed directly to the SCN and transmit principal information to master clocks [10, 11]. Furthermore, light stimuli at the beginning of the active period cause phase delays in the SCN and its associated activity rhythms [10], whereas light stimuli at the end of the active period induce a phase advance of the associated rhythms. Therefore, the effects of external stimuli on the circadian system depend on the time of day (this phenomenon is discussed further in "Time-of-day dependency of non-photic entrainment").

Food also has the potential to entrain peripheral clocks but only has small effects on the master clock, since the light signal is the most important stimulus in the SCN [12, 13]. Furthermore, scheduled feeding during the inactive period in mice produces changes in sleep–wake cycles, hormonal and temperature rhythms, and the expression of clock genes in peripheral tissues. In addition to light and food, scheduled stress or exercise stimulations have also been reported to be important entrainment factors in mammals.

In this review, we focus on the entrainment of the mammalian circadian clock and discuss the type of stress (e.g., restraint, social defeat, sleep deprivation, or oxidative stress) or exercise (e.g., endurance or resistance exercise), timing of stimulation (e.g., morning or evening), duration of stimulation (e.g., acute or chronic), and signaling pathways (e.g., sympathetic nerve activation or glucocorticoid release). We also review circadian variation in responses to stressor stimuli at different times of the day, as well as the relationship between stress and exercise-induced entrainment. Because both stress and exercise activate the hypothalamic–pituitary–adrenal (HPA) and sympathetic–adrenal–medullary (SAM) axes [14], we suggest that these pathways could be involved in entrainment. In addition, we discuss the beneficial effects of exercise on circadian disturbances.

Stress-induced entrainment of the circadian clock

Effects of stress and sleep deprivation on the SCN and behavior

Several studies have shown the phase-resetting effects of acute stress stimuli such as sleep deprivation and social defeat on the sleep–wake cycle of hamsters [15, 16]. For example, in constant darkness, phase-shifts in locomotor activity rhythms were strongly induced by 3 h of sleep deprivation that was maintained using gentle handling [15, 16]. In addition, 3 h of wheel running also caused clear phase entrainment of the behavioral rhythms in hamsters [17], and 3 h of social defeat stress also caused a phase shift. However, 3 h of restraint stress did not affect the behavior of hamsters [16], and the treatments that did induce acute phase-shift effects were comparatively small, or not observed in rats [18]. Thus, the type of stimuli and species affected are both important in phase entrainment of the sleep–wake cycle.

The sleep–wake cycle is thought to be the main output rhythm controlled by the SCN clock. In hamsters or mice, for example, sleep deprivation causes rapid reduction in the expression of C-FOS and PER1 proteins and *Per1/2* mRNA in the SCN, although the phase entrainment after these changes was not examined [15, 19]. However, in mice, we demonstrated that, under normal light–dark cycles, the SCN clock remains unchanged following 3 days of 2-h restraint stress [20], which suggests that short-term stressors have little effect on the SCN and SCN-regulated activity rhythms in mice. This could be because the glucocorticoid receptor is not expressed in the SCN [21].

However, the SCN clock is sometimes affected by long-term stressors [22–25]. Kinoshita et al. [23], for example, demonstrated that 3 h of restraint stress at Zeitgeber time

(ZT)6–9 for 7 consecutive days produced elevated glycogen synthase kinase (GSK)-3β phosphorylation and blunted PER2 rhythms in the SCN of mice (ZT0 and 12 are defined as the start and end of the light period, respectively). In addition, 19 days of social defeat stress during the day or night induced changes in the expression of *Per2* and *Cry1* in the SCN of mice [22]. Moreover, chronic (4 weeks) mild stress caused decreased amplitude of PER2 rhythms in the SCN of rats, whereas 7 days of mild stress caused no alterations [25]. Thus, the sleep–wake cycle and the SCN clock could be entrained or manipulated by stressful stimuli; however, the effects are dependent on the duration and type of stimuli, as well as on the animals affected.

Effect of stress on peripheral circadian clocks

We recently reported that both acute and sub-acute physiological/psychological stress have tremendous potential to entrain the phases of peripheral circadian clocks in mice, similar to food-induced entrainment (Fig. 2) [20]. We demonstrated that several days of restraint stress or social defeat stress could cause strong phase changes in the PER2::LUC bioluminescence rhythms of the liver, kidney, and submandibular gland in mice and that the effects of the stimuli depended on the time of day and varied with the length (number of days) of stimulation [20]. In fact, we demonstrated that 3 days of restraint stress at ZT4–6 caused a phase advance (4–6 h) of peripheral PER2::LUC rhythms (Fig. 2) [20]. Furthermore, we also determined the stress-induced entrainment of the adrenal gland, cortex, and hippocampus and found that, in contrast to peripheral tissues, the SCN was not affected [20].

Other previous studies have attempted to identify the effect of stressful stimuli on the peripheral clocks in depression models of mice and rats; however, only small phase changes were observed, with no reduction in amplitude. For example, Takahashi et al. [25] demonstrated that 7 days of chronic mild stress induced phase

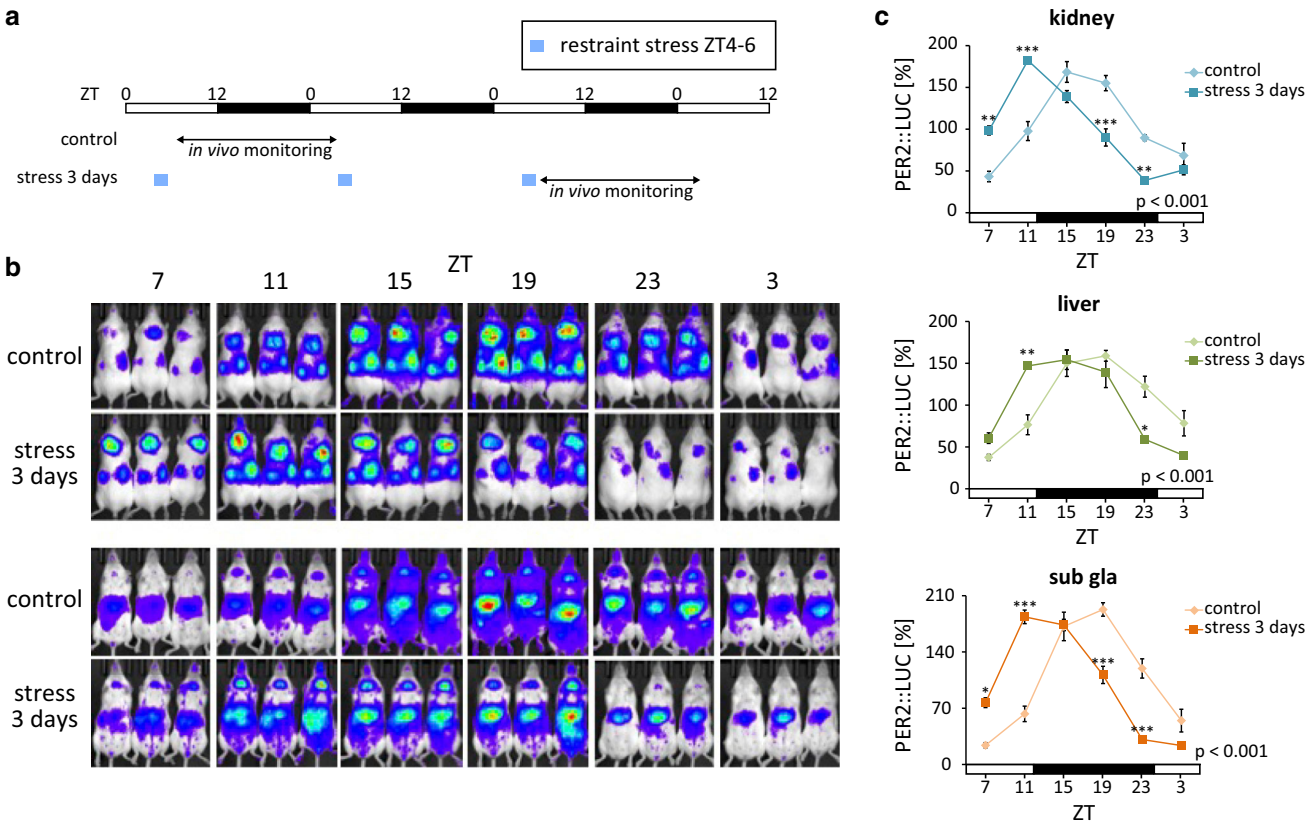

Fig. 2 Stress-induced phase shift of peripheral PER2::LUC rhythms. **a** Experimental schedule; 2-h restraint stress was performed for 3 days at Zeitgeber time (ZT)4–6 in PER2::LUC mice and, subsequently, the rhythm of in vivo bioluminescence was monitored. **b** Representative images of in vivo PER2::LUC bioluminescence in kidney (*upper panels*), liver, and submandibular gland (sub gla) tissues (*lower panels*). **c** Normalized PER2::LUC oscillations in control and stress groups show phase advancement in the stressed group. Values are expressed as mean ± SEM. The *P* values shown on the *lower right* side of the graphs indicate the results of two-way ANOVA (with Tukey post hoc test) between the control and stress groups. $*P < 0.05$, $***P < 0.001$ (modified from [16])

advancement of the rhythmic expression of liver clock genes in BALB/c mice; however, the phenomenon was not observed in C57BL/6 mice. Chronic (2-week) daytime social stress was also shown to cause phase advancement (1–2 h) in the PER2::LUC rhythms of cultured adrenal and pituitary glands [24], and in our most recent study, we found that 4 weeks of restraint stress (3 days $week^{-1}$) elicited habituated responses in the phase entrainment of peripheral PER2::LUC rhythms, with no reductions in amplitude [20]. Thus, it seems that the phases of peripheral clocks could generally be changed by acute or sub-acute stressful stimuli, although habituation to chronic stressful stimuli can reduce these effects.

Entrainment pathways of stress-induced phase changes

The pathways involved in stress-induced entrainment of peripheral clocks have also been investigated, and along the HPA axis, glucocorticoids, which are secreted from the adrenal gland in response to stressful stimuli, have been identified as powerful factors, both in vitro and in vivo [21]. Functional glucocorticoid response elements (GREs) in the promoter regions of *Per1, Per2,* and *E4bp4* have also been reported as possible factors in the signaling mechanisms of molecular clocks [26, 27], and the expression of *Rev-erbα* in the liver has been reported to decrease in response to glucocorticoid treatment via GREs [28]. In our most recent study, we also confirmed that dexamethasone (an analog of corticosterone) induced phase entrainment of peripheral PER2 rhythms in the liver, kidney, and submandibular gland [20]. Restraint stress-induced *Per1* expression in the liver through GRE has also been reported [29], and the ablation of glucocorticoid effects via adrenalectomy was shown to disrupt PER2 oscillations in the bed nucleus of the stria terminalis (BNST) [30], suggesting that adrenal hormones play an important role in maintaining appropriate circadian rhythms in peripheral tissues in vivo.

Furthermore, sympathetic activation of the SAM axis during stressful stimulation also causes phase changes in peripheral clocks [20], and the administration of adrenaline or noradrenaline induces *Per1* and *Per2* expression through the cAMP response element-binding protein (CREB) signaling pathway [31–33]. Thus, the SAM axis is another pathway involved in stress-induced peripheral clock entrainment.

In addition, restraint stress also induces strong expression of the *HO-1* gene and causes oxidative stress by reducing levels of superoxide dismutase (SOD), glutathione-*S*-transferase (GST), and catalase [34]. Because cellular oxidative stress from the administration of H_2O_2 has been reported to reset the expression of clock genes in vitro [35], it is also likely that oxidative stress, as a consequence of physiological stress, could be one of the important pathways in stress-induced phase shifts in vivo. Therefore, several pathways, including the HPA and SAM axes and oxidative stress, may all be involved in the regulation of stress-induced peripheral clock entrainment.

Time-of-day dependency of non-photic entrainment

The construction of phase response curves (PRCs), in which phase shift values are plotted against the timing of stimuli, is helpful for understanding the properties of entraining stimuli. In a previous study [20], for example, we constructed the PRC of restraint stress-induced peripheral PER2::LUC entrainment and found that phase and amplitude changes were dependent on time of day (Fig. 3): stress at ZT4–6 caused phase-advancement (positive shifts) and stress at ZT18–20 caused phase-delay (negative shifts).

Interestingly, we also found that stress at ZT0–2 caused desynchronization of PER2::LUC among tissues and decreased PER2::LUC amplitude in the kidney (Fig. 3b). This phenomenon in the kidney has been previously attributed to singularity behavior, which constitutes a potent entraining stimulus delivered at the critical transition from phase-delay to phase-advancement, resulting in desynchronization of individual cellular clocks [36–38]. Ukai et al. [37] also observed this phenomenon (i.e., stopping the oscillation of clock gene expression) in melanopsin-transfected NIH3T3 cells in vitro and in SCN clocks in vivo, in response to light perturbation. The PRC of stress entrainment follows a similar trend to that of light-induced singularity, since ZT0–2 is the transition phase of the PRC (Fig. 3).

In addition, we recently constructed the PRC of caffeine-induced peripheral PER2::LUC phase entrainment in vivo and demonstrated that similar singularity behaviors occur in the liver, kidney, and submandibular gland, as a result of caffeine injections at ZT1 (Fig. 4) [39]. Administration of caffeine induces potent arousal through adenosine receptors. Thus, non-photic entrainment might be induced by caffeine injections. However, for dexamethasone-induced entrainment, Balsalobre et al. [21] constructed the PRC of liver *Dbp* expression rhythms and found no singularity phenotypes at the transition phase, since singularity could be shown by an infinitesimal range of perturbation strengths and timing [37]. Therefore, the construction of PRCs that represent various timings and strengths of stimuli will be necessary to further understand the entraining stimuli of the circadian clock system.

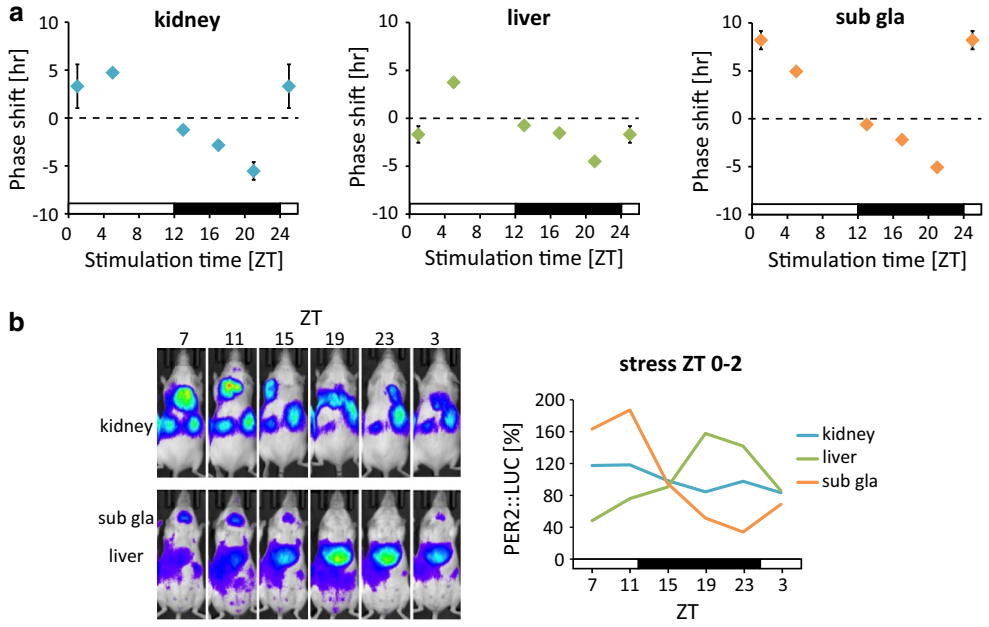

Fig. 3 Time-of-day dependence of circadian changes in response to restraint stress. **a** Phase-response curves of the response of peripheral clocks to 2-h restraint stress at Zeitgeber time (ZT)0–2, 4–6, 12–14, 16–18, and 20–22 (PER2::LUC rhythms). Increased and decreased phase shifts indicate phase-advance and -delay, respectively. Data for ZT25 were copied from ZT1. Graphs include all rhythmic and arrhythmic data. **b** Representative images of in vivo PER2::LUC bioluminescence (*left*) and normalized waveforms (*right*) after restraint stress at ZT0–2 for 3 days (modified from [16])

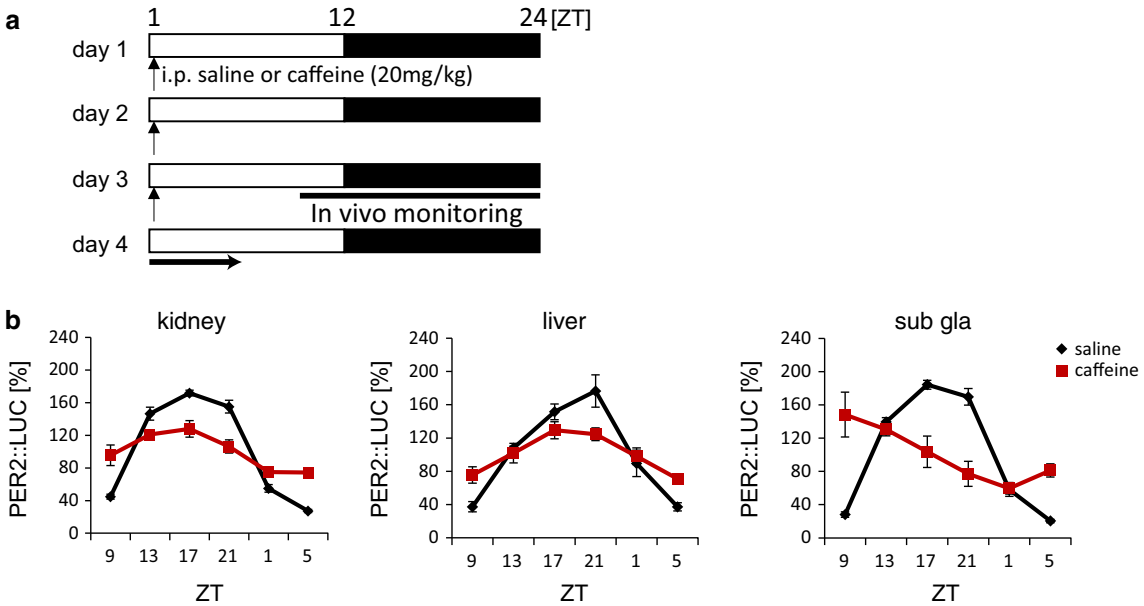

Fig. 4 Decreased amplitude of PER2::LUC rhythms in peripheral tissues after daily caffeine injections. **a** Experimental schedule; mice were maintained under 12:12 h light–dark conditions and given intraperitoneal (IP) injections of saline (control; VEH) or 20 mg kg^{-1} caffeine (CAF) for 3 consecutive days at Zeitgeber time (ZT)1; in vivo monitoring was initiated at ZT9. **b** Normalized waveforms of PER2::LUC rhythms in saline- or caffeine-injected mice

Circadian clock regulation in the stress response

Circadian regulation of the HPA axis

The HPA axis is regulated by the circadian clock system [40]. Elevated levels of circulating glucocorticoids have been observed at the end of the resting phase and are thought to be released in preparation for waking up in the morning. The HPA axis comprises endocrine negative feedback loops that involve the neuropeptides corticotropin-releasing hormone and arginine vasopressin in the paraventricular nucleus (PVN), adrenocorticotropic hormone (ACTH) from the pituitary, and glucocorticoids from the adrenal glands. Each phase of the HPA axis is controlled by circadian rhythms. For example, the expression of *c-Fos* (a marker of neural activity) in the PVN exhibits circadian changes, with high expression levels at the beginning of the dark phase in mice [41, 42]. In addition, serum ACTH and corticosterone concentrations exhibit similar circadian oscillations. Moreover, since these rhythms were not observed in animals with SCN lesions [43, 44] or in knockout (KO) mice with clock gene mutations [45, 46], the HPA axis may be regulated by the master clock.

However, Son et al. [47] demonstrated that knockdown of the adrenal-specific *Bmal1* in mice resulted in disrupted rhythms of corticosterone production, via rhythmic expression of the *StAR* gene in the adrenal gland, suggesting that local clock genes are also important regulators of the circadian cycle of the HPA axis. Furthermore, these mice exhibited abnormal locomotor activity and abnormal expression of clock genes in other peripheral tissues, which suggests that the adrenal clock moderates time-related communication among tissues [47]. However, adrenalectomized mice exhibit no alteration in the expression of clock genes in the liver [48, 49].

Although circadian rhythms of basal corticosterone circulation exist, restraint stress-induced corticosterone levels are similar, whether in response to daytime or nighttime stress [42]. Therefore, the ratio of corticosterone release in response to stress is higher at the beginning of the light phase than at the onset of the dark phase. In addition, *Bmal1* KO mice exhibit lower levels of corticosterone induction in response to restraint stress and lower feedback activity of dexamethasone-induced suppression of corticosterone secretion than wild type (WT) mice. *Bmal1* KO mice also display manic-like behavior in the forced swim test [45]. Thus, the hypothalamic and adrenal clocks regulate both the HPA axis and the stress response.

Furthermore, dysfunction of the HPA axis induces mood spectrum disorders, such as major depression [50]. Rotating nighttime shift work, for example, increases the risk of depressive symptoms [51, 52], and in the mouse model of chronic jet lag, exposure to a 7-h light–dark cycle (3.5 h:3.5 h = light:dark) caused depressive behavior with increased serum corticosterone, demonstrating that disrupted sleep–wake cycles are linked to mood disorders.

However, in rodents, clock gene mutations (e.g., *Bmal1* KO mice and *Per2* or *Clock* mutants) cause hyperactivity, manic-like behavior, and low anxiety that could be attributed to an increase in the dopaminergic activity of the ventral tegmental area (VTA) via changes in the genes for tyrosine hydroxylase and monoamine oxidase A [45, 53–55]. In addition, changes in the genes for tyrosine hydroxylase and monoamine oxidase A also increase the risk of cocaine addiction [56]. Therefore, impairments in the expression of clock genes are, in turn, linked to antidepressive behavior.

On the other hand, there are many reports of single-nucleotide polymorphisms (SNPs) found in clock genes of patients with mood spectrum disorders, such as bipolar disorder, unipolar disorder, and seasonal affective disorder [57]. Thus, further research is required to investigate the relationship between moods and the circadian clock.

Circadian regulation of oxidative stress

Responses of the antioxidant pathway to oxidative stress also exhibited day–night differences. For example, the severity of bleomycin-induced lung fibrosis in mice exhibited an association with the timing of treatment; fibrosis was more severe in mice treated at ZT12 than in those treated at ZT0 [58]. This was owing to circadian variation of a key antioxidant regulator, nuclear factor erythroid-derived 2-like 2 (*Nrf2*), which is regulated by CLOCK/BMAL1 through the E-box [58, 59]. Miura et al. [60] also demonstrated that cadmium-induced mortality is affected by circadian variations, since the toxicity of cadmium was higher at ZT8 than at ZT20, and hepatic glutathione (GSH) was lower at ZT8 than at ZT20.

In addition to *Nrf2* and GSH, many other antioxidants and antioxidant genes exhibit day–night fluctuations as well, including glutathione *S*-transferases, cyclooxygenase-2, catalase, and hepatic metallothionein [61–63]. However, the disruption of circadian systems in *Bmal1* KO mice results in increased levels of reactive oxygen species in peripheral tissues, compared to the levels in WT mice, and accelerates aging [64]. Thus, the circadian clock system regulates the responses of oxidative stressors by regulating antioxidant pathways.

Exercise and the circadian clocks

Exercise and the entrainment of the circadian clocks

Exercise represents another non-photic phase-shifting cue that entrains circadian clocks. Some studies have shown that exercise shifts the phase of circadian rhythm of wheel running behavior in rodents under constant dark conditions [17, 65]. For example, Maywood et al. [19] reported that, under constant dark conditions, the expression of *Per1* and *Per2* in the SCN was changed by wheel running.

In addition, the timing of exercise is also involved the regulation of circadian clocks. Wheel running at the onset of the active phase decreases the amplitude of *Per2* in the SCN more than that at the end of the active phase [66], and scheduled exercise can entrain the molecular clocks of skeletal muscle and lungs, but not the SCN, under light–dark conditions [67]. Recently, we also demonstrated scheduled exercise-induced entrainment of *Per2* in the submandibular gland [68]. These results suggest that scheduled exercise entrains the molecular clock in both the SCN and peripheral tissues, although exercise-induced entrainment of the master clock is limited under non-light conditions.

Similar to the studies in mice and rats, exercise-induced phase shifts of the circadian rhythm have also been observed in humans [69–74]. For example, Barger et al. [69] reported that exercise accelerated forced sleep-induced phase delays of circadian rhythms in humans. During their study, the daily rhythm of plasma melatonin levels was used as a parameter of circadian rhythms, and the 9-h sleep schedule-induced phase delay of the circadian melatonin rhythm was facilitated by bicycle ergometer exercise under dim light conditions.

Yamanaka et al. [75] also reported that exercise had differential effects on the circadian melatonin rhythm and the sleep–wake cycle. Apparently, exercise accelerated the re-entrainment of the sleep–wake cycle, but not the melatonin rhythm, under dim light and a restricted phase-advanced sleep schedule [75]. Moreover, Yamanaka et al. [74] investigated the effects of exercise on the circadian melatonin rhythm and sleep–wake cycle under bright light and 8-h phase-advance shifted sleep–wake schedule. The sleep–wake cycle was entrained by the sleep schedule, regardless of the presence of exercise, but phase-advancement of the circadian rhythm of melatonin was dependent on exercise. Thus, the combination of light and exercise is a strong entrainment cue for circadian rhythms in humans.

Zambon et al. reported that resistance exercise changed the expression of the molecular clock in human skeletal muscle [76]. The resistance exercise (ten sets of eight repetitions of isotonic knee extension at 80 % of the predetermined one-repetition maximum) changed the gene expression of circadian clocks in the skeletal muscle of humans, suggesting that both resistance and endurance exercise are capable of producing phase shifts in circadian genes of skeletal muscle.

Entrainment pathways of exercise-induced phase changes

The potential pathways involved in exercise-induced entrainment of peripheral clocks includes the HPA and SAM axes, since several studies have reported their activation by both exercise and stress [77–81]. However, plasma corticosterone levels exhibit day-to-night fluctuations and are highest at the end of the resting phase. Some reports have demonstrated that wheel running only increases corticosterone levels at the end of the resting phase [82, 83], and Fediuc et al. [78] reported that sustained exercise gradually reduced both corticosterone releases.

It is thought that central and peripheral catecholamines regulate the exercise-induced elevation of plasma corticosterone [84]. Although the stress-induced elevation of plasma corticosterone is thought to involve ACTH secretion, the elevation of ACTH is not observed during voluntary exercise, such as wheel running. However, stressful exercise, such as treadmill running, has been shown to increase both ACTH and stress levels in rodents. These findings suggest that the mechanisms of exercise-induced elevations in corticosterone levels differ depending on the type and intensity of the exercise.

Exercise and circadian disturbance

Some studies have demonstrated beneficial effects of exercise on circadian disturbance. For example, skeletal muscle in *Clock* mutant mice exhibits decreased mitochondrial content and exercise intolerance [85]; however, endurance exercise for 8 weeks increases skeletal muscle mitochondrial levels and exercise tolerance. Schroeder et al. [66] also reported that the rhythmic deficits observed in vasointestinal polypeptide (VIP)-deficient mice were improved by wheel running. The VIP-deficient mice displayed advanced phases in activity, heart rate, and body temperature rhythms, and a decreased amplitude of *Per2* expression in the SCN.

However, the VIP-deficient mice only improved in response to wheel running at the end of the active phase, not at its onset [66], and we recently demonstrated that wheel running at the end of the active phase controlled high-fat diet-induced obesity in mice more than at the onset

of the active phase [86]. Therefore, although much research has focused on the beneficial effects of exercise itself, the work of Schroeder et al. and ourselves has demonstrated the importance of exercise timing in the resolution of circadian disturbance and metabolic disorder [66, 86].

Conclusions and perspectives

Based on recent findings, stress and exercise are potent entraining cues for peripheral clocks and sometimes for the central clock. The disturbance of circadian rhythms occurs in several disorders such as cardiovascular disease, obesity, and diabetes [87]. Recent studies have also shown that scheduled feeding can enhance the circadian oscillations of clock genes and metabolic genes, potentially conferring tolerance to high-fat diet-induced obesity and age-related cardiovascular failure [88, 89]. These findings suggest that the timing of meals is an important factor for good health. In addition, exercise may also be a beneficial and powerful tool for the maintenance of circadian rhythms and good health. However, further evidence is needed.

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Compliance with ethical standards

Conflict of interest The authors declare no competing financial interests.

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