**REVIEW ARTICLE**

# Energy-responsive timekeeping

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## Abstract

An essential component of energy homeostasis lies in an organism's ability to coordinate daily patterns in activity, feeding, energy utilization and energy storage across the daily 24-h cycle. Most tissues of the body contain the molecular clock machinery required for circadian oscillation and rhythmic gene expression. Under normal circumstances, behavioural and physiological rhythms are orchestrated and synchronized by the suprachiasmatic nucleus (SCN) of the hypothalamus, considered to be the master circadian clock. However, metabolic processes are easily decoupled from the primarily light-driven SCN when food intake is desynchronized from normal diurnal patterns of activity. This dissociation from SCN based timing demonstrates that the circadian system is responsive to changes in energy supply and metabolic status. There has long been evidence for the existence of an anatomically distinct and autonomous food-entrainable oscillator (FEO) that can govern behavioural rhythms, when feeding becomes the dominant entraining stimulus. But now rapidly growing evidence suggests that core circadian clock genes are involved in reciprocal transcriptional feedback with genetic regulators of metabolism, and are directly responsive to cellular energy supply. This close interaction is likely to be critical for normal circadian regulation of metabolism, and may also underlie the disruption of proper metabolic rhythms observed in metabolic disorders, such as obesity and type-II diabetes.

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## Introduction

A primary role of the circadian clock is to entrain the organism to environmental cues, so that an animal is able to anticipate fluctuations in the environment that dictate such things as food availability, predator risk, and the likelihood of reproductive success. The circadian system is also critical to the synchronization and relative phasing of diverse internal physiological processes and molecular pathways (Reppert and Weaver 2002). Such internal coordination is essential to optimize responses to environmental fluctuation and strengthen homeostatic control mechanisms. In mammals, the circadian system is headed by a master biological clock located within the suprachiasmatic nucleus (SCN). Daily and seasonal light cycles are probably the most consistent and conspicuous of environmental time cues. Photic information is relayed to the SCN via the retino-hypothalamic tract (RHT), and serves as the primary entraining stimulus (*Zeitgeber*) for the SCN. Nevertheless, as a true clock, the SCN can initiate and sustain near 24-h rhythms, even in the absence of external entraining agents such as light.

The most dramatic demonstration of the dominant role played by the SCN in generating rhythmic behaviours has involved transplantation of donor SCN tissue into animals in which the SCN had been previously ablated (Sawaki *et al*. 1984; Ralph *et al*. 1990; Silver *et al*. 1996; Meyer-Bernstein *et al*. 1999; Guo *et al*. 2006). Impressively, transplanted tissue is able to restore locomotor rhythmicity, and confer the circadian profile (free-running period) of the donor animal to the recipient. Interestingly, unlike locomotor activity, rhythms of melatonin and glucocorticoid secretion are not recovered by such transplantation (Ralph *et al*. 1990; Silver *et al*. 1996; Meyer-Bernstein *et al*. 1999; Sujino *et al*. 2003; Guo *et al*. 2006). SCN transplantation also reestablishes rhythmic expression of clock genes in some peripheral tissues (liver, kidney), but not others (heart, spleen) (Guo *et al*. 2006). Together, these findings demonstrate that both humoral factors and direct neuronal contact are required for the full dissemination of SCN-based timing information. It also implies that the influence of the SCN is not uniform across the body.

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Despite its primacy, the expression of the molecular clock gene machinery is not limited to the SCN, and many other brain regions and peripheral tissues are capable of selfsustained circadian oscillation (Reick *et al*. 2001; Abe *et al*. 2002; Cermakian and Sassone-Corsi 2002; Panda *et al*. 2002; Storch *et al*. 2002; Schibler 2003; Granados-Fuentes *et al*. 2004; Yoo *et al*. 2004; Lamont *et al*. 2005). Under normal circumstances it is likely that these extra-SCN clocks are subordinate to and synchronized by the SCN. Gene microarray studies involving a variety of tissues show that 5-10% of transcribed genes exhibit rhythmic oscillations in mRNA expression (Panda *et al*. 2002; Oishi *et al*. 2003, 2005a; McCarthy *et al*. 2007; Miller *et al*. 2007). Interestingly, there is relatively little overlap observed in the genes that cycle between different tissues, demonstrating that the circadian system can influence diverse physiological processes in a tissue-specific manner. This also implies that the circadian machinery interacts directly with tissue-specific transcriptional regulators. Local timing systems are clearly important for individual tissue/organ function. For example, deletion of the clock gene, *BMAL1* specifically within the liver causes fasting hypoglycaemia, exaggerated glucose clearance, and loss of rhythmic expression of hepatic glucose regulatory genes (Lamia *et al*. 2008). Therefore, we must concede that, ultimately, circadian rhythms in behaviour and physiology are likely to be directed by a network of oscillators, distributed across the body. This may be especially true when light is no longer the dominant *Zeitgeber*, such as during restricted food availability (figure 1 and below).

The role of the circadian system in regulating metabolism has received increasing attention over recent years (Wijnen and Young 2006; Kohsaka and Bass 2007; Ramsey *et al*. 2007; Laposky *et al*. 2008), driven in part by indications that disruption of daily metabolic rhythms is an exacerbating factor in metabolic syndrome (obesity, diabetes and cardiovascular disease) (Karlsson *et al*. 2001; Gangwisch *et al*. 2005; Chaput *et al*. 2006; Gallou-Kabani *et al*. 2007). Many metabolic processes, such as feeding behaviour, and

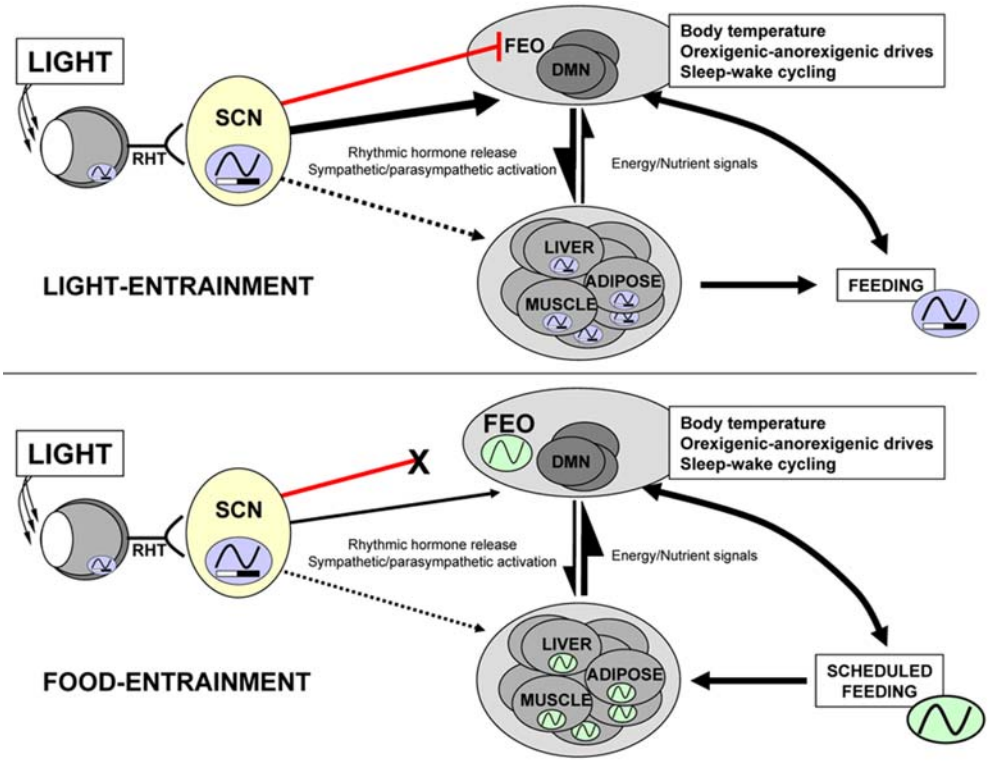


**Figure 1.** Entrainment of circadian clocks by light and feeding. Light entrainment: photic timing information is relayed to the SCN via the retino-hypothalamic tract (RHT), where it serves as the principal *Zeitgeber* for the SCN clock. Under normal circumstances, the SCN synchronizes other oscillators throughout the body, via direct neuronal contacts and the rhythmic release of humeral factors, to dictate daily behavioural and physiological rhythms. Food entrainment: when placed on a restricted feeding schedule (RFS), peripheral clocks rapidly entrain to meal times, and decouple from SCN-driven rhythms. It is likely that peripheral rhythms and diffusible energy signals potentiate food-driven oscillations within a food-entrainable oscillator (FEO), possibly by dampening the repression of such rhythms by the SCN. It remains unclear whether the FEO exists as a single anatomically discrete site, driving all food-anticipatory rhythms, or may be a network of oscillators distributed across many brain regions, with specific sites driving individual components of food-anticipatory behaviour.

glucose and lipid metabolism, exhibit coordinated circadian oscillation (Rutter *et al*. 2002; Kaasik and Lee 2004; Tu and McKnight 2006), and many genes involved in metabolic control are rhythmically expressed (Akhtar *et al*. 2002; Duffield *et al*. 2002; Panda *et al*. 2002; Storch *et al*. 2002; Walker and Hogenesch 2005; Kornmann *et al*. 2007). The importance of a functional circadian system in the regulation of metabolism is evident from studies of animals with disrupted clock gene expression or function (Turek *et al*. 2005; Oishi *et al*. 2006; Bechtold *et al*. 2008; Kudo *et al*. 2008). For example, *clock* mutant mice exhibit reduced metabolism and obesity, reminiscent of metabolic syndrome (Turek *et al*. 2005). Moreover, restricted feeding cycles are perhaps the dominant *Zeitgeber* for circadian clocks outside of the SCN (Schibler 2003), suggesting not only that the circadian system is important in regulating metabolism, but also that the timing systems themselves are responsive to energy status.

The present review highlights the connections that exist between circadian timing systems and regulators of metabolism, and how the clock is responsive to the energy status of an organism at both an anatomical and molecular level. This includes the ability of timed feeding to entrain the circadian system, the molecular connections through which clock components interact with genetic regulators of metabolic processes at a molecular level, and the surprising degree to which the clock itself may be influenced by local (cellular) energy supplies.

## Food-entrainable rhythms

### *An anatomically distinct food-entrainable oscillator*

In normal animals, light-driven diurnal behaviour can be easily overcome by alterations in energy supply, such as during restricted feeding schedules (RFS) (Mistlberger 1994; Stephan 2002). During RFS, food is only available to animals during set periods that typically occur outside of their normal feeding period (such as during the day for nocturnal rodents). Under RFS numerous physiological and metabolic functions become entrained to the availability of food, e.g., locomotor activity, body temperature, insulin and corticosterone release. Strong support for the existence of a food-entrainable timing system is the circadian pattern of food anticipatory activity (FAA) rhythms that emerge in intact and SCN-ablated animals maintained on RFS (Krieger 1972; Stephan and Zucker 1972; Boulos and Terman 1980; Mistlberger 1994; Stephan 2002). Further, feeding-related anticipation is not dictated simply by a threshold of energy depletion, as such behaviours are not observed in fasted animals with no prior RFS conditioning, nor during the first few days of RFS. This implies the existence of other food-entrainable oscillators (FEO), located outside of the SCN, capable of coordinating behaviour and physiology with daily feeding schedules (Mistlberger 1994; Stephan 2002). Once established by RFS, the FEO appear to be robust, as anticipatory activity can continue for several cycles after RFS is stopped and animals are subsequently fasted or returned to *ad libitum* feeding (Davidson *et al*. 2001b). FAA also displays limits of entrainment in the circadian range (Mistlberger and Marchant 1995) and phase-shifts in feeding time during RFS leads to transients in the behavioural rhythms as the animal re-entrains (Davidson and Stephan 1998), both characteristics of a true circadian oscillator.

Attempting to identify which parts of the clock underlie circadian rhythms in food anticipatory behaviour, a number of groups have tested clock gene mutant and knockout animals (*CLOCK*, and its homologue *NPAS2, CRY1/CRY2, BMAL1, PER1*) for their ability to entrain to scheduled feeding regimes and display FAA (Dudley *et al*. 2003; Pitts *et al*. 2003; Iijima *et al*. 2005; Feillet *et al*. 2006; Landry and Mistlberger 2007). Somewhat surprisingly, most retain relatively normal anticipation of feeding time. One exception has been reported by Feillet *et al*. (2006), in which FAA rhythms in wheel running and body temperature were severely attenuated in $PER2^{brdm1}$ mutant mice. Interestingly, food-entrained clock gene rhythms were still observed in the liver and kidney of $PER2^{brdm1}$ mice (Feillet *et al*. 2006). This suggests that while PER2 may be critical for the establishment of the FEO (and the expression of FAA), peripheral oscillators remain responsive to energy status. This finding also seems to discount the liver and kidney as potential sites of the FEO. High rates of mortality in response to RFS have been reported for some clock mutant/knockout strains (Dudley *et al*. 2003; Fuller *et al*. 2008). Even when surviving animals go on to display FAA, it should acknowledged that a reduced ability of these animals to rapidly entrain to feeding cycles may underlie this mortality, and may therefore be indicative of a compromised food-entrainable circadian system.

Identifying the anatomical location of the FEO has also proved challenging. Attractive candidate sites of an FEO are of course the neural centres of the hypothalamus that are central to the regulation of energy homeostasis and arousal, including the arcuate nucleus (ARC), paraventricular nucleus (PVN), dorsomedial nucleus (DMN) and lateral hypothalamic area (LH) (Cone *et al*. 2001; Rodgers *et al*. 2002; Saper *et al*. 2005a,b). All of these neuronal populations receive significant input from the SCN (Saper *et al*. 2005b), and it is likely that much of the anatomical interaction between circadian and metabolic regulatory pathways involves such intrahypothalamic connections. A number of studies attempting to employ discrete lesioning of candidate brain regions have failed to fully disrupt the appearance of FAA (Mistlberger and Rechtschaffen 1984; Mistlberger and Rusak 1988; Mistlberger and Mumby 1992; Davidson *et al*. 2001a,b; Stephan 2002; Landry *et al*. 2006, 2007). One exception involved lesions of the parabrachial nucleus in rats (Davidson *et al*. 2000); however, as the authors of this study point out, the attenuation of FAA in these animals may be best interpreted as a loss of gut–brain signalling, rather than the destruction of a true FEO.

A site that is often implicated in the regulation of metabolic rhythms, food-entrainment, and FAA is the DMN. DMN activity in nocturnal rodents, as measured by *c-fos* expression, is highest during the dark (active) phase, but shifts to anticipate meal time when the animals are placed under RFS (Angeles-Castellanos *et al*. 2004). Restricted feeding also induces robust circadian expression in *PER2* in a subset of DMN neurons, which persist during two days of fasting subsequent to RFS entrainment (Mieda *et al*. 2006). Unfortunately, the ability of FAA to persist in animals with whole and partial lesions of the DMN is somewhat unclear due to conflicting reports (Gooley *et al*. 2006; Landry *et al*. 2006, 2007; Fuller *et al*. 2008). Nonetheless, the ability of at least one group to observe FAA activity in DMN-lesioned animals (Landry *et al*. 2006, 2007) implies that although the DMN may house a genuine FEO, it cannot be the only area capable of directing food-entrainable circadian behaviour.

It is also possible that the FEO may be located within a metabolically important peripheral tissue. Peripheral energy signals and rhythmic outputs are probably an important factor in entraining an animal to food intake, as well as in the initiation and fortification of FEO rhythms. However, dissociations of behavioural FAA rhythms and those of peripheral clock gene expression are not uncommon (for e.g., Davidson *et al*. 2003; Feillet *et al*. 2006), suggesting that the FEO resides within the nervous system.

#### *Routes of food entrainment*

Rhythmic feeding appears to the primary entraining stimulus controlling the phase of peripheral circadian oscillators, presumably to ensure optimal synchrony between metabolic processes and the daily rhythm of food intake (figure 1) (Damiola *et al*. 2000; Stokkan *et al*. 2001; Wakamatsu *et al*. 2001; Schibler *et al*. 2003). For example, clock gene rhythms in the liver can entrain to RFS within two days, prior to the expression of FAA, and even though SCN activity remains locked to light–dark cues throughout the duration of RFS (Stokkan *et al*. 2001). The mechanism(s) by which feeding cycles so rapidly entrain peripheral oscillators, and allow them to dissociate from the SCN remain unclear.

Direct neural communication, originating from the SCN, via the autonomic nervous system is important in the entrainment of peripheral oscillators to light cycles (Bartness *et al*. 2001; Ishida *et al*. 2005; Bando *et al*. 2007; Vujovic *et al*. 2008). In addition, sympathetic and parasympathetic nerve fibres provide a direct link between the hypothalamus and metabolically important peripheral tissues (Berthoud 2002; Ruiter *et al*. 2006). For example, it has been demonstrated that the liver, the pancreas, and the visceral adipose tissue all share a common and specific neuronal connection with the PVN, DMN, and SCN (Bartness *et al*. 2001). It therefore seems likely that autonomic pathways are involved in the entrainment and synchronization of peripheral tissues by energy-related stimuli. However, vagal nerve signalling is not required for the expression of FAA in food-restricted rats (Comperatore and Stephan 1990), indicating that the autonomic nervous system cannot be the sole route for the dissemination of food-anticipatory timing information. Nonetheless, an imbalance in autonomic input to peripheral organs has been proposed to underlie the dampening of circadian rhythms observed in obesity and type-II diabetes (Kalsbeek *et al*. 2007; Cailotto *et al*. 2008).

In addition to direct neural contacts, energy-related release of hormones or other factors may serve to synchronize numerous peripheral (and brain) oscillators to meal times. For example, glucocorticoid receptors (GR) and retinoic acid receptors are capable of resetting peripheral clocks (Balsalobre *et al*. 2000; McNamara *et al*. 2001), and circulating glucocorticoids rapidly entrain to meal times during restricted feeding (Mistlberger 1994; Stephan 2002). However, disruption of GR signalling enhances, rather than disrupts, the synchronization of peripheral clock gene rhythms with altered feeding cycles (Le Minh *et al*. 2001), indicating that glucocorticoids may normally act to keep peripheral oscillators synchronized with the SCN. There are of course a number of additional factors, including nutrient signals themselves (glucose, fatty acids etc.), that may be capable of modulating the circadian system and thus contributing to the overall expression of FAA. As discussed in the following section, it is becoming clear that a number core clock genes are directly responsive to cellular energy status, and subject to reciprocal regulation by metabolic and energy-responsive genes.

## Molecular interface between clock and metabolic genes

#### *The molecular clock*

The molecular machinery that provides circadian timekeeping consists of a complex circuitry of transcriptional/translational regulatory feedback loops (figure 2). The current model involves a primary loop with CLOCK and BMAL1 as transcriptional activators, and two period proteins (PER1 and PER2) and two cryptochrome proteins (CRY1 and CRY2) as transcriptional repressors (Shearman *et al*. 2000; Ripperger and Schibler 2001; Reppert and Weaver 2002; Lowrey and Takahashi 2004). Within this loop, CLOCK and BMAL1 heterodimers bind to E-box enhancer elements within the *PER* and *CRY* genes to activate their transcription. As levels of cytosolic PER and CRY proteins rise, they associate, translocate to the nucleus, and repress their own gene transcription through direct interaction with CLOCK/BMAL1. In the mammalian clock, this primary feedback loop is also acted upon by additional interlocking loops, most notably the loop involving the orphan nuclear receptors, REV-ERB and ROR. REV-ERB represses, while ROR activates *BMAL1* transcription through shared ROR-binding elements (ROREs) within the *BMAL1* promoter

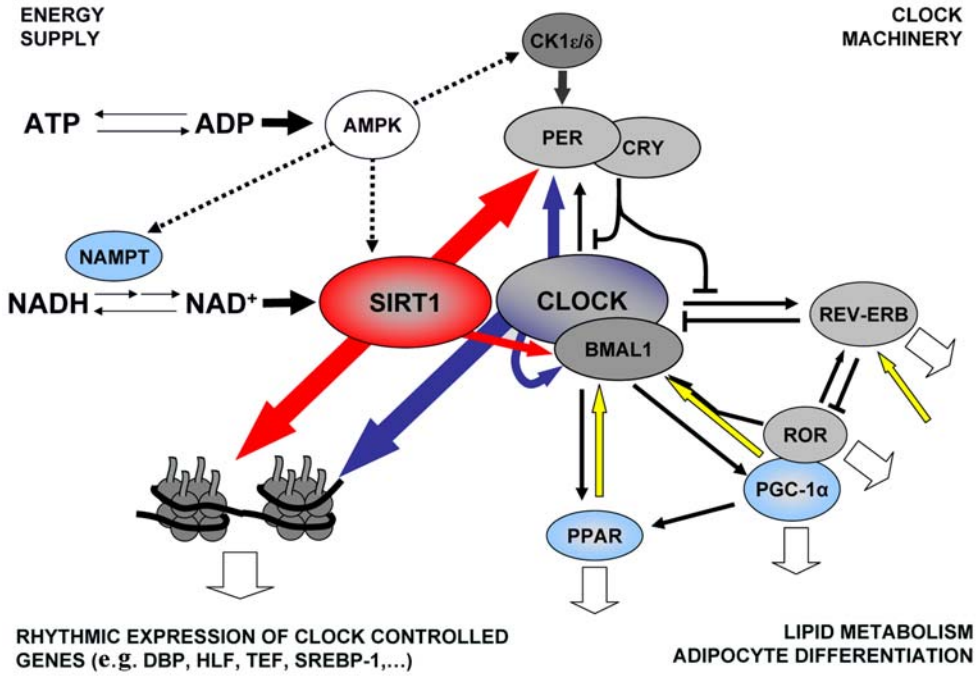


**Figure 2.** Molecular interactions of the clock and metabolic regulators. The molecular clock: the transcriptional regulatory feedback loops of the clock incorporate CLOCK, BMAL1 and ROR as transcriptional activators, PER, CRY, and REV-ERB as transcriptional repressors, and casein kinase 1 as a posttranslational regulator (grey circles). This circadian clockwork dictates the expression of numerous metabolic regulatory genes (output pathways represented by fat white arrows) to coordinate metabolism. SIRT1: recent evidence suggests that CLOCK-mediated acetylation (blue arrows) and SIRT1 deacetylation (red arrows) cycles are a central mechanism by which the clock orchestrates the rhythmic expression of clock-responsive genes. In addition to histone acetylation dynamics, SIRT1 and CLOCK also modulate core clock feedback loops through the acetylation of PER and BMAL1. An energy-responsive clock: clock genes including BMAL1 and REV-ERBα receive direct regulatory feedback from transcription factors involved in metabolism including PPARα and PGC-1α (yellow arrows). In addition, cellular energy supply (as reflected in ATP/ADP and $NAD^+$/NADH ratio) can directly influence clock activity. For example, SIRT1 requires $NAD^+$ as a co-substrate during deacetylation, thereby tying its activity to cellular energy metabolism. Further, AMPK activity is able to modify the clock directly through actions on CK1ε, SIRT1, and NAMPT (an enzyme involved in the $NAD^+$ cycle). Energy-related regulation of clock genes may therefore be a major factor in the entrainment of peripheral clocks to feeding cycles.

(Preitner *et al*. 2002; Emery and Reppert 2004). Both REV-ERB and ROR are constitutively transcribed, and are also involved in reciprocal regulation (Adelmant *et al*. 1996; Raspe *et al*. 2002b).

Together these feedback cycles provide near 24 h timing to the cell/tissue/organism, and drive the rhythmic expression of a number of clock-controlled genes, many of which are involved in regulating metabolic processes. For example, the albumin D-site binding protein (DBP), the expression of which is directly regulated by CLOCK/BMAL1, is involved in the rhythmic transcription of several metabolic enzymes (Ripperger and Schibler 2001; Reppert and Weaver 2002; Lowrey and Takahashi 2004). Moreover, the direct involvement of clock genes in aspects of metabolism is clear. Expression of *REV-ERBα* and *BMAL1* is required for adipogenesis and adipocyte differentiation (Chawla and Lazar 1993; Fontaine *et al*. 2003; Wang and Lazar 2008), and altered lipid metabolism is observed in *REV-ERBα* knockout mice (Raspe *et al*. 2001, 2002a). Importantly, the clock gene machinery is also responsive to metabolic status and energy supply. For example, fluctuations in glucose levels can modulate and entrain circadian oscillations in cells grown in culture (Hirota *et al*. 2002), suggesting that changes in energy supply can directly modify clock gene expression or activity.

### *Metabolic feedback onto clock genes*

Our understanding of the molecular connections that link the circadian system to metabolism has been greatly advanced by a series of observations detailing the interactions of CLOCK and BMAL1 with nuclear hormone receptors (NHRs) and other transcriptional regulators. The breadth and impact of these interactions have been highlighted in a number of recent reviews (for example, see Yang *et al*. 2007; Duez and Staels 2008; Teboul *et al*. 2008). The present discussion

will focus on three factors that are central not only to the clock's output onto metabolism, but may also modulate the clock itself in response to metabolic cues. These include the peroxisome proliferator-activated receptor (PPAR) family, PPARγ-coactivator-1α (PGC-1α), and the sirtuin protein, SIRT1 (McNamara *et al*. 2001; Inoue *et al*. 2005; Oishi *et al*. 2005b; Canaple *et al*. 2006; Liu *et al*. 2007). All three transcriptional regulators have been implicated in adaptive responses to feeding cues (Kersten *et al*. 1999; Yoon *et al*. 2001; Liu *et al*. 2007), and are well positioned to modulate circadian function during altered energy status and contribute to food-entrainment.

***PGC-1α***

PGC-1α is a stress-inducible and nutrient-inducible factor that regulates adaptive energy metabolism in numerous tissues, and plays a central role in the maintenance of glucose, lipid and energy homeostasis (Leone *et al*. 2005; Lin *et al*. 2005a). PGC-1α acts as a coactivator of transcription through its recruitment of proteins involved in chromatin remodelling (such as the histone acetyltransferases, CBP and p300) to the gene promoter. It is known to interact with a number of transcription factors involved in metabolic pathways, including FOXO1, thyroid hormone receptor β (TRβ), GR, and the PPARs (Liang and Ward 2006). As mentioned, PGC-1α is responsive to energy status, and its expression is rapidly induced in response to fasting in rats (Yoon *et al*. 2001).

Rhythmic expression of *PGC-1α* has been demonstrated in mouse liver and muscle, with protein levels peaking in the early dark phase, coinciding with *BMAL1* induction and mRNA accumulation (Liu *et al*. 2007). Importantly, PGC-1α can stimulate *BMAL1* and *REV-ERBα* transcription through coactivation of RORα (Liu *et al*. 2007). *PGC-1α* knockout mice display both metabolic and circadian abnormalities. Specifically, these mice exhibit disrupted weight control, muscle dysfunction, and hepatic steatosis, as well as altered diurnal rhythms of activity, body temperature, and metabolic rate (Leone *et al*. 2005; Liu *et al*. 2007). Interestingly, *PGC-1α* knockout mice appear to have a reduced ability to phase-reset liver clock gene expression in response to a shift from night-restricted to day-restricted feeding (Liu *et al*. 2007). Although a more detailed study is required, this may indicate that feedback between *PGC-1α* and core clock genes is required for optimal entrainment of peripheral clocks to energy-related cues. Equally, imposing of chronic and inappropriate metabolic inputs onto the clock through metabolic regulators such as PGC-1α might contribute to dampening of metabolic rhythms observed in obesity.

***PPAR***

One of the targets of both PGC-1α and CLOCK/BMAL1 is the PPAR family of transcription factors. PPARα is involved in the regulation of numerous genes involved in lipid metabolism, including fatty acid transport and uptake, catabolism and storage (Desvergne and Wahli 1999), and PPARα activity has been shown to have a role in adaptive responsive to feeding cues (Kersten *et al*. 1999). *PPARα* is rhythmically expressed (in a CLOCK/BMAL1-dependent manner) in peripheral tissues, including liver, heart and kidney, and to a lesser extent within the SCN (Lemberger *et al*. 1996; Panda *et al*. 2002). Like PGC-1α, PPARα is capable of modifying CLOCK and BMAL1 activity and expression (McNamara *et al*. 2001; Inoue *et al*. 2005; Oishi *et al*. 2005b; Canaple *et al*. 2006). PPARα has been shown to bind directly to the *BMAL1* promoter by chromatin immunoprecipitation, and fibrate agonists of PPARα can induce *BMAL1* expression in the liver. Further, the retinoid X receptor-α (RXRα), a dimerization partner of PPARα, inhibits CLOCK/BMAL1-induced transcriptional activation at E-box promoter sites (McNamara *et al*. 2001). PPAR-response elements are also found within the REV-ERBα promoter, and REV-ERBα expression has been shown to be responsive to PPARα and PPARγ both *in vitro* and *in vivo* (Chawla and Lazar 1993; Gervois *et al*. 1999; Fontaine *et al*. 2003; Laitinen *et al*. 2005).

***SIRT1***

Chromatin remodelling is now recognized as being a central component in facilitating clock-regulated gene expression (Nakahata *et al*. 2007) and CLOCK has been shown to function as a histone acetyltransferase (HAT) (Doi *et al*. 2006). HAT activity (acetylation) attaches an acetyl group to the histone, which serves to loosen chromatin structure and facilitate gene transcription. CLOCK-mediated histone acetylation presumably follows CLOCK/BMAL1 binding of E-box sites (Doi *et al*. 2006; Etchegaray *et al*. 2003). In line with this, transcriptional rhythms in clock gene expression in mouse liver are accompanied by rhythms in H3 histone acetylation, including the promoter regions of the *PER1, PER2* and *CRY1* genes (Etchegaray *et al*. 2003). In order to achieve rhythmic cycles of acetylation, the activity of a histone deacetylase (HDAC) is required to oppose any HAT activity. Two groups have recently identified SIRT1, a protein extensively linked to energy metabolism and ageing (Michan and Sinclair 2007), as an HDAC that counteracts CLOCK-mediated acetylation (Asher *et al*. 2008; Nakahata *et al*. 2008).

Targets of CLOCK and SIRT1 acetylation/deacetylation cycles include not only histones (Doi *et al*. 2006), but also clock components (e.g. BMAL1, PER2) and metabolic regulators (e.g. PGC-1α) (Hirayama *et al*. 2007; Asher *et al*. 2008; Nakahata *et al*. 2008; Rodgers *et al*. 2008). While *SIRT1* expression is reported to be is required for high-amplitude transcriptional rhythms of several core clock components *in vitro*, including *BMAL1* and *PER2*, it does not appear to be essential for the maintenance of clock gene transcriptional oscillations *per se* (Asher *et al*. 2008; Nakahata *et al*. 2008). This suggests that rhythmic histone acetylation

serves primarily to confer circadian transcriptional regulation to clock-controlled genes (Etchegaray *et al*. 2003; Curtis *et al*. 2004; Naruse *et al*. 2004; Ripperger and Schibler 2006), whereas nonhistone acetylation of clock genes, including *BMAL1* and *PER2* might be important in modifying the strength and phase of clock gene rhythms. For example, both PER2 (Asher *et al*. 2008) and BMAL1 (Nakahata *et al*. 2008) are stabilised through acetylation, thus modifying the dynamics of the transcriptional feedback loops of the clock. Several transcription factors and co-activators involved in metabolism, including members of the FOXO protein family, the nuclear receptor LXR, and PGC-1α, are also subject to regulation by SIRT1 HDAC activity (Brunet *et al*. 2004; Motta *et al*. 2004; Rodgers *et al*. 2005; Bordone *et al*. 2006; Dali-Youcef *et al*. 2007; Li *et al*. 2007).

Taken together, these findings suggest that the interaction of CLOCK and BMAL1 with PPARα, PGC1α, and SIRT1 constitute a reciprocal transcription loop linking metabolism with clock gene oscillation. The ability of energy-responsive genes to modify clock gene expression and activity, in essence renders the clock itself responsive to metabolic cues. Further, the adaptability of different body clocks to metabolic input may be dictated to a great extent by the tissue-specific expression of energy-responsive genes such as *PPARα, PGC1α*, and *SIRT1*.

## Adaptability of the clock to cellular energy status

The transcriptional activity of CLOCK/BMAL1 has been shown to be strongly influenced by the intracellular ratio of reduced to oxidized nicotinamide adenine dinucleotide (NAD) cofactors, a ratio which is closely tied to cellular energy metabolism (Rutter *et al*. 2001, 2002). Equally, SIRT1 activity is dependent on NAD ratio, since it requires $NAD^+$ as a cosubstrate during deacetylation reactions (Sauve *et al*. 2006). The direct dependence of clock activity on cellular energy supply provides a mechanism by which alterations in metabolic cues (such as RFS, hyperphagia, or desynchronised feeding / activity patterns) can modulate timing systems at a cell / tissue / organism level. These findings also suggest that SIRT1 may be a key physiological control switch through which changes in cellular energy ($NAD^+$/NADH ratios) impact on clock gene expression and function.

An intriguing question is the degree to which fluctuations in SIRT1 activity and $NAD^+$ supply are confined to individual cells/tissues, or whether they may also be subject to system-wide modification. Nicotinamide phosphoribosyltransferase (NAMPT, also referred to as visfatin), a key enzyme involved in the $NAD^+$/NADH cycle, is released from visceral adipocytes, and detectable at relatively high levels in the circulation (Revollo *et al*. 2007). NAMPT is responsive to cellular energy supply, being strongly induced in the livers of rats following a 48 h fast (Yang *et al*. 2007) and increased circulating NAMPT has been linked to obesity and insulin resistance in type-II diabetes (Chen *et al*. 2006; Retnakaran *et al*. 2008). NAMPT is also responsive to AMP-activated protein kinase (AMPK) activity, and capable of regulating the activity and expression of sirtuin proteins, including SIRT1 (presumably through its actions on $NAD^+$) (Revollo *et al*. 2004; Wang *et al*. 2006; Yang *et al*. 2007; Fulco *et al*. 2008). In a comprehensive gene array study, Dupré and colleagues have recently demonstrated that NAMPT is under strong circadian and seasonal control within the pars tuberalis of sheep (Dupré *et al*. 2008). This group revealed NAMPT to be one of only a handful of genes within this structure to be directly responsive to melatonin. These findings suggest that the $NAD^+$ cycle may be central to linking circadian machinery (via SIRT1 and CLOCK), to both cellular energy supplies (e.g. glucose availability and electron transport chain activity) and systemic timing signals (melatonin), to orchestrate and adapt metabolic gene expression on a circadian and circannual level.

Another attractive candidate for linking cellular energy supply to clock function is AMPK. AMPK is activated in response to increases in the cellular AMP:ATP ratio, and acts to switch the cellular metabolic programme from ATP consumption to ATP production. AMPK activation is observed in fasted and calorie-restricted animals, and it has been identified as an essential pathway involved in regulating energy balance within the hypothalamus (Kahn *et al*. 2005; Carling 2007). Interestingly, the SIRT1 agonist resveratrol induces the phosphorylation and activation of AMPK (Baur *et al*. 2006; Dasgupta and Milbrandt 2007), and activation of AMPK induces NAMPT transcription during glucose restriction (Fulco *et al*. 2008). AMPK has recently been shown to heighten the activity of casein kinase 1ε (CK1ε) (Um *et al*. 2007), an enzyme central to determining the period of clock transcriptional feedback loops (Gallego and Virshup 2007; Loudon *et al*. 2007; Meng *et al*. 2008).

## Concluding remarks

The ability of restricted food availability to rapidly entrain behavioural and metabolic rhythms indicates the degree to which the circadian system is responsive to energy cues. Although the mechanisms of entrainment remain uncertain, it seems clear that modification of clock gene rhythms at a molecular level by energy-responsive metabolic genes will play a central role. Additionally, the uncoupling of peripheral circadian oscillators like those in the liver from SCN during altered energy status raises the distinct possibility that abnormal energy supply (including unrestricted hypercalorific food intake and feeding schedules that are out of synchrony with normal patterns of behaviour) may be effective at dampening hypothalamic control of metabolism. Recent evidence suggests that dampening of our daily physiological rhythms is a contributing factor in metabolic syndrome (diabetes, cardiovascular disease) (Boden *et al*. 1999; Calvani *et al*. 2004; Yildiz *et al*. 2004; Ando *et al*. 2005), and clinical reports demonstrate that sleep restriction, shift work,

and night-eating conditions are all strong risk factors for obesity and other aspects of metabolic syndrome (Blundell and Gillett 2001; Buijs and Kreier 2006; Wolk and Somers 2007; Young and Bray 2007; Zvonic *et al*. 2007). Therefore, understanding how circadian systems are entrained, or conversely desynchronized, by alterations in food supply, may provide novel therapeutic avenues for the treatment of metabolic disorders.

A key issue that remains to be resolved, is how much (or perhaps more accurately how little) of the clock machinery is required to facilitate food-entrainment. It is possible that rhythmic expression of core metabolic genes due to cycles in food intake needs only a fraction of the molecular clock structure to provide a circadian basis to the timing. From an evolutionary point of view, the lack of specificity at both an anatomical and a molecular level in the food-entrainable circadian system may be required to allow flexibility in an organism's response to food cues, and to minimize the vulnerability of the food-entrainment system to disruption.

## References


Abe M., Herzog E. D., Yamazaki S., Straume M., Tei H., Sakaki Y. *et al*. 2002 Circadian rhythms in isolated brain regions. *J. Neurosci*. **22**, 350–356.

Adelmant G., Begue A., Stehelin D. and Laudet V. 1996 A functional Rev-erb alpha responsive element located in the human Rev-erb alpha promoter mediates a repressing activity. *Proc. Natl. Acad. Sci. USA* **93**, 3553–3558.

Akhtar R. A., Reddy A. B., Maywood E. S., Clayton J. D., King V. M., Smith A. G. *et al*. 2002 Circadian cycling of the mouse liver transcriptome, as revealed by cDNA microarray, is driven by the suprachiasmatic nucleus. *Curr. Biol.* **12**, 540–550.

Ando H., Yanagihara H., Hayashi Y., Obi Y., Tsuruoka S., Takamura T. *et al*. 2005 Rhythmic messenger ribonucleic acid expression of clock genes and adipocytokines in mouse visceral adipose tissue. *Endocrinology* **146**, 5631–5636.

Angeles-Castellanos M., Aguilar-Roblero R. and Escobar C. 2004 c-Fos expression in hypothalamic nuclei of food-entrained rats. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **286**, R158–R165.

Asher G., Gatfield D., Stratmann M., Reinke H., Dibner C., Kreppel F. *et al*. 2008 SIRT1 regulates circadian clock gene expression through PER2 deacetylation. *Cell* **134**, 317–328.

Balsalobre A., Brown S. A., Marcacci L., Tronche F., Kellendonk C., Reichardt H. M. *et al*. 2000 Resetting of circadian time in peripheral tissues by glucocorticoid signaling. *Science* **289**, 2344–2347.

Bando H., Nishio T., van der Horst G. T., Masubuchi S., Hisa Y. and Okamura H. 2007 Vagal regulation of respiratory clocks in mice. *J. Neurosci.* **27**, 4359–4365.

Bartness T. J., Song C. K. and Demas G. E. 2001 SCN efferents to peripheral tissues: implications for biological rhythms. *J. Biol. Rhythms* **16**, 196–204.

Baur J. A., Pearson K. J., Price N. L., Jamieson H. A., Lerin C., Kalra A. *et al*. 2006 Resveratrol improves health and survival of mice on a high-calorie diet. *Nature* **444**, 337–342.

Bechtold D. A., Brown T. M., Luckman S. M. and Piggins H. D. 2008 Metabolic rhythm abnormalities in mice lacking VIP-VPAC2 signaling. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **294**, R344–R351.

Berthoud H. R. 2002 Multiple neural systems controlling food intake and body weight. *Neurosci. Biobehav. Rev.* **26**, 393–428.

Blundell J. E. and Gillett A. 2001 Control of food intake in the obese. *Obes. Res.* **9**, suppl. 4, 263S–270S.

Boden G., Chen X. and Polansky M. 1999 Disruption of circadian insulin secretion is associated with reduced glucose uptake in first-degree relatives of patients with type 2 diabetes. *Diabetes* **48**, 2182–2188.

Bordone L., Motta M. C., Picard F., Robinson A., Jhala U. S., Apfeld J. *et al*. 2006 Sirt1 regulates insulin secretion by repressing UCP2 in pancreatic beta cells. *PLoS Biol*. **4**, e31.

Boulos Z. and Terman M. 1980 Food availability and daily biological rhythms. *Neurosci. Biobehav. Rev.* **4**, 119–131.

Brunet A., Sweeney L. B., Sturgill J. F., Chua K. F., Greer P. L., Lin Y. *et al*. 2004 Stress-dependent regulation of FOXO transcription factors by the SIRT1 deacetylase. *Science* **303**, 2011–2015.

Buijs R. M. and Kreier F. 2006 The metabolic syndrome: a brain disease? *J. Neuroendocrinol.* **18**, 715–716.

Cailotto C., van Heijningen C., van der Vliet J., van der Plasse G., Habold C., Kalsbeek A. *et al*. 2008 Daily rhythms in metabolic liver enzymes and plasma glucose require a balance in the autonomic output to the liver. *Endocrinology* **149**, 1914–1925.

Calvani M., Scarfone A., Granato L., Mora E. V., Nanni G., Castagneto M. *et al*. 2004 Restoration of adiponectin pulsatility in severely obese subjects after weight loss. *Diabetes* **53**, 939–947.

Canaple L., Rambaud J., Dkhissi-Benyahya O., Rayet B., Tan N. S., Michalik L. *et al*. 2006 Reciprocal regulation of brain and muscle Arnt-like protein 1 and peroxisome proliferator-activated receptor alpha defines a novel positive feedback loop in the rodent liver circadian clock. *Mol. Endocrinol.* **20**, 1715–1727.

Carling D. 2007 The role of the AMP-activated protein kinase in the regulation of energy homeostasis. *Novartis Found. Symp.* **286**, 72–81; discussion 81–85.

Cermakian N. and Sassone-Corsi P. 2002 Environmental stimulus perception and control of circadian clocks. *Curr. Opin. Neurobiol.* **12**, 359–365.

Chaput J. P., Brunet M. and Tremblay A. 2006 Relationship between short sleeping hours and childhood overweight/obesity: results from the 'Quebec en Forme' Project. *Int. J. Obes. (London)* **30**, 1080–1085.

Chawla A. and Lazar M. A. 1993 Induction of Rev-ErbA alpha, an orphan receptor encoded on the opposite strand of the alpha-thyroid hormone receptor gene, during adipocyte differentiation. *J. Biol. Chem.* **268**, 16265–16269.

Chen M. P., Chung F. M., Chang D. M., Tsai J. C., Huang H. F., Shin S. J. and Lee Y. J. 2006 Elevated plasma level of visfatin/pre-B cell colony-enhancing factor in patients with type 2 diabetes mellitus. *J. Clin. Endocrinol. Metab.* **91**, 295–299.

Comperatore C. A. and Stephan F. K. 1990 Effects of vagotomy on entrainment of activity rhythms to food access. *Physiol. Behav.* **47**, 671–678.

Cone R. D., Cowley M. A., Butler A. A., Fan W., Marks D. L. and Low M. J. 2001 The arcuate nucleus as a conduit for diverse signals relevant to energy homeostasis. *Int. J. Obes. Relat. Metab. Disord.* **25**, suppl. 5, S63–S67.

Curtis A. M., Seo S. B., Westgate E. J., Rudic R. D., Smyth E. M., Chakravarti D. *et al*. 2004 Histone acetyltransferase-dependent chromatin remodeling and the vascular clock. *J. Biol. Chem.* **279**, 7091–7097.

Dali-Youcef N., Lagouge M., Froelich S., Koehl C., Schoonjans K. and Auwerx J. 2007 Sirtuins: the 'magnificent seven', function, metabolism and longevity. *Ann. Med.* **39**, 335–345.

Damiola F., Le Minh N., Preitner N., Kornmann B., Fleury-Olela F. and Schibler U. 2000 Restricted feeding uncouples circadian oscillators in peripheral tissues from the central pacemaker in the suprachiasmatic nucleus. *Genes Dev.* **14**, 2950–2961.

Dasgupta B. and Milbrandt J. 2007 Resveratrol stimulates AMP kinase activity in neurons. *Proc. Natl. Acad. Sci. USA* **104**, 7217–7222.

Davidson A. J. and Stephan F. K. 1998 Circadian food anticipation persists in capsaicin deafferented rats. *J. Biol. Rhythms* **13**, 422–429.

Davidson A. J., Cappendijk S. L. and Stephan F. K. 2000 Feeding-entrained circadian rhythms are attenuated by lesions of the parabrachial region in rats. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **278**, R1296–R1304.

Davidson A. J., Aragona B. J., Houpt T. A. and Stephan F. K. 2001a Persistence of meal-entrained circadian rhythms following area postrema lesions in the rat. *Physiol. Behav.* **74**, 349–354.

Davidson A. J., Aragona B. J., Werner R. M., Schroeder E., Smith J. C. and Stephan F. K. 2001b Food-anticipatory activity persists after olfactory bulb ablation in the rat. *Physiol. Behav.* **72**, 231–235.

Davidson A. J., Poole A. S., Yamazaki S. and Menaker M. 2003 Is the food-entrainable circadian oscillator in the digestive system? *Genes Brain Behav.* **2**, 32–39.

Desvergne B. and Wahli W. 1999 Peroxisome proliferator-activated receptors: nuclear control of metabolism. *Endocr. Rev.* **20**, 649–688.

Doi M., Hirayama J. and Sassone-Corsi P. 2006 Circadian regulator CLOCK is a histone acetyltransferase. *Cell* **125**, 497–508.

Dudley C. A., Erbel-Sieler C., Estill S. J., Reick M., Franken P., Pitts S. and McKnight S. L. 2003 Altered patterns of sleep and behavioral adaptability in NPAS2-deficient mice. *Science* **301**, 379–383.

Duffield G. E., Best J. D., Meurers B. H., Bittner A., Loros J. J. and Dunlap J. C. 2002 Circadian programs of transcriptional activation, signaling, and protein turnover revealed by microarray analysis of mammalian cells. *Curr. Biol.* **12**, 551–557.

Duez H. and Staels B. 2008 The nuclear receptors Rev-erbs and RORs integrate circadian rhythms and metabolism. *Diab. Vasc. Dis. Res.* **5**, 82–88.

Dupré S. M., Burt D. W., Talbot R., Downing A., Mouzaki D., Waddington D. *et al*. 2008 Identification of melatonin-regulated genes in the ovine pituitary pars tuberalis, a target site for seasonal hormone control. *Endocrinol.* **149**, 5527–5539.

Emery P. and Reppert S. M. 2004 A rhythmic Ror. *Neuron* **43**, 443–446.

Etchegaray J. P., Lee C., Wade P. A. and Reppert S. M. 2003 Rhythmic histone acetylation underlies transcription in the mammalian circadian clock. *Nature* **421**, 177–182.

Feillet C. A., Ripperger J. A., Magnone M. C., Dulloo A., Albrecht U. and Challet E. 2006 Lack of food anticipation in Per2 mutant mice. *Curr. Biol.* **16**, 2016–2022.

Fontaine C., Dubois G., Duguay Y., Helledie T., Vu-Dac N., Gervois P. *et al*. 2003 The orphan nuclear receptor Rev-Erbalpha is a peroxisome proliferator-activated receptor (PPAR) gamma target gene and promotes PPARgamma-induced adipocyte differentiation. *J. Biol. Chem.* **278**, 37672–37680.

Fulco M., Cen Y., Zhao P., Hoffman E. P., McBurney M. W., Sauve A. A. and Sartorelli V. 2008 Glucose restriction inhibits skeletal myoblast differentiation by activating SIRT1 through AMPK-mediated regulation of Nampt. *Dev. Cell* **14**, 661–673.

Fuller P. M., Lu J. and Saper C. B. 2008 Differential rescue of light- and food-entrainable circadian rhythms. *Science* **320**, 1074–1077.

Gallego M. and Virshup D. M. 2007 Post-translational modifications regulate the ticking of the circadian clock. *Nat. Rev. Mol. Cell Biol.* **8**, 139–148.

Gallou-Kabani C., Vige A. and Junien C. 2007 Lifelong circadian and epigenetic drifts in metabolic syndrome. *Epigenetics* **2**, 137–146.

Gangwisch J. E., Malaspina D., Boden-Albala B. and Heymsfield S. B. 2005 Inadequate sleep as a risk factor for obesity: analyses of the NHANES I. *Sleep* **28**, 1289–1296.

Gervois P., Chopin-Delannoy S., Fadel A., Dubois G., Kosykh V., Fruchart J. C. *et al*. 1999 Fibrates increase human REV-ERBalpha expression in liver via a novel peroxisome proliferator-activated receptor response element. *Mol. Endocrinol.* **13**, 400–409.

Gooley J. J., Schomer A. and Saper C. B. 2006 The dorsomedial hypothalamic nucleus is critical for the expression of food-entrainable circadian rhythms. *Nat. Neurosci.* **9**, 398–407.

Granados-Fuentes D., Prolo L. M., Abraham U. and Herzog E. D. 2004 The suprachiasmatic nucleus entrains, but does not sustain, circadian rhythmicity in the olfactory bulb. *J. Neurosci.* **24**, 615–619.

Guo H., Brewer J. M., Lehman M. N. and Bittman E. L. 2006 Suprachiasmatic regulation of circadian rhythms of gene expression in hamster peripheral organs: effects of transplanting the pacemaker. *J. Neurosci.* **26**, 6406–6412.

Hirayama J., Sahar S., Grimaldi B., Tamaru T., Takamatsu K., Nakahata Y. and Sassone-Corsi P. 2007 CLOCK-mediated acetylation of BMAL1 controls circadian function. *Nature* **450**, 1086–1090.

Hirota T., Okano T., Kokame K., Shirotani-Ikejima H., Miyata T. and Fukada Y. 2002 Glucose down-regulates *Per1* and *Per2* mRNA levels and induces circadian gene expression in cultured Rat-1 fibroblasts. *J. Biol. Chem.* **277**, 44244–44251.

Iijima M., Yamaguchi S., van der Horst G. T., Bonnefont X., Okamura H. and Shibata S. 2005 Altered food-anticipatory activity rhythm in Cryptochrome-deficient mice. *Neurosci. Res.* **52**, 166–173.

Inoue I., Shinoda Y., Ikeda M., Hayashi K., Kanazawa K., Nomura M. *et al*. 2005 CLOCK/BMAL1 is involved in lipid metabolism via transactivation of the peroxisome proliferator-activated receptor (PPAR) response element. *J. Atheroscler. Thromb.* **12**, 169–174.

Ishida A., Mutoh T., Ueyama T., Bando H., Masubuchi S., Nakahara D. *et al*. 2005 Light activates the adrenal gland: timing of gene expression and glucocorticoid release. *Cell Metab.* **2**, 297–307.

Kaasik K. and Lee C. C. 2004 Reciprocal regulation of haem biosynthesis and the circadian clock in mammals. *Nature* **430**, 467–471.

Kahn B. B., Alquier T., Carling D. and Hardie D. G. 2005 AMP-activated protein kinase: ancient energy gauge provides clues to modern understanding of metabolism. *Cell Metab.* **1**, 15–25.

Kalsbeek A., Kreier F., Fliers E., Sauerwein H. P., Romijn J. A. and Buijs R. M. 2007 Minireview: Circadian control of metabolism by the suprachiasmatic nuclei. *Endocrinol.* **148**, 5635–5639.

Karlsson B., Knutsson A. and Lindahl B. 2001 Is there an association between shift work and having a metabolic syndrome? Results from a population based study of 27,485 people. *Occup. Environ. Med.* **58**, 747–752.

Kersten S., Seydoux J., Peters J. M., Gonzalez F. J., Desvergne B. and Wahli W. 1999 Peroxisome proliferator-activated receptor alpha mediates the adaptive response to fasting. *J. Clin. Invest.* **103**, 1489–1498.

Kohsaka A. and Bass J. 2007 A sense of time: how molecular clocks organize metabolism. *Trends Endocrinol. Metab.* **18**, 4–11.

Kornmann B., Schaad O., Bujard H., Takahashi J. S. and Schibler U. 2007 System-driven and oscillator-dependent circadian transcription in mice with a conditionally active liver clock. *PLoS Biol.* **5**, e34.

Krieger D. T. 1972 Circadian corticosteroid periodicity: critical period for abolition by neonatal injection of corticosteroid. *Science* **178**, 1205–1207.

Kudo T., Kawashima M., Tamagawa T. and Shibata S. 2008 Clock mutation facilitates accumulation of cholesterol in the liver of mice fed a cholesterol and/or cholic acid diet. *Am. J. Physiol. Endocrinol. Metab.* **294**, E120–E130.

Laitinen S., Fontaine C., Fruchart J. C. and Staels B. 2005 The role of the orphan nuclear receptor Rev-Erb alpha in adipocyte differentiation and function. *Biochimie* **87**, 21–25.

Lamia K. A., Storch K. F. and Weitz C. J. 2008 Physiological significance of a peripheral tissue circadian clock. *Proc. Natl. Acad. Sci. USA* **105**, 15172–15177.

Lamont E. W., Robinson B., Stewart J. and Amir S. 2005 The central and basolateral nuclei of the amygdala exhibit opposite diurnal rhythms of expression of the clock protein Period2. *Proc. Natl. Acad. Sci. USA* **102**, 4180–4184.

Landry G. J. and Mistlberger R. E. 2007 Food entrainment: methodological issues. *J. Biol. Rhythms* **22**, 484–487.

Landry G. J., Simon M. M., Webb I. C. and Mistlberger R. E. 2006 Persistence of a behavioral food-anticipatory circadian rhythm following dorsomedial hypothalamic ablation in rats. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **290**, R1527–R1534.

Landry G. J., Yamakawa G. R., Webb I. C., Mear R. J. and Mistlberger R. E. 2007 The dorsomedial hypothalamic nucleus is not necessary for the expression of circadian food-anticipatory activity in rats. *J. Biol. Rhythms* **22**, 467–478.

Laposky A. D., Bass J., Kohsaka A. and Turek F. W. 2008 Sleep and circadian rhythms: key components in the regulation of energy metabolism. *FEBS Lett.* **582**, 142–151.

Le Minh N., Damiola F., Tronche F., Schutz G. and Schibler U. 2001 Glucocorticoid hormones inhibit food-induced phase-shifting of peripheral circadian oscillators. *EMBO J.* **20**, 7128–7136.

Lemberger T., Saladin R., Vazquez M., Assimacopoulos F., Staels B., Desvergne B. *et al*. 1996 Expression of the peroxisome proliferator-activated receptor alpha gene is stimulated by stress and follows a diurnal rhythm. *J. Biol. Chem.* **271**, 1764–1769.

Leone T. C., Lehman J. J., Finck B. N., Schaeffer P. J., Wende A. R., Boudina S. *et al*. 2005 PGC-1alpha deficiency causes multisystem energy metabolic derangements: muscle dysfunction, abnormal weight control and hepatic steatosis. *PLoS Biol.* **3**, e101.

Li X., Zhang S., Blander G., Tse J. G., Krieger M. and Guarente L. 2007 SIRT1 deacetylates and positively regulates the nuclear receptor LXR. *Mol. Cell* **28**, 91–106.

Liang H. and Ward W. F. 2006 PGC-1alpha: a key regulator of energy metabolism. *Adv. Physiol. Educ.* **30**, 145–151.

Lin J., Handschin C. and Spiegelman B. M. 2005a Metabolic control through the PGC-1 family of transcription coactivators. *Cell. Metab.* **1**, 361–370.

Lin J., Yang R., Tarr P. T., Wu P. H., Handschin C., Li S. *et al*. 2005b Hyperlipidemic effects of dietary saturated fats mediated through PGC-1beta coactivation of SREBP. *Cell* **120**, 261–273.

Liu C., Li S., Liu T., Borjigin J. and Lin J. D. 2007 Transcriptional coactivator PGC-1alpha integrates the mammalian clock and energy metabolism. *Nature* **447**, 477–481.

Loudon A. S., Meng Q. J., Maywood E. S., Bechtold D. A., Boot-Handford R. P. and Hastings M. H. 2007 The biology of the circadian Ck1epsilon tau mutation in mice and Syrian hamsters: a tale of two species. *Cold. Spr. Harb. Symp. Quant. Biol.* **72**, 261–271.

Lowrey P. L. and Takahashi J. S. 2004 Mammalian circadian biology: elucidating genome-wide levels of temporal organization. *Annu. Rev. Genomics Hum. Genet.* **5**, 407–441.

McCarthy J. J., Andrews J. L., McDearmon E. L., Campbell K. S., Barber B. K., Miller B. H. *et al*. 2007 Identification of the circadian transcriptome in adult mouse skeletal muscle. *Physiol. Genomics* **31**, 86–95.

McNamara P., Seo S. P., Rudic R. D., Sehgal A., Chakravarti D. and FitzGerald G. A. 2001 Regulation of CLOCK and MOP4 by nuclear hormone receptors in the vasculature: a humoral mechanism to reset a peripheral clock. *Cell* **105**, 877–889.

Meng Q. J., Logunova L., Maywood E. S., Gallego M., Lebiecki J., Brown T. M. *et al*. 2008 Setting clock speed in mammals: the CK1 epsilon tau mutation in mice accelerates circadian pacemakers by selectively destabilizing PERIOD proteins. *Neuron* **58**, 78–88.

Meyer-Bernstein E. L., Jetton A. E., Matsumoto S. I., Markuns J. F., Lehman M. N. and Bittman E. L. 1999 Effects of suprachiasmatic transplants on circadian rhythms of neuroendocrine function in golden hamsters. *Endocrinology* **140**, 207–218.

Michan S. and Sinclair D. 2007 Sirtuins in mammals: insights into their biological function. *Biochem. J.* **404**, 1–13.

Mieda M., Williams S. C., Richardson J. A., Tanaka K. and Yanagisawa M. 2006 The dorsomedial hypothalamic nucleus as a putative food-entrainable circadian pacemaker. *Proc. Natl. Acad. Sci. USA* **103**, 12150–12155.

Miller B. H., McDearmon E. L., Panda S., Hayes K. R., Zhang J., Andrews J. L. *et al*. 2007 Circadian and CLOCK-controlled regulation of the mouse transcriptome and cell proliferation. *Proc. Natl. Acad. Sci. USA* **104**, 3342–3347.

Mistlberger R. E. 1994 Circadian food-anticipatory activity: formal models and physiological mechanisms. *Neurosci. Biobehav. Rev.* **18**, 171–195.

Mistlberger R. E. and Marchant E. G. 1995 Computational and entrainment models of circadian food-anticipatory activity: evidence from non-24-hr feeding schedules. *Behav. Neurosci.* **109**, 790–798.

Mistlberger R. E. and Mumby D. G. 1992 The limbic system and food-anticipatory circadian rhythms in the rat: ablation and dopamine blocking studies. *Behav. Brain. Res.* **47**, 159–168.

Mistlberger R. E. and Rechtschaffen A. 1984 Recovery of anticipatory activity to restricted feeding in rats with ventromedial hypothalamic lesions. *Physiol. Behav.* **33**, 227–235.

Mistlberger R. E. and Rusak B. 1988 Food-anticipatory circadian rhythms in rats with paraventricular and lateral hypothalamic ablations. *J. Biol. Rhythms.* **3**, 277–291.

Motta M. C., Divecha N., Lemieux M., Kamel C., Chen D., Gu W. *et al*. 2004 Mammalian SIRT1 represses forkhead transcription factors. *Cell* **116**, 551–563.

Nakahata Y., Grimaldi B., Sahar S., Hirayama J. and Sassone-Corsi P. 2007 Signaling to the circadian clock: plasticity by chromatin remodeling. *Curr. Opin. Cell Biol.* **19**, 230–237.

Nakahata Y., Kaluzova M., Grimaldi B., Sahar S., Hirayama J., Chen D. *et al*. 2008 The NAD+-dependent deacetylase SIRT1 modulates CLOCK-mediated chromatin remodeling and circadian control. *Cell* **134**, 329–340.

Naruse Y., Oh-hashi K., Iijima N., Naruse M., Yoshioka H. and Tanaka M. 2004 Circadian and light-induced transcription of clock gene *Per1* depends on histone acetylation and deacetylation. *Mol. Cell Biol.* **24**, 6278–6287.

Oishi K., Miyazaki K., Kadota K., Kikuno R., Nagase T., Atsumi G. *et al*. 2003 Genome-wide expression analysis of mouse liver reveals CLOCK-regulated circadian output genes. *J. Biol. Chem.* **278**, 41519–41527.

Oishi K., Amagai N., Shirai H., Kadota K., Ohkura N. and Ishida N. 2005a Genome-wide expression analysis reveals 100 adrenal gland-dependent circadian genes in the mouse liver. *DNA Res.* **12**, 191–202.

Oishi K., Shirai H. and Ishida N. 2005b CLOCK is involved in the circadian transactivation of peroxisome-proliferator-activated receptor alpha (PPARalpha) in mice. *Biochem. J.* **386**, 575–581.

Oishi K., Atsumi G., Sugiyama S., Kodomari I., Kasamatsu M., Machida K. and Ishida N. 2006 Disrupted fat absorption attenuates obesity induced by a high-fat diet in *Clock* mutant mice. *FEBS Lett.* **580**, 127–130.

Panda S., Antoch M. P., Miller B. H., Su A. I., Schook A. B., Straume M. *et al*. 2002 Coordinated transcription of key pathways in the mouse by the circadian clock. *Cell* **109**, 307–320.

Pitts S., Perone E. and Silver R. 2003 Food-entrained circadian rhythms are sustained in arrhythmic *Clk/Clk* mutant mice. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **285**, R57–R67.

Preitner N., Damiola F., Lopez-Molina L., Zakany J., Duboule D., Albrecht U. and Schibler U. 2002 The orphan nuclear receptor REV-ERBalpha controls circadian transcription within the positive limb of the mammalian circadian oscillator. *Cell* **110**, 251–260.

Ralph M. R., Foster R. G., Davis F. C. and Menaker M. 1990 Transplanted suprachiasmatic nucleus determines circadian period. *Science* **247**, 975–978.

Ramsey K. M., Marcheva B., Kohsaka A. and Bass J. 2007 The clockwork of metabolism. *Annu. Rev. Nutr.* **27**, 219–240.

Raspe E., Duez H., Gervois P., Fievet C., Fruchart J. C., Besnard S. *et al*. 2001 Transcriptional regulation of apolipoprotein C-III gene expression by the orphan nuclear receptor RORalpha. *J. Biol. Chem.* **276**, 2865–2871.

Raspe E., Duez H., Mansen A., Fontaine C., Fievet C., Fruchart J. C. *et al*. 2002a Identification of Rev-erbalpha as a physiological repressor of apoC-III gene transcription. *J. Lipid Res.* **43**, 2172–2179.

Raspe E., Mautino G., Duval C., Fontaine C., Duez H., Barbier O. *et al*. 2002b Transcriptional regulation of human Rev-erbalpha gene expression by the orphan nuclear receptor retinoic acid-related orphan receptor alpha. *J. Biol. Chem.* **277**, 49275–49281.

Reick M., Garcia J. A., Dudley C. and McKnight S. L. 2001 NPAS2: an analog of clock operative in the mammalian forebrain. *Science* **293**, 506–509.

Reppert S. M. and Weaver D. R. 2002 Coordination of circadian timing in mammals. *Nature* **418**, 935–941.

Retnakaran R., Youn B. S., Liu Y., Hanley A. J., Lee N. S., Park J. W. *et al*. 2008 Correlation of circulating full-length visfatin (PBEF/Nampt) with metabolic parameters in subjects with and without diabetes: a cross-sectional study. *Clin. Endocrinol. (Oxf.)* (in press).

Revollo J. R., Grimm A. A. and Imai S. 2004 The NAD biosynthesis pathway mediated by nicotinamide phosphoribosyltransferase regulates Sir2 activity in mammalian cells. *J. Biol. Chem.* **279**, 50754–50763.

Revollo J. R., Korner A., Mills K. F., Satoh A., Wang T., Garten A. *et al*. 2007 Nampt/PBEF/Visfatin regulates insulin secretion in beta cells as a systemic NAD biosynthetic enzyme. *Cell Metab.* **6**, 363–375.

Ripperger J. A. and Schibler U. 2001 Circadian regulation of gene expression in animals. *Curr. Opin. Cell. Biol.* **13**, 357–362.

Ripperger J. A. and Schibler U. 2006 Rhythmic CLOCK-BMAL1 binding to multiple E-box motifs drives circadian Dbp transcription and chromatin transitions. *Nat. Genet.* **38**, 369–374.

Rodgers R. J., Ishii Y., Halford J. C. and Blundell J. E. 2002 Orexins and appetite regulation. *Neuropeptides* **36**, 303–325.

Rodgers J. T., Lerin C., Haas W., Gygi S. P., Spiegelman B. M. and Puigserver P. 2005 Nutrient control of glucose homeostasis through a complex of PGC-1alpha and SIRT1. *Nature* **434**, 113–118.

Rodgers J. T., Lerin C., Gerhart-Hines Z. and Puigserver P. 2008 Metabolic adaptations through the PGC-1 alpha and SIRT1 pathways. *FEBS Lett.* **582**, 46–53.

Ruiter M., Buijs R. M. and Kalsbeek A. 2006 Hormones and the autonomic nervous system are involved in suprachiasmatic nucleus modulation of glucose homeostasis. *Curr. Diabetes Rev.* **2**, 213–226.

Rutter J., Reick M., Wu L. C. and McKnight S. L. 2001 Regulation of clock and NPAS2 DNA binding by the redox state of NAD cofactors. *Science* **293**, 510–514.

Rutter J., Reick M. and McKnight S. L. 2002 Metabolism and the control of circadian rhythms. *Annu. Rev. Biochem.* **71**, 307–331.

Saper C. B., Cano G. and Scammell T. E. 2005a Homeostatic, circadian, and emotional regulation of sleep. *J. Comp. Neurol.* **493**, 92–98.

Saper C. B., Lu J., Chou T. C. and Gooley J. 2005b The hypothalamic integrator for circadian rhythms. *Trends Neurosci.* **28**, 152–157.

Sauve A. A., Wolberger C., Schramm V. L. and Boeke J. D. 2006 The biochemistry of sirtuins. *Annu. Rev. Biochem.* **75**, 435–465.

Sawaki Y., Nihonmatsu I. and Kawamura H. 1984 Transplantation of the neonatal suprachiasmatic nuclei into rats with complete bilateral suprachiasmatic lesions. *Neurosci. Res.* **1**, 67–72.

Schibler U. 2003 Circadian rhythms. Liver regeneration clocks on. *Science* **302**, 234–235.

Schibler U., Ripperger J. and Brown S. A. 2003 Peripheral circadian oscillators in mammals: time and food. *J. Biol. Rhythms* **18**, 250–260.

Shearman L. P., Sriram S., Weaver D. R., Maywood E. S., Chaves I., Zheng B. *et al*. 2000 Interacting molecular loops in the mammalian circadian clock. *Science* **288**, 1013–1019.

Silver R., LeSauter J., Tresco P. A. and Lehman M. N. 1996 A diffusible coupling signal from the transplanted suprachiasmatic nucleus controlling circadian locomotor rhythms. *Nature* **382**, 810–813.

Stephan F. K. 2002 The "other" circadian system: food as a Zeitgeber. *J. Biol. Rhythms* **17**, 284–292.

Stephan F. K. and Zucker I. 1972 Circadian rhythms in drinking behavior and locomotor activity of rats are eliminated by hypothalamic lesions. *Proc. Natl. Acad. Sci. USA* **69**, 1583–1586.

Stokkan K. A., Yamazaki S., Tei H., Sakaki Y. and Menaker M. 2001 Entrainment of the circadian clock in the liver by feeding. *Science* **291**, 490–493.

Storch K. F., Lipan O., Leykin I., Viswanathan N., Davis F. C., Wong W. H. and Weitz C. J. 2002 Extensive and divergent circadian gene expression in liver and heart. *Nature* **417**, 78–83.

Sujino M., Masumoto K. H., Yamaguchi S., van der Horst G. T., Okamura H. and Inouye S. T. 2003 Suprachiasmatic nucleus grafts restore circadian behavioral rhythms of genetically arrhythmic mice. *Curr. Biol.* **13**, 664–668.

Teboul M., Guillaumond F., Gréchez-Cassiau A. and Delaunay F. 2008 The Nuclear hormone receptors family round the clock. *Mol. Endocrinol.* (in press).

Tu B. P. and McKnight S. L. 2006 Metabolic cycles as an underlying basis of biological oscillations. *Nat. Rev. Mol. Cell Biol.* **7**, 696–701.

Turek F. W., Joshu C., Kohsaka A., Lin E., Ivanova G., McDearmon E. et al. 2005 Obesity and metabolic syndrome in circadian *Clock* mutant mice. *Science* **308**, 1043–1045.

Um J. H., Yang S., Yamazaki S., Kang H., Viollet B., Foretz M. and Chung J. H. 2007 Activation of 5′-AMP-activated kinase with diabetes drug metformin induces casein kinase I epsilon(CKIepsilon)-dependent degradation of clock protein mPer2. *J. Biol. Chem.* **282**, 20794–20798.

Vujovic N., Davidson A. J. and Menaker M. 2008 Sympathetic input modulates, but does not determine, phase of peripheral circadian oscillators. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **295**, R355–R360.

Wakamatsu H., Yoshinobu Y., Aida R., Moriya T., Akiyama M. and Shibata S. 2001 Restricted-feeding-induced anticipatory activity rhythm is associated with a phase-shift of the expression of *mPer1* and *mPer2* mRNA in the cerebral cortex and hippocampus but not in the suprachiasmatic nucleus of mice. *Eur. J. Neurosci.* **13**, 1190–1196.

Walker J. R. and Hogenesch J. B. 2005 RNA profiling in circadian biology. *Methods Enzymol.* **393**, 366–376.

Wang J. and Lazar M. A. 2008 Bifunctional role of Rev-erbalpha in adipocyte differentiation. *Mol. Cell Biol.* **28**, 2213–2220.

Wang T., Zhang X., Bheda P., Revollo J. R., Imai S. and Wolberger C. 2006 Structure of Nampt/PBEF/visfatin, a mammalian NAD+ biosynthetic enzyme. *Nat. Struct. Mol. Biol.* **13**, 661–662.

Wijnen H. and Young M. W. 2006 Interplay of circadian clocks and metabolic rhythms. *Annu. Rev. Genet.* **40**, 409–448.

Wolk R. and Somers V. K. 2007 Sleep and the metabolic syndrome. *Exp. Physiol.* **92**, 67–78.

Yang X., Lamia K. A. and Evans R. M. 2007 Nuclear receptors, metabolism, and the circadian clock. *Cold. Spr. Harb. Symp. Quant. Biol.* **72**, 387–394.

Yang H., Yang T., Baur J. A., Perez E., Matsui T., Carmona J. J. *et al*. 2007 Nutrient-sensitive mitochondrial NAD+ levels dictate cell survival. *Cell* **130**, 1095–1107.

Yildiz B. O., Suchard M. A., Wong M. L., McCann S. M. and Licinio J. 2004 Alterations in the dynamics of circulating ghrelin, adiponectin, and leptin in human obesity. *Proc. Natl. Acad. Sci. USA* **101**, 10434–10439.

Yoo S. H., Yamazaki S., Lowrey P. L., Shimomura K., Ko C. H., Buhr E. D. *et al*. 2004 PERIOD2::LUCIFERASE real-time reporting of circadian dynamics reveals persistent circadian oscillations in mouse peripheral tissues. *Proc. Natl. Acad. Sci. USA* **101**, 5339–5346.

Yoon J. C., Puigserver P., Chen G., Donovan J., Wu Z., Rhee J. *et al*. 2001 Control of hepatic gluconeogenesis through the transcriptional coactivator PGC-1. *Nature* **413**, 131–138.

Young M. E. and Bray M. S. 2007 Potential role for peripheral circadian clock dyssynchrony in the pathogenesis of cardiovascular dysfunction. *Sleep Med.* **8**, 656–667.

Zvonic S., Floyd Z. E., Mynatt R. L. and Gimble J. M. 2007 Circadian rhythms and the regulation of metabolic tissue function and energy homeostasis. *Obesity (Silver Spr.)* **15**, 539–543.

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