Endocrine regulation of circadian physiology

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Abstract

Endogenous circadian clocks regulate 24-h rhythms of behavior and physiology to align with external time. The endocrine system serves as a major clock output to regulate various biological processes. Recent findings suggest that some of the rhythmic hormones can also provide feedback to the circadian system at various levels, thus contributing to maintaining the robustness of endogenous rhythmicity. This delicate balance of clock–hormone interaction is vulnerable to modern lifestyle factors such as shiftwork or high-calorie diets, altering physiological set points. In this review, we summarize the current knowledge on the communication between the circadian timing and endocrine systems, with a focus on adrenal glucocorticoids and metabolic peptide hormones. We explore the potential role of hormones as systemic feedback signals to adjust clock function and their relevance for the maintenance of physiological and metabolic circadian homeostasis.

Key Words

- ▶ circadian rhythms
- ▶ glucocorticoid
- ▶ HPA axis
- ▶ insulin
- ▶ leptin

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Introduction

Endogenous circadian clocks regulate a broad spectrum of biological functions via multiple routes. A major output pathway of the circadian clock is the endocrine system which allows for a systemic coordination of various physiological target systems according to the time of day. It has long been appreciated that many hormones show circadian rhythms in the circulation (Pincus *et al.* 1954, Moore & Eichler 1972). Both central and peripheral tissue clocks impinge on such endocrine rhythms. On the other hand, hormonal signals have been shown to feed back on circadian clock regulation. Modern life styles compromise the integrity of this feedback balance, and targeting the interaction between the two systems may provide novel solutions to improve general well-being. Various previous reviews have discussed clock regulation of specific hormonal systems (Haus 2007, Kalsbeek & Fliers 2013) as well as the impact of circadian misalignment in metabolic disorders (Marcheva *et al.* 2013). Here, we

describe the clock–endocrine crosstalk with a focus on the hypothalamic–pituitary–adrenal (HPA) stress axis and peptide hormones involved in energy homeostasis (Fig. 1).

Molecular and anatomical makeup of the mammalian circadian system

The mammalian cellular clockwork consists of a transcriptional–translational feedback loop (TTL) of a set of core clock genes, with a positive and a negative arm active during subjective night and day time, respectively. The positive arm comprised circadian locomotor output cycles kaput (CLOCK) (in neural and vascular tissues, CLOCK can be functionally replaced by neuronal PAS domain-containing protein 2 (NPAS2)) and brain and muscle aryl hydrocarbon receptor nuclear translocator-like 1 (BMAL1). These transcription factors form

Figure 1

Schematic summary of circadian-endocrine crosstalk. Clocks in the SCN are reset by the external light-darkness cycle. The SCN regulates peripheral physiology via controlling behaviors, hormonal factors, and autonomic innervations. The HPA axis is one major hormonal output of the SCN, which is controlled by direct innervation of the PVN and the subparaventricular zone and further modulated by SCN-controlled melatonin (MEL) secretion. On the other hand, adrenocortical clocks provide a circadian gating mechanism regulating ACTH sensitivity of the adrenal cortex. GC rhythms act as synchronizing signals of peripheral tissues, but not the SCN, by directly resetting clock gene expression in target tissues. Peripheral clocks are also reset by food intake mediated by hormonal factors such as insulin and oxyntomodulin, as well as by various metabolites such as glucose and fatty acids. Some metabolic hormones such as leptin, ghrelin, and FGF21 are regulated by interplay of the clock and food intake, but they also provide metabolic feedback to the SCN to modify circadian behaviors. SCN, suprachiasmatic nucleus; HPA, hypothalamic-adrenocortical axis; MEL, melatonin; ACTH, adrenocorticotrophic hormone; GC, glucocorticoid; FGF21, fibroblast growth factor.

heterodimers which bind to *E-box* promoter elements to activate the negative arm genes, period (*Per1-3*) and cryptochrome (*Cry1/2*), as well as several other clock-controlled genes (CCGs). During the night, CRY and PER proteins accumulate in the cytoplasm and translocate into the nucleus where they inhibit CLOCK:BMAL1 activity and, thus, shut down their own transcription. Subsequent degradation of PER and CRY relieves the inhibition on CLOCK:BMAL1 toward the morning, followed by resumed transcription of *Per/Cry* and other CCGs. The cycle is further stabilized by accessory TTLs such as the one composed of the nuclear receptors REV-ERB α/β and ROR α/β , repressing and activating *Bmal1* transcription, respectively (Zhang & Kay 2010).

The mammalian circadian system is organized in a hierarchical manner. The molecular clockwork described above is present in essentially all cells, but the nature of CCGs differs between tissues (Zhang *et al.* 2014). In order

to generate physiologically meaningful rhythms, these tissue clocks have to be properly aligned with each other and external time. In mammals, light is the major *Zeitgeber* (German for 'time giver'). A master pacemaker located in the hypothalamic suprachiasmatic nucleus (SCN) acts as the major interface between endogenous rhythms and environmental time cues such as the light-darkness cycle (Hussey *et al.* 2015). The SCN receives photic input from intrinsically photoreceptive retinal ganglion cells (ipRGCs) expressing the photopigment melanopsin to entrain SCN clock gene expression and neuronal activity (Hankins *et al.* 2008). The majority of efferent projections from the SCN target hypothalamic structures such as the subparaventricular zone (sPVZ), the arcuate nucleus (ARC), the paraventricular nucleus (PVN), and the dorsomedial hypothalamic nucleus (DMH). Through these, the SCN regulates a plethora of physiological systems (Saeb-Parsy *et al.* 2000). Mice with focal SCN lesions lose circadian

behavioral and physiological rhythms and no longer entrain to light–darkness cycles (Moore & Eichler 1972, Stephan & Zucker 1972). It is still a matter of debate as to which of these functions require rhythmic input from the SCN and which are primarily controlled by clocks in downstream central or peripheral tissues. Environmental factors other than light can serve as *Zeitgebers* of the circadian system. For example, temporally restricted food availability is a potent synchronizer of peripheral tissue and some central nervous system (CNS) clocks, but has little effect on the SCN itself (Damiola *et al.* 2000, Stephan 2002).

Circadian regulation of the HPA axis

Many hormones and most of the major endocrine axes show robust circadian rhythms. Of these, circadian regulation of the HPA axis is particularly well studied, since blood levels of glucocorticoids (GCs) are among the most rhythmic functions observed in the mammalian system and because both GCs and catecholamines have been implicated in the synchronization of circadian clocks and rhythms in other tissues (Balsalobre *et al.* 2000, Terazono *et al.* 2003). HPA axis activity coordinates different physiological systems and behavior in response to stress. GCs are the end products of the activation of the HPA axis. Acute stress activates hypothalamic release of corticotropin-releasing hormone (CRH) to the anterior pituitary, where it stimulates the release of adrenocorticotrophic hormone (ACTH) into the bloodstream. ACTH activates adrenocortical steroidogenesis through the melanocortin 2 receptor (MC2R), via a cyclic adenosine monophosphate/protein kinase A (cAMP/PKA)-dependent pathway (Miller & Bose 2011). Under nonstressed conditions, blood GC levels oscillate in both circadian and ultradian manners. Ultradian (aka. pulsatile) GC rhythms are controlled by a negative feedback loop in which GCs suppress ACTH production via the hypothalamus and the pituitary (Spiga *et al.* 2014). The circadian GC rhythm, in contrast, involves HPA activity, SCN-controlled autonomic innervation, and adrenocortical clocks. The peak of the circadian GC rhythm is phase-locked to the beginning of the active phase in order to organize various biological processes to prepare for the active behavior during the wake time (Moore & Eichler 1972). Circadian GC rhythms have long been established as a function of endogenous circadian clocks as they persist even under constant conditions. At the same time, surgical ablation

of the SCN completely abolishes the circadian release of GCs into the blood (Moore & Eichler 1972). Retrograde neuronal tracing experiments revealed that the adrenal is connected to the SCN via the intermediolateral (IML) column of the spinal cord and the PVN (Buijs *et al.* 1999). Sympathetic nerve stimulation potentiates GC responses, suggesting a role of adrenal sympathetic innervation in the regulation of GC rhythms (Edwards & Jones 1993). The SCN projects inhibitory efferents to pre-autonomic and CRH-producing neurons in the PVN which ultimately lead to a suppression of adrenal GC secretion (Buijs *et al.* 1997). On the other hand, HPA axis activity upstream of the adrenal is also rhythmic, so circadian GC release may be an indirect response to SCN-controlled CRH expression. The latter view has been challenged by the discovery that the timing of expression of CRH in the hypothalamus and pro-opiomelanocortin (POMC) in the anterior pituitary and the plasma surge of GC is not organized in the expected sequential manner (Girotti *et al.* 2009). Moreover, in hypophysectomized rats, the implantation of constant-release ACTH pellets is sufficient to restore GC rhythmicity (Ottenweller & Meier 1982). Along this line, light signals have been found to be capable of modulating adrenal GC secretion via the SCN directly and independent of ACTH (Buijs *et al.* 1999, Ishida *et al.* 2005).

Experiments from the early 1960s suggested that the responsiveness of the adrenal steroidogenic machinery to ACTH stimulation shows circadian variations (Ungar & Halberg 1962). More than 40 years later, our group described an SCN-independent, adrenal clock-controlled gating mechanism underlying this observation (Oster *et al.* 2006). As a consequence, surgical or genetic ablation of adrenal clock function in mice results in dampened rhythms of GC secretion compared with sham-treated or wild-type controls (Oster *et al.* 2006, Son *et al.* 2008). Son and coworkers further showed that steroidogenic acute regulatory protein (StAR), one of the pacemakers of GC biosynthesis, is a direct target of CLOCK:BMAL1, suggesting a mechanistic function of adrenocortical clocks in the regulation of GC production (Son *et al.* 2008). The light pulse data discussed above suggest that adrenal clocks are entrained by neuronal mechanisms (Buijs *et al.* 1999, Ishida *et al.* 2005). However, Yoder and coworkers recently found that ACTH itself can also shift the phase of the adrenal *Per2* rhythm (Yoder *et al.* 2014). One might speculate that, in this way, stress-induced HPA axis activation can reset adrenal clocks, thus affecting circadian GC release. Also, under acute stress conditions, the circadian clock plays a role in HPA axis regulation. SCN-lesioned animals show

exaggerated GC secretion under acute stress, in line with an inhibitory role of the SCN on HPA axis activity (Buijs *et al.* 1997, 1999). Interestingly, we recently reported that *Bmal1*-deficient mice show a blunted stress-induced GC release along with reduced behavioral responses (Leliavski *et al.* 2014). Together, these data suggest that repetitive or chronic stress may alter the timing of GC-regulated metabolic processes. Not only GC production but also GC action has been found to be gated by the molecular clock. GC receptors (GRs) are rhythmically expressed in various tissues and subject to acetylation (and subsequent inactivation) by CLOCK (Charmandari *et al.* 2011). Recently, CRY1/2 proteins have been shown to directly repress the transactivational function of GR in a ligand-dependent manner (Lamia *et al.* 2011), providing another layer of complexity to the circadian regulation of GR signaling.

The pineal hormone melatonin may serve as an additional mean for the SCN to further modulate HPA axis activity. Melatonin secretion is controlled via multisynaptic innervation by the SCN pacemaker and plays a role in synchronizing peripheral tissue clocks (Hardeland *et al.* 2012). Melatonin administration suppresses HPA axis activity (Konakchieva *et al.* 1997, Torres-Farfan *et al.* 2003), and timed melatonin administration can entrain adrenal gland rhythms (Torres-Farfan *et al.* 2011). Together, melatonin and GC rhythms appear to act in concert to stabilize circadian phase and precision of different physiological systems.

Circadian regulation of metabolic hormones

Recent studies highlight the importance of the circadian clock in metabolic regulation. Behaviorally arrhythmic mice under constant light conditions (LL) or SCN-lesioned animals show increased body-weight gain together with impaired glucose tolerance and insulin sensitivity (Fonken *et al.* 2010, Coomans *et al.* 2013). Likewise, various metabolic phenotypes have been reported for different clock gene mutations (Bechtold & Loudon 2013). For instance, *Bmal1*-knockout (KO) mice display impaired glucose homeostasis with reduced gluconeogenesis and glucose intolerance (Rudic *et al.* 2004, Lamia *et al.* 2008, Marcheva *et al.* 2010, Kennaway *et al.* 2013), while *Clock* Δ 19-mutant mice are obese and show hyperglycemia and hyperlipidemia (Turek *et al.* 2005). These and other metabolic disturbances are accompanied by altered endocrine functions. Both the master SCN clock and local clocks in peripheral tissues

are involved in regulating the production and function of several metabolic hormones. Below, we summarize recent findings on the circadian regulation of insulin and its function in glucose homeostasis and on the ghrelin-leptin system controlling feeding behavior.

Circadian gating of insulin function in glucose homeostasis

Circulating plasma glucose levels, insulin concentrations, and whole-body insulin sensitivity display SCN-dependent circadian variations (La Fleur *et al.* 1999, Rudic *et al.* 2004, Lamia *et al.* 2008, Shi *et al.* 2013). Local clocks in pancreatic beta cells provide a gating mechanism for insulin secretion. Disruption of the positive arm of this clock (i.e. tissue-specifically deleting *Clock* or *Bmal1*) results in hypoinsulinemia (Marcheva *et al.* 2010, Sadacca *et al.* 2011), whereas deletion of the clock's negative regulators (i.e. the *Pers* or *Crys*) is associated with hyperinsulinemia (Barclay *et al.* 2012, Zhao *et al.* 2012). In rodent and human pancreatic beta cells, the main functional targets of the clock machinery are a number of CCGs involved in peptide secretory pathways (Perelis *et al.* 2015, Saini *et al.* 2016). This mechanism further appears to be sensitive to the cellular redox status. Normalizing reactive oxygen species (ROS) levels can partially rescue the impairment of insulin secretion in *Bmal1*-deficient pancreatic beta cells (Sadacca *et al.* 2011). In line with these observations, mice with behaviorally disrupted circadian rhythms also exhibit hypoinsulinemia (Sadacca *et al.* 2011). Intriguingly, SCN-lesioned mice show hyperinsulinemia, but this may rather be an effect of elevated body weight and systemic insulin resistance (Coomans *et al.* 2013). Further studies will be needed to elucidate how SCN and local pancreatic clocks interact in regulating insulin secretion.

Circadian clocks play a further role in regulating insulin sensitivity at target tissues. Insulin resistance, a hallmark of the prediabetic state, has been associated with extended shift work in humans (Esquirol *et al.* 2012). Liver, skeletal muscle, and adipose tissues are the major effector organs of insulin's hypoglycemic effects. Cell-type-specific *Bmal1*-mutant mice have been used to assess the role of the molecular clock in regulating insulin sensitivity in these tissues. *Bmal1*-knockout mice show impaired systemic insulin sensitivity accompanied by hyperglycemia over the course of a day (Rudic *et al.* 2004, Lamia *et al.* 2008, Shi *et al.* 2013). In contrast, mice with liver-specific deletion of *Bmal1* show improved glucose tolerance, lowered blood glucose, but normal systemic

insulin sensitivity (Lamia *et al.* 2008). Hypoglycemia in these mice may be explained by blunted expression of GLUT2, which mediates the export of glucose from liver to the blood stream (Lamia *et al.* 2008). Alternatively, CRY1 has been shown to modulate gluconeogenesis by its interaction with the G-protein involved in glucagon signaling pathway (Sun *et al.* 2015) and PER2 binds to regulatory regions of the glucose-6-phosphatase gene, a key player in maintaining glucose levels during fasting periods (Schmutz *et al.* 2010). Skeletal muscle clocks have been suggested to play a role in preparing the transition from the rest/fasting to the active/feeding phase of the day when glucose becomes the predominant fuel. Skeletal muscle-specific *Bmal1*-knockout mice show impaired insulin-stimulated glucose uptake due to downregulated GLUT4 expression. However, the canonical insulin signaling pathway appears unaltered in these animals, as do systemic insulin sensitivity and blood glucose concentrations (Dyar *et al.* 2014). Skeletal muscle itself is an endocrine organ which secretes a number of peptide hormones known as myokines. Using human primary skeletal myotubes as a model, a recent study has unveiled that the clock machinery plays a pivotal role in regulating basal and circadian secretion of several myokines (Perrin *et al.* 2015). Given that many myokines are established regulators of energy metabolism, disruption of muscle clocks may link circadian misalignment to metabolic diseases. Adipose physiology shows strong variations over the course of the day. Adipocyte-specific *Bmal1*-knockout mice develop obesity. Surprisingly, though, these mice display normal systemic insulin sensitivity and glucose homeostasis (Paschos *et al.* 2012). Instead, the obesity phenotype appears to stem from mistimed feeding induced by altered adipose production of polyunsaturated fatty acids (Paschos *et al.* 2012).

Circadian regulation of leptin and ghrelin

The timing of food intake has recently been found to play an unexpected key role in body energy homeostasis (Zarrinpar *et al.* 2016). For example, scheduled feeding of a high-fat diet (HFD) during the inactive phase in mice leads to significant increase in body weight compared with feeding during the normal active phase, despite comparable caloric intake (Kohsaka *et al.* 2007). In line with that, scheduled feeding during the active phase (i.e. the night in nocturnal rodents) is protective against the metabolic dysregulation induced by HFD compared with chow fed controls *ad libitum* (Chaix *et al.* 2014).

In a recent study in humans, restricting food intake to 12 h during the day had beneficial effects on body-weight control (Gill & Panda 2015). The relative abundance of the antagonistic hormone duo, ghrelin and leptin, plays a major role in determining appetite regulation via signaling to the mediobasal hypothalamus (MBH) (Begg & Woods 2013). Blood levels of both hormones display circadian rhythms and are subject to acute regulation by food intake (see below).

Leptin is a cytokine-like peptide secreted from adipocytes to suppress food intake. In most obese individuals, leptin fails to suppress appetite despite increased blood leptin concentrations; a condition that has, in reference to insulin resistance in type 2 diabetes, been termed leptin resistance, though the mechanism of this lack of leptin action has still to be determined (Begg & Woods 2013). Baseline plasma leptin levels show SCN-dependent circadian variations (Kalsbeek *et al.* 2001) which are blunted and elevated in *ClockΔ19*, *Bmal1*-knockout, as well as adipose-specific *Bmal1*-deficient mice (Turek *et al.* 2005, Paschos *et al.* 2012, Kennaway *et al.* 2013). Owing to increased fat mass in these genetic models, it has not yet been conclusively shown to which extent *in vivo* leptin secretion rhythms are directly regulated by adipocyte clocks or rather follow systemic cues such as food intake. Nevertheless, *in vitro* leptin secretion rhythms persist in cultured adipocytes (Otway *et al.* 2009). A recent study has identified an unexpected dual role of BMAL1:CLOCK in *Leptin* (*Lep*) transcription via an interaction with CCAAT/enhancer-binding protein (C/EBPα) at the proximal *Lep* promoter. When blood leptin levels are at their trough (corresponding to the early inactive phase in mice), CLOCK:BMAL1 modestly enhances the C/EBPα-mediated upregulation of *Lep* transcription, while acting in a suppressive way at high leptin blood levels (i.e. during the late inactive phase) due to direct competition with C/EBPα for *Lep* promoter binding (Kettner *et al.* 2015). In the same study, the authors also demonstrated that central leptin sensitivity is impaired in mice with genetically or behaviorally disrupted circadian rhythms (Kettner *et al.* 2015). How the molecular clock influences hypothalamic leptin signaling, however, remains unclear.

Ghrelin, on the other hand, is an orexinergic hormone secreted from the gastrointestinal (GI) tract in response to fasting. Both circulating ghrelin and gastric *prepro-Ghrelin* (*Ghrl*) mRNA levels display circadian rhythms which are lost in *Bmal1*-mutant mice (LeSauter *et al.* 2009, Laermans *et al.* 2015). Intriguingly, local GI clocks appear to be dispensable for regulating ghrelin secretion, as

siRNA-mediated downregulation of *Bmal1* failed to affect ghrelin secretion from ghrelinoma cells (Laermans *et al.* 2015). Despite its role as a peripheral feedback signal to the central circadian system (see below), very little is still known about how the circadian system affects ghrelin secretion and sensitivity.

Endocrine feedback on the circadian system

Recent data suggest that endocrine functions are not merely an output of the circadian clock system, but also serve as feedback signals to regulate the circadian system at various levels. Alterations of such endocrine feedback have been implicated in the circadian disruption associated with conditions such as sleep disorders or shift work. In the following paragraphs, we will discuss the physiological relevance of hormones on the regulation of circadian rhythms with a focus on GCs and metabolic peptide hormones.

GC circadian clock feedback

As outlined above, the rhythmic secretion of GCs is involved in entraining clocks of peripheral and CNS tissues. GR is ubiquitously expressed throughout the body, with the notable exception of the SCN (Okamura 2007). It exerts a plethora of physiological effects by binding to GC-responsive elements (*GREs*) in the promotor of target genes and upregulating their expression (Yamazaki *et al.* 2009). The mechanism of GC-induced resetting of local clocks has been described. The proximal promoters of *Per* genes contain *GREs* and, thus, are activated by GCs to reset the phase of the TTL, very comparable to light-induced resetting of SCN clocks (Balsalobre *et al.* 2000). Very recently, a novel consensus promoter GR regulatory sequence (*nGRE*) has been discovered, binding of which results in repression of target gene transcription (Surjit *et al.* 2011). An auxiliary clock gene (*Dec1*) contains an *nGRE* in its promoter (Surjit *et al.* 2011). The two DEC proteins (DEC1/2; aka. BHLHE40/1) have been shown to modify the molecular clock in a tissue-specific manner (Rossner *et al.* 2008, Tsang *et al.* 2012). How GC-induced *Dec* suppression may affect tissue clock function, however, has not yet been studied.

Given the stimulatory role of GCs in arousal and alertness, it is not surprising that due to disruption of GC rhythms (such as in Cushing's (hypercortisolemia), Addison's (hypocortisolemia), and chronic stress

diseases) patients often suffer from sleep and circadian rhythm disorders (Leliavski *et al.* 2015). For Addison's patients, the standard therapeutic approach involves life-long supplementation of GCs which often fails to replicate the normal circadian GC rhythm, thus compromising the patients' quality of life (Arlt & Allolio 2003). Attempts to modify the release profiles of GC replacement medications aimed to mimic the natural GC circadian rhythm have shown promising improvements in clinical studies (Chan & Debono 2010), highlighting the physiological importance of the circadian GC rhythm.

Transcontinental flight travel across multiple time zones results in jetlag which manifests in transient physiological and behavioral disturbances such as decreased alertness during the day and sleep problems during the night. It has been shown that GC rhythms are involved in mediating the adaptation of internal rhythms under jetlag conditions. In mice, by manipulating GC secretion phase during jetlag, behavioral adaptation after a shift of the light–darkness cycle can be accelerated (Kiessling *et al.* 2010). The potential clinical use of this treatment in humans warrants further pursuit.

Metabolic hormone circadian clock feedback

As outlined above, the timing of food intake is a major *Zeitgeber* to clocks residing in, both, the periphery and the CNS. When food access is restricted to the inactive phase of mice, it uncouples peripheral clocks from the SCN pacemaker (Damiola *et al.* 2000). In consequence, mistimed feeding alters circadian rhythms of locomotor activity and of various endocrine functions (Zarrinpar *et al.* 2016). Interestingly, already a mere change in nutrient composition can affect circadian rhythm regulation. Mice fed a high-fat diet *ad libitum* show blunted behavioral and molecular circadian rhythms (Kohsaka *et al.* 2007). These effects are correlated with altered regulation of metabolic hormone secretion.

All three metabolic hormones discussed above can provide feedback to the circadian clock system. Insulin has been shown to regulate food-induced resetting of liver clocks *in vitro* and *in vivo*, though the underlying mechanism has not yet been described (Tahara *et al.* 2011, Yamajuku *et al.* 2012). Our group has recently identified the incretin hormone oxyntomodulin (OXM) as an additional effector of food entrainment of peripheral tissues clocks (Landgraf *et al.* 2015). OXM is a 37-amino acid peptide of the glucagon family secreted from GI cells after meal intake. It promotes gastric acid secretion

and gut motility, but suppresses appetite. Both glucagon (GCGR) and glucagon-like peptide 1 receptors (GLP-1R) have been shown to mediate a part of OXM signaling, but an, as yet uncharacterized, additional pathway has been suggested (Pocai 2014). In our study, we found that, in the inactive phase, postprandial increases of blood OXM levels are sufficient to reset the molecular clock and clock output gene rhythms in liver via a glucagon receptor-dependent signaling mechanism and induction of hepatic *Per* expression (Landgraf *et al.* 2015). Paradoxically, at a different time of day, glucagon itself can enhance fasting-induced liver *Bmal1* expression (Sun *et al.* 2015). Further studies are needed to evaluate the temporal order and relative contributions of these and other metabolic hormones in mediating feeding-associated resetting of circadian transcriptional programs in peripheral tissues. Along this line, using a novel screening approach, Gerber and coworkers identified serum response factor (SRF) as an immediate early response transcription factor in the liver relaying signals from as yet unidentified oscillating blood-borne factors to control liver clock gene expression (Gerber *et al.* 2013).

Fibroblast growth factor 21 (FGF21) is a metabolic hormone that has recently been found to directly regulate circadian behavior and energy homeostasis via the SCN (Bookout *et al.* 2013). FGF21 is mainly produced by the liver, but is also secreted from muscle and white adipose tissues. Its signals are mediated via its cognate receptors (FGF receptors FGFR1c, FGFR2c, or FGFR3c) in complex with β -Klotho abundantly expressed in metabolic tissues (Degirolamo *et al.* 2016). FGF21 plays a major role in adaptive responses under starvation. The secretion of FGF21 is stimulated by fasting to enhance energy mobilization through gluconeogenesis, fatty acid oxidation, and ketogenesis (Degirolamo *et al.* 2016). FGF21 was also found to enhance insulin sensitivity after overfeeding (Xu *et al.* 2009). Together, much attention has been drawn to the therapeutic potential of FGF21 in treating metabolic syndromes. A recent study showed that the expression of the β -Klotho-encoding *Klb* gene is highly enriched in the SCN. Overexpression of FGF21 in mice was found to blunt circadian locomotor activity rhythms and suppress insulin, but to enhance GCs secretion and reduce body weight. However, mice with conditional genetic ablation of *Klb* in the SCN lack these phenotypes, suggesting that the metabolic FGF21 effects are dependent of SCN clock function (Stephan 2002). Additionally, the FGF21–SCN axis has been found to play a key role in regulating female fertility via vasopressin–kisspeptin signaling

controlling the proestrus surge of luteinizing hormone (Owen *et al.* 2013).

Both leptin and ghrelin can also directly regulate SCN function. In explant slices, leptin stimulation can reset the phase of SCN neuron firing rhythms (Prosser & Bergeron 2003). *In vivo*, systemic leptin injections result in modest induction of *Per* expression in the SCN and potentiate the phase-shifting effects of light in female, but not in male mice (Mendoza *et al.* 2011). *Ob/ob* mice (carrying a loss-of-function mutation of the *Lep* gene) show altered photic responses of the circadian clock at both behavioral and molecular levels, which can be normalized by timed injections of leptin. In the same study, however, the authors found that systemic leptin injections failed to stimulate canonical leptin signaling cascades in the SCN, suggesting an indirect mechanism for leptin's circadian resetting effects (Grosbellet *et al.* 2015b). *Db/db* mice (expressing a nonfunctional version of the long isoform of leptin receptor gene, *Obrb*) show severely disrupted locomotor activity and feeding rhythms together with exaggerated molecular photic responses in the SCN (Grosbellet *et al.* 2015a). Similar to leptin, ghrelin has been shown to directly impact on the SCN. *In vitro*, treatment of ghrelin phase resets the circadian neuronal firing and *Per* expression rhythms in organotypic cultured SCN-containing slices (Yannielli *et al.* 2007). Likewise, application of a synthetic ghrelin analog in *in vivo* phase resets circadian locomotor activity rhythms (Yannielli *et al.* 2007), but attenuates light-induced phase-shifts, which may involve inhibitory innervations from ghrelin-sensitive neurons in the ARC to the SCN (Yi *et al.* 2008). A recent study has discovered an unexpected role of ghrelin as a circadian regulator of the sleep/wake cycle. Ghrelin-positive neurons, receiving projections from the SCN and the visual system via the intergeniculate leaflet (IGL), suppress the activity of arousal-promoting orexinergic neurons in the lateral hypothalamus (LH) (Horvath *et al.* 2012).

Anticipatory behavioral activity before scheduled feeding (food anticipatory activity, FAA) is seen in animals with time-restricted access to food (RF) and is characterized by increases in locomotor activity, body temperature, and GC secretion just before feeding time (Krieger *et al.* 1977). It is believed to reflect foraging in anticipation of food intake. FAA rhythms represent a form of food entrainment of the circadian system as they develop in the absence of other time cues (such as the light–darkness cycle) and persist even when the scheduled feeding condition is lifted (i.e. they free-run) (Mistlberger 2009). Although the anatomical and molecular makeup of this food-entrainable

oscillator (FEO) underlying FAA rhythms is still largely unknown, both leptin and ghrelin have been shown to play a role in regulating FAA rhythms. *ob/ob* mice and *Obrb*-mutant Zucker rats show increased FAA under RF, which can be suppressed by the administration of recombinant leptin (Mistlberger & Marchant 1999, Ribeiro *et al.* 2011). In contrast, ghrelin receptor (*Ghsr*)-deficient mice show impaired FAA (Blum *et al.* 2009, LeSauter *et al.* 2009, Lamont *et al.* 2014); though intriguingly, ghrelin-deficient mice are normal under these conditions (Szentirmai *et al.* 2010). The mechanisms that mediate leptin and ghrelin effects on FAA remain unknown. Two neural substrates have been identified to modify FAA rhythms, which are also established targets of leptin and ghrelin: the dopaminergic reward circuitry (Gallardo *et al.* 2014) and the mediobasal hypothalamic appetite-regulating circuitries centers (Bechtold & Loudon 2013). The SCN itself has been recognized as a negative regulator of FAA rhythms (Storch & Weitz 2009, Acosta-Galvan *et al.* 2011). Given that both of these two hormones can directly act on the SCN clock, it is plausible that the circadian pacemaker may mediate part of their FAA-regulating effects. Alternatively, it has been shown that the DMH is a positive regulator of FAA through suppression of SCN neuronal activity (Acosta-Galvan *et al.* 2011). The DMH receives input from several metabolic state-sensing brain nuclei such as the ARC (Bouret *et al.* 2004), thus acting as a relay mediating the FAA effects of metabolic hormones.

Concluding remarks

The endocrine system serves as a major output of the circadian clock. Circadian disruption is a frequent consequence of modern urban lifestyles. Occupations requiring shift work or irregular working hours, chronic stress, mistimed light exposure, e.g. through artificial lighting or the use of light-emitting electronic devices (Chang *et al.* 2015), and the frequent intake of arousal stimulating beverages such as coffee at night (Burke *et al.* 2015) are all established disruptors of the circadian system. Altered circadian hormonal regulation compromises one's health such as by promoting the development of metabolic disorders. At the same time, many hormones have been shown to feed back on the circadian clock system at various levels, thus supporting the maintenance of robust physiological and behavioral rhythms. This central role of endocrine signals within the circadian system makes them attractive targets to manipulate

physiological functions via the circadian clock, e.g. to affect circadian stabilization during jetlag (Kiehl *et al.* 2010) or shift work. The recent discovery of drugs directly impinging on molecular clock function (Hirota *et al.* 2010, Solt *et al.* 2012), on the other hand, offers the possibility to ameliorate disrupted endocrine regulation under desynchrony conditions through the circadian clock. Finally, reinstating behavioral and physiological rhythms, e.g. by restricting food intake to the active phase, may protect against metabolic dysregulation (Chaix *et al.* 2014, Gill & Panda 2015), providing a highly accessible mean for improving the general well-being.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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