Circadian regulation of metabolism

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Abstract

In association with sleep–wake and fasting–feeding cycles, organisms experience dramatic oscillations in energetic demands and nutrient supply. It is therefore not surprising that various metabolic parameters, ranging from the activity status of molecular energy sensors to circulating nutrient levels, oscillate in time-of-day-dependent manners. It has become increasingly clear that rhythms in metabolic processes are not simply in response to daily environmental/behavioral influences, but are driven in part by cell autonomous circadian clocks. By synchronizing the cell with its environment, clocks modulate a host of metabolic processes in a temporally appropriate manner. The purpose of this article is to review current understanding of the interplay between circadian clocks and metabolism, in addition to the pathophysiologic consequences of disruption of this molecular mechanism, in terms of cardiometabolic disease development.

Key Words
- circadian rhythms
- glucose metabolism
- lipid
- metabolism

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Introduction

Both energetic supply and demand fluctuate as a function of time-of-day, concomitant with daily sleep–wake and fasting–feeding cycles. It is therefore not surprising that marked diurnal variations in metabolism are observed at multiple levels. Metabolic parameters ranging from circulating nutrient levels and substrate utilization to energy expenditure and thermogenesis have been reported to fluctuate over the course of the day. For example, body temperature and energy expenditure are both elevated in the laboratory rodent during the awake period, in association with behaviors known to elicit a positive thermic effect (e.g. increased physical activity and food intake; Alberts *et al.* 2006, Yang *et al.* 2010, Bray *et al.* 2013). In contrast to the laboratory rodent or the typical human in the civilized world, rhythms in distinct metabolic parameters are presumably less predictable for the animal in the wild; physical activity is anticipated to be elevated during the awake (vs sleep) phase in association with behaviors such as foraging for food, avoidance of predation, and reproduction, while food availability is somewhat less predictable on a daily basis. The organism must therefore 'hedge its bets', by maintaining metabolic flexibility, such that homeostasis can be achieved whether or not foraging is successful during the active period. Undoubtedly, endocrine factors play critical roles in this process, signaling transition of both activity and feeding status. However, what is becoming increasingly clear is that behavior-independent endogenous mechanisms also contribute toward daily rhythms in metabolism; one such mechanism is the cell autonomous circadian clock, which allows the cell to anticipate a predictable daily stimulus before its onset. In this review, we will discuss current knowledge regarding the regulation of time-of-day-dependent oscillations in metabolism, with a specific focus on the interplay between extracellular (e.g. endocrine) and intracellular (e.g. circadian clock) factors.

Extrinsic vs intrinsic regulation

It has become increasingly clear that 24 h rhythms in multiple biological processes, including metabolism, are

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mediated not only by environmental (i.e. extrinsic) factors but also by endogenous (i.e. intrinsic) influences. Dissociation of these two influences is possible when environmental conditions are maintained constant over the course of the day (i.e. constant lighting and food availability in the absence of synchronizing environmental cues); under such conditions, behavioral (sleep–wake and feeding–fasting), endocrine, and metabolic cycles persist in both humans and rodent models (with periodicities slightly longer and shorter than 24 h respectively) (Aschoff 1965, Pittendrigh & Daan 1976). Time-of-day-dependent oscillations in both endocrine and metabolic rhythms are closely associated with, and have therefore been classically attributed to, fluctuations in daily behaviors. However, various studies have directly challenged an obligatory relationship between the two, revealing that distinct 24 h endocrine and metabolic rhythms can be dissociated from behaviors. For example, oscillations in plasma cortisol and thyroid-stimulating hormone persist in human subjects when sleep is prevented through enforcement of a state of arousal during the night (Van Cauter *et al*. 1991, Van Cauter & Copinschi 1999, Van Cauter & Spiegel 1999). Twenty-four hour rhythms in epinephrine and plasminogen activator inhibitor 1 similarly persist in humans subjected to contiguous 20 or 28 h days (known as forced dyssychrony; Scheer *et al*. 2010, 2011, Shea *et al*. 2011, Scheer & Shea 2014). With regards to metabolism, oscillations in circulating blood glucose levels persist during this forced dyssychrony protocol, highlighting that rhythms in carbohydrate metabolism are not simply secondary to alterations in physical activity and/or food intake during the day (Scheer *et al*. 2009). Collectively, these observations suggest that 24 h oscillations in specific endocrine and metabolic parameters are not driven solely by environmental/behavioral rhythms, but are instead mediated (at least in part) by endogenous mechanisms. One such likely candidate mechanism is the circadian clock.

The circadian clocks are cell autonomous molecular mechanisms that confer the selective advantage of anticipation, thereby allowing the cell/organ/organism to prepare for an extracellular stimulus/stress before its onset (Edery 2000, Takahashi *et al*. 2008). In doing so, this mechanism facilitates temporally appropriate responses, through orchestration of cellular processes over the course of the day. Circadian clocks (found within essentially all mammalian cells) comprise transcriptional–translational feedback loops, the components of which oscillate with a free-running periodicity of ~24 h (Edery 2000, Takahashi *et al*. 2008). A scheme illustrating the core components of the circadian clock mechanism is provided in Fig. 1. At the heart of the mammalian mechanism are two transcription factors, circadian locomotor output cycles kaput (CLOCK) and brain and muscle aryl hydrocarbon nuclear translocator (ARNT)-like 1 (BMAL1) (Gekakis *et al*. 1998, Hogenesch *et al*. 1998). Upon heterodimerization, CLOCK and BMAL1 bind to E-boxes in the promoter region of multiple target genes, including core components of the circadian clock mechanism. The latter include multiple period (PER) and cryptochrome (CRY) isoforms, which, upon accumulation of their translation products in the cytosol, heterodimerize and translocate back into the nucleus, subsequently inhibiting the transcriptional activity of CLOCK–BMAL1 (Miyamoto & Sancar 1998, Zylka *et al*. 1998). A second well-characterized negative feedback loop involves REV–ERBα (encoded by the nuclear receptor subfamily 1, group D, member 1 gene, *NR1D1*); accumulation of REV–ERBα protein results in repression of *BMAL1* (*ARNTL*) transcription, through binding of REV–ERBα to the retinoid-related orphan receptor (ROR) response element within the *BMAL1* promoter (Preitner *et al*. 2002). Additional feedback loops also exist, including involvement of deleted in esophageal cancer 1–2 (DEC1–2; Honma *et al*. 2002). Post-translational modifications (PTMs) are extremely important not only for appropriate operation of the clock mechanism itself (e.g. both phosphorylation and ubiquitination events are essential for temporal control of clock component protein turnover), but also for entrainment/synchronization of the mechanism with the environment (Lee *et al*. 2001, Harms *et al*. 2004). *BMAL1* is an excellent example of a clock component whose activity is tightly controlled by PTMs (including phosphorylation, acetylation, ADP-ribosylation, SUMOylation, and *O*-GlcNAcylation), resulting in a multitude of PTM permutations over the course of the day (Kloss *et al*. 1998, Millar 2000, Cardone *et al*. 2005, Hardin & Yu 2006, Asher & Schibler 2011, Durgan *et al*. 2011). An imbalance in PTMs will result in aberrant regulation of the clock mechanism, as discussed in greater detail in subsequent sections.

In addition to understanding the inner workings of the circadian clock, it is important to appreciate the manner by which the mechanism is regulated, as well as the identity of the processes that it modulates (i.e. clock output). When considering regulation, it is important to note that clocks are separated into two broad categories based on location. The central circadian clock is located within a distinct region of the hypothalamus, known as the suprachiasmatic nucleus (SCN), whereas peripheral circadian clocks are located within non-SCN regions of the

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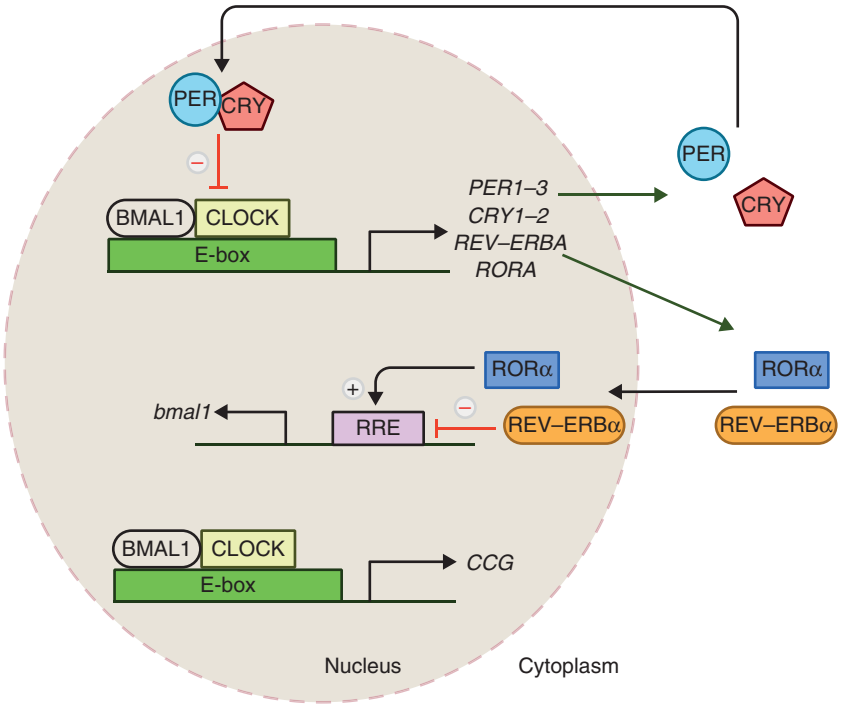

Figure 1
The mammalian circadian clock mechanism. The core circadian clock mechanism relies on a transcriptional–translational feedback loop comprising the transcription factors BMAL1 and CLOCK. On the positive side of loop, BMAL1 and CLOCK heterodimerize and bind E-box elements in *PER* and *CRY* genes that encode negative members of the feedback loop PER1–3 and CRY1–2. The PER and CRY proteins repress their own transcription by interfering with CLOCK–BMAL1 activity. A second feedback loop involving opposing actions of REV–ERBα and RORα nuclear receptors controls the rhythmic expression of BMAL1, which is essential for the generation of circadian clock rhythms. CLOCK–BMAL1 also promotes the transcription of many noncore clock and metabolic genes; a.k.a., clock-controlled genes. *BMAL1*, brain and muscle ARNT-like 1; *CLOCK*, circadian locomotor output cycles kaput; *CCG*, clock controlled gene; *CRY1–2*, cryptochrome 1–2; *PER1–3*, period 1–3; *REV–ERBA* or α, nuclear receptor subfamily 1, group D; *RORA* or α, RAR-related orphan receptor alpha; *RRE*, retinoid response element.

organism, including other regions of the CNS (Takahashi *et al.* 2008). Zeitgebers ('time-givers') are time cues that phase shift circadian clocks. Light is one of the most well-characterized zeitgebers, which resets the central SCN clock via the retino-hypothalamic tract (Berson 2003). In contrast, peripheral circadian clocks are influenced by various neurohumoral factors, including (in specific cases) direct innervation from the SCN (e.g. heart) (Scheer *et al.* 2001, Hirota & Fukada 2004). Relevant to this review article, the quantity, quality, and timing of food intake differentially influence peripheral circadian clocks, with little or no impact on the SCN central clock (Damiola *et al.* 2000, Kohsaka *et al.* 2007, Bray *et al.* 2013). Output from the clock can manifest initially at the levels of both transcription and PTMs. In the former case, it has been estimated that between 8 and 13% of a cell's transcriptome is regulated by cell autonomous clocks (Storch *et al.* 2002, Kornmann *et al.* 2007, Bray *et al.* 2008). Clock-controlled genes (CCGs) include, but are not limited to, genes encoding for proteins that impact transcription, translation, signaling, cell cycle/survival, and metabolism. The remainder of this review will focus on clock control of metabolic processes.

Circadian clock control of metabolism

A diverse number of metabolic pathways have now been shown to be regulated by the circadian clock, both directly (e.g. a key metabolic enzyme is regulated transcriptionally by the CLOCK–BMAL1 heterodimer) and indirectly (e.g. clock regulation of endocrine factor release influences metabolically active tissues in a time-of-day-dependent manner). Within this sub-section, we summarize what is currently known regarding circadian clock control of carbohydrate, lipid, protein, and NAD^+ metabolism.

Clock control of carbohydrate metabolism

Dramatic time-of-day-dependent oscillations in glucose metabolism are observed in both humans and rodent

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models, at both the whole body level and the organ/cellular level. During periods of increased physical activity, non-insulin-mediated glucose utilization increases; the relative contribution of aerobic to anaerobic utilization being dependent upon exercise intensity (Rose & Richter 2005, Alberts *et al*. 2006, Calvo *et al*. 2008). Similarly, food consumption results in insulin-mediated glucose disposal (Woerle *et al*. 2003). It is therefore not surprising that indirect calorimetry reveals increased glucose utilization during the awake period (relative to the sleep period). However, as highlighted in the preceding section, recent studies have strongly supported the concept that rhythms in glucose metabolism are not mediated purely by fluctuations in behaviors. Additional evidence includes the observation that circulating glucose levels increase before waking, in both humans and rodents, an event known as the dawn phenomenon (Bolli *et al*. 1984). Similarly, rhythms in blood glucose levels persist when rats are fasted (La Fleur *et al*. 1999). Collectively, these observations reveal an important role of an endogenous circadian mechanism in whole body glucose metabolism. Indeed, surgical ablation of the central clock (SCN) or genetic manipulation of circadian clock components disrupts glucose homeostasis (La Fleur *et al*. 1999, la Fleur *et al*. 2001). In the case of the dawn phenomenon, multiple studies suggest that the SCN–paraventrciular nucleus–autonomic nervous system axis plays a critical role in daily rhythms in hepatic glucose output, as recently reviewed by Kalsbeek *et al*. (2014).

Glucose homeostasis is achieved through the coordinated regulation of exogenous (ingestion/digestion/absorption) and endogenous (gluconeogenesis) glucose input vs disposal (utilization) mechanisms. Evidence exists that the hepatocyte circadian clock plays an important role in several processes involved in glucose homeostasis, including gluconeogenesis and glycogen turnover. In the latter case, hepatic glycogen levels display a diurnal variation in a variety of species including rats, mice, rabbits, guinea pigs, chickens, and human as highlighted in a study by Sollberger (1964). Interestingly, time-of-day-dependent rhythms in glycogen levels persist in fasted rodents (albeit at lower amplitude), suggesting that these rhythms are not simply secondary to feeding–fasting cycles (Ishikawa & Shimazu 1976). Not only do glycogen levels oscillate over the course of the day, but so do the activities of key glycogen metabolism enzymes; glycogen synthase displays maximum levels during the dark (active) phase in rodents, whereas glycogen phosphorylase peaks toward the end of the light (sleep) phase (Peret *et al*. 1976, Ishikawa & Shimazu 1980). Evidence in support of circadian clock involvement in the mediation of these oscillations comes from recent studies by Doi *et al*. (2010), which have reported diminished oscillations in both hepatic glycogen levels and glycogen synthase expression/activity in *Clock*$^{\Delta 19}$ mutant mice. Similar to glycogen turnover, glucogenogenesis exhibits a diurnal variation; increased rates are observed at the sleep-to-wake phase transition (in comparison to the wake-to-sleep transition), which is paralleled by a diurnal rhythm of phosphoenolpyruvate carboxykinase (PEPCK) activity, a key regulatory enzyme in gluconeogenesis (Kida *et al*. 1980). Using hepatocyte-specific *BMAL1* knockout mice, Lamia *et al*. (2008) found that the hepatocyte's circadian clock was critical for rhythms in PEPCK expression. More recently, Zhang *et al*. (2010) reported that the core clock component CRY modulates hepatic gluconeogenesis in a time-of-day-dependent manner through the regulation of β-adrenergic signaling and activation of cAMP response element-binding protein.

Both insulin-dependent and insulin-independent whole-body glucose disposal exhibits diurnal variations in humans and rodents (Whichelow *et al*. 1974, Lee *et al*. 1992, la Fleur *et al*. 2001). Extra-hepatic tissues, such as muscle, contribute in a significant manner to glucose homeostasis. Diurnal variations in glucose utilization of both skeletal and cardiac muscles persist *ex vivo*, suggesting that an intrinsic mechanism may contribute toward these rhythms (Leighton *et al*. 1988, Young *et al*. 2001). In the case of the heart, genetic disruption of the cardiomyocyte circadian clock abolishes time-of-day-dependent rhythms in cardiac glucose oxidation, glycolysis, and glycogen synthesis, as well as protein *O*-GlcNAcylation (an indirect marker of flux through the hexosamine biosynthetic pathway; Durgan *et al*. 2011). More recently, Dyar *et al*. (2014) have reported decreased glucose uptake and oxidation by soleus and diaphragm muscles in skeletal myocyte-specific *Bmal1* null mice, concomitant with dysregulation of pyruvate dehydrogenase. Collectively, these observations suggest that circadian clocks within cardiac and skeletal myocytes significantly influence glucose utilization.

Clock-mediated regulation of glucose homeostasis also involves the temporal regulation of endocrine factor release and sensitivity. Insulin and glucagon play important roles in the maintenance of blood glucose homeostasis (Voet & Voet 2004). *In vitro* studies by Peschke & Peschke (1998) showed that insulin secretion from isolated pancreatic rat islets display a circadian rhythm that originates within the islet. Further, plasma insulin concentrations in rats exhibit daily oscillations with distinct

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increments at every meal (Kalsbeek & Strubbe 1998). Studies also show that disruption of the circadian clock causes impaired insulin secretion and consequent hypoinsulinemia (Marcheva *et al.* 2010, Coomans *et al.* 2013). Using melatonin receptor null mice as a model of circadian clock dysregulation, Muhlbauer *et al.* (2009) reported altered circadian rhythms of insulin transcripts and plasma insulin levels. Insulin sensitivity also exhibits a time-of-day dependence, which appears to be circadian clock dependent. For example, both glucose and insulin tolerance are impaired in SCN ablated rats, as well as $Clock^{\Delta 19}$ mutant and *Bmal1* null mice (la Fleur *et al.* 2001, Rudic *et al.* 2004). Similarly, insulin signaling is impaired in various tissues isolated from germline *Bmal1* null, *Per2* mutant, and cardiomyocyte-specific $Clock^{\Delta 19}$ mutant mice (Anea *et al.* 2009, Durgan *et al.* 2010, Carvas *et al.* 2012). In addition to insulin, glucagon also plays a crucial role in the regulation of blood glucose homeostasis, and has similarly been shown to display diurnal patterns of release (Gagliardino *et al.* 1978, Tasaka *et al.* 1980). A study by Ruiter *et al.* (2003) demonstrated that 24 h plasma glucagon concentrations are regulated by feeding and the circadian clock. Experiments by Bahr *et al.* (2011) demonstrate that melatonin (an important synchronizer of circadian rhythms) influences pancreatic glucagon expression, as well as peripheral glucagon action. Collectively, these observations raise the possibility that cell autonomous circadian clocks contribute toward rhythms in glucose homeostasis, through regulation of endocrine factors (e.g. insulin and glucagon) release and/or sensitivity.

Clock control of lipid metabolism

Similar to glucose, it is well documented that lipid metabolism displays time-of-day-dependent rhythms, which align with daily rhythms in behaviors, such as sleep–wake and feeding–fasting cycles. Significant evidence obtained using genetic mouse models of clock disruption supports the concept that rhythms in lipid metabolism are mediated by intrinsic molecular clocks. The purpose of this subsection is to provide a brief overview of current knowledge regarding clock control of lipid digestion/absorption, as well as oxidative and nonoxidative metabolism of lipids and fatty acids.

Uptake of dietary fat by the body involves mechanical emulsification, lipolytic breakdown, and absorption into intestinal epithelial cells. The digestive tract displays daily rhythms at multiple levels, including gastrointestinal motility, exocrine secretion, macronutrient absorption, and digestive enzyme activities. Using an *in situ* jejunal loop preparation and isolated primary enterocytes, Pan & Hussain (2009) reported higher rates of cholesterol and lipid absorption during periods of high activity (dark phase) in mice and lower absorption during periods of low activity (light phase). Importantly, this study revealed that $Clock^{\Delta 19}$ mutant mice absorbed similar amounts of macronutrients during both the day and night, indicating a loss of rhythm in intestinal absorption and supporting a role for the circadian clock in the regulation of nutrient absorption. Indeed, robust expression of clock genes in different regions and cell types in the gastrointestinal tract has been observed by several groups (Pardini *et al.* 2005, Hoogerwerf *et al.* 2007, Sladek *et al.* 2007). Furthermore, studies have shown that many of the genes involved in lipid uptake and metabolism in the intestine, including apolipoprotein B (*Apob*), *Apo AIV* (*Apoa4*), intestinal microsomal triglyceride transport protein (*Mtp* (*Mttp*)), and intestinal fatty acid binding protein (*Fabp* (*Fabp2*)), display diurnal rhythms (Pan & Hussain 2007, 2009, Pan *et al.* 2010). Additional evidence for clock control of lipid digestion/absorption comes from the observations that mice with genetic ablation of nocturnin (a known clock controlled gene) are resistant to high-fat diet-induced obesity due to aberrant chylomicron excretion from the intestinal epithelial cells (Douris *et al.* 2011). While the importance of the intrinsic clock in the regulation of lipid metabolism-related functions in the intestinal tract is established, rhythms in these processes and others can be phase-shifted in response to restricted feeding regimens and attenuated by different lighting conditions (e.g. constant darkness or constant light), pointing to the importance of both feeding behavior and the light–dark cycle in time-of-day-dependent regulation of intestinal function (Pan & Hussain 2009, Polidarova *et al.* 2011, Malloy *et al.* 2012). Moreover, Mukherji *et al.* (2013) have recently shown that proper functioning of the circadian clock in intestinal epithelial cells is necessary for maintaining homeostasis between the intestinal epithelium and gut microbiota. The importance of this relationship is showcased by work demonstrating that disrupting the intestinal circadian clock causes gut leakiness and hepatic inflammation (Swanson *et al.* 2011). Thus, continued investigation and improved understanding of the intestinal circadian clock are important especially with the newly recognized role of the intestine–microbiome relationship in influencing metabolic syndrome (Vinje *et al.* 2014).

In addition to the processes described above, several lipid metabolism species exhibit daily rhythms. For example, circulating nonesterified fatty acids (NEFA) are known to display diurnal rhythms. Multiple studies have

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reported higher circulating levels of NEFA in rodents during their inactive phase (Stavinoha *et al*. 2004, Shostak *et al*. 2013). Similarly, humans have higher levels of NEFA at night due to increased lipolytic activity (Schlierf & Dorow 1973). In support of an underlying circadian regulation of NEFA homeostasis, studies comparing circulating NEFA levels in fasted human volunteers revealed that plasma NEFA levels remained higher in the evening compared with the morning, despite lack of food intake (Carroll & Nestel 1973, Gibson *et al*. 1975). Furthermore, a recent study by Dallmann *et al*. (2012) has found that plasma lipid levels remain rhythmic in human subjects maintained in constant dim light, even when food intake and wakefulness were kept constant (i.e. hourly iso-caloric food intake and sleep deprivation). Taken together, these studies provide strong evidence that rhythms in circulating lipid species (and presumably lipid metabolism) are not simply secondary to behavioral cycles.

Circadian regulation of triglyceride metabolism is achieved in part through the rhythmic gene expression of several enzymes involved in triglyceride biosynthesis (Shostak *et al*. 2013, Adamovich *et al*. 2014). Lipid biosynthesis is known to be regulated by sterol regulatory element-binding proteins (SREBP), a family of membrane-bound, basic helix–loop–helix leucine zipper transcription factors (Goldstein *et al*. 2006). Emerging studies reveal a transcriptional regulatory link between SREBP and the circadian clock. By the use of a combination of genetic loss- and gain-of-function experiments, Le Martelot *et al*. (2009) found that REV–ERBα regulates the daily rhythm in activity and expression of SREBP, as well as SREBP targets (e.g. fatty acid synthase and acetyl-CoA carboxylase α), independently of feeding regimen. Regulation of lipid uptake, biosynthesis, and breakdown are tightly coupled. Therefore it is not surprising that lipid turnover and fatty acid β-oxidation are also diurnally regulated. Enzymes such as carnitine palmitoyltransferase 1, medium-chain acyl-CoA dehydrogenase, adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL), and diacylglycerol acyltransferase 2 (DGAT2) have been shown to exhibit circadian oscillations in various tissues at the gene expression level (Alenghat *et al*. 2008, Tsai *et al*. 2010, Filiano *et al*. 2013, Shostak *et al*. 2013). In support of clock control of these genes, Shostak *et al*. (2013) have shown that *Hsl* (*Lipe*) and *Atgl* (*Pnpla2*) oscillations are absent in white adipose tissue isolated from *Bmal1* null mice, while Tsai *et al*. (2010) have reported loss of *Dgat2* oscillations in the hearts of cardiomyocyte-specific $Clock^{\Delta 19}$ mutant mice. More recently, Bass *et al*. have proposed time-of-day-dependent regulation of hepatic β-oxidation through the circadian clock by protein acetylation (as discussed in greater detail in subsequent sections; Peek *et al*. 2013). Taken together, it is clear that cell autonomous circadian clocks likely regulate lipid metabolism at multiple levels.

Clock control of protein and amino acid metabolism

An important example of temporal regulation of biologic processes by cell autonomous circadian clocks is DNA synthesis and repair. DNA repair is increased during the active period, when oxidative stress is high, while DNA synthesis is restricted to the less active/sleep phase (Edery 2000). In doing so, the clock minimizes transmittance of mutations to daughter cells. An analogous form of regulation may occur for protein turnover. Oxidative stress is predicted to cause protein damage primarily during the active phase, while increased protein degradation and autophagy are observed during the less active/sleep phase (presumably as a means to remove damaged proteins/organelles, in anticipation of the subsequent active period). The nature of protein rhythms in protein synthesis appear to be less consistent; skeletal muscle net protein synthesis peaks during the active/awake phase, which is in marked contrast to cardiac muscle, for which protein synthesis peaks during the sleep/inactive phase (Garlick *et al*. 1973, Rau & Meyer 1975). Consistent with these metabolic observations, several microarray studies have reported marked diurnal variations in genes known to modulate protein turnover, including ubiquitin ligases, proteasome subunits, and autophagy proteins and markers (Duffield *et al*. 2002, Reddy *et al*. 2006). Classically, stimulation of protein synthesis (e.g. skeletal muscle) and concomitant repression of protein degradation (e.g. liver) during the active/awake phase has been attributed to increased food intake at that period of time (Garlick *et al*. 1973). Indeed, circulating insulin levels (a potent anabolic signal) are increased during the active phase (Fulks *et al*. 1975, Rannels *et al*. 1975). Similarly, circulating amino acid levels are elevated during the awake phase, which act both as a substrate and stimulus for protein synthesis (Wurtman *et al*. 1968). Interestingly, diurnal variations in circulating amino acid levels persist both during fasting and consumption of protein-free diet, suggesting that ingestion of dietary protein during the active period is not mediating rhythms in circulating amino acids (or protein synthesis; Fernstrom *et al*. 1979). These observations raise the possibility that oscillations in protein degradation are independent of dietary status

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(i.e. feeding–fasting cycles), releasing amino acids into the circulation in a time-of-day-dependent manner.

Evidence has begun to accumulate, suggesting a role for circadian clocks in the regulation of protein turnover. Indeed, time-of-day-dependent turnover of circadian clock proteins is essential for the functioning of this mechanism. This is exemplified by the E3 ubiquitin ligases F-box and leucine-rich repeat protein 3 (FBXL3) and FBXL21, which are essential for turnover of CRY proteins (Yoo *et al.* 2013). Similarly, microarray analyses highlight multiple components of the ubiquitin/proteasome system as being regulated by circadian clock (Duffield *et al.* 2002, Reddy *et al.* 2006). One such component, ubiquitin-specific protease 2 (important for deubiquitination of proteins), is considered a direct Clock–Bmal1 target gene that influences hepatic gluconeogenesis (Molusky *et al.* 2012). Interestingly, this clock output gene oscillates in a number of additional metabolically active tissues, including skeletal and cardiac muscles (McCarthy *et al.* 2007, Bray *et al.* 2008). As highlighted above, insulin is a potent anabolic signal, and evidence suggests that cell autonomous circadian clocks influence insulin sensitivity; clock-mediated diurnal rhythms in insulin sensitivity may therefore contribute toward oscillations in protein turnover. Similarly, whether clock-driven oscillations in amino acid metabolism (particularly branched chain amino acids (BCAA)) impact protein turnover is an attractive hypothesis. Indeed, microarray analyses suggest regulation of the BCAA alpha ketoacid dehydrogenase by the circadian clock at the transcriptional level (ME Young, unpublished observations).

Clock control of NAD^+ metabolism

NAD^+ is traditionally considered as a key source of reducing equivalents for numerous oxidation–reduction reactions being interconverted between its oxidized (NAD^+) and reduced (NADH) forms. However, NAD^+ may also function as a cell signaling molecule via roles in PTMs; ADP-ribosylation and NAD^+-dependent deacetylation. For example, NAD^+ activates sirtuin 1 (SIRT1) deacetylase thereby altering the acetylation status and presumably the function of cellular proteins (Imai *et al.* 2000, Landry *et al.* 2000). There are two metabolic pathways that control the levels of NAD^+: the biosynthesis pathway from tryptophan and the salvage pathway (Imai 2010). Notably, the salvage pathway functions to preserve cellular NAD^+ levels when NAD^+ is used as a cofactor for signaling reactions. For example, when NAD^+ is used as a co-factor for SIRT1 it is degraded to nicotinamide (NAM). In the salvage pathway, NAM is converted to nicotinamide mononucleotide (NMN) by the enzyme nicotinamide phosphoribosyltransferase (NAMPT), the rate-limiting enzyme in the pathway. NMN is then reacted with ATP by the enzyme NAM/nicotinic acid mononucleotide adenylytransferase to regenerate NAD^+. Importantly, the NAD^+ salvage pathway operates in a circadian fashion because *NAMPT* gene expression is regulated by CLOCK–BMAL1 through DNA binding (Nakahata *et al.* 2009, Ramsey *et al.* 2009). The consequence of this is daily oscillations in NAD^+ and NAD^+-dependent reactions (e.g. SIRT1 activity). Importantly, daily rhythms in *NAMPT* and NAD^+ are absent in tissues and cells from animal models with a nonfunctional circadian clock mechanism, and pharmacological inhibition of NAMPT activity also dampens NAD^+ oscillations (Nakahata *et al.* 2009, Ramsey *et al.* 2009, Peek *et al.* 2013). Together, these results demonstrate that the molecular clock plays an important role in the regulation of the levels of a key cellular metabolite, NAD^+, which, in turn can feedback and regulate clock activity (see section on 'Acetylation'). With this said there are still gaps in this area of NAD^+ biology that require attention. For example, it is not clear what role the molecular clock plays in the regulation of different sub-cellular pools (nuclear, cytosolic, and mitochondrial) of NAD^+. This is an important question as most studies have only looked at total cellular or whole tissue levels of NAD^+ and we now know that organelle compartmentation and microenvironments are critical aspects in control of metabolism. Furthermore, measurements done using isolated organelles (e.g. mitochondrial and/or nuclear fractions) may be invalid as NAD^+ content and/or the NAD^+/NADH ratio will likely be altered during the sub-cellular fractionation procedure. However, investigations using a new mitochondrially targeted poly(ADP-ribose) polymerase 1 (PARP1) derivative as a tool for NAD^+ detection have shed some light into the mechanisms involved in generation of mitochondrial NAD^+ (Nikiforov *et al.* 2011). It is also important that investigators explicitly report the nutritional state (fed vs fasting), feeding strategy (*ad libitum* vs time-restricted), dietary formulations, and environmental conditions (light intensity and temperature) used in experimental studies, as all these factors most likely impact NAD^+ rhythms.

Circadian clock regulation of mitochondrial bioenergetics

Mitochondria are dynamic organelles that provide the majority of cellular energy needed for metabolic processes, through oxidative phosphorylation. In addition to ATP

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generation, mitochondria mediate the production of controlled reactive oxygen species (ROS) for redox signaling, regulate cytosolic Ca^{2+} levels, participate in the biosynthesis of amino acids and heme, generate heat via thermogenesis, and serve as a gatekeeper for apoptotic and necrotic signaling. Highlighting the importance of these processes and others in the maintenance of cellular homeostasis and health is the fact that mitochondrial damage and dysfunction are linked to numerous diseases. Because of the tight connection between circadian rhythms and metabolism, it has been proposed that various mitochondrial functions may be regulated by the circadian clock, and possibly may serve as a central coordinator between the clock and cellular energy metabolism (Langmesser & Albrecht 2006). Although substantial evidence suggests that specific mitochondrial functions (e.g. carbohydrate oxidation) are circadian controlled, much less is known regarding time-of-day-dependent changes in mitochondrial bioenergetics and the importance of the circadian clock in this vital process.

Daily oscillations in mitochondrial energy metabolism were first suggested by studies that examined gene expression in the SCN; Panda *et al*. (2002) reported circadian oscillations in the mRNA levels of several nuclear-encoded mitochondrial proteins involved in oxidative phosphorylation. Several databases of circadian gene expression (e.g. CircaDB (Circadian Expression Profiles Data Base), bioinf.itmat.upenn.edu/circa) provide evidence supporting circadian oscillations in specific respiratory chain subunits in various tissues from mice, including the SCN (Pizarro *et al*. 2013). Studies have also shown diurnal oscillations in other key bioenergetic parameters in the SCN, including mitochondrial membrane potential, cytochrome *c* oxidase activity (Isobe *et al*. 2011), and coordination of mitochondrial Ca^{2+} handling in SCN astrocytes (Burkeen *et al*. 2011). Interestingly, cytochrome *c* oxidase activity, as well as expression of subunits I and IV, is increased in the brain during wakefulness compared with sleep, presumably to meet increased energy demands when awake (Nikonova *et al*. 2005). Together, these findings support the concept of temporal organization of mitochondrial bioenergetics within important brain regions.

Accumulating evidence also supports circadian and/or diurnal oscillations in mitochondrial energy metabolism and associated oxidative pathways in peripheral tissues. For example, myocardial oxygen consumption exhibits daily oscillations in experimental rodent models (Young *et al*. 2001, Bray *et al*. 2008), purely during the active phase, when cardiac function is elevated. Yet, how these temporal changes in mitochondrial metabolism and bioenergetics are mediated is not as well understood. To address this question and assign the relative contribution of the molecular clock in these processes, recent studies have been performed using tissues, cells, and/or isolated organelles from mice deficient in core clock components. Notably, this work suggests that there are several different levels of clock control over mitochondrial metabolism, including both transcriptional and post-transcriptional mechanisms.

Using isolated mitochondria from germline *Bmal1* null mice, Bass *et al*. reported reduced mitochondrial oxygen consumption when fatty acids were provided as an oxidizable substrate, but not in the presence of substrates that supply electrons directly to complex I or II of the mitochondrial respiratory chain (Peek *et al*. 2013). This finding suggests that a clock-mediated defect in β-oxidation, as opposed to respiratory chain components themselves, is likely responsible for lower respiration in liver mitochondria of *Bmal1* null mice. Additional experiments from this study suggest that reduced oxidative metabolism was associated with hyperacetylation of mitochondrial proteins in *Bmal1* null mice, potentially due to low levels of NAD^+ and decreased activity of SIRT3 (the mitochondrial NAD^+-dependent deacetylase). Importantly, repletion of NAD^+ with NMN normalized protein acetylation and partially restored respiration rates in mitochondria from *Bmal1* null mice. Given that NAD^+ salvage is directly controlled by cell autonomous clocks, these observations suggest that circadian control of fatty acid β-oxidation is mediated by rhythmic oscillations in NAD^+, SIRT3 activity, and post-translational acetylation of mitochondrial proteins. In support of this, Sassone-Corsi *et al*. (Masri *et al*. 2013) have also reported that many mitochondrial proteins are differentially acetylated and linked to circadian alterations of the liver metabolome. Together, these results suggest that the circadian clock regulates mitochondrial energy metabolism, in part, by a nontranscriptional mechanism, namely PTM (i.e. acetylation) of proteins.

Similar to numerous metabolic processes, mitochondrial biogenesis is controlled transcriptionally by various nuclear receptors, including estrogen-related receptor alpha and nuclear respiratory factor 1 (NRF1) and NRF2. Genetic control over mitochondrial biogenesis by these factors is coordinated by the peroxisome proliferator-activated receptor-γ coactivator 1 (PGC1) family of transcriptional coactivators. PGC1α and PGC1β dock with the DNA-binding transcription factors NRF1 or NRF2 to stimulate the metabolic gene network involved in

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mitochondrial biogenesis and oxidative phosphorylation (Scarpulla 2008). Expression of these coactivators is increased in response to a variety of environmental inputs, nutritional stimuli, mitochondrial outputs (e.g. ROS and/or Ca^{2+}), and circadian signals (Lin 2009). Notably, rhythmic expression of PGC1α and PGC1β mRNA and protein has been reported in several peripheral tissues, and mice deficient in these coactivators have lower levels of metabolic and mitochondrial genes (Liu *et al*. 2007, Sonoda *et al*. 2007). In addition to PGC1, a second level of transcriptional control over mitochondrial metabolism that is linked to the molecular clock is the nuclear receptor REV–ERBα; a known repressor of *BMAL1* transcription and other target genes (Duez & Staels 2009). Duez *et al*. (Woldt *et al*. 2013) showed that REV–ERBα deficiency in skeletal muscle impairs mitochondrial biogenesis and lowers the content of respiratory chain subunit genes resulting in decreased mitochondrial oxygen consumption and reduced exercise endurance in mice. Conversely, pharmacological activation of REV–ERBα significantly improved mitochondrial respiration by stimulating mitochondrial biogenesis through the AMP-dependent protein kinase (AMPK)–SIRT1–PGC1α pathway (Woldt *et al*. 2013). A novel role of REV–ERBα in mitochondrial metabolism has also been shown where REV–ERBα functions as a negative regulator of adaptive thermogenesis via repression of mitochondrial uncoupling protein 1 in brown adipose tissue (Gerhart-Hines *et al*. 2013). Thus, PGC1 and REV–ERB may serve unique roles as potential integrators of the circadian clock and mitochondria to fine-tune mitochondrial metabolism under changing environmental conditions.

The studies described earlier raise the question as to whether mitochondrial content oscillates in a time-of-day-dependent manner with a control of mitochondrial content regulated by a balance between mitochondrial biogenesis and mitochondrial turnover (e.g. mitophagy and/or the Lon protease). Clearly, the work of Duez *et al*. (Woldt *et al*. 2013) indicates that some parameters of mitochondrial biogenesis and turnover are negatively affected in skeletal muscle in REV–ERBα null mice; however, the time-of-day dependence of these two key metabolic programs was not examined in this study. Further, these alterations in mitochondrial function could be independent of the circadian clock as REV–ERB is a transcription factor for multiple noncircadian target genes. Furthermore, Peek *et al*. (2013) showed that the levels of several markers of mitochondrial biogenesis (e.g. mtDNA content and PGC1α protein) were normal in liver of *Bmal1* null mice. Nonetheless, these markers were only measured at one or two time points during the day; thus, it is difficult to draw a solid conclusion from this study as too few time points were measured. Thus, more comprehensive studies are required to address this question, especially in a tissue-specific manner, as it is anticipated that different tissues will have different regulatory mechanisms due to tissue-specific rates of mitochondrial turnover (Lipsky & Pedersen 1981, Miwa *et al*. 2008). With this said, determination of the time-of-day dependence in mitochondrial quality control is not a trivial undertaking. In addition to biogenesis and mitophagy, studies need to consider time-of-day changes in the cellular mitochondrial network (governed by mitochondrial fusion and fission), as alterations in mitochondrial dynamics also impact cellular bioenergetics.

Additional examples illustrating the importance of the molecular clock in the regulation of mitochondrial function include pancreatic β-cell dysfunction in germline *Bmal1* null mice (Lee *et al*. 2011). Impairment in insulin secretion in *Bmal1* null mice islets appears to occur due to a consequence of lowered mitochondrial membrane potential and ATP generation (Lee *et al*. 2011). Investigation of skeletal muscle mitochondria in *Bmal1* null and $Clock^{\Delta 19}$ mutant mice reveal reduced volume, altered morphology, and increased uncoupled respiration (Andrews *et al*. 2010). Moreover, heart mitochondria isolated from cardiomyocyte-specific $Clock^{\Delta 19}$ mutant mice exhibit decreased state 3 and state 4 respiration in the presence of multiple substrates (Bray *et al*. 2008).

In summary, the studies presented in this section provide compelling evidence that normal mitochondrial respiratory chain function and bioenergetics are dependent on the molecular clock. We hypothesize that the circadian clock synchronizes mitochondrial ATP production in a time-of-day-dependent manner, to meet daily fluctuations in cellular energy demands. This appears to be achieved by a variety of transcriptional and post-translational dependent mechanisms. For example, circadian control over mitochondrial turnover (a balance between biogenesis, mitophagy, and fusion/fission) should be considered as a potential mechanism regulating cellular bioenergetics. Moreover, recent evidence has suggested that clock control over mitochondrial fatty acid oxidation is mediated, in part, by metabolite cycling (e.g. NAD^+) and protein acetylation (Peek *et al*. 2013). Future studies should be directed at characterizing the influence of other metabolites and PTMs (e.g. nitrosation) on time-of-day dependent changes in cellular bioenergetics. A disrupted clock would also desynchronize the expression of respiratory chain subunits, resulting in a

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damaged electron transport system. One consequence of an improperly 'put together' respiratory chain might include slippage in electron flow among the complexes resulting in increased ROS production and decreased ATP production. Thus, perturbations in the circadian clock may be a key initiating factor in diseases linked to mitochondrial damage.

Role of circadian clocks in anticipating metabolic demands

The concept of anticipation is not new to the field of endocrinology, particularly in the context of metabolism. The 'fight-or-flight' response is a classic example, in which a rise in adrenaline levels facilitates mobilization of intracellular energy stores (i.e. glycogen and triglyceride) in anticipation of imminent physical activity. A second example includes the 'dawn phenomenon', characterized by an elevation in blood glucose levels before awaking (secondary to alterations in hepatic glucose output and insulin sensitivity). Although the exact biological significance of this phenomenon is unknown, it has been hypothesized that the rise in blood glucose is in anticipation of increased energetic demand upon awaking. Despite appreciation of the importance of anticipation, and the regulation of metabolism by circadian clocks, several fundamental questions remain unanswered regarding the interplay between extrinsic (e.g. endocrine factors) and intrinsic (e.g. circadian clock) factors, and their contribution toward time-of-day-dependent metabolic homeostasis. This includes an understanding of how a cell/organ is able to simultaneously anticipate seemingly opposing metabolic scenarios (e.g. successful forage for food vs prolongation of the sleep phase fast). This subsection proposes an evidence-based hypothetical model in an attempt to begin addressing these questions.

In general terms, organisms have two 'major' behavioral oscillations to contend with on a daily basis. These are active/inactive and feeding/fasting rhythms. During the awake period, increased physical activity associated with foraging for food, avoidance of predation, and/or reproduction are energetic demands that are anticipated to occur, even if the animal in the wild is not successful in its forage for food. Organisms that anticipate this scenario (i.e. physical activity/energetic demand rhythms independent of feeding status) would undoubtedly have an evolutionary-selective advantage. At the same time, it is essential that upon successful foraging of food, cells/organs maintain adequate metabolic flexibility, facilitating efficient storage of nutrients (in anticipation of the next period of fasting). We hypothesize that circadian clocks have an integral relationship with endocrine factors, enabling anticipation of both fasting and feeding during the active period. In this study, discussion will focus initially on the greater selective pressure (i.e. the less favorable scenario of unsuccessful foraging for food during the active period). The model in Fig. 2 predicts that cell autonomous clocks directly regulate metabolic processes, promoting maximal oxidative metabolism capacity during the awake period (particularly in muscle), in anticipation of increased energetic demands during continued foraging for food; conversely, these processes are repressed during the sleep phase. Cell autonomous circadian clocks within metabolically active tissues would therefore be predicted to induce metabolic genes/proteins facilitating glucose uptake, glycogen utilization, and oxidative metabolism during the awake phase. Similarly, clock-mediated sensitization to 'physical activity' signals (e.g. β-adrenergic stimulation) would amplify metabolic responsiveness (i.e. endocrine-clock interaction). Conversely, reversal of circadian clock-mediated effects during the sleep phase would minimize excessive energy expenditure and oxidative stress during the sleep phase (a time at which organelle and cellular repair likely occurs). Cell autonomous circadian clocks would enable metabolically active tissues to 'hedge their bets', by concomitantly increasing sensitivity to insulin during the active phase. Should the animal be successful in its forage for food at that time, stimulus (insulin) and responsiveness (insulin sensitivity) would be synchronized, facilitating efficient uptake and storage of substrates. Thus, cell autonomous circadian clocks are predicted to have direct (increase maximal metabolic capacity during the active period) and indirect (to simultaneously sensitize to 'activity' and 'feeding' signals) modes of action.

For the hypothetical model depicted in Fig. 2 to be accurate, tissues with a high energetic demand during the active phase (e.g. muscle) would be expected to exhibit circadian clock-mediated augmentation of substrate uptake and oxidative capacity, as well as β-adrenergic and insulin sensitivity, during the active period. Evidence exists in support of this hypothesis, particularly in the heart. AMPK activity oscillates markedly in the hearts of WT mice, but not of cardiomyocyte-specific *Clock*$^{\Delta 19}$ mutant mice, paralleled by clock-dependent rhythms in glucose uptake and utilization. Should fatty acid availability increase during the active phase (due to, for example, prolongation of the sleep phase fast) increased AMPK activity at this time would facilitate β-oxidation. Both cardiac β-adrenergic responsiveness and activation

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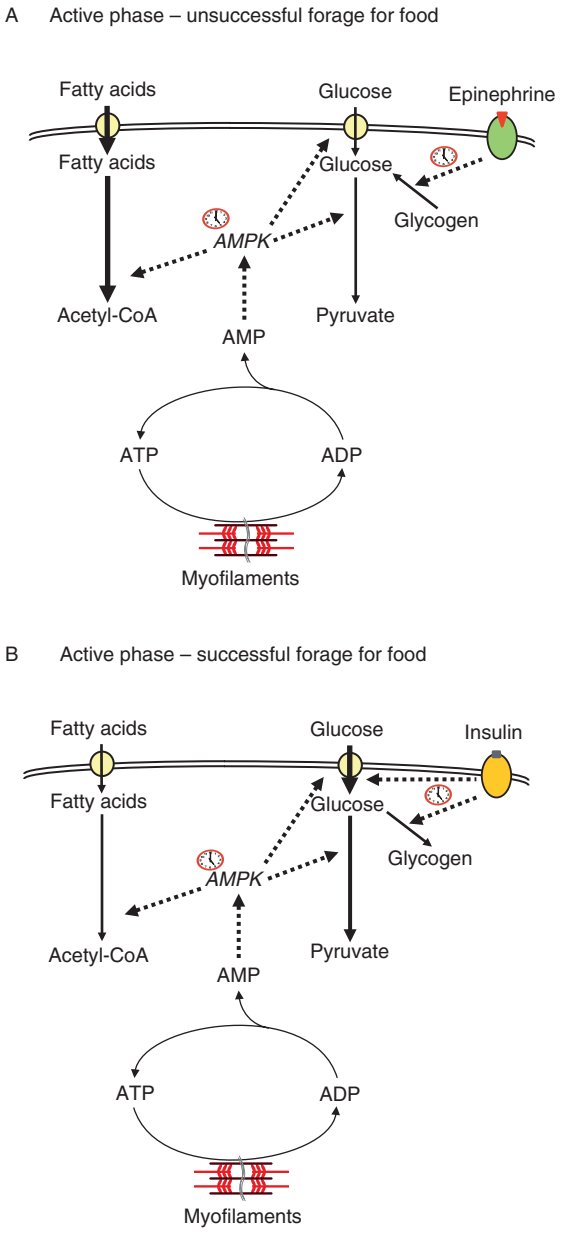

Figure 2
Hypothetical role for the circadian clock in anticipation of fasted (A) vs fed (B) states. As outlined in the text, we hypothesize that the circadian clock within skeletal and/or cardiac myocytes anticipate increased energetic demand during the active period, through mechanisms such as AMPK activation (possibly through the NAMPT/SIRT1/LKB1/AMPK axis), which promotes substrate uptake and utilization. Similarly, clock-mediated augmentation of β-adrenergic sensitivity during the active period would facilitate efficient energy store breakdown, for continued contraction. Should the animal be successful in its forage for food (B), increased clock-mediated augmentation of insulin sensitivity during the active phase would promote efficient uptake and storage of nutrients. Clock symbol represents a clock-controlled process; dashed lines indicate positive regulation on a process; thickness of solid lines represents relative flux through a pathway. Acetyl CoA, acetyl coenzyme A; AMPK, AMP-activated protein kinase; LKB1, liver kinase B1; NAMPT, nicotinamide phosphoribosyltransferase; SIRT1, sirtuin 1.

of insulin signaling components are increased during the active phase, in a clock-dependent manner. More recently, we have found that the phosphoinositide 3-kinase component p85a is under direct clock control (ME Young, unpublished observations), in a manner consistent with clock increased insulin sensitivity during the active phase (in anticipation of successful foraging of food). Collectively, these observations suggest that cell autonomous circadian clocks are an essential link between endocrinology and metabolic homeostasis.

Metabolic regulation of the molecular circadian clock

It is now widely accepted that metabolism is not only an output from the clock, but that various metabolic processes influence function and timing of the clock (Peek *et al.* 2012, Sahar & Sassone-Corsi 2012). An excellent example of this is protein turnover. For the clock to function, components must be synthesized and degraded in a time-of-day-dependent fashion; pharmacological interference with protein turnover drastically impairs clock function. The purpose of this subsection is to review current knowledge regarding the impact of metabolism on the circadian clock. We will focus on redox status, acetylation, ADP-ribosylation, phosphorylation, *O*-GlcNAcylation, heme, and reactive species (a number of which are summarized in Fig. 3).

Redox status

One of the earliest studies supporting the concept that metabolism can affect clock function investigated the role of cellular redox state (Rutter *et al.* 2001). This work showed that DNA binding of the CLOCK–BMAL1 heterodimer could be influenced by the relative ratio of NAD(P)H and $NAD(P)^+$. Rutter *et al.* (2001) demonstrated that high levels of NAD(P)H increased binding of CLOCK–BMAL1 (or neuronal PAS domain protein 2 (NPAS2)–BMAL1) to DNA E-box motifs, whereas $NAD(P)^+$ decreased binding. Notably, high levels of lactate dehydrogenase A (*LDHA*) mRNA accumulate in cells transfected with expression vectors encoding NPAS2 and BMAL1, demonstrating that *LDHA* is a transcriptional target of NPAS2–BMAL1. LDH plays a critical role in the maintenance of cellular redox state, as its co-factor for the reaction catalyzing the conversion of lactate to pyruvate (or *vice versa*) is NAD^+ (or NADH). Thus, *LDH*, a target gene of NPAS2–BMAL1 has the ability to feedback and regulate clock activity by changing the cellular redox potential *in vivo*. Recent work by Yoshii *et al.* (2013) has confirmed that DNA binding

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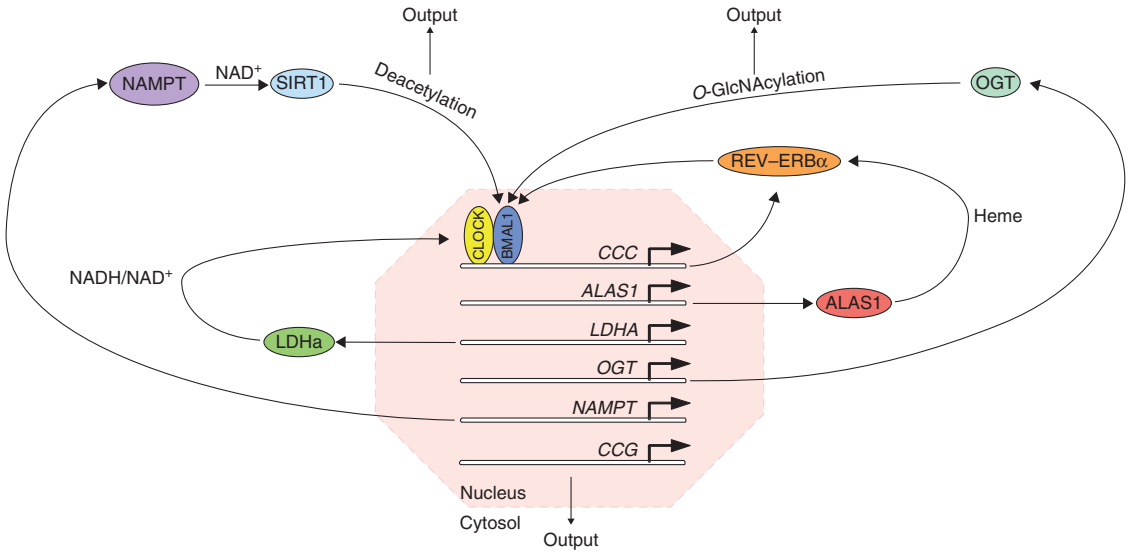

Figure 3
Metabolic feedback loops of the mammalian circadian clock. Clock-mediated induction of ALAS1, LDHa, OGT, and NAMPT, likely form feedback loops through regulation of heme biosynthesis, redox status, protein *O*-GlcNAcylation, and protein deacetylation respectively (for additional details, please see relevant text within the 'Metabolic regulation of the molecular circadian clock' subsection. ALAS1, δ-aminolevulinate synthase; BMAL1, brain and muscle ARNT-like 1; CLOCK, circadian locomotor output cycles kaput; CCC, circadian clock components; CCG, clock controlled genes; LDHA, lactate dehydrogenase A; NAMPT, nicotinamide phosphoribosyltransferase; OGT, *O*-GlcNAc transferase; REV–ERBα, nuclear receptor subfamily 1, group D; SIRT1, sirtuin 1.

of NPAS2–BMAL1 is enhanced by NAD(P)H; however, $NAD(P)^+$ had no effect on DNA binding: these studies also localized the NAD(P)H enhancement binding site to the N-terminal (1–61 residues) region of NPAS2. Together, these studies strongly support the concept that transcriptional activity of the clock is responsive to daily fluctuations in NAD(P)H levels.

Acetylation

The influence of NAD^+ on the clock is highlighted further by work showing that the NAD^+-dependent deacetylase SIRT1 has an impact on clock activity. As discussed in previous sections, intracellular NAD^+ levels oscillate significantly due to NAMPT regulation by CLOCK–BMAL1. More recently, evidence suggests that SIRT1 deacetylates BMAL1 and PER2 in an NAD^+-dependent manner (Asher *et al.* 2008, Nakahata *et al.* 2008), thereby counteracting the known acetylase activity of CLOCK (which is important for normal clock function) (Doi *et al.* 2006). SIRT1 also regulates NAD^+ levels because it is recruited to the *NAMPT* promoter (Nakahata *et al.* 2009, Ramsey *et al.* 2009). Therefore, circadian NAD^+ oscillations influence the function of the molecular clock indirectly by controlling rhythms in SIRT1 activity. Evidence exists suggesting that NAD^+ levels influence the circadian clock *in vivo*; Sahar *et al.* (2011) reported that *Cd38* null mice (with chronically elevated NAD^+ levels) exhibited disrupted circadian behavior (e.g. shortened period length and altered rest-activity rhythms) and altered clock and metabolic gene expression in liver.

ADP-ribosylation

Another NAD^+-mediated mechanism for clock regulation has been described, which involves PARP1 (Asher & Schibler 2011), a protein known to catalyze the transfer of ADP-ribose units from NAD^+ to various target proteins (Kraus & Hottiger 2013). Asher *et al.* (2010) showed that PARP1 binds to and poly ADP-ribosylates CLOCK, thereby decreasing its binding with DNA. Conversely, loss of PARP1 enhances CLOCK–BMAL1 binding to DNA, which was found to alter the expression of known clock output genes. While PARP1 activity exhibits diurnal changes, this activity rhythm persists in livers following disruption of the hepatocyte clock, suggesting mediation by extrinsic factors (Asher *et al.* 2010). Indeed, experiments show that PARP1 activity is potentially regulated by feeding time, as the peak in poly ADP-ribosylation of PARP1 can be shifted by restricted feeding protocols (Asher *et al.* 2010). Therefore, unlike that of SIRT1, circadian oscillations in NAD^+ are unlikely to be responsible for PARP1 activity

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rhythms, as NAD^+, *NAMPT* expression, and PARP1 activity oscillations are not synchronized and PARP1 activity rhythms do not require CLOCK–BMAL1 activity (Asher *et al*. 2010). Nevertheless, these findings support a mechanism whereby PARP1 activity links nutritional status to phase shifting of peripheral clocks.

AMP-dependent protein kinase

AMPK is another key metabolic sensor central for the transmission of nutrient and energy-dependent signals to the molecular clock (Jordan & Lamia 2013). AMPK functions as an energy sensor, being exquisitely sensitive to the AMP/ATP ratio in cells. When AMP levels are elevated, structural changes in AMPK enhance phosphorylation by liver kinase B1 (LKB1), resulting in activation. AMPK catalyzes the phosphorylation of the clock repressor proteins CRY1 and CRY2, targeting them for proteasomal degradation (Lamia *et al*. 2009). AMPK also targets PER proteins for degradation by phosphorylating casein kinase 1ε (CK1ε), which subsequently stimulates CK1ε-mediated phosphorylation of PERs (Um *et al*. 2007). *Ampkα* null mice have increased PER2 levels (Um *et al*. 2007), supporting the hypothesis that AMPK impacts the circadian clock *in vivo*. Conversely, the AMPK activators AICAR (Um *et al*. 2007) and metformin (Barnea *et al*. 2012) shift the phase of the liver clock. A mechanistic connection also appears to exist between SIRT1 and AMPK; studies show that SIRT1 deacetylates LKB1 influencing the activity, localization, and ability of LKB1 to activate AMPK (Lan *et al*. 2008). Collectively, these observations have led to the hypothesis that AMPK may re-set (i.e. entrain) peripheral circadian clocks during specific physiologic and pathophysiologic states.

O-GlcNAcylation

Modification of proteins by *O*-linked β-*N*-acetylglucosamine (*O*-GlcNAc) has emerged as a new regulator linking metabolism to the circadian clock. Reminiscent of phosphorylation, *O*-GlcNAcylation of proteins is regulated by the balance between *O*-GlcNAc transferase (OGT; which catalyzes the addition of *O*-GlcNAc to protein serine and threonine residues) and *O*-GlcNAcase (OGA; which hydrolyzes *O*-GlcNAc residues) (Hart *et al*. 2011). The substrate for *O*-GlcNAcylation is the high-energy compound UDP-*N*-acetylglucosamine; a product of the hexosamine biosynthetic pathway. Studies by Young *et al*. showed coordinated diurnal variations in glucose metabolism, OGT, and OGA leading to peak *O*-GlcNAcylation of cardiac proteins in the middle of the active (dark) phase (Durgan *et al*. 2011). These diurnal changes were absent in hearts of cardiomyocyte-specific $Clock^{\Delta 19}$ mutant mice, suggesting that these pathways are under direct clock control. Importantly, they demonstrated that BMAL1 is a target for *O*-GlcNAcylation and that pharmacological inhibition of OGA shifted the phase of the heart clock (Durgan *et al*. 2011). Related studies in *Drosophila* and mice also support a role of this PTM in regulation of the circadian clock, as *O*-GlcNAcylation of CLOCK and PER2 affects their transcriptional activities and alters the timing of the clock (Kim *et al*. 2012, Kaasik *et al*. 2013). Furthermore, *O*-GlcNAcylation prevents BMAL1 and CLOCK degradation by inhibiting their ubiquitination. In addition, liver-specific knockdown of OGT decreased hepatic *BMAL1* transcripts late in the active (dark) phase and altered diurnal rhythms in glucose homeostasis (by affecting hepatic gluconeogenic gene expression) (Li *et al*. 2013). Together, these studies demonstrate that *O*-GlcNAc is a novel metabolic signal connecting metabolism and the circadian clock.

Heme and reactive species

The iron-containing protein, heme, influences clock function by binding to distinct clock components, including CRY1–2, NPAS2, and REV–ERBα (Burris 2008). Heme binding to REV–ERB nuclear receptors causes the recruitment of the nuclear receptor co-repressor (NCoR) histone deacetylase (HDAC) co-repressor complex to REV–ERB homodimers, leading to the repression of target genes (e.g. *BMAL1*; Yin & Lazar 2005, Raghuram *et al*. 2007). The rate-limiting enzyme in heme biosynthesis, δ-aminolevulinate synthase (ALAS1), exhibits a circadian rhythm at the gene level (Rogers *et al*. 2008) due to activation by NPAS2 and PGC1α, resulting in circadian clock-mediated oscillations in heme levels (Kaasik & Lee 2004, Handschin *et al*. 2005). Importantly, ligation of heme to REV–ERBα in turn inhibits its own biosynthesis through REV–ERBα-mediated inhibition of PGC1α (Wu *et al*. 2009). This feedback loop functions to tightly maintain heme levels within a physiologic range in the cell. Thus, heme metabolism appears to constitute an additional metabolic feedback loop of the molecular clock.

An important characteristic of heme is its ability to bind gaseous signaling molecules including nitric oxide (NO), carbon monoxide (CO), and hydrogen sulfide (H_2S). The ability of gaseous signaling molecules to influence clock function was first recognized when binding of CO to the heme in NPAS2 decreased the formation of

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NPAS2–BMAL1 heterodimers *in vitro* (Dioum *et al*. 2002). Transcriptional regulation by REV–ERBs may be similarly influenced by interaction of heme with these gaseous molecules. Pardee *et al*. (2009) reported that the NO donor (DETA NONOate) blocked REV–ERB-mediated repression of gene transcription in HEK 293 cells. Work by Gupta & Ragsdale (2011) have expanded on this novel concept by showing that the redox state of a thiol-disulfide redox switch controls heme affinity to the ligand-binding domain in REV–ERBβ. This study demonstrated that formation of a disulfide bond between Cys-384 and Cys-374 in the REV–ERBβ ligand-binding domain lowers the affinity for heme, whereas the reduced dithiol between these two Cys residues binds heme more tightly. As thiol-disulfide switches are sensitive to PTM by ROS and reactive nitrogen species, conditions involving oxidative stress may cause perturbation of REV–ERB-controlled pathways including the clock. With regards to H_2S, much less is known about the impact this signaling molecule may have on the molecular clock. Incubation of cultured mouse hepatocytes with sodium hydrosulfide was shown to maintain oscillations of distinct clock genes (Shang *et al*. 2012). Furthermore, inhaled H_2S was found to increase cardiac *Per1* gene expression relative to rats exposed to room air (SM Bailey, unpublished observations). Together, the results from these studies strongly suggest that the interaction of heme with multiple reactive gaseous species may be important for the maintenance of clock function, whereas aberrant production of reactive species could potentially dysregulate the clock. The importance of this level of control is strengthened further by recent reports that peroxiredoxin, the main hydrogen peroxide detoxification enzyme, has a 24 h cycle in the oxidation state of its catalytic site (Edgar *et al*. 2012). Indeed, future studies should be aimed at understanding circadian regulation of the enzymatic pathways responsible for the production and removal of the gaseous signaling molecules and other reactive species (e.g. ROS), as mounting evidence support their role in clock function.

Cardiometabolic consequences of disrupted circadian rhythms

It has become clear that metabolism and the circadian clock are inseparably interlinked (Fig. 3). As highlighted above, the circadian clock not only regulates metabolism, but in turn, metabolism influences the circadian clock. In certain instances, metabolic processes have emerged as integral components of the mammalian circadian clock. It is therefore not surprising that disruption or misalignment among internal biological clocks and the external environment, or among internal clocks in different tissues, perturbs metabolic homeostasis, leading to metabolic diseases. In this context, cardiometabolic disease as a consequence of circadian misalignment in humans has received the greatest attention in individuals that perform night and/or shift work; night-shift workers have greater risk for obesity, diabetes mellitus, and cardiovascular disease compared with day-shift counterparts (see reviews by Knutsson (2003) and Esquirol *et al*. (2011)). More recently, studies on both animal models and humans suggest that circadian misalignment occurs during meal feeding, ethanol consumption, obesity, and diabetes, leading to speculation that aberrant circadian clock function during these conditions potentially contributes toward the etiology of cardiometabolic dysfunction and disease. This sub-section will consider the evidence for each of these.

Shift work

Night-shift workers often exhibit dyslipidemia (e.g. high triglycerides and/or low HDL cholesterol), increased postprandial serum glucose and insulin (Lund *et al*. 2001), and increased circulating levels of several biomarkers of inflammation (Sookoian *et al*. 2007), associated with increased incidence of obesity and diabetes (Karlsson *et al*. 2001, Nagaya *et al*. 2002, Morikawa *et al*. 2005, Kroenke *et al*. 2007, Copertaro *et al*. 2008, De Bacquer *et al*. 2009, Lin *et al*. 2009, Burgueno *et al*. 2010, Chen *et al*. 2010). Controlled laboratory-based studies clearly showed that circadian misalignment disrupts metabolism in humans. For example, Scheer *et al*. (2009) induced circadian misalignment in healthy adults by using an 11-day forced dyssynchrony protocol consisting of repeated '28 h days'; during this protocol, all subjects ate four isocaloric meals each '28 h day' and slept at all phases of the circadian cycle. The results showed that circadian misalignment (defined as eating and sleeping 12 h out of phase from their habitual times) increased circulating glucose and insulin, decreased leptin, and increased blood pressure. Indeed, some subjects in this study exhibited pre-diabetic symptoms in response to circadian misalignment. More recently, Van Cauter *et al*. have reported augmentation of insulin resistance in sleep-deprived subjects following circadian misalignment (Leproult *et al*. 2014). Together, these results support the concept that circadian misalignment in shift workers may contribute toward development of cardiometabolic disease.

The influence of sleep disturbances (e.g. too little sleep) and/or psychosocial stressors should not be

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overlooked as additional risk factors for metabolic disease in shift workers (Clougherty *et al.* 2010, Bannai & Tamakoshi 2014). For example, a combination of sleep deprivation and circadian disruption ('28 h days') caused decreased metabolic rate and increased postprandial glucose in healthy adults (Buxton *et al.* 2012). Sleep deprivation and sleep restriction alone have been shown to alter endocrine regulators of glucose and energy metabolism, which may lead to insulin resistance, obesity, and other pathologies (Zizi *et al.* 2010, Lucassen *et al.* 2012). Studies show that acute sleep restriction (three consecutive nights of shortened sleep – 4 h of sleep/night) reduced insulin sensitivity in adolescent boys (Klingenberg *et al.* 2013). Schmid *et al.* (2007) reported a significant decrease in plasma glucagon levels following one night of total sleep deprivation in healthy young men aged 20–40 years. Interestingly, plasma glucagon levels were significantly decreased in the morning following only one night of mild sleep restriction (one night of 4.5 h of sleep) as compared with levels measured in healthy men allowed to sleep for 7 h (Schmid *et al.* 2009). In this study, plasma glucagon levels also remained depressed throughout a 240 min step-wise hypoglycemic clamp in the sleep restricted group. Sleep deprivation (24 h of continual wakefulness) significantly decreased energy expenditure (resting and postprandial), increased morning plasma glucose (postprandial), and elevated morning levels plasma ghrelin levels, and increased nighttime and daytime levels of cortisol as compared with the control group that was allowed 8 h of sleep during a normal 24 h sleep–wake cycle (Benedict *et al.* 2011). While the mechanisms responsible for these effects remain unknown, they provide compelling evidence to support a linkage among disturbed sleep, dysregulated glucose and energy metabolism, and a predisposition to adverse metabolic consequences.

Experimental animal models have also been utilized to demonstrate that circadian misalignment causes metabolic disturbances. Using a 'night-work' model in rats, Salgado-Delgado *et al.* (2010) showed that forced activity (and/or food consumption) during the normal rest phase increased body weight, adiposity, and glucose intolerance compared with rats with forced activity in the normal active phase. Furthermore, this experimental protocol disrupted the normal daily rhythms in both clock and metabolic genes and caused hepatic steatosis (Salgado-Delgado *et al.* 2013). Similarly, dim-light-at-night (dLAN) has been shown to increase weight gain and disrupt circadian rhythms in both the SCN and peripheral tissues (Fonken *et al.* 2010, 2013*a*), as well as increase peripheral inflammation when combined with a high-fat diet (Fonken *et al.* 2013*b*). Interestingly, re-exposure to a dark night can reverse metabolic disturbances following exposure to dLAN (Fonken *et al.* 2013*c*). These data support the hypothesis that activity and/or light in the normal rest (or sleep) phase causes misalignment among different organ systems and intracellular metabolic pathways. Accordingly, circadian misalignment or dyssynchrony may partially explain why night work and shiftwork are strongly associated with obesity and related metabolic diseases. An additional cause of circadian misalignment during shift work is potentially the timing of food intake (as discussed below).

Timing of feeding

Food consumption is a potent zeitgeber for peripheral circadian clocks, as first demonstrated by Damiola *et al.* (2000); restricting food access to the sleep-phase shifted circadian clocks in the liver, kidney, and heart, with no effect in the SCN, thereby result in circadian dyssynchrony between central and peripheral clocks. More recently, studies have reported that this experimental protocol differentially influences clocks within metabolically active tissues (e.g. liver, skeletal muscle, and adipose), suggesting that meal feeding also causes dyssynchrony between peripheral clocks (Bray *et al.* 2013). This is associated with perturbations in metabolic homeostasis, resulting in increased adiposity, decreased glucose tolerance, and dyslipidemia, a metabolic profile often observed in subjects with night-eating syndrome (Stunkard & Allison 2003, Arble *et al.* 2009, Bray *et al.* 2013). Conversely, restricting food intake to the normal activity phase in rodents prevents metabolic disturbances and weight gain associated with high-fat diets (Hatori *et al.* 2012, Tsai *et al.* 2013). Evidence also suggests that the timing of macronutrient ingestion within the active/awake period markedly impacts metabolic outcomes. More specifically, consumption of a calorically dense high-fat meal at the end of the active/awake period increases adiposity, decreases glucose tolerance, and increases circulating insulin and leptin levels in mice (relative to consumption of the exact same meal during the beginning of the active period; Bray *et al.* 2010). This experimental paradigm phase shifts peripheral circadian clocks (ME Young, unpublished observations). Interestingly, when human subjects were forced to consume the majority of their calories immediately before overnight sleep, metabolic perturbations were observed (e.g. dissociation between circulating insulin and glucose levels; Qin *et al.* 2003). Collectively, these observations suggest that consumption of nutrients at an inappropriate

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time of the day can result in circadian dyssynchrony, associated with metabolic imbalances.

Alcohol consumption

In addition to high-fat diets, recent studies have reported that other lifestyle factors such as chronic alcohol consumption can alter circadian rhythms in peripheral tissues like gut (Swanson *et al.* 2011, Forsyth *et al.* 2013, Summa *et al.* 2013) and liver (Filiano *et al.* 2013, Zhou *et al.* 2014), thus contributing to circadian misalignment and tissue injury. Work from our laboratories revealed that diurnal oscillations in clock genes and CCGs were altered in the liver of ethanol-fed mice exhibiting steatosis (Filiano *et al.* 2013). Importantly, ethanol feeding induced a phase advance in clock gene expression in liver, but not in SCN, indicating dyssynchrony between the master clock in the SCN and the peripheral clock in the liver. Ethanol consumption also altered the diurnal rhythms in several lipid, carbohydrate, and energy metabolism genes (Filiano *et al.* 2013), which were confirmed by findings of Zhou *et al.* (2014). These findings are important because they revealed that chronic alcohol consumption perturbs the circadian clock in the liver and associated downstream metabolic targets. Notably, these results support the hypothesis that ethanol, such as high fat, induces circadian misalignment between molecular oscillators. As a consequence, the peripheral liver clock is no longer in sync with its environment during alcoholic and nonalcoholic fatty liver disease.

Obesity/diabetes

It is clear that circadian dyssynchrony negatively impacts cardiometabolic parameters. What has also become apparent is that cardiometabolic diseases result in circadian dyssynchrony. For example, Young *et al.* (2002) reported that circadian clock gene expression was phase shifted in the rat heart following streptozotocin (STZ)-induced diabetes, an effect that has been confirmed for various peripheral clocks (Oishi *et al.* 2004). Several classic parameters of clock gene expression (e.g. acrophase, amplitude, and mesor) were found to be altered in liver of out-bred male rats treated with STZ or in liver of male spontaneous type 1 diabetes LEW.1AR1-*Iddm* rats (Hofmann *et al.* 2013). Specifically, the acrophase of *Bmal1* and other clock component genes were phase advanced in liver of STZ-treated rats and *Iddm* rats, with insulin treatment normalizing some of the dysregulated clock rhythms. Furthermore, peripheral clocks also appear to be phase shifted in rodent models of type 2 diabetes (e.g. *db/db* mice; Kudo *et al.* 2004). Diet-induced obesity, from unrestricted access to a high-fat diet, altered rhythms in circadian behaviors (activity and feeding), neuropeptides in the hypothalamus, and clock and metabolism gene expression in liver and adipose tissue of mice (Kohsaka *et al.* 2007). Other studies have reported similar findings in response to diet-induced obesity in highly metabolic tissues (Lizier *et al.* 2013, Pendergast *et al.* 2013, Prasai *et al.* 2013, Shi *et al.* 2013, Bravo *et al.* 2014). Recent work by Sassone-Corsi *et al.* has also shown that a high-fat diet disrupts normal circadian oscillations of the molecular clock and clock-controlled metabolites and transcripts in the liver (Eckel-Mahan *et al.* 2013); they propose that these high-fat diet-mediated alterations in metabolism are linked to impaired CLOCK–BMAL1 chromatin recruitment and induction of peroxisome proliferator-activated receptor gamma-mediated oscillations in noncyclic genes (Eckel-Mahan *et al.* 2013). Taken together, these studies support the hypothesis that circadian misalignment consequent to environmental, life-style, and dietary factors most likely contributes to the development of cardiometabolic diseases.

Summary

Time-of-day-dependent oscillations in metabolic homeostatic parameters are consequent to a complex interplay between exogenous (e.g. behavioral) and endogenous (e.g. circadian clock) influences. Cell autonomous circadian clocks regulate metabolism through a number of direct (e.g. control of enzymes within a distinct metabolic pathway) and indirect (e.g. modulation of sensitivity to endocrine factors) mechanisms (Figs 2 and 3). Furthermore, many clock-controlled metabolic processes 'feedback' on the clock mechanism, such that metabolism should be considered an integral component. In general, the primary function of clock control of processes is to prepare the cell/tissue for a predictable event before its onset; through regulation of metabolism, circadian clocks likely allow anticipation of daily fluctuations in energy demand and/or nutrient availability (e.g. increased physical activity during the awake phase). Common behavioral/environmental risk factors for cardiometabolic diseases (e.g. food intake, physical activity, lighting, etc.) are known to influence circadian clocks in a tissue-specific manner, leading to the suggestion that circadian misalignment contributes toward obesity, diabetes mellitus, and cardiovascular disease. Accordingly, strategies designed to normalize circadian clock function represent an attractive therapeutic approach for the treatment of cardiometabolic diseases.

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Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review.

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