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Circadian control of white and brown adipose tissues

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White and brown adipose tissues are highly dynamic organs anticipating and responding to changes in the environment. The circadian timing system facilitates anticipation, and it is therefore not surprising that circadian disturbances, a prominent feature of modern 24/7 society, increase the risk for (cardio)metabolic diseases. In this mini-review, we will address mechanisms and strategies to mitigate disease risk associated with circadian disturbances. In addition, we discuss the opportunities arising from the knowledge we gained about circadian rhythms in these adipose tissues, including the application of chronotherapy, optimizing endogenous circadian rhythms to allow for more effective intervention, and the identification of novel therapeutic targets.

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Introduction

The concept of adipose tissue has radically changed in the past decades. While the classical view of white adipose tissue (WAT) is a passive lipid-storing tissue, it actually is a very dynamic organ anticipating and responding to changes in nutrient availability. Adding to this, the presence of the thermogenic and lipid-combusting brown adipose tissue (BAT) in adult humans was only established 15 years ago, and more recent insight into the physiology also here suggests anticipation and response to, for example, changes in environmental temperature.

Anticipation and adaptation of adipose tissue

Dealing with daily and seasonal fluctuations in nutrient availability and environmental temperature is, for a large part, facilitated through the circadian timing system. For this, adipocytes and all other cell types in adipose tissue possess a cell-autonomous transcription–translation feedback loop. Core clock genes serve as the molecular basis for endogenous oscillations under constant environmental conditions. Rhythms are fine-tuned to run at exactly 24 h through, among others, post-translational modifications as a result of variation in cellular energy status, and by synchronization to the outside world via hormones, the autonomic nervous system, temperature, and nutrient availability. In turn, circadian variation in WAT function leads to, for example, a circadian rhythm in leptin levels independent of meal timing, and the circadian activity in BAT likely contributes to the rhythm in body core temperature to which other bodily organs and even the central clock in the brain respond. Interestingly, circadian rhythms in BAT also seem to adapt to (seasonal) variation in daily light exposure [1], thereby possibly anticipating upcoming changes in environmental temperature. And while our knowledge on circadian rhythms in specific BAT and WAT functions is increasing, a more or less understudied phenomenon is the circadian rhythm in more general housekeeping processes such as cell proliferation. Notably, both the circadian clock machinery and diurnal feeding patterns have been implicated in adipocyte progenitor proliferation, and may therefore be critical determinants of adipose tissue expansion and health over time [2].

Implications of circadian disturbance

Regulation of circadian rhythms at multiple levels, including the entrainment to the environment via so-called Zeitgebers (e.g. light and food cues), on the one hand, facilitates anticipation and adaptation, but on the other hand, also makes us vulnerable for circadian disturbances, often with consequences for metabolic and cardiovascular disease risk. In addition, modern-day society characterized by all-day electrical lighting, continuous access to food, and need for shift work causes misalignment of behavior and endogenous anticipatory circadian rhythms. As an example, WAT shows mild insulin resistance during the night to redirect glucose produced by the liver to the brain as an essential energy source. The implication, however, is that eating at night or even late-evening meals have been shown to cause spikes in blood glucose levels and increase the risk of type-2 diabetes [3]. To

make things worse, circadian disruption additionally attenuates glucose-stimulated insulin secretion by the pancreas [4]. Thus, eating during a night shift, especially readily digestible carbohydrates in sweets and soft drinks, constitutes a strong risk for cardiometabolic disorders due to a combination of insufficient insulin secretion and adipose tissue responding to a lesser extent to this insulin. Interestingly, time-restricted eating appears to be a feasible strategy to alleviate cardiometabolic risks associated with shift work [5], and also daytime eating prevents circadian misalignment and glucose intolerance in simulated shift work [6]. Nevertheless, the multifactorial disease risk in shift workers likely requires a personalized, multidisciplinary approach [7].

Identification of the mechanisms driving circadian rhythms in adipose tissue may help us to select promising prevention or intervention strategies. In subcutaneous adipose tissue biopsies of healthy subjects, approximately 800 rhythmic transcripts (2% of target genes in the assay) can be detected under 'constant routine' conditions [8]. In such a protocol, exogenous time cues are minimized through exposure to constant light, evenly distributed food intake, and no sleep for at least 24 h. The number of oscillating transcripts dramatically increases under less-stringent diurnal conditions. With 'normal' meal sleep timing, at least 25% of the genes show different expression levels during the course of the day, and time-restricted eating additionally changes the rhythmicity of 450 genes [9]. Specifically, circadian expression of core clock genes, glucoregulatory genes, and genes involved in cell proliferation and differentiation are altered in WAT upon time-restricted eating in humans [9], patterns that have been linked to healthy adipose function and expansion in mice [2]. In murine BAT, approximately 40% of all expressed genes was found to be oscillating in unrestricted conditions [10]. These numbers indicate a role for core clock genes, and possibly an even bigger role for external factors. Indeed, a landmark study by Turek et al. [11] demonstrated that whole-body circadian locomotor output cycle kaput (CLOCK) mutant mice are obese and develop features of the metabolic syndrome when fed a high-fat diet. Adipocyte-specific loss of brain and muscle ARNT-like 1 (BMAL1) has also been reported to increase adiposity due to defective lipolytic activity in WAT [12]. Nuclear receptor subfamily-1 group-D member 1 (NR1D1), also known as REV–ERBα, was identified as one of the main regulators of diurnal variation in body temperature and BAT activity through its suppressive effects on uncoupling protein-1 (UPC1) expression [13].

With regard to the environmental factors, we previously demonstrated in mice that prolonged daily light exposure increases adiposity through attenuation of BAT activity [14]. In line with these data, it has been reported that artificial light at night while sleeping is associated with risk of weight gain and obesity in humans [15]. Mechanistically, we identified in mice a physiological rhythm in glucocorticoids as an important regulator of diurnal BAT function, although this effect was likely mediated via altered sympathetic outflow toward BAT [16]. Interestingly, others have also reported weight gain upon flattening of daily glucocorticoid oscillations in mice, and attributed this to a direct effect of continuous versus pulsatile glucocorticoids on peroxisome proliferator-activated receptor gamma (PPARγ)-mediated white adipocyte differentiation [17]. Thus, beyond the well-known effects of hypercorticism (e.g. in chronic stress) on adipose tissue function, a circadian rhythm in glucocorticoids also seems critical for metabolic health. Nocturnin, a circadian-regulated deadenylase, has also been reported to regulate adipocyte differentiation in a PPARγ-dependent manner [18], and nocturnin-deficient mice are resistant to diet-induced obesity. Likewise, period 2 was found to directly interact with PPARγ to regulate adipogenesis [19]. Most strikingly, time-restricted feeding was shown to protect from obesity and metabolic syndrome in the context of circadian disruption due to genetic loss of clock genes in mice, highlighting the relative importance of external timing cues [20].

Beyond the effects of genetic or environmental circadian disruption, it is tempting to speculate that alterations in the circadian system also contribute to the increased risk of cardiometabolic diseases with increasing age. Aging is typically associated with reduced amplitude or even loss of rhythmicity. In WAT and BAT of aged mice, the fraction of oscillating lipids decreases from approximately 22–14% and 18%, respectively [21]. In line with this, we recently reported that peak abundance of lipoprotein lipase (LPL), a critical regulator of triglyceride-derived fatty acid uptake, was strongly attenuated in BAT of middle-aged female mice [22]. Combined with the lower expression of genes involved in fat oxidation, the net result was increased adiposity and attenuated rhythms in core body temperature. Provided these findings can be translated to humans, these data suggest BAT-targeted interventions may particularly benefit the aged population.

Opportunities arising from circadian rhythms in adipose tissue

Before addressing the question whether circadian cycles in adipose tissue should be considered when therapeutically targeting the tissue, it is imperative to note that the existence of circadian variation in WAT and BAT function also implies that potential rhythmic activity should be taken into account when performing measurements. As an example, we previously demonstrated that angiopoietin-like 4 (ANGPTL4), a protein

that inhibits LPL activity, redirects triglycerides from WAT to BAT uptake during cold [23]. Those experiments were, mostly for practical reasons, performed during the light phase. Only later, we realized that when experiments would have been performed during the dark phase, when ANGPTL4 levels are low/absent [1,10], this effect would probably have been missed. Thus, knowledge of circadian rhythms in the body is useful, if not critical, in the design and interpretation of experiments, but also when interpreting patient data.

The presence of metabolically active BAT is associated with cardiometabolic health in humans [24], indicating that stimulating BAT — despite its relative low abundance in humans — might have therapeutic potential. Cold exposure is the most effective way to activate thermogenesis in BAT and simultaneously promotes lipolysis in WAT, but comes with practical limitations. We therefore recently asked ourselves the question whether time of day is an important determinant in the metabolic effects of cold [25]. In males, cold-induced energy expenditure was found to be higher in the morning than in the evening. This effect was accompanied by an elevation in free fatty acids in the morning, but not evening. In females, there was no (statistical) difference in cold-induced energy expenditure between morning and evening, but free fatty acids as well as triglycerides and cholesterol levels were increased after cold to a higher extent in the morning than in the evening. Whether these differences have implications for the therapeutic potential of cold strategies remains to be investigated.

Chronotherapy can be considered to optimize therapeutic effectiveness as shown for cold exposure, and/or to minimize side effects. In the context of adipose-targeted therapy, the latter may be particularly relevant when using sympathomimetics to stimulate lipolysis in WAT and thermogenesis in BAT. In humans, both processes are primarily driven by signaling through the β2-adrenergic receptor [26], but this receptor also exerts prominent functions in the vasculature. It would be of high interest to investigate if, for example, β2-adrenergic receptor-mediated vasodilation also shows a circadian rhythm.

As an alternative strategy to the timing of therapeutic interventions, one might also consider optimizing endogenous circadian rhythms to promote resilience against circadian disruption or to allow for more effective pharmacological intervention. A fascinating development in treatment of cardiometabolic disorders is the generation of dual- or even triple agonists, with recent successes in clinical trials reported for combined glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonism. The impressive weight-lowering effect of dual-GIP and GLP-1 receptor agonism is most likely mediated via promotion of satiety and a reduction in food intake [27], but preclinical evidence also suggests improvement of the lipid-buffering capacity of WAT, with increased lipid uptake in postprandial state and potentiated lipolysis in the fasted state contributing to better overall metabolic health (reviewed in [28]). Given the differential regulation of WAT in the fast-fed state, it would be of interest to investigate if time-restricted eating can potentiate the health benefits of dual-GIP/GLP-1 receptor agonism. Of note, time-restricted eating does not seem to be more beneficial than calorie restriction when it comes to promoting weight loss in humans [29]. However, it does attenuate daily glucose levels in blood accompanied by increased GIP levels following dinner and > 300 genes being differentially regulated in subcutaneous adipose tissue [30]. Late eating on the other hand increases hunger and decreases energy expenditure as (partly) explained by lower adipose-derived leptin levels and changes in the adipose transcriptome consistent with decreased lipolysis and increased adipogenesis [31].

Last but not least, one could ask the question if defining the molecular on- and off-switches in diurnal WAT or BAT functioning would yield novel therapeutic targets. To explore this further, we recently performed RNA sequencing in BAT samples collected from C57BL/6J mice at three-hour interval throughout a 24-hour period [10]. In the gene cluster that shows expression patterns overlapping with the previously reported rhythm in metabolic BAT activity [1], we found marked enrichment for lipid catabolic processes, with *Lpl* as the gene with the largest amplitude. Of the known LPL modulators, *Angptl4* showed the largest diurnal amplitude in antiphase with *Lpl* expression, and both *Angptl4* knockout and overexpression attenuated oscillations in LPL and triglyceride-derived fatty acid uptake by BAT. These data suggest that time of day is essential when targeting LPL activity through ANGPTL4 modulation. In addition, transcription factor enrichment analysis identified PPARγ as one of the potential drivers of the circadian transcriptional activity in BAT, and chromatin immunoprecipiation (ChIP) sequencing revealed six rhythmic binding sites for PPARγ in the promoter region of *Lpl* [10]. Next, questions to address are how rhythms in PPARγ-mediated transcription are generated, and if a PPARγ agonist with a short half-life can be used to stimulate thermogenic activity.

Concluding remarks

Taken together, adipose tissues show strong variation in activity during the course of the day with implications for nutrient handling and cardiometabolic disease risk. Circadian disruption following shift work, or attenuated circadian amplitudes as occurring during aging are associated with adipose dysfunction and accelerated disease

development. Incremental evidence suggests that circadian rhythms in adipose tissue should be considered when measuring WAT or BAT function, and when targeting these tissues in the treatment of cardiometabolic disorders.

CRediT authorship contribution statement

Kaiming Yue, Patrick Rensen, Sander Kooijman: Writing – original draft, Writing – review & editing.

Data Availability

No data were used for the research described in the article.

Declaration of Competing Interest

Nothing declared.

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