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Nutrient Sensing and the Circadian Clock

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Abstract

The circadian system synchronizes behavioral and physiologic processes with daily changes in the external light-dark cycle, optimizing energetic cycles with the rising and setting of the sun. Molecular clocks are organized hierarchically, with neural clocks orchestrating the daily switch between periods of feeding and fasting, and peripheral clocks generating 24hr oscillations of energy storage and utilization. Recent studies indicate that clocks respond to nutrient signals, and that high-fat diet influences the period of locomotor activity under free-running conditions, a core property of the clock. A major goal is to identify the molecular basis for the reciprocal relationship between metabolic and circadian pathways. Here, we highlight the role of peptidergic hormones and macromolecules as nutrient signals integrating circadian and metabolic systems.

Circadian Regulation of Metabolic Function

Circadian rhythms (derived from the Latin “*circa diem*”, which means “about a day”) were first discovered in plants nearly three centuries ago, and have since been observed in nearly all kingdoms of life [1, 2]. The core circadian clock is critical not only in the synchronization of behavioral and physiological processes with the external light-dark cycle, but also in the temporal partitioning of incompatible biochemical and energetic processes, in order to prevent futile energetic cycles such as the separation of oxygenic photosynthesis and nitrogen fixation in plants, or glycolytic and oxidative pathways in vertebrates. Circadian rhythms are generated by a transcription-translation autoregulatory feedback loop which cycles with a periodicity of ~24 hours (reviewed in [3–5]). The positive limb of this loop is driven by the transcriptional activators CLOCK and BMAL1, which activate transcription of the *Period (Per)* and *Cryptochrome (Cry)* genes (figure 1), both of which drive the negative limb. Upon reaching a critical threshold concentration, PER and CRY translocate to the nucleus where they inhibit the activity of the CLOCK:BMAL1 heterodimer, thus leading to a decrease in *Per* and *Cry* expression. Furthermore, AMPK and Casein Kinase I α and δ (CKI α /CKI δ) trigger the phosphorylation and ubiquitin-mediated degradation of PER and CRY in the cytoplasm, thus providing an additional layer of regulation of the core clock machinery [6, 7]. The nuclear hormone receptors (NHRs) REV-ERB α and RAR-related orphan receptor alpha (ROR α), both transcriptional targets of the

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CLOCK/BMAL1 complex, are also involved in the regulation of clock genes and comprise a short negative feedback loop that modulates *Bmal1* transcription; REV-ERB α represses, while ROR α activates, *Bmal1* transcription [8, 9].

The core molecular clock as described above is found in neurons of the hypothalamic suprachiasmatic nucleus (SCN) and is essential for entrainment of locomotor activity and the sleep-wake cycle to light. However, a surprising discovery has been that the entire core clock mechanism is also expressed in extra-SCN regions of the brain and in nearly all peripheral tissues [10, 11]. The presence of clocks in metabolic tissues such as liver, adipose, pancreas, and muscle suggests a critical role of circadian oscillations in metabolic physiology. Indeed, mice with both global and tissue-specific loss-of-function mutations in core clock genes display increased susceptibility to metabolic diseases. For example, *Clock* ^{$\Delta 19/\Delta 19$} mutant mice, which express a dominant negative mutant form of the CLOCK protein, display diet-induced obesity, hyperlipidemia, hepatic steatosis, and diabetes characterized by hypoinsulinemic hyperglycemia [12–14], and global *Bmal1*^{−/−} mutant mice display impaired glucose tolerance, increased insulin sensitivity, and age-related myopathy and arthropathy [13–17]. The use of tissue-specific circadian mutant mice has further elucidated the physiologic function of molecular clocks. For example, pancreatic beta cell-specific deletion of *Bmal1* results in impaired insulin secretion, reduced islet size, and impaired glucose tolerance [13]. Circadian timing also impacts organismal homeostasis through non-cell-autonomous mechanisms, and recent evidence in mice has revealed that simply restricting high-fat feeding to the normal rest period results in exaggerated obesity [18]. Thus, both genetic and environmental factors underlie the linkage between circadian and metabolic homeostasis.

However, just as disruption of the circadian network influences metabolism, it has also been shown that the reciprocal relationship exists, as altered feeding behavior and metabolism affect the clock [19, 20]. For example, mice fed a high-fat diet were found to have alterations in period length and in the expression and cycling of canonical clock genes, of clock-target genes involved in metabolic homeostasis, and of NHRs that regulate the clock itself [19]. Together, these studies reveal a reciprocal relationship between circadian and metabolic regulation that may hold important clues to the development of metabolic disease.

Recent focus has turned towards identifying the key factors or metabolites that might connect circadian transcriptional networks with nutrient sensing pathways. In this regard, the observation that clocks in metabolic peripheral tissues such as liver and adipose can be entrained by food [21, 22] raises several important questions: 1) What are the metabolic ‘sensors’ of feeding and fasting cycles in peripheral cells? 2) How are peripheral clocks entrained by nutrient flux (e.g., lipid vs carbohydrate)? 3) How does the molecular clock influence nutrient sensing at the level of individual tissues and cells?

Interplay between circadian clocks, NAD⁺ biosynthesis, and sirtuins

Several recent studies have demonstrated that the circadian clock regulates the synthesis of the essential metabolic cofactor nicotinamide adenine dinucleotide (NAD⁺). Because of its central role in numerous biochemical redox reactions, NAD⁺ is an attractive candidate as an integrator of circadian rhythms and nutrient sensing pathways. Indeed, CLOCK:BMAL1 directly regulates the transcript encoding the rate-limiting enzyme in the NAD⁺ salvage pathway, nicotinamide phosphoribosyltransferase (NAMPT), and NAD⁺ levels likewise display rhythmicity, at least in the liver and in embryonic fibroblasts [23, 24] (Figure 1). Importantly, abrogation of the clock activator arm (CLOCK/BMAL1) leads to reduced NAD⁺ levels, whereas ablation of clock repressors CRY1/2 leads to elevated NAD⁺, indicating that the counter-balance between expression of clock activators and repressors

(i.e., a functional molecular clock transcriptional network) controls hepatic NAD^+ turnover. Moreover, NAD^+ oscillations persist in animals maintained in constant darkness, consistent with dependency on the core molecular clock [23, 25].

In addition to its role in biochemical redox reactions, NAD^+ is an important cofactor for the Class III histone and protein deacetylase SIRT1, a member of the sirtuin family of NAD^+ -dependent deacetylases that regulates a range of metabolic processes, including gluconeogenesis, insulin sensitivity, and life span [26–28]. Many of the transcription factors regulated by SIRT1 are involved in the cellular response to stress and nutrient flux, such as Peroxisome Proliferator-activated Receptor Gamma Coactivator 1-alpha (PGC-1 α), Forkhead Box Protein O1 (FOXO1), Transducer of Regulated CREB Protein 2 (TORC2), Sterol Regulatory Element-Binding Protein 1c (SREBP-1c), and Signal Transducer and Activator of Transcription 3 (STAT3) [26–29]. Given that the activity of SIRT1 depends on levels of NAD^+ , clock-driven oscillations of NAD^+ likely contribute to daily rhythms in the multitude of metabolic pathways regulated by SIRT1. Intriguingly, it has been reported that in addition to being regulated by the clock, SIRT1 also regulates clock function itself (28–30) through deacetylation of both BMAL1 and PER2, leading to altered CLOCK/BMAL1 transcriptional activity [30–32] (figure 1). While the direction of effect of SIRT1 on clock activity appears to be complicated, as reports have demonstrated both activation and repression of CLOCK/BMAL1 [30–32] (it is clear that SIRT1 plays an important role in clock function. It is thus possible that circadian-driven oscillation of NAD^+ biosynthesis may in turn modulate SIRT1 and CLOCK/BMAL1 activity, thus “priming” the organism to anticipate the daily transitions between nutrient alternans, corresponding with the fasting/feeding and sleep/wake cycle. Consistent with this idea, SIRT1 has been implicated in the metabolic switch between periods of feeding and fasting, as SIRT1 activity increases upon fasting and in response to caloric restriction [33–35]. For example, during fasting, increased SIRT1 activity activates PGC1 α , allowing nutrient-deprived cells to transition from glycolytic ATP production to mitochondrial oxidative ATP synthesis [34]. Whether this increase in SIRT1 activity during nutrient deprivation is dependent upon cyclic NAD^+ metabolism, and the extent to which the NAD^+ /SIRT1 pathway acts as a switch coupling metabolic and circadian oscillators, remain questions for further investigation.

In addition to SIRT1, recent evidence suggests a role for other NAD^+ -dependent enzymes in metabolic regulation, each of which may also be influenced by clock-control of NAD^+ turnover. For example, the sirtuin orthologs SIRT2 to 7, which are distributed across a number of subcellular compartments (i.e., SIRT2 is cytoplasmic, SIRT3–5 are mitochondrial, SIRT6 is nuclear, and SIRT7 is nucleolar), act on a wide range of proteins including histones, transcription factors, and enzymes involved in intermediary metabolism. Interestingly, activity of the mitochondrial sirtuins SIRT3 to 5 is intimately involved in the adaptive response to fasting [36]. For example, SIRT3 deacetylates and activates the fatty acid oxidation enzyme long-chain acyl coenzyme A dehydrogenase (LCAD) in mouse liver in response to a 24 hr fast, thereby facilitating fuel for β -oxidation. Consistently, *Sirt3*^{−/−} mice display defects in fasting fatty acid oxidation [37]. Similar studies revealed that SIRT3 also deacetylates and activates enzymes involved in other mitochondrial pathways including ketogenesis, urea cycle, electron transport, acetate metabolism, and production of reactive oxygen species [38–42]. While SIRT4 has not been shown to possess deacetylase activity, it has instead been shown to catalyze the NAD^+ -dependent ADP-ribosylation of glutamate dehydrogenase 1 (GLUD1), an enzyme involved in ammonia detoxification and the citric acid cycle [43]. SIRT5 also plays an important role in urea cycle regulation via deacetylation of carbamoyl phosphate synthetase (CPS1) [44]. Thus, the NAD^+ -dependent sirtuin superfamily participates in both protein deacetylation and ADP-ribosylation, establishing a rapid means of upregulating mitochondrial energy production during nutrient deprivation. The potential control of SIRT3–5 activity through clock-mediated NAD^+ biosynthesis

suggests a possible mechanism by which circadian oscillations of feeding and fasting metabolic pathways are controlled.

Finally, recent studies have also implicated the NAD⁺-dependent ADP-ribosyltransferase PARP-1 as a mediator of the circadian clock. When activated by NAD⁺, liver PARP-1 binds to and ADP-ribosylates CLOCK, thus altering the interaction of CLOCK/BMAL1 with DNA and the clock repressor proteins PER and CRY [45] (figure 1). While still at an early stage of investigation, the possibility that clock control of NAD⁺ biosynthesis may mediate the function of sirtuins and of PARP not only within nuclei, but also within other subcellular compartments, remains an intriguing question. Together, these studies raise the possibility that circadian control of NAD⁺ metabolism couples internal energetic cycles with oscillation in the external nutrient environment.

A role for cellular redox and ROS in regulating circadian clocks

Whereas only recently has the circadian clock been tied to cycles of NAD⁺ metabolism, a role for cellular redox flux in regulating circadian rhythms was initially proposed by McKnight and coworkers in 2001, who demonstrated that the oxidation state of NAD(P) cofactors influences the binding of BMAL1 complexes to DNA [46]. Increased levels of oxidized NAD⁺ and NADP⁺ lead to decreased binding of CLOCK/BMAL1 and the Neuronal PAS Domain-containing Protein 2 (NPAS2) /BMAL1 to DNA, suggesting that the redox state *per se* may entrain molecular clock activity, and in turn couple circadian and metabolic cycles.

Two recent studies have further demonstrated that the redox state of peroxiredoxin proteins exhibit properties of a self-sustained circadian oscillator, controlling circadian rhythms of metabolic proteins even in the absence of ongoing gene transcription [47, 48]. Circadian rhythms of metabolic enzyme activities in anucleate mature human red blood cells have been observed for decades [49–51]. However, only recently has a potential mechanism for these rhythms been uncovered. O'Neill *et al.* demonstrated that the redox state of peroxiredoxin antioxidant proteins oscillates with a periodicity of ~24 hours. Oscillating peroxiredoxin redox state affects its antioxidant activity, generating self-sustained rhythms of cellular redox status (i.e., NADH/NADPH levels), which may in turn generate rhythms of metabolic enzyme activity [47]. Similar to clock-dependent circadian rhythms, these oscillations are temperature-entrainable and temperature-compensated. Independent studies in the single-celled alga *Ostreococcus tauri* identified ~24h rhythms of peroxiredoxin oxidation, which were sustained in the absence of functional molecular clock components [48]. These studies indicate that certain metabolic oscillations exhibit circadian properties independent of active gene transcription rhythms, and raise the possibility that other nutrients may act independently of transcriptional control to generate rhythms of metabolic pathways.

Crosstalk between circadian clocks and nuclear hormone receptors

REV-ERBs and RORs

Emerging evidence has also recently indicated that NHRs and their cognate ligands may also act as 'nutrient sensors', coupling circadian and metabolic pathways. NHRs represent a large family of homologous transcription factors that contain both DNA and ligand binding domains that bind a wide range of metabolic intermediates, including the classical endocrine hormones (e.g. GR, TR, ER), lipid- and steroid-derived molecules (e.g. PPARs, LXR, RORs), xenobiotics (e.g. PXR), and other metabolites (REV-ERBs, RARs) [52]. Also, many NHRs are classified as orphan receptors since their endogenous ligands have not been identified (e.g. ERRα). Of note, in addition to direct NHR transcriptional regulation of

Bmal1 via REV-ERB and ROR [8, 9, 52], (more than half of the ~50 known NHRs display circadian oscillations in metabolic tissues such as liver, adipose, and skeletal muscle [8, 53–56], demonstrating a complex feedback loop, whereby the clock both regulates and is regulated by NHRs.

Indeed, mice lacking REV-ERB α display a shortened circadian period in constant darkness [9], as well as several metabolic abnormalities including altered lipid and bile metabolism [57, 58]. These observations are consistent with the recent discovery of coordinated binding of REV-ERB α to lipogenic targets in the hepatic cistrome [59]. Likewise, ROR α -deficient (*staggerer*) mice also display altered circadian rhythms and are predisposed to several aging-related phenotypes, including atherosclerosis [52, 60–62]. Therefore, NHRs directly integrate nutrient signals with transcriptional regulation of the clock [63].

Interestingly, the metabolic transcriptional regulator PGC1 α acts as a coactivator for ROR α and β at the *Bmal1* promoter [64]. Consistently, mice lacking PGC1 α display disrupted clock gene oscillations, abnormal locomotor activity, and slight changes in free-running period length [64, 65], in addition to defects in mitochondrial oxidative metabolic pathways such as respiration and fatty acid oxidation [66–68]. PGC1 α also acts as a coactivator for the metabolic orphan nuclear hormone receptor Estrogen Related Receptor α (ERR α), which has recently been shown to display circadian rhythms of transcriptional activity and is directly regulated by the molecular clock [69–72]. Finally, activity of PGC1 α is dependent upon NAD⁺-dependent deacetylation by SIRT1, so it is tempting to speculate that clock regulation of NAD⁺ may in turn drive an additional metabolic feedback loop involving PGC1 α [29, 64]. Several studies implicate ROR α as a lipid sensor, and x-ray crystallography evidence indicates that cholesterol and oxysterol function as ROR α ligands [73, 74]. ROR α activates lipogenic pathways, including expression of the transcription factor SREBP1c [75]. Interestingly, REV-ERB α controls the circadian expression of Insulin-induced Gene 2 (Insig2), a negative regulator of SREBP1c activity [57]. Thus, sterols may also play an important role in circadian clock oscillations, and in turn, in the temporal control of lipogenesis.

Finally, heme is an additional metabolite that may act as a metabolic signal coupling metabolic and circadian oscillations. Heme, a cofactor for oxidative reactions including mitochondrial oxidative phosphorylation, is present in a complex with REV-ERB α and promotes its activity as a transcriptional repressor [55, 76, 77]. Thus, heme may represent an additional node linking environmental nutrient flux with circadian oscillation [55, 78, 79].

Glucocorticoid-regulated NHRs

Glucocorticoids (GC) and the glucocorticoid receptor (GR) in peripheral tissues have also emerged as an important link between circadian clocks and feeding/fasting cycles [80]. GCs are steroid hormones produced in the adrenal cortex that participate in adaptive pathways during fasting in liver, adipose, and skeletal muscle. GCs exhibit well-characterized circadian oscillations, arising through relays from the SCN to the hypothalamic-pituitary-adrenal (HPA) axis (figure 2). Light entrains the GC rhythm, generating a zenith in the early morning in humans [81, 82]. While the detailed mechanisms have not yet been fully defined, several studies have suggested that GCs in turn affect clock activity in peripheral tissues and may act as important mediators between central and peripheral clocks [56]. Pharmacological activation of the GR by dexamethasone resets the clock in several peripheral tissues, including liver, kidney, and heart, and GR has been shown to regulate *Rev-erba* and *Per1* expression [83–85] (figure 2). GR may also regulate the clock through direct binding to PER2 [86]. Furthermore, in liver, GR has been proposed to be a key physiological entrainment signal of clock oscillations, leading to coupling of the food- and SCN-derived resetting cues [83, 87]. In fact, it has been proposed that SCN-controlled GC release can

oppose food entrainment of peripheral clocks, and liver-specific GR knockout mice display accelerated phase shifting in response to restricted daytime feeding [87]. Since GC signaling is not present within the SCN [83], this pathway may be essential for altering circadian clock oscillations in peripheral metabolic tissues in response to stress and changes in nutrient availability.

Other circadian metabolite-regulated NHRs

While many additional NHRs are rhythmically expressed, less is known about the metabolites that regulate these factors and whether they might affect the circadian clock. For example, retinoic acid was shown to shift *Per2* rhythmicity in muscle cells through the retinoic acid-responsive NHRs RAR and RXR [54, 88]. Members of the PPAR family of NHRs also directly regulate clock gene expression. PPAR α is a positive regulator of both *Bmal1* and *Rev-erba* in liver [54, 63, 86]. Likewise, synthesis of several PPAR proteins, including PPAR α γ δ are regulated by the circadian clock [63]. Ligands for PPARs include fatty acids and eicosanoids, including the diurnally-regulated gut metabolite oleylethanolamide (OEA). OEA is synthesized in the small intestine during the rest period and suppresses food intake in a PPAR α -dependent manner [89, 90]. Thus, OEA acts as another nutrient signal that may feedback to the clock within either local tissues or as a circulating signal to regulate circadian behaviors. In addition, PPAR γ regulates *Bmal1* expression in blood vessels and helps maintain daily rhythms of blood pressure and heart rate [91]. PPAR γ is regulated by the prostaglandins, and it is thus possible that oscillations of these molecules are essential for the maintenance of circadian rhythms in the vasculature. Metabolite profiling studies will be necessary to determine the importance of other lipid-derived PPAR ligands as effectors of the molecular clock.

Circadian regulation of metabolic peptide hormones

In addition to NHRs, several metabolic peptide hormones, such as leptin and ghrelin, display circadian oscillations that may act to coordinate nutrient signals from peripheral tissues with central behavioral outputs (e.g. feeding, physical activity) to maintain whole body energy homeostasis. Several studies have implicated the rhythmic release of adipocyte-derived hormone leptin and stomach-derived hormone ghrelin as important for relaying food cues to the brain to establish food anticipatory behaviors [92–97]. For example, humans display increased levels of leptin at night, contributing to nocturnal appetite suppression by hypothalamic neurons [98]. In contrast, ghrelin levels increase before meal times and have been suggested to play a role in food anticipatory behavior [99]. Although the mechanisms controlling the rhythmic release of leptin and ghrelin from peripheral tissues remain unclear, it is known that their effects can modulate the SCN-derived clock [92, 96]. As a potential inverse to the GC/GR pathway, these hormones may play a key role in providing information from peripheral food-responsive clocks to the central pacemaker (SCN).

Concluding remarks

Recent publications have shed light on the molecular pathways connecting circadian rhythms and metabolism. One of the most intriguing aspects of this connection is the reciprocal nature of the crosstalk between nutrient sensing pathways and the clock. Coupling of circadian and metabolic oscillators also raises intriguing evolutionary questions. That certain biochemical oscillations exist in cells in the absence of transcription (e.g. peroxiredoxin oxidation in human red blood cells and algae), and that circadian phosphorylation cycles of cyanobacteria can be reproduced *in vitro* [47, 48, 100, 101], support the hypothesis that metabolic oscillators represent the most ancient biological clock [102]. From this vantage point, the emergence of clocks encoded by an autoregulatory transcription feedback loop in plants, fungi and metazoa, may represent a more recent

adaptation in the evolution of circadian systems. However, it is important to note that even in cyanobacteria, most biochemical oscillators are coupled to transcriptional oscillators —so the question is a bit of a “chicken or the egg” puzzle [1]. Indeed, the diverse pathologies associated with circadian disruption in mammalian clock mutants highlights the interdependence of metabolic and circadian systems and provides new avenues to consider the impact of sleep and circadian timing on disorders including obesity, cardiovascular disease and diabetes mellitus [12].

In summary, two central questions remain in understanding the mechanism through which molecular clocks contribute to metabolic homeostasis (1) the identity of metabolic ‘sensors’ that coordinate circadian cycles within and between peripheral tissues across the feeding/fasting cycle, and (2) the mechanism through which cell autonomous and non-autonomous signals are integrated within peripheral tissues to produce coherent oscillation in physiologic systems. One approach has been to examine classical neuroendocrine factors on a candidate basis, while unbiased metabolomics surveys have also been deployed to identify metabolic-circadian coupling mechanisms [103]. One short-term benefit to emerge from metabolomics profiling may be the development of surrogate biomarkers for circadian time and in so doing, advance our ability to tell time in experimental and clinical settings. As we further explore the role of peripheral clocks in metabolic homeostasis, it will be important to dissect the patterns of oscillations of not only gene transcripts, but also metabolites and hormones. Circadian clocks represent an ensemble of oscillators both within the brain and in peripheral tissues, and it is the phasic synchrony of these multiple tissue clocks that gives rise to overt rhythms of behavior and physiology necessary for metabolic health.

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Figure 1. Circadian control of NAD⁺ and NAD⁺-dependent enzymes

The core circadian clock is composed of a feedback loop involving a series of activators (CLOCK/BMAL1) and repressors (CRYs/PERs) that generate ~24h rhythms of gene transcription. Targets of the circadian clock include genes involved in the production and utilization of nutrient metabolites, including the NAD⁺ biosynthetic enzyme NAMPT. NAD⁺ is an important cofactor for the metabolic regulators, SIRT1, SIRT3–5 and PARP1, which may mediate rhythms of oxidative metabolism.

Figure 2. Coordination of central and peripheral clocks by glucocorticoids

Light-derived cues stimulate hormonal signaling from hypothalamus/SCN to the adrenal cortex (via the autonomic nervous system (ANS) or via the pituitary gland), producing daily rhythms of glucocorticoid release. Glucocorticoids activate the glucocorticoid receptor in peripheral tissues, which 'resets' the molecular clocks and metabolic pathways.