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REVIEW

Consequences of circadian dysregulation on metabolism

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Abstract: Most organisms display endogenously produced rhythms in physiology and behavior of ~24 hours in duration. These rhythms, termed circadian rhythms, are entrained to precisely 24 hours by the daily extrinsic light–dark cycle. Circadian rhythms are driven by a transcriptional–translational feedback loop that is hierarchically expressed throughout the brain and body; the suprachiasmatic nucleus of the hypothalamus is the master circadian oscillator at the top of the hierarchy. Precise timing of the circadian clocks is critical for many homeostatic processes, including energy regulation and metabolism. Many genes involved in metabolism display rhythmic oscillations. Because circadian rhythms are most potently synchronized with the external environment by light, exposure to light at night potentially disrupts circadian regulation. Other potential disruptors of circadian organization include night shift work, social jet lag, restricted sleep, and misaligned feeding. Each of these environmental conditions has been associated with metabolic changes and obesity. The goal of this review is to highlight how disruption of circadian organization, primarily due to night shift work and exposure to light at night, has downstream effects on metabolic function.

Keywords: circadian disruption, light at night, obesity, shift work

Introduction

The prevalence of obesity and metabolic diseases has been increasing since the late 20th century, despite major efforts in raising public health awareness. More than two-thirds of Americans are considered overweight and obese (body mass index [BMI] >25 and >30, respectively).[1] Estimates of global obesity prevalence are about half this rate, but are no less susceptible to these dramatic increases, nearly doubling since 1980.[2,3] In addition to overall increased mortality, obesity is associated with the development of diabetes, cardiovascular diseases, certain cancers, reproductive dysfunction, as well as depression; all of these adverse health outcomes contribute to the increasing health care costs.[4–16]

Although obesity is considered to be the result of an energy imbalance, genetics and environmental factors play a role in affecting the magnitude of obesity in individuals.[17–19] The increased availability of food, especially calorie-dense foods, and shift toward a more sedentary lifestyle are considered primary contributors to obesity, but do not account for all the environmental changes that have occurred during the past 40 years. The rise of industrialization in the 20th century has increased human productivity, with the advent of electrical lighting to extend the workday, allow night shift work, as well as other social activities, to occur during the night. However, this technological intervention was accepted prior to a modern understanding of the circadian system and

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the detrimental effects of circadian disruption on physiology, behavior, and health.

Circadian rhythms are approximately, but not exactly, endogenous 24-hour rhythms in behavior and physiology that are synchronized to precisely 24 hours by the environmental day–night cycle. A functional and synchronized, or entrained, circadian system maintains homeostasis and temporally compartmentalizes energetically incompatible processes in order to maximize physiological efficiency. The circadian clock is deeply involved in maintaining metabolic, endocrine, and immunological homeostasis. It is therefore not unexpected that disrupting synchronizing signals would have severe consequences on metabolic functions. Many facets of an urban lifestyle exist in opposition to circadian synchrony: shift work, physical jet lag, social jet lag, exposure to light at night, sleep restriction, and misaligned feeding. Each of these environmental conditions have been associated with metabolic alterations.

This review highlights the associations between circadian disrupting lifestyle changes that have come about over the past century and their impact on metabolic functions. First, it provides a brief introduction to the circadian system. Then, it explores the influence of the circadian system on metabolism and reciprocal feedback from metabolic cues. Next, it presents insights gathered from experimental models of circadian disruption, namely forced desynchrony, light at night, and misaligned feeding and compares these findings with clinical and epidemiological data. Finally, the directions for future research are proposed.

Circadian rhythms

Circadian rhythms are a highly conserved system that maintains homeostasis by anticipating daily environmental changes. The suprachiasmatic nuclei (SCN) are a paired structure located in the anterior hypothalamus, which is considered the "master clock," responsible for setting the phase of clocks located throughout the body. Timekeeping in the SCN is maintained by an autoregulatory transcriptional–translational feedback loop with a period of ~24 hours. The precise 24-hour period is imposed by the environmental light–dark cycle. Light is the most potent synchronizing cue, or zeitgeber, to the SCN. Light stimulates the intrinsically photosensitive retinal ganglion cells of the retina, which signal along the retinohypothalamic tract to the SCN.[20] These signals cause rapid molecular changes in the cells of the SCN, altering the phase of the transcriptional–translational feedback loop and aligning it to the external time of day.[21,22]

The loop is initiated by proteins, namely circadian locomotor output cycles kaput (CLOCK) and brain muscle Arnt-like protein 1 (BMAL1). CLOCK and BMAL1 heterodimerize and drive expression of *Period* (*Per)* and *Cryptochrome (Cry)* genes through E-box enhancers. PER and CRY proteins form a secondary heterodimer that translocates back to the nucleus to inhibit their own transcription. This inhibitory arm of the loop is released by casein kinases, which tag PER for ubiquitin-mediated degradation. In addition to E-box motifs in the *Per* and *Cry* promoter regions, CLOCK and BMAL1 bind to E-boxes in promoter regions of various other genes (reviewed in Ko and Takahashi[23]).

One such target of CLOCK and BMAL1 are the nuclear receptors RAR-related orphan receptor alpha (RORα) and reverse-ErbA alpha (REV-ERBα), which enhance and repress *Bmal1*, respectively. This process acts as an auxiliary loop to fine-tune the primary loop. In addition to functions within the clock, CLOCK and BMAL1 regulate the expression of clock-controlled genes.[23] Between direct targets and downstream effects of cycling clock genes, these molecular cycles regulate gene expression in various different systems, including, but not limited to, metabolism.

Circadian rhythms and metabolism

The SCN comprises the so-called master clock, but all cells in the body exhibit circadian rhythms. In mammals, it is the sole endogenous clock possessing the ability to be reset directly by light; therefore, peripheral clocks must rely on neural or humoral signaling from the SCN in order to maintain proper alignment with the time of day.[24,25] It directly innervates local targets within the brain, such as the paraventricular nucleus, which through a polysynaptic pathway regulates rhythmic expression of melatonin.[20,26] Similarly, SCN-derived vasopressin expressing neurons synapse upon the dorsomedial hypothalamus to regulate the daily rhythm in corticosterone by upstream regulation of the hypothalamus–pituitary–adrenal axis.[27,28] These hormones act as humoral signals of circadian time to peripheral tissues.[29] SCN connections in the paraventricular nucleus also regulate circadian rhythms in autonomic tone. Pre-autonomic fibers in the paraventricular nucleus synapse onto metabolic, immune, and endocrine tissues driving circadian rhythms in various physiological systems.[30–37]

In addition to these SCN-derived signals, peripheral tissues also incorporate signals relevant to their homeostatic function, such as feeding state and metabolite

abundance.[38–41] The liver plays an important role in maintaining metabolic homeostasis and is under heavy circadian control. Approximately 10% of the liver transcriptome and 20% of the proteome are circadian rhythmic; this stands on the higher end of the estimated circadian regulation of the mammalian transcriptome.[42–47] Most notably, hepatic glucose and triglyceride homeostasis, processes linked to functional expression of clock genes, are regulated in a circadian manner.[48–50]

Animal models of circadian gene knockouts have played a crucial role in establishing the importance of clock genes in maintaining metabolic homeostasis. Knockouts of *Clock* and/or *Bmal1* exhibit poor glucose tolerance and insulin sensitivity, as well as increased circulating triglycerides and cholesterol, and hepatic steatosis.[51–54] Loss of the inhibitory arm of the feedback loop similarly impairs glucose and lipid metabolism. *Per*-deficient mice exhibit altered lipid metabolism, decreasing body mass, and circulating lipids.[55] Mutations in *Cry* genes impair gluconeogenesis.[56] Elimination of *REV-ERBs* impairs lipid homeostasis,[57] whereas addition of synthetic *REV-ERBs* to diet-induced obese mice resolves hyperlipidemia and hyperglycemia.[58]

As a peripheral clock, liver also incorporates external signals to determine local time. Food can entrain peripheral circadian clocks and food restriction can alter the phase of several circadian rhythms including glucocorticoid secretion.[59–62] Glucocorticoids can regulate 60% of the circadian transcripts in the liver in the absence of a functional SCN.[63] Although traditionally considered stress hormones, glucocorticoids are primarily mediators of metabolism, generally favoring energy storage and fat deposition.[64] High-fat diet consumption, in addition to weight gain, disrupts locomotor and molecular circadian rhythms in the adipose tissue and the liver.[65] Specifically, the function of the liver clock is altered by inducing the production of additional metabolites in a PPARγ-dependent manner and impairing CLOCK:BMAL1 chromatin recruitment.[66] The CLOCK:BMAL1 complex interacts with chromatin in a circadian manner through Sirtuin 6 (SIRT6), which polarizes transcription toward factors involved in lipid and carbohydrate metabolism.[67] Sirtuins are NAD^+-dependent deacetylases that act as integrators of cellular metabolism into circadian clock function.[68,69] Specifically, SIRT6 is also activated by fatty acids, providing additional metabolite integration.[70] Together, these studies suggest that altered glucocorticoid rhythms, feeding patterns, and food type may contribute to functional desynchrony between the master pacemaker and the liver.

Circadian disruption and metabolism

A properly entrained circadian system is central to maintaining metabolic homeostasis; it is therefore not unexpected that poor circadian hygiene alters metabolism. Although clock gene mutations have been associated with obesity, the majority of the population does not possess these mutations. Instead, modern society participates in lifestyles that are incongruent with entrainment to the natural lighting environment.[71,72] Disruption of entrainment occurs by shifting work schedules (shift work), travel and social life (physical and social jet lag), food intake (misaligned feeding) late into the night, or exposure to light late into the night (light at night), all of which have been on the rise during the past century and have been associated with adverse health outcomes. In the following sections, experimental, clinical, and epidemiological studies implicating circadian disruption in the global rise in obesity are discussed.

Circadian desynchrony

Experimentally, forced desynchrony exposes an animal to a photoperiod, or day length, longer or shorter than the natural day, or forcibly shifts activity patterns to the inactive phase. Exposure to a 20-hour light/dark cycle, incongruous to the natural 24-hour period, results in increased body mass, hyperleptinemia, and hyperinsulinemia independent of changes in circulating glucocorticoids.[73] Chronic phase advances increase body mass, fat mass, adipocyte size, and circulating triglycerides.[74] Forced activity during an 8-hour window of the inactive phase increases body mass, flattens glucose rhythms, alters glucose tolerance, shifts the peak in serum triglycerides to the daytime, and overall alters rhythmicity in the hypothalamus and the liver.[75–77] Nighttime food restriction in rats exposed to this forced activity protocol restores glucose rhythms and baseline body mass.[75]

Approximately 20% of the global population works in night shifts, forcing individuals to be physically, mentally, and metabolically active out of circadian phase. Shift work has been associated with increased prevalence for obesity, diabetes, systemic inflammation, and other metabolic comorbidities.[78–85] Human participants exposed to a forced desynchrony protocol display hyperglycemia, insulin resistance, poor glucose tolerance, increased arterial pressure, and reversed cortisol rhythms when they are ~12 hours out of phase with the environmental light–dark cycle.[86] The 12-hour phase shifts also increase blood pressure, C-reactive protein, and inflammatory mediators and decrease vagal tone,

all contributing to increased cardiovascular disease risk.[87] To replicate the multimodal disruption induced by shift work, Buxton et al subjected healthy adults to a combined sleep restriction and circadian disruption protocol for 3 weeks.[88] This challenge reduced metabolic rate and induced postprandial hyperglycemia due to hypoinsulinemia.

Jet lag occurs when a person travels rapidly over multiple time zones leading to a discrepancy between internal time and the external light–dark cycle. People who experience repeated shifts across time zones exhibit increased serum cholesterol.[89] Social jet lag, on the other hand, is the discrepancy that occurs between circadian time and social schedules, which results in circadian disruption and often sleep loss. Social jet lag is associated with increased BMI, independent of sleep duration.[90] In a cohort of specifically nonshift workers, individuals with higher social jet lag scores (greater discrepancy) had higher BMI and fat mass and were more likely to have metabolic syndrome. Additionally, social jet lag was also associated with indicators of inflammation and diabetes in "metabolically unhealthy" obese participants.[91] Delaying bedtime by 8.5 hours for 4 days decreases insulin sensitivity and inflammation.[92] Endocrine rhythms, specifically leptin and melatonin, are depressed in night active individuals, defined as having an average sleep onset of 01:30 hours relative to 22:30 hours in control participants.[93]

Delayed feeding

Food can act as an entraining cue to the liver clock, which has been established as central to metabolic homeostasis. Delayed food consumption or feeding during the inactive phase has been associated with increased weight and metabolic dysfunction. Restriction of feeding to the inactive phase, during the light phase in nocturnal rodents, increases body mass, fat mass, and liver clock gene profile.[75,76,94] When compounded with a high-fat diet, mice develop obesity, altered circadian endocrine, and locomotor profiles.[60,95–97] Restricting high-fat diet consumption to the active phase, in contrast, can protect against reduced clock gene amplitude, weight gain, and metabolic disease.[98–100]

Delayed eating in humans is associated with increased risk of obesity. An extreme example of delayed eating is called night eating syndrome, a clinical manifestation of a shift in nighttime food consumption. Night eating syndrome is defined by nighttime hyperphagia and awakenings to eat. Night eating syndrome is associated with an increased risk of obesity, dampened or phase delayed diurnal endocrine rhythms, and a shift in metabolism toward carbohydrate oxidation suggesting altered metabolic function.[101]

In otherwise healthy individuals, nighttime eating is associated with increased calorie consumption and weight gain.[102] This weight gain phenotype is supported by a shift toward carbohydrate oxidation and away from lipid oxidation, as well as increased low density lipoprotein (LDL), suggesting increased circulating cholesterol.[103,104] Nighttime eating also confers postprandial hyperglycemia and hyperinsulinemia and a loss of association between plasma glucose and insulin concentrations.[93] In a study on eating patterns, more than a third of food intake occurred after 18:00 hours, with half the participants eating over the course of >14 hours a day.[105] Overweight individuals exhibiting this eating patterns reduced weight when food intake was restricted to a self-determined 10-hour window.

Light at night

As mentioned earlier, light is the most potent cue to the circadian system. Exposure to constant light desynchronizes locomotor and temperature rhythms in rodents. Mice exposed to constant light experience increased body mass and impaired glucocorticoid rhythmicity, glucose processing, and insulin sensitivity.[94,106] These metabolic alterations are associated with elevated food intake during the inactive phase. Exposure to constant light also causes circadian arrhythmia and desynchronizes SCN neuronal networks.[106,107]

Nightly exposure to dim white light, in contrast to constant light, does not induce locomotor or glucocorticoid arrhythmicity.[94,108] Nonetheless, light levels as low as 5 lux induce changes in central and peripheral clock gene expression. Specifically, amplitude of *Bmal1*, *Per1*,2, *Cry1*,2, and *REV-ERB-*α gene expression rhythms are dampened in the liver in response to exposure to dim light at night.[108] Mice exposed to dim light at night experience increased body and fat mass, as well as impaired glucose processing with no change in locomotor activity.[94] Much of this metabolic phenotype is attributed to increased food intake during the inactive phase. Light at night has additive effects on weight gain induced by high-fat diet and contributes to the inflammatory pathology of obesity.[109] Much like misaligned feeding models, changes in metabolism are reversed by restricting food intake to the active phase and engaging in locomotor exercise.[94,110] Additionally, return to a dark night environment resolves weight gain and glucose tolerance within 3 weeks.[111]

Among humans, recent epidemiological data have begun drawing a connection between nighttime light exposure and body mass. Over 99% of the population of the United States and Europe are exposed to nighttime light. In a study of 100,000 women in the UK, the chances of obesity increased with elevated levels of exposure to light at night.[112] Obesity

was assessed by BMI, waist:hip and waist:height ratios, and waist circumference, independent of sleep duration. In elderly individuals, exposure to >3 lux of light was associated with higher body weight, BMI, and waist circumference, as well as hyperlipidemia.[113]

Sleep restriction

Sleep is strongly regulated by the circadian system, but can also have important feedback effects on circadian functions. Disrupted sleep can impair energy metabolism (reviewed in Laposky et al[114]), and conversely obesity and leptin deficiency disrupt sleep.[115,116] Total sleep restriction does induce changes in metabolism but has paradoxical effects on weight.[117,118] Additionally, total sleep restriction alters glucose, triglyceride, and adipokine expression.[119] Animal models of shift work employ timed sleep restriction, which increases inactive phase locomotor activity, food intake, and clock gene expression. Mice exposed to timed sleep restriction experience increased body mass, despite impaired gluconeogenesis and decreased circulating triglycerides.[120] This phenotype is blunted in mice unable to express *Per1/2,* suggesting their involvement and the necessity of a functional clock.[121]

Approximately 30% of adults report short sleep durations (<6 hours per night); the prevalence of people experiencing reduced sleep duration has increased substantially since 1985.[122] Short sleep duration has also been associated with increased risk for obesity,[123,124] increased BMI, and altered metabolic endocrine profile.[125–127] Experimental sleep restriction to <5 hours a night increased body mass gain by increasing nighttime intake of calories derived from fat.[128] Similar sleep restriction also increases glucose, insulin, cortisol, and leptin, induces insulin resistance in adipocytes, and decreases whole body insulin sensitivity and glucose tolerance, suggesting a functional impairment of carbohydrate metabolism.[129–132] This metabolic endocrine disruption is exacerbated by increased sympathetic tone, and altered circadian rhythm in cortisol secretion, which occurs independent of changes in adrenocorticotropic hormone (ACTH), suggesting a deficit at the adrenal level. [129,133]

Conclusion

The past century has been a time of booming advances in technology and industrialization bringing about benefits to productivity, efficiency, safety, and convenience. Unfortunately, this has come at a cost to the signals necessary to maintain circadian and physiological homeostasis. During the past decade, experimental and epidemiological studies have suggested detrimental effects of circadian disruption on lipid and carbohydrate metabolism, obesity, and metabolic dysfunction. Delayed feeding, exposure to light at night, and sleep disruption seem to converge in shift workers, producing the most dramatic increases in obesity in epidemiological studies. Individually, these disruptors are much more commonly experienced in the population and have been tied to metabolic disruption. Data from animal studies offer some insight into the mechanisms that may mediate these changes. At the level of the circadian clock, disruption of synchronizing signals impair entrainment and abolish rhythmic and functional endocrine responses; glucose and insulin become uncoupled or insulin sensitivity is abolished, and leptin and glucocorticoids no longer exhibit rhythms. In addition to central disruption, peripheral clocks lose a functional signal of time of day. Within the liver, a critical organ for maintaining lipid and carbohydrate metabolism, this can eliminate temporal compartmentalization of metabolite production, leading to impaired energy allocation and fat deposition. Circadian disruption also is associated with inflammation, both centrally and in the periphery, further exacerbating associated metabolic and cardiovascular diseases.[109,134]

Although much research has been conducted associating circadian disruption and obesity, the mechanisms by which these phenomena are linked remain unspecified. It seems that disruption of peripheral clocks, by targeted gene knockouts to the liver or pancreas, dim light at night, and restricted feeding, is sufficient to recapitulate the weight gain and metabolic disruption exemplified in epidemiological data. But central disruption can also play a role in mediating weight gain phenotypes. The disruption in endocrine function can be both downstream of weakened central circadian cues and upstream of peripheral disruption, as exemplified by glucocorticoid secretion. Despite an unclear etiology, many of these models show that metabolic shifts toward obesity can be ameliorated when individuals are returned to conditions of good circadian hygiene; that is, feeding restricted to the active phase, return to dark nights, >8 hours of sleep a night, as well as exercise.

There is now substantial evidence that circadian disruption affects human health. Promoting awareness of circadian biology and the consequences of poor circadian hygiene in both the scientific community and the general public are important for improving human health. Reduction of exposure to short wavelength light (blue) at night is consistent with good circadian hygiene. Obesity rates have also increased among human companion animals and laboratory animals. For example, laboratory animals have inexplicably become obese over the past 30 years.[135] Perhaps reducing nighttime light exposure in animal colony rooms (typical

sources include glass windows on doors, ventilated racks, etc) could improve lab animal housing conditions and make research outcomes more consistent. Similarly, exposure to their human companions' nighttime lighting or late feeding times may be contributing to the increasing obesity rates among companion animals.

Future research should establish the pathways through which light exposure alters circadian clock genes and determine the elements of this pathway that are crucial for inflammation and metabolic disruption. Very few clinical studies assessing the effects of nighttime light exposure exist. Future clinical studies should evaluate the effects of different light levels in home environments, as well as nursing homes and hospitals where people may be particularly vulnerable to the negative effects of circadian dysregulation. Development of lighting parameters that do not derange circadian organization is critical for human and nonhuman animal health.

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Disclosure

The authors report no conflicts of interest in this work.

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