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Sleep and Circadian Regulation of Cortisol: A Short Review

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Abstract

The central circadian pacemaker (CCP) located in the suprachiasmatic nucleus (SCN) of the hypothalamus drives the 24-hour pattern in cortisol, which functions as the main central synchronizing signal that coordinates peripheral clocks in organs that control whole body metabolism. A superimposed pulsatile pattern of cortisol allows rapid responses that fine tune the body's reaction to changes in the environment. In addition to coordinating metabolic processes to predictable environmental events, cortisol is the main catabolic signal which acts with testosterone, the quintessential male anabolic hormone, to maintain catabolic-anabolic homeostasis in men. Sleep restriction, when sufficiently substantial, increases late afternoon/early evening cortisol, but does not alter 24-hour cortisol; whereas even maximal acute circadian misalignment only slightly delays the cortisol rhythm. Prolonged circadian misalignment decreases overall cortisol exposure. The implications of these regulatory changes on health and disease requires further evaluation.

Keywords

Glucocorticoid; Insulin resistance; catabolic; Adrenal; pulsatile

I. INTRODUCTION

The hypothalamo-pituitary adrenal (HPA) axis controls cortisol secretion, including maintaining an underlying diurnal (i.e. 24 hour) pattern of cortisol upon which ultradian (i.e. pulsatile) oscillations in secreted cortisol permit a rapid dynamic response to threats in the environment [1]. This diurnal rhythm in cortisol, where circulating concentrations peak at the habitual sleep-wake transition and gradually decrease to a nadir during the late evening/early night, is of endogenous origin because it is driven by the central circadian pacemaker (CCP) located in the suprachiasmatic nucleus (SCN) of the hypothalamus. Cortisol's rhythm is therefore more precisely described as a circadian rhythm, and this

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signal coordinates and optimizes metabolic responses that are predictable in relation to the environmental day, particularly to the light-dark cycle and its consequent behaviors [2]. In contrast, the superimposed pulsatile pattern of cortisol allows rapid responses that fine tune the body's reaction to changes in both the external as well as the internal environment that may not be as predictable [3, 4]. Accordingly, discerning both the circadian and ultradian rhythms in cortisol is essential to understanding the HPA response to disruptions in the sleep-wake cycle. Consideration of both sleep and wake is also necessary because of the cortisol awakening response [2, 5]. The cortisol awakening response refers to the increase in cortisol which occurs within the first hour after awakening, is separate from the cortisol increase that happens during the second half of the night, and appears to be independent of circadian control [2, 5].

Cortisol is the predominant glucocorticoid secreted by the adrenal gland in humans. It is the main catabolic signal and a potent anti-inflammatory agent that restrains the cytokine cascade and limits self-harm [4, 6, 7]. While adaptation to novel situations may be helpful in certain situations, chronic changes in the HPA axis from cumulative and ongoing exposures to stress can lead to a new dynamic equilibrium set-point, in a process known as allostasis [4]. Accordingly, cross sectional studies show that chronically increased glucocorticoid concentrations correlate with: (1) cardiovascular disease, obesity and metabolic syndrome (indicative of metabolic dysfunction); predisposition to infection and cancer (suggesting immune suppression); and physical frailty, mood disorders, impaired spatial cognition and memory deficits [1, 2, 4, 6]. Although it is believed that hypercortisolemia leads to these deficits, the direction of these relationships cannot be established solely by correlational studies, and the possibility that bidirectional effects remains. Nevertheless, the well-recognized cardiometabolic deficits, susceptibility to infection and other mood and cognitive impairments that typify Cushing's syndrome suggest a causal relationship. These data are consistent regardless of the cause of Cushing's syndrome, including from exogenous glucocorticoid use, as well as increased endogenous cortisol exposure from either pituitary dependent or pituitary independent disease.

This review will discuss important findings concerning the sleep and circadian regulation of cortisol, particularly high-quality studies where diurnal secretion of cortisol was assessed across an entire 24-hour period, or where hormone pulsatility could be accurately assessed because blood sampling was sufficiently frequent. Recently published findings within the past 5 years will be emphasized. The sympatho-adrenomedullary axis, and other steroids secreted by the adrenal cortex (such as mineralocorticoids and sex steroids) are beyond the scope of this short review. Studies of disrupted sleep due to obstructive sleep apnea are also excluded because the multiple awakenings, hypoxia and sympathetic overactivity that typify this condition may confound interpretation of the sleep and circadian regulation of cortisol.

II. CIRCADIAN REGULATION OF CORTISOL

Acute and chronic circadian misalignment has differential effects on cortisol

Circadian misalignment is characterized by desynchrony between the CCP and behavioral cycles (sleep/wake, feeding/fasting, activity/rest). Night and evening shift work, rotating shifts, split shifts, or an otherwise irregular work schedule, as well as with jet lag, are

common causes of circadian misalignment. Shift work is associated with adverse health consequences including increased susceptibility to infection and cancer, and increased risk of inflammation-related disorders including cardiovascular and cardiometabolic diseases [8–12].

Studying the effects of circadian misalignment on endogenously regulated cortisol rhythms is complicated by the confounding effects of external environmental or behavioral influences – including sleep and wake. Use of a 24-hour constant routine protocol, with constant wakefulness and devoid of external mediators, is needed to interrogate the endogenous temporal patterns of circulating cortisol [13]. The constant routine protocol is the gold-standard method to remove or uniformly distribute external and behavioral influences that may affect the expression of endogenous rhythms [13–15]. The rhythms so observed under constant routine conditions are therefore not passive responses to changes in external or behavioral factors such as sleep-wake, feeding-fasting, posture, activity and light, but are internally generated by the circadian clock.

Two recent studies utilized a constant routine to properly evaluate the effect of circadian misalignment on cortisol rhythms. The first allocated 14 healthy young adults at random to three days of either a simulated night shift schedule (7 participants) or a simulated day shift (i.e., control) schedule (7 participants) – followed by a 24-hour constant routine protocol, during which blood was collected at 3-hour intervals through an intravenous catheter [7]. The degree of circadian misalignment was maximal since those undergoing simulated night shift work had behavioral cycles that were inverted (delayed by 12 hours). Cortisol concentrations were measured in blood collected across the 24-hour constant routine, and analyzed with cosinor analysis for 24-hour rhythmicity with a trend for time awake, implemented as non-linear mixed effect regression. Circadian rhythmicity was apparent under both shiftwork conditions ($P<0.001$), and there was a small but significant delay in the timing (i.e. acrophase) of the cortisol peak which occurred at approximately the same time of day in both conditions but was slightly but significantly delayed during night shift by 26.5 minutes ($P=0.04$). There was no difference in the average (i.e. mesor) or amplitude (the difference between peak and trough levels). These data indicate that acute circadian misalignment, as occurs with shift work, has minimal effects on the endogenous circadian rhythm of cortisol.

A complementary non-randomized study of 14 healthy young adults examined the effect of chronic circadian misalignment by forced desynchrony where cortisol rhythms were assessed every 30 minutes under constant routine [16]. The forced desynchrony protocol misaligned the biological clock with behavioral cycles by creating a 24.6-hour day where lights off and lights on during the 8-hour sleep period were both 36 minutes later each day for 21 consecutive days (misaligned group, n=6) whereas the aligned group (n=8) maintained the same lights off and lights on during the 8-hour sleep period in a 24-hour day. Comparisons of the change in cortisol patterns between groups and within groups indicated a substantial reduction in overall cortisol (24-hour area under the curve) of 120 mcg/day. The misaligned group had greater variability in the timing of the peak in cortisol for each individual, but formal cosine analyses were not performed so a delay or advance in timing could not be reported. Furthermore, there is a possibility that the peaks identified represent

the morning cortisol awakening response, rather than the circadian-driven acrophase, and the increased variability in the timing of these peaks in the misaligned group was due to greater variability in wake time.

Although the forced desynchrony protocol has merit, sustained circadian misalignment in dim light enforced by such protocols do not reflect real-life shift work – a limitation recognized by others [17]. Since simulated day and night shift work in the first study was also conducted under dim light [7], and both studies utilized a constant routine, the complementary findings (delayed acrophase versus more variable peaks) could alternatively represent the effect of prolonged versus acute circadian misalignment, instead of differences in the analytical methods utilized. Furthermore, the possibility that the differences in findings are due to discrepancies in other aspects of the study design, such the frequency of blood sampling and the analytical methods utilized, cannot be entirely excluded.

Cortisol is the main metabolic central synchronizing signal

Under fully circadian-aligned conditions, the CCP (located in the SCN of the hypothalamus) synchronizes peripheral clocks throughout the body by hormonal and neural signals [18, 19]. Neural signaling from the SCN is also mediated hormonally by the adrenal axis, and therefore by cortisol [20]. Relevant for metabolism, the principal storage sites for glycogen, protein, and fat are the liver, muscle, and adipose tissue, respectively. Cortisol synchronizes peripheral clocks in these tissues: examination of target tissues from rodents or human explant cell systems, after timed glucocorticoid administration, shows that cortisol directly synchronizes peripheral clocks in liver, muscle, and adipose tissue, and putatively also in pancreas and gut [2, 21]. The latter two organs (pancreas and gut) are also relevant for metabolism because each has a role in the control of macronutrient absorption. Both the peripheral clocks and the glucocorticoid receptors are present in these tissues [2], so direct interaction between these molecular elements is possible. Furthermore, the ligand-activated glucocorticoid receptor has the opportunity to bind to glucocorticoid-response elements, located in the regulatory regions of the core clock genes - *Bmal1, Cry1, Per1* and *Per2*. The binding to these elements is required for action, because genomic deletion of the glucocorticoid-response elements from these core clock genes prevents signal transduction by glucocorticoids [20, 22]. Accordingly, cortisol is accepted to be the key *metabolic* central synchronizing signal [2, 20], although other effects are possible since shifting the peak of the cortisol rhythm can speed the re-entrainment of locomotor activity in mice exposed to jet lag conditions [23]. In addition to this central synchronizing function, cortisol is the main hormone controlling catabolism, acting with testosterone, the quintessential male anabolic hormone, to maintain catabolic-anabolic homeostasis in men [12].

Implications of the bidirectional circadian regulation of cortisol

Acute and substantial 12-hour circadian misalignment shifts the timing of the peak of the cortisol rhythm by less than 30 minutes and has no effect on overall cortisol levels, whereas sustained but smaller degrees of circadian misalignment increases the variability in the timing of the peak cortisol and decreases overall cortisol concentrations considerably. Since cortisol is the main signal synchronizing peripheral clocks in organs important for metabolism, changes in the cortisol rhythm may alter the timing and coordination of

metabolic processes throughout the body. Although it is possible that a quantitatively small shift in cortisol can cause substantial disruption to these processes, it seems to be unlikely. An important consideration is that the increased variability in the timing of peak cortisol with sustained circadian misalignment suggests that the retiming of the metabolic signal could be greater in certain individuals, less in others, and unchanged when averaged across all. Further investigation is warranted to ascertain whether this variability is due to inter-individual differences (including from genetic factors) in response to circadian misalignment and the impact of these changes on the synchronization of metabolic processes.

III. SLEEP AND THE REGULATION OF CORTISOL

Cortisol pulsatility is fundamental to its signaling

Cortisol is secreted in a pulsatile fashion (i.e. in short bursts) from the adrenal glands, and the time-specific 6.6 fold variation in the size (i.e. amplitude) of these bursts that occur every 60 to 90 minutes creates the circadian rhythms observed in the human [1, 24]. Cortisol levels are regulated via feedback mechanisms to maintain equilibrium control and homeostasis [4]. The ultradian rhythm is not regulated by the SCN because neither electrolytic destruction of the SCN in rodents, nor surgical disconnection of the hypothalamus from the pituitary in sheep, alters glucocorticoid pulsatility [25, 26]. Additional studies show that there is a discrepancy between the hypothalamic corticotrophin-releasing hormone pulse frequency from the hypothalamus, which occurs 3 times per hour, and the pulse frequencies of ACTH and glucocorticoids, which occur hourly. These findings suggest that glucocorticoid pulsatility is regulated at a subhypothalamic site and that glucocorticoid pulsatility is driven by ACTH. Pulsatile ACTH induces adrenal glucocorticoid production, but not when an identical dose is administered continuously without pulsation [27]. Episodic transcription of rate limiting enzymes crucial for steroidogenesis under pulsatile - not continuous - ACTH drive, may explain this observation [28]. Furthermore, adrenal sensitivity to ACTH is altered by autonomic projections of the paraventricular nucleus via the splanchnic nerve [29].

Continuous glucocorticoid infusion causes non-pulsatile target gene expression, whereas pulsatile glucocorticoid exposure drives pulsatile gene expression which may be from intermittent histone acetylation and cyclical accessibility to chromatin in certain cells [30, 31]. Specifically, rapid cycling of the glucocorticoid receptor and transcription factors on and off chromatin occurs because the low levels of glucocorticoids during the pulse nadir are insufficient to maintain glucocorticoid receptor activation and DNA binding throughout the interpulse interval [4]. An example of how these molecular differences may modulate physiological processes is the behavioral response to startling noise, which differs depending on timing around an infused glucocorticoid pulse [31, 32] implying that the inter-individual variability in these responses may also be due to hypothalamo-pituitary adrenal axis pulsatility [32].

A recent study extends these findings to humans [33]. This randomized order, placebo-controlled crossover trial in 15 young men compared the effect of 5 days of hydrocortisone delivered in a manner that replicated both the ultradian and circadian rhythms versus delivery that replicated only the circadian rhythm. The total dose of hydrocortisone administered was identical in both conditions, and endogenous cortisol secretion was

pharmacologically prevented. Replicating both the ultradian and circadian rhythms resulted in better performance in working memory capacity (N-back test), reduced the perception of negative facial expressions, and caused subtle differences in the neural processing of emotional input assessed by functional MRI.

Late afternoon/early evening cortisol is important for its signaling

The fall in cortisol across the late afternoon and early evening permits low cortisol concentrations during the 4–6 hours of the circadian nadir, which is necessary to avoid the effects of glucocorticoid excess on peripheral tissues [34]. This is because under usual conditions, these low cortisol levels are insufficient to activate the glucocorticoid receptor [4]. A failure for cortisol levels to fall sufficiently is believed to underlie the increased insulin resistance observed with aging [2, 35, 36], as well as impaired physical performance [37] and neurocognitive deficits [38]. Preventing the fall in late afternoon/early evening cortisol experimentally, by administering glucocorticoids to bolster cortisol levels, induces insulin resistance [34, 35, 39]. Hepatic and peripheral insulin resistance is itself induced by post-receptor mechanisms and distinct molecular processes [40–42]. Accordingly, assessing late afternoon/early evening cortisol levels specifically, in addition to understanding the 24-hour dynamics of cortisol, provides additional insights that are relevant to the consequences of time-dependent hypercortisolemia.

This finding complements a recent randomized, crossover study that utilized the same total daily dose between conditions while comparing the effects of hydrocortisone delivery that did or did not replicate a fall in late afternoon/early evening cortisol in 64 adults with primary adrenal insufficiency [43]. Oral administration for 12 weeks of a dual release hydrocortisone preparation reduced the late afternoon and 24-hour cortisol exposure compared to 12 weeks of thrice daily dosing of conventional hydrocortisone. The dual release preparation further optimized weight, blood pressure and glucose metabolism [43].

Sleep restriction bolsters late afternoon/early evening cortisol

Table 1 summarizes the 12 studies showing the effect of sleep restriction on cortisol concentrations in men and women, ordered by the frequency of sampling, and then by sample size [16, 44–54]. Only studies that included at least 24 hours of blood sampling across each sleep condition are included. Six of these studies show an increase in the afternoon or evening cortisol levels where sleep opportunity was reduced to no more than 5.5 hours per night [16, 44–46, 51,52]. Three studies showed no change in afternoon/evening cortisol [48, 49, 53]; however, two of these studies allowed more sleep (6 hours per night) in sleep restriction condition [48, 49] and the third sampled cortisol much less frequently at 2 hour intervals, so that the peak in afternoon cortisol may have been missed [53]. These findings suggest the possibility that substantial sleep loss is required to induce an increase in the afternoon/evening cortisol. These data are also consistent with one of the earliest reports showing that partial or total sleep loss causes an elevation of cortisol levels the next evening [55].

In contrast, no consistent pattern in morning cortisol was observed in the 7 studies that measured morning levels: two studies show an increase [16, 53], two studies reveal a

decrease [48, 49], and three other studies report no consistent change [44, 46, 51]. These contradictory findings could be explained by the cortisol awakening response which occurs within the first hour after awakening [2, 5]. This phenomenon was controlled for only in 2 of the 7 studies: one by utilizing a consistent wake time of 0700 for both sleep conditions [53] and the other by best-fit polynomial regression which may have lessened the impact of an acute cortisol peak [46]. Indeed, changes in the timing of the peak cortisol level that are determined in the absence of cosine or similar analysis may actually reflect changes in wakening. The concept is important because if the intent is to examine circadian rhythmicity and the acrophase of the cortisol rhythm, then the cortisol peak that occurs with wakening needs to be excluded because it is independent of circadian control [2, 5]. Accordingly, the 1–2 hour advance in cortisol peak reported by some studies likely reflects the 2 hour advance in wake time, rather than a true circadian shift in the timing of the cortisol rhythm [45, 48, 49]. Furthermore, none of the 12 studies shown in Table 1 has included individual wake times as part of the analytical plan.

The majority of studies (n=7) examining 24-hour cortisol have reported no change in measures of overall cortisol (mesor, mean or area under the curve), although three other studies show an increase [16, 51, 54]. However, all subjects underwent strenuous exercise in the one of these three studies [54], which may have confounded findings. Accordingly, there are insufficient data to be sure that sleep restriction alters overall cortisol.

A new contribution to the study of sleep restriction and the HPA axis is a prospective, randomized, crossover study of total sleep deprivation (complete nighttime wakefulness) and 8 hours of nighttime sleep in 18 older men (average age 63.9 ± 4.0) and 17 young male adults (average age 24 ± 2.9 years) [44]. Cortisol was assessed every 10 minutes for a 24-hour period, which allowed estimation of the timing of pulses; the mass per pulse; the basal, total and pulsatile secretion; and its biexponential elimination [3, 56–58]. Total sleep deprivation did not alter any of these pulse characteristics when assessed over the full 24-hour period or in the morning (0600 to 0900), but analysis of a specific 3-hour time window in the afternoon (1500 to 1800) revealed an increase in cortisol concentrations and pulsatile secretion specifically in older men (and not in young men). This study is notable in that it is the first study performed in older men, and shows that the effect of sleep restriction on late afternoon/early evening cortisol observed in young men in other studies (see Table 2) is also present with advancing age. One limitation of this study is that the afternoon time window was relatively early. Older men have a phase-advanced acrophase of almost 3 hours, so the 1500 to 1800 time period represents a later circadian time compared to young men [6]. This may explain why sleep restriction did not alter early afternoon cortisol in the young men examined in this study. Accordingly, if sampling had continued for an additional 3 hours in the young men in this study (i.e. from 1800 to 2100), then increases in cortisol levels with sleep deprivation might have been detected [55].

IV. SUMMARY AND CONCLUSIONS

This review demonstrates that the HPA axis is regulated by circadian factors, as well as the sleep-wake cycle. Experimental studies also show that a dynamic and responsive HPA axis, which is necessary for proportional reactions to threats in the internal and external

environments, is predicated on ultradian rhythms. Quantifying circadian cycles by cosine analysis and ultradian pulses by mathematical deconvolution should therefore allow a more complete understanding of the physiological processes that regulate cortisol, secretion and action.

Future studies should examine the effect of sleep restriction or circadian misalignment on adrenocorticotropic hormone (ACTH) to better understand the network regulation of the HPA axis [59]. However, a single defect anywhere within the HPA axis leads to secondary changes at other nodes due to interlinked control by corticotropin releasing hormone (CRH), ACTH and cortisol, which confounds interpretation. The solution is to perform "clamp" experiments to prevent secondary changes from occurring, by isolating specific nodes that secrete each hormone individually, such as by blocking steroidogenesis and examining feedback effects on ACTH secretion [60]. Such studies will unveil the specific hypothalamic, pituitary and adrenal processes that are impaired by sleep restriction or circadian misalignment. Future studies should also examine how these regulatory changes alter cortisol and other metabolically active hormones such as testosterone, modify catabolic-anabolic balance, induce insulin resistance, and impair other fundamental metabolic processes that are known to impact health and disease. Such studies that are longitudinal or longer-term would be particularly useful in an older population, which is the population at risk for metabolic diseases and in whom a lifetime of sleep debt has accumulated.

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Table 1:

Effect of Sleep Restriction on 24 hour Cortisol

Study	Subjects (n)	Age (yr) Mean ± SD	BMI (kg/m^2) Mean ± SD	Sleep Restriction (days × hr); sleep opportunity	Control Sleep (days × hr); sleep opportunity	Study Design	Cortisol measurement frequency and duration	AM Cortisol	PM Cortisol	24 Hr Cortisol
Liu 2020 [44]	17 M "young men"	24.1 ± 2.9	Median 25.0 (IQR 22.9 – 27.5)	1 × 0 hr	1 × 8 hr 2200 – 0600	Randomized order	Q10 min ×24 hr 1800 – 1800	No change 0600 – 0900	No change 1500 –1800	No change
	16 M "older men"	63.9 ± 4.0	Median 29.5 (IQR 26.4 – 31.7)	1 × 0 hr	1 × 8 hr 2200 – 0600	Randomized order	Q10 min ×24 hr 1800 – 1800	No change 0600 – 0900	Increased 1500 – 1800	No change
Broussard 2015 [45]	19 M	23.5 ± 3.1	23.4 ± 1.7	4 × 4.5 hr 0100 – 0530	4 × 8.5 hr 2300 – 0730	Randomized order	Q15-30 min ×24 hr 2130 – 2130	NR	Increased 1900 – 2130, 2300 – 0100	NR
Nedeltcheva 2009 [46]	6 M 5 F "Sedentary"	39 ± 5	26.5 ± 1.5	14 × 5.5 hr ~0030 – ~0600[&]	14 × 8.5 hr ~2315 – ~0740[&]	Randomized order	Q15-30 min ×24 hr 2000 – 2000	No change AM peak cortisol	Increased 2000 – 2200	No change
Leproult 2011 [47]	10 M	24.3 ± 4.3	23.5 ± 2.4	8 × 5 hr 0030 – 0530	3 × 10 hr 2200 – 0800	Fixed order	Q15-30 min ×24 hr 1400 – 1400	NR	NR	No change
Vgontzas 2004 [48]	12 M 13 F	M:25.6 ± 4.1 F: 24.8 ± 3.4	M: 24.6 ± 1.5 F: 23.1 ± 2.7	8 × 6 hr 2230 – 0430	4 × 8 hr 2230 – 0630	Fixed order	Q30 min ×24 hr 0800 – 0730	Decreased AM peak cortisol	No change	No change
Wright 2015 [16]	14 M 3 F	31.7 ± 6.1	NR	1 × 0 hr	6 × 8 hr "Habitual" sleep time	Fixed order	Q30 min ×24 hr 2400 – 2400[#]	Increased ~0900 – 1100	Increased ~1300, ~1600	Increased
Pejovic2013 [49]	16 M 14 F	24.7 ± 3.5	23.6 ± 2.4	6 × 6 hr 2230 – 0430	4 × 8 hr 2230 – 0630	Fixed order	Q1 hr ×24 hr 0800 – 0800	Decreased AM peak cortisol	No change	No change
Ackermann 2013 [50]	12 M	23 ± 5	NR	1 × 0 hr	1 × 8 hr 2300 – 0700	Fixed order	Q1 hr ×24 hr 1200 – 1200[#]	NR	NR	No change
Benedict 2011 [51]	14 M	22.6 ± 3.0	23.9 ± 1.9	1 × 0 hr	1 × 8 hr 2300 – 0630-0700	Randomized balanced order	1800, 2100, then Q90 min 2400 – 0900, Q60 min 1000 – 1300, then 1500 & 1800	Decreased 0730 Increased 0900	Increased 1200, 1500	Increased
Axelsson 2013 [52]	9 M	Range 23–28	Range 21–26	5 × 4 hr 0300 – 0700	2 × 8 hr 2300 – 0700	Fixed order	Q1 hr 2300 – 0800, then Q3 hr 0800 – 2300	NR	Increased 2000	No change

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Study	Subjects (n)	Age (yr) Mean ± SD	BMI (kg/m^2) Mean ± SD	Sleep Restriction (days × hr); sleep opportunity	Control Sleep (days × hr); sleep opportunity	Study Design	Cortisol measurement frequency and duration	AM Cortisol	PM Cortisol	24 Hr Cortisol
Simpson 2016 [53]	8 M 8 F	24.9 ± 4.4	24.8 ± 3.2	5 × 4 hr 0300 – 0700	5 × 8 hr 2300 – 0700	Randomized balanced order	Q2 hr ×24 hr 2330 – 2130	Increased 0730	No change	NR
Dattilo 2019 [54]	10 M Undergoing strenuous exercise	24.5 ± 2.9	22.7 ± 2.3	2 × 0 hr	2 × 8 hr 2300 – 0700	Randomized order	Q2 hr ×24 hr 1900 – 1900	NR	NR	Increased

BMI - body mass index; F – females; Hr – hours; IQR - interquartile range; M – males; Min – minutes; NR - not reported; Q – every; SD - standard deviation; SR - sleep restriction; Wk – week; Yr - year

[&]Sleep opportunities are listed as approximate times because the lights-off and wakeup times were moved proportionally to avoid shift in circadian phase throughout each 14-day study period

[#]Blood sampled for 2 consecutive 24-hour periods for total of 48 hours