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Circadian Control of Neuroendocrine Function: Implications for Health and Disease

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Abstract

The circadian timing system orchestrates daily rhythms in physiology and behavior via the suprachiasmatic nucleus (SCN), the master brain clock. Because endocrine secretions have far-reaching influence on the brain and periphery, circadian regulation of hormones is essential for normal functioning and disruptions to circadian timing (e.g., irregular sleep patterns, limited exposure to sunlight, jet lag, nighttime light exposure) have detrimental health consequences. Herein, we provide an overview of circadian timing in three major endocrine axes, the hypothalamo-pituitary-gonadal (HPG), hypothalamo-pituitary-adrenal (HPA) and hypothalamo-pituitary-thyroid (HPT) axes, and then consider the negative health consequences of circadian disruptions in each of these systems. For example, disruptions to HPG axis circadian timing lead to a host of negative reproductive outcomes such as irregular menstrual cycles, low sperm density and increased rates of miscarriages and infertility. Dysregulation of HPA axis timing is associated with obesity and metabolic disease, whereas disruptions to the HPT axis are associated with dysregulated metabolic gene rhythms in the heart. Together, this overview underscores the significance of circadian endocrine rhythms in normal health and disease prevention.

Keywords

biological rhythms; circadian; hormone; reproduction; HPA; HPG; HPT

1. Introduction

Walter Cannon coined the term homeostasis (standing the same) to describe the remarkable precision with which brain and bodily processes are maintained within stable operating parameters to promote optimal health and prevent illness [1]. However, physiological and behavioral needs vary markedly and predictably over the course of the day, necessitating that

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biological systems adjust correspondingly. he circadian timing system synergizes with homeostatic drive to anticipate changing daily requirements and modify central and peripheral physiology accordingly. Under ideal circumstances, exposure to sunlight during the day and darkness at night optimally entrains (synchronizes) endogenously-generated circadian rhythms to environmental time to temporally coordinate neural and hormonal events for optimal health and functioning. Unfortunately, a major consequence of the modern lifestyle is increased exposure to sun-free environments during the day and artificial lighting at night, resulting in an incongruence between the endogenous circadian timing system and the external environment [2,3]. Such concerns have attracted the attention of the medical community, with the American Medical Association adopting a policy statement on the dangers of light at night for a number of maladies [4].

Hormones are substantial regulators of biological and behavioral events, including sexual motivation and reproduction, feeding and metabolism, sleep and vigilance, and immune function. Given the broad functional implications of hormones and their ability to travel long distances through the bloodstream, rhythms in endocrine secretions have far-reaching consequences for physiology and behavior [5–8]. Likewise, circadian-controlled rhythms in physiology and behavior (e.g., feeding) can influence rhythmic endocrine secretion (e.g., [9]; Figure 1). In the present overview, we consider circadian timing in three major endocrine axes (the hypothalamo-pituitary-gonadal (HPG), hypothalamo-pituitary-adrenal (HPA) and hypothalamo-pituitary-thyroid (HPT) axes) their functional significance, and clinical implications when their circadian timing is disrupted.

2. The Circadian Timing System

The circadian system includes a master brain clock in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus that is synchronized to environmental time via a direct retinal pathway [10]. The SCN has direct access to environmental time cues and uses neural, diffusible and autonomic communication to convey timing information to the whole organism [5,11]. By communicating to hypothalamic neuroendocrine cells and hormone-producing glands, the SCN has widespread influence over the timing of physiology and behavior. At the cellular level, circadian rhythms are generated by a autoregulatory transcription-translation feedback loop consisting of clock genes and their protein products [12]. The core feedback loop begins in the morning with the clock protein, CLOCK, binding to BMAL1 to drive the transcription of the *Period* (*Per1* and *Per2*) and *Cryptochrome* (*Cry1* and *Cry2*) genes. Over the course of the day, *Per* and *Cry* transcripts are translated into their respective proteins that inevitably feed back to the cell nucleus to repress CLOCK:BMAL1-mediated transcription until the next morning when transcription resumes. Circadian timekeeping is a ubiquitous property of cells throughout the brain and body, with virtually all cells exhibiting circadian timekeeping [13]. However, in the absence of light input, the SCN maintains indefinite circadian rhythms at the tissue level due to unique coupling among independent oscillators in this master pacemaker. In contrast, in the absence of master clock communication or other entraining stimuli, extra-SCN brain loci and peripheral organs exhibit loss of rhythmicity after several cycles [14,15]. This loss of rhythmicity in extra-SCN systems results from loss of coupling among cellular oscillators having slightly different periods [16]. Disruptions to this circadian timing through night or rotating shift

work, international travel, irregular sleep patterns, limited exposure to sunlight, and exposure to light pollution and electronic devices at night precipitates a host of illnesses, including obesity and metabolic disease [17,18], breast cancer [19], prostate cancer [20], mental illness [21,22], and reproductive deficits [23,24].

3. The Hypothalamo-Pituitary Gonadal Axis

The HPG axis controls reproduction, including the generation and maintenance of gametes and sexual motivation and behavior. Secretion of hypothalamic gonadotropin-releasing hormone (GnRH) triggers the release of the gonadotropins, luteinizing hormone (LH) and follicle-stimulating hormone (FSH), from the anterior pituitary. In turn, LH and FSH stimulate gonadal sex steroid (i.e., estradiol, progesterone, and testosterone) synthesis and secretion and gamete maturation, respectively. Sex steroids and gonadotropins feed back onto the HPG axis to regulate its activity. Hormones produced by the HPG axis are under strong circadian control [5,6], with male and female reproductive function negatively affected by disruptions to circadian timing [23–25].

3.1 Circadian timing and female reproduction

Converging lines of evidence implicate a critical role for circadian timing in successful female reproduction across mammalian species, including humans (see [23,24,26–28] for comprehensive reviews on this topic). Ovulation, behavioral estrus, fertilization, pregnancy maintenance, and birth each require specific temporal patterns of hormone secretion regulated by the circadian system [29–33]. The negative consequences of chronic circadian disruption for female reproductive health are underscored in studies investigating women or animals with marked circadian deficits. Women with irregular work or sleep cycles, for example, exhibit abnormal menstrual cycles [34,35], reduced fertility [36,37] and increased miscarriage rates [37–39]. In rodents, destruction of the SCN, its neural output, or the genes regulating cellular clock function lead to pronounced abnormalities in ovulation and fecundity [40–44].

Because the majority of functional studies have explored the role of the circadian system in ovulation, the present overview will focus on this aspect of the female reproductive cycle. In spontaneously ovulating mammals, estradiol secretion from maturing ovarian follicles maintains LH at low concentrations through estradiol negative feedback during the follicular phase of the ovulatory cycle. Just prior to ovulation, estradiol negative feedback is suppressed and estradiol acts through positive feedback to stimulate the LH surge that initiates ovulation. Findings across rodent species by our group and others have shown that the SCN acts to coordinate the timing of negative and positive feedback via actions on the inhibitory neuropeptide, gonadotropin-inhibitory hormone (GnIH; also know as RFamide-related peptide 3) and the stimulatory neuropeptide, kisspeptin (reviewed in [45–47]). At the time of the preovulatory LH surge that stimulates ovulation, the SCN suppresses estradiol negative feedback by acting on GnIH neurons and stimulates estradiol positive drive via actions on the kisspeptin and GnRH systems. In addition to these monosynaptic projections to neuroendocrine cells, the SCN may be communicating via autonomic outflow through the PVN to the ovary [48,49]. Finally, circadian timekeeping at the level of GnIH, GnRH and

kisspeptin neurons furthers precision in the balance of these negative and positive and regulators [50–53] (Figure 1).

In addition to actions at the level of the brain, cellular clocks in the ovary have been implicated in follicular growth, hormone synthesis, and ovulation [54], with clock gene expression observed in theca, granulosa, and luteal cells [55]. Additionally, abnormal rhythms of *Per2* are seen in ovary in a mouse model of polycystic ovarian syndrome [56], suggesting abnormal ovarian rhythmicity may contribute to the symptoms of the disease. Using RT-qPCR, rhythms in clock genes are observed in the rat ovary across the ovulatory cycle [57]. Likewise, in rats with a luciferase reporter for *Per1*, circadian rhythms are seen in the ovary *in vitro* with large phase adjustments observed in response to LH and FSH [58]. *In vivo*, rats treated with LH during the subjective night ovulate more frequently and produced more oocytes than animals treated during the subjective day[59]. Together, these results suggest that ovarian timers mediate the sensitivity of the ovary to LH across the day, further establishing an important role for the circadian system in ovulation. The generation of ovarian cell-phenotype-specific clock gene knockout/knockdown mice will help to clarify the specific role of ovarian clocks.

3.2 Circadian timing and male reproductive function

Although the significance of circadian timing in male reproduction has received less attention than that of females, several lines of evidence point to an important role for rhythmicity in males. Men exhibit daily changes in semen quality and sperm numbers [60,61], and those who work irregular shifts exhibit compromised fertility and lower sperm density, motile count, and testosterone [20]. Global knockout of *Bmal1* leads to loss of circadian rhythmicity and infertility in male mice, presumably due to abnormal hormone secretion, small testes and seminal vesicles, and low sperm count [62]. However, testes from these mice still produce viable sperm, suggesting infertility may be due to alterations in behavior in these mice. More recent findings reveal that *Bmal1* knockout males fail to mate with receptive females [63]. Interestingly, this deficit appears to be due abnormal olfactory processing. Although the vomeronasal organ (VNO) responds appropriately to pheromonal stimulation, hypothalamic targets of the VNO do not respond properly to downstream signaling from the VNO. These findings indicate that, although *Bmal1* knockout mice may be capable of sexual behavior, the motivation to engage is such behavior is abolished due to deficits in olfactory processing. Whether these deficits result from loss of rhythmicity in neural targets of the olfactory system or through pleiotropic effects resulting from the loss of *Bmal1* remains to be determined. Together, these findings point to several factors that may contribute to infertility in *Bmal1* knockout mice, deficits in hormone secretion, reduced sperm production, and reduced sexual motivation.

In mice, clock genes are expressed in the testes, but do not exhibit detectable rhythms [64–66]. In *Clock* mutant mice, *Per1* expression is not altered relative to wild-type mice, indicating that typical CLOCK:BMAL1-mediated transcription may not drive *Period* gene production in mouse testis [66]. Mice lacking *Bmal1* have reduced steroidogenic acute regulatory protein (StAR), the rate-limiting enzyme in steroidogenesis, reduced serum testosterone levels, and elevated LH concentrations [62], pointing to a central role for this

clock gene in normal testicular function. Intriguingly, in Syrian hamster testis, *Per1* and *Bmal1* are expressed rhythmically [67]. This same study identified two *Per1* transcripts in testis that differed from those seen in mice and other hamster organs, with these transcript variants lacking a nuclear localization signal and lacking a putative CRY1-binding domain. Whether or not these hamster transcript variants account for the apparent rhythmicity of testicular clock gene expression in this species remains to be determined.

4. Hypothalamo-Pituitary Adrenal Axis

The HPA axis regulates arousal and energy mobilization under typical conditions and rapidly mobilizes energy from stored sources to facilitate the fight or flight response. Analogous to the HPG axis, the hypothalamic peptide, corticotropin-releasing hormone (CRH), is released into the anterior pituitary blood supply and stimulates the release of adrenocorticotropic hormone (ACTH). ACTH released into systemic circulation, in turn, acts on the adrenal cortex to stimulate glucocorticoid (GC) (i.e., cortisol and corticosterone) release. GC acts broadly within the brain and body through negative feedback to inhibit its own production. Humans, non-human primates, and rodents exhibit pronounced daily GC rhythms that persist in constant conditions, with GC concentrations rising prior to waking, decreasing throughout the day, and falling in anticipation of sleep [5,68,69]. Like the ovaries, the adrenal glands exhibit rhythms in clock gene expression that likely drive daily changes in responsiveness to ACTH stimulation and stress [70–73]. Rhythms in adrenal GC secretion and adrenal clock gene expression are eliminated by SCN lesions [74,75], suggesting that circadian rhythms in individual cells of the adrenal become uncoupled in the absence of SCN input.

The SCN drives rhythmic secretion of GC through several pathways (Figure 1). The first pathway indirectly targets CRH neurons in the paraventricular nucleus of the hypothalamus (PVN) through SCN arginine vasopressin-ergic projections to an area just below the PVN (the subPVN) and the dorsomedial hypothalamus (DMH) [76–78]. In turn, the subPVN and DMH regulate CRH production. Secondly, the SCN continues through this PVN pathway, sending autonomic outflow through a multisynaptic projection to the adrenal cortex [79]. As removal of the pituitary (and resulting abolition of ACTH secretion) does not alter clock gene rhythmicity in the adrenal cortex [72], it is likely that SCN control of autonomic input to the adrenals is responsible for the coordination/maintenance of adrenal cellular clocks. Finally, feeding influences GC rhythms, underscoring the importance of circadian-controlled behavior in maintaining typical endocrine rhythmicity [9].

GC can act throughout the periphery to set the phase of oscillators in individual peripheral systems [9,80–82]. As a result, disruptions to GC rhythms have far-reaching,negative impact on normal physiology, particularly metabolism (see [83] a review of this topic). Travel in humans and experimental jet lag in rodents increases GC [84,85], contributing to negative health consequences of circadian disruption. In addition, advancing the sleep-wake and light-dark cycles by 8 hours in humans results in elevated nighttime cortisol concentrations, likely contributing to difficulty falling asleep at the new circadian phase. Individuals suffering from depression have abnormal cortisol and ACTH rhythms, with the trough of

both hormones advanced 3 h [86,87]. Whether disruptions to the cortisol rhythm are a cause or consequence of depressive symptoms remains to be determined.

Given the role of GC in energy mobilization and utilization, disruptions to HPA axis rhythmicity are implicated in obesity and metabolic disease. Chronic stress, for example, results in elevated GC concentrations and abnormal GC rhythmicity and is associated with obesity, insulin resistance, dyslipidemia, hypertension, and hyperglycemia [83]. Obese mice and humans exhibit flattened GC rhythms, further pointing to HPA axis dysregulation in obesity [88,89]. People with select polymorphisms in the *Clock* gene are at greater risk for obesity and metabolic disease [90,91]. Furthermore, patients with abnormal HPA axis functioning and receiving cortisol replacement at tonic high levels (rather than mimicking the endogenous rhythm) are at greater risk for cardiovascular and metabolic bone disease [92]. Likewise, *Cry* deficient mice exhibit HPA axis deficits and are vulnerable to obesity and enhanced fat deposition when fed a high fat diet [93]. Similarly, mice deficient in *Clock* or *Bmal1* exhibit abnormal glucose and triglycerides rhythms, and develop obesity, hyperlipidemia and diabetes mellitus [94,95]. Although these disease risks have not been directly linked to disruptions in HPA axis rhythmicity in these knockout mice, it is noteworthy that glucocorticoid excess results in the same negative outcomes across studies [83]. Whereas it has been challenging to specifically link alterations in HPA axis rhythms directly to metabolic outcomes, these converging lines of evidence, along with established functions of GC, suggest that disrupted HPA rhythms contribute to metabolic dysregulation.

4. Hypothalamo-Pituitary Thyroid Axis

The HPT axis is responsible for regulating metabolism. Hypothalamic release of thyrotropin-releasing hormone (TRH) into the anterior pituitary stimulates production and release of thyroid-stimulating hormone (TSH) in the general circulation. TSH stimulates production of thyroid hormones from the thyroid gland. Thyroid hormones are initially produced as thyroglobulin, which is converted primarily to thyroxine (T4). T4 is considered inactive and is further converted into the active thyroid hormone, triiodothyronine (T3) in target tissues. In humans, the HPT axis is under circadian control, with free T3 and TSH being low during the day and high at night [96,97]. In rats, TSH is rhythmic and in antiphase to that of humans (low during the night and high during the day), with rhythmic secretion abolished by SCN lesions [98–100]. As with the adrenals, clock genes (*Per1* and *Bmal1*) are rhythmically expressed in the rat thyroid [101]. Whereas daily rhythms in thyroid hormones are abolished by hypophysectomy, rhythms in clock gene expression are unaffected, suggesting that thyroid clock maintenance is accomplished through SCN autonomic innervation of the thyroid gland. Indeed, retrograde transneuronal tracing from the thyroid gland reveals multisynaptic projections from the SCN [100]. This same study found direct projections to TSH neurons located in the PVN, indicating that, as with the HPA and potentially the HPG axes, the SCN regulates thyroid hormone secretion both via actions on TSH neuroendocrine cells and via autonomic outflow to the thyroid (Figure 1).

Relative to the HPA and HPG axis, less work has focused on the negative effects of disrupted HPT axis rhythms. Given the contribution of circadian disruption to obesity and metabolic disease, it is feasible that disruptions to the HPT axis contribute to these

outcomes. Thyroidectomy followed by ‘flat’ T3 replacement negatively impact clock and metabolic genes in the heart and may contribute to heart conditions associated with hypo- and hyperthyroid disease [102]. In mice, exposure to constant light reduces TSH concentrations and abolishes day-night rhythms in free T3 and leptin [103], indicating that entraining stimuli likely contribute to HPT axis rhythmicity and underscore the importance of stable exposure to day-night cycles in maintaining HPT axis health. Finally, thyroid cancer is associated with dysregulated clock gene expression in thyroid cells during the transition from a benign to malignant state [104,105]. Whether dysregulated clock gene expression is a cause or consequence of this transition remains to be determined.

5. Conclusions and Considerations

Circadian control of physiological functioning is ubiquitous throughout the brain and body and contributes to the maintenance of optimal health. The endocrine system provides a mechanism of circadian control by which systemic chemical communicators can broadly influence organismal rhythms. Disruptions to endocrine rhythms are associated with deteriorating health and vulnerability to disease. Given that circadian disruption is virtually inescapable in the modern world, it is imperative to develop strategies to maximize circadian health in the face of such chronic disruptions. Likewise,this overview underscores the importance of educating patients suffering from chronic or recurrent disease, as well as healthy individuals, about the importance of consistent sleep-wake patterns, exposure to sunlight, and avoidance of nighttime lighting wavelengths that markedly alter circadian timing.

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Highlights

- The circadian system coordinates physiology and behavior with time of day
- Hormones broadly affect central and peripheral physiology and behavior.
- The circadian system coordinates endocrine timing via direct communication to neuroendocrine cells, autonomic outflow to endocrine glands and through and rhythmic behavior.
- Disruptions to endocrine timing have marked, negative impact on normal physiology and behavior and are associated with a variety of disease states.

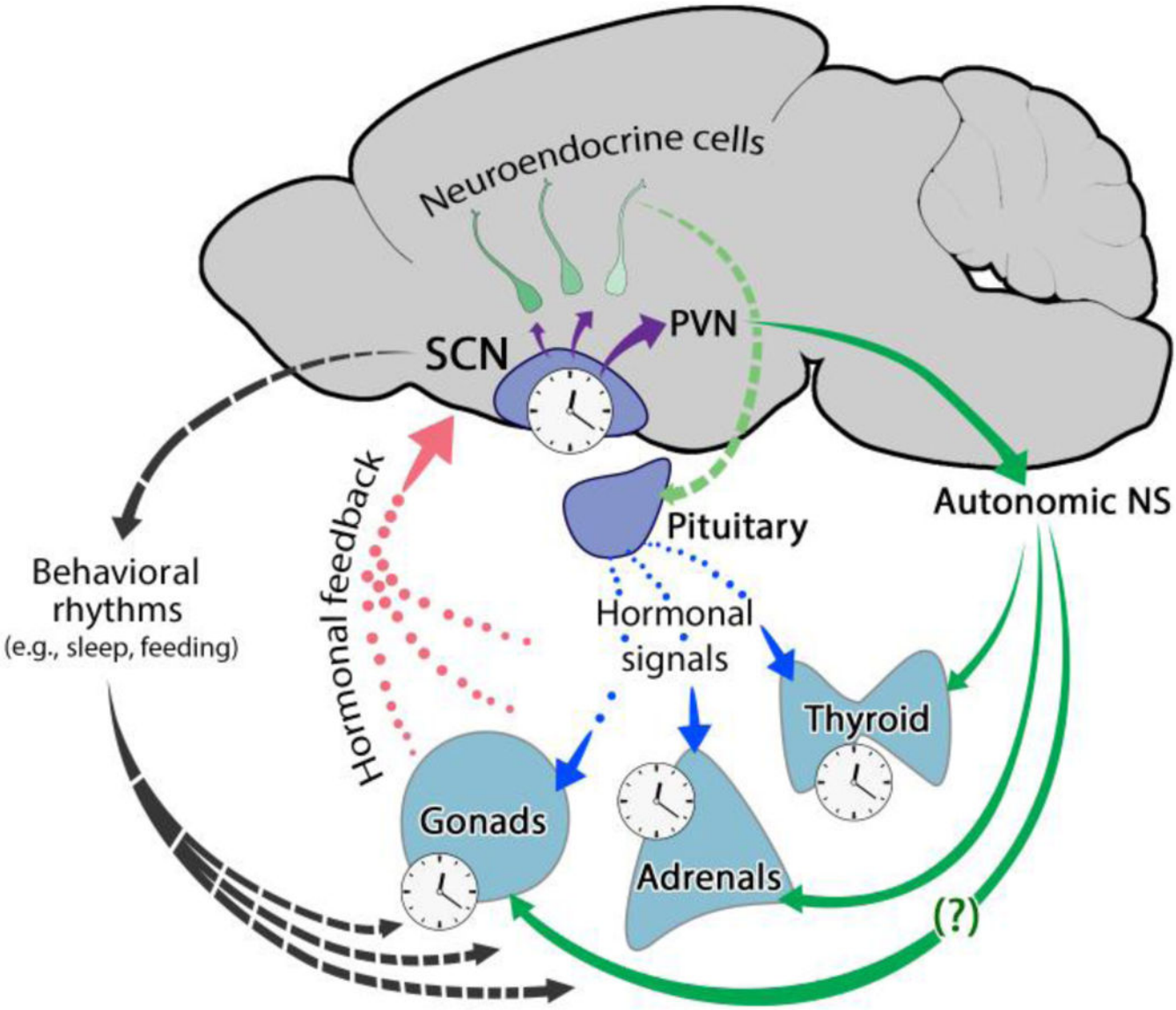

Figure 1.

The SCN influences endocrine timing via projections to neuroendocrine cells in the brain, autonomic outflow through initial projections to the PVN, and rhythmic behavioral output. Autonomic outflow from the SCN to the gonads, while likely, has not been specifically examined. Peripheral clocks are found in the gonads, adrenals, and thyroid, keeping their own circadian time coordinated by the SCN. Peripheral clock functioning likely serves to further control hormonal output from these glands. Finally, hormones from these glands feed back to the hypothalamus and pituitary to further regulate their own production and secretion.