Autonomic Neuroscience: Basic and Clinical 219 (2019) 66–70

Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

journal homepage: www.elsevier.com/locate/autneu

Review

The circadian clock control of adipose tissue physiology and metabolism

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ARTICLE INFO

Keywords:
Circadian clock
Adipose tissue
Lipolysis
Lipogenesis
Thermogenesis
Food intake

ABSTRACT

The circadian clock organizes the timing of physiological processes in anticipation of diurnal environmental changes that originate from the rotation of the Earth. Several of the metabolic functions of adipose tissues are under regulation by the circadian clock to achieve temporal coordination and whole body homeostasis. Adipose tissues, once believed to only express physiological phenotypes that are downstream of central nervous system regulation, are now well described to communicate not only to other peripheral tissues, but also to the central nervous system for temporal orchestration of metabolism. In this review, we will cover the involvement of the circadian clocks, both master and adipocyte clocks, in the regulation of adipose tissue physiology and the associated consequences for energy homeostasis.

1. Introduction

Life has adapted to daily environmental fluctuations, governed by the Earth's rotation, by evolving mechanisms that anticipate change and adjust physiological processes at the most advantageous time of day. As a result, the majority of biological functions, including adipose tissue physiology, exhibit daily rhythmicity. These diurnal oscillations are evoked by circadian clocks (Takahashi, 2017). Moreover, the intricacy of this circadian regulation manifests in what has been described in the literature as a complex suite of cellular, physiological, and behavioral interactions. Naturally, such complexity extends to adipose tissue as various aspects of its biology fall within the purview of a clock-controlled regulatory paradigm. To address the nature and extent of circadian involvement in adipose tissue, the following is a discourse on the specific clock components that have been found to exercise control over various physiological phenomena both locally in adipose tissue and more universally in whole-body energy homeostasis.

2. The circadian clock

Circadian rhythmicity in mammals involves a central cell-autonomous transcriptional-translational feedback loop (TTFL) comprising a positive (activating) and a negative (inhibiting) regulatory arm. The transcription factors Brain and Muscle ARNT-Like 1 (BMAL1) (also known as ARNTL) and either of Circadian Locomotor Output Cycles Kaput (CLOCK) or Neuronal PAS domain protein 2 (NPAS2) comprise the core of the positive arm and bind to the *E*-box domains of genes during the day to drive expression of core repressor elements of the negative arm, Period (PER) 1, 2, 3, and Cryptochrome (CRY) 1, 2. During the early night, PERs and CRYs translocate to the nucleus, form large complexes (Kim et al., 2014b), and repress the transcriptional activity of BMAL1:CLOCK/NPAS2, thus downregulating their own expression. Degradation of PER and CRY during the late night ends this repression and allows the start of a new transcriptional cycle with a period of approximately 24 h. Additionally, BMAL1:CLOCK/NPAS2 activates the transcription of several key nuclear hormone receptors including REV-ERB (also known as nuclear receptor subfamily 1, group D (NR1D) α and β, and RAR-related orphan receptor (ROR) α, β, and γ, which in turn suppress (REV-ERBs) or activate (RORs) *Bmal1* expression via binding to RRE regulatory elements. The function and timing of the transcriptional feedback loops is regulated by post-translational modifications affecting the stability and degradation of the transcription factors (Hurley et al., 2016) and epigenomic regulation of their transcriptional activity (Sahar and Sassone-Corsi, 2013). This molecular oscillator, called the circadian clock, exists in almost all cells/tissues in mammals. The rhythmic binding of BMAL1:CLOCK/NPAS2 and REV-ERB/ROR to their DNA binding sites drives the rhythmic expression of a substantial number of genes that ultimately generates rhythms of physiology.

The circadian clocks of different cells/tissues are organized to achieve circadian rhythm coordination. The circadian clocks of the suprachiasmatic nucleus (SCN), located in the anterior hypothalamus of the brain, comprise a central pacemaker that receives light information from specialized melanopsin expressing, intrinsically photosensitive ganglion cells in the retina via the retinohypothalamic tract. The SCN pacemaker synchronizes its phase to light phase (Dibner et al., 2010)

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https://doi.org/10.1016/j.autneu.2019.05.001
Received 12 March 2019; Received in revised form 8 April 2019; Accepted 7 May 2019

and transmits circadian clock phase information to other brain regions and peripheral organs, including the adipose tissue, via neuronal connections (Vujovic et al., 2008) and endocrine signals (Balsalobre et al., 2000; Reddy et al., 2007; Vujovic et al., 2008). In addition to direct synchronization cues from the SCN, circadian clocks of peripheral organs respond to entrainment signals – known as *zeitgebers* (German: literally "time givers") such as food intake (Damiola et al., 2000; Stokkan et al., 2001) and temperature (Buhr et al., 2010). Synchronization of peripheral clocks to food intake and temperature may be in phase with the SCN as a result of the feeding rhythms and body temperature rhythms imposed by the SCN, or out of phase with the SCN due to environmental change or temporally aberrant behavior. Communication between circadian clocks within and between tissues, as well as feedback signaling from peripheral clocks to the central clock, facilitates circadian organization at the level of the organism. However, the details of this communication remain elusive.

3. Adipose tissue types and their relevant characteristics

The molecular makeup of the circadian clock is essentially identical among cell types, including the neurons of the SCN and the cells of adipose tissues. Adipose tissue presents in three distinct categories: white, brown, and beige/brite. These delineations are both biologically relevant to form and function and physiologically meaningful for circadian regulatory architecture.

The first and most abundant adipose tissue type in mammals is white adipose tissue (WAT). Anatomically, WAT is characterized by cellular heterogeneity, consisting of pre-adipocytes, adipocytes, stem cells, fibroblasts, neutrophils, macrophages, lymphocytes, and endothelial cells (Esteve Rafols, 2014). While clock genes have been found in most of these cell types (Hayashi et al., 2007; Nagoshi et al., 2004; Takeda et al., 2007; Wu et al., 2007), the phase of clock gene rhythmicity, as well as relative cellular constituency, is driven by temporal factors within various biochemical pathways and by anatomical location (e.g. subcutaneous depots vs. visceral depots) (Lee et al., 2013; Zanquetta et al., 2012). In addition to its cellular makeup, white adipose contains uniocular lipid droplets which signify its status as a major storage and regulatory center for energy in the form of triacylglycerides (TAGs). While it was originally believed to play a passive role in balancing energy budgets, the discovery of its ability to serve as an endocrinological entity in the late 1980s, coupled with the subsequent discovery of leptin, a key cytokine-like hormone factor, resulted in a paradigm shift within the metabolic literature. Ultimately, much of what has been garnered in the literature regarding nuanced clock homeostatic energetics comes from work done on this tissue.

Brown adipose tissue (BAT), despite being a class of adipose, is derived from a different cellular precursor than WAT, as exemplified by a (rather complicated) developmental lineage that is more akin to that of muscle cells (Seale et al., 2008). This relates to its distinction of having high mitochondrial density, which in turn is correlated with its claim to fame as a temperature regulator. More precisely, BAT converts chemical energy (ATP) into heat through the uncoupling of lipid oxidation in mitochondria – a phenomenon phenotypically referred to as non-shivering thermogenesis. To achieve this, BAT mitochondria contain a larger proportion of a transmembrane protein known as uncoupling protein 1 (UCP1). UCP1 effectively decreases the normal proton gradient established via oxidative phosphorylation through a shift in the permeability of the inner mitochondrial membrane. In doing so, protons pumped into the intermembrane space by ATP synthase are able to return to the mitochondrial matrix, thus disrupting the relative concentration of protons on either side of the membrane. What would normally result in a predominance of ATP production is now lost as heat through oxidation in an uncoupled system. In addition to dense mitochondrial presence, BAT can be identified histologically by its multi-ocular lipid droplets. Unlike WAT, BAT is restricted to depots within the interscapular region and, barring cold-induction manipulations, is more prevalent in human infants and small mammals.

Lastly, beige or brite (literally "brown-in-white") adipose tissue is developmentally related to WAT, but exhibits functional plasticity in terms of its ability to function like BAT (Wu et al., 2013). As its name suggests, it is found within WAT and represents an interesting case of adaptive and inducible transdifferentiation. Beige adipose is multiocular, expresses UCP1, and exhibits a mitochondrial density comparable to BAT despite WAT origins. Its status presents a conundrum to the current classification scheme, and research in this domain is currently in its infancy (Rosen and Spiegelman, 2014).

4. Circadian clock and adipocyte differentiation

Findings from both *in vitro* and *in vivo* studies implicate the circadian clock with adipocyte differentiation. In an early study by Shimba and colleagues, mouse embryonic fibroblasts from *Bmal1* knockout mice failed to differentiate into adipocytes (Shimba et al., 2005). In contrast, a later study from Guo and colleagues showed increased adipogenic differentiation in mouse embryonic fibroblasts from Bmal1 knockout mice (Guo et al., 2012). In this study, BMAL1 is found to activate the Wnt signaling pathway and suppress adipogenesis (Guo et al., 2012). In agreement with the findings of this study, animals with global deletion of *Bmal1* (Guo et al., 2012; Kennaway et al., 2013), as well as adipocyte specific deletion of *Bmal1* (Paschos et al., 2012), show increased adiposity. Although increased adiposity in mice lacking *Bmal1* may be the result of changes in lipogenesis and/or lipolysis, as we discuss further below, the increased adiposity of these animal models does not support the requirement of *Bmal1* for adipocyte differentiation. While the involvement of BMAL1 in the Wnt pathway is tied to its repressive impact in white adipocyte differentiation, BMAL1 also functions as a repressor in brown adipocyte differentiation, specifically in mesenchymal lineage commitment, yet its path of influence is via the TGFβ cascade and associated BMP signaling pathways (Nam et al., 2015b). Since REV-ERBα is not only the negative regulator of *Bmal1*, but also a repressor of several TGFβ pathway components (Nam et al., 2015a), its positive role in adipocyte differentiation is not altogether surprising. That said, much less is currently known regarding control and regulation of brown adipocyte differentiation when compared with white adipocytes. REV-ERBα is found to exert transcriptional repression of key genes of the TGF-β pathway, e.g. *Tgfbr2* and *Smad3*, and is therefore a positive regulator in brown adipocyte generation *in vivo* (Nam et al., 2015a). Additional *in vitro* analysis and *ex vivo* studies determined that REV-ERBα operates in a cell-autonomous manner (Nam et al., 2015a).

PPARγ, a master regulator of adipogenesis, is required for adipocyte differentiation (Kim et al., 2014a; Rosen et al., 1999). *In vivo* mouse knock-out studies have shown that a lack of PPARγ from the embryonic stage results in an absence of postnatal adipogenic capability (Kubota et al., 1999). PER2 has been found to directly bind to PPARγ and block its recruitment to promotor targets (Grimaldi et al., 2010). By blocking PPARγ transcriptional activity, PER2 was shown to downregulate mouse embryonic fibroblast differentiation to adipocytes (Grimaldi et al., 2010). Another Period protein, PER3, appears to inhibit differentiation of mesenchymal stem cells into adipocytes. Overexpression of PER3 was found to prevent differentiation into adipocytes, while deletion of PER3 enhanced differentiation (Costa et al., 2011). More recently, endogenous adipose-depot resident bona fide adipocyte precursor cells (APCs) were used to show that PER3 downregulates adipogenesis by direct regulation of Kruppel-Like factor 15 (KLFL5) expression in complex with BMAL1 (Aggarwal et al., 2017). In addition to Period proteins, the circadian clock regulated protein nocturnin binds to PPARγ in adipocytes to increase adipogenesis (Kawai et al., 2010).

REV-ERBα protein expression was found to be required for early cell proliferation during adipocyte differentiation with a concomitant nadir in associated mRNA levels; however, this pattern reverses at later

stages, and expression of *Rev-erbα* mRNA effectively prevents adipogenesis via repression of PPARγ while protein levels are low (Wang and Lazar, 2008). Despite this, *in vivo* studies on *Rev-erbα* knockout mice yielded individuals with normal amounts of adipose tissue (Chomez et al., 2000; Delezie et al., 2012). This result, however, may be attributed to compensation by REV-ERBβ.

5. Circadian control of lipid metabolism

White adipose tissue serves as an important storage depot for lipids in the form of triglycerides. In response to diurnal variations in energy demands and availability, fatty acids are released from WAT through hydrolysis of triglycerides to free fatty acids and glycerol (lipolysis) and are synthesized with glucose into triglycerides for storage in lipid droplets (lipogenesis). The circadian clock coordinates the timing of these processes by controlling key enzymes in the respective pathways. PER2 interacts with PPARγ to repress its transcriptional activity and reduce the synthesis of saturated and monounsaturated fatty acids in WAT (Grimaldi et al., 2010). Deletion of *Per2* in mice increases fatty acid oxidation with a concurrent reduction in triglyceride levels in white adipose tissue (Grimaldi et al., 2010). Administration of synthetic REV-ERBα/β agonists reduces the expression of the genes encoding diacylglycerol O-acyltransferases (*Dgat1, 2*) that catalyze the conversion of diacylglycerides to triacylglycerides, Perilipin 1 (*Plin1*) that surrounds lipid droplets and inhibits the initiation of lipolysis, and hormone sensitive lipase (*Hsl*) that catalyzes lipolysis in white adipose tissue (Solt et al., 2012). Mice fed synthetic REV-ERBα/β agonists present lower levels of plasma triacylglycerides and non-esterified fatty acids (Solt et al., 2012).

As further proof of the involvement of REV-ERBs in adipose lipid metabolism, *Rev-erbα* knockout mice show an upregulation of expression for the gene encoding lipoprotein lipase in the adipose tissue, coupled with lower plasma levels of non-esterified fatty acids (Delezie et al., 2012). Ablating the master clock in the SCN of mice affected the expression of genes encoding proteins of the cholesterol and lipid biosynthetic pathways in WAT, suggesting that the SCN clock is involved in the regulation of lipid metabolism in adipose (Kolbe et al., 2016). This is unsurprising given the central role of the sympathetic activation of lipolysis via sympathetic signaling from hypothalamic nuclei to WAT (Geerling et al., 2014). Additionally, the circadian clock of adipocytes is found to control adipose triglyceride lipase (ATGL) and hormone sensitive lipase (HSL) that serve lipolysis, as well as lipoprotein lipase (LPL) and Stearoyl-CoA desaturase-1 (SCD1) that serve lipogenesis (Paschos et al., 2012; Shostak et al., 2013).

Lipolysis in response to fasting is defective in mice with a dominant negative mutation of *Clock* (*Clock*$^{\Delta 19}$) (Shostak et al., 2013), and the diurnal rhythm of fatty acid and glycerol plasma concentrations is disrupted not only in *Clock*$^{\Delta 19}$ mice, but also in mice with adipocyte specific disruption of *Bmal1* that have functional clocks in all cells but adipocytes (Paschos et al., 2012; Shostak et al., 2013). This latter finding suggests a role of the adipocyte circadian clock in the regulation of lipolysis independent from the central clock regulation of lipolysis. In agreement with decreased lipolysis, mice with defective adipocyte clocks display increased adiposity (Paschos et al., 2012; Shostak et al., 2013). The independent role of the adipocyte clock in the regulation of lipid metabolism in adipose tissue is further highlighted by a reduction in unsaturated fatty acids in triglycerides from WAT and an increase in short chain fatty acids in triglycerides from BAT of mice with an adipocyte-specific deletion of Bmal1 (Castro et al., 2015).

6. Circadian clock control of adipose tissue endocrine function

The participation of adipose tissue in whole-body energy metabolism involves the secretion of peptide hormones called adipokines to coordinate energy intake, storage, and utilization. As such, the timing of adipokine secretion is critical for maintaining diurnal rhythms of metabolism. Despite this, very little is currently known on the regulation of adipokine secretion by the circadian clock with the exception of a number of reports regarding leptin. A diurnal rhythm of plasma concentrations of adiponectin was shown in mice (Rudic et al., 2004) and humans (Gavrila et al., 2003), while diurnal variation of plasma leptin has been shown in mice (Ahren, 2000), rats (Bodosi et al., 2004), and humans (Gavrila et al., 2003; Heptulla et al., 2001). The oscillations of plasma leptin levels in mice correlate with the fed state of the animals, with higher plasma leptin during the active/feeding phase and lower levels during the rest/fasting phase of the daily cycle (Arble et al., 2011). Altering feeding schedules by constraining mice to eat exclusively during their rest phase reverses the rhythm of plasma leptin levels (Arble et al., 2011). The involvement of the circadian clock in the generation of plasma leptin rhythms has been assessed in humans kept at a constant routine and fed isocaloric meals every 2 h for 38 h (Shea et al., 2005). The study revealed a persistent rhythm of plasma leptin that was independent of feeding and behavior (Shea et al., 2005). In mice, the role of the master clock was examined by lesion of the SCN. Mice with no SCN showed arrhythmic plasma leptin levels; however, the contribution of this change to the feeding rhythms of mice without SCN was not directly assessed (Kalsbeek et al., 2001). The contribution of the adipocyte clock to the rhythms of plasma leptin, conversely, has not been established. *In vitro* examination of differentiated, synchronized white adipocytes failed to show circadian rhythm in leptin gene expression (Otway et al., 2009). Similarly, gene expression of leptin in WAT from *ad libidum* fed mice was not rhythmic (Zhang et al., 2014). In agreement with the lack of a role of the adipocyte clock in the rhythmic synthesis and secretion of leptin, leptin gene expression did not change in mice without a functional adipocyte clock (Paschos et al., 2012). Furthermore, the arrhythmic plasma leptin levels of *Clock*$^{\Delta 19}$ mice and adipocyte-*Bmal1* knockout mice correlate with the attenuation of the feeding rhythm in these mice, suggesting that the feeding status may drive the arrhythmicity of plasma leptin instead of a direct effect of the circadian clock (Paschos et al., 2012; Turek et al., 2005). The direct role of the master clock and adipocyte clocks in the synthesis and secretion of leptin will have to be evaluated in carefully designed studies that control for the effect of circadian clock-mediated feeding status.

7. Circadian clock and food intake control

The orchestration of daily feeding rhythm by the circadian clock has been suggested by early studies showing that lesions of the SCN attenuated the feeding rhythm in rats (Nagai et al., 1978). The projections from the SCN to numerous hypothalamic nuclei involved in the regulation of feeding behavior further support the involvement of the master clock in food intake regulation (Buijs et al., 1994; Saper et al., 2005). On the other hand, mice with forebrain deletion of *Bmal1* that lack a functional SCN clock show intact food anticipatory activity when access to food is restricted to a specific time of day (Izumo et al., 2014). This observation highlights the complexity of food intake regulation which involves homeostatic and reward pathways. The multiple animal models of circadian disruption that present attenuation of feeding rhythms, i.e. the *Clock*$^{\Delta 19}$ mouse (Turek et al., 2005), the postnatal *Bmal1* knockout mouse (Yang et al., 2016), the *Per2* knockout mouse (Yang et al., 2009), and the *Per1/2* deficient mouse (Thaiss et al., 2014), support the role of the circadian clock in the regulation of food intake. In line with a role of PER1 in food intake regulation, mice with the PER1^{S714G} mutation prohibiting PER1 phosphorylation at the site and accelerating degradation of PER1 advanced their feeding rhythm by 4–5 h (Liu et al., 2014). Feedback from the periphery to the hypothalamic centers that control feeding supports the idea that peripheral clocks may organize the timing of feedback signals to the hypothalamus in order to generate feeding rhythms. Indeed, ablating the adipocyte clock in mice attenuates their feeding rhythm (Paschos et al., 2012).

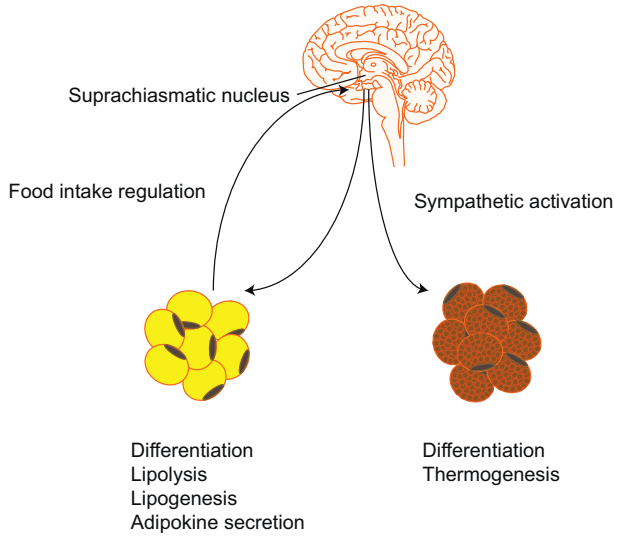

Fig. 1. Communication between the master clock at the suprachiasmatic nucleus and adipocyte clocks coordinates both adipose tissue physiology and whole body energy homeostasis.

8. Circadian clock and brown adipose tissue

The circadian clock in BAT appears to generate rhythmic expression in approximately 8% of the protein encoding genes, roughly double the number of genes with rhythmic expression in WAT (Zhang et al., 2014). Shifting the light phase changed not only circadian, but also thermogenic gene expression in BAT and induced brown to white adipocyte transformation with accumulation of lipids (Herrero et al., 2015). Constant exposure to light throughout the 24-h cycle increased adiposity in mice by decreasing adrenergic signaling to BAT that reduced glucose and fatty acid uptake in BAT (Kooijman et al., 2015). β-oxidation of fatty acids fuels BAT thermogenesis, and the uptake of both glucose and fatty acids by BAT increases with the activation of thermogenesis (Cannon and Nedergaard, 2011). Glucose and fatty acid uptake by BAT was found to be rhythmic in mice, and the capacity of BAT to clear postprandial lipids is time dependent (van den Berg et al., 2018; van der Veen et al., 2012). Similarly, glucose utilization in human BAT is rhythmic with a peak during the start of the active phase (Lee et al., 2016) – the same phase of peak thermogenic activity in mice. Mice deficient in PER2 exhibit reduced utilization of fatty acids and UCP1 expression in BAT that is dependent on PPARα activity and ultimately results in a reduced ability to maintain temperature in response to cold exposure (Chappuis et al., 2013). Conversely, REV-ERBα deficient mice show constant increased levels of whole-body energy expenditure, arrhythmic UCP1 levels, and increased core body temperature with attenuated diurnal rhythm (Gerhart-Hines et al., 2013). More recently, *ex vivo* respiration in BAT and WAT were found to be higher in tissue from RORα-deficient mice and accompanied by both browning of WAT and an increase of UCP1 in WAT (Monnier et al., 2018). Sympathetic innervation of BAT originates from hypothalamic nuclei including the SCN, suggesting a central regulation of BAT thermogenesis rhythms (Bartness et al., 2001). The ventromedial hypothalamus (VMH) is another hypothalamic nuclei that innervates BAT and is known to regulate diet-induced thermogenesis (Kim et al., 2011). Ablating the VMH clock in mice increased BAT thermogenic capacity and sympathetic signaling to BAT, resulting in increased whole body energy expenditure (Orozco-Solis et al., 2016).

9. Conclusion

The many different aspects of adipose tissue physiology under circadian clock control highlight the significance of proper timing in whole body metabolism coordination (Fig. 1). It is apparent that coordination of physiology requires communication between the central nervous system and the periphery. Signaling between the master clock at the SCN and the adipocyte clocks in both WAT and BAT is a great example of the need for bidirectional communication to achieve coordination.

Declaration of interests

The authors declare no competing interests.

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