The Clockwork of Metabolism

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Abstract

The observation that cycles of sleep and wakefulness occur with a periodicity fixed in time to match the rotation of the Earth on its axis provided a key to unlock the first genetic code for a neurobehavioral pathway in flies and ultimately in mice. As a remarkable outcome of this discovery, we have gained an unprecedented view of the conserved genetic program that encodes a sense of time across all kingdoms of life. The tools are now in hand to begin to understand how important processes such as energy homeostasis and fuel utilization are coordinated to anticipate daily changes in environment caused by the rising and setting of the sun. A better understanding of the impact of circadian gene networks on nutrient balance at the molecular, cellular, and system levels promises to shed light on the emerging association between disorders of diabetes, obesity, sleep, and circadian timing.

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OPENING QUOTE

> We have unlocked time, as in the seventeenth century we unlocked space, and now have at our disposal what are, in effect, temporal microscopes and temporal telescopes of prodigious power . . . . In this way, stuck though we are in our own speed and time, we can, in imagination, enter all speeds, all time.—Oliver Sacks (127)

INTRODUCTION: THE TEMPORAL BIOLOGY OF METABOLISM

Although humans have been acutely aware of the cyclical nature of their external environment since ancient times, the idea of the existence of an internal timekeeping system was not considered until the early 1700s when French astronomer Jean Jacques d'Ortous de Marian observed that daily leaf movement of the *Mimosa* plant persisted for several days in constant darkness. Nearly a century later, Alphonse de Candolle demonstrated not only that endogenous rhythmicity was sustained in the absence of external environmental cues,

Circadian rhythm:
a biological rhythm that persists under constant conditions with a period length of ∼24 hours

Clock: a central mechanism controlling circadian rhythms

Zeitgeber: an entraining agent such as light or food; German for "time giver"

but also that in constant darkness, this rhythmicity advanced to an earlier start each day. However, despite these early observations, it was not until the mid-1900s that it became accepted that circadian rhythms were not merely passive reflections of the environmental light/dark cycle, but were rather dependent upon an underlying internal endogenous clock.

Circadian rhythms are such an innate part of our behavior that we rarely pause to speculate why they even exist. Many physiological processes, such as sleep-wake cycles, locomotor activity, body temperature, hormone secretion, and metabolism, are under the control of circadian clocks. The approximately 24-hour nature of the endogenous clock maintains a periodicity fixed in time to match the Earth's rotation around its axis, hence the term circadian (derived from the Latin phrase *circa diem*, or about a day). To remain in sync with their environment, circadian clocks are reset or entrained on a daily basis by zeitgebers, environmental cues such as light that provide information about the external time. A presumed advantage of the

circadian system is that it enables organisms to anticipate, rather than simply react to, daily changes in the external light/dark environment, and it also allows synchronization of behavioral and physiological processes to the environment in order to optimize energy utilization, reproduction, and survival. The ubiquity of the circadian clock in organisms as diverse as cyanobacteria, fungi, fruit flies, birds, and mammals implies that it confers an adaptive advantage to the organism. In plants, for example, transcripts encoding proteins involved in flowering, nitrogen fixation, and photosynthesis are synthesized and degraded according to a 24-hour cycle that matches the availability of sunlight and conserves protein biogenesis during darkness (62). Direct demonstration for a distinct survival and competitive advantage to having properly tuned circadian clocks and "circadian resonance" came from clever experiments performed in *Arabidopsis thaliana* (49). When plants harboring mutations that result in altered period lengths were placed in an environment with light/dark cycles that were shorter, equal to, or longer than the endogenous period length, those plants whose endogenous clock matched that of the external light/dark cycle had increased photosynthesis, growth, and survival (49).

In vertebrates, reproductive function has been shown to be under circadian control (24, 171). Furthermore, mice with genetically disrupted circadian rhythms have reduced gonadotropin production, irregular estrous cycles, and high pregnancy failure rates (106). A more general example suggesting a link between clock function and fitness in vertebrates is offered by the observation that chronic reversal of the light/dark cycle results in decreased survival time in cardiomyopathic hamsters (117). These observations suggest that the ability to sustain an internal timekeeping mechanism may have important implications for maintenance of fitness, health, and longevity of the organism.

LINKS BETWEEN CIRCADIAN RHYTHMS, SLEEP, AND HUMAN HEALTH

There is now reason to speculate that disruption of circadian rhythms of physiology and behavior may have broader implications for human health. A long history of clinical epidemiology in humans indicates that myocardial infarction, pulmonary edema, and hypertensive crises all peak at certain times during the day (98, 149). With advances in automation, communication, and travel, the pressure to extend wakefulness or repeatedly invert the normal sleep-wake cycle has become widespread. Interestingly, association studies have demonstrated an increased incidence of obesity and cardiovascular disease among shift workers, who are routinely subjected to extended and/or fragmented working hours (47, 77, 78). Furthermore, the average nighttime sleep duration has decreased dramatically in the past few decades, in parallel with a rampant increase in obesity (147). Indeed, a number of epidemiological investigations have reported that voluntary short sleep duration is associated with increased body mass index and elevated incidence of type 2 diabetes (65, 68, 102, 108, 155). Clinical studies have also identified changes in many aspects of energy metabolism following even just a few days of partial sleep restriction. For example, healthy subjects restricted to four hours of sleep for six consecutive nights exhibited impaired glucose tolerance and reduced insulin responsiveness following a glucose challenge, a pattern indicative of aging and early diabetes (169). Furthermore, self-reported short sleepers had significantly reduced circulating levels of the anorectic hormone leptin and increased levels of the orexigenic hormone ghrelin (155). These neuroendocrine changes could explain, in part, reports of increased appetite following sleep loss (148). Other changes related to metabolic function in the short sleepers included increased sympathoadrenal tone, hypercortisolemia, and altered thyroid hormone turnover (148). Although these

Period: duration of one complete cycle in a rhythmic variation

epidemiological and clinical studies have provided clues to possible links between sleep and metabolic regulatory processes, specific mechanisms underlying the effects of sleep loss on energy metabolism need to be further elucidated.

Circadian control of glucose metabolism was recognized from early studies demonstrating variation in glucose tolerance and insulin action across the day (61, 163). In humans, it has been repeatedly demonstrated that oral glucose tolerance is impaired in the afternoon and evening compared to the morning hours (10, 22, 29, 74, 123). A similar decrease in glucose tolerance toward the evening hours was observed in subjects exposed to a constant rate of intravenous glucose infusion for 24 hours (137, 162). The cyclical nature of glucose tolerance has been ascribed to a circadian effect on insulin sensitivity of the peripheral tissues (13, 85, 88, 166) as well as to a relative decrease in insulin secretion during the evening hours (19, 29, 88, 103). Although circadian fluctuations in plasma levels of corticosterone have also been hypothesized to account for the circadian rhythms of glucose metabolism, this hypothesis remains controversial because corticosterone, which is known to decrease insulin sensitivity, peaks at a time of day when insulin sensitivity is greatest (10, 48, 163). Another example of circadian regulation of glucose metabolism is demonstrated by the so-called dawn phenomenon, whereby glucose levels peak before the onset of the activity period (11, 20). Together, these data suggest that humans are most tolerant to glucose when the plasma glucose concentrations are highest prior to the onset of activity. Finally, circadian regulation of glucose metabolism is further indicated by recent studies showing that destruction of the hypothalamic suprachiasmatic nucleus (SCN), believed to contain the "master circadian pacemaker," abolishes diurnal variation in glucose metabolism in rats (85), and that degeneration of the autonomic tracts linking the SCN to liver similarly diminishes the 24-hour rhythms in glucose levels (27).

However, despite the well-documented diurnal variation in glucose tolerance and insulin sensitivity, the molecular mechanisms underlying these phenomena are not yet well understood.

Finally, evidence suggests that loss of circadian rhythmicity of glucose metabolism may contribute to the development of metabolic disorders, such as type 2 diabetes, in both rodents (115, 142, 165) and humans (146, 163). For example, daily cycles of insulin secretion and glucose tolerance are lost in patients with type 2 diabetes (18, 163), as are daily variations in plasma corticosterone levels and locomotor activity in streptozotocin-induced diabetic rats (115, 165). These findings indicate that a critical relationship exists between endogenous circadian rhythms and diabetes. The findings also suggest that time of day may be an important consideration for the diagnosis and treatment of metabolic disorders such as type 2 diabetes (134, 159). As discussed below, clues from studies on the molecular genetics of circadian clock genes may offer insight into the molecular mechanisms underlying the diurnal variation in glucose metabolism.

MOLECULAR CLOCK COMPONENTS

Amid much skepticism that single gene mutations could affect such complex behavioral processes as circadian rhythms, the first clock mutant, *period*, was identified in *Drosophila melanogaster* in 1971 (82). However, it was not until more than two decades later that the first mammalian circadian gene, *circadian locomotor output cycles kaput* (*Clock*), was identified in a large-scale chemical mutagenesis screen for circadian variants in mice (167). *Clock* is a semidominant mutation, and homozygous *Clock* mutant animals have an initial free-running period of approximately 27–28 hours and become arrhythmic in constant darkness. Positional cloning and genetic rescue experiments identified *Clock* as a member of the basic helix-loop-helix period-ARNT-single-minded (bHLH-PAS) transcription factor

family (80, 167). Since this initial discovery more than a decade ago, the identification of additional genes that are expressed with pronounced circadian rhythmicity has progressed rapidly and has revealed that circadian gene expression in mammals is controlled by autoregulatory transcription-translation feedback loops, similar to those found in other prokaryotes and eukaryotes (17).

CLOCK heterodimerizes with another bHLH-PAS family protein, BMAL1 (brain and muscle ARNT-like; also known as MOP3), and this heterodimer constitutes the positive limb of the circadian feedback loop mechanism (**Figure 1**). The CLOCK/BMAL1 complex activates transcription of target genes containing E-box *cis*-regulatory enhancer elements (5′-CACGTG-3′), including the *period* (*Per1*, *2*, and *3*) and *cryptochrome* (*Cry 1* and *2*) genes (26, 64, 79, 84, 180). The PER and CRY proteins comprise the negative limb of the feedback loop; upon translation, PER and CRY proteins multimerize and subsequently translocate to the nucleus and directly inhibit the transcriptional activity of the CLOCK/BMAL1 complex (64, 89, 113, 133, 138). PER and CRY are phosphorylated and degraded, in part through the action of the casein kinases I epsilon and delta (CKIε/δ) (6, 51, 89, 94), and as a result, the CLOCK/BMAL1 heterodimer is released from inhibition and is free to reinitiate transcription. In addition to the *Per* and *Cry* targets, CLOCK/BMAL also activates transcription of the orphan nuclear receptors *Rev-erbα* and *Rorα* (5, 118, 132, 158). REV-ERBα and retinoic acid–related orphan receptor RORα subsequently compete for binding to the retinoic acid–related orphan receptor response elements (ROREs) in order to repress or activate, respectively, transcription of *Bmal1* (5, 66, 118, 132). This entire autoregulatory cycle takes approximately 24 hours to complete before cycling anew.

Targeted gene knockout strategies have revealed functional roles for each of the core clock components in the generation of circadian rhythms. Mice lacking *Bmal1* exhibit a complete loss of circadian rhythmicity in constant darkness (25), and as described above, mice with a dominant-negative *Clock* mutation have a four-hour increase in period length and become arrhythmic in constant darkness (80, 167). However, a recent report has questioned the absolute requirement for CLOCK in the generation of circadian rhythms because of the finding that *Clock* knockout mice retain rhythmic activity (50). A possible explanation for the lack of an observable effect on circadian rhythms in these animals is that the *Clock* homolog neuronal PAS domain protein 2 (*Npas2*) could functionally compensate for the lack of *Clock* (50). Knockout studies targeting components in the negative limb of the circadian clock have revealed additional examples of functional redundancy within the clock machinery. Although mice lacking any one of the *Per* or *Cry* genes individually have subtle circadian phenotypes that alter period length by ~1 hour or less (with the exception of *Per2*, which shortens the period by 1.5 hours and leads to eventual arrhythmicity in constant darkness), the double mutants *Per1/Per2* and *Cry1/Cry2* experience a complete loss of circadian rhythmicity (12, 30, 164, 168, 180, 181). While our knowledge of the clock machinery has attained a level of detail perhaps exceeding that of any other neurobehavioral gene pathway, it is likely that additional genes and components of the core clock machinery have yet to be identified.

LOCALIZATION OF THE CIRCADIAN CLOCK

Studies of the molecular components of the clock have provided a powerful new framework to better understand the temporal control of physiology and behavior at the cell and whole animal levels. The concept that distinct circadian centers, or pacemakers, direct organismal timekeeping was validated by studies performed in the 1960s and 1970s that identified circadian pacemaker centers in insects (in the optic lobe), mollusks (in the eye), and birds (in the pineal gland) (56, 63,

109). In mammals, lesioning studies in rats revealed that rhythmic locomotor and feeding activity required the central circadian pacemaker in the SCN within the anterior ventral hypothalamus. Evidence for a definitive role for the SCN as a "master pacemaker" came from studies wherein the circadian locomotor activity rhythm of SCN-lesioned hamsters with a short period was restored by transplantation of the SCN from a wild-type animal (121). Interestingly, such transplantation studies also revealed that the restored rhythms of the host always matched the rhythms of the donor, implying that circadian period length is determined by the SCN (121). Furthermore, despite lack of neuronal connections between the grafted SCN and the host brain, transplantation of donor SCN tissue into hosts with lesioned SCN partially restored their circadian rhythms, suggesting that a diffusible secreted molecule, such as transforming growth factor-α or prokineticin-2, might be responsible for generation of circadian rhythms from the SCN (2, 34, 83, 143). However, while circadian locomotor activity is restored by SCN transplants, circadian endocrine rhythms of corticosteroid or melatonin secretion are not (104), suggesting that in addition to secreted factors, neural efferents must also be critical for generation of certain circadian rhythms.

Intriguingly, a major transformation in our understanding of circadian biology came from the discovery that circadian rhythms and the core clock machinery are also present in most, if not all, peripheral tissues, as well as in extra-SCN regions of the brain (**Figure 2**). Maintenance of sustained rhythms in cultured fibroblasts following a serum shock was the first demonstration that non-neuronal mammalian cells have the autonomous capacity for generating circadian rhythms (14). It was subsequently demonstrated that self-sustaining oscillations could be observed in explants in a variety of tissues including muscle and liver by using luciferase as a reporter of *Per1* or *Per2* expression (173, 174, 177, 178). The SCN, which is directly entrained by photic input from the retinohypothalamic tract, synchronizes the timing of the clocks in the peripheral tissues; destruction of the SCN in rats abolishes synchronization of peripheral oscillators (128). Furthermore, the phase of peripheral clocks is delayed approximately four hours compared to that of the SCN (14). Interestingly, the phase of the peripheral clocks can be uncoupled from that of the SCN in response to hormonal signals (such as glucocorticoids) and restricted feeding (15, 41, 151). Restricting the availability of food to a limited period during the light cycle rapidly entrains the peripheral tissues of mice; within two days of the start of a restricted feeding regimen, circadian rhythms in the periphery are essentially inverted while rhythms in the SCN remained unchanged (41, 151). Thus, feeding time, rather than light, appears to be the dominant zeitgeber for peripheral clocks.

Although the mammalian core circadian components are well defined, the molecular effectors acting downstream of the core circadian clock machinery that link the circadian regulation to metabolism and physiological processes are much less clear. One example of a well-studied *Clock-controlled gene* is the *D-element binding protein* (*Dbp*), encoding a helix-loop-helix winged transcription factor that regulates the transcription of genes containing an insulin-response element. Oscillations in the *Clock* gene in liver induce 100-fold changes in the expression of *Dbp*, which, in turn, regulates the rhythmic transcription of key genes involved in gluconeogenesis and lipogenesis (87).

The development of DNA microarray technology has greatly expanded our ability to examine the downstream effectors of the core clock machinery, particularly in peripheral tissues. Gene expression profiling has revealed that a surprisingly large number of transcripts (approximately 5%–10% of the transcriptome) display a 24-hour variation in mRNA expression levels within the SCN, liver, heart, vasculature, and fat (116, 119, 152, 161). Furthermore, very few of these

genes show coordinate circadian regulation between tissues, suggesting a high degree of tissue specificity in the output of the *Clock-controlled genes*. Profiling of the circadian proteome has further revealed that up to 20% of proteins are subject to circadian control in the liver (122). Surprisingly, however, almost half of these cycling proteins did not have correspondingly cycling transcripts, suggesting that circadian regulation also exists at a post-transcriptional level (122). Importantly, both the transcriptome and proteome studies have highlighted a key role for the circadian regulation of a number of genes and/or proteins involved in intermediary metabolic processes, including oxidative phosphorylation, carbohydrate metabolism and transport, lipid biogenesis, cholesterol biosynthesis, and proprotein processing (116, 119, 152, 161). These studies suggest that circadian regulation may provide a temporal mechanism to coordinate and/or separate a diverse range of interdependent chemical reactions in the cell.

COMMUNICATION BETWEEN SCN AND CNS CENTERS CONTROLLING ENERGY BALANCE AND METABOLISM

Map of Circadian Centers

There are several levels at which circadian and metabolic systems may affect metabolism within the whole animal. In taking a top-down approach, it is useful to consider first how circadian signaling centers within the brain are connected to regions involved in appetite control, energy expenditure, and metabolism (**Figure 3**). For example, neural tracing studies have revealed numerous projections from the SCN to hypothalamic cell clusters that express orexigenic and anorexigenic neuropeptides (154, 170). The largest output of SCN projections is directed toward the subparaventricular zone (SPZ) and the dorsomedial nucleus of the hypothalamus (DMH) (131). The role of each of these hypothalamic regions in

the regulation of circadian rhythms was determined by elegant studies using neurotrophic toxins (35, 95). Destruction of the ventral SPZ (vSPZ) reduced circadian rhythms of sleep-wakefulness and locomotor activity but had little effect on circadian regulation of body temperature (95). Conversely, degeneration of the dorsal SPZ (dSPZ) disrupted circadian regulation of body temperature with minimal effect on sleep-wakefulness and locomotor activity (95), thus demonstrating a dissociation of circadian regulation of sleep-wakefulness and body temperature (131). Electrode ablation of the DMH cell bodies, which receive inputs from both the SCN and the SPZ, resulted in severe impairment of circadian-regulated sleep-wakefulness, locomotor activity, corticosteroid secretion, and feeding (35). Furthermore, the DMH has many outputs to other regions of the brain, including the ventrolateral preoptic nucleus, the paraventricular nucleus, and the lateral hypothalamus, which regulate sleep, corticosteroid release, and wakefulness/feeding, respectively. Thus, the DMH constitutes a gateway between the master pacemaker neurons of the SCN and cell bodies located within brain centers important in energy homeostasis (**Figure 3**). Interestingly, the DMH has also been implicated in the ability of organisms to be entrained by restricted feeding; a subset of DMH neurons show robust *Per2* oscillations following restricted feeding, and ablation of the DMH eliminates the altered sleep-wake, activity, and feeding rhythms characteristic of food-restricted animals (64a, 105). However, controversy remains concerning the precise anatomic localization of the food-entrainable oscillator because Landry et al. (85a) have reported that DMH ablation fails to disrupt this phenomena.

Map of Energy Centers

While studies of SCN architecture have advanced our understanding of CNS timekeeping, a distinct line of investigation has focused on the localization of neuronal centers

SPZ: subparaventricular zone

DMH: dorsomedial hypothalamus

involved in energy balance and feeding behavior (71). Classical lesioning studies performed more than 50 years ago demonstrated that distinct regions of the hypothalamus control hunger and satiety. Destruction of the ventromedial hypothalamic (VMH), PVH, and DMH regions resulted in obesity (7, 23, 69, 70), whereas ablation of the lateral hypothalamus (LH) resulted in anorexia (7). Although these relatively nonselective approaches did not provide a molecular entrée into understanding the hypothalamic regulation of appetite and food intake, they did provide an anatomical framework for future studies examining the integration of hormonal and nutrient signals at the level of specific hypothalamic regions. The suggestion that humoral factors might be responsible for the control of appetite and energy expenditure was first made by Coleman and colleagues (37, 38) in the late 1960s and early 1970s, following parabiosis experiments between two genetic mouse models of obesity, the *obese* (*ob/ob*) and *diabetic* (*db/db*) mice, that suggested that the *ob/ob* gene encoded a secreted factor, whereas the *db/db* gene encoded its cognate receptor. Ultimately, a major breakthrough in our molecular understanding of hypothalamic regulation of energy balance came with the positional cloning of leptin, a secreted adipocyte-derived factor, as the product of the *ob/ob* gene (179). Subsequently, expression and positional cloning identified the protein product deficient in *db/db* mice as the leptin receptor (33, 36, 90, 156). Administration of leptin to *ob/ob* mice decreased food intake and body weight and corrected neuroendocrine abnormalities (28, 67, 117). Importantly, Ahima et al. (3) showed that low levels of leptin during fasting suppress reproductive function and energy expenditure. The fact that leptin is secreted from adipocytes in proportion to total body adipose mass (59, 96), that leptin is expressed in a circadian fashion in addition to fluctuating in response to fasting and feeding (4, 76, 91, 92, 135, 145), and that the leptin receptor is highly expressed in various regions within the hypothalamus, including

the arcuate nucleus (ARC), DMH, and VMH nuclei (54), suggests that humoral signals derived from peripheral tissues may communicate the nutritional status of the organism to the hypothalamic centers controlling hunger and satiety in a circadian-dependent manner.

Additional insight into the neural control of energy homeostasis came with the discovery of the melanocortin system as downstream of leptin (57, 72). Leptin, a satiety signal, stimulates pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART)-expressing neurons within the ARC to produce α-melanocyte-stimulating hormone (α-MSH), which subsequently activates the melanocortin receptor subtype 4 (MC4) and results in decreased food intake and increased energy expenditure (1, 39). Leptin also suppresses a distinct set of neuropeptide Y (NPY) and agouti-related protein (AgRP)-expressing ARC neurons that, when active, antagonize the effect of α-MSH on the MC4 receptor through release of AgRP (114, 120, 124) and inhibit the POMC/CART-expressing neurons through release of the small inhibitory amino acid neurotransmitter γ-aminobutyric acid (40). In the absence of leptin, such as during the fasted state, the orexigenic NPY/AgRP neuropeptides cause decreased energy expenditure and increased appetite (16, 52, 53, 99, 150). The integration of signaling by agonists (α-MSH) and antagonists (AgRP) of the melanocortin receptor is pivotal in the weight-regulating effects of leptin in the central nervous system.

Both POMC/CART and NPY/AgRP ARC neurons project to multiple nuclei involved in feeding behavior, some of which also receive input from the SCN and display pronounced circadian rhythms of gene expression (40, 52, 54, 55). These include neurons in the lateral hypothalamic area that produce the hunger-stimulating neuropeptides melanin-concentrating hormone (MCH) and orexins A and B (58, 60, 136). Targeted deletion studies of MCH resulted in hypophagic lean mice with a high metabolic rate and demonstrated that MCH acts downstream of leptin and the

melanocortin system (140). Orexins A and B are two neuropeptides generated from a single transcript that display a circadian rhythm of expression and are strongly induced by fasting (153, 172). Intracerebroventricular injection of orexin A stimulates food intake acutely in rats, in part through excitation of NPY in the ARC (130, 153); however, the long-term effects of orexins on energy balance are not yet fully established.

Genetic studies have also uncovered a role for the orexins in the regulation of sleep-wake rhythms. Mutations in the orexin B receptor were found to cause narcolepsy in two independent canine populations (93, 172), and deletion of the orexin gene results in narcolepsy in mice (31). Narcoleptic humans also have decreased orexin levels (111) and, interestingly, increased body mass index levels (110). Furthermore, the finding that orexin-producing neurons project to extensive regions within both the cortex and brainstem is consistent with a role for these neuropeptides in modulating arousal and autonomic function (45, 46). It is also important to note that additional neuromodulators involved in both feeding and alertness, including the histaminergic and serotinergic transmitters, may have combined effects on alertness, circadian rhythmicity, and metabolism (100, 101, 157). The complete identity of both chemical and anatomic pathways through which organisms balance the homeostatic needs of sleep and fuel metabolism remains an active area of investigation.

INTERCONNECTIONS BETWEEN CIRCADIAN GENE PATHWAYS AND METABOLISM

A unifying principle to have emerged from studies of circadian timekeeping and energy balance is that both of these dynamic processes exhibit a hierarchical organization in which the brain drives the function of peripheral tissues. Furthermore, as reviewed above, the circadian and energetic centers are intimately connected at both a neuroanatomical and neuroendocrine level. More recent studies suggest that such interconnections also extend to coregulation of metabolic and circadian transcription networks within individual peripheral tissues and cells. A major advance in our awareness of the temporal organization of metabolic processes stemmed from the landmark discovery by Schibler and colleagues (14) that peripheral tissues express self-sustained periodic oscillators. The following sections focus on recent evidence that suggests that a reciprocal relationship exists between the circadian and metabolic gene pathways.

Circadian Transcriptional Networks Promote Metabolic Homeostasis

Mounting evidence suggests that many essential metabolic pathways are subject to circadian control. For example, a vast number of nuclear receptor (NR) proteins exhibit circadian patterns of gene expression in a variety of metabolic tissues (175). NR proteins are transcription factors activated by the binding of endocrine hormones, such as steroid and thyroid hormones, vitamins, and dietary lipids, and these proteins regulate a diverse range of metabolic processes, including lipid and carbohydrate metabolism (32). Thus, it is possible that the circadian rhythmicity of NRs will contribute in part to the well-documented diurnal variations in lipid and glucose metabolism.

As described above, CLOCK/BMAL heterodimers positively regulate the transcription of the orphan nuclear receptor *Rev-erbα*, which subsequently inhibits transcription of *Bmal1* as part of a cell-autonomous feedback loop (66, 118). In addition to its regulation by the core clock complex, *Rev-erbα* is also regulated by a host of metabolic processes, including adipogenesis and carbohydrate metabolism, which in turn may affect the circadian clock through their actions on *Rev-erbα*. For example, *Rev-erbα* mRNA levels increase dramatically during adipocyte differentiation (31), and REV-ERBα is

phosphorylated and stabilized by glycogen synthase kinase 3 (176). Furthermore, *Reverbα* transcription is inhibited by retinoic acid (31), levels of which are increased in the metabolic syndrome (175), and the retinoic acid–related orphan receptor RORα has been shown to regulate lipogenesis and lipid storage in muscle in addition to its role as a positive transcriptional regulator of *Bmal1* (95).

The circadian rhythmicity of another NR family member, peroxisome proliferator-activated receptor α (PPARα), provides a further example of a reciprocal link between circadian and metabolic processes. As with RORα, the CLOCK/BMAL heterodimer activates transcription of PPARα, which subsequently binds to the peroxisome-proliferator response element and activates transcription of *Bmal1*. PPARα regulates the transcription of genes involved in lipid and glucose metabolism upon binding of endogenous free fatty acids to its receptor. These data are concordant with the finding that BMAL1-deficient embryonic fibroblasts fail to differentiate into adipocytes (141) and demonstrate that PPARα may also play a unique role at the intersection of circadian and metabolic pathways.

Emerging studies from experimental genetic models support a central role for clock genes in the regulation of energy balance and metabolism. Both *Clock* mutant and *Bmal1*$^{-/-}$ mice develop not only circadian defects, but also metabolic deficits in glucose and lipid homeostasis (125, 160). An analysis performed on C57BL/6J *Clock/Clock* mutant and coisogenic wild-type mice revealed that *Clock* mutant mice have an attenuated diurnal feeding pattern, are hyperphagic and obese, and develop metabolic abnormalities, including hyperleptinemia, hyperlipidemia, hepatic steatosis, hyperglycemia, and hypoinsulinemia. Furthermore, *Clock* mutant mice had reduced levels of the orexigenic neuropeptides orexin and ghrelin (160). On mixed genetic backgrounds, Rudic et al. (125) reported decreased gluconeogenesis in both *Clock* mutant and *Bmal1*$^{-/-}$ mice, in addition to suppres-

sion of the normal diurnal variation in glucose and triglycerides. Additional studies, recently reviewed by Kohsaka & Bass (81), have also pointed to a role for the clock genes in adipocyte hypertrophy and the response to diet-induced obesity in vivo, in addition to the importance of considering strain background. A fascinating question remains as to whether the metabolic phenotypes of the *Clock* and *Bmal1* mutant animals are dependent or independent on the circadian function of these conserved genes. A deeper understanding of the cell-autonomous function of each gene will lead to better insight into their phenotypes and open new windows on manipulations to enhance metabolic function under circumstances of circadian disruption. Finally, it is interesting to speculate that clock genes represent an example of convergent evolution because the pressure to preserve energy and to adhere to a light/dark cycle may have coexisted during the origins of life.

Nutrient and Metabolic Signaling in Circadian Rhythms and Sleep

Feeding and sleep/circadian rhythmicity. Although the aforementioned studies clearly demonstrate that many central metabolic pathways are subject to circadian control, several studies have revealed that the reciprocal relationship also holds true: i.e., alterations in metabolism disrupt sleep-wake patterns and/or circadian rhythmicity. For example, mice fed a high-fat diet have increased sleep time, particularly in the nonrapid eye movement (NREM) stage, but decreased sleep consolidation (75). On the other hand, food deprivation results in decreased sleep time (43, 107) and a more fragmented sleep pattern in rats (21). The refeeding period following food deprivation in these animals is accompanied by lengthened sleep time (139) and varies as a function of the nutritional content of the food (107). In addition to diet-induced alterations in sleep architecture, genetic mouse models of obesity have similarly demonstrated disrupted sleep-wake patterns. The

leptin-deficient *ob/ob* mouse exhibits hyperphagia, obesity, and stigmata of the metabolic syndrome, including hyperglycemia, insulin resistance, and dyslipidemia (73, 179). These mice have recently been shown to have increased NREM sleep time, decreased sleep consolidation, decreased locomotor activity, and a smaller compensatory rebound response to acute sleep deprivation (86). Similarly, rats harboring mutations in the leptin receptor display increased sleep time and decreased sleep consolidation (42, 102). Evidence has begun to emerge suggesting that metabolic disorders may also affect circadian rhythmicity. For example, the circadian expression of a number of genes is attenuated in the fat and liver of obese KK-A(y) mice, a polygenic model for noninsulin-dependent diabetes mellitus (8, 9).

Molecular sensors linking metabolism and circadian rhythmicity. A major question resulting from these studies concerns the nature of the molecular link between the regulation of metabolism and circadian rhythmicity, particularly in the peripheral tissues. Is there a molecular "sensor" common to the regulation of both of these processes? One possible explanation for the interdependence of metabolic and circadian processes stems from the finding that changes in the cellular redox status of cells, represented by the nicotinamide adenine dinucleotide cofactors NAD(H) and NADP(H), regulate the transcriptional activity of the bHLH proteins CLOCK and its homolog NPAS2. The reduced forms of these redox cofactors enhance DNA binding of the CLOCK/BMAL1 and NPAS2/BMAL1 heterodimers, whereas the oxidized forms inhibit binding (126). Thus, it is possible that direct modulation of the redox state in response to feeding, for example, may provide an additional level of regulation of the circadian clock and may serve as a molecular link between metabolic and circadian processes. However, how metabolic sensors affect circadian processes in vivo remains an area of active investigation.

Hormones and sleep. Within the whole animal, numerous studies have revealed that various hormones and neuromodulators have overlapping roles in regulating metabolism and sleep, and by extension, may be involved in synchronizing these processes. For example, acute administration of leptin, an adipocyte-derived circulating hormone that acts at specific receptors in the hypothalamus to suppress appetite and increase metabolism, decreases REM and increases NREM sleep time in rats (144). Furthermore, leptin-deficient mice have significantly disrupted sleep architecture with impaired sleep consolidation and diurnal rhythmicity, as described above (86). Increased levels of other anorectic hormones, including gastrointestinal tract–derived cholecystokinin and pancreatic β cell–derived insulin also increase sleep time in rodents (44, 97). Ghrelin, an orexigenic stomach-derived hormone, has been shown to increase NREM sleep in both rodents and humans (112, 171), whereas orexin/hypocretin neuropeptides, produced by a small subset of neurons within the lateral, posterior, and perifornical hypothalamus in response to fasting, stimulate food intake, locomotor activity, and wakefulness (46, 129). Interestingly, the receptor for orexin/hypocretin has been shown to be the causative genetic defect in the most common form of canine narcolepsy (93). The regulation of both metabolism and wakefulness by these neuroendocrine factors suggests that coordination of periods of fasting with sleep and feeding with wakefulness is important. These observations also have potential implications for the pharmacological development of therapies for both sleep and metabolic disease. Lack of sleep or altered metabolism may disrupt these homeostatic conditions, resulting in activation of metabolic pathways that lead to increased food intake or altered sleep architecture, respectively.

CONCLUSIONS/PERSPECTIVES

Remarkable advances in mammalian experimental genetics heralded by the discoveries

of leptin in 1994 and the *Clock* gene in 1997 have transformed our understanding of both metabolism and circadian rhythmicity. A major theme to have emerged has been the finding that perturbation of either CNS pathways or those within peripheral metabolic tissues contribute to diabetes and obesity and are important in basal homeostasis. Compelling new evidence reviewed above has uncovered an interconnection between temporal regulation and metabolic processes that may have implications for understanding human diseases such as sleep disorders and diabetes. With the molecular road map now in hand to unlock the key to internal timekeeping, new opportunities are available to integrate studies of behavior and metabolism. One conclusion that can already be drawn is that metabolic processes are highly dynamic and subject to strong variation across the 24-hour light/dark cycle at both the molecular and physiologic levels. One implication is that introducing temporal analyses in studies of metabolism may lead to the discovery of previously unrecognized phenotypes. At the cellular level, the challenge will be to define the impact of the clock gene network on specific metabolic processes. At the organismal level, the integration of circadian and metabolic analyses may lead us closer to a unified understanding of how internal systems have evolved to optimize survival across the daily light/dark changes in environment.

DISCLOSURE STATEMENT

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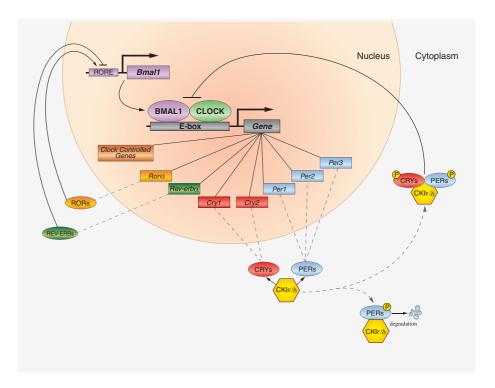
Figure 1

Central mechanism of the clock in all cells. The mammalian circadian clock consists of a network of transcription-translation feedback loops. The transcription factors circadian locomotor output cycles kaput (CLOCK) and brain and muscle ARNT-like (BMAL)1 heterodimerize and activate transcription of downstream targets, including the *period*, *cryptochrome*, *Ror*, and *Rev-Erb* genes, which contain E-box enhancer elements within their promoters. Upon translation, the period (PER) and cryptochrome (CRY) proteins multimerize and inhibit the action of the CLOCK/BMAL1 complex. Phosphorylation of PERs and CRYs by casein kinases I epsilon and delta (CKIε/δ), and the subsequent degradation of the PERs, is an important modulator of circadian rhythmicity. The retinoic acid–related orphan receptors (RORs) and REV-ERBs constitute another regulatory feedback loop through regulation of *Bmal1* transcription.
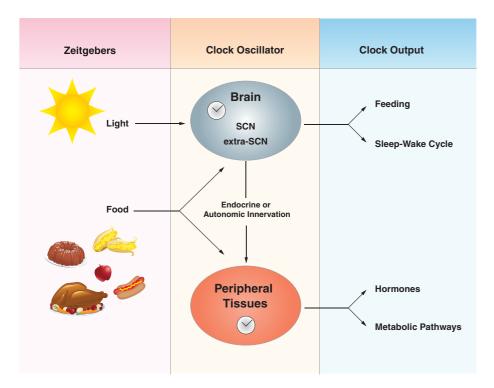
Figure 2

Clocks coordinate feeding and metabolism with environmental cues. Although the mammalian master pacemaker is located in the suprachiasmatic nucleus (SCN), the core clock machinery has been identified in most peripheral tissues, as well as in extra-SCN regions of the brain. These oscillators are entrainable, responding to extrinsic stimuli such as light and food, and the master pacemaker coordinates peripheral clocks through both endocrine signals and autonomic innervation. The clock output includes behavioral and metabolic responses, such as feeding, sleep-wakefulness, hormone secretion, and metabolic homeostasis. Not drawn are extensive reciprocal loops that connect clock output in both brain and peripheral tissues with the clock oscillators.
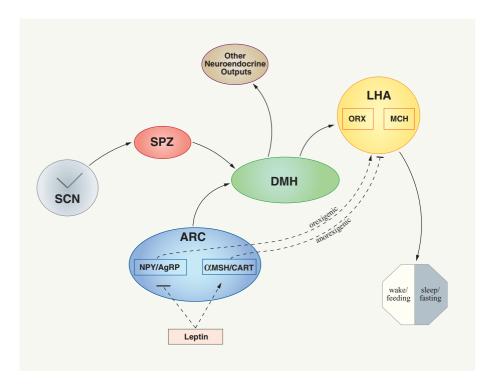
Figure 3

Neuroanatomic and neuroendocrine connections within the hypothalamus. The largest output of neural projections from the suprachiasmatic nucleus (SCN) extends toward the subparaventricular zone (SPZ) and continues from the SPZ to the dorsomedial hypothalamus (DMH). The DMH has many outputs to other regions of the brain, including the lateral hypothalamus (LHA), which controls circadian regulation of coordination of the alternans of sleep/wakefulness and fasting/feeding. The LHA also receives neuroendocrine input from the arcuate nucleus (ARC). Leptin activates neuronal cells within the ARC that express the anorexigenic neuropeptides α-MSH/CART, which in turn results in inhibition of production of orexigenic peptides orexin (ORX) and melanin concentrating hormone (MCH) in the LHA. In the absence of leptin, orexigenic neurons in the ARC produce neuropeptide Y (NPY)/agouti-related protein (AgRP) and stimulate hunger and decreased energy expenditure via signaling to the LHA.

Contents

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Errata

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