

# Central and Peripheral Circadian Clocks in Mammals

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## Keywords

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## Abstract

The circadian system of mammals is composed of a hierarchy of oscillators that function at the cellular, tissue, and systems levels. A common molecular mechanism underlies the cell-autonomous circadian oscillator throughout the body, yet this clock system is adapted to different functional contexts. In the central suprachiasmatic nucleus (SCN) of the hypothalamus, a coupled population of neuronal circadian oscillators acts as a master pacemaker for the organism to drive rhythms in activity and rest, feeding, body temperature, and hormones. Coupling within the SCN network confers robustness to the SCN pacemaker, which in turn provides stability to the overall temporal architecture of the organism. Throughout the majority of the cells in the body, cell-autonomous circadian clocks are intimately enmeshed within metabolic pathways. Thus, an emerging view for the adaptive significance of circadian clocks is their fundamental role in orchestrating metabolism.

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## INTRODUCTION

Living systems possess an exquisitely accurate internal biological clock that times daily events ranging from sleep and wakefulness in humans to photosynthesis in plants (Takahashi et al. 2008). These circadian rhythms represent an evolutionarily conserved adaptation to the environment that can be traced back to the earliest life forms. In animals, circadian behavior can be analyzed as an integrated system—beginning with genes and leading ultimately to behavioral outputs. In the past 15 years, the molecular mechanism of circadian clocks has been uncovered by the use of phenotype-driven (forward) genetic analysis in a number of model systems (Lowrey & Takahashi 2011). Circadian oscillations are generated by a set of genes forming

a transcriptional autoregulatory feedback loop. In mammals, these include *Clock*, *Bmal1*, *Per1*, *Per2*, *Cry1*, and *Cry2*. Researchers have identified another dozen candidate genes that play additional roles in the circadian gene network such as the feedback loop involving *Rev-erba*.

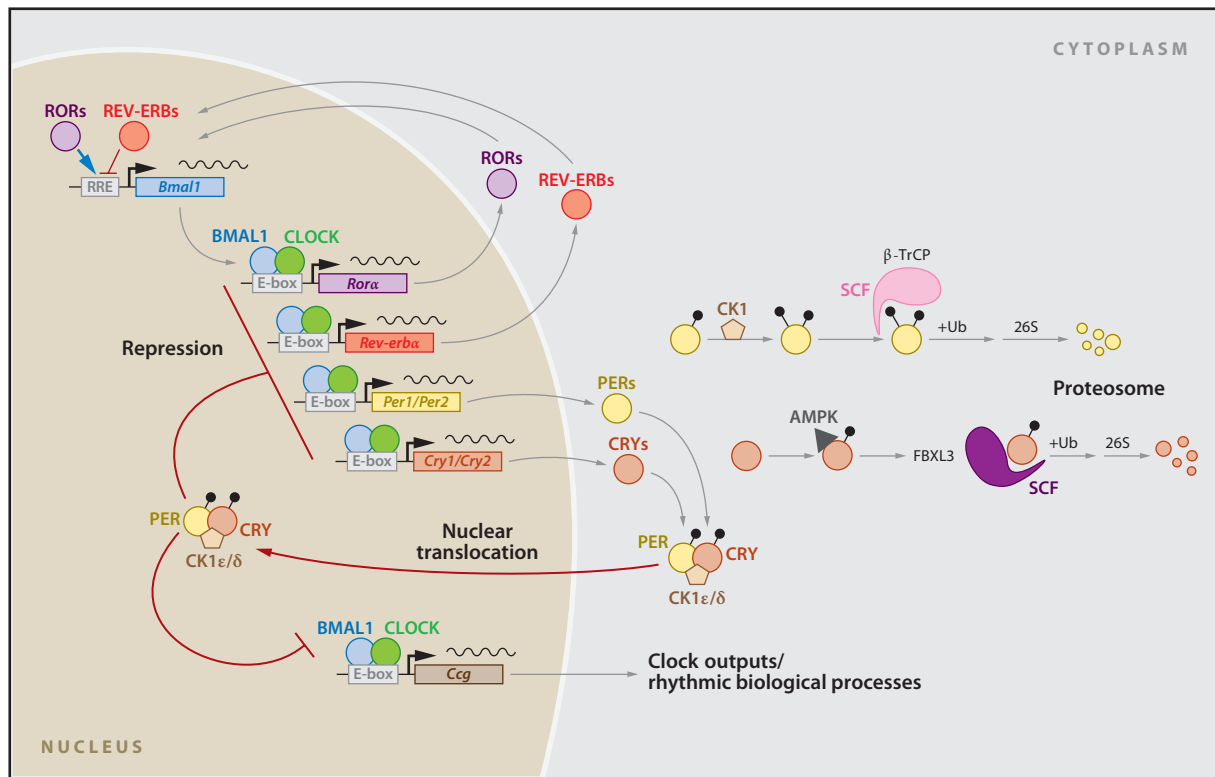
Early work on mammalian rhythms used rhythmic behavior as a readout of the clock, and the hypothalamic suprachiasmatic nucleus (SCN) was identified as the dominant circadian pacemaker driving behavioral rhythms (Welsh et al. 2010). However, the discovery of “clock genes” led to the realization that the capacity for circadian gene expression is widespread throughout the body (Dibner et al. 2010). Using circadian gene reporter methods, one can demonstrate that most peripheral organs and tissues can express circadian oscillations in isolation yet still receive, and may require, input from the SCN in vivo. The cell-autonomous clock is ubiquitous, and almost every cell in the body contains a circadian clock (Balsalobre et al. 1998, Nagoshi et al. 2004, Welsh et al. 2004, Yoo et al. 2004). It is now evident that the circadian oscillators within individual cells respond differently to entraining signals, control different physiological outputs, and interact with each other and with the system as a whole. These discoveries have raised a number of questions concerning the synchronization and coherence of rhythms at the cellular level as well as the architecture of circadian clocks at the systems level (Hogenesch & Ueda 2011). Here we discuss recent work that addresses these organizational issues and examines a number of levels of complexity within the circadian system. We review mechanisms by which circadian clocks govern biological processes as well as mechanisms by which these processes feed back into the circadian system. Perhaps the most important example of this is the intimate and reciprocal interaction between the circadian clock system and fundamental metabolic pathways (Bass & Takahashi 2010, Green et al. 2008, Rutter et al. 2002). In addition, there exist additional oscillatory processes in the circadian time domain that are observable in the presence of scheduled meals or methamphetamine

### Circadian rhythm:

an endogenously generated oscillation with a period of ~24 h; can entrain to external cues and is temperature compensated

### Suprachiasmatic nucleus (SCN):

the site of the master circadian pacemaker in mammals, comprising ~20,000 individual neurons that couple to form a robust oscillatory network



**Figure 1**

The molecular mechanism of the circadian clock in mammals. Constituting the core circadian clock is an autoregulatory transcriptional feedback loop involving the activators CLOCK and BMAL1 and their target genes *Per1*, *Per2*, *Cry1*, and *Cry2*, whose gene products form a negative-feedback repressor complex. In addition to this core transcriptional feedback loop, other feedback loops are also driven by CLOCK:BMAL1. One feedback loop involving *Rev-erba* and *Rora* that represses *Bmal1* transcription leads to an antiphase oscillation in *Bmal1* gene expression. CLOCK:BMAL1 also regulates many downstream target genes known as clock-controlled genes (*Ccg*). At a post-transcriptional level, the stability of the PER and CRY proteins is regulated by SCF (Skp1-Cullin-F-box protein) E3 ubiquitin ligase complexes involving  $\beta$ -TrCP and FBXL3, respectively. The kinases, casein kinase 1 $\epsilon/\delta$  (CK1 $\epsilon/\delta$ ) and AMP kinase (AMPK), phosphorylate the PER and CRY proteins, respectively, to promote polyubiquitination by their respective E3 ubiquitin ligase complexes, which in turn tag the PER and CRY proteins for degradation by the 26S proteasome complex.

treatment. These oscillators can generate behavioral rhythms in vivo in the absence of the SCN (Honma & Honma 2009).

## MOLECULAR MECHANISM OF THE CIRCADIAN CLOCK IN MAMMALS

In mammals, the mechanism of the circadian clock is cell autonomous and arises from an autoregulatory negative-feedback transcriptional network (Lowrey & Takahashi 2004, Takahashi et al. 2008) (**Figure 1**). At the core

of this clock network are the transcriptional activators, CLOCK (and its paralog, NPAS2) and BMAL1, which positively regulate the expression of the *Period* (*Per1*, *Per2*) and *Cryptochrome* (*Cry1*, *Cry2*) genes at the beginning of the cycle. *Per* and *Cry* gene products accumulate, dimerize, and form a complex that translocates into the nucleus to interact with CLOCK and BMAL1, repressing their own transcription. This feedback cycle takes  $\sim 24$  h, and the turnover of the PER and CRY proteins is tightly regulated by E3 ubiquitin ligase complexes. There are additional feedback loops interlocked

with the core CLOCK-BMAL1/PER-CRY loop. Prominent among these is a loop involving *Rev-erb $\alpha$*  (*Nr1d1*) and *Rora*, which are also direct targets of CLOCK-BMAL1. The feedback effects of this loop impinge on the transcription of *Bmal1* (and to a lesser extent on *Clock*) to cause an antiphase oscillation of BMAL1. Other feedback loops involve the PAR-bZip family members, DBP, HLF, and TEF; the bZip protein, E4BP4 (*Nfil3*); and the bHLH proteins, DEC1 and DEC2 (*Bhlhb2*, *Bhlhb3*), all of which are transcriptional targets of CLOCK-BMAL1 (Gachon 2007, Lowrey & Takahashi 2004, Takahashi et al. 2008).

The discovery of a ubiquitous, cell-autonomous clock in mammals has led to a re-evaluation of central and peripheral oscillators: Are they fundamentally similar in mechanism, how do they function in different cellular contexts, and what role does coupling in the central SCN clock play in its functional properties?

## CENTRAL CIRCADIAN OSCILLATORS

The hypothalamic SCN acts as a master pacemaker for the generation of circadian behavioral rhythms in mammals (for a review, see Welsh et al. 2010). Classic work not reviewed here has shown that the SCN is both necessary and sufficient for the generation of circadian activity rhythms in rodents. The SCN receives direct photic input from the retina from a recently discovered photoreceptor cell type termed the intrinsically photoreceptive retinal ganglion cell (ipRGC) (reviewed in Do & Yau 2010). These ipRGCs express a novel photopigment, melanopsin, that renders them intrinsically photosensitive to short-wavelength irradiation. Interestingly, ipRGCs are depolarizing photoreceptors that employ a phototransduction mechanism that is analogous to that seen in invertebrate photoreceptors. The photoreponse in ipRGCs has slow kinetics and a relatively high threshold to light, making them ideally suited to function as circadian photoreceptors, which must integrate light information over relatively long durations and must be

insensitive to transient light signals that are not associated with the solar light cycle. Although ipRGCs appear to be optimal circadian photoreceptors, they do not act alone; rod and cone photoreceptors also have photic inputs to the SCN. Interestingly, these nonvisual inputs from rods and cones to the SCN are mediated by the ipRGCs (Chen et al. 2011, Guler et al. 2008). An emerging theme is that melanopsin-positive ipRGCs are involved in a surprisingly broad array of nonvisual photic responses in mammals. The complexity of the ipRGCs and their contribution to circadian rhythms and other behaviors are beyond the scope of this discussion, but recent reviews have covered this topic in depth (Do & Yau 2010, Schmidt et al. 2011).

## Suprachiasmatic Nucleus

The SCN is composed of ~20,000 neurons, each of which is thought to contain a cell-autonomous circadian oscillator. The SCN functions as a network in which the population of SCN cells are coupled together and oscillate in a coherent manner (Herzog 2007). The dynamics of the spatial and temporal coordination of rhythms in the SCN have been studied recently, enabled by the advent of single-cell circadian reporter technology, which has revealed unexpected complexity in the temporal architecture of the nucleus (Evans et al. 2011, Foley et al. 2011, Yamaguchi et al. 2003). At the single-cell level, SCN neurons exhibit a wide range in cell-autonomous circadian periods that vary from 22 h to 30 h (Ko et al. 2010, Liu et al. 1997, Welsh et al. 1995). Intercellular coupling among SCN neurons acts to mutually couple the entire population to a much narrower range that corresponds to the circadian period of the locomotor activity rhythm, which is extremely precise (a standard deviation in period that is ~0.2 h or 12 min in mice) (Herzog et al. 2004). The heterogeneity in intrinsic period of the SCN cells confers at least two important functions: phase lability and phase plasticity. The phases of the rhythms of individual SCN neurons are highly stereotyped

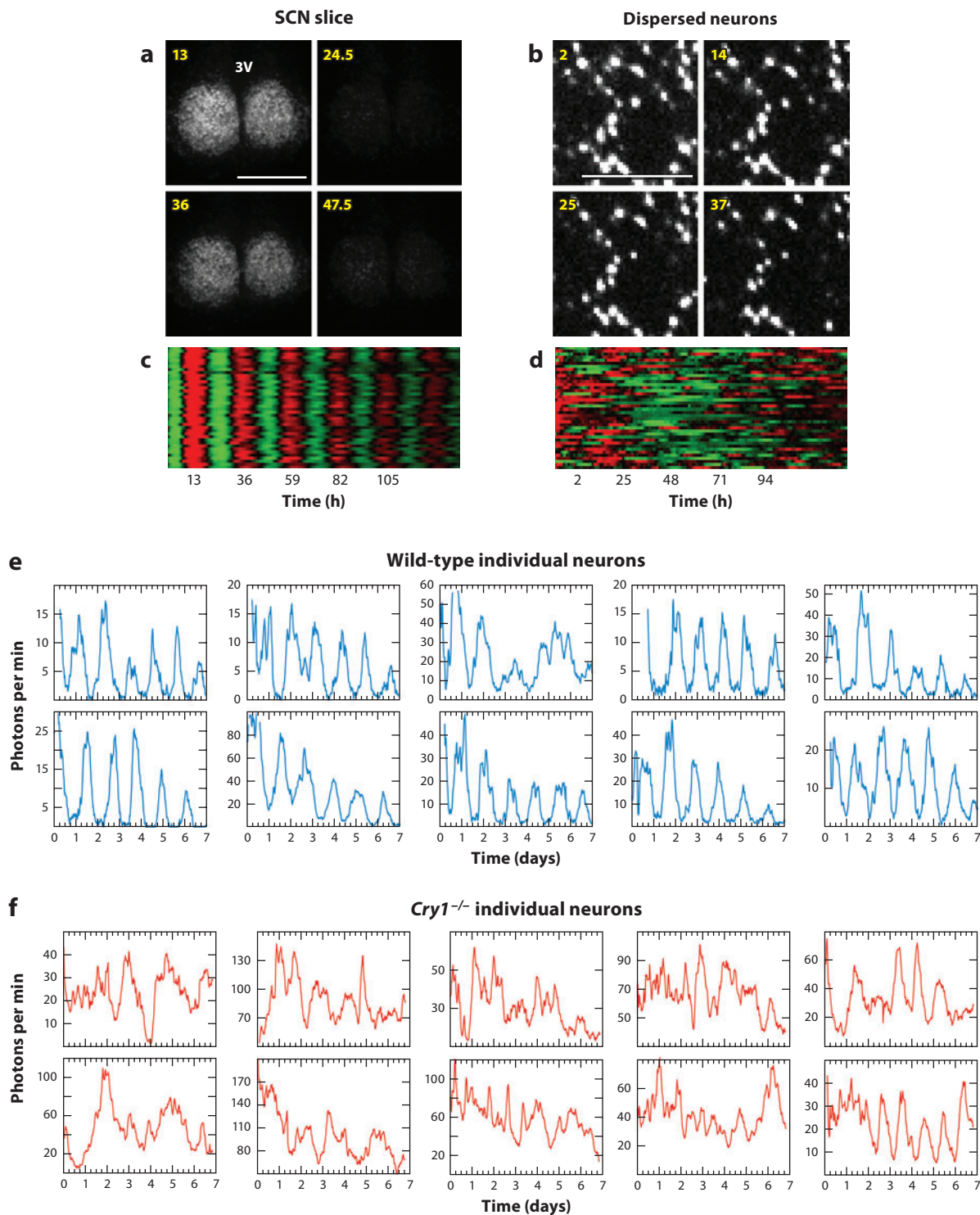
anatomically and appear as a wave that spreads across the nucleus over time (Evans et al. 2011, Foley et al. 2011, Yamaguchi et al. 2003). Intrinsically shorter-period cells have earlier phases and intrinsically longer-period cells have later phases within the SCN, reflecting phase lability (Yamaguchi et al. 2003). Under different photoperiods (e.g., long- versus short-photoperiod light cycles), the waveform of the SCN population rhythm is modulated such that in short photoperiods the SCN waveform is narrow and has a high amplitude, whereas in long photoperiods the SCN waveform is broad and has a low amplitude, reflecting phase plasticity (Inagaki et al. 2007, VanderLeest et al. 2007). In addition to the heterogeneity of SCN oscillator period and phase, it has been proposed that the cell-autonomous SCN oscillators are not intrinsically uniformly robust (Webb et al. 2009). Rather, the intercellular coupling of SCN neurons appears critical to the robustness of the SCN network oscillatory system.

With the discovery of peripheral oscillators (Balsalobre et al. 1998, Yamazaki et al. 2000, Yoo et al. 2004) and the apparent ubiquity of clock mechanisms (Yagita et al. 2001), a critical question arises concerning the similarity and differences in the SCN pacemaker as compared with peripheral oscillators. To address this question, Liu et al. (2007a) examined whether canonical clock mutations previously assessed *in vivo* affected the SCN and peripheral oscillators in a similar manner. Using *Per2::luciferase* reporter mice, they found that the effects of the *Period* and *Cryptochrome* loss-of-function mutations were the same in SCN explants as those seen previously at the behavioral level. By contrast, in peripheral tissues, single loss-of-function mutations that are subtle at the behavioral level, such as *Per1* or *Cry1* knockouts, produced very strong loss-of-rhythm phenotypes. Interestingly, the effects of these mutations are cell autonomous in both fibroblasts and in isolated SCN neurons, supporting the idea that the cell-autonomous clock is similar in these two cell types. However, when the SCN population is coupled, the effects of

these mutations are non-cell autonomous. This occurs as a consequence of the intercellular coupling in the SCN network, which is capable of rescuing a cell-autonomous defect in the individual cells (**Figure 2**). This transformation of the oscillatory capability of SCN neurons from damped to self-sustained is an important illustration of the robustness of the SCN network. Indeed, Ko et al. (2010) have found that the SCN network is capable of generating oscillations in the circadian domain in the complete absence of cell-autonomous oscillatory potential. In *Bmal1*-knockout mice, which are arrhythmic at the behavioral level, SCN explants unexpectedly express stochastic oscillations in the circadian range that are highly variable. When the individual cells are no longer rhythmic, the coupling pathways within the SCN network can propagate stochastic rhythms that are a reflection of both feed-forward coupling mechanisms and intracellular noise. Thus, in a manner analogous to central pattern generators in neural circuits, rhythmicity can arise as an emergent property of the network in the absence of the component pacemaker or oscillator cells.

In addition to the generation of sustained oscillations by the SCN network, the SCN is also robust to perturbations from environmental inputs. In wild-type mice, the phase-resetting curve to light pulses is characteristic of Type 1 or weak resetting (low amplitude) (Vitaterna et al. 2006). This is a reflection of the robustness of the SCN pacemaker because inputs such as light can perturb the phase of the oscillation only to a limited extent. In contrast, genetic mutations that lower the amplitude of the molecular oscillation in the SCN lead to increases in the sensitivity to light-induced phase shifts (Type 0 resetting) without changing the strength of the light signals impinging on the SCN (Vitaterna et al. 2006). Similar effects are seen with temperature cycles. Peripheral oscillators are exquisitely sensitive to the phase-shifting effects of temperature and can be entrained strongly by low-amplitude temperature cycles that are equivalent to the circadian fluctuation in core body temperature





( $\sim 2.5^{\circ}\text{C}$  oscillation in mice) (Brown et al. 2002, Buhr et al. 2010). Interestingly, the SCN is resistant to entrainment by low-amplitude temperature cycles, and this resistance depends on the intercellular coupling of SCN neurons (Abraham et al. 2010, Buhr et al. 2010). As was the case for genetic mutations on the generation of rhythms, the effects of temperature perturbations on the SCN are cell autonomous when intercellular coupling is eliminated. Thus, both SCN and peripheral oscillators are sensitive to temperature cycles at the cell-autonomous level; however, coupling within the SCN network confers robustness and makes the SCN network resistant to temperature perturbations. As discussed below, the temperature resistance of the SCN makes functional sense because the SCN drives the body-temperature rhythm, and this temperature signal, which can serve as an entraining signal for peripheral clocks, may otherwise feed back and interfere with the SCN (Buhr et al. 2010).

## PERIPHERAL CLOCKS

Rhythms of clock gene and/or protein expression have been observed in cells and tissues throughout the body in mammals, and these rhythms persist in culture, demonstrating that non-SCN cells also contain endogenous circadian oscillators (Balsalobre et al. 1998, Yamazaki et al. 2000, Yoo et al. 2004). Although the core clock machinery is conserved in these different cellular clocks, there are significant differences in the relative contributions of the individual clock components, as well as

in the manner in which these peripheral clocks are reset and in the output pathways that are under their control. These endogenous cellular clocks drive extensive rhythms of gene transcription, with 3–10% of all mRNAs in a given tissue showing circadian rhythms in steady-state levels (Akhtar et al. 2002, Duffield et al. 2002, Hughes et al. 2009, Miller et al. 2007, Panda et al. 2002, Storch et al. 2002). However, the genes that are under circadian control are largely nonoverlapping in each tissue, reflecting the need for temporal control of the cellular physiology relevant to each unique cell type. As a result, the circadian clock exerts broad-ranging control over many biological processes, including many aspects of metabolism such as xenobiotic detoxification (Gachon et al. 2006), glucose homeostasis (Lamia et al. 2008, Marcheva et al. 2010, So et al. 2009, Turek et al. 2005), and lipogenesis (Gachon et al. 2011, Le Martelot et al. 2009).

## ORGANIZATION OF THE CIRCADIAN SYSTEM

For biological clocks to be effective, they must accurately keep time and adjust to environmental signals. In an organized circadian system, this requires SCN control of peripheral oscillators, and loss of the SCN results in peripheral circadian clocks that become desynchronized (Yoo et al. 2004). However, tissue-specific gene expression patterns are likely to be regulated by both “local” as well as central mechanisms. This concept was elegantly demonstrated through genetic disruption of the

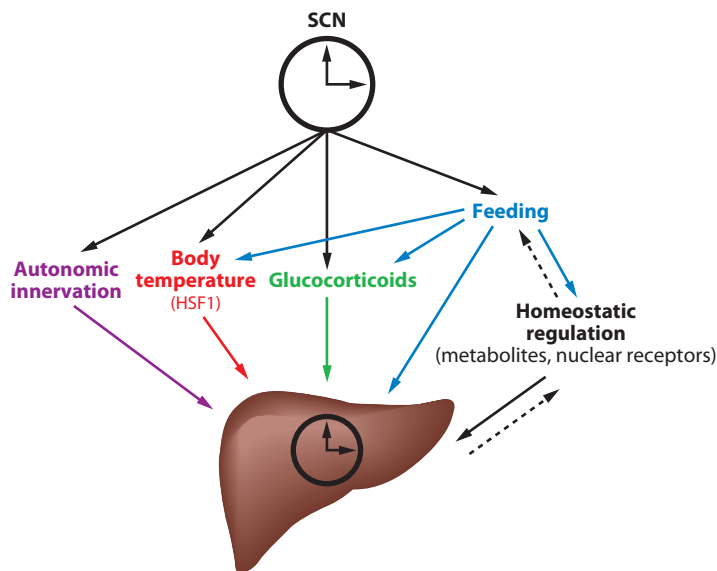
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**Entrainment:**  
synchronization and phase control of a rhythm to a regularly occurring environmental cycle (usually  $\sim 24$  h)

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### Figure 2

Network and autonomous properties of suprachiasmatic nucleus (SCN) neurons. Network properties of the SCN can compensate for genetic defects affecting rhythmicity at the cell-autonomous level. (a) Bioluminescence images of a *Cry1<sup>-/-</sup>* SCN in organotypic slice culture. Note the stable, synchronized oscillations. Numbers indicate hours after start of imaging; 3V indicates the third ventricle. (b) Bioluminescence images of dissociated individual *Cry1<sup>-/-</sup>* SCN neurons showing cell-autonomous, largely arrhythmic patterns of high bioluminescence intensity. (c,d) Heat-map representations of bioluminescence intensity of individual *Cry1<sup>-/-</sup>* neurons in an (a) SCN slice and (b) dispersed culture. Values above and below the mean are shown in red and green, respectively, for 40 SCN neurons in each condition. (e,f) Ten single SCN neuron rhythms from (e) wild-type and (f) *Cry1<sup>-/-</sup>* mice. Imaging began immediately following a media change at day 0. Dissociated *Cry1<sup>-/-</sup>* SCN neurons are largely arrhythmic, whereas dissociated wild-type cells are rhythmic. By contrast, in organotypic slice cultures, both wild-type and *Cry1<sup>-/-</sup>* SCN cells are robustly rhythmic and tightly synchronized. Figure and legend adapted and reprinted from Liu et al. (2007a), with permission from Elsevier.



**Figure 3**

Pathways of peripheral clock entrainment. The master circadian pacemaker within the suprachiasmatic nucleus (SCN) relays temporal information to peripheral oscillators through autonomic innervation, body temperature, humoral signals (such as glucocorticoids), and feeding-related cues. Independent of the SCN, local signaling pathways can also affect peripheral oscillators.

circadian clock mechanism specifically in the hepatocytes of mice, while leaving the circadian clock intact in the SCN and other cell types throughout the body (Kornmann et al. 2007). Microarray analysis of mRNAs in the livers from these mice demonstrated that the disruption of the circadian molecular feedback loop specifically within the liver results in arrhythmicity of most hepatic transcripts. Thus, most circadian oscillations of hepatic function rely on an intact liver clock. However, a subset of transcripts, including the core clock component *Per2*, continued to cycle robustly even in the absence of a functional liver clock. In livers maintained in explant culture, rhythms in *Per2* transcription were observed in livers with intact clocks but were absent in livers with inactivated clocks. Thus, rhythmic gene expression can be driven by both local intracellular clocks and by extracellular systemic cues.

What are these systemic cues? The photically entrained SCN is thought to convey signals to light-insensitive peripheral clocks to

synchronize these systems, and SCN transplant studies (Ralph et al. 1990, Silver et al. 1996) and parabiosis experiments in mice (Guo et al. 2005) have demonstrated that both humoral and non-humoral pathways are important for SCN coordination of circadian output rhythms. In addition, complex feedback loops link the circadian clock with rhythmic metabolic networks, integrating these systems in a light-independent manner. Circadian control of metabolism occurs at the central (SCN) as well as local levels and involves clocks within a number of peripheral tissues including the liver, pancreas, skeletal muscle, intestine, and adipose tissue (for a review, see Bass & Takahashi 2010, Green et al. 2008). This intimate relationship between clocks and metabolism is an example of how the circadian “system” is integrated with, and influenced by, the physiology that is under its control. Therefore, organization of the circadian system requires a combination of (a) autonomic innervation of peripheral tissues, (b) endocrine signaling, (c) temperature, and (d) local signals (Figure 3).

### Neural Control of Peripheral Oscillators: The Autonomic Nervous System

The SCN controls peripheral oscillators through both sympathetic and parasympathetic pathways (Kalsbeek et al. 2010, Ueyama et al. 1999). SCN projections through the paraventricular nucleus–superior cervical ganglia (PVN-SCG) pathway provide the dominant entraining signal for the submandibular salivary glands (Ueyama et al. 1999, Vujovic et al. 2008). Sympathetic innervation from the SCN to the PVN to the liver results in daily rhythms of plasma glucose, presumably by directly influencing the rhythm of hepatic gluconeogenesis (Cailotto et al. 2005, Kalsbeek et al. 2004).

Autonomic pathways from the SCN relay photic information to oscillators in the adrenal gland and liver (Buijs et al. 1999, Cailotto et al. 2009, Ishida et al. 2005). Sympathetic innervation also modulates the sensitivity of the adrenal to adrenocorticotrophic hormone (ACTH) and



directly influences glucocorticoid release (Buijs et al. 1999, Kalsbeek et al. 2010, Kaneko et al. 1981). Oscillators in both the adrenal cortex and medulla respond to neural inputs emanating from the SCN (Buijs et al. 1999, Mahoney et al. 2010). The adrenal clock is of particular interest given the strong case for glucocorticoids as a humoral entraining signal for peripheral clocks.

## Hormonal Control of Peripheral Oscillators

Although a number of hormones may have roles in mammalian circadian organization, glucocorticoids have received the most attention. Rhythmic glucocorticoids result both from the sympathetic inputs discussed above and from an underlying rhythm of corticotropin releasing hormone (CRH) and ACTH function (Kaneko et al. 1980, Kaneko et al. 1981). The adrenal clock also provides temporal control of sensitivity to ACTH-induced glucocorticoid release (Oster et al. 2006).

The demonstration that dexamethasone (a glucocorticoid analog) could shift the phase of peripheral tissues in vivo (Balsalobre et al. 2000) provided the first definitive evidence that glucocorticoids were entraining signals for peripheral oscillators. Dexamethasone was initially shown to shift the phase of clock gene expression in the liver, kidney, and heart as well as cultured fibroblasts. What provides glucocorticoid input into the clock at the local level? Glucocorticoid-response elements exist in the regulatory regions of the core clock genes, *Bmal1*, *Cry1*, *Per1* (Reddy et al. 2007, Yamamoto et al. 2005), and *Per2* (So et al. 2009). These glucocorticoid-response elements may lead to the transcriptional activation of a number of clock genes and clock-controlled genes by glucocorticoids.

Glucocorticoids can synchronize circadian expression of much of the oscillatory component of the liver transcriptome in SCN-lesioned mice (Reddy et al. 2007). This is accomplished, in part, through activation of the nuclear receptor (and hepatic transcription

factor) HNF4 $\alpha$ . HNF4 $\alpha$  is responsive to glucocorticoids (Reddy et al. 2007), contains E-boxes, which may allow for transcriptional control by CLOCK:BMAL1 (Reddy et al. 2007), and can interact with PER2 (Schmutz et al. 2010). Other metabolically relevant nuclear receptors, including peroxisome proliferator-activated receptor (PPAR) $\alpha$ , also respond to glucocorticoids (Lemberger et al. 1994). Nuclear receptor activation by clock components and glucocorticoids provides another point of circadian input to metabolic pathways as described below.

## Temperature

In most organisms, temperature is a powerful entraining agent for circadian rhythms. However, in mammals, external temperature cycles are very weak entraining agents (Refinetti 2010); this has been attributed to the fact that homeotherms regulate their body temperature and can defend their body temperature against environmental fluctuations. It has long been known that body temperature is circadian and the rhythm is driven by the SCN. Peripheral oscillators, including fibroblasts, liver, kidney, and lung, are exquisitely sensitive to temperature changes (Abraham et al. 2010, Brown et al. 2002, Buhr et al. 2010, Kornmann et al. 2007). These oscillators can be strongly reset by low-amplitude temperature pulses that mimic the range of circadian variation, and temperature profiles that match circadian body temperature rhythms strongly entrain peripheral clocks (Brown et al. 2002, Buhr et al. 2010). However, as described above, the SCN is resistant to temperature cycles in the circadian range. Because of this system design, the SCN is ideally situated to utilize circadian temperature cycles as a universal entraining signal for peripheral oscillators. The influence of temperature on peripheral oscillators likely occurs through the transcription factor heat shock factor 1 (HSF1). HSF1 transcriptional activity oscillates with a circadian rhythm in the liver and can be driven by temperature cycles (Reinke et al. 2008). HSF1 inhibitors block temperature-induced resetting in extra-SCN

**PPAR:** peroxisome proliferator-activated receptor

**HSF1:** heat shock factor 1

**NAD:** nicotinamide  
adenine dinucleotide

oscillators (Buhr et al. 2010). Because HSF1 is influenced by a wide range of signaling pathways in the cell (Akerfelt et al. 2010), temperature and HSF1 may form a final common pathway for the integration of resetting signals in peripheral clocks.

### **Behavioral and Homeostatic Regulation: Local Cues Feed Back into the Clock**

In addition to controlling hormone secretion and body temperature directly, the SCN coordinates rhythms in behavioral processes, such as locomotor activity and feeding, which can influence endocrine function and body temperature. These behaviors, feeding in particular, can regulate peripheral clocks at the local level, modulating local signaling pathways and metabolic processes. Homeostatic signaling pathways also affect peripheral clocks and their function, allowing for extra SCN control of circadian processes. Studies in which mealtime has been experimentally manipulated to occur antiphase to the normal SCN-driven feeding rhythm have attempted to elucidate local mechanisms for controlling clocks in peripheral tissues.

The liver clock, unlike the SCN, is particularly sensitive to resetting by feeding. Hepatic rhythms of clock gene and protein expression rapidly shift their phase to follow the timing of a scheduled meal (Damiola et al. 2000, Stokkan et al. 2001). Similarly, livers of *Cry1/Cry2*-null mice display rhythms in many transcripts (including a number of transcripts involved in metabolic processes) when fed in regular 24-h intervals (Vollmers et al. 2009). Feeding appears to result in cues that bypass the core circadian feedback loop to drive these rhythms. These cues may include feeding-induced changes in temperature and HSF1 activity (Kornmann et al. 2007) or activation of other metabolically sensitive pathways.

A number of local mediators of both core clock components and clock-controlled rhythmic transcripts have been identified, and can respond to SCN-driven inputs as well as local signals related to homeostasis and metabolic

state. These mediators include members of the nuclear receptor family of transcription factors, many of which exhibit circadian rhythms of transcription within the liver and other metabolically relevant tissues (Yang et al. 2006). These rhythmic nuclear receptors regulate transcription of downstream metabolic pathways. Among the rhythmic nuclear receptors are PPARs and members of the REV-ERB and ROR families. As described above, ROR $\alpha$  and REV-ERB $\alpha$  participate directly in the clock mechanism by regulating *Bmal1* transcription (Preitner et al. 2002, Sato et al. 2004), but they are also important for many aspects of metabolic regulation. Similar to REV-ERBs and RORs, many of the other rhythmic nuclear receptors are regulators of clock function, providing a mechanism by which signals of metabolic status can influence rhythmicity. Glucocorticoid receptors, as discussed above, induce transcription of *Per* and potentially a number of other clock and clock-controlled genes (Reddy et al. 2007, So et al. 2009, Yamamoto et al. 2005). PPAR $\alpha$ , which responds to lipid status and glucocorticoids, may also regulate *Bmal1* transcription (Canaple et al. 2006).

PPAR $\gamma$  coactivator-1 $\alpha$  (PGC-1 $\alpha$ , a transcriptional coactivator) provides a link between the clock and changes in metabolic status. PGC-1 $\alpha$  is critical for adaptive responses to nutritional and metabolic state, particularly following fasting (reviewed in Lin et al. 2005). PGC-1 $\alpha$  is rhythmic and activates expression of *Bmal1* and *Rev-erb $\alpha$*  through coactivation of RORs (Liu et al. 2007b). PGC-1 $\alpha$ -null mice display disruptions in a number of circadian outputs including locomotor activity, oxygen consumption rate, and expression of both clock and metabolic genes (Liu et al. 2007b). PGC-1 $\alpha$  also interacts with SIRTUIN 1 (SIRT1), a nicotinamide adenine dinucleotide (NAD)-dependent histone deacetylase (Rodgers et al. 2005).

Another mechanism by which metabolic signals can feed into the clock is through the adenosine monophosphate-activated protein kinase (AMPK) (Bass & Takahashi 2010). This kinase is a central mediator of metabolic

signals. AMPK activity is robustly rhythmic in mouse liver and is regulated by nutrient status, as reflected in the ratio of AMP to ATP. Active AMPK directly regulates the central clock mechanism by phosphorylating and destabilizing the clock component CRY1 (Lamia et al. 2009).

Cellular redox state can also serve as a mechanism by which the metabolic status of the cell can impact the circadian system. NAD levels exhibit circadian oscillations in the liver, likely owing to transcriptional regulation of nicotinamide phosphoribosyltransferase (*Nampt*, encoding the rate-limiting enzyme in the NAD<sup>+</sup> salvage pathway) by CLOCK:BMAL1 (Nakahata et al. 2009, Ramsey et al. 2009). NAD levels also vary with cellular redox state as a consequence of metabolic changes, which, in turn, can directly impact clock function. The ratio of NAD<sup>+</sup> to NADH influences binding of NPAS2:BMAL1 and CLOCK:BMAL1 to DNA in vitro, suggesting one way in which NAD could interact with clock components (Rutter et al. 2001).

NAD<sup>+</sup>-dependent SIRT1 also displays daily oscillations and feeds back onto the circadian clock. SIRT1 forms a complex with CLOCK:BMAL1, leading to the deacetylation of PER2 (Asher et al. 2008) and BMAL1 (Nakahata et al. 2008). SIRT1 also suppresses CLOCK:BMAL1-mediated transcription, resulting in decreased expression of *Per2* (Nakahata et al. 2008, Ramsey et al. 2009) and the clock-controlled gene *Dbp* (Nakahata et al. 2008).

Another molecule with NAD<sup>+</sup>-sensitive activity, poly(ADP-ribose) polymerase 1 (PARP-1), was recently shown to interact with the circadian clock (Asher et al. 2010). PARP-1 activity is rhythmic in the liver, and this rhythm persists even in the absence of a functional hepatic circadian clock. The rhythm of PARP-1 activity can be entrained by scheduled meals, however, suggesting that the circadian activity of PARP-1 is driven by feeding-related cues. PARP-1 interacts with CLOCK:BMAL1 in a rhythmic fashion and inhibits DNA binding by the CLOCK:BMAL1 complex. PARP-1 also

polyADP-ribosylates CLOCK and appears to temporally regulate the interaction of CLOCK:BMAL1 with PER2 and CRYs. The circadian regulation of PARP-1 by feeding, and subsequent consequences for the circadian clock, are likely not entirely mediated through NAD<sup>+</sup>. Regardless of the mechanism, PARP-1 provides another way for metabolic signals to influence timekeeping by the core molecular clock.

## OTHER OSCILLATORS: FOOD AND DRUGS

The circadian system consists of a web of interconnected oscillators and feedback loops. The core molecular clock within cells keeps time and responds to cues from the SCN (through neural, hormonal, and activity-driven pathways) as well as signals from the local cellular environment. These cell- and tissue-level clocks result in rhythms of physiologically relevant outputs, including glucose production, fat storage, and hormone production. These outputs, in turn, become circadian time-keeping cues relayed to other clocks throughout the body, likely ultimately feeding back to the central nervous system and the SCN. Under normal circumstances, the SCN maintains temporal organization of body temperature, activity, feeding, and neural output rhythms. This keeps local and systemic circadian signals aligned. In the absence of the SCN, however, the system becomes disorganized. Activity is nonrhythmic and peripheral tissues and cells drift out of phase with one another. There are two striking exceptions to this phenomenon. Scheduled, restricted feeding and chronic administration of methamphetamine, a psychostimulant drug of abuse, are both capable of organizing the circadian outputs in the absence of the SCN.

### The Food-Entrainable Oscillator

It is not surprising that food and food-related cues are salient for many biological processes, including circadian rhythms. The ability of animals to anticipate food availability is well

**FEO:** food-entrainable oscillator

**DMH:** dorsomedial hypothalamus

**Free-running period:** the period of an oscillation in the absence of entraining signals; reflects the intrinsic period of the oscillator uninfluenced by environmental timing cues

**MASCO:** methamphetamine-sensitive circadian oscillator

established and persists even when food is provided at a time that is out of phase with the animal's normal feeding time (Richter 1922, Stephan et al. 1979). When food is temporally restricted to the daytime (the normal rest period), nocturnal rodents will anticipate the arrival of the meal with an increase in activity; if the timing of that meal is shifted, rats will display transients, gradually shifting their food-anticipatory activity bout each day until it again precedes the start of food availability.

In animals with lesions of the SCN, temporal food restriction will induce circadian rhythmicity of locomotor behavior (Stephan et al. 1979) and an accompanying temperature rhythm (Krieger et al. 1977). Food-anticipatory activity persists on days of total food deprivation, demonstrating that these cycles are not merely an hourglass phenomenon but are driven by an underlying oscillator (Stephan 2002). This food-entrainable oscillator (FEO) can take on pacemaking functions—organizing rhythms of activity, body temperature, and peripheral tissues in SCN-lesioned animals. Peripheral tissues from both SCN-intact and SCN-ablated mice are sensitive to temporally restricted feeding. In SCN-intact animals, phase desynchrony among peripheral oscillators can occur: Some tissues remain in phase with the (food-unaffected) SCN, and some follow the phase of food availability (Damiola et al. 2000, Pezuk et al. 2010). Cues related to the meal must be the dominant entraining signals in this latter group of tissues. In SCN-lesioned mice, food entrainment organizes rhythms throughout the periphery, and stable phase relationships are observed among tissues (Hara et al. 2001, Pezuk et al. 2010).

Interestingly, the FEO does not appear to require a functional molecular clock, as *Bmal1*<sup>-/-</sup> and *Per1/Per2*<sup>-/-</sup> mice can entrain to restricted feeding (Pendergast et al. 2009, Storch & Weitz 2009). The mechanism by which food drives oscillatory behavior throughout the organism is unknown. It is possible that the FEO exploits some of the same pathways used by the SCN, such as hormone- and temperature-dependent cues, to organize

peripheral tissues. The locus (or loci) of the FEO is also unknown. A number of structures, including the olfactory bulbs (Davidson et al. 2001), the ventromedial hypothalamus (Mistlberger & Rechtschaffen 1984), the paraventricular thalamic nucleus (Landry et al. 2007), and a large portion of the digestive system (Davidson et al. 2003), have been ruled out.

The dorsomedial hypothalamus (DMH) has received considerable attention for its role in food entrainment. Data supporting a role for the DMH in the generation of food-anticipatory circadian activity are controversial (Gooley et al. 2006, Landry et al. 2006, Moriya et al. 2009), and the DMH may not be essential for the expression of the FEO (Landry et al. 2006, Moriya et al. 2009). The DMH does, however, interact with the SCN under conditions of food restriction and may influence the strength of the FEO output, particularly in SCN-intact animals (Acosta-Galvan et al. 2011).

## The Methamphetamine-Sensitive Circadian Oscillator

Chronic or scheduled methamphetamine treatment affects circadian outputs in a manner similar to food restriction (Honma & Honma 2009). Methamphetamine, provided in the drinking water of rats and mice, is capable of driving circadian rhythms of locomotor behavior in the absence of the SCN (Honma et al. 1987, Tataroglu et al. 2006). In SCN-intact animals, this appears as a lengthening of the free-running period of locomotor activity, and in some cases, two activity components (relatively coordinated with each other) are observed. Much like the FEO, these rhythms persist when the stimulus (in this case, methamphetamine) is withdrawn (Tataroglu et al. 2006) as well as in the absence of a functional molecular clock (Honma et al. 2008, Mohawk et al. 2009). The methamphetamine-sensitive circadian oscillator (MASCO) is capable of functioning as a pacemaker driving rhythms in locomotor activity, body temperature, endocrine function, and the oscillators of peripheral

tissues (Honma et al. 1988, Pezuk et al. 2010). In the presence of the SCN, methamphetamine results in desynchrony among internal oscillators, as some follow the SCN and some follow the presumed phase of the MASCO (Pezuk et al. 2010). When the SCN is ablated, however, the MASCO organizes oscillators in tissues throughout the organism, resulting in a coordinated system (Pezuk et al. 2010).

The site of the MASCO is also unknown. It is possible that the FEO and MASCO share an anatomical and mechanistic basis, or, indeed, that they represent a single oscillator. Research focused on understanding how the MASCO and FEO relay circadian information to peripheral tissues will likely uncover novel (or underappreciated) mechanisms that control circadian rhythms. The role of these oscillators in the absence of food restriction and methamphetamine must also be determined. It is unlikely that these oscillators are dormant under normal conditions; instead, the FEO, MASCO, and SCN probably cooperate in a hierarchically organized, perhaps necessarily redundant, timing network.

## SUMMARY

It is now clear that there is feedback at nearly every level of the circadian system. “Outputs” such as body temperature and feeding become inputs to other oscillators and are capable of influencing the core molecular clockwork, generating complex interconnectivity between the circadian system and the biological outputs it controls. Reciprocity between the circadian and metabolic systems makes it likely that perturbations in one system affect the other. This

idea is supported both genetically—circadian mutants have metabolic phenotypes—and environmentally—nutrient intake can modulate circadian rhythms (Bass & Takahashi 2010). In recent years, considerable progress has been made in unraveling the connections between the circadian clock and metabolism. The role of circadian clocks in governing many other physiological systems has been established, but is far less well characterized.

We still know very little about how oscillators and timing cues are integrated at the local and organismal levels to coordinate the circadian architecture of the animal. Peripheral clocks must balance (sometimes conflicting) inputs arising from the SCN with those signaling local cellular and metabolic state. Moreover, recent work has revealed that the cell-autonomous oscillator, which normally lies at the foundation of the circadian clockwork, is not absolutely crucial for the expression of rhythms by other components of the system. Within the SCN, coupling among individual neurons gives rise to a heterogeneous, yet elegantly organized, robust oscillatory network, which can overcome impaired rhythmicity at the cellular level (Ko et al. 2010, Liu et al. 2007a). Food- and drug-sensitive oscillators (FEO, MASCO) can influence circadian rhythms and drive rhythmic outputs in the absence of the core molecular clock mechanism (Honma et al. 2008, Mohawk et al. 2009, Pendergast et al. 2009, Storch & Weitz 2009). The ability of rhythmic circadian outputs to persist in the absence of the SCN necessitates that any model of the circadian network include alternative mechanisms for controlling circadian rhythms at the cell, tissue, and organism levels.

## DISCLOSURE STATEMENT

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## Errata

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