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CHAPTER 10

Interaction of central and peripheral clocks in physiological regulation

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Abstract: In mammals, circadian rhythms of physiology and behavior are regulated by a complex network of cellular molecular oscillators distributed throughout the brain and peripheral tissues. A master clock in the hypothalamic suprachiasmatic nuclei (SCN) synchronizes internal time with the external light–dark cycle, thus entraining the overall rhythmicity of the organism. Recent findings have challenged the dominant role of the SCN in physiological regulation and it becomes increasingly evident that close interaction between different central and peripheral clocks is necessary to maintain robust circadian rhythms of physiology and metabolism. In this review, we summarize recent findings regarding circadian organization in the SCN and in other central and peripheral tissues. We outline the communication pathways between different tissue clocks and, exemplified by the regulation of glucocorticoid release from the adrenal gland and glucose homeostasis in the blood, characterize the interaction between different clocks in the regulation of physiological processes.

Keywords: SCN; adrenal; circadian clock; glucose; metabolism; glucocorticoids; liver; clock genes; mammals; pancreas.

Introduction

Living organisms—from unicellular prokaryotes to multicellular metazoans—have evolved diverse strategies to internalize the diurnal environmental changes brought about by Earth's rotation around its axis. The biological timing system that organizes such 24-h oscillations is known as the circadian clock. The two major functions of the circadian clock are to optimize the temporal manifestations of different biological activities along the course of a day through anticipating recurring environmental fluctuation and to separate incompatible biological processes such as feeding and sleeping. Unicellular organisms can internalize external diurnal rhythms by employing a single set of

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molecular clockwork; multicellular organisms, such as mammals, on the other hand, have developed a highly complex circadian timing system that is intricately intertwined with different physiological systems. Mammalian circadian rhythms are a result of a close interaction between different central (i.e., inside the central nervous system or CNS) and peripheral oscillators. An ever-growing body of evidence has demonstrated that a misalignment of central and peripheral circadian clocks (*internal desynchrony*) predisposes individuals to physiological complications and diseases. This chapter describes the current state of knowledge concerning the properties of clocks in the CNS and the periphery. We then discuss general mechanisms of central-to-peripheral clock interaction in the regulation of physiology using two extensively studied processes, glucose metabolism and glucocorticoid (GC) secretion.

Molecular clockworks

In the past decades, our knowledge of the molecular make-up of the cellular circadian clock has been significantly advanced. The current model suggests that the central mechanism of the mammalian molecular clock is composed of a set of clock genes intertwined with a delayed interlocked transcriptional–translational feedback loop (TTL) with several auxiliary mechanisms reinforcing robustness and stability (Zhang and Kay, 2010). The positive limb of this TTL comprises the basic helix–loop–helix transcription factors—circadian locomotor output cycles kaput (CLOCK) and brain and muscle aryl hydrocarbon receptor nuclear translocator like (BMAL1 or ARNTL). They form heterodimers via their PER–ARNT–SIM (PAS) domains and activate E-box element containing genes (Hardin, 2004; Zhang and Kay, 2010) by recruiting several transcriptional co-activators, chromatin modifying proteins, and finally, RNA polymerase II. In certain tissues such as forebrain or the vasculature, CLOCK is functionally replaced by its homologue neuronal PAS domain protein 2 (NPAS2; McNamara et al., 2001; Reick et al., 2001). Period (PER1–3) and cryptochrome (CRY1–2) constitute the negative limb of the core clock. CLOCK–BMAL1 complexes activate the expression of *Per* and *Cry* genes during the subjective day. PER and CRY interact to form complexes and translocate into the nucleus. When PER/CRY complexes accumulate to a critical concentration, they interact with CLOCK and BMAL1 and thereby inhibit their transactivator function, thus shutting down *Per* and *Cry* transcription (Lee et al., 2001). The progressive degradation of PER/CRY complexes throughout the subjective night releases the inhibition on CLOCK–BMAL1 transcriptional activity and, thereby, completes the negative feedback loop of the circadian clock.

In addition to the core clock TTL described above, additional auxiliary TTLs have also been described. Though principally dispensable, they stabilize the oscillation of the core clock TTL and help to translate time-of-day information into physiological signals via transcriptional control of clock target genes (Zhang and Kay, 2010). Such loops include the nuclear receptors REV-ERBα (NR1D1) and RORα (NR1F1) that regulate *Bmal1* expression via retinoid orphan receptor-responsive elements (ROREs) (Preitner et al., 2002; Ueda et al., 2002) as well as the PAR basic leucine zipper (bZIP) proteins, D-box albumin-binding protein (DBP) and E4 promoter-binding protein (E4BP; NFIL3; Cowell, 2002; Ripperger and Schibler, 2006), that feedback on the expression of *Per* genes via D-box promoter elements (Ripperger et al., 2000).

Recently, there are accumulating evidences showing that the circadian clock is tightly intertwined with multiple metabolic pathways. While the temporal manifestation of several metabolic functions is one of the most important functional outputs of the circadian clock (see below), the cellular circadian clock, on the other hand, constantly receives the feedbacks from the metabolic signalings of the cells. For example, the redox status of the cells has been demonstrated to regulate the molecular clock, in both direct and indirect manners. The ratio of oxidized to reduced

nicotinamide adenine dinucleotide (phosphate) ($NAD(P)^+$/NAD(P)H) reflects the cellular redox and metabolic status. This ratio oscillates in a circadian manner (Nakahata et al., 2009; Ramsey et al., 2009). The binding of the CLOCK–BMAL1 and NPAS2–BMAL1 heterodimeric complexes to the E-box elements is inhibited by the oxidized NAD^+ and NADP but stimulated by the reduced NADH and NADPH (Rutter et al., 2002). NAD is an important cofactor that involves in many cellular enzymatic reactions, for example, sirtuins-mediated protein deacetylation. SIRT1 catalyzes the removal of acetyl group from acetylated lysine residues of proteins thereby modulating their activities in the expense of NAD(P)H. It has recently been shown that the activity and level of SIRT1 oscillate in a circadian manner (Asher et al., 2008; Nakahata et al., 2008). Importantly, SIRT1 physically interacts with the CLOCK–BMAL1 complex and mediates BAML1 and histone H3 deacetylation, which is important for the transcriptional activating activity of the CLOCK–BMAL1 complex (Nakahata et al., 2008). In addition to acting on the positive limb components, SIRT1 also deacetylates PER2, which promotes its degradation (Asher et al., 2008). More recently, another NAD-dependent poly (ADP-ribose) polymerase-1 (PARP-1)-mediated protein poly (ADP-ribosyl)ation also showed a circadian oscillation pattern (Asher et al., 2010). PARP-1, on the other hand, can also poly (ADP-ribosyl)ate CLOCK and thereby inhibit the CLOCK–BMAL1 DNA-binding capacity (Asher et al., 2010). The nutrient-sensing AMP-dependent protein kinase (AMPK) represents another elegant example integrating the metabolism to the circadian clock. AMP/ATP ratio is another indicator of the metabolic status of the cells. AMPK is the major sensor of such ratio. The elevated AMP level stimulates the AMPK activity via liver kinase B1 (LKB1; Mihaylova and Shaw, 2011). The activation of AMPK acts on the negative limb of the core clock TTL in both direct and indirect manners. AMPK directly phosphorylates CRY1 (Lamia et al., 2009) and indirectly leads to the phosphorylation of PER2 via casein kinase 1ε (CK1ε) (Um et al., 2007). In both scenarios, AMPK activation promotes their degradation and thereby influences the core clock oscillation cycle.

These and other similar examples illustrate that the molecular clockwork and several metabolic signaling pathways are so tightly intertwined that the clear distinction between them is becoming somewhat blurrier. Here, we only reviewed a few examples of such metabolic feedback pathways on the circadian clock. Several elegant reviews discussing the orchestration of the metabolic homeostasis and the circadian clock and the deleterious consequences if this orchestration is disrupted have recently been published (Asher and Schibler, 2011; Huang et al., 2011; Reddy and O'Neill, 2010). Most of these metabolic feedback mechanisms have been implicated in the food entrainment of the peripheral clock but have only a little if not no effect on the suprachiasmatic nuclei (SCN) clock. However, it would be interesting to know how these pathways influence the extra-SCN clocks in the brain, particularly for those regions involved in organizing the feeding schedule.

The master circadian pacemaker of the SCN

In vertebrates, almost all cells express clock genes. Without synchronization on a systemic level, these autonomous clocks could not produce physiologically meaningful signals. In mammals, circadian regulation is organized in a hierarchical fashion with the hypothalamic SCN housing the master circadian pacemaker. The SCN is a bilaterally paired compact brain nucleus comprising about 20,000 neurons in mice, located directly adjacent to the third ventricle and atop the optic chiasm (Welsh et al., 2010). Electrical ablation of the SCN renders animals behaviorally arrhythmic (Moore and Eichler, 1972; Stephan and Zucker, 1972). Transplanting SCN tissue to SCN-lesioned animals restores circadian rhythmicity (Ralph et al., 1990). Importantly, the restored rhythm of recipients is determined by the donor SCN period, indicating that the SCN indeed generates the

timing information that synchronizes oscillators throughout the body (Ralph et al., 1990). SCN explants as well as dispersed neurons display robust circadian oscillations in firing rate *in vitro*, suggesting that the rhythmicity of the SCN is autonomous in nature (Green and Gillette, 1982; Groos and Hendriks, 1982; Shibata et al., 1982; Welsh et al., 1995).

The endogenous circadian clock in mammals possesses a rhythm with an approximate 24-h free-running period. However, the daily fluctuation of the external environment is not constant, and variables such as photoperiod, temperature, and food availability are subject to seasonal changes. In order to synchronize the internal circadian rhythm to the external diurnal fluctuation patterns, circadian clocks are constantly reset by external environmental cues, so-called zeitgebers, every day in a process known as entrainment. The major zeitgeber in mammals is light, with the SCN acting as a relay between the external light–dark cycle and the endogenous timing system (Hankins et al., 2008). Other, nonphotic zeitgebers exist, some of which act through the SCN, for example, arousal (Welsh et al., 2010), while others, such as food intake, are more directly affecting the peripheral circadian machinery (Huang et al., 2011).

The SCN makes use of the same TTL molecular timekeeping machinery as the peripheral oscillators (see below). However, the particular robustness and resilience of SCN circadian rhythmicity are achieved through the formation of a tight interneuronal network (Welsh et al., 2010). SCN slices cultured *in vitro* exhibit robust and persistent circadian oscillations in electrophysiological activity and clock gene expression for several weeks, while rhythms in slice explants from most other brain regions and peripheral tissues dampen after a couple of days (Guilding and Piggins, 2007; Guilding et al., 2009). SCN explant rhythms are also more resistant to temperature fluctuations or clock gene mutations (Abraham et al., 2010; Buhr et al., 2010; Liu et al., 2007). This rigidity and robustness has been attributed to the intercellular coupling of individual SCN neurons (Aton et al., 2005; Buhr et al., 2010; Liu et al., 2007; Welsh et al., 1995).

The SCN innervates numerous brain nuclei, thereby passing time information to other CNS clocks. The paraventricular hypothalamic nucleus (PVN) is one of the main regions transducing SCN circadian function to the periphery (Saeb-Parsy et al., 2000). The PVN is a relay hub for energy homeostasis and projects predominantly to the pituitary where it regulates the release of hormones such as adrenocorticotrophin (ACTH; see below) and thyroid-stimulating hormone. The PVN also innervates the sympathetic limb of the autonomous nervous system which allows the SCN to indirectly control melatonin release from the pineal gland (Buijs et al., 2003b). Further projections of the SCN have been described to the dorsomedial hypothalamic nucleus (DMH; Luiten et al., 1987), the nucleus accumbens (NAc; Phillipson and Griffiths, 1985), and the paraventricular thalamic nucleus (Watts and Swanson, 1987; Watts et al., 1987) enabling the SCN to affect a plethora of physiological processes such as the reward system, feeding–fasting cycles, cognitive function, locomotor activity, and body temperature (Dibner et al., 2010). In addition, the SCN secretes diffusible factors which can function as timing cues. This notion has been substantiated by an elegant experiment showing that membrane-encapsulated fetal SCN tissue grafts, which only allowed for small molecule passage, could restore the periodicity of locomotor activity in SCN-lesioned hamsters in the absence of axonal outgrowth (Silver et al., 1996). Transforming growth factor (TGF) alpha (Kramer et al., 2001; Li et al., 2002), prokineticin-2 (PK-2) (Cheng et al., 2002), and cardiotrophin-like cytokine (CLC) (Kraves and Weitz, 2006) have been implicated as SCN-secreted peptides capable of regulating behavioral rhythmicity.

Extra-SCN clocks in the brain

The classical view of the role of SCN as the exclusive circadian pacemaker that controls all circadian

aspects of behavior (Fig. 1a) has been changing (Guilding and Piggins, 2007). The emerging theory is that the SCN synchronizes and coordinates numerous semiautonomous circadian clocks residing in different brain regions and peripheral tissues (Fig. 1b). Thanks to recent technical advancements, long-lasting and self-sustained circadian oscillations of clock genes have been revealed in a number of brain nuclei *in vitro* (Abe et al., 2002; Guilding and Piggins, 2007). These data provide compelling evidence for the existence of other circadian clocks in the brain. Here, we discuss some examples of these extra-SCN neural oscillators.

The retina was the first neuronal tissue outside the SCN shown to possess a circadian oscillator. Cultured hamster retinae show a circadian pattern of melatonin synthesis *in vitro* (Tosini and Menaker, 1996). Importantly, this rhythm persists in constant darkness (*self-sustainment*) but can be reset by a light–dark cycle (*entrainment*). Moreover, the period of the retina clock is resistant to

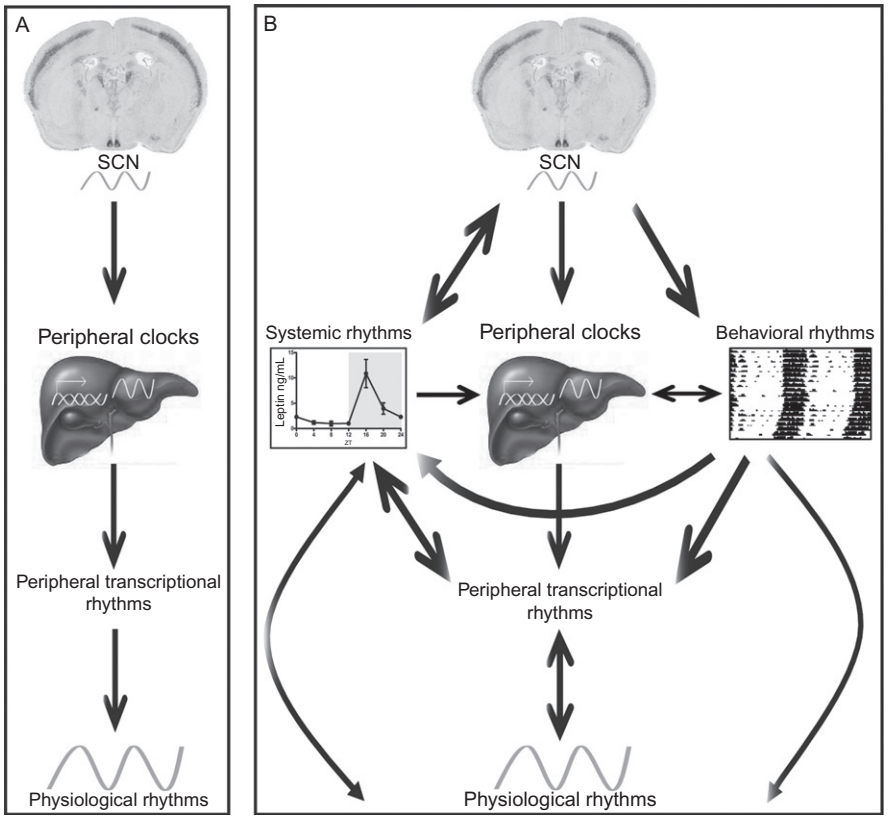

Fig. 1. Communication routes of the mammalian circadian timing system. (a) The SCN pacemaker entrains peripheral clocks. Via transcriptional regulation of clock controlled genes in target tissues, peripheral physiological functions are reset and synchronized to the light–dark cycle. (b) Pathways of interaction between central and peripheral clocks. The SCN resets physiological rhythms via the entrainment of peripheral tissue clocks, but at the same time regulates behavioral and systemic (e.g., endocrine) functions in a more direct manner. Peripheral rhythms may, in turn, directly or indirectly feedback on the SCN. This interlocked balance system creates plasticity in the entrainment of the circadian timing system and promotes adaptation to complex changes in environmental parameters.

temperature changes (*temperature compensation*), thereby fulfilling all the formal requirements of a true autonomous circadian oscillator (Tosini and Menaker, 1996). More recently, circadian oscillations of clock gene expression have also been detected in the retina, further supporting the clock properties of this tissue (Kamphuis et al., 2005). Genetic disruption of retinal clock function results in the loss of circadian rhythm of electrical responses to light (Storch et al., 2007). The olfactory bulbs (OBs), similar to the retina, have also been shown to comprise an autonomous circadian clock (Granados-Fuentes et al., 2004a,b). OB *Per1* expression and electrophysiological activity display rhythmic circadian patterns. Importantly, these rhythms persist in SCN-lesioned animals and under constant light conditions—when behavioral rhythms are disrupted—indicating that the OB's circadian oscillation is autonomous and independent from the SCN (Granados-Fuentes et al., 2004a). Circadian rhythms of clock gene expression and of odor responses have been described in the OB (Granados-Fuentes et al., 2006), but molecular evidence for an autonomous OB clock is still missing.

The mediobasal hypothalamus (MBH), situated posterior to the optic chiasm and overlying the pituitary, is a collective anatomical structure comprising the DMH, ventromedial (VMH), PVN, supraoptic, and arcuate (ARC) nuclei. The MBH is deemed as an integrating center regulating a diverse array of physiological processes such as growth, feeding, maturation, and reproduction (Luiten et al., 1987). Clock gene rhythms have been demonstrated in the DMH (see below), the PVN, and the ARC, as well as in the adjacent median eminence and the pituitary (Abe et al., 2002; Guilding et al., 2009). However, the physiological relevance of potential MBH clocks remains largely unknown. A recent study revealed that, despite the fact that ARC slices in culture possess a sustained (more than 1 week) molecular rhythm, electrical firing rate rhythms dampen within 48 h, suggesting that in the MBH molecular clocks may not—or only weakly—couple to electrical activity (Guilding et al., 2009). A subpopulation of dopaminergic (DA) ARC neurons displays robust circadian oscillations of *Per1* and *Per2* transcripts (Sellix et al., 2006). These neurons receive projections from the SCN (Gerhold et al., 2001) and themselves project to the anterior pituitary, where they regulate prolactin secretion. The DA turnover in these neurons exhibits a circadian rhythm which is light entrainable and has an approximate 24-h free-running period in constant conditions (Sellix and Freeman, 2003). It has been reported that several ARC neuropeptides display circadian/diurnal expression patterns including Agouti-related protein (AgRP; Lu et al., 2002), cocaine and amphetamine-regulated transcript (CART; Vicentic et al., 2005), neuropeptide Y (NPY), and pro-opiomelanocortin (POMC; Kalra et al., 1999). Also, orexin, secreted from the lateral hypothalamic area (LHA), shows rhythmic expression (Willie et al., 2001). Importantly, many of these rhythms are altered in diet-induced obese animals (Kohsaka et al., 2007), suggesting a link between the hypothalamic clock and metabolic regulation.

The reward system controls and regulates animal behavior by inducing pleasurable sensations upon perceiving certain stimuli. Such stimuli can be primary, that is, in response to food, sex, and water, which are important for the survival of individuals and propagation of species, or secondary, for example, in the context of money/profits and power/reputation (Chen et al., 2010). The major anatomical structure of reward is found in the mesolimbic DA system. DA neurons from the ventral tegmental area in the midbrain signal to the NAc, the dorsal striatum, and the frontal cortex (Chen et al., 2010). The links between circadian rhythms and the reward system are multifaceted (Dibner et al., 2010; Webb et al., 2009). Patients that suffer from defective reward function, for example, in bipolar disorder or major depression, often show altered behavioral rhythms and sleep patterns (Westrich and Sprouse, 2010). Conversely, patients with genetic sleep disorders are often predisposed to addiction (Shibley et al., 2008). The most striking example, seasonal

affective disorder (SAD), provides a mechanistic link between altered mood status and altered circadian behavior. SAD patients suffer from depressive episodes upon seasonal change, mostly in winter, suggesting that alterations in circadian light entrainment might trigger disease states (Levitan, 2007). Along the same line, psychostimulants such as cocaine and methamphetamine that can activate the mesolimbic reward system and induce pleasurable effects are known to affect circadian clock. Early studies revealed that chronic exposure to methamphetamine can disrupt the circadian rhythms of rats (Honma et al., 1986). On the other hand, many aspects of addictive behavior show a time-of-day-dependent pattern with a period of approximately 24 h (Abarca et al., 2002). Drug intake can induce clock gene expression in several brain areas including the NAc and the striatum (Uz et al., 2005; Yuferov et al., 2003). In rodents, clock genes have been shown to modify psychostimulant responses (Abarca et al., 2002; Rosenwasser et al., 2005; Spanagel et al., 2005). Importantly, *Clock*$^{\Delta 19}$ mutant mice show increased excitability of DA neurons and a higher rate of DA synthesis, indicating a general excited, mania-like state of the DA circuitry (McClung et al., 2005; Roybal et al., 2007). Recently, *Per2* has been identified as a positive regulator of monoamine oxidase A (MAOA) expression and activity, a degrading enzyme of DA, and hence a negative regulator or DA release (Hampp et al., 2008). Taken together, these data illustrate an active role of the circadian clock in modulating the mesolimbic reward pathway. It remains to be shown, however, whether the DA neurons themselves contain a functional circadian clock and how such a system affects reward responses to different stimuli.

Two phenomena tightly linked to the reward system suggest that circadian rhythms may also emerge from structures that are potentially very differently organized than the cellular TTL clocks described above. The food-entrainable oscillator or FEO is a putative timing system that has drawn much attention in the past 30 years. It has been shown that the lost rhythmic locomotor activity of SCN-lesioned arrhythmic rats can be partly restored by temporally restricted feeding (RF) schedules (Stephan et al., 1979), a phenomenon known as food anticipatory activity (FAA; Boulos and Terman, 1980; Mistlberger, 1994). RF can also restore the rhythmicity of pineal melatonin release (Feillet et al., 2008), thermogenesis, plasma rhythms of nutrient-related blood-borne hormones, and drinking patterns (Boulos and Terman, 1980; Mistlberger, 1994; Stephan, 2002). Such feeding-related rhythms, once established, can persist (or *free-run*) for several days with an approximate 24-h period under fasting conditions. Lesion studies have tried to determine the anatomical locus of the FEO, but to date, no study has unequivocally identified a structure essential for the generation of feeding-related rhythms (Davidson, 2009). Moreover, it remains controversial whether the known clock genes are involved in the regulation of FAA (Challet et al., 2009; Feillet et al., 2006; Storch and Weitz, 2009). The current prevailing opinion is that the FEO is a diffuse system emerging from the interplay of different circuits within the CNS, and likely even within peripheral organs. Within the CNS it may comprise multiple brain regions as well as various signaling pathways.

The concept of the methamphetamine-sensitive oscillator (MASCO) originated in the 1980s; Honma and colleagues showed that chronic treatment of SCN-lesioned rats with methamphetamine could reinitiate circadian locomotor activity, core body temperature, and plasma corticosterone rhythms (Honma et al., 1987, 1988), which can persist for up to 2 weeks after withdrawal from the drug (Ruis et al., 1990). The emergence of methamphetamine-induced rhythms is independent of functional circadian clock machinery (Honma et al., 2008; Masubuchi et al., 2001). Interestingly, methamphetamine treatment can reset the rhythm of clock gene expression in several brain areas such as the caudate putamen, the striatum, and the parietal cortex, but not the SCN (Masubuchi et al., 2000). The anatomical structure, the endogenous

zeitgebers, and the output pathways of the MASCO, however, remain largely unknown.

Peripheral clocks

Outside the brain, "canonical" circadian clocks have been identified in several peripheral organs and tissues, capable of generating oscillations with a periodicity of approximately 24 h. The intrinsic properties of such peripheral clocks have been characterized using primary cell culture models and tissue explants cultures (Yoo et al., 2004). Immortalized rat fibroblast (Rat-1) cells display robust oscillations of clock gene expression after brief stimulation with high concentrations of serum (*serum shock*; Balsalobre et al., 1998). Using single cell imaging techniques, Nagoshi et al. showed that individual fibroblasts possess sustained endogenous circadian expression rhythms of clock genes, although populations of cells quickly become desynchronized from each other because of individual differences in period (Nagoshi et al., 2004). Serum shock (or stimulation with forskolin, GCs, or phorbol esters) synchronizes the individual cells, yielding a transiently phase coherent population (Nagoshi et al., 2004). These results point to the notion that the peripheral cellular clock is actually self-sustained and autonomous in nature but fails to maintain the coherence with neighboring cells, in contrast to the coupled nature of SCN (see above). In other words, at the cellular level, fibroblasts do not differ from SCN neurons in terms of the molecular circadian machinery (Liu et al., 2007). In line with this observation, tissue explants from a wide array of peripheral organs including heart, lung, kidney, liver, spleen, pancreas, stomach, cornea, thyroid gland, and adrenal gland all show robust clock gene expression rhythms (Yamazaki et al., 2000; Yoo et al., 2004). It is still not fully understood how the SCN transmits its timing signal to peripheral clocks. Endocrine signals such as GCs play a role (Balsalobre et al., 2000; Kiessling et al., 2010). Some clocks respond to neuronal cues (Ishida et al., 2005; Kalsbeek et al., 2004; Oster et al., 2006a), while others are affected by behavior-associated changes in temperature (Brown et al., 2002; Dibner et al., 2010). Circadian transcriptome profiling studies suggest that local peripheral clocks, while being reset by the SCN, independently control tissue physiology via the regulation of output genes comprising 5–10% of the active transcriptome (Akhtar et al., 2002; Hughes et al., 2009; Kornmann et al., 2007a; McCarthy et al., 2007). In line with this, peripheral clocks have been implicated in a plethora of physiological functions such as cardiac contraction (Bray and Young, 2009), renal excretion (Firsov et al., 2011), adipogenesis and lipid metabolism (Gimble et al., 2011), digestive processes (Gimble and Floyd, 2011), and xenobiotic metabolism (Claudel et al., 2007), to name but a few. However, recent data suggest that the organization of circadian molecular and physiological functions is more complex than originally thought and involves tight interaction between different central and peripheral clocks (Kornmann et al., 2007b; Fig. 1b). In the following section, we will discuss glucose metabolism and the regulation of GC secretion from the adrenal cortex to exemplify the intricate interplay between the central and peripheral circadian clocks which is essential for the maintenance of physiological homeostasis.

Glucocorticoid (GC) secretion

GCs are steroids produced in the adrenal gland, cortisol in humans and corticosterone in rodents, which are essentially involved in energy metabolism, immune function, and stress responses. Disruption of GC secretion is associated with severe pathophysiology. Patients affected with Cushing's Syndrome, characterized by excess GC levels, often present with diabetes mellitus, osteoporosis, hypertension, dyslipidemia, and sleep disorders (Carroll and Findling, 2010). Conversely, GC insufficiency results in Addison's disease, which is characterized by stress sensitivity, hypoglycemia, hypotension, mood disturbances, and weight loss

(Anglin et al., 2006). In addition, chronic fatigue syndrome is associated with perturbations in GC regulation (Chung et al., 2011b). Clock-related lifestyle factors can affect GC levels, such as shift work, jet lag, and nighttime eating, and are associated with diabetes and metabolic syndrome and increased risk of heart attack and cancer (Boivin et al., 2007). GC secretion shows a very prominent diurnal/circadian rhythm peaking around wake-up time (morning in humans, evening in rodents). SCN and adrenal clocks are both required for the circadian production of GCs. Further, GC actions are circadian gated through the rhythmic expression of its receptors. Finally, GC feedback directly affects the phase of clock gene transcription in other peripheral oscillators, completing an elegant cycle of integration.

The nycthemeral production of GCs occurs through the hypothalamus/pituitary/adrenal (HPA) axis. The role of the SCN was determined in the 1970s and 1980s, with studies demonstrating that the ACTH release from the pituitary is no longer rhythmic in SCN-lesioned animals, disrupting adrenal GC secretion rhythms (Cascio et al., 1987; Moore and Eichler, 1972; Szafarczyk et al., 1983). The neuropeptide arginine vasopressin (AVP) is released rhythmically from SCN neurons (Earnest and Sladek, 1986; Gillette and Reppert, 1987) projecting into the rostral PVN. There, it inhibits the production of corticotrophin-releasing hormone (CRH; Buijs et al., 1993; Gomez et al., 1997; Kalsbeek et al., 1992), which is ultimately responsible for ACTH release from hypophyseal adrenocorticotrophs in the pituitary. In this manner, circadian rhythms in the SCN result in the circadian release of ACTH, peaking at the beginning of the active phase. ACTH then regulates the production and release of GC from the adrenal gland.

Anatomically, the adrenal gland is divided into the cortex and the medulla, which are structurally and functionally discrete. The medulla is responsible for the secretion of epinephrine and norepinephrine, while the cortex produces various steroid hormones. GCs are produced in the *zona fasciculata* cells of the cortex, which express ACTH receptors (Chung et al., 2011a). Rhythmic GC secretion is regulated by an intrinsic circadian clock located in the cortex of the adrenal gland (Oster et al., 2006a,b; Son et al., 2008). Using a model of adrenal transplantation between wild-type and mutant mice lacking a functional clock, the role of the adrenal clock was elucidated (Oster et al., 2006b). In the absence of an SCN clock, GC rhythms remain entrainable by light, but in the absence of light, the rhythm is rapidly lost. Conversely, in the absence of a functional adrenal clock, GC rhythms are dampened, suggesting that the function of the adrenal clock is to gate the responsiveness of the adrenal to ACTH through the rhythmic expression of steriodogenic enzymes or modulators. A *Bmal1 knockdown* study supports these findings, suggesting that the adrenal clock plays a dominant role in the regulation of local GC production in the adrenal, though not of circulating GC levels in the blood (Son et al., 2008).

In addition to HPA axis control, GC release is regulated by neuronal signals. Virus tracing studies reveal multisynaptic autonomic connections between the SCN and the adrenal gland (Buijs et al., 1999). Jasper et al. showed that splanchnic denervation results in dampening of diurnal GC rhythms and increased sensitivity to ACTH stimulation (Jasper and Engeland, 1997). A direct effect of light on the adrenal gland was characterized by Ishida et al., who showed that light exposure induces *Per* gene expression in the adrenal gland via the SCN sympathetic nervous system, resulting in an upregulation of GC release (Ishida et al., 2005), thus offering a mechanism for the observed light entrainment of adrenal clock transplants in otherwise arrhythmic animals mentioned above (Oster et al., 2006b).

GC receptors are expressed throughout the periphery and the brain, with the notable exception of the SCN (Rosenfeld et al., 1988). Activated GC receptors act as transcription factors via activation or repression of GC target genes (Surjit et al., 2011). Disruption of GC signaling, for example, by adrenalectomy, affects gene transcription in the periphery and the brain. In the central nucleus of

the amygdala, it causes a loss of PER2 rhythmic expression, while in the liver, it alters the regulation of numerous genes involved in metabolism (Lamont et al., 2005; Oishi et al., 2005). Timed GC or GC analog treatment in mice has a powerful resetting effect on liver (clock) gene rhythms (Balsalobre et al., 2000; Reddy et al., 2007; Segall et al., 2006; Son et al., 2008). Additionally, GC receptors are rhythmically transcribed in various tissues and subjected to acetylation—and subsequent inactivation—by CLOCK (Nader et al., 2009; Yao et al., 2006). In conclusion, GC production, secretion, and signaling are an example of the complex system of integration afforded by the presence of multiple circadian clocks organized in a hierarchical manner.

Glucose metabolism

The maintenance of glucose homeostasis is essential for mammalian physiology. Plasma glucose levels display diurnal rhythms in mammals, peaking before the onset of activity while remaining constant throughout the remainder of the day. This peak does not coincide with food intake, clearly illustrating the extent of endogenous regulation dedicated to glucose circulation (La Fleur et al., 1999). Circulating glucose is altered by absorption from the gut following feeding, glucose uptake into tissues, and glucose production. These latter processes are tightly regulated in a temporal manner to assure sufficient glucose availability, for example, for the brain, while avoiding extended postprandial hyperglycemia. The liver plays a pivotal role in this process as a site of glucose uptake from the circulation, as well as being the major source of *de novo*-synthesized glucose in times of need (Kalsbeek et al., 2010). The regulation of the diurnal glucose rhythm has been shown to be maintained by both neuroendocrine and neuronal pathways and involve a large number of different central and peripheral circadian clocks.

Early studies on the autonomic innervation of the liver in regard with glucose homeostasis show that sympathetic input predominantly increases hepatic glucose output, while parasympathetic input stimulates insulin-dependent glucose uptake and storage in the form of glycogen (Puschel, 2004). The influence of the master clock on glucose regulation was shown by Buijs and colleagues using SCN-lesioned rats, which have no diurnal glucose rhythm, compared to fasted and arrhythmic-fed (six daily feeds) animals, which retain their glucose rhythms (La Fleur et al., 1999). The precise nature of this regulation has been dissected in a series of studies using euglycemic hyperinsulinemic clamps in combination with selective autonomic denervation of the liver. Initial retrograde tracing studies from the liver revealed projections via both sympathetic and parasympathetic systems to third-order neurons in the hypothalamus, specifically the SCN (La Fleur et al., 2000). Studies designed to distinguish between sympathetic and parasympathetic output from the SCN showed that exclusive populations of neurons within the SCN are responsible for each of these signals, projecting to preautonomic neurons in the PVN (Buijs et al., 2003a). In 2004, it was shown that the SCN-derived sympathetic inputs to the PVN were inhibitory GABAergic inputs, and their inhibition resulted in increased hepatic glucose production (Kalsbeek et al., 2004). It was additionally demonstrated that these GABAergic inputs provide the circadian timing information for the liver as well as for the insulin response of the pancreas (Kalsbeek et al., 2008). Interestingly, it was shown that complete denervation of the liver in conjunction with constant feeding does not abolish diurnal glucose rhythms; however, this can be achieved by inactivation of either the sympathetic or the parasympathetic inputs (Cailotto et al., 2008). Collectively, these studies indicate that the autonomic modulation of glucose rhythms requires a balance in both branches of the autonomic nervous system by the SCN.

Further studies revealed that orexin, a hypothalamic neuropeptide involved in wakefulness and feeding behavior, is an important regulator of glucose homeostasis and the main effector in the preactive phase glucose peak (Yi et al., 2009).

Intracerebroventricular infusion of orexin results in increased glucose production. Inhibition of GABAergic inputs—originating from the SCN—to the perifornical orexin area (PF-Oa) has a similar effect, correlating with activation of orexin-positive neurons. Given that GABAergic inhibition of hyperglycemia, GABAergic inputs to orexin neurons in the PF-Oa, and orexin release all show clear diurnal rhythmicity (Alam et al., 2005; Kalsbeek et al., 2008; Zhang et al., 2004), it is feasible to propose that orexin-containing PF-Oa neurons translate SCN-derived GABAergic rhythms into glucose rhythms via the sympathetic nervous system.

Interestingly, hepatic sympathetic denervation of the liver results in the loss of diurnal glucose rhythms, without affecting gene expression rhythms of liver clock genes, indicating that the liver clock is not essential in this process (Cailotto et al., 2005). However, glucose production is generally thought to be further regulated via clock target genes involved in glucose metabolism in the liver. The liver clock has been well described, and rhythmic liver genes are highly enriched for metabolic function (Lamia et al., 2008; Oishi et al., 2003; Panda et al., 2002; Storch et al., 2002). SCN ablation studies show that liver clock gene and clock output gene rhythmicity are abolished or severely dampened in the absence of synchronization by the central clock (Akhtar et al., 2002). The liver clock is highly responsive to RF regimes, which change the phase of core clock gene expression as well as the diurnal rhythm of circulating glucose (Damiola et al., 2000; Escobar et al., 1998). Interestingly, these RF-induced changes to the liver clock are inhibited by GCs (Le Minh et al., 2001). Conversely, regular short-period feeding paradigms prevent disturbances in clock gene expression in the liver and leave circulating glucose rhythms intact (La Fleur et al., 1999).

Many clock-deficient animal models show perturbations in glucose metabolism. *Clock* mutant mice display impaired glycogen storage, which correlates with dampened glycogen synthase 2 (*Gys2*) expression rhythms in the liver (Doi et al., 2010). Microarray analyses of the $Clock^{\Delta 19}$ mutant liver transcriptome reveal that metabolic gene rhythmicity is dampened (Oishi et al., 2003). $Clock^{\Delta 19}$ mutant and $Bmal1^{-/-}$ mice show impaired gluconeogenic potential, correlating with decreased phosphoenolpyruvate carboxykinase 1 (*PEPCK*) expression in the liver (Rudic et al., 2004). More recently, studies have shown that CRY1 negatively regulates gluconeogenesis through the inhibition of G-protein-coupled receptor-mediated cAMP accumulation (Zhang et al., 2010). Perhaps most significantly, liver-specific $Bmal1^{-/-}$ ($L\text{-}Baml1^{-/-}$) mice display perturbations in rhythmic expression of glucose regulatory genes and glucose metabolism, including circulating blood glucose (Lamia et al., 2008). These mice display hypoglycemia in the middle and end of the inactive phase and increased glucose uptake during this time, arguing for a significant role of hepatic clocks in the maintenance of glucose homeostasis.

Glucose uptake is dependent on insulin and can be influenced by insulin release from the pancreas or by insulin sensitivity in peripheral tissues. Insulin levels display diurnal rhythms, and similarly to glucose, time-RF results in changes to this rhythm in rodents (Diaz-Munoz et al., 2000). In the case of insulin, however, the diurnal rhythm is lost following fasting and appears to be primarily dependent on feeding rhythms rather than being clock driven (La Fleur et al., 1999). On the other hand, feeding-stimulated insulin responses are rhythmic (Kalsbeek and Strubbe, 1998). Indeed, changes in glucose uptake over the course of the day correlate to alterations in insulin sensitivity rather than insulin release, and this rhythm is lost in SCN-lesioned animals, indicating central clock involvement (La Fleur et al., 2001). Conflictingly, SCN-lesioned animals display increased glucose uptake as well as decreased meal-induced insulin secretion. This is hypothesized to be due to insulin-independent glucose uptake, perhaps via autonomic inputs to muscle tissues (La Fleur, 2003). Functional clocks have been identified in the pancreatic β-cells (Marcheva et al., 2010; Sadacca et al., 2011).

In *Clock*$^{\Delta 19}$ mutant mice, a diabetic phenotype comprising increased blood glucose levels, loss of active phase insulin peak, reduced glucose tolerance, and retarded glucose-stimulated insulin release is seen (Marcheva et al., 2010). Generation of a β-cell-specific *Bmal1*$^{-/-}$ mouse confirmed that these phenotypes are due to the loss of a functioning clock in islets of Langerhans and seem to be the result of impaired glucose-stimulated insulin release rather than insulin production (Sadacca et al., 2011).

As discussed above, euglycemia is maintained in the fasting state predominantly through hepatic production and release of glucose. Of note, GCs can increase gluconeogenesis directly through the activation of a number of key enzymes involved in this pathway (Jin et al., 2004; Sasaki et al., 1984; Vander Kooi et al., 2005) as well as through the production of suitable substrates from increased lipolysis (Campbell et al., 2011), thus suggesting indirect effects of adrenal—and possibly adipose—clocks in glucose regulation. GCs further affect gluconeogenesis by decreasing the sensitivity of the liver to insulin, the major inhibitor of gluconeogenesis. This is achieved in two ways, first, by directly decreasing the release of insulin from β-cells in the pancreas and, second, by decreasing the insulin-mediated glucose uptake in adipocytes and muscle (Delaunay et al., 1997; Sakoda et al., 2000; Weinstein et al., 1998), potentially involving further circadian clocks active in the respective tissues. Under conditions of HPA axis dysregulation where GC rhythms are affected, abnormal glucose homeostasis is observed, promoting the development of diabetes.

The hypothalamus contains distinct populations of neurons, identifiable according to their signature expression profiles of receptors and neurotransmitters. These nuclei form a complex network of excitatory and inhibitory signals that regulate peripheral nutritional status and both homeostatic and hedonic feeding. These feeding nuclei receive inputs from the SCN, as discussed above, and many have been suggested to contain functional molecular clocks (Guilding et al., 2009). Arguably the most important input in the regulation of feeding is leptin, which shows a diurnal circulation rhythm, and is disrupted in mouse models lacking a functional clock (Turek et al., 2005). Leptin signals predominantly in the ARC, which contains two distinct populations of neurons: the first expressing NPY and AgRP and possessing orexigenic function and the second expressing POMC and CART and possessing anorexigenic function. In addition to receiving leptin signals, these cells may also be directly responsive to glucose and function as sensors of peripheral glucose fluctuations. Some studies have demonstrated that NPY neurons are inhibited by glucose, whereas POMC neurons are excited, although it should be noted that other studies have failed to see these effects (Claret et al., 2007; Fioramonti et al., 2007; Ibrahim et al., 2003; Muroya et al., 1999). Despite discrepancies, it seems plausible that ARC neurons are capable of responding directly to changes in circulating glucose levels. ARC neurons signal to various regions of the brain such as the LHA, the VMH, the mediodorsal nucleus of the thalamus, the dentate gyrus, the piriform cortex, the ventral basolateral amygdala, and the bed nucleus of stria terminalis (DeFalco et al., 2001; Muroya et al., 2004), and some of these neurons may also possess glucose-sensing properties. For example, orexin/hypocretin-containing neurons of the LHA are activated by hypoglycemia (Cai et al., 2001) and inhibited by glucose in mice (Guyon et al., 2009). Melanin-concentrating hormone (MCH)-containing neurons—also in the LHA—respond to glucose stimulation (Burdakov et al., 2005). Given the apparent opposing functions of these subsets of neurons, with orexin/hypocretin neurons involved in wakefulness and MCH-containing neurons involved in sleep and decreased activity, circulating glucose levels can feedback to the hypothalamus to direct appropriate behaviors. How clock disruption in these neurons affects metabolic homeostasis and glucose levels, however, remains to be shown.

Conclusion

While the circadian clock is traditionally seen as a top-down-controlled system in which the SCN pacemaker synchronizes peripheral clocks throughout

the body, which, in turn, regulate local physiological rhythms via transcriptional programs (Fig. 1a), recent data clearly suggest that a coordinated interplay between different central and peripheral clocks is necessary to maintain robust rhythms of certain humoral factors (e.g., GCs) or restrict fluctuations in others within physiologically tolerable ranges (e.g., blood glucose; Fig. 1b). We are only now developing the genetic tools to dissect the role of organ-specific circadian clocks in these processes in living animals, and new technologies will be needed to specifically manipulate several tissue clocks in a coordinated manner which would allow the interactivity of the circadian oscillatory network at the systemic level to be analyzed.

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