



# Circadian rhythms, sleep, and metabolism

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**The discovery of the genetic basis for circadian rhythms has expanded our knowledge of the temporal organization of behavior and physiology. The observations that the circadian gene network is present in most living organisms from eubacteria to humans, that most cells and tissues express autonomous clocks, and that disruption of clock genes results in metabolic dysregulation have revealed interactions between metabolism and circadian rhythms at neural, molecular, and cellular levels. A major challenge remains in understanding the interplay between brain and peripheral clocks and in determining how these interactions promote energy homeostasis across the sleep-wake cycle. In this Review, we evaluate how investigation of molecular timing may create new opportunities to understand and develop therapies for obesity and diabetes.**

## Introduction: circadian clocks and metabolism from molecular systems to physiology

Studies in plants dating from the 18th century originally established that 24-hour periodic phenomena arise from biological oscillators that internally track the rotation of the Earth. These so-called “circadian clocks” (the term is derived from “circa diem,” or “about a day”) are entrained by light and synchronize energy-harvesting and utilization processes with the rising and setting of the sun (ref. 1 and Figure 1A). At the molecular level, circadian rhythms are encoded by an autoregulatory loop composed of a set of transcription activators (CLOCK:NPAS2/BMAL1 [MOP3]) that induce expression of repressors (PER1–3/CRY1–2) that feedback to inhibit the forward limb. Discovery of this mechanism stemmed from deliberate mutagenesis experiments in flies (2), and forward genetics in mice ultimately led to the discovery of the first mammalian *Clock* gene (3–5). Subsequent work has revealed that the mammalian molecular clock is not only expressed within the master suprachiasmatic nucleus (SCN) pacemaker neurons, but also within nearly all cells (6, 7). In addition to this core loop, CLOCK/BMAL1 also induce expression of the orphan nuclear hormone receptors (NHRs) ROR $\alpha$  and REV-ERB $\alpha$ , which activate and repress *Bmal1* transcription, respectively. Posttranslational regulation of clock transcription factors by casein kinase I $\epsilon$  and I $\delta$  (CKI $\epsilon/\delta$ ),  $\beta$ -TrCP, FBXL3, and ARF-BP1/PAM, in addition to cAMP signaling (8), further modulates circadian oscillations (1). The purpose of this Review is to provide an overview of the genetic and neurobiological evidence linking circadian and energetic systems and to highlight gaps in our understanding of the molecular pathways that couple these processes.

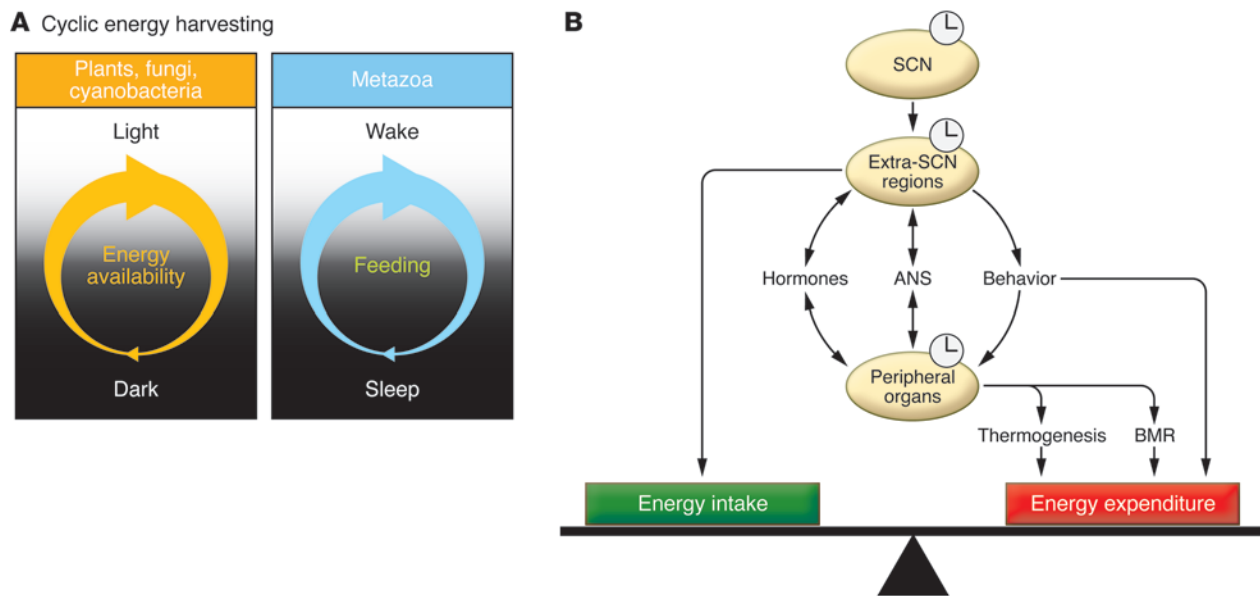
## Neural networks linking circadian and energetic centers

In vertebrates, circadian systems are organized hierarchically with master pacemaker neurons within the hypothalamic SCN presiding over a distributed network of extra-SCN and peripheral clocks (9). The environmental light-dark cycle provides the principal entraining signal to the SCN, which in turn produces synchronized rhythms of behavior and physiology through alignment of circadian gene oscillation within both extra-SCN neu-

rons and peripheral tissues (Figure 1B). Wiring of the neural circuit generating circadian rhythms involves projections of the SCN to a wide range of cell bodies within both the hypothalamus (including the arcuate nucleus [ARC], paraventricular nucleus [PVN], lateral hypothalamic area [LHA], and dorsomedial hypothalamus [DMH]; refs. 10–16) and the brainstem (including the ventral tegmental area [VTA] and dorsomedial nucleus of vagus [DMV] via relay at the medial preoptic area [MPO] and PVN, respectively refs. 17, 18) (Figure 2). Within the ARC, neurons expressing orexigenic neuropeptide Y/Agouti-related protein (NPY/AgRP) and anorexigenic pro-opiomelanocortin/cocaine- and amphetamine-regulated transcript (POMC/CART) peptides form reciprocal connections with cells located within the SCN (10, 11). In addition, NPY/AgRP- and POMC/CART-expressing neurons and SCN neurons project to cell bodies within the PVN and LHA that modulate autonomic (18) and sleep-wakefulness (19, 20) behavior, respectively. While peptidergic signaling within NPY/AgRP and POMC/CART neurons has been shown to influence long-term body weight constancy (see refs. 21–24 for more complete reviews), less is known concerning circadian modulation of signaling within these cells. For instance, clock genes are expressed cell-autonomously within cell bodies that receive projections from the SCN; thus it is possible that oscillation of key transcripts important in the response to anorexigenic and orexigenic hormones may be subject to circadian control. Interestingly, feeding an isocaloric high-fat diet at the incorrect circadian time has been shown to result in increased weight gain in mice (25), suggesting that circadian alignment of feeding and activity is critical in the homeostatic control of body weight. It is also intriguing that projections originating in the SCN directly synapse at the orexin-producing (ORX-producing, also referred to as hypocretin-producing) neurons within the LHA (14, 26, 27). ORX neurons in the LHA are important in peripheral glucose metabolism (28) and also participate in long-term weight homeostasis, since ORX receptor knockout mice are susceptible to diet-induced obesity (29). Finally, since dopaminergic signaling in the VTA neurons is implicated in reward systems associated with feeding (30, 31), an intriguing question is whether hedonic drive might similarly display circadian variation (32). Further studies are needed to define the repertoire of connections between SCN and energetic neurons, to determine the impact of feeding rhythms on function and entrainment of extra-SCN clocks, and to elucidate how clocks participate in melanocortinergic and dopaminergic signaling.

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**Figure 1** Circadian control of energy metabolism. **(A)** In plants, cyanobacteria, and fungi, energy is available during the light period within the light/dark cycle, while in metazoa, alternating periods of sleep and wakefulness, closely associated with the light/dark cycle, impart cyclicality on feeding behavior and fuel utilization. **(B)** The master clock in the SCN sends signals to the extra-SCN regions, which in turn entrain peripheral tissues via hormonal, autonomic nervous system (ANS), and behavioral pathways in order to regulate peripheral clock control of fuel utilization and energy harvesting. Extra-SCN regions also regulate energy homeostasis by controlling cyclic energy intake and locomotor activity. Through regulation of food intake, physical activity, and metabolic processes, both brain and peripheral clocks contribute to long-term weight stability by maintaining a precise balance between energy intake and energy expenditure. A positive energy balance deposits stored energy mostly into adipose tissue, leading to obesity, while a negative energy balance results in leanness. BMR, basal metabolic rate.

**Interaction of circadian and metabolic systems at the cell and molecular levels**

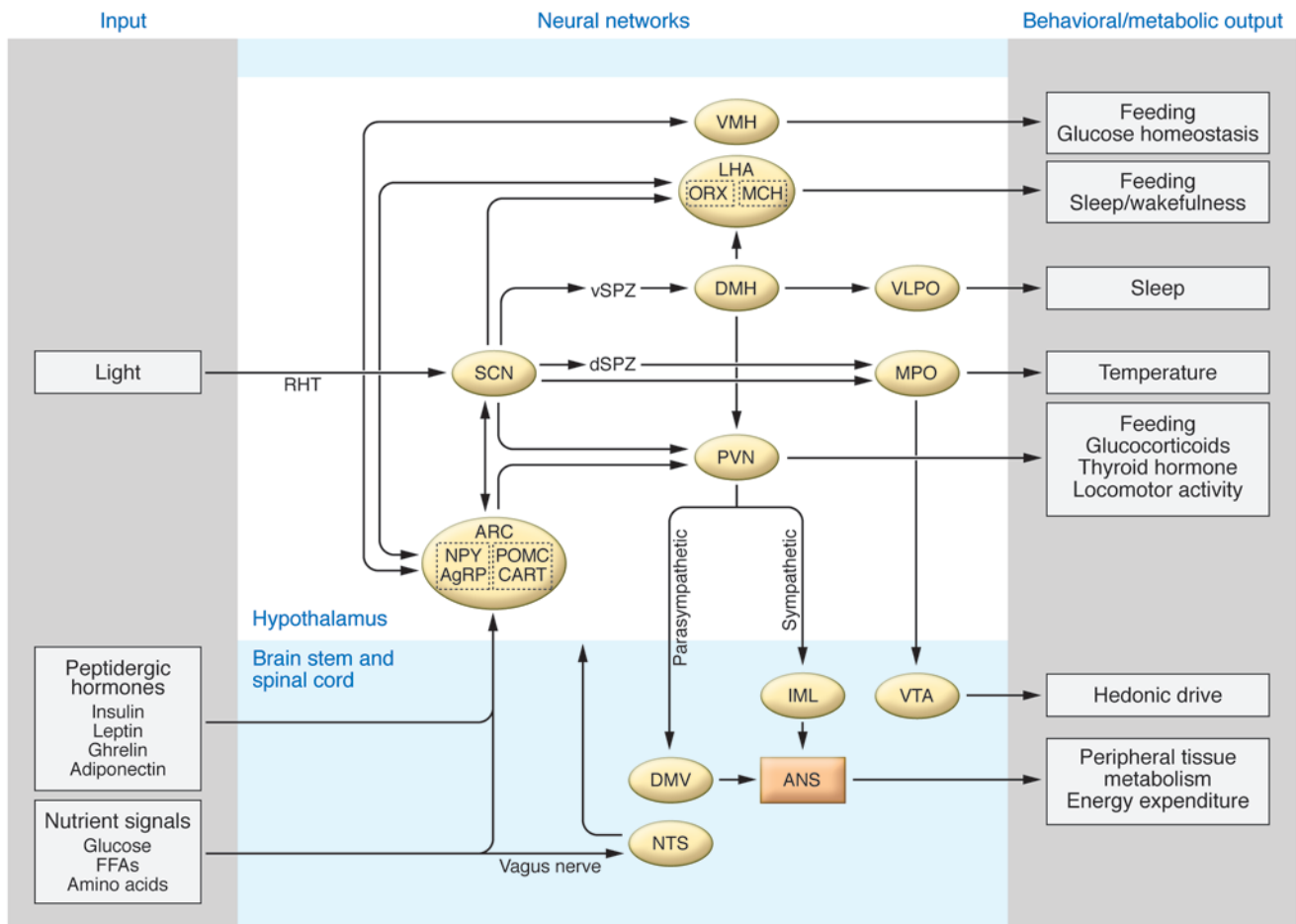
Integration of circadian systems with the light/dark environment involves a widely distributed network of local tissue clocks within both the brain and periphery (33–36) (Figure 3). Interestingly, a variety of factors including food availability, glucocorticoid level, and temperature, so called “zeitgebers” (“time givers”), are able to reset the phase of peripheral clocks. In contrast, the SCN is entrained only to light but not to feeding; thus shifts in feeding time uncouple the phase of peripheral tissue clocks from that of the SCN (37–40).

*Feedback loops between nutrient sensors and molecular clocks in peripheral tissues (NAD<sup>+</sup>, NAMPT, SIRT1, AMPK).* Recent studies have demonstrated that various nutrient sensors are able to relay information regarding the cellular nutrient status to the circadian clock. For example, early studies indicated that the reduced forms of the redox cofactor NADH increase CLOCK/BMAL1 and NPAS2/BMAL1 heterodimer activity, whereas the oxidized forms (NAD<sup>+</sup>) inhibit their activity (41). The NAD<sup>+</sup>-dependent deacetylase sirtuin 1 (SIRT1), which is induced by acute nutrient withdrawal (42) or calorie restriction (43), also directly binds to the CLOCK/BMAL1 complex to regulate expression of clock genes (44–47). AMP kinase (AMPK) serves as another highly conserved cellular nutrient sensor that, when activated by exercise, fasting, or hypoxia (48), leads to phosphorylation and degradation of CRY1 (49), as well as activation of NAMPT, the rate-limiting enzyme in NAD<sup>+</sup> salvage biosynthesis (50). Interestingly, the connection between nutrient sensors and molecular clocks is bidirectional. Levels of NAMPT, as well as NAD<sup>+</sup> itself, exhibit circadian oscillations, and *Nampt*

gene transcription is directly regulated by CLOCK (46, 47). As such, SIRT1 activity is indirectly regulated by the clock network. Together, these data demonstrate on a molecular level that there is a complex crosstalk between highly conserved nutrient sensors and the molecular clock networks, at least at the level of peripheral tissues (see below for discussion regarding potential roles of CNS nutrient sensors in circadian control of metabolism).

*Metabolic transcription factor and transcriptional co-activator feedback on the core clock in peripheral tissues (REV-ERB, ROR, PPAR, DBP, PGC1α).* NHRs are ligand-activated transcription factors, a majority of which, including REV-ERBα, RORs and PPARs, demonstrate circadian expression in peripheral tissues (51). REV-ERBα regulates hepatic gluconeogenesis, adipocyte differentiation, and lipid metabolism, and also represses *Bmal1* transcription (52, 53). RORα competes with REV-ERBα in binding to the *Bmal1* promoter and induces *Bmal1* expression (54) in addition to regulating lipid metabolism (55). PPARα, when activated by endogenous fatty acids (FAs), stimulates FA oxidation, regulates genes controlling lipid homeostasis, and prevents atherosclerosis (56). In addition, PPARα positively regulates *Bmal1* expression, while BMAL1 likewise activates PPARα, generating a positive feedback loop (57). Another subtype, PPARγ, plays an important role in adipocyte differentiation and triglyceride synthesis (58). PPARγ induces *Bmal1* expression in the blood vessels, and vasculature-specific PPARγ knockout leads to marked reduction in the circadian variation in blood pressure and heart rate (59).

In addition to NHRs, *Dbp*, a known clock target gene, regulates expression of key metabolic genes involved in gluconeogenesis and lipogenesis (60). Because DBP levels change 100-fold in response

**Figure 2**

Map of neural circuits linking SCN and extra-SCN regions important in circadian and energetic control. CNS centers receive dual input of light and metabolic signals. Light reaches the SCN via the RHT, which in turn sends neural projections to various extra-SCN regions in the hypothalamus and brainstem that are critical for energy homeostasis and sleep, including the ARC, PVN, and ventrolateral preoptic nucleus (VLPO). The hypothalamus also receives metabolic inputs, including peptidergic hormones and nutrient metabolites, which modulate the CNS signaling. Thus signals from the exogenous environment (i.e., light) and endogenous metabolism (i.e., metabolic cues) are integrated in the CNS, the output of which in turn imparts rhythmicity on sleep and a variety of metabolic outputs, such as thermogenesis, feeding behavior, hormone secretion, and locomotor activity. IML, intermediolateral nucleus; NTS, nucleus tractus solitarius. dSPZ, dorsal subparaventricular zone; RHT, retinohypothalamic tract; vSPZ, ventral subparaventricular zone; MCH, melanocyte concentrating hormone.

to CLOCK/BMAL1 activation, it is conceivable that DBP generates circadian oscillation in metabolic processes such as gluconeogenesis. Additionally, the transcriptional co-activator PPAR $\gamma$  co-activator 1 $\alpha$  (PGC-1 $\alpha$ ) (61) also displays circadian oscillations and regulates *Bmal1* and *Rev-erba* expression. Knockout of *Pgc1a* leads to abnormal diurnal rhythms of activity, body temperature, and metabolic rate, in addition to aberrant expression of clock and metabolic genes (62). Interestingly, SIRT1 suppresses PPAR $\gamma$  (63) but activates PGC-1 $\alpha$  (64), and thus affects the clock network through multiple mechanisms.

*Possible molecular integrators of circadian and metabolic systems in the CNS.* Molecular analyses of interplay between circadian and metabolic pathways have primarily emerged from studies in liver and other peripheral tissues, yet it remains uncertain whether similar mechanisms might also couple these processes within the brain. One question is whether specific metabolites that vary according to time of day and nutrient state (fasting vs. feeding), may also affect

circadian function of energy-sensing neurons. For instance, 24-hour oscillation in levels of glucose and FAs may in turn influence expression of circadian genes and rhythmic transcriptional outputs within hypothalamic neurons involved in glucose homeostasis (65), food intake (66), and energy expenditure (67–70). Perturbation of metabolic homeostasis with a high-fat diet is sufficient to alter both period length and amplitude of locomotor activity (71). These observations indicate that changes in FA metabolism per se may either alter clock gene function within SCN pacemaker neurons and/or interrupt communication between SCN and extra-SCN neurons.

Additional nutrient factors that may participate in circadian oscillations of SCN and extra-SCN neurons include AMPK, SIRT1, and the mammalian target of rapamycin (mTOR). Hypothalamic AMPK is regulated by nutrient state and hormones such as leptin and insulin (72), and manipulation of its expression alters food intake and body weight (73); however the impact of AMPK on CNS control of locomotor behavior and physiologi-







entrainment of peripheral clocks by specific hormones may be phase dependent (80); that is, local tissue clocks may only respond to phase-resetting hormones and/or metabolites when these are present within a narrow window of time during the 24 hour light/dark cycle. For instance, glucocorticoid secretion from adrenal glands in response to adrenocorticotropin is dependent on time of day (81). In addition to metabolite and hormonal input into the clock, recent studies by Buhr et al. suggest that temperature and heat shock signaling pathways play a central role in entrainment of peripheral tissues (39). Importantly, since alteration in temperature and/or the heat shock pathway is closely associated with other synchronizing signals including feeding and glucocorticoid secretion, it may serve as a unifying signal in entraining peripheral clocks. A major objective in future research will thus be to delineate the role of nutrient signaling in entrainment of CNS and peripheral clocks, and to determine how these signals interact with synchronizing signals such as feeding and neuroendocrine hormones (e.g., glucocorticoids) to maintain phase alignment of behavioral and metabolic rhythms within the whole organism at the levels of both physiology and pathophysiology.

### **Role of the circadian system in energy balance, metabolism, and sleep**

*Evidence for circadian integration of energetics, metabolism, and sleep in humans.* In humans, many aspects of metabolism display circadian cycles, including 24-hour variation of glucose, insulin, and leptin levels (82, 83). Genome-wide association studies have also suggested connections between clock gene variation and fasting glucose levels (84, 85), obesity, and metabolic syndrome (86), raising interest in understanding the impact of circadian systems on human disease. One common clinical condition suggestive of interactions between circadian rhythms and metabolism in humans is that of shift work. Numerous reports have indicated that shift workers have a higher incidence of diabetes, obesity, and cardiovascular events (1, 87), although the mechanism underlying this association is uncertain. Scheer et al. recently tested the impact of forced circadian misalignment (a simulation of shift work) on neuroendocrine control of glucose metabolism and energetics (88). In participants subjected to circadian misalignment, the investigators observed hypoleptinemia, insulin resistance, inverted cortisol rhythms, and increased blood pressure (88). It is also interesting to note that patients with diabetes exhibit dampened amplitude of rhythms of glucose tolerance and insulin secretion (89); thus the relationship between circadian disruption and metabolic pathologies appears to be bidirectional in humans, suggesting that circadian disruption may lead to a vicious cycle and contribute to augmentation and progression of metabolic disease.

Direct genetic evidence in humans has linked the molecular clock with sleep (90, 91) through the positional cloning of mutations causing familial advanced sleep phase syndrome, which is characterized by early sleep onset and awakening (92). In the general population, observational studies have also found that short sleep, sleep deprivation, and poor sleep quality are associated with diabetes, metabolic syndrome (82, 93), hypoleptinemia, increased appetite, and obesity (94, 95). A recent study showed that sleep duration correlates with the magnitude of weight loss as fat in response to caloric restriction; short sleepers appear to have more difficulty losing fat compared to long sleepers despite similar amount of weight loss (96). Narcolepsy, a sleep disorder in which patients present with extreme daytime sleepiness due to loss of hypocretin-producing

neurons (97, 98), has been associated with elevated BMI (99) and increased incidence of obesity (100, 101). Night eating syndrome (NES) is another instance in which disrupted rhythmic patterns of sleep and eating correlate with altered metabolism (102) and obesity (103). Patients with NES consume significantly more of their daily energy intake at night, although their total daily food intake is similar to that of control subjects (104, 105). They also have abnormal rhythms of metabolic hormones, including decreased nocturnal rise in leptin, a phase shift in insulin, cortisol, and ghrelin, and inverted 24-hour rhythms of blood glucose (104, 106). Interestingly, the nocturnal pattern of eating observed in NES patients is reminiscent of feeding alterations in the *Clock* mutant mouse. These animals exhibit increased feeding during the normal sleep period together with increased susceptibility to diet-induced obesity (107). A major goal is to determine whether the adverse metabolic consequences of sleep loss (and accompanying feeding alterations) are due to the disrupted circadian rhythms per se, to the altered sleep, or to some combination of the two. Nonetheless, the above observations in humans demonstrate that synchronization of feeding/fasting and active/rest periods with the environmental light/dark cycle influences body weight constancy.

*Integration of circadian rhythms and energy homeostasis in animal models.* Studies in rodents have also attempted to experimentally simulate shift work in order to further probe mechanisms linking circadian disruption with metabolic disorders. When rats were exposed to a daily eight-hour activity schedule during their normal resting phase, they succumbed to diminished rhythms of glucose and locomotor activity, as well as obesity, which correlated with increased food intake during their resting phase (108). However, shifting food intake back to the active phase restored their metabolic rhythms and prevented obesity in these same animals (108), suggesting that the normal alignment of feeding and activity with the environment light cycle is critical for the maintenance of energy homeostasis. Furthermore, feeding wild-type mice ad libitum exclusively during the daytime resulted in greater weight gain than in animals fed exclusively at night (25). Similarly, when genetically obese mice with disrupted diurnal feeding patterns were fed exclusively at night, their obesity and metabolic disorders improved (109).

Genetic animal models of clock gene disruption have provided an additional approach to specifically dissect the effects of molecular clock genes on energy homeostasis. For example, *Clock* mutant mice are obese and hyperphagic (107), although this phenotype may be modified by genetic background (110). Moreover, introgression of the *Clock* mutation into the *ob/ob* strain exacerbates obesity (111). In addition to causing metabolic disorders, both *Clock* mutant and *Npas2*<sup>-/-</sup> mice display abnormalities in sleep architecture, so it will be critical to determine the cause-and-effect relationship between alterations in sleep and feeding in these models (112, 113). In addition, *Npas2*<sup>-/-</sup> mice display increased activity during the “siesta” that wild-type mice normally take during the mid-active period (112). In contrast, *Clock* mutants have increased locomotor activity and food intake during the period when wild-type mice are at rest and fasting (107), suggesting non-redundant functions between the *Clock* and *Npas2* paralogs with regard to energy balance. Global *Bmal1* knockout mice are arrhythmic and display increased adiposity at early ages (114); however, these animals also develop arthropathy and myopathy, resulting in decreased activity and weight (115). Interestingly, brain rescue of *Bmal1*-knockout mice only restores behavioral circadian rhythms, whereas muscle rescue restores activity levels and body weight, but



not behavioral rhythms (116, 117), suggesting that BMAL1 function within the brain controls period length and activity rhythms, whereas its expression in muscle affects mitochondrial function and exercise tolerance (117). Curiously, mice with mutations in the *Period* genes display increased adiposity (118). Future application of neuron-specific targeting approaches will be important to identify selective effects of circadian gene disruption on the inter-relationship between sleep and energy homeostasis.

*Integration of circadian rhythms and glucose homeostasis in animal models.* Glucose homeostasis is under circadian control at the level of both peripheral tissues and the SCN. Ad libitum glucose levels peak and glucose tolerance is enhanced at the beginning of the active phase compared with the rest phase (119, 120). The morning peak of glucose is postulated to result from increased hepatic gluconeogenesis (120) as well as low insulin secretion (121), whereas the improved glucose tolerance (early in the active period) is likely due to elevated glucose uptake at skeletal muscle and adipose tissues (119, 122). Genetic disruption of components of the clock network has identified a role of core clock genes in glucose homeostasis. For example, multi-tissue *Clock* mutant mice develop age-dependent hyperglycemia and hypoinsulinemia (107, 123), in part due to impaired insulin secretion and defects in proliferation of pancreatic islets. *Cry*-knockout animals have increased hepatic gluconeogenesis, in part due to upregulation of cAMP signaling (124). A major advance toward understanding the tissue-specific roles of peripheral clocks in glucose homeostasis came with the development of conditional gene-targeting approaches. While deletion of *Bmal1* within liver causes hypoglycemia (114), deletion of *Bmal1* within pancreas causes hyperglycemia and hypoinsulinemia (123); thus at the physiological level, the actions of clock activator genes in the liver oppose those in the pancreas. Interestingly, both *Clock* mutant and *Bmal1*-knockout mice are hypersensitive to insulin, although the mechanism for this remains to be defined (115). While the above genetic models demonstrate a role for peripheral clocks in regulation of glucose metabolism, the SCN also plays a critical role in controlling the circadian variation of glucose and glucose tolerance (119), in part through rhythmic modulation of autonomic nervous system efferents (125). An important remaining question is whether peripheral clocks are necessary for the proper alignment of behavioral states (sleep/wakefulness, fasting/feeding) with peripheral metabolism in liver, muscle, adipose tissue, and pancreas.

*Integration of circadian rhythms and lipid homeostasis in animal models.* In addition to glucoregulatory pathways, the circadian system also regulates lipid homeostasis and adipose tissue metabolism. Both intestinal lipid transport and de novo lipid synthesis exhibit circadian variation (126), as do levels of adipose tissue hormones such as adiponectin (127) and leptin (128). Hypertriglyceridemia is evident in *Clock* mutant mice (107), likely due to both intestinal overabsorption (129) and hepatic overproduction (130). One node of coupling circadian and lipogenic pathways involves REV-ERB $\alpha$  (52). REV-ERB $\alpha$  controls SREBP signaling and bile acid homeostasis, both of which are essential for lipid metabolism (131). Furthermore, BMAL1 is necessary for adipogenesis, as embryonic fibroblasts from *Bmal1* knockout mice fail to differentiate into adipocytes (132). Clock genes may also indirectly regulate adipogenesis via PPARs. Finally, the SCN has also been shown to be critical for regulation of the diurnality of leptin release (133, 134). Further studies are necessary to assess the potential impact of clock genes on additional functions of the adipocytes, including thermogenesis and lipokine secretion.

*Reciprocal effects of nutrient signaling on circadian rhythms and sleep.* The relationship between circadian rhythms and metabolism is bidirectional; as noted above, a high-fat diet lengthens the intrinsic period length of locomotor activity, alters the circadian rhythms of feeding, reduces the amplitude, and shifts the phase of metabolic gene expression cycles in liver, fat, and hypothalamus (71). Similarly, genetically obese *ob/ob* and *db/db* mice (135, 136) have disrupted circadian rhythms of activity and sleep/wake patterns. In addition, glucocorticoid, a metabolic hormone involved in numerous biological processes such as gluconeogenesis, also entrains peripheral clocks (40) and increases expression of multiple clock genes, including *Per1* and *Per2* (137).

Restricted feeding studies have further suggested that nutrient conditions influence rhythmic locomotor activity and peripheral clock gene entrainment, although the role of clock genes per se in activity rhythms remains controversial. Whereas the period of locomotor activity programmed by the SCN remains constant even when food is restricted each day to the light period, food-restricted animals display an anticipatory increase in locomotor activity (138), temperature, and glucocorticoid secretion that persists even when the food is removed (139). Moreover, food availability can entrain rhythms in peripheral tissues such as liver and kidney, but not in the SCN (37, 38), suggesting the existence of a food-entrainable oscillator (FEO) (140). The anatomic location of the FEO has been a topic of intensive investigation, although efforts to understand the mechanism for this process have produced inconclusive results. While several studies have suggested that the DMH is necessary and sufficient to induce food-entrainable circadian rhythms (141, 142), other studies have questioned the role of the DMH as the FEO (143).

An important remaining question concerns the identity of the synchronizing signals that adjust circadian oscillations according to feeding time. Potential signals involved in resetting peripheral clocks are numerous, including glucose, lipids, sterols, peptidergic molecules, and catecholamines. Elucidating mechanisms involved in circadian entrainment of feeding may lead to improved interventions for clinical pathologies associated with shift work and jet lag.

### Concluding remarks

Advances in genetic studies of circadian rhythms have led to the recognition that the circadian system is tightly coupled with processes controlling both sleep and metabolism. These dynamic interactions ensure that energy metabolism is coordinated in a proper temporal pattern and that circadian control is also subject to modulation by the energy status of the organism. Disruption of either the circadian clock or metabolism can lead to derangement of the other, thus predisposing to metabolic disorders such as obesity and type 2 diabetes. Future research will continue to focus on expanding our understanding of how brain and peripheral clocks coordinately regulate metabolic processes at both the cell-autonomous and non-autonomous level, how nutrient flux translates information regarding environmental milieu to the clock, and the impact of circadian rhythms in human health and disease.

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