Mini-Review

Contributions of White and Brown Adipose Tissues to the Circadian Regulation of Energy Metabolism

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Abbreviations: AgRP, agouti-related peptide; AMPK, adenosine monophosphate–activated protein kinase C; Atgl, adipose triglyceride lipase; Bmal1, brain and muscle aryl hydrocarbon receptor nuclear translocator-like protein 1; BAT, brown adipose tissue; CD36, cluster of differentiation 36; Clock, circadian locomotor output cycles kaput; Cry1/2, cryptochrome 1 and 2; DIT, diet-induced thermogenesis; FAs, fatty acids; FGF21, fibroblast growth factor 21; GCs, glucocorticoids; GLUT4, glucose transporter 4; IL, interleukin; LPL, lipoprotein lipase; mRNA, messenger RNA; Nampt, nicotinamide phosphoribosyltransferase; Npas2, neuronal PAS domain protein 2; Per1-3, period 1-3; PGC-1, PPAR gamma coactivator 1; POMC, proopiomelanocortin; PUFAs, polyunsaturated fatty acids; REV-ERBα/β, reverse erythoblastoma; RORα-γ, retinoic acid-related orphan receptors; ROREs, retinoic acid-related orphan receptor response elements; SCN, suprachiasmatic nucleus; SNS, sympathetic nervous system; SREBP-1c, stimulatory factor-1/2/regulatory element-binding protein-1c; TGs, triglycerides; TNF-α, tumor necrosis factor α; TTFL, transcriptional-translational feedback loop; UCP1, uncoupling protein 1; WAT, white adipose tissue 20211623114

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Abstract

The term energy metabolism comprises the entirety of chemical processes associated with uptake, conversion, storage, and breakdown of nutrients. All these must be tightly regulated in time and space to ensure metabolic homeostasis in an environment characterized by cycles such as the succession of day and night. Most organisms evolved endogenous circadian clocks to achieve this goal. In mammals, a ubiquitous network of cellular clocks is coordinated by a pacemaker residing in the hypothalamic suprachiasmatic nucleus. Adipocytes harbor their own circadian clocks, and large aspects of adipose physiology are regulated in a circadian manner through transcriptional regulation of clock-controlled genes. White adipose tissue (WAT) stores energy in the form of triglycerides at times of high energy levels that then serve as fuel in times of need. It also functions as an endocrine organ, releasing factors in a circadian manner to regulate food intake and energy turnover in other tissues. Brown adipose tissue (BAT) produces heat through nonshivering thermogenesis, a process also controlled by the circadian clock. We here review how WAT and BAT contribute to the circadian regulation of energy metabolism. We describe how adipose rhythms are regulated by the interplay of systemic signals and local clocks and summarize how adipose-originating circadian factors feed-back on metabolic homeostasis. The role of adipose tissue in the circadian control...
of metabolism becomes increasingly clear as circadian disruption leads to alterations in adipose tissue regulation, promoting obesity and its sequelae. Stabilizing adipose tissue rhythms, in turn, may help to combat disrupted energy homeostasis and obesity.

Key Words: circadian clocks, energy metabolism, adipose tissue, BAT, WAT, circadian rhythm, hormones, adipokines, cytokines, thermogenesis, obesity

Molecular and Cellular Circadian Networks

Many aspects of the environment show regular rhythms. For many organisms the most prominent of these rhythms is the 24-hour solar cycle resulting in changes in, for example, illumination, temperature, or food availability. Species throughout all phyla have adapted to these predictable variations by evolving internal timekeepers, so-called circadian clocks (from the Latin “circa diem,” meaning “around a day”).

At the molecular level, the circadian clock of mammals consists of clock genes such as brain and muscle aryl hydrocarbon receptor nuclear translocator-like protein 1 (Bmal1), aka Arntl, circadian locomotor output cycles kaput (Clock) and its analogue, neuronal PAS domain protein 2 (Npas2), cryptochrome 1 and 2 (Cry1/2), and period 1-3 (Per1-3) (Fig. 1A) (1). They interact in a transcriptional-translational feedback loop (TTFL), which comprises the heart of the clock machinery (2). Briefly, in the morning BMAL1 and CLOCK heterodimerize and bind to E-box enhancers in the promoters of Per and Cry genes (3). Over the course of the day PER and CRY proteins translocate into the nucleus, where they inhibit CLOCK:BMAL1-mediated transcription, including their own (4). Gradual degradation of PER and CRY during the night is controlled by the casein kinases and F-box ubiquitin transferases, thus resulting in disinhibition of CLOCK:BMAL1 toward the next morning (1). This core loop is stabilized by a second TTFL in which retinoic acid-related orphan receptors (RORα-γ) and reverse erythroblastoma (REV-ERBα, aka NR1D1/2) proteins compete for binding to retinoic acid-related orphan receptor response elements (ROREs) in the promoter of Bmal1 (5). Thereby, RORs activate whereas REV-ERBs inhibit Bmal1 gene expression. A third feedback loop consists of D-site albumin promoter binding protein and nuclear factor interleukin 3 regulated (Nfil3, aka E4bp4), which modulate gene expression by binding to D-boxes in the promoters of several clock genes, for example, Per1-3, Rev-Erbβ, Roraβ, and Cry1 (5-10). The role of D-boxes as additional feedback loops is still a current research topic. So far it is assumed that D-box regulation is involved in circadian signaling. However, mice deficient for E4bp4 do not show differences in circadian oscillation (6). These interlocked TTFLs drive circadian gene expression of thousands of tissue-specific clock-controlled genes throughout the day (11, 12).

Molecular clocks are found in all cells and tissues. This circadian clock network is organized in a hierarchical manner with a master pacemaker located in the suprachiasmatic nucleus (SCN) of the hypothalamus (13). The most prominent, the zeitgeber—an external time signal entraining the endogenous circadian clock—is light. Light reaches melanopsin (OPN4) expressing intrinsically photosensitive retinal ganglion cells that directly project to the SCN through the retinohypothalamic tract (14, 15). In this way, the SCN aligns its internal rhythm with the external light-dark cycle. In the absence of regular light input, the endogenous circadian rhythm is maintained, showing a “free-running” species-specific period close to 24 hours (2). From the SCN, behavioral, neuronal, and humoral signals transmit internal time to peripheral tissues (Fig. 1B) (16). Apart from light, other zeitgebers can influence the circadian clock network. The timing of food intake, for example, is a potent zeitgeber of peripheral tissue clocks while only marginally affecting the master pacemaker (17, 18).

Adipose Functions in Metabolism

Most adipose tissue depots in mammals are classified as “white” (19) with spherical cells of variable size (25-200 µm) and a single large lipid droplet. Brown adipocytes, on the other hand, are smaller (15-60 µm) and contain multiple small lipid droplets as well as much more mitochondria (20). One main function of white adipose tissue (WAT) is the storage of energy. Stimulated by insulin, glucose and lipoprotein-derived fatty acids (FAs) are taken up by the adipocyte where they are converted into triglycerides (TGs) (21, 22). If energy levels drop, stored TGs are broken down during lipolysis and released as glycerol and FAs that can then both be used as energy sources by other organs (23, 24). WAT is also an important endocrine organ. White adipocytes release adipokines such as leptin and adiponectin to regulate metabolic functions in other peripheral tissues and the brain (24).

Brown adipose tissue (BAT) differs morphologically from WAT. Brown adipocytes convert energy into heat by nonshivering thermogenesis (20). Cold exposure as well as noradrenergic stimulation lead to β-adrenergic excitation, which then induces lipolysis in brown adipocytes (22, 25). The resulting FAs activate uncoupling protein 1 (UCP1), which forms a proton leak in
Oscillating Signals Regulate White Adipose Tissue Metabolism

Metabolic homeostasis is regulated by the interaction of different organs, including liver, pancreas, adrenal, and adipose tissue, in a circadian manner. Involved tissues release factors or stimulate the autonomic nervous system to mediate the metabolic state to other participating organs. WAT is a target tissue that receives and integrates numerous signals. WAT metabolism is strongly controlled by the interplay of 2 pancreatic hormones, β-cell–derived insulin and α-cell–derived glucagon, both of which are regulated by energy intake while also showing underlying circadian rhythms in plasma levels controlled by the SCN (27). Besides regulation by the SCN, cell-autonomous clocks in α and β cells control the circadian release of locally produced hormones (28-31). α- and β-Cell clocks show distinct phases in vivo and in vitro, with the α-cell clock being phase delayed by 1 to 2 hours compared to β cells. Cell type–specific clocks regulate the transcription of key genes involved in glucose sensing and hormone release (28). Together, the findings show that insulin—but also glucagon—release is regulated by the intrinsic clock in the distinct cell types and is affected by metabolic state. Food intake increases circulating FAs, amino acids, and glucose, which triggers the release of insulin from pancreatic β cells, resulting in a peak of blood insulin levels in the middle of the active phase (27, 28). In adipocytes, insulin inhibits lipolysis and activates lipogenesis (Fig. 2) (32-34). Insulin-mediated repression of lipolysis is regulated via the mammalian target of rapamycin complex 1 (mTORC1)-early growth response element 1 pathway, which inhibits adipose triglyceride lipase (Atgl) promoter activity, encoding a key enzyme of lipolysis (32), and other key proteins of the lipolytic pathway including hormone-sensitive lipase (HSL) and perilipin (35-39). On the other hand, insulin increases glucose and FA uptake as well as FA synthesis and TG storage by glucose transporter 4 (GLUT4, aka SLC2A4) translocation and activating upstream stimulatory factor-1/2/regulatory element-binding protein-1c (SREBP-1c)- and carbohydrate-response element binding protein-α/β (ChREBP-α/β)-mediated target gene expression, respectively (40). Insulin sensitivity is gated by the clock (41-43). In vitro studies suggest that insulin action, that is, activation of the protein kinase B–pathway, depends on adipose clock function at least in subcutaneous adipose tissue (41). Glucagon, released from pancreatic α cells as a signal of low energy, is a strong counterregulatory signal of insulin and displays high levels in the transition of rest to activity phase. Although it is still not clear whether adipocytes actually express the glucagon receptor, the hormone induces adipose lipolysis. Glucagon’s effects may be mediated by stimulation of the sympathetic nervous system (SNS), which induces lipolysis via β-adrenergic pathways (44-47).

Fibroblast growth factor 21 (FGF21) is regulated by NFIL3 (aka E4BP4) and peaks during the fasting period (48). It is predominantly synthesized in the liver and regulates carbohydrate and lipid metabolism (48-50). In lean
mice, FGF21 increases adipose lipid uptake through cluster of differentiation 36 (CD36) and lipoprotein lipase (LPL). Conversely, in insulin-resistant obese mice, FGF21 increases catabolism of TGs in BAT while inducing WAT browning by an increase in PGC-1α protein levels (51-53).

FGF21 potently lowers blood glucose levels by increasing glucose uptake into the liver, WAT, and BAT (54, 55) via adiponectin (56, 57). Moreover, adiponectin seems to mediate FGF21-induced energy expenditure (57). Ghrelin, a stomach-derived hormone, shows a diurnal oscillation with increased levels during fasting and low levels during feeding phases (58-60), and its messenger RNA (mRNA) expression and release are disrupted in Bmal1 knockouts (60). Ghrelin promotes lipogenic gene expression in WAT via autonomic stimulation (61, 62) or directly through activation of its receptor, growth hormone secretagogue receptor, which is expressed in adipocytes of old, but hardly detectable in young, mice (63).

Glucocorticoids (GCs) are secreted from the adrenal in a circadian manner and in response to stress. The adrenal clock gates the sensitivity to incoming signals and regulates GC rhythms (64). The local clock is important for rhythmic production of steroidogenic genes but seems to be dispensable for rhythmic GC output (65, 66). Global clock disruption deletes rhythmic GC output (64, 67). GCs promote adipocyte differentiation (68-70). Dampered GC rhythms result in increased lipid accumulation and body weight gain due to upregulation of the FA transporter Cd36 (71). Hypercortisolemia increases lipolysis while at the same time promoting visceral adiposity, probably by enhanced preadipocyte differentiation (69, 72). GCs stimulate the expression of Hsl, Atgl, and Lpl, key enzymes of the lipolytic pathway, in a dose-dependent manner (73-76). At the same time, GCs promote adipose insulin resistance by downregulating the expression of GLUT4 plasma membrane translocation (77-79). GC effects are dependent on 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1), which might be a promising target to counteract GC-mediated adiposity and insulin resistance (74). In subcutaneous, but not in visceral adipose tissue, GC decreases lipolysis by reducing the expression of Hsd (80). This strongly suggests that the effects of GCs on adipose tissue metabolism are depot dependent.

Together, WAT physiology is regulated by numerous incoming oscillating signals in a circadian manner. Insulin and ghrelin, signaling the feeding:fasting state, activate lipogenic gene expression. Insulin and FGF21 increase lipid and glucose uptake at different times of day to maintain energy homeostasis. Glucagon and GCs, both peaking around activity onset, stimulate lipolysis to fuel the body in the transition from rest to the active state.

**Figure 2.** White adipose tissue (WAT) function is regulated by numerous rhythmic signals originating from other peripheral or central tissues. The circadian clocks in white adipocytes are essential for proper WAT function. WAT releases adipokines and cytokines in a circadian manner, regulating food intake, insulin sensitivity, and inflammation. ANS indicates autonomic nervous system; IL, interleukin; TNF, tumor necrosis factor.
adipose tissue adapts to daily variations of energy availability and needs to maintain energy homeostasis. Adipocyte clocks regulate the local transcriptome in a circadian manner including key enzymes of lipogenesis and lipolysis, for example, Atgl, Hsl, caveolin 2, acyl-CoA synthetase (Acs1l), phosphatidate phosphatase (Lpin1), Lpl, peroxisome proliferator-activated receptor α (Ppara), PPAR gamma coactivator 1-β (Pgc1β), Srebp-1α, and Ppary2 (81-86). BMAL1:CLOCK activate gene expression of Atgl and Hsl via binding to E-box promoter elements (81). Most of those diurnal rhythms are lost in obese individuals with type 2 diabetes (83, 87). The physiological significance of adipose tissue clocks has been demonstrated in numerous studies. Bmal1-deficient embryonic fibroblasts show impaired differentiation into adipocytes (82). BMAL1:CLOCK dimers regulate adipogenesis via the Wnt signaling pathway (88, 89). Genetic disruption of the circadian clock by mutations in Clock leads to increased adiposity on regular chow in a genetic background-dependent manner. In both strains, Clock mutants show blunted or lost rhythms in serum TGs, FAs, and glycerol, indicating impairments in fat absorption and lipolysis (81, 90). The latter was attributed to decreased transcription of Atgl and Hsl (81). Adipocyte-specific knockout of Bmal1 leads to obesity under high-fat diet conditions, probably due to changes in circulating polyunsaturated FAs that centrally affect food intake rhythms. This idea is supported by the aberrant expression of hypothalamic neuropeptides involved in appetite regulation in those mice (91). Together, the existence of a circadian adipocyte-hypothalamus axis emphasizes the importance of a functional adipose tissue clock for the circadian regulation of energy homeostasis.

Overexpression of Bmal1 increases the expression of lipogenesis-related genes in WAT (82). BMAL1:CLOCK induce Ppar expression via E-box binding (92, 93). PPARγ in particular is crucial for adipocyte differentiation and adipogenesis (94-96). PPARs also feed-back on Clock gene expression. PPARγ induces Rev-Erbα expression in adipose tissue whereas PPARα activates Bmal1 transcription in the liver (97, 98). PER2, being part of the negative limb of the core TTFL, directly inhibits expression of PPARγ target gene expression by suppressing PPARγ binding to PPAR response elements (99). The clock modulator—differentiated embryo chronicodrocyte protein 1 (DECI) prevents PPARγ-mediated target gene expression, thereby promoting circadian oscillations in these genes. In line with this, Dec1 deficiency leads to a pronounced increase in gene expression related to FA biosynthesis, lipid storage, and lipolysis in the dark phase as well as a loss of circadian variation in serum FAs (100). Expression of the nuclear receptors Rev-Erbαβ and ROARαβ peaks at the end of the light phase in mice. Srebp-1c, Ppary, as well as adiponectin and leptin also exhibit diurnal mRNA rhythms peaking at night (101). Genetic disruption of Rev-Erbα is associated with decreased SREBP1 and SREBP2 activity (102). REV-ERBα regulates SREBP activity and bile acid metabolism in the liver (102). In muscle, REV-ERBβ is recruited to the Srebp-1c promoter, inducing gene expression (103). Thus, REV-ERB agonists may be promising candidates to treat obesity by increasing energy expenditure and, thereby, improving dyslipidemia and hyperglycemia through alterations in circadian gene expression of metabolic genes (104).

In summary, the circadian clock is important for adipocyte differentiation and the rhythmic expression of lipogenic and lipolytic genes. Clock proteins regulate the activity of proteins involved in WAT metabolism that, in turn, control rhythmic FA release. FAs signal the metabolic state to the brain, adjusting food intake. Circadian disruptions in WAT metabolism lead to alterations in adipogenesis, lipid mobilization, and food intake, promoting obesity.

**Rhythmic Output from White Adipose Tissue Regulates Metabolism**

Metabolic homeostasis is regulated by factors released by, inter alia, WAT in a circadian manner. Such factors modulate the physiology of other tissues and are integrated at a central level to control food intake. One of the main functions of WAT is the storage of lipids and release of lipolytic products. The latter—as FAs and glycerol—exhibits a prominent circadian rhythm in mice and humans that is only partly driven by food intake (81, 90, 100, 105). A loss of polyunsaturated FA (PUFA) rhythms induces alterations in the expression of appetite-regulating neuropeptides and increases food intake. Decreased PUFA levels are accompanied by reduced expression of long-chain fatty acid elongase 5/6 (Elov5/6) and stearoyl-CoA desaturase 1 (Scd1), key enzymes in PUFA biosynthesis (91, 106). Restoration of PUFA content in the hypothalamus rescues food intake rhythms, body weight development, appetite-regulated neuropeptide expression, and energy homeostasis (91). This clearly shows the crucial role of oscillating lipolytic output for whole-body metabolic homeostasis.

WAT is also an endocrine organ releasing adipokines in a circadian manner that contribute to the regulation of metabolism throughout the body (Fig. 2). Secretion of leptin, one of the best studied adipokines, is stimulated by insulin but is also regulated by adipose tissue clocks (107, 108). The diurnal leptin pattern is maintained under regular feeding of 6 meals a day but is abolished by lesioning the SCN, which suggests that leptin secretion is controlled by the circadian clock (109). In vitro studies reveal that the adipocyte clock regulates leptin secretion. Although mRNA expression of
Adiponectin increases the role in the regulation of energy expenditure and insulin resistance (129). As mentioned earlier, it plays a crucial β-adrenergic receptor expression. Furthermore, leptin stimulates β-adrenergic receptors and, thereby, increases expression of Ucp1 in BAT (124). Despite the effects on BAT, leptin activates β-oxidation in peripheral tissues, for example, muscle and liver, via adenosine monophosphate-activated protein kinase C (AMPK) signaling (125). Thereby, leptin prevents lipid accumulation in such tissues. Furthermore, leptin directly suppresses the release of GCs, which play an important role in glucose and lipid homeostasis (70, 126, 127). Adiponectin is expressed in a circadian manner in adipose tissue (128) as a target gene of PPARγ and PGC1α and stimulating the expression of anorexigenic Pmc. Chronic jet lag promotes obesity probably by central leptin resistance and downregulation of leptin transcription (122). Leptin’s effects on energy expenditure may in part be mediated by BAT activation. A recent discovery suggests that the thermogenic effect of leptin may be regulated by PGC-1α. Adiponectin seems to inhibit Ucp1 expression via inhibition of β-adrenergic receptor expression (135). Expression of adiponectin receptors (Adipor1 and 2) exhibits a circadian oscillation in adipose tissue and in the mediobasal hypothalamus (128, 136). The adipokine signals the peripheral metabolic state to the brain, which in combination with blood glucose levels results in adjustment of food intake (137, 138). Its action is mediated by AMPK signaling (139). Adiponectin also induces Bmal1 expression in the mediobasal hypothalamus that then locally regulates the expression of orexigenic neuropeptides (136). These findings suggest a mechanism by which peripheral circadian clock disruption may alter food intake rhythms, promoting the development of metabolic disorders.

Serum visfatin levels, encoded by nicotinamide phosphoribosyltransferase (Nampt), exhibit a diurnal rhythm that is inversely related to leptin (140-143). Nampt expression rhythms are shifted by sleep deprivation, negatively affecting glucose homeostasis (142). Visfatin/NAMPT also catalyzes the rate-limiting step in the nicotinamide adenine dinucleotide (NAD+) salvage pathway. Nampt expression is regulated by the circadian clock and modulates the core TTFL by regulating the activity of the histone deacetylase SIRT1 (143). Its insulin-mimetic function is controversial and still under investigation (144-146). However, it has become more evident that visfatin has a proinflammatory function and most studies agree on a positive correlation between fat mass and visfatin levels (147-150). Infiltrated immune cells might be a major source of visfatin expression (149, 151). Circulating visfatin levels are positively correlated with proinflammatory cytokines such as interleukin-6 (IL-6) and C-reactive protein, and visfatin expression is strongly correlated with expression of tumor necrosis factor α (Tnf-α) and IL-6 (148, 150, 152). Thus, increased visfatin may have deleterious effects on energy homeostasis. In fact, visfatin induces insulin resistance in the liver partly via induction of inflammatory pathways and induces FA-mediated neuroinflammation (152, 153).

Resistin reduces insulin sensitivity and shows a circadian rhythm trailing that of insulin and suggesting a negative feedback on insulin action (154). Circadian rhythms in resistin expression are stimulated by rhythmic input of insulin. In obesity, concomitant with insulin resistance, rhythmic resistin expression is blunted or abolished (155, 156). In humans, resistin is mainly expressed by macrophages whereas its main source in rodents are adipocytes. Gene and protein structures differ between humans and rodents, accounting for their different functional roles (157). Human resistin activates circadian expression of proinflammatory cytokines, such as TNFα, IL-6, and IL-12, which contribute to development of insulin resistance and inflammation (158, 159). In turn, such cytokines enhance resistin expression (160). Neutrophils are the first immune cells to infiltrate adipose tissues after a dietary challenge (161). Neutrophils, in turn, attract further immune cells including macrophages, which then reduce insulin sensitivity and induce chronic inflammation (162, 163). TNFα, predominantly released by macrophages, promotes lipolysis (164) and inhibits the expression of perilipin, a protein associated with fat storage (164, 165). Furthermore, it decreases GLUT4 and LPL expression (166). As such, high TNFα levels inhibit insulin-mediated glucose uptake (167, 168) and promote the development of insulin resistance, for example, in obese individuals (167, 169). GC treatment inhibits TNFα-mediated insulin resistance but also
Circadian Aspects of Brown Adipose Tissue Metabolism Crosstalk

The main function of BAT is the conversion of energy into heat by nonshivering thermogenesis (20). Heat production in BAT is achieved by β-oxidation or through uncoupling of mitochondrial proton transport from energy production by UCP1 (171). BAT heat generation allows mammals to keep their body temperature more constant and cope with cold temperature environments. On a cold stimulus, autonomic activation leads to a release of noradrenaline at BAT terminals. Activation of β1-adrenergic receptors in brown adipocytes results in G protein–controlled activation of the protein kinase A pathway and further gene expression of metabolic genes, including Ucp1 (171). Additionally, this pathway activates ATGL to yield FAs that then further stimulate UCP1 (26, 171).

Heat production in BAT is also induced by a carbohydrate-rich meal (diet-induced thermogenesis or DIT; Fig. 3) through autonomic adrenergic activation (172, 173). Hormones originating from the gut as well as bile acids are also able to stimulate DIT (174). Gut-derived cholecystokinin (CCK) and secretin activate BAT thermogenesis via vagal afferents and sympathetic efferents and UCP1 activation (174). Ghrelin rhythms affect Ucp1 expression, and its secretion is reduced after food intake (175, 176). By using DIT, our body is able to partly reduce excessive energy uptake from food and thereby avoid energy storage in the form of fat (171). The induction of BAT postprandial thermogenesis leading to glucose and FA uptake might be stimulated by insulin (173). Interestingly, UCP1 seems to be essential because mice with ablated UCP1 no longer show diet-induced thermogenesis but gain weight instead (177). Endocrine circadian factors such as the pineal hormone melatonin (156, 157) modulate the capacity of BAT for nonshivering thermogenesis (171). In rodents, GCs downregulate UCP1 and, thereby, BAT thermogenesis. In humans, they have the opposite effect (178).

Like WAT, BAT is also involved in the circadian regulation of energy metabolism. However, because BAT function is not primarily endocrine, the focus of metabolic regulation is connected to the clearance of metabolic factors from the bloodstream as well as affecting the capacity of thermogenesis in brown adipocytes. The circadian clock and metabolic regulation of BAT are tightly connected. Chronic rhythm disruption by repeated shifting of the light-dark cycle leads not only to whitening of the BAT but also reduces UCP1 expression in rats (179).

Glucose as well as TG/FA uptake in BAT is rhythmic, with a maximum at the end of the inactive or in the beginning of the active phase, respectively (180-183). Enzymes involved in TG breakdown such as LPL also show their maximum activity and expression in the beginning of the active phase (180, 183). This indicates a role of BAT in circadian gating of FA, TG, as well as glucose clearance (180, 183, 184). In line with this, thermogenesis is higher in the active phase (182). Because high BAT activity in humans is associated with reduced glycemia, these data suggest that sufficient BAT could stabilize glucose fluctuations throughout the day and thereby maintain glucose homeostasis (184). Interestingly, glucose uptake in human BAT is increased in the morning, correlating with high Ucp1 and Glut4 gene expression (184, 185). FGF21 seems to be important for BAT glucose clearance. It inhibits temperature decreases in BAT and ameliorates normal glucose clearance by controlling stable BAT temperature and, thereby, BAT thermogenesis (186). Interestingly, BAT thermogenic activity also increases the local release of FGF21, indicating the existence of a paracrine feedback (187).

Circadian thermogenic plasticity is controlled by REV-ERBα as shown in mice that cope better with cold temperatures at times of low REV-ERBα expression (189). REV-ERBα represses UCP1. In turn, cold temperatures downregulate Rev-Erbα, leading to an induction of UCP1 to increase thermogenesis. REV-ERBα depletion leads to the complete loss of body temperature rhythms and BAT activity with overall higher body temperature (189). This emphasizes the importance of the circadian regulation of BAT metabolism. Interestingly, the SCN itself is involved in plasma TG variations by regulating lipid uptake into BAT through the control of REV-ERBα (182, 190). This fuels the assumption that disturbed circadian rhythms contribute to hyperlipidemia (190).

In summary, circadian regulation of metabolism by BAT mainly involves regulating the uptake and clearance of glucose and lipids from the circulation. In addition, the capacity of thermogenesis is regulated by the circadian clock within BAT, but also by circadian hormones such as melatonin and GCs (see Fig. 3).

Conclusion

The role of WAT and BAT depots in the circadian regulation of metabolism becomes increasingly clear. Both fat depots harbor intrinsic clocks that regulate the tissue-specific
transcription of many key genes involved in lipogenesis and lipolysis in WAT and thermogenesis in BAT. WAT regulates feeding behavior, carbohydrate metabolism, and energy expenditure by releasing adipokines and FAs in a circadian manner. In this way, metabolism is modulated as a function of the peripheral energy state through central integration of feedback signals to respond to the organism’s needs. BAT, in turn, contributes to the circadian regulation of energy substrates in the circulation. In recent years, research has mostly focused on characterizing the effects of (tissue) clock disruption on energy metabolism. Circadian studies have helped us understand how incoming signals and WAT physiology are integrated at the tissue level to generate coherent output that, in turn, regulates food intake and modulates the physiology of other organs involved in metabolic homeostasis. Thus, adipose tissues not only possess a lipid storage and thermogenesis function, but are important regulators of energy homeostasis. From a clinical point of view, it will be important to dissect the regulatory mechanisms controlling circadian rhythms in adipose tissues. Together, recent findings have changed our view on adipose tissue as storage tissue and emphasize its role as a possible therapeutic target. Such knowledge may help us devise adipose depot-specific chronopharmacological approaches to counteract the misbalanced energy homeostasis that has become so prevalent in modern societies.

Clock modulators like nobiletin, a RORα/β agonist, may be putative therapeutic agents. Nobiletin promotes adipocyte differentiation, stimulates lipolysis by induction of, for example, Pparγ expression, improves insulin resistance, and decreases adipocytokine expression (191-194). Another possible therapeutic approach may be the use of light. Very recent findings show that light increases lipolysis and mitochondrial activity via Opsin3 signaling in adipose tissues (195, 196). Chronotargeted approaches might be useful to modulate adipose tissue activity, and future studies are needed to evaluate their beneficial effects in humans.

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**Additional Information**

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**Figure 3.** Brown adipose tissue (BAT) function is modulated by numerous rhythmic signals originating from other peripheral or central tissues as well as circulating metabolites such as glucose and fatty acids (FAs). The circadian clock in brown adipocytes is essential for proper BAT function. BAT produces heat via nonshivering thermogenesis, affecting body temperature. ANS indicates autonomic nervous system; CCK, cholecystokinin; SNS, sympathetic nervous system.
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