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Circadian regulation of endocrine systems

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ABSTRACT

Hormones are major systemic regulators of homeostatic functions. Not surprisingly, most endocrine signals show some extent of variation across the day. This holds true for the three major hormonal axes of the body originating from the hypothalamus, relayed by the pituitary and terminating in the adrenal (HPA axis), the thyroid (HPT axis), and the gonads (HPG axis), respectively. The rhythmicity of endocrine axis formation has important functions for the maintenance of homeostasis and stabilizes physiological functions against external perturbations. In some cases, such as cortisol, hormonal signals are themselves implicated in circadian regulation and, thus, endocrine disruption may affect the function of the circadian clock network to alter further downstream processes.

1. Introduction

The circadian clock system adjusts the body's physiological functions to changes in environmental demands brought about by the Earth's rotation around its axis. Most cells and tissues of our body harbor molecular clocks synchronized with the external light-dark cycle by a master pacemaker residing in the hypothalamic suprachiasmatic nucleus (SCN). At the cellular level, these clocks are based on a set of clock genes whose activity is controlled *via* interlocked transcriptional-translational feedback loops (Hastings et al., 2018). For the communication, synchronization and orchestration of biological processes across the body's organs, the endocrine glands release messenger hormones into the circulatory system. Many of these hormones show pronounced circadian rhythmicity, thereby conferring time-of-day information to physiological processes across the body. On the other hand, endocrine signals can affect molecular clock function in peripheral tissues and the brain, thus adjusting internal timekeeping and clock-controlled processes to changes in environmental conditions (Tsang et al., 2016). This delicate crosstalk is sensitive to external perturbations, *e.g.* by nocturnal light exposure and food intake or by endocrine pathologies promoting internal desynchrony and the development of a range of associated disorders, from obesity to major depression and even cancer.

2. Anatomy & physiology

The three major endocrine systems of the body are the hypothalamus-pituitary-adrenal (HPA) axis, which plays a crucial role in the adaptation to stress, the hypothalamus-pituitary-gonadal (HPG) axis, most important for reproduction, and the hypothalamus-pituitary-thyroid (HPT) axis, a key regulator of metabolism and energy homeostasis. All three axes share a similar hierarchical organization originating in the hypothalamus. *Via* peptide "releasing" hormones the hypothalamus induces production and release of secondary modulators (stimulating hormones) in the anterior pituitary, which in turn act on target tissues to induce the secretion of the final effector hormones. Many hypothalamic regions show robust tissue clock rhythmicity (Guilding et al., 2009), as do the pituitary and most peripheral target tissues (Yoo et al., 2004). Therefore, the major endocrine systems are multi-oscillatory axes with endogenous tissue clocks found at all hierarchical levels (Fig. 1). The different axis elements are balanced *via* feed-forward and feedback mechanisms.

3. HPA axis rhythms and clocks

Glucocorticoids (GCs) are the major output of the HPA axis and produced in response to stress (Cheifetz, 1971; Lefcourt et al., 1993). HPA axis activation involves secretion of corticotropin releasing hormone (CRH) from hypophysiotropic neurons of the hypothalamic paraventricular nucleus (PVH), adrenocorticotropic hormone (ACTH) release from the pituitary and subsequent activation of steroidogenesis in the adrenal cortex (Smith and Vale, 2006). Under non-stressed conditions plasma GC levels show pulsatile and circadian patterns with highest levels before the onset of activity. While hourly pulsatile GC

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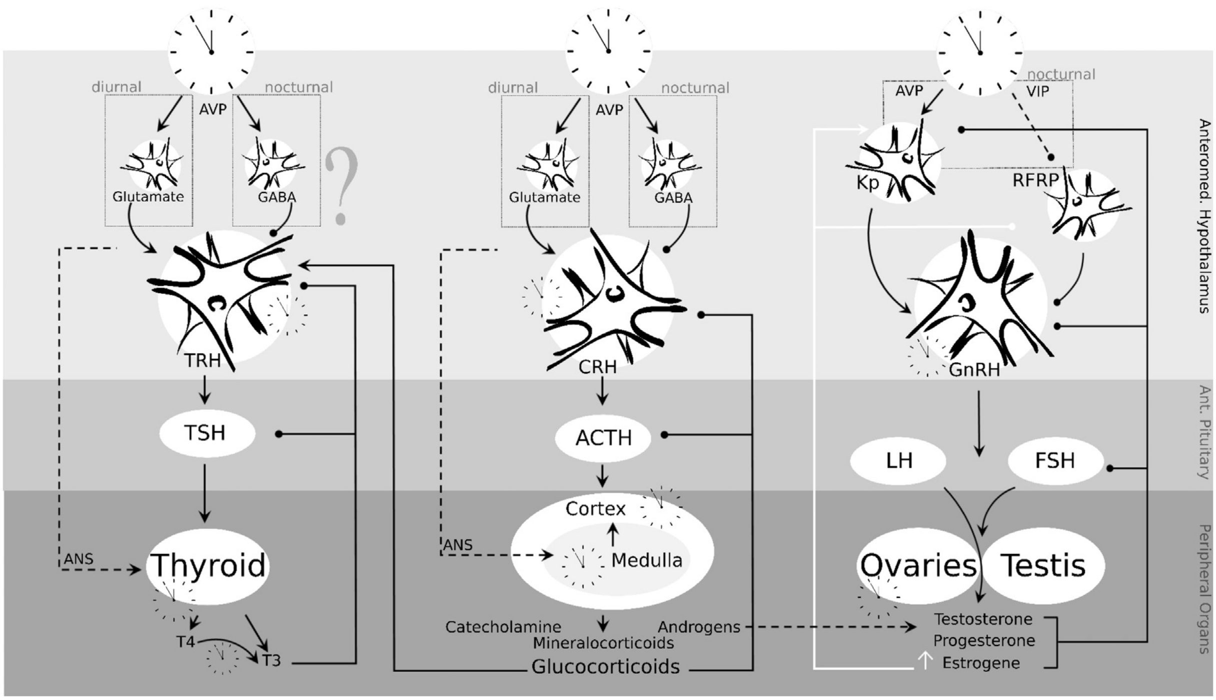

Fig. 1. Circadian regulation of the major endocrine axes. The suprachiasmatic nucleus (SCN, shown as master clock) stimulates *via* its different neurotransmitter outputs (arginine vasopressin, AVP, and vasoactive peptide, VIP) inhibitory (γ-aminobutyric acid, GABA, or RFamide-related peptide, RFRP) and excitatory neurons (Glutamate or Kisspeptin, Kp), that further regulate the activity of hypothalamic tropic hormones-releasing neurons. Endogenous tissue clocks within these neurons, the anterior pituitary and target organs fine-tune circadian rhythmicity. *Via* the autonomous nervous system (ANS) the SCN exerts additional regulation of endocrine target organs. Crosstalk between the different axes possibly supports synchronicity. Thyroid hormone target tissues (*e.g.* hypothalamus and anterior pituitary) show circadian regulation of thyroxine (T4) to triiodothyronine (T3) conversion. Furthermore, effector hormones feedback to all levels of the regulatory hierarchy to inhibit their own production. Estrogens have the unique property to induce gonadal axis activity when concentrations exceed a certain threshold to initiate pre-ovulatory luteinizing hormone (LH) surge (white lines). Arrows represent stimulation, dots inhibition, dashed lines indirect mechanisms. TRH thyrotropin-releasing hormone, TSH thyroid-stimulating hormone, CRH corticotropin-releasing hormone, ACTH adrenocorticotropic hormone, GnRH gonadotropin-releasing hormone, FSH follicle-stimulating hormone.

rhythms result from a negative feedback loop in which GCs inhibit ACTH secretion from the pituitary, circadian GC rhythms are regulated on multiple levels (Spiga et al., 2014; Walker et al., 2012).

Early animal experiments show that SCN lesions result in abolished GC rhythms, suggesting a role of the SCN in circadian GC regulation (Moore and Eichler, 1972). Arginine vasopressin (AVP) containing SCN neurons directly project to the dorsomedial hypothalamic nucleus (DMH) and the PVH to control the timing of CRH production (Kalsbeek et al., 1996a, b, 2010). In nocturnal species SCN-derived AVP has a strong inhibitory effect on the regulation of the HPA axis. Consequently, increased AVP release results in low GC levels in the first part of the rest period (*i.e.* the light phase) (Kalsbeek et al., 1996a). In contrast, high GC levels just before waking result from stimulation of the HPA axis by absence of AVP and increased release of an additional, yet unknown, stimulatory input from the SCN (Kalsbeek et al., 1996b). In diurnal species such as humans, AVP seems to have an opposite excitatory effect, activating glutamatergic neurons in the DMH and the PVH (Kalsbeek et al., 2012).

While ACTH has been shown to reset adrenal circadian clocks *in vitro* (Yoder et al., 2014), GC rhythms persist in hypophysectomized animals, suggesting that ACTH may contribute to phase adjustment of GC production, but is not essential for the generation of daily GC rhythms *per se* (Engler et al., 1990; Ottenweller and Meier, 1982). In addition, the SCN regulates the sensitivity of the adrenal cortex to ACTH *via* the autonomic nervous system (ANS) (Buijs et al., 1999; Ishida et al., 2005; Ulrich-Lai et al., 2006). Transection of the thoracic splanchnic nerve, the primary conduit for autonomic innervation to the adrenal, results in dampened circadian rhythms of GC secretion (Holgert et al., 1998; Kleitman and Holzwarth, 1985; Ulrich-Lai et al., 2006). Demedullation experiments reveal that the adrenal medulla is required for the autonomic influence on glucocorticoid release (Ulrich-Lai et al., 2006). The adrenal gland clock itself plays a special role in regulating the sensitivity of the adrenal cortex to ACTH. In mice, knockout of the core clock gene *Bmal1* leads to a lack of responsiveness of the adrenal gland to ACTH, impaired GC production, and inadequate responses to stress (Leliavski et al., 2014). Similarly, adrenal specific ablation of the circadian clock in mice, either by conditional knockdown or by tissue transplantation, results in dampened GC rhythms under constant darkness conditions, suggesting that the adrenal clock gene machinery regulates circadian GC production (Oster et al., 2006; Son et al., 2008). In summary, circadian release of GCs is regulated by interplay of the endocrine activity of the HPA axis, SCN signaling, and the action of peripheral adrenal clocks.

4. HPT axis rhythms and clocks

Hypothalamic thyrotropin-releasing hormone (TRH) activates the production thyroid-stimulating hormone (TSH, also known as thyrotropin) in the anterior pituitary, which, in turn, stimulates the synthesis and release of both thyroid hormones (THs), triiodothyronine (T3) and thyroxine (T4). Physiological TH levels are maintained by a negative feedback loop, in which high TH serum levels inhibit synthesis and release of TRH and TSH at the level of the hypothalamus and pituitary (Ortiga-Carvalho et al., 2016). Besides THs, other circulating hormones modulate HPT axis activity. High GC levels have been shown to suppress TSH secretion (Brabant et al., 1987), possibly by attenuating the hypophyseal response to TRH (Jameson et al., 2016). GCs may modulate TRH synthesis at the transcriptional level, however both inhibitory (Kakucska et al., 1995) and stimulatory (Luo et al., 1995) effects have been reported (Mariotti and Beck-Peccoz, 2000). Melatonin may further modulate the response of the pituitary to TRH and of the thyroid to TSH (Mazzoccoli et al., 2004).

In humans and animals, TRH and TSH serum levels show a clear circadian rhythm, with higher levels during the inactive phase (Jordan et al., 1980, 1987; Mazzoccoli et al., 2004; Persani et al., 1995; Philippe and Dibner, 2016; Rookh et al., 1979; Russell et al., 2008). Moderate daily rhythms of T3 und T4 have been reported in rat serum (Campos-Barros et al., 1997; Jordan et al., 1980), whereas in humans, daily rhythmicity for T4 is less evident (Philippe and Dibner, 2016; Russell et al., 2008). There is evidence for the circadian regulation of the HPT axis by the SCN (Kalsbeek and Fliers, 2013). Thermic SCN lesions in rats, for instance, disrupt circadian AVP and circulating TSH and TH oscillations (Kalsbeek et al., 2000). Indeed, SCN fibers have been shown to contact TRH neurons in the PVH and modulate circadian expression of *Trh* mRNA (Kalsbeek and Fliers, 2013). The mechanisms for this circadian modulation of TRH neuron activity by the SCN, however, are still poorly understood (Kalsbeek and Fliers, 2013; Roelfsema et al., 2017). Interestingly, circadian rhythms of PVH neuronal activity and TSH release are antiphasic between nocturnal and diurnal species, suggesting an opposite response of the PVH to SCN neurotransmitter, similar to the circadian regulation of the HPA axis (Bertani et al., 2010; Kalsbeek et al., 2010; Martin-Fairey et al., 2015). Furthermore, the SCN might modulate TH release *via* the autonomic nervous system (Kalsbeek et al., 2000). Retrograde trans-neuronal tracing experiments identified multisynaptic connections between the SCN and the thyroid gland (Kalsbeek et al., 2000). In conclusion, there are two possible mechanisms by which the SCN may modulate TH secretion; firstly, by affecting the neuroendocrine control of TSH release through TRH neurons in the PVH, and, secondly, *via* autonomic input into the thyroid gland (Kalsbeek et al., 2000).

Target tissue clocks modulate TH activity. In rats, the TH activating deiodinase 2 (D2), which converts T4 into the biologically much more active T3, has been reported to show rhythmic activity in several tissues, such as pituitary and hypothalamus (Kalsbeek et al., 2005). At the same time, the TH inactivating deiodinase 3 (D3) is rhythmically expressed in pituitary of fish (Jones et al., 2013). Moreover, circadian gene expression patterns of D3 are in phase with those of TSH, suggesting that local TH conversion is an important component of HPT axis negative feedback control (Jones et al., 2013). The clock component REV-ERBα (NR1D1) has been shown to interact with nuclear corepressor 1 (NCoR1) to regulate expression of the TSH beta subunit (*Tshb*) (Aninye et al., 2014), suggesting direct involvement of molecular clock components in the regulation of TSH production. Self-sustained circadian oscillators have been described in human primary thyrocytes (Mannic et al., 2013) and the thyroid gland of rats (Fahrenkrug et al., 2017). In hypophysectomised rats, circadian TH rhythms are eliminated, but expression of the circadian clock genes *Bmal1* and *Per1* in the thyroid is unaffected, indicating that circadian TH secretion is controlled by rhythmic TSH release rather than by thyroid clocks (Fahrenkrug et al., 2017).

5. HPG axis rhythms and clocks

Hypothalamic neurons that secrete gonadotropin releasing hormone (GnRH) are the major driving force for the activity of reproductive organs. Projecting to the median eminence they activate secretion and release of hypophyseal gonadotropins into the blood stream. These gonadotropins, namely luteinizing (LH) and follicle-stimulating hormone (FSH), trigger sex steroid production as well as follicular growth and ovulation in females. Kisspeptin (Kp)-expressing neurons were shown to be heavily involved in sexual differentiation and reproduction with projections to GnRH cell bodies (Clarkson and Herbison, 2006). Kp is a potent stimulant of GnRH secretion and gonadal activity (Navarro et al., 2005) which in turn is inhibited by RFamide-related peptide (RFRP) (Pineda et al., 2010). Interestingly, in males, testosterone inhibits Kp and GnRH expression, while in females the effect is more complex depending on estradiol concentrations and menstrual stage (Simonneaux et al., 2017). Here, this effect is almost exclusively mediated by regulation of Kp neurons, since GnRH neurons do not express the required estrogen receptor (ERα) (Gottsch et al., 2004).

HPG axis regulation is rhythmic at various levels: GnRH secretion is pulsatile and circadian while regulation along the ovarian cycle is in the range of days to weeks. Finally, reproduction shows marked seasonal variations in many species. Interestingly, not only 24-hour rhythms are affected by circadian clock function: while the role of the circadian system in seasonality remains poorly understood (Nishiwaki-Ohkawa and Yoshimura, 2016), clock gene mutations affect GnRH pulsatility (Chappell et al., 2003). Moreover, the circadian clock acts as a timing signal for the ovulation-inducing LH surge in females, which usually occurs at the end of the daily resting phase. In nocturnal animals, the SCN clock directly communicates with GnRH neurons *via* vasoactive intestinal polypeptide (VIP) signaling (Kriegsfeld et al., 2002). At the same time, Kp neurons receive input from the SCN *via* AVP (Williams et al., 2011). Moreover, Kp neuronal responses to AVP are estradiol-dependent (Piet et al., 2015) whereas GnRH neurons show a temporally gated responsiveness to Kp (Williams et al., 2011) regulated by circadian expression of Kp receptor (Poling et al., 2017) and clock genes (Hickok and Tischkau, 2010). Thus, GnRH and Kp neurons together fine-tune LH surge timing. RFRP neurons are also innervated by the SCN *via* VIP, but RFRP expression is reduced *prior* to the LH surge (Russo et al., 2015). Estrogen feedback mechanisms on Kp and RFRP neurons are present in males, too, but without an underlying gating mechanism (Poling et al., 2017). Studies with a gonadotrope-specific disruption of the clock gene *Bmal1* indicate that intrinsic pituitary clocks are not essential for LH surge regulation but might contribute to estrous cycle robustness (Chu et al., 2013). Interestingly, males may lack a robustly functional clock in the testis (Morse et al., 2003; Mazzoccoli et al., 2012), but gonadosteroids, testosterone and estradiol, show marked diurnal rhythms in plasma concentrations in human males and females, respectively (Bao et al., 2003; Barberia et al., 1973). The regulatory mechanisms behind this rhythmicity are still unclear. Moreover, despite the numerous effects the circadian system can have on HPG axis activity, it is debatable to which extent it is required for reproduction in general. In some cases, disruption of the clock machinery by knock-out of core clock genes leads to reduction or loss of fertility in female and male mice alike (Miller et al., 2004; Ratajczak et al., 2009; Xu et al., 2016). Male infertility is not fully understood yet and sperms are still functional *in vitro*, but mating behavior appears to be impaired (Schoeller et al., 2016). Female infertility involves implantation failure and marked neuroendocrine dysregulation (Liu et al., 2014; Ratajczak et al., 2009). The clock gene *Bmal1* is essential for oocyte fertilization (Xu et al., 2016) and, while spontaneous ovulation is unaffected in global Bmal1 KO mice, it is disrupted in mice with a conditional deletion of Bmal1 in ovarian theca cells (Mereness et al., 2016). Hence, in an intact circadian system the theca cells can act as a pacemaker for ovulation.

While the circadian system to various extent modulates activity of the three major endocrine axes rhythmic endocrine signals may feedback on central and peripheral circadian clocks, thus providing systemic cues to orchestrate circadian behavior and physiological functions.

6. GC clock feedback

GCs have been shown to reset peripheral clocks *in vitro* and *in vivo*. Acute treatment with the glucocorticoid analogue dexamethasone leads to synchronization of various cell culture systems and induces phase shifts in circadian clocks of several mouse peripheral tissues, such as liver, kidney and heart (Balsalobre et al., 2000). GCs modulate clock gene expression at the transcriptional level, in a glucocorticoid receptor (GR)-dependent fashion (Son et al., 2011). While *Per1* expression is acutely induced *via* GR binding to GC-responsive elements (GREs) in the *Per1* promoter (Yamamoto et al., 2005), *Rev-erbα* (*Nr1d1*) expression is repressed (Torra et al., 2000). Additionally, GC rhythms themselves can also produce rhythms of their physiological target genes, in a more direct manner, without affecting local clocks. DNA microarray analysis revealed that 100 out of 169 cycling hepatic genes lose circadian rhythmicity after adrenalectomy, while circadian clock gene expression remains intact (Oishi et al., 2005).

In rodents, disruption of GC rhythms, either genetically (Son et al., 2008) or surgically (Soták et al., 2016), results in reduced amplitudes of circadian clock gene expression profiles in various peripheral organs, such as liver, kidney and others, but does usually not completely abolish circadian clock gene oscillations. Adrenalectomy also does not affect the phasing of peripheral clock gene oscillations (Soták et al., 2016). Therefore it can be concluded, that GC rhythms are not essential for molecular clock operation in peripheral tissues (Spencer et al., 2018) and that, besides GCs, other humoral factors are involved in resetting tissue clock gene oscillations (Spencer et al., 2018).

Instead, GC rhythms have stabilizing effects on overt physiological rhythms (Chung et al., 2011). For instance, they prevent uncoupling of peripheral clocks from central clocks during non-natural feeding times (Le Minh et al., 2001). Ablation of GC rhythms by adrenalectomy in nocturnal mice results in faster phase shifts of peripheral oscillators during daytime-restricted feeding conditions compared to sham-operated animals (Le Minh et al., 2001), showing that GC rhythms play a modulatory role in food entrainment (Dickmeis, 2009). Similarly, pharmacological suppression of GC production may inhibit or accelerate behavioral adaptation under jetlag conditions in mice, depending on treatment time (Kiessling et al., 2010).

7. TH clock feedback

At present, surprisingly little is known about the relationship between thyroid function and circadian clocks, but there is mounting evidence for a circadian modulation of TH action. BMAL1 complexes include the thyroid hormone receptor-associated protein 150 (TRAP150), a positive clock element, which promotes binding of CLOCK-BMAL1 complexes to target gene promoters, and thus might be involved in timing and reactivation of circadian transcription (Lande-diner et al., 2013). Interestingly, in rat hearts, besides known T3 target genes also core clock components such as *Bmal1* are acutely induced by T3 treatment (Peliciari-Garcia et al., 2016). Moreover, in hypo- and hyperthyroid rats, mRNA levels of *Bmal1*, *Per2*, *Nr1d1* and *Rorα* are altered (Peliciari-Garcia et al., 2018) indicating modulatory effects of T3 on local clock gene expression. Finally, short-term cultivation of human hair follicles with T4 leads to a dampening *Bmal1* and *Per1* expression at transcriptional and translational levels (Hardman et al., 2015) providing further evidence for modulatory TH effects on peripheral clocks.

8. Gonadal steroid clock feedback

It is very well known that gonadal hormones regulate clocks in several tissues including the brain, reproductive and non-reproductive peripheral tissues (Nakamura et al., 2001, 2005, 2008). For instance, estrogen modulates clock gene expression in the SCN, uterus, liver and kidney, *in vivo* (Nakamura et al., 2001, 2005). In addition, *ex-vivo* experiments using estrogen treatments on tissue explant cultures of ovariectomized *PER2*::*LUCIFERASE* knock-in mice revealed shortened periods of rhythmic PER2 oscillations in the uterus, but no effect in SCN slices (Nakamura et al., 2008).

Furthermore, estrogens modulate circadian activity rhythms. In female rodents, estrogen has been shown to influence free-running period and phase angle of entrainment of wheel-running behavior (Morin et al., 1977a, b; Royston et al., 2014). Ovariectomy reduces the amount of total daily activity in female mice, an effect which is reversed by subsequent estradiol administration (Royston et al., 2014). To which extent estrogen's effects on circadian activity are mediated by the SCN is still not clear and there is contradictory data regarding the expression of estrogen receptors (ERs) in the SCN (Hagenauer and Lee, 2011; Karatsoreos and Silver, 2007; Kriegsfeld and Silver, 2006). More likely, these effects are mediated through indirect mechanisms, including estrogen effects on SCN afferents or effects on general activity levels (*i.e.* masking) (Karatsoreos and Silver, 2007). In rodents, both ERs, ERα and ERβ, are expressed in the major input tissues of the SCN, including retina, the retino-hypothalamic and geniculo-hypothalamic tract, and raphe nuclei-derived serotonergic inputs (Simonneaux, 2015).

Androgens also affect circadian activity rhythms. Surgical or photoperiodic castration in hamsters increases the variation of wheel-running onset and increases the number of activity bouts with short duration. Subsequent testosterone replacement restores running patterns (Morin and Cummings, 1981). Androgen receptors (ARs) are expressed in the SCN core region (Karatsoreos et al., 2007). Thus, androgens may affect circadian activity through direct action on the SCN (Kriegsfeld and Silver, 2006). It is also possible that testosterone effects are at least partly mediated *via* conversion to estradiol (Karatsoreos et al., 2007; Kriegsfeld and Silver, 2006).

9. The circadian clock in endocrine pathologies

Alternations of the circadian system greatly impact the endocrine systems and *vice versa*. Disruption of the sleep-wake cycle and light during the night, as during night-shift work, is linked to internal desynchronization (Vogel et al., 2012) and metabolic and endocrine dysfunction (Herichova, 2013; Wang et al., 2014). Additionally, genetic clock gene variants are associated with a broad range of diseases including multiple sclerosis (Golalipour et al., 2017) neurodegenerative disorders (Gu et al., 2015), diabetes, or affective disorders (Valenzuela et al., 2016). While little is known about the impact of HPT axis rhythms on health and well-being, accumulating data suggest that the maintenance and robustness of circadian HPA and HPG axis regulation may be an important factor of physiological homeostasis and disease resistance.

10. Rhythmic HPA axis activity and human health

Sleep disruption affects both ACTH and GC rhythms. Travel by long-distance flights affects daily GC rhythms for up to three weeks depending on flight direction (Désir et al., 1981). Similarly, shift workers suffer from dampened GC rhythms (Diez et al., 2011) and reversed salivary cortisol rhythms during night working (Niu et al., 2015). Rhythmic GC secretion promotes the synchronization of the body's circadian system and GC arrhythmicity has been linked to diseases, from metabolic disorders to depression (Liyanarachchi et al., 2017).

Cushing's patients experience pronounced abnormalities of the HPA axis with dampened GC rhythms as well as overall elevated levels (Liyanarachchi et al., 2017) that may account for a diverse range of metabolic complications. Chronic fatigue syndrome patients, on the other hand, show mild hypocortisolism (Wyller et al., 2016) with attenuated daily rhythms (Nater et al., 2008) accompanied by sleep problems. Adrenal insufficiency leads to a number of comorbidities (Charmandari et al., 2014) including the disruption of daily rhythms in serum glucose and insulin (Björnsdottir et al., 2015; Meyer et al., 2012), blood pressure (Fallo et al., 1994), sleep (García-Borreguero et al., 2000), as well as attenuation of endocrine rhythms of cortisol, renin, angiotensin, TSH, aldosterone, and sex steroids (Björnsdottir et al., 2015; Cugini et al., 1993; Samuels, 2000). Additionally, treatment of adrenal insufficiency with a constant-dose GCs is associated with, among others, increased cardiovascular mortality (Debono et al., 2009). These examples emphasize the importance of a functional HPA axis with circadian GC secretion patterns for health and underline the clinical relevance of a physiological rhythm. A more detailed review of the HPA axis rhythms and physiological homeostasis is provided in

Oster et al. (2016).

11. Rhythmic HPT axis activity and human health

Thyroid hormones are crucial for the regulation of energy metabolism, growth and healthy ageing. Hence, disruptions of thyroid hormones levels come with several comorbidities. Patients suffering from the various forms of hypothyroidism also show changes in thyroid hormone rhythmicity (Roelfsema et al., 2017). Data on diurnal TH rhythms in hyperthyroidism are rare. In one patient, a 24-h rhythm with elevated TSH was observed (Custro et al., 1992). Brabant et al. showed normal rhythms in three patients of TSH-induced hyperthyroidism and an abolished rhythm in tumor-induced thyroid hyperfunction (Brabant et al., 1990a). Depending on the extent of hyperthyroidism, TH rhythms appeared increasingly suppressed in another study (Vardarli et al., 1989). The underlying pathophysiology distinctly impacts TSH rhythmicity and needs to be considered. Besides, it was shown that the heart circadian clock is sensitive to high or low TH levels alike, which might contribute to the pathogenesis of cardiac dysfunction associated with hypo- or hyperthyroidism (Peliciari-Garcia et al., 2018). Moreover, hyperthyroidism patients show blunted daily blood pressure and heart rate rhythms (Klüglich and Middeke, 1992; Kohno et al., 1998).

Due to a strong link between HPT and HPA axis regulation, disruption of the HPA axis is often accompanied by HPT alternations and causality is often difficult to determine. We discussed HPA axis disturbances by jetlag or shift work above. Sleep deprivation also dampens all HPT rhythms (Parker et al., 1987). In regular night shift workers, TSH rhythms and core body temperature remain synchronized but are phase-delayed (Weibel et al., 1995). During sleep withdrawal the TSH pulse frequency is unaltered, but amplitudes rise during the working hours and fall in recovery, strongly dampening the diurnal rhythm (Brabant et al., 1990b). It could be argued that all of these effects are a secondary consequences of abnormal GC and melatonin rhythms. Additionally, insomnia and the risk of developing thyroid cancer were linked (Luo et al., 2013). In thyroid malignant nodules changes in expression of the molecular clock components *Bmal1* and *Cry2* were observed (Mannic et al., 2013).

12. Rhythmic HPG axis activity and human health

Generally speaking, pulsatile GnRH secretion appears to be the most important determinant of HPG axis activation. Discontinuous administration of GnRH is capable of restoring reproductive activity in patients suffering from Kallmann's syndrome (Crowley and McArthur, 1980) and diurnal testosterone levels in patients with idiopathic hypogonadotropic hypogonadism (IHH) (Simoni et al., 1992). Not much is known about the impact of HPG disorders on sex steroid rhythms except overall abolishment in IHH (Simoni et al., 1992) and Klinefelter's syndrome (Montanini et al., 1987). Interestingly, in female patients with both Kallmann's syndrome and IHH, nocturnal melatonin levels are increased, probably due to changes in the negative central feedback of estradiol (Kadva et al., 1998). Contrary, men with Klinefelter's syndrome (hypogonadism with high estradiol concentrations) show low nocturnal melatonin levels (Luboshitzky et al., 1996). On another note, young patients of Turner syndrome show alternations of circadian blood pressure (Nathwani et al., 2000).

Even though not much is known about how HPG disorders effect circadian rhythms, clock disruptions seem to impact the reproductive system. As described earlier, circadian SCN output plays a crucial role in the generation of the LH surge in females and its downstream mechanisms. Female shift workers have an increased risk of irregular menstrual cycles, miscarriage and low-weight newborns (Gamble et al., 2013; Lawson et al., 2011; Rocheleau et al., 2012). Genetic variations in clock genes were associated with several dysregulations of the reproductive system. Women with a single-nucleotide polymorphism (SNP) in *BMAL1* suffer more from miscarriages and pregnancies, while carriers of a *NPAS2* SNP appear protected (Kovanen et al., 2010). The *CLOCK* gene SNP rs1801260 is associated with irregular menstrual cycles in Korean adolescents (Kim et al., 2015) and idiopathic male infertility in the Han-Chinese population (Shen et al., 2015). Other *CLOCK* gene SNPs are liked to an increased risk of idiopathic recurrent spontaneous abortion (Hodžić et al., 2018) and, again, male infertility (Hodžić et al., 2013).

13. Conclusion

In summary, it becomes increasingly clear that circadian clocks and the endocrine system are intimately linked. On one hand, clocks provide temporal modulation to hormonal axis activity, thus providing systemic timing cues to major physiological processes. On the other hand, hormones serve as mediators between different parts of the circadian clock network as well as conferring state information from the body back to circadian centers in the brain. Disruption of this circadian-endocrine crosstalk affects well-being and promotes the development of various disease complexes, from infertility to metabolic and psychiatric disorders. At the same time, endocrine malfunction affects circadian synchrony, thus impinging on various further biological systems and elevating the risk of secondary pathologies. Stabilization of circadian endocrine regulation may improve therapeutic strategies for hormone disorders and may stabilize both systems against external perturbations.

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