The Effects of Light at Night on Circadian Clocks and Metabolism

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Most organisms display endogenously produced ~24-hour fluctuations in physiology and behavior, termed circadian rhythms. Circadian rhythms are driven by a transcriptional-translational feedback loop that is hierarchically expressed throughout the brain and body, with the suprachiasmatic nucleus of the hypothalamus serving as the master circadian oscillator at the top of the hierarchy. Appropriate circadian regulation is important for many homeostatic functions including energy regulation. Multiple genes involved in nutrient metabolism display rhythmic oscillations, and metabolically related hormones such as glucagon, insulin, ghrelin, leptin, and corticosterone are released in a circadian fashion. Mice harboring mutations in circadian clock genes alter feeding behavior, endocrine signaling, and dietary fat absorption. Moreover, misalignment between behavioral and molecular circadian clocks can result in obesity in both rodents and humans. Importantly, circadian rhythms are most potently synchronized to the external environment by light information and exposure to light at night potentially disrupts circadian system function. Since the advent of electric lights around the turn of the 20th century, exposure to artificial and irregular light schedules has become commonplace. The increase in exposure to light at night parallels the global increase in the prevalence of obesity and metabolic disorders. In this review, we propose that exposure to light at night alters metabolic function through disruption of the circadian system. We first provide an introduction to the circadian system, with a specific emphasis on the effects of light on circadian rhythms. Next we address interactions between the circadian system and metabolism. Finally, we review current experimental and epidemiological work directly associating exposure to light at night and metabolism. **(*Endocrine Reviews* 35: 648–670, 2014)**

I. Introduction

Over the course of the 20th century, the prevalence of obesity and metabolic disorders rapidly increased worldwide. By the year 2000, the number of adults with excess body fat surpassed those who were underweight for the first time in evolutionary history (1). The growth in obesity has been exponential in recent decades, particularly for the highest weight categories. For example, from 2000 to 2005, the number of individuals with a body mass index (BMI) over 50 (for reference, obesity is defined as BMI >30) increased 75% in the United States (2). Obesity is a pathogenic condition defined by the accumulation of excess adipose tissue and is associated with serious health issues including diabetes, cardiovascular disease, hypertension, asthma, cancer, and reproductive dysfunction (3). Obesity reduces quality of life, results in significant health-related complications, and more than doubles healthcare

ISSN Print 0163-769X ISSN Online 1945-7189
Printed in U.S.A.

Received May 12, 2013. Accepted March 18, 2014.
First Published Online March 27, 2014

Abbreviations: BMAL1, brain and muscle arnt-like protein 1; BMI, body mass index; CLOCK, circadian locomotor output cycles kaput; CNS, central nervous system; Cry, cryptochrome; LDL, low-density lipoprotein; PER, period; SCN, suprachiasmatic nuclei.

Figure 1.

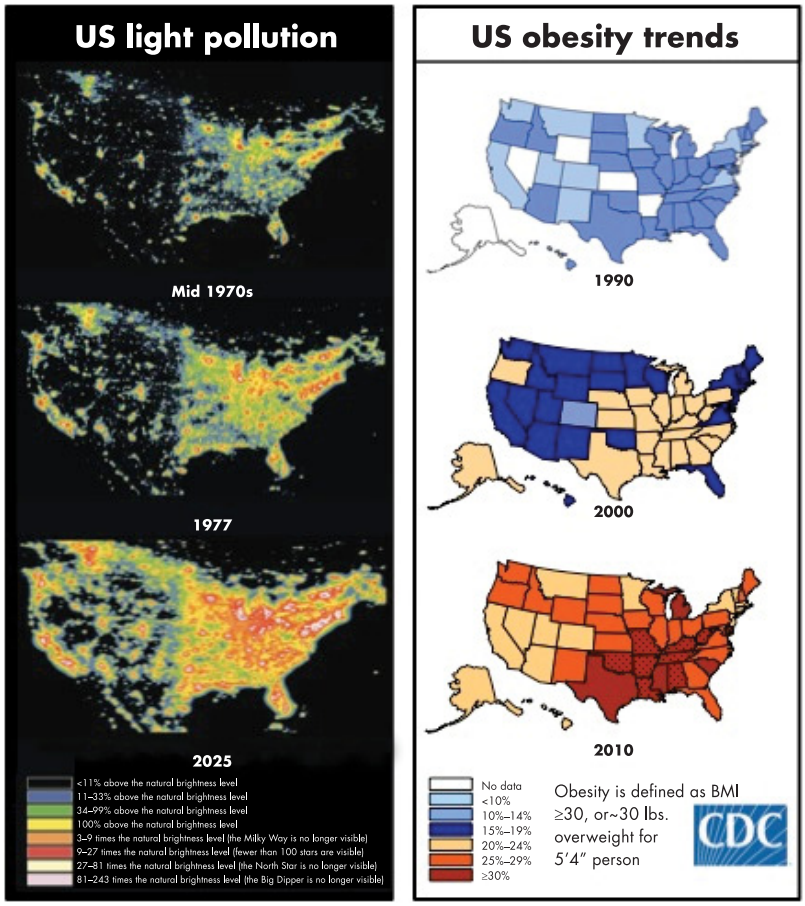

Figure 1. Exposure to light at night and obesity are increasing in tandem. The left panel shows light pollution trends in the United States from the mid-1970s through projected levels in 2025. The right panel shows obesity trends in the United States from 1990, 2000, and 2010.

costs. In addition to traditional risk factors (high-calorie diet, sedentary lifestyle, etc) contributing to obesity, other environmental factors are likely involved in the development and maintenance of this condition (4).

Multiple historic transitions in human lifestyle occurred during the past century, such as advances in travel and communication, greater urbanization, and the eradication of several diseases (5). One environmental change that had a particularly dramatic effect on human lifestyle was the widespread adoption of electrical lighting. Electric lights provide many societal advances. Brightening the night has shed the negative stigma of night as a time solely for crime, sickness, sleep, and death (6). The use of electric light at night played a major role in the industrial revolution, allowing for the creation of shift work. Furthermore, electrical lighting has given individuals the ability to self-select their sleep/wake schedule. Because the invention of electrical lighting occurred before an understanding of circadian biology, little concern was given for how exposure to unnatural light schedules may affect human mental and physical health. It is reasonable to suggest that exposure to electric light affects physiology and behavior because of the importance of the circadian system in regulating homeostatic functions in many organisms. Circadian rhythms are endogenously driven 24-hour rhythms in physiology and behavior that are most potently synchronized by light information. It is now becoming apparent that disruption of the circadian system with exposure to light at night causes significant physiological repercussions (7, 8). In a sense, shift workers, who are exposed to high levels of light at night in the workplace, have served as society's canaries in the coal mine for maladaptive consequences of nighttime light exposure. Epidemiological evidence from shift workers suggests that prolonged exposure to light at night increases the risk of developing cancer (9), sleep disturbances (10), mood disorders (11), metabolic dysfunction (12–17), and cognitive impairments (18, 19). Additionally, the increase in exposure to light at night parallels the global increase in the prevalence of obesity and metabolic disorders (Figure 1).

Here we propose that increases in exposure to light at night during the 20th century and concomitant changes in lifestyle are associated with alterations in metabolism. We will first provide an introduction to the circadian system (Section II), with a specific emphasis on the effects of light on circadian rhythms (Section II.E). We will then address interactions between the circadian system and metabolism (Section III). Animal models have provided insight about the effects of circadian rhythm disruption on metabolism (Section III.A) as well as the effects of disrupted metabolism on the circadian system (Section III.B). Next, we will review current experimental (Section IV.A) and epidemiological (Section IV.B) work directly associating exposure to light at night and metabolism. Finally, we will present alternative pathways through which light at night may affect metabolism (Section V).

II. Circadian Clockwork

The rotation of the Earth about its axis produces a highly consistent cycle of light and dark (that varies latitudinally

and on a seasonal basis). For more than 3 billion years, life on Earth evolved under natural lighting conditions. This led most organisms, from unicellular cyanobacterium to fruit flies and humans, to develop an endogenous timekeeping system that synchronizes physiological and behavioral processes to the external solar cycle (20). Biological clocks can coordinate an individual's interactions with the external environment (eg, having an internal reference to the time of day can help animals avoid predation or engage in mating) and synchronize an individual's internal physiological and biochemical processes (eg, rhythmic hormone release in anticipation of food availability and sleep). Circadian rhythms are specifically defined as internally driven oscillations that meet several characteristics, including 1) the period of the rhythm is about 24 hours in the absence of environmental cues (21), 2) rhythms are buffered against changes in environment such as temperature fluctuations and behavioral feedback (22), and 3) rhythms can shift under the influence of certain factors, but entrainment is limited to a specific range (23).

One common example of a circadian rhythm in mammals is the presence of a sleep/wake cycle. In diurnal species, such as humans, sleep typically occurs during the dark part of the day, whereas nocturnal animals, such as house mice (*Mus musculus*), generally sleep during the light part of the day (see Section II.D for more details on diurnal vs nocturnal species). Sleep and activity rhythms parallel endogenous hormone rhythms. For example, cortisol secretion spikes in the early morning directly before awakening in humans and then drops throughout the day, reaching its nadir around the time of sleep onset (24). Overall, circadian rhythms influence many physiological functions, and the importance of the circadian system is clearly demonstrated by considering pathogenic conditions that result from altering the circadian system (25). Circadian rhythm disruptions contribute to a wide range of disorders including cognitive impairments, mood disturbances, and increased risk of cardiometabolic disorders (26). To understand why these pathogenic conditions arise from disruption of the circadian clock, we review how and where circadian oscillations originate.

A. The suprachiasmatic nucleus is the master circadian oscillator

The suprachiasmatic nuclei (SCN) of the hypothalamus comprise the master circadian clock in mammals (26), at the top of a hierarchy of independent self-sustaining oscillators. The SCN is located in the anterior hypothalamus directly above the optic chiasm and is composed of approximately 50 000 densely packed small neurons in humans and 8000 to 20 000 neurons in rodents (27–29). The cellular make-up of the SCN is diverse, and the SCN contains several different peptides and neurotransmitters (30). There are multiple lines of evidence confirming that the SCN is the master circadian oscillator in mammals: 1) SCN lesions abolish circadian rhythms (31–33), 2) electrical and chemical stimulation of the SCN induce phase shifts (34, 35), 3) transplanting an SCN into an animal whose own SCN has been ablated restores circadian activity (36), and 4) individual neurons dissociated from the SCN display long-term (<1 month) self-sustaining oscillations (37, 38). Cellular synchrony within the SCN is established through multiple mechanisms such as sodium-dependent action potentials and humoral signals (39).

B. Molecular mechanisms of the circadian clock

The circadian clock in mammals is driven by an autoregulatory feedback loop of transcriptional activators and repressors (reviewed in Refs. 40 and 41) (Figure 2). Circadian locomotor output cycles kaput (CLOCK) and brain and muscle arnt-like protein 1 (BMAL1) form heterodimers that induce expression of period (*Per1*, *Per2*, and *Per3*) and cryptochrome (*Cry1* and *Cry2*) through E-box enhancers (42–44). Period (PER) and cryptochrome (CRY) proteins accumulate in the cytoplasm throughout the circadian day. Upon reaching critical levels, PER and CRY form a complex that translocates back to the nucleus to associate with CLOCK and BMAL1 and repress their own transcription (45–47). This process takes approximately 24 hours to complete a full cycle. In addition to the primary feedback loop, other regulatory loops influence the circadian clockwork. For example, the CLOCK:BMAL1 heterodimer also activates transcription of retinoic acid- related orphan nuclear receptors, *Rev-erbα* and *Rora*, which have feedback effects primarily on *Bmal1* (48).

Core clock components are defined as genes with protein products that are essential for the generation and regulation of circadian rhythms (49). Ablation of any of the core clock genes, *Clock* or *Bmal1* (50), *Per1* or *Per2* (51), or *Cry1* or *Cry2* (52), disrupts circadian physiology (see Table 1 in Ref. 53). A number of other secondary and tertiary clock components are necessary for generation of precise circadian rhythms (54), and the criteria for what constitutes core clock genes are constantly evolving. *Rev-Erb* and *Per3* were not initially considered critical for maintaining clock function; however, the importance of these genes for circadian regulation is now widely accepted (55, 56).

C. Additional clocks exist outside the SCN

Circadian oscillators are present in most, if not all, tissues of multicellular organisms. The SCN serves as the master circadian clock at the top of a hierarchically orga-

Figure 2.

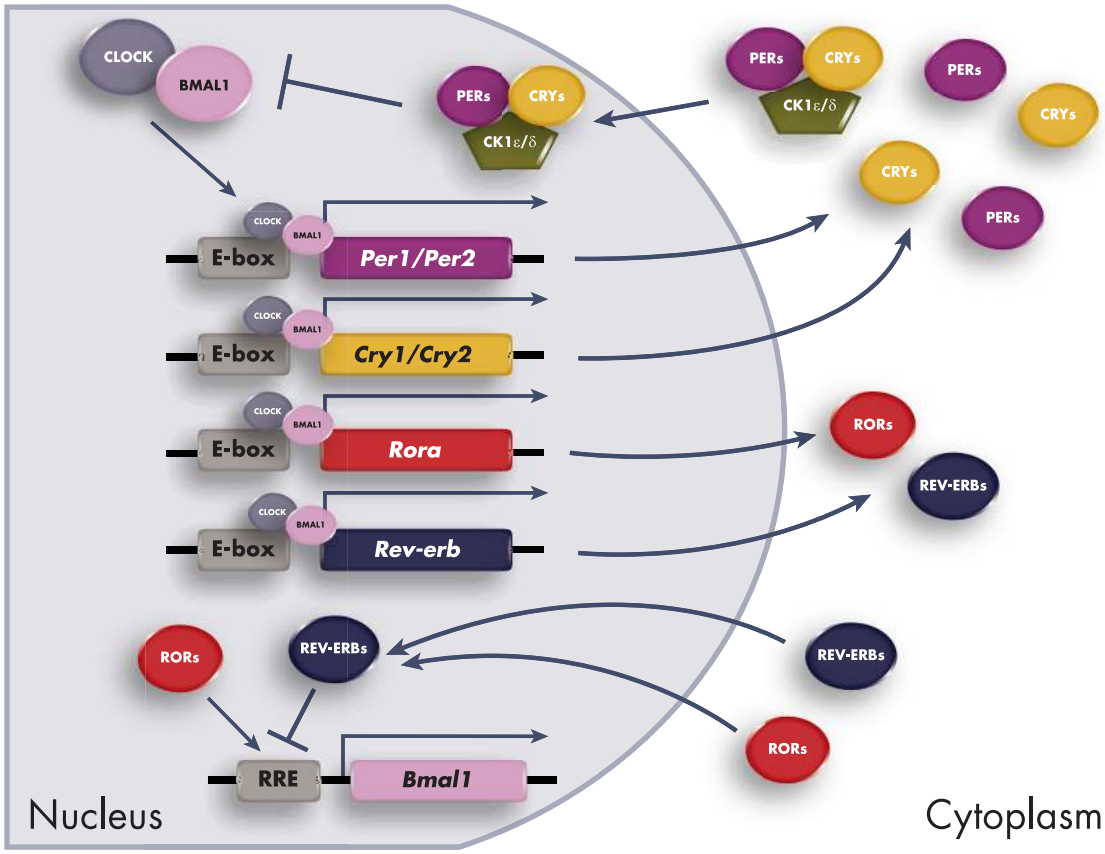

Figure 2. Simplified version of the molecular mechanisms of the circadian clock in mammals. The circadian clock is driven by an autoregulatory feedback loop. CLOCK and BMAL1 form a heterodimer that induces expression of *Per* and *Cry* through E-box enhancers. PER and CRY proteins accumulate in the cytoplasm throughout the circadian day. Upon reaching critical levels, PER and CRY form a complex that translocates back to the nucleus to associate with CLOCK and BMAL1 and repress their own transcription. This process takes approximately 24 hours to complete a full cycle. Additionally, the CLOCK:BMAL1 heterodimer regulates transcription of *Rev-erbα* and *Rora*, which have feedback effects on *Bmal1*.

nized system (41). Tissue-specific clocks contain the molecular machinery necessary for self-sustaining oscillations (57) and have virtually the same molecular makeup as circadian oscillators in the SCN. Peripheral clocks are entrained by the SCN through both neural and hormonal signals (58–60) as well as local factors such as nutritional signals (61). Peripheral clocks do not appear to communicate with each other, but they are coupled to the SCN (62). Ablation of the SCN in vivo has profound effects on peripheral oscillators (63) and peripheral oscillators show more rapid dampening of circadian rhythms in vitro (64). Although SCN rhythms can persist for more than 1 month in vitro, peripheral rhythms decay within 2 to 7 cycles (38).

D. Diurnality vs nocturnality

Most basic research is conducted in nocturnal rodents, whereas epidemiological and clinical results refer to diurnal humans. What are some of the key differences between nocturnal and diurnal mammals? The circadian timekeeping system coordinates a biological day and a biological night that transition in a cyclic fashion. The biological night is considered the circadian time period that occurs during the dark part of the day. In diurnal (day-active) species, behavioral inactivity or rest characterizes biological night, whereas behavioral activity is typical during this time in nocturnal (night-active) species, although this is often relative because individuals of many species are only minimally active through much of the day. Despite activity profiles that are 180° out of phase, the fundamental function of the circadian system and mechanisms of the molecular clock appear conserved between nocturnal and diurnal species (65). Indeed, the structural and chemical make-up of the SCN is similar in nocturnal and diurnal rodents of the same genus (66). However, the downstream products of this conserved system can vary greatly between nocturnal and diurnal mammals. For example, temporal information for circadian control of corticosterone

secretion is carried along the same pathways in nocturnal and diurnal rodents, but the response of the target tissue to the signal is quite different. Vasopressin in the SCN inhibits or stimulates adrenal corticosterone in nocturnal and diurnal rodents, respectively (67). Importantly, the effect of light on entraining the circadian system (described in Section II.D) and photic inhibition of melatonin is similar between nocturnal and diurnal animals, although sensitivity to light can vary greatly (68). Light also has some opposite effects on masking in diurnal and nocturnal rodents. Light pulses during the dark reduce activity in nocturnal rodents (negative masking) but increase activity in diurnal rodents (positive masking) (69). Furthermore, many endocrine signals related to metabolism occur out of phase in nocturnal and diurnal mammals because feeding patterns are reversed.

E. Light entrains the circadian system

Exposure to constant dim light or total darkness results in a free-running circadian system (ie, a rhythm that is not entrained to the 24-hour day-night cycle). In most organisms, the circadian system functions with a period close to, but not exactly, 24 hours when free-running (21). Therefore, circadian clocks require external input to entrain them to the environment (70). Light is the most potent synchronizing factor for the SCN. Light information travels directly from intrinsically photosensitive melanopsin-containing retinal ganglion cells through the retinohypothalamic tract to the SCN (71). The SCN receives additional indirect input from intrinsically photosensitive melanopsin-containing retinal ganglion cells via the intergeniculate nucleus and input from rods and cones (72–74). Indeed, photo entrainment persists in melanopsin-deficient mice but not in triple knockouts that lack melanopsin, rod, and cone function (75). Within the SCN, light induces rapid changes in cellular activities that have been extensively characterized by examining the expression of immediate early genes (76–78).

At the molecular level, exposure to light rapidly induces *Per1* (79, 80). A pulse of light during the dark phase can phase advance or delay the circadian clock depending on the timing, duration, and intensity of the light signal (81, 82). In nocturnal rodents, light at the end of the dark phase advances the clock through advancing the onset of the *Per1* rhythm and acutely increasing mRNA transcription, whereas light at the beginning of the dark phase delays the clock through delaying the offset of *Per2* (82). Higher intensities of light are required earlier as compared with later in the dark phase to induce these phase shifts in rodents (83). Moreover, the duration of light exposure is critical in determining whether a light pulse phase shifts circadian rhythms in both humans (84) and rodents (85). Light intensities well below those produced by natural sunlight (10 000 lux) can induce phase shifting (light intensities around 180 lux phase shift activity rhythms in humans) (86). The circadian system also appears to be sensitive to light intensities below the threshold that induces phase shifts (for example, see Ref. 87).

The SCN can rapidly adjust to light shifts, whereas peripheral tissues shift more slowly and in different ways (38). Although light is the most potent signal for the mammalian circadian system, other factors such as food availability and locomotor activity can feed back and influence circadian clock function (88, 89). These types of stimuli can leave SCN rhythms intact, specifically altering clock gene expression in peripheral tissues (61, 90).

As discussed above (Section II.A), multiple characteristics of the circadian system are conserved between nocturnal rodents and diurnal humans. In humans, specifically timed light pulses can also shift the circadian clock (91, 92). Moreover, both humans and rodents are most responsive to blue wavelength nighttime light exposure (93–95). Long wavelengths of light, such as red light, do not activate the melanopsin-containing retinal ganglion cells that project to the SCN (75) and therefore minimally influence the circadian system (96).

F. Light at night and the circadian system

In contrast to constant dark or dim light, exposure to continuous bright light produces locomotor activity arrhythmicity and flattens circadian rhythms in glucocorticoids and body temperature, two principle outputs of the circadian system (Table 1) (97–102). This is likely due to desynchrony among mammalian clock neurons in constant lighting conditions (103).

There is evidence that dim levels of light at night can also influence the mammalian circadian system (104, 105). Our lab and others have extensively characterized the effects of chronic exposure to ecologically relevant levels of dim light at night (~5 lux) on rodent circadian systems (Table 1); 5 lux of nighttime light exposure is comparable to levels of light pollution found in urban areas (106, 107) and sleeping environments (14). Exposure to chronic low levels of light at night alters circadian clock genes in both the SCN and peripheral tissue in mice (108, 109). Exposure to dim light at night specifically attenuates the rhythm in Per1 and Per2 gene and protein expression in the SCN around the light/dark transition (108, 109). Furthermore, expression of *Bmal1*, *Per1*, *Per2*, *Cry1*, *Cry2*, and *Rev-Erb* are all suppressed in the liver by exposure to dim light at night (109). Nocturnal light may affect the liver through both autonomic and hormonal pathways (110). The changes in clock gene expression associated with exposure to dim light at night do

Table 1. Effects of Chronic (>1 Week) Light Disruption on the Circadian System

		Findings				
Light Manipulation	**Species**	**Brain**	**Periphery**	**Endocrine**	**Behavior**	**Ref.**
Constant light	Diurnal fat sand rat		Body temp rhythm attenuated			101
Constant light	Mouse (Swiss Webster)			Blunted corticosterone rhythm	Arrhythmic activity	97, 279
Constant light	Mouse (C57BL/6J)	Dampening of SCN rhythm amplitude		Blunted corticosterone rhythm	Arrhythmic activity	98
Constant light	Mouse (BALB/c)	Per2 expression dampened			Lengthened activity period, arrhythmic activity	99
Constant light	Mouse (B6C3HF1)	SCN neurons desynchronized			Arrhythmic and split activity	103
Constant light	Mouse (C3H/He)	Constitutively elevated PER2			Lengthened activity period	100
Constant light	Rat (Wistar)	Reduced *c-fos* activity in SCN		Loss of corticosterone rhythm, melatonin suppressed	Arrhythmic activity	102
Dim (20 lux) LAN	Mouse (CD1)	Reduced amplitude of Per oscillations in SCN			Elevated daytime activity, altered light responsiveness	108
Dim (5 lux) LAN	Mouse (Swiss Webster)	Attenuated Per1 and 2 rhythms in hypothalamus	Reduced amplitude of core clock genes in liver and fat	Corticosterone unaffected	Home cage activity unaffected wheel running rhythm disrupted	97, 109, 215
Dim (5 lux) LAN	Diurnal nile grass rat			Elevated corticosterone	Activity rhythm unaffected	278
Dim (5 lux) LAN	Siberian hamster	Attenuated Per1 and 2 rhythms in SCN		Abolished cortisol rhythm	Reduced activity rhythm amplitude	111
Shifts: daily 6-h phase advance	Rat (F344)		Altered clock gene rhythm in NK cells		Disrupted activity rhythm	114
Ultradian (LD 3.5:3.5)	Mice (B6/129)	Intact SCN Per rhythm	Liver Per rhythm intact, body temp rhythm intact	Corticosterone rhythm unaffected	Activity rhythm unaffected	112
Ultradian (LD 3:3)	Mice (ICR)				Arrhythmic activity	113
Ultradian (LD 10:10)	Mice (C557BL/6)		Body temp rhythm disrupted			216

Abbreviations: LD, light/dark; temp, temperature; LAN, light at night.

not result in disruption of either the glucocorticoid rhythm or locomotor activity rhythm (97, 109). Similar changes in circadian clock function are also apparent in the SCN of Siberian hamsters (*Phodopus sungorus*) exposed to low levels of light at night (111). Hamsters exposed to dim light suppress PER1 and PER2 protein rhythms in the SCN independent of changes in activity rhythm. In contrast to mice, however, hamsters exposed to dim light at night display a flattening of the cortisol and melatonin rhythm. Other light manipulations such as chronic daily phase shifts or ultradian light schedules also affect the circadian system (Table 1) (112–114). Overall, these results indicate that exposure to levels of nighttime lighting commonly experienced in urban settings can affect the circadian system. One important caveat to this work is that rodents are typically more sensitive to lower-intensity lighting than humans (94, 115).

Exposure to electric light also influences the circadian system in humans. A recent study by Wright and colleagues (116) examined the effects of electric light exposure on the circadian system in humans by measuring characteristic circadian and sleep patterns in adults maintained in a standard electrical lighting environment (ie, light that reflects daily routines of work, school, social activities, and self-selected sleep schedule) compared with a natural lighting environment (outdoor camping). People exposed to only natural light were more accurately synchronized to solar time. Furthermore, exposure to natural lighting reduced individual variability in melatonin and sleep rhythms making late chronotypes more similar to early chronotypes (116).

Exposure to low levels of light at night influence a diverse array of functions associated with circadian disruption in other animals. For example, European blackbirds (*Turdus merula*), exposed to 0.3 lux of light at night develop their reproductive system up to 1 month earlier and molt sooner than birds maintained in dark nights (117). Diurnal Nile Grass rats (*Arvicanthis niloticus*) exposed to light at night have impaired learning and memory and increase depressive-like responses compared with rats maintained in dark nights (118). Furthermore, exposure to light at night affects foraging and predation (119–121) and migration in multiple species (122–124).

III. The Circadian System Regulates Metabolism and Vice Versa

The circadian system is involved in maintaining energy homeostasis (125). Approximately 10% of the mammalian transcriptome display circadian oscillations (126–128). Among the rhythmic genes identified, many have a specific role in coordinating nutrient metabolism (128, 129). For example, glucose transporters and the glucagon receptor, as well as multiple enzymes involved in the metabolism of sugars and the biosynthesis of cholesterols, are rhythmically expressed (109–111). Metabolically related

hormones such as glucagon, insulin, ghrelin, leptin, and corticosterone oscillate in a circadian manner (130–132). There is rhythmic expression of orexigenic signals including neuropeptide Y, galanin, and preopiomelanocortin within the hypothalamus, an area critical for coordinating metabolic signals (133, 134). Circadian fluctuations in hunger and appetite have also been reported (135). Moreover, neuroanatomical organization provides evidence of interactions between metabolism and the circadian system; hypothalamic nuclei such as the paraventricular nucleus receive direct neuronal input from the SCN (reviewed in Ref. 136).

A. Knocking out the circadian clock and obesity

In addition to fluctuations in metabolic processes suggesting an association between the circadian and metabolic systems, disrupting the clock network through genetic manipulations has provided insight into the role of the circadian system in maintaining metabolic homeostasis (Table 2). Mice harboring mutations in various components of the circadian clock are susceptible to obesity and metabolic syndrome. Turek and colleagues (137) were the first to report that *Clock* mutant mice on a BALB/c and C57BL/6J background are susceptible to diet-induced obesity. *Clock* mutants display profound changes in circadian rhythmicity as well as disruptions in diurnal food intake and increased body mass. This phenotype may partially result from changes in endocrine regulation as serum leptin, glucose, cholesterol, and triglyceride levels are all increased in *Clock* mutants compared with wild-type mice. Deletion of *Clock* on an ICR background also results in metabolic alterations. In contrast to *Clock* deletion in a BALB/c and C57BL/6J background, ICR *Clock*-deficient mice are protected against weight gain due to impairments in dietary fat absorption (138). The contrary effects of *Clock* deletion on energy balance in these strains may indicate that CLOCK protein affects metabolism through interactions with other strain-specific loci in the murine genome (138).

Disruption of other core circadian clock genes also affects metabolism. Mice deficient in *Bmal1* alter glucose and insulin secretion (139, 140). *Bmal1*$^{-/-}$ mice increase concentrations of circulating fatty acids resulting in formation of ectopic fat in the liver and skeletal muscle (141). When rhythmicity is rescued in *Bmal1*$^{-/-}$ mice with *Bmal2*, insulin secretion and activity patterns are restored (140). Furthermore, rescuing *Bmal1* in the central nervous system (CNS) restores locomotor activity rhythms but not changes in metabolism (142). This indicates disruption of *Bmal1* in peripheral tissue is important for changes in metabolism. Mutation of *Cry1* produces symptoms of diabetes mellitus in mice (143). *Cry1/2*$^{-/-}$ mice are more susceptible to diet-induced obesity, display hyperinsulinemia, and alter lipid storage (144). Furthermore, mice deficient in *mPer1/2/3* increase weight gain on a high-fat diet (145). Single disruption of the *Per2* gene alters glucose homeostasis, disrupts feeding and glucocorticoid rhythms, and results in significant weight gain and elevated adiposity (146–149). Conversely, *Per1*^{Brd} mice show increased glucose efficiency and weight loss compared with wild-type controls (150).

Table 2. Circadian Clock Disruptions and Metabolism

Gene	Background	Tissue	Principal Findings	Ref.
Bmal1	Mixed background	Whole body	Altered endocrine signaling, reduced islet size	139
Bmal1	C57BL/6J	Whole body	Lack insulin rhythmicity, ectopic fat formation	140, 141
Bmal1	Mixed background	Pancreas	Impaired glucose tolerance, defective insulin production	139, 152
Bmal1	C57BL/6 and 129	Liver	Altered glucose regulation	153
Bmal1	C57BL/6J	Adipocytes	Prone to obesity, altered feeding rhythm	155
Bmal1	C57BL/6J	CNS	Altered feeding rhythm	156
Clock	ICR	Whole body	Decreased body mass, impairments in fat absorption	138
Clock$^{\Delta 19}$	BALB/c and C57BL/6J	Whole body	Prone to obesity, increased daytime food intake, altered endocrine signaling	137
Clock$^{\Delta 19}$	C57BL/6J	Whole body	Altered endocrine signaling, reduced pancreatic islet size	139
Clock$^{\Delta 19}$	DBA	Liver and skeletal muscle	Altered glucose regulation	151
Cry1		Whole body	Diabetic-like phenotype	143
Cry1/2	C57BL/6J	Whole body	Prone to obesity, hyperinsulinemic, altered lipid storage	144
Per1/2/3^{tm1Drw}		Whole body	Prone to obesity	145
Per1^{Brd}	C57BL/6	Whole body	Decreased body mass, altered feeding, increased glucose efficiency	150
Per2	C57BL/6J	Whole body	Prone to obesity, altered feeding rhythm, altered endocrine signaling	146–149
Per3^{tm1Drw}		Whole body	Prone to obesity	145
Rev-Erbα and *-β*	C57BL/6	Whole body	Altered endocrine signaling	55

Loss of clock function in peripheral tissues similarly affects metabolism. For example, altering *Clock* gene expression in liver and skeletal muscle impairs glucose processing and alters insulin secretion (151). Deletion of pancreatic *Bmal1* reduces glucose and insulin processing abilities, independent of changes in activity or feeding rhythms in mice (139, 152). Mice with liver-specific deletion of *Bmal1* exhibit hypoglycemia during the fasting phase, exaggerated glucose clearance, and loss of rhythmic expression of hepatic glucose regulatory genes (153, 154). Changes in glucose processing with liver-specific *Bmal1* deletion occur without changes in feeding behavior or locomotor activity, indicating a primary defect in metabolic responses (153). In contrast, deletion of *Bmal1* in adipocytes alters daily feeding rhythms and results in obesity (155). Finally, *Bmal1* deletion in the CNS produces deficits in locomotor activity entrainment by periodic feeding, reductions in food intake, and subsequent loss of body weight (156).

Alterations in secondary clock genes are also associated with metabolic changes in mice. Modulation of *Per3* may be responsible for weight gain in *Per1/2/3*$^{-/-}$ mice, because single deletion of *Per3* results in significant weight gain (145). Mice lacking the VIP-VPAC2 (Vasoactive Intestinal Peptide-VIP receptor type II) pathway, which plays an important role in SCN communication (157), have dampened feeding rhythms and decreased metabolic rate (158). Furthermore, mice lacking Nocturnin, a gene involved in the posttranscriptional regulation of rhythmic gene expression (159), remain lean on a high-fat diet (160). This appears to reflect either changes in lipid uptake or utilization because Nocturnin$^{-/-}$ mice lack rhythmicity in several lipid pathway genes (160, 161). Recently, *Rev-Erb* has been implicated in the modulation of both metabolism and the circadian system (162). Dual deletion of *Reb-Erb*α and *Rev-Erb*β disrupts gene networks involved in lipid metabolism (55) and markedly affects circadian rhythms. *Rev-Erb* likely regulates hepatic lipid homeostasis through the recruitment of histone deacetylase 3 (163). Treatment with a Rev-Erb agonist increases energy expenditure and promotes weight loss in mice fed a high-fat diet (164).

Associations between clock genes and metabolism are also apparent in humans. Glycemic control in people with type 2 diabetes varies by chronotype; night owls (ie, people with a late chronotype) who eat a larger dinner tend to have poorer glycemic control independently of sleep disturbances (165). Furthermore, BMI correlates with clock gene expression in peripheral adipose tissue depots (166). *Per2* expression levels in visceral adipose tissue inversely correlate with waist circumference (167), and *Bmal*, *Per2*, and *Cry1* levels negatively correlate with total cholesterol and low-density lipoprotein (LDL) concentrations. The methylation pattern of different CpG sites of *Clock*, *Bmal*, and *Per1*, are significantly associated with metabolic parameters including BMI, adiposity, and metabolic syndrome score (168). Moreover, a common clock polymorphism is coupled to the presence of metabolic syndrome in humans (169).

B. Metabolism and the circadian clock are reciprocally related

The relationship between the circadian system and metabolism appears to be bidirectional. In addition to circadian system disruptions causing obesity, metabolic abnormalities alter circadian rhythms. For example, in humans, metabolically related diseases such as obesity and anorexia nervosa are associated with altered hormone and body temperature rhythms (170). Obese individuals lack typical daily rhythms in glucose and insulin sensitivity (171). Moreover, obese women have significantly lower wrist temperature and a flattened temperature rhythm compared with normal-weight controls (172).

Animal research also indicates metabolism can affect the circadian system. Mice fed a high-fat diet lengthen their circadian period of activity, attenuate diurnal feeding rhythms, and dampen circadian rhythms in clock gene expression in peripheral metabolically related tissues (173, 174). These changes appear to occur rapidly, because liver rhythms are phase advanced 5 hours, within 1 week of initiating a high-fat diet (175). Furthermore, mice fed a high-fat diet delay re-entrainment of behavioral and physiological rhythms after a 6-hour phase shift (176).

Modulation of leptin in mice and rats provides further support for the hypothesis that disrupting metabolism affects the circadian system. Zucker obese rats, a widely used obesity model produced by a single mutation in the gene encoding the leptin receptor (177), exhibit phase-advanced circadian rhythms and an attenuated amplitude of body temperature, activity, and sleep (178, 179). Zucker rats increase daytime food intake when compared with lean controls (180, 181), and preventing food intake during the light (inactive) phase ameliorates weight gain in Zucker rats (179). Furthermore, db/db mice, which lack the leptin receptor, alter rhythms of multiple metabolically related hormones (182) and clock genes in peripheral tissues (183). The ob/ob leptin-deficient mice attenuate rhythms in activity, heat production, and clock gene expression (184). Disruptions in circadian rhythms, however, may occur before the onset of obesity in ob/ob mice (185).

Other rodent models of obesity display similar changes in circadian rhythms. Rats with ventromedial hypothalamic lesions become obese and alter the daily pattern of

food intake and circadian gene expression (186). KK-A^y mice, a mouse model of obesity and type 2 diabetes, attenuate clock gene rhythms in adipose tissue and the liver (187, 188). Moreover, a subset of Mexican volcano mice (*Neotomodon asltoni*), are naturally susceptible to obesity and display phase-advanced activity-onset and attenuated locomotor activity rhythms compared with nonobese volcano mice (189). Of note, one common feature in many of the obesity models discussed above is that rodents shift diurnal rhythms in food intake.

C. You are what *when* you eat?

Food is an important entraining signal for the circadian system. Restricting food intake to certain times of day can lead to anticipatory increases in wakefulness, locomotor activity, body temperature, and glucocorticoid secretion (190). Food-entrainable oscillators appear dependent on extra-SCN signaling and likely involve the dorsomedial hypothalamus (191). Indeed, although the SCN remains phase locked to light/dark cues, restricting feeding to certain times of day rapidly entrains circadian rhythms in the liver (192). Additionally, in the absence of light cues, time-restricted feeding is capable of affecting the SCN. Restricting food intake to the same 3 h/d rescues both activity rhythms and *Per2* rhythms in the SCN of rats maintained in constant light (193). In contrast, timed feeding does not reliably produce anticipatory activity in mice made arrhythmic with SCN lesions (194). In a study by Marchant and Mistlberger (194), only 2 of 9 mice with complete SCN ablations consistently anticipated food availability.

Timing of food intake is now recognized as a critical factor in energy acquisition, storage, and expenditure. Mice fed a high-fat diet only during the 12-hour light (resting) phase gain significantly more weight than mice fed only during the dark (active) phase (195). This change in body mass may be dependent on leptin signaling (196). Importantly, in this experimental model, total daily caloric intake and locomotor activity did not significantly differ between groups, indicating changes in body mass can occur independently of changes in energy intake and output (195). A more thorough examination of metabolic characteristics in food-restricted mice revealed light-phase–fed mice exhibit a higher respiratory exchange ratio (indicating decreased reliance on fat oxidation), tissue-specific alterations in metabolically related genes and circadian clock genes, changes in the circadian pattern of humoral factors (ie, corticosterone), and increased weight gain (197). In the study by Bray and coauthors (197), mice also differed in food intake; mice fed during the light phase increased food intake and ate larger meals. Similarly, rats fed during the light phase increase weight gain compared with rats fed only during the dark phase (198). The time of day at which dietary fat is eaten also influences multiple cardiometabolic parameters (199). High-fat meals eaten at the end, as compared with the beginning, of the dark phase lead to features of metabolic syndrome including weight gain, elevated adiposity, reductions in glucose processing, hyperinsulinemia, hyperleptinemia, and hypertriglyceridemia (199).

As discussed above, multiple rodent models of obesity increase food intake during the inactive phase. This has led to recent research assessing whether preventing rest-phase feeding can ameliorate weight gain. Mice fed a high-fat diet that are food restricted to either 4 (200) or 8 (201) h/d during the dark (active) phase are protected against diet-induced obesity. Food-restricted mice consume equivalent calories as mice with ad libitum food access and yet are buffered against obesity, inflammation, hepatic steatosis, hypercholesterolemia, and hyperinsulinemia. Changes in metabolism in food-restricted mice are associated with improved intracellular signaling and nutrient utilization as well as greater circadian clock oscillations (200, 201). Similarly, restricting food access to the 14-hour dark (active) phase reduces weight gain in Zucker obese rats (179).

Accumulating epidemiological and experimental evidence in humans supports the hypothesis that when energy intake occurs is important in determining energy utilization. Timing of food intake predicts BMI in humans, even when controlling for variables such as sleep timing and duration. People who consume more food after 8:00 PM tend to have higher BMI (202, 203). Moreover, weight loss therapy (combinatorial dietary and behavioral weight reduction plan) is more effective for individuals who eat early as compared with late eaters (204). Women who eat their largest meal in the morning compared with the evening lose more weight and have a larger reduction in waist circumference even when consuming the same amount of total daily calories (205). Evidence indicates late night snacking reduces fat oxidation and increases LDL cholesterol in women (206). Short-duration sleepers also have increased risk for obesity, weight gain over time, and higher body fat composition (207). Controlling for factors such as preference for fatty food, skipping breakfast, snacking, and eating out only partially accounts for the effects of short-duration sleep on obesity. This indicates that changes in metabolic homeostasis at different times of day may partially account for different body weight regulation (208). Indeed, people with night eating syndrome, a disorder characterized by evening hyperphagia and nocturnal awakenings accompanied by food intake (209), show alterations in metabolically related hormones and are more likely to be obese (210, 211).

IV. Exposure to Light at Night and Obesity

Given the well-established role of light in modulating the circadian system, and the relationship between circadian and metabolic functions, it is not surprising that exposure to light at unnatural times affects metabolism. Increases in nocturnal illumination parallel increases in obesity and metabolic syndrome worldwide. Here we propose that exposure to light at night may be contributing to increasing rates of obesity. In this section, we will discuss evidence from animal models and epidemiological studies implicating exposure to light at night in the growing obesity epidemic.

A. Evidence from nonhuman animals

Exposure to continuous-light, non–24-hour light schedules, and dim light at night are all associated with metabolic changes in rodents. As discussed, exposure to constant light desynchronizes circadian activity in rodents (98). Swiss Webster mice maintained in constant light as compared with standard light/dark cycles increase body mass and reduce glucose processing without changing total daily home cage activity or food intake (97). C57BL/6J mice similarly alter metabolism in constant light, with body weight gain, reductions in insulin sensitivity, and a higher fat to lean mass ratio (98, 140). After 4 weeks of constant light, C57BL/6J mice lack a circadian rhythm in both food intake and energy expenditure. These changes are associated with reductions in circadian rhythm amplitude as measured by in vivo electrophysiological recordings of the SCN (98). Although rats maintained in constant light do not appear to increase weight gain, they do increase visceral adiposity and demonstrate higher feed efficiency than rats exposed to either a standard light/dark cycle or constant dim light (212).

One limitation to studying the effects of constant light exposure on metabolism is that the circadian system becomes arrhythmic under bright constant-light conditions (97, 193). Furthermore, with the exception of high latitudes, exposure to constant light in natural settings is rare. In contrast to constant light exposure, mice maintained in a bright light/dim light cycle maintain circadian locomotor activity and glucocorticoid rhythmicity (97). Mice exposed to dimly lit, as compared with dark, nights impair glucose processing, increase white adipose tissue depots, and elevate body mass gain (97). Changes in metabolism occur independently of changes in total daily food intake or home cage activity. However, mice exposed to dim light at night shift timing of food intake, consuming more during the light (rest) phase. Restricting food intake to the active (dim) phase, prevents weight gain in mice maintained in dim light at night. Placing mice back in dark nights after exposure to dim light at night partially reverses increases in body mass, suggesting changes in metabolism associated with nighttime light exposure are not permanent (213). Exposure to dim light at night also interacts with more traditional obesogenic risk factors. Mice exposed to dimly lit nights exaggerate weight gain on a high-fat diet (214) and weight gain is diminished with access to a functional running wheel (215).

Studies of circadian desynchrony provide further support for an association between exposure to altered light schedules and changes in metabolism. Mice maintained on a 20-hour light/dark cycle incongruous with their endogenous ~24-hour circadian period accelerate weight gain and alter metabolically related hormones (216). Rodent models of shift work have demonstrated altered light or activity patterns can disrupt liver transcriptome rhythms (217), flatten glucose rhythms, increase abdominal fat (198), and conversely reduce body mass when shift work schedules are combined with other environmental challenges (218). Notably, preventing daytime food intake may rescue metabolic changes in rats undergoing a shift-work lighting schedule (198).

B. Evidence in humans

Light exposure >180 lux phase shifts the human circadian pacemaker (86), but even lower light intensities appear to affect the circadian system and suppress melatonin concentrations (219). Importantly, 320 lux is the minimum required light level in offices and infirmaries by the Occupational Health and Safety Administration in the United States and industrial accident prevention guidelines often call for even brighter light for night shift workers to prevent job-related accidents. This indicates night shift workers are typically exposed to light levels well beyond those that affect the circadian system.

Multiple epidemiological studies in shift-working populations link exposure to light at night to metabolic impairments (220). Healthcare personnel that work night shifts, as compared with day shifts, are at elevated risk for developing metabolic syndrome (221). Shift work is associated with increased blood pressure, cholesterol, obesity, and hypertriglyceridemia in men (12, 222) and increased risk for obesity, hypertension, and hypertriglyceridemia in women (12). A study of offshore personnel either chronically working day shifts or transitioning between day and nights shifts demonstrated that the number of years of shift work is positively associated with BMI in day/night workers. In contrast, age is the greatest predictor for BMI in the day shift population (15). This suggests that chronic exposure to light at night can affect BMI to a greater extent than typical predictors of body mass. Several other studies indicate that working rotating shift

schedules as compared with day schedules increases risk for developing metabolic syndrome (223–227). Importantly, the effects of shift work on metabolism may be long lasting because former shift workers show an elevated risk of being obese (17). Changes in metabolic signals may contribute to increased body mass in shift workers. For example, brief behavioral and endogenous circadian misalignment in a controlled laboratory setting alters leptin, insulin, and cortisol secretion and elevates blood pressure (228). Moreover, forced desynchrony can produce postprandial glucose responses comparable to a prediabetic state (228).

There are several limitations to drawing conclusions about light at night and metabolism based on epidemiological studies in shift workers. First, not only are shift workers exposed to light at night, but they also undergo behavioral circadian desynchrony, which makes it difficult to tease apart the influence of light alone. This is why animal models in which light can be manipulated in isolation and apart from sleep disruption are important in determining the direct effects of light on metabolism. Regardless, addressing the effects of light at night in shift workers remains valid because exposure to bright light at night does not typically occur in the absence of other circadian system disrupters.

Second, the light levels that shift workers are exposed to at night are not representative of the general population. In industrialized economies, approximately 20% of the population work night or rotating shifts (229, 230). However, exposure to light at night occurs beyond the scope of shift work. Over 99% of the population in the United States and Europe experience nighttime light exposure (231). Importantly, associations between exposure to light at night and increases in BMI are also apparent outside the shift working population. A recent study reported that increased light exposure in an uncontrolled home setting is associated with obesity and other metabolic consequences (14). People with nocturnal light levels >3 lux had significantly higher body weight, elevated BMI, increased waist circumference, and elevated triglyceride and LDL cholesterol levels (14). Moreover, a large-scale epidemiological study demonstrated that social jetlag is associated with increased BMI, even when controlling for factors such as sleep duration (232). Exposure to light at night can also lead to disrupted sleep as well as poor sleep quality (233). Insufficient sleep is also associated with metabolic impairments (see Section V.C).

One final piece of evidence linking exposure to light at night and obesity comes from a population where nighttime light exposure is minimal, the Old Order Amish. The Amish abstain from using public power and, therefore, are not exposed to common sources of light at night such as televisions, computers, and electrical lights (234). The prevalence of obesity among the Amish is far lower than the general population in the United States (235). Lower obesity rates among the Amish are for the most part attributed to changes in activity and diet (235, 236). However, other environmental factors are likely involved in limiting disease rates among the Amish. For example, the Amish also suffer disproportionately lower rates of breast and prostate cancer (237). Controlling for known carcinogenic variables such as tobacco use does not completely account for the disparate rates of cancer. Importantly, exposure to light at night is also associated with increased risk for developing both breast and prostate cancer (238, 239).

V. Additional Pathways Through Which Light Affects Metabolism

There are several additional mechanisms through which nighttime light exposure can affect physiology. Thus far, this review specifically focused on how light at night influences metabolism via disruption of circadian clock genes. Exposure to unnatural light at night may also affect metabolic function through melatonin suppression, alterations in glucocorticoids, and changes in sleep architecture (Figure 3). These additional pathways are distinct, but not independent, from changes in the circadian clock.

A. Melatonin and metabolism

Melatonin is an endogenously synthesized molecule that is secreted by the pineal gland during the night in both nocturnal and diurnal mammals (240). This means that melatonin rhythms are 12 hours out of phase in diurnal and nocturnal mammals. Melatonin secretion is potently inhibited by exposure to sufficient levels and durations of nighttime lighting in both rodents and humans (241). For example, exposing people to 1 hour of approximately 45 lux of nighttime light decreases plasma melatonin by ~60% (219). The threshold for melatonin suppression is even lower in rodents with light intensities of 1.08 lux reducing pineal melatonin content (115). In both humans and rodents, melatonin suppression occurs at significantly lower light levels than those required to phase shift the circadian system. Similar to disruption of circadian clock genes, suppressing melatonin secretion is associated with increased risk for developing cancer (242, 243), obesity (244, 245), and mood disorders (246).

The influence of melatonin on body weight in the context of photoperiodism is well documented in rodents. During the short days of winter, when resources are scarce, individuals of many seasonally breeding rodents dramat-

Figure 3.

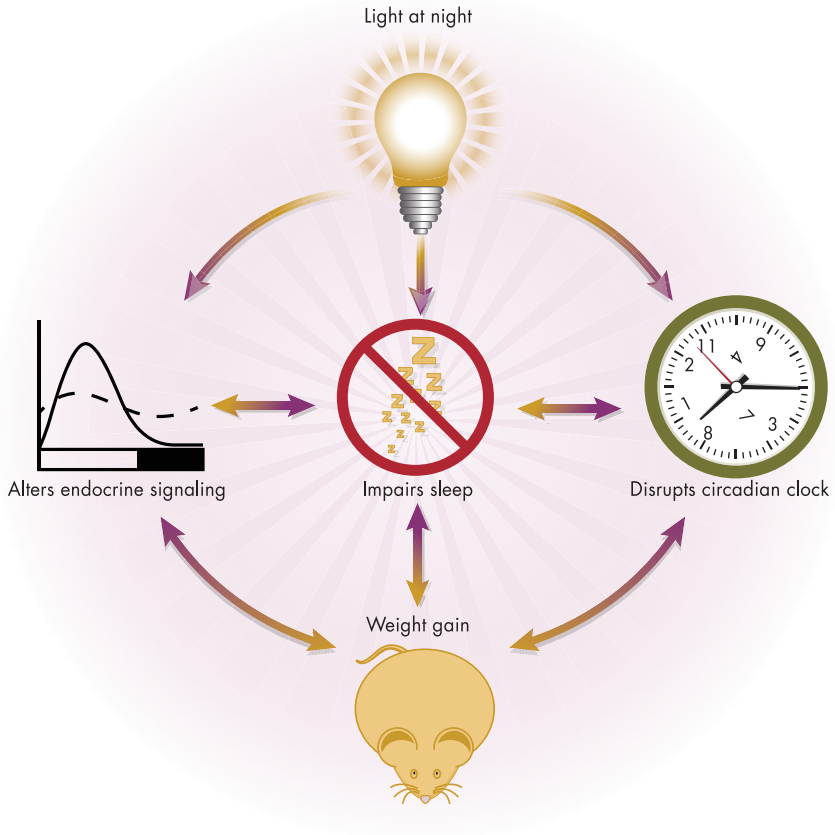

Figure 3. Pathways through which light at night can affect metabolism. Exposure to light at night can disrupt glucocorticoid and melatonin signaling, impair sleep, and attenuate circadian clock gene expression.

ically reduce body mass (247). Seasonal changes in body mass in some photoperiodic rodents such as Siberian hamsters (*P. sungorus*) are dependent on changes in the circadian pattern of melatonin secretion (248). However, melatonin appears to decrease body mass in this context by signaling time-of-day information (249); continuously administering melatonin to Siberian hamsters does not decrease body mass and even prevents short-day reductions in body mass (250).

Exogenous melatonin treatment reduces body mass in rats. Although melatonin administered through the drinking water does not directly affect metabolism, melatonin-treated rats increase nocturnal activity, resulting in reduced body weight gain (251). Furthermore, melatonin treatment improves glucose homeostasis in Zucker obese diabetic fatty rats (252) and reduces weight gain in rats fed a high-fat diet (253). Melatonin treatment similarly improves glucose homeostasis in mice fed a high-fat diet but does not prevent increases in weight gain when compared with vehicle-treated mice (254). Melatonin treatment protects against glucose toxicity in pancreatic β-cells (255). β-Cell function and survival often deteriorates in type 2 diabetes even with therapeutic intervention (256), implicating melatonin as a potential nontraditional treatment.

Melatonin treatment has been proposed as an effective antiobesity therapeutic tool (244, 257–261); however, there has been little work investigating the effects of melatonin treatment on weight regulation in humans. One study reported an association between melatonin and BMI in obese women but not in normal-weight controls or men (262). Furthermore, low nocturnal melatonin secretion is associated with increased risk of developing type 2 diabetes (263). Genome-wide association studies implicate non-coding variants in the melatonin receptor 1B with elevated fasting blood glucose and diabetes risk (264–266). Melatonin receptors are also expressed in human pancreatic islets. Melatonin treatment stimulates human islet α-cells and elevates glucagon release leading to increased insulin secretion (267). These results contrast with reports in rodents demonstrating melatonin de-

creases insulin secretion (268). However, Ramracheya and colleagues (267) propose that melatonin may have this opposing role in rodents and humans because humans are inactive during the dark when melatonin levels are high. Thus, it may be adaptive for melatonin to stimulate glucagon secretion, ensuring the brain has fuel during the extended overnight fast.

Although there is compelling evidence that suppression of melatonin secretion can contribute to weight gain, there are also several limitations suggesting melatonin may not be the primary means through which light affects metabolism, including 1) pineal melatonin suppression requires higher intensities of nocturnal illumination (45 lux) (241) than those typically reported in sleeping environments, 2) nighttime light exposure below the threshold for melatonin suppression is associated with changes in metabolism in humans (14), and 3) multiple strains of laboratory mice that lack pineal melatonin demonstrate changes in metabolism with nighttime light exposure (97, 98, 140).

B. Glucocorticoids and metabolism

Diurnal variations in other hormones may also be disrupted by exposure to light at night. Glucocorticoids are of particular interest in the context of nighttime light exposure because 1) light at night may be interpreted as a stressor (269, 270) and 2) glucocorticoids are a primary output of, and feedback signal for, the circadian system (271, 272). There is substantial evidence that stress and glucocorticoids are associated with changes in metabolism. Nondiabetic male volunteers increase energy intake and weight gain when treated with methylprednisolone (273). Endogenous cortisol secretion is association with obesogenic factors, metabolism, and hemodynamic variables (274). Cushing's disease, which is characterized by hypercortisolism, is associated with obesity (275), and Addison's disease, which is characterized by hypocortisolism, is associated with low body weight (276). Moreover, chronic stress is associated with increases in high-fat food intake and obesity (reviewed in Ref. 277).

Although changes in stress steroids are known to affect weight gain, nighttime light exposure has been reported to elevate, reduce, or not affect glucocorticoid concentrations. For example, diurnal Nile grass rats (*A. niloticus*) increase serum corticosterone concentrations after chronic exposure to dim light at night (278). In contrast, corticosterone concentrations are unaffected in mice exposed to dim light at night and Siberian hamsters exposed to dim light at night show a dampening of the cortisol rhythm resulting in an overall reduction in cortisol (109, 111). Furthermore, exposure to constant light reduces (97, 98, 279) or conversely elevates (269, 270) corticosterone concentrations in mice. In humans, sleep disruption and shift work are associated with disrupted cortisol rhythms (280, 281) and light exposure has been reported to increase (282–284), decrease (285, 286), or not affect cortisol levels (282, 284, 287). This suggests that in common with melatonin suppression, the duration and intensity of the light pulse are likely important factors in determining the effect nighttime light exposure has on glucocorticoids (286).

Despite disparate effects of light at night on glucocorticoids, rodents show similar changes in physiology and behavior after exposure to light at night (118, 279, 288) and exposure to light at night alters metabolism independent of changes in glucocorticoids (97). This indicates that alterations in glucocorticoids are not critical for changes in metabolism associated with nocturnal illumination.

C. Sleep and metabolism

Finally, exposure to light at night may affect metabolism through disturbing sleep. Sleep disruptions can profoundly affect physiology and contribute to multiple pathological conditions including metabolic syndrome (289, 290). Short-duration sleep is associated with elevated risk for obesity at all ages in humans (291–294), and as few as 5 days of insufficient sleep can cause excess energy intake (particularly during the evening) and weight gain (295). Along with exposure to light at night, sleep disruption is common among shift workers (296). Importantly, nighttime light exposure is associated with weight gain but does not disrupt sleep in mice (297), suggesting sleep disturbances may not be the primary mechanisms for light-induced changes in weight gain.

Overall, melatonin suppression, circadian disruption, changes in the hypothalamic-pituitary-adrenal axis, and sleep disturbances likely co-occur with nighttime light exposure and all contribute to the deleterious outcomes associated with exposure to light at night. However, there are several caveats of melatonin, glucocorticoids, or sleep disruptions mediating changes in metabolism associated with exposure to light at night. Considered together, light at night appears to primarily affect metabolism through disruption of the circadian system.

VI. Implications and Interventions

Modern society now functions on a 24-hour schedule. Although there are economic and societal benefits to such a schedule, there is converging evidence from epidemiological and experimental work that light at night has unintended, maladaptive consequences. Over 99% of the population in the United States and Europe is exposed to urban light pollution (231), and many people bring light at night into their homes by turning on electric lights after sunset, watching TV

late into the night, and using computers directly before bed. It is estimated that two-thirds of the population experience social jet lag (232). Moreover, shift workers make up approximately 20% of the populations and are exposed to high and prolonged levels of light at night (229, 230).

It is important to note that exposure to light at night is not just a human issue. Many plant and animal species are affected by nighttime light exposure, as lighting from infrastructure strays into the atmosphere creating a general nighttime glow termed light pollution (8). Unnatural exposure to light at night may have significant ecological implications. Indeed, exposure to light at night affects mating (117, 298), foraging and predation (119–122), and migration (123) in multiple species.

Preventing the general population from excessive exposure to light at night can be achieved with relatively low-cost manipulations, such as using blackout curtains or sleep masks to block out street lights, turning off hallway lights, and removing televisions and computers from bedrooms. Adhering to a consistent schedule and avoiding rapid phase shifts can also minimize social jet lag (232). In shift-working populations, avoiding phase shifts and nighttime light exposure is often impossible. However, not all nocturnal illumination equally affects the circadian system. The intrinsically photosensitive retinal ganglion cells that project to the SCN are most responsive to the blue region of the visible spectrum (ranging from 450–485 nm) with longer wavelengths of lighting minimally influencing the circadian system (93, 94, 299). Manipulation of lighting wavelength may prove effective in blocking out light-induced physiological changes. To that end, ongoing research is investigating the effectiveness of preventing exposure to blue wavelength light with specially designed goggles and light fixtures. Providing people with goggles excluding wavelengths of light less than 530 nm prevents nocturnal suppression of melatonin in a simulated shift work environment (300). Rescuing endogenous melatonin production in this study did not impair measures of performance or alertness (300). Alternatively, other studies have investigated correcting circadian disruption with light (301). Reversing shift-workers' biological clock by exposing them to bright light pulses during the night shift and providing dark goggles during the morning commute home increases daytime sleep episodes (301).

VII. Conclusions

Overall, exposure to light at night can disrupt circadian clock mechanisms in the SCN and peripheral tissues. Disruptions in circadian clock mechanisms are associated with weight gain in rodents and humans. Furthermore, exposure to light at night and shift work lead to changes in timing of food intake, which are also associated with increases in weight gain. The global increase in the prevalence of obesity and metabolic disorders coincides with the increase of exposure to light at night and shift work. These converging lines of evidence indicate that exposure to light at night may cause metabolic changes in mammals.

Throughout this review, we focused on how circadian disruption due to nighttime light exposure affects metabolism. We predict, however, that circadian disruption caused by other sources would similarly affect metabolism. Factors that disrupt the circadian system often co-occur, making it difficult to tease apart the effects of one specific element. The reason that we focus on light in this review is that exposure to light at night is generally considered an innocuous environmental factor but, in fact, has clear consequences for the circadian system.

There is now substantial evidence that nighttime light exposure affects human health. Promoting awareness of circadian biology and the consequences of nighttime light exposure in both the scientific community and general public are critical. For example, reducing nighttime light exposure in animal colony rooms (typical sources include glass windows on doors, ventilated racks, etc,) could improve animal housing conditions and make research outcomes more consistent.

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 metabolic disruption. Additionally, there are very few clinical studies assessing the effects of nighttime light exposure in the human population. Future studies should determine what light levels are like in home environments and also places such as nursing homes and hospitals where people may be particularly vulnerable to the negative effects of nighttime light exposure. Better characterizing electric light environments and determining the consequences of nighttime light exposure on human health can be used to develop indoor and outdoor lighting that is optimized to prevent negative effects of nighttime light exposure.

Acknowledgments

We thank Zachary M. Weil for his helpful comments on this manuscript.

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L.K.F. was supported by an American Heart Association Predoctoral fellowship; portions of the research described from our lab were supported by National Science Foundation (NSF) Grants IOS 08-38098 and

11-18792. R.J.N. was supported by NSF Grant 11-18792 during the preparation of this review.

Disclosure Summary: The authors have no conflicts of interest to declare.

References

1. **Caballero B.** The global epidemic of obesity: an overview. *Epidemiol Rev*. 2007;29:1–5.
2. **Sturm R.** Increases in morbid obesity in the USA: 2000–2005. *Public Health*. 2007;121(7):492–496.
3. **Guh DP, Zhang W, Bansback N, et al.** The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. *BMC Public Health*. 2009; 9:88.
4. **Symonds ME, Sebert S, Budge H.** The obesity epidemic: from the environment to epigenetics - not simply a response to dietary manipulation in a thermoneutral environment. *Front Genet*. 2011;2:24.
5. **National Academy of Engineering.** Greatest engineering achievements of the 20th Century. *Engineering*. 2000. http://www.greatachievements.org/.
6. **Ekirch AR.** *At Day's Close: Night in Times Past*. New York, NY: WW Norton; 2005.
7. **Fonken LK, Nelson RJ.** Illuminating the deleterious effects of light at night. *F1000 Med Rep*. 2011;3:18.
8. **Navara KJ, Nelson RJ.** The dark side of light at night: physiological, epidemiological, and ecological consequences. *J Pineal Res*. 2007;43(3):215–224.
9. **Stevens RG.** Light-at-night, circadian disruption and breast cancer: assessment of existing evidence. *Int J Epidemiol*. 2009;38(4):963–970.
10. **Kohyama J.** A newly proposed disease condition produced by light exposure during night: asynchronization. *Brain Dev*. 2009;31(4):255–273.
11. **Bedrosian TA, Nelson RJ.** Influence of the modern light environment on mood. *Mol Psychiatry*. 2013;18(7):751–757.
12. **Karlsson B, Knutsson A, Lindahl B.** Is there an association between shift work and having a metabolic syndrome? Results from a population based study of 27,485 people. *Occup Environ Med*. 2001;58(11):747–752.
13. **Knutsson A.** Health disorders of shift workers. *Occup Med*. 2003;53(2):103–108.
14. **Obayashi K, Saeki K, Iwamoto J, et al.** Exposure to light at night, nocturnal urinary melatonin excretion, and obesity/dyslipidemia in the elderly: a cross-sectional analysis of the HEIJO-KYO study. *J Clin Endocrinol Metab*. 2013;98(1): 337–344.
15. **Parkes KR.** Shift work and age as interactive predictors of body mass index among offshore workers. *Scand J Work Environ Health*. 2002;28(1):64–71.
16. **van Amelsvoort LG, Schouten EG, Kok FJ.** Duration of shiftwork related to body mass index and waist to hip ratio. *Int J Obes Relat Metab Disord*. 1999;23(9):973–978.
17. **Puttonen S, Viitasalo K, Härmä M.** Effect of shiftwork on systemic markers of inflammation. *Chronobiol Int*. 2011; 28(6):528–535.
18. **Cho K.** Chronic 'jet lag' produces temporal lobe atrophy and spatial cognitive deficits. *Nat Neurosci*. 2001;4(6): 567–568.
19. **Vetter C, Juda M, Roenneberg T.** The influence of internal time, time awake, and sleep duration on cognitive performance in shiftworkers. *Chronobiol Int*. 2012;29(8):1127–1138.
20. **Bell-Pedersen D, Cassone VM, Earnest DJ, et al.** Circadian rhythms from multiple oscillators: lessons from diverse organisms. *Nat Rev Genet*. 2005;6(7):544–556.
21. **Aschoff J.** Circadian rhythms in man. *Science*. 1965; 148(3676):1427–1432.
22. **Ruby NF, Burns DE, Heller HC.** Circadian rhythms in the suprachiasmatic nucleus are temperature-compensated and phase-shifted by heat pulses in vitro. *J Neurosci*. 1999; 19(19):8630–8636.
23. **Ralph MR, Menaker M.** A mutation of the circadian system in golden hamsters. *Science*. 1988;241(4870):1225–1227.
24. **Bailey SL, Heitkemper MM.** Circadian rhythmicity of cortisol and body temperature: morningness-eveningness effects. *Chronobiol Int*. 2001;18(2):249–261.
25. **Takahashi JS, Hong HK, Ko CH, McDearmon EL.** The genetics of mammalian circadian order and disorder: implications for physiology and disease. *Nat Rev Genet*. 2008;9(10):764–775.
26. **Zee PC, Attarian H, Videnovic A.** Circadian rhythm abnormalities. *Continuum*. 2013;19(1 Sleep Disorders):132–147.
27. **Van den Pol AN.** The hypothalamic suprachiasmatic nucleus of rat: intrinsic anatomy. *J Comp Neurol*. 1980; 191(4):661–702.
28. **Lydic R, Albers HE, Tepper B, Moore-Ede MC.** Three-dimensional structure of the mammalian suprachiasmatic nuclei: a comparative study of five species. *J Comp Neurol*. 1982;204(3):225–237.
29. **Lydic R, Schoene WC, Czeisler CA, Moore-Ede MC.** Suprachiasmatic region of the human hypothalamus: homolog to the primate circadian pacemaker? *Sleep*. 1980; 2(3):355–361.
30. **van den Pol AN, Tsujimoto KL.** Neurotransmitters of the hypothalamic suprachiasmatic nucleus: immunocytochemical analysis of 25 neuronal antigens. *Neuroscience*. 1985;15(4):1049–1086.
31. **Moore RY, Eichler VB.** Loss of a circadian adrenal corticosterone rhythm following suprachiasmatic lesions in the rat. *Brain Res*. 1972;42(1):201–206.
32. **Stephan FK, Zucker I.** Circadian rhythms in drinking behavior and locomotor activity of rats are eliminated by hypothalamic lesions. *Proc Natl Acad Sci U S A*. 1972; 69(6):1583–1586.
33. **Stephan FK, Nunez AA.** Elimination of circadian rhythms in drinking, activity, sleep, and temperature by isolation of the suprachiasmatic nuclei. *Behav Biol*. 1977;20(1):1–61.
34. **Albers HE, Ferris CF, Leeman SE, Goldman BD.** Avian pancreatic polypeptide phase shifts hamster circadian rhythms when microinjected into the suprachiasmatic region. *Science*. 1984;223(4638):833–835.
35. **Rusak B, Groos G.** Suprachiasmatic stimulation phase shifts rodent circadian rhythms. *Science*. 1982;215(4538): 1407–1409.
36. **Silver R, LeSauter J, Tresco PA, Lehman MN.** A diffusible

coupling signal from the transplanted suprachiasmatic nucleus controlling circadian locomotor rhythms. *Nature*. 1996;382(6594):810–813.
37. **Welsh DK, Logothetis DE, Meister M, Reppert SM.** Individual neurons dissociated from rat suprachiasmatic nucleus express independently phased circadian firing rhythms. *Neuron*. 1995;14(4):697–706.
38. **Yamazaki S, Numano R, Abe M, et al.** Resetting central and peripheral circadian oscillators in transgenic rats. *Science*. 2000;288(5466):682–685.
39. **Yamaguchi S, Isejima H, Matsuo T, et al.** Synchronization of cellular clocks in the suprachiasmatic nucleus. *Science*. 2003;302(5649):1408–1412.
40. **Reppert SM, Weaver DR.** Coordination of circadian timing in mammals. *Nature*. 2002;418(6901):935–941.
41. **Mohawk JA, Green CB, Takahashi JS.** Central and peripheral circadian clocks in mammals. *Annu Rev Neurosci*. 2012;35:445–462.
42. **Gekakis N, Staknis D, Nguyen HB, et al.** Role of the CLOCK protein in the mammalian circadian mechanism. *Science*. 1998;280(5369):1564–1569.
43. **Hogenesch JB, Gu YZ, Jain S, Bradfield CA.** The basic-helix-loop-helix-PAS orphan MOP3 forms transcriptionally active complexes with circadian and hypoxia factors. *Proc Natl Acad Sci U S A*. 1998;95(10):5474–5479.
44. **Jin X, Shearman LP, Weaver DR, Zylka MJ, de Vries GJ, Reppert SM.** A molecular mechanism regulating rhythmic output from the suprachiasmatic circadian clock. *Cell*. 1999;96(1):57–68.
45. **Griffin EA Jr, Staknis D, Weitz CJ.** Light-independent role of CRY1 and CRY2 in the mammalian circadian clock. *Science*. 1999;286(5440):768–771.
46. **Kume K, Zylka MJ, Sriram S, et al.** mCRY1 and mCRY2 are essential components of the negative limb of the circadian clock feedback loop. *Cell*. 1999;98(2):193–205.
47. **Lee C, Etchegaray JP, Cagampang FR, Loudon AS, Reppert SM.** Posttranslational mechanisms regulate the mammalian circadian clock. *Cell*. 2001;107(7):855–867.
48. **Preitner N, Damiola F, Lopez-Molina L, et al.** The orphan nuclear receptor REV-ERBα controls circadian transcription within the positive limb of the mammalian circadian oscillator. *Cell*. 2002;110(2):251–260.
49. **Takahashi JS.** Finding new clock components: past and future. *J Biol Rhythms*. 2004;19(5):339–347.
50. **Bunger MK, Wilsbacher LD, Moran SM, et al.** Mop3 is an essential component of the master circadian pacemaker in mammals. *Cell*. 2000;103(7):1009–1017.
51. **Bae K, Jin X, Maywood ES, Hastings MH, Reppert SM, Weaver DR.** Differential functions of mPer1, mPer2, and mPer3 in the SCN circadian clock. *Neuron*. 2001;30(2):525–536.
52. **van der Horst GT, Muijtjens M, Kobayashi K, et al.** Mammalian Cry1 and Cry2 are essential for maintenance of circadian rhythms. *Nature*. 1999;398(6728):627–630.
53. **Ko CH, Takahashi JS.** Molecular components of the mammalian circadian clock. *Hum Mol Genet*. 2006;15(Spec No 2):R271–R277.
54. **Zhang EE, Liu AC, Hirota T, et al.** A genome-wide RNAi screen for modifiers of the circadian clock in human cells. *Cell*. 2009;139(1):199–210.
55. **Cho H, Zhao X, Hatori M, et al.** Regulation of circadian behaviour and metabolism by REV-ERB-α and REV-ERB-β. *Nature*. 2012;485(7396):123–127.
56. **Pendergast JS, Niswender KD, Yamazaki S.** Tissue-specific function of Period3 in circadian rhythmicity. *PLoS One*. 2012;7(1):e30254.
57. **King DP, Zhao Y, Sangoram AM, et al.** Positional cloning of the mouse circadian clock gene. *Cell*. 1997;89(4):641–653.
58. **Reddy AB, Maywood ES, Karp NA, et al.** Glucocorticoid signaling synchronizes the liver circadian transcriptome. *Hepatology*. 2007;45(6):1478–1488.
59. **McNamara P, Seo SB, Rudic RD, Sehgal A, Chakravarti D, FitzGerald GA.** Regulation of CLOCK and MOP4 by nuclear hormone receptors in the vasculature: a humoral mechanism to reset a peripheral clock. *Cell*. 2001;105(7):877–889.
60. **Guo H, Brewer JM, Champhekar A, Harris RB, Bittman EL.** Differential control of peripheral circadian rhythms by suprachiasmatic-dependent neural signals. *Proc Natl Acad Sci U S A*. 2005;102(8):3111–3116.
61. **Vollmers C, Gill S, DiTacchio L, Pulivarthy SR, Le HD, Panda S.** Time of feeding and the intrinsic circadian clock drive rhythms in hepatic gene expression. *Proc Natl Acad Sci U S A*. 2009;106(50):21453–21458.
62. **Liu AC, Welsh DK, Ko CH, et al.** Intercellular coupling confers robustness against mutations in the SCN circadian clock network. *Cell*. 2007;129(3):605–616.
63. **Akhtar RA, Reddy AB, Maywood ES, et al.** Circadian cycling of the mouse liver transcriptome, as revealed by cDNA microarray, is driven by the suprachiasmatic nucleus. *Curr Biol*. 2002;12(7):540–550.
64. **Balsalobre A, Damiola F, Schibler U.** A serum shock induces circadian gene expression in mammalian tissue culture cells. *Cell*. 1998;93(6):929–937.
65. **Smale L, Lee T, Nunez AA.** Mammalian diurnality: some facts and gaps. *J Biol Rhythms*. 2003;18(5):356–366.
66. **Cohen R, Kronfeld-Schor N, Ramanathan C, Baumgras A, Smale L.** The substructure of the suprachiasmatic nucleus: Similarities between nocturnal and diurnal spiny mice. *Brain Behav Evol*. 2010;75(1):9–22.
67. **Kalsbeek A, Verhagen LA, Schalij I, et al.** Opposite actions of hypothalamic vasopressin on circadian corticosterone rhythm in nocturnal versus diurnal species. *Eur J Neurosci*. 2008;27(4):818–827.
68. **Challet E.** Minireview: Entrainment of the suprachiasmatic clockwork in diurnal and nocturnal mammals. *Endocrinology*. 2007;148(12):5648–5655.
69. **Shuboni DD, Cramm S, Yan L, Nunez AA, Smale L.** Acute behavioral responses to light and darkness in nocturnal *Mus musculus* and diurnal *Arvicanthis niloticus*. *J Biol Rhythms*. 2012;27(4):299–307.
70. **Golombek DA, Rosenstein RE.** Physiology of circadian entrainment. *Physiol Rev*. 2010;90(3):1063–1102.
71. **Hattar S, Liao HW, Takao M, Berson DM, Yau KW.** Melanopsin-containing retinal ganglion cells: architecture, projections, and intrinsic photosensitivity. *Science*. 2002;295(5557):1065–1070.
72. **Altimus CM, Güler AD, Alam NM, et al.** Rod photoreceptors drive circadian photoentrainment across a wide range of light intensities. *Nat Neurosci*. 2010;13(9):1107–1112.

73. **Guler AD, Ecker JL, Lall GS, et al.** Melanopsin cells are the principal conduits for rod-cone input to non-image-forming vision. *Nature*. 2008;453(7191):102–105.
74. **Hattar S, Kumar M, Park A, et al.** Central projections of melanopsin-expressing retinal ganglion cells in the mouse. *J Comp Neurol*. 2006;497(3):326–349.
75. **Hattar S, Lucas RJ, Mrosovsky N, Thompson S, Douglas RH, Hankins MW, Lem J, Biel M, Hofmann F, Foster RG, Yau KW.** Melanopsin and rod-cone photoreceptive systems account for all major accessory visual functions in mice. *Nature*. 2003;424(6944):76–81.
76. **Rusak B, Robertson HA, Wisden W, Hunt SP.** Light pulses that shift rhythms induce gene expression in the suprachiasmatic nucleus. *Science*. 1990;248(4960):1237–1240.
77. **Morris ME, Viswanathan N, Kuhlman S, Davis FC, Weitz CJ.** A screen for genes induced in the suprachiasmatic nucleus by light. *Science*. 1998;279(5356):1544–1547.
78. **Porterfield VM, Piontkivska H, Mintz EM.** Identification of novel light-induced genes in the suprachiasmatic nucleus. *BMC Neurosci*. 2007;8:98.
79. **Albrecht U, Sun ZS, Eichele G, Lee CC.** A differential response of two putative mammalian circadian regulators, mper1 and mper2, to light. *Cell*. 1997;91(7):1055–1064.
80. **Shigeyoshi Y, Taguchi K, Yamamoto S, et al.** Light-induced resetting of a mammalian circadian clock is associated with rapid induction of the mPer1 transcript. *Cell*. 1997;91(7):1043–1053.
81. **Miyake S, Sumi Y, Yan L, et al.** Phase-dependent responses of Per1 and Per2 genes to a light-stimulus in the suprachiasmatic nucleus of the rat. *Neurosci Lett*. 2000; 294(1):41–44.
82. **Schwartz WJ, Tavakoli-Nezhad M, Lambert CM, Weaver DR, de la Iglesia HO.** Distinct patterns of Period gene expression in the suprachiasmatic nucleus underlie circadian clock photoentrainment by advances or delays. *Proc Natl Acad Sci U S A*. 2011;108(41):17219–17224.
83. **Sharma VK, Chandrashekaran MK, Singaravel M, Subbaraj R.** Relationship between light intensity and phase resetting in a mammalian circadian system. *J Exp Zool*. 1999;283(2):181–185.
84. **Dewan K, Benloucif S, Reid K, Wolfe LF, Zee PC.** Light-induced changes of the circadian clock of humans: increasing duration is more effective than increasing light intensity. *Sleep*. 2011;34(5):593–599.
85. **Comas M, Beersma DG, Spoelstra K, Daan S.** Phase and period responses of the circadian system of mice (*Mus musculus*) to light stimuli of different duration. *J Biol Rhythms*. 2006;21(5):362–372.
86. **Boivin DB, Duffy JF, Kronauer RE, Czeisler CA.** Dose-response relationships for resetting of human circadian clock by light. *Nature*. 1996;379(6565):540–542.
87. **Gorman MR, Evans JA, Elliott JA.** Potent circadian effects of dim illumination at night in hamsters. *Chronobiol Int*. 2006;23(1–2):245–250.
88. **Fuller PM, Lu J, Saper CB.** Differential rescue of light- and food-entrainable circadian rhythms. *Science*. 2008; 320(5879):1074–1077.
89. **Mistlberger RE, Antle MC.** Entrainment of circadian clocks in mammals by arousal and food. *Essays Biochem*. 2011;49(1):119–136.
90. **Damiola F, Le Minh N, Preitner N, Kornmann B, Fleury-Olela F, Schibler U.** Restricted feeding uncouples circadian oscillators in peripheral tissues from the central pacemaker in the suprachiasmatic nucleus. *Genes Dev*. 2000;14(23): 2950–2961.
91. **Smith MR, Revell VL, Eastman CI.** Phase advancing the human circadian clock with blue-enriched polychromatic light. *Sleep Med*. 2009;10(3):287–294.
92. **Ruger M, St Hilaire MA, Brainard GC, et al.** Human phase response curve to a single 6.5 h pulse of short-wavelength light. *J Physiol*. 2013;591(Pt 1):353–363.
93. **Brainard GC, Sliney D, Hanifin JP, et al.** Sensitivity of the human circadian system to short-wavelength (420-nm) light. *J Biol Rhythms*. 2008;23(5):379–386.
94. **Brainard GC, Lewy AJ, Menaker M, et al.** Effect of light wavelength on the suppression of nocturnal plasma melatonin in normal volunteers. *Ann N Y Acad Sci*. 1985;453: 376–378.
95. **Brainard GC, Richardson BA, King TS, Reiter RJ.** The influence of different light spectra on the suppression of pineal melatonin content in the Syrian hamster. *Brain Res*. 1984;294(2):333–339.
96. **Figueiro MG, Rea MS.** The effects of red and blue lights on circadian variations in cortisol, alpha amylase, and melatonin. *Int J Endocrinol*. 2010;2010:829351.
97. **Fonken LK, Workman JL, Walton JC, et al.** Light at night increases body mass by shifting the time of food intake. *Proc Natl Acad Sci U S A*. 2010;107(43):18664–18669.
98. **Coomans CP, van den Berg SA, Houben T, et al.** Detrimental effects of constant light exposure and high-fat diet on circadian energy metabolism and insulin sensitivity. *FASEB J*. 2013;27(4):1721–1732.
99. **Sudo M, Sasahara K, Moriya T, Akiyama M, Hamada T, Shibata S.** Constant light housing attenuates circadian rhythms of mPer2 mRNA and mPER2 protein expression in the suprachiasmatic nucleus of mice. *Neuroscience*. 2003;121(2):493–499.
100. **Muñoz M, Peirson SN, Hankins MW, Foster RG.** Long-term constant light induces constitutive elevated expression of mPER2 protein in the murine SCN: a molecular basis for Aschoff's rule? *J Biol Rhythms*. 2005;20(1):3–14.
101. **Schwimmer H, Mursu N, Haim A.** Effects of light and melatonin treatment on body temperature and melatonin secretion daily rhythms in a diurnal rodent, the fat sand rat. *Chronobiol Int*. 2010;27(7):1401–1419.
102. **Tapia-Osorio A, Salgado-Delgado R, Angeles-Castellanos M, Escobar C.** Disruption of circadian rhythms due to chronic constant light leads to depressive and anxiety-like behaviors in the rat. *Behav Brain Res*. 2013;252:1–9.
103. **Ohta H, Yamazaki S, McMahon DG.** Constant light desynchronizes mammalian clock neurons. *Nat Neurosci*. 2005;8(3):267–269.
104. **Evans JA, Elliott JA, Gorman MR.** Circadian entrainment and phase resetting differ markedly under dimly illuminated versus completely dark nights. *Behav Brain Res*. 2005;162(1):116–126.
105. **Jasser SA, Hanifin JP, Rollag MD, Brainard GC.** Dim light adaptation attenuates acute melatonin suppression in humans. *J Biol Rhythms*. 2006;21(5):394–404.
106. **Gaston KJ, Davies TW, Bennie J, Hopkins J.** Reducing the ecological consequences of night-time light pollution: op-

tions and developments. *J Appl Ecol*. 2012;49(6):1256–1266.
107. **Kloog I, Haim A, Portnov BA.** Using kernel density function as an urban analysis tool: investigating the association between nightlight exposure and the incidence of breast cancer in Haifa, Israel. *Comput Environ Urban*. 2009;33(1):55–63.
108. **Shuboni D, Yan L.** Nighttime dim light exposure alters the responses of the circadian system. *Neuroscience*. 2010;170(4):1172–1178.
109. **Fonken LK, Aubrecht TG, Meléndez-Fernández OH, Weil ZM, Nelson RJ.** Dim light at night disrupts molecular circadian rhythms and increases body weight. *J Biol Rhythms*. 2013;28(4):262–271.
110. **Cailotto C, Lei J, van der Vliet J, et al.** Effects of nocturnal light on (clock) gene expression in peripheral organs: a role for the autonomic innervation of the liver. *PLoS One*. 2009;4(5):e5650.
111. **Bedrosian TA, Galan A, Vaughn CA, Weil ZM, Nelson RJ.** Light at night alters daily patterns of cortisol and clock proteins in female Siberian hamsters. *J Neuroendocrinol*. 2013;25(6):590–596.
112. **LeGates TA, Altimus CM, Wang H, et al.** Aberrant light directly impairs mood and learning through melanopsin-expressing neurons. *Nature*. 2012;491(7425):594–598.
113. **Oishi K, Itoh N.** Disrupted daily light-dark cycle induces the expression of hepatic gluconeogenic regulatory genes and hyperglycemia with glucose intolerance in mice. *Biochem Biophys Res Commun*. 2013;432(1):111–115.
114. **Logan RW, Zhang C, Murugan S, et al.** Chronic shift-lag alters the circadian clock of NK cells and promotes lung cancer growth in rats. *J Immunol*. 2012;188(6):2583–2591.
115. **Brainard GC, Richardson BA, Petterborg LJ, Reiter RJ.** The effect of different light intensities on pineal melatonin content. *Brain Res*. 1982;233(1):75–81.
116. **Wright KP Jr, McHill AW, Birks BR, Griffin BR, Rusterholz T, Chinoy ED.** Entrainment of the human circadian clock to the natural light-dark cycle. *Curr Biol*. 2013;23(16):1554–1558.
117. **Dominoni D, Quetting M, Partecke J.** Artificial light at night advances avian reproductive physiology. *Proc Biol Sci*. 2013;280(1756):20123017.
118. **Fonken LK, Kitsmiller E, Smale L, Nelson RJ.** Dim nighttime light impairs cognition and provokes depressive-like responses in a diurnal rodent. *J Biol Rhythms*. 2012;27(4):319–327.
119. **Dwyer RG, Bearhop S, Campbell HA, Bryant DM.** Shedding light on light: benefits of anthropogenic illumination to a nocturnally foraging shorebird. *J Anim Ecol*. 2013;82(2):478–485.
120. **Rydell J.** Exploitation of Insects around Streetlamps by Bats in Sweden. *Funct Ecol*. 1992;6(6):744–750.
121. **Davies TW, Bennie J, Gaston KJ.** Street lighting changes the composition of invertebrate communities. *Biol Lett*. 2012;8(5):764–767.
122. **Stone EL, Jones G, Harris S.** Street lighting disturbs commuting bats. *Curr Biol*. 2009;19(13):1123–1127.
123. **Wang Z, Lin A, Yuan Q, Zhou W, Zhang W, Yang XJ.** Attraction of night-migrating birds to light-blue structures causes mass bird deaths. *Environ Sci Technol*. 2011;45(24):10296–10297.
124. **Rowan W.** Relation of light to bird migration and developmental changes. *Nature*. 1925;115:494–495.
125. **Froy O.** Metabolism and circadian rhythms–implications for obesity. *Endocr Rev*. 2010;31(1):1–24.
126. **Storch KF, Lipan O, Leykin I, et al.** Extensive and divergent circadian gene expression in liver and heart. *Nature*. 2002;417(6884):78–83.
127. **Panda S, Antoch MP, Miller BH, et al.** Coordinated transcription of key pathways in the mouse by the circadian clock. *Cell*. 2002;109(3):307–320.
128. **Eckel-Mahan KL, Patel VR, Mohney RP, Vignola KS, Baldi P, Sassone-Corsi P.** Coordination of the transcriptome and metabolome by the circadian clock. *Proc Natl Acad Sci U S A*. 2012;109(14):5541–5546.
129. **Eckel-Mahan K, Sassone-Corsi P.** Metabolism control by the circadian clock and vice versa. *Nat Struct Mol Biol*. 2009;16(5):462–467.
130. **Sinha MK, Ohannesian JP, Heiman ML, et al.** Nocturnal rise of leptin in lean, obese, and non-insulin-dependent diabetes mellitus subjects. *J Clin Invest*. 1996;97(5):1344–1347.
131. **Kalsbeek A, Fliers E, Romijn JA, et al.** The suprachiasmatic nucleus generates the diurnal changes in plasma leptin levels. *Endocrinology*. 2001;142(6):2677–2685.
132. **Ruiter M, La Fleur SE, van Heijningen C, van der Vliet J, Kalsbeek A, Buijs RM.** The daily rhythm in plasma glucagon concentrations in the rat is modulated by the biological clock and by feeding behavior. *Diabetes*. 2003;52(7):1709–1715.
133. **Jhanwar-Uniyal M, Beck B, Burlet C, Leibowitz SF.** Diurnal rhythm of neuropeptide Y-like immunoreactivity in the suprachiasmatic, arcuate and paraventricular nuclei and other hypothalamic sites. *Brain Res*. 1990;536(1–2):331–334.
134. **Xu B, Kalra PS, Farmerie WG, Kalra SP.** Daily changes in hypothalamic gene expression of neuropeptide Y, galanin, proopiomelanocortin, and adipocyte leptin gene expression and secretion: effects of food restriction. *Endocrinology*. 1999;140(6):2868–2875.
135. **Scheer FA, Morris CJ, Shea SA.** The internal circadian clock increases hunger and appetite in the evening independent of food intake and other behaviors. *Obesity*. 2013;21(3):421–423.
136. **Kalra SP, Dube MG, Pu S, Xu B, Horvath TL, Kalra PS.** Interacting appetite-regulating pathways in the hypothalamic regulation of body weight. *Endocr Rev*. 1999;20(1):68–100.
137. **Turek FW, Joshu C, Kohsaka A, et al.** Obesity and metabolic syndrome in circadian Clock mutant mice. *Science*. 2005;308(5724):1043–1045.
138. **Oishi K, Atsumi G, Sugiyama S, et al.** Disrupted fat absorption attenuates obesity induced by a high-fat diet in Clock mutant mice. *FEBS Lett*. 2006;580(1):127–130.
139. **Marcheva B, Ramsey KM, Buhr ED, et al.** Disruption of the clock components CLOCK and BMAL1 leads to hypoinsulinaemia and diabetes. *Nature*. 2010;466(7306):627–631.
140. **Shi SQ, Ansari TS, McGuinness OP, Wasserman DH,**

Johnson CH. Circadian disruption leads to insulin resistance and obesity. *Curr Biol*. 2013;23(5):372–381.
141. **Shimba S, Ogawa T, Hitosugi S, et al.** Deficient of a clock gene, brain and muscle Arnt-like protein-1 (BMAL1), induces dyslipidemia and ectopic fat formation. *PLoS One*. 2011;6(9):e25231.
142. **McDearmon EL, Patel KN, Ko CH, et al.** Dissecting the functions of the mammalian clock protein BMAL1 by tissue-specific rescue in mice. *Science*. 2006;314(5803):1304–1308.
143. **Okano S, Akashi M, Hayasaka K, Nakajima O.** Unusual circadian locomotor activity and pathophysiology in mutant CRY1 transgenic mice. *Neurosci Lett*. 2009;451(3):246–251.
144. **Barclay JL, Shostak A, Leliavski A, et al.** High-fat diet-induced hyperinsulinemia and tissue-specific insulin resistance in Cry-deficient mice. *Am J Physiol Endocrinol Metab*. 2013;304(10):E1053–E1063.
145. **Dallmann R, Weaver DR.** Altered body mass regulation in male mPeriod mutant mice on high-fat diet. *Chronobiol Int*. 2010;27(6):1317–1328.
146. **Grimaldi B, Bellet MM, Katada S, et al.** PER2 controls lipid metabolism by direct regulation of PPARγ. *Cell Metab*. 2010;12(5):509–520.
147. **Zhao Y, Zhang Y, Zhou M, Wang S, Hua Z, Zhang J.** Loss of mPer2 increases plasma insulin levels by enhanced glucose-stimulated insulin secretion and impaired insulin clearance in mice. *FEBS Lett*. 2012;586(9):1306–1311.
148. **Yang S, Liu A, Weidenhammer A, et al.** The role of mPer2 clock gene in glucocorticoid and feeding rhythms. *Endocrinology*. 2009;150(5):2153–2160.
149. **Carvas JM, Vukolic A, Yepuri G, et al.** Period2 gene mutant mice show compromised insulin-mediated endothelial nitric oxide release and altered glucose homeostasis. *Front Physiol*. 2012;3:337.
150. **Dallmann R, Touma C, Palme R, Albrecht U, Steinlechner S.** Impaired daily glucocorticoid rhythm in Per1 (Brd) mice. *J Comp Physiol A Neuroethol Sens Neural Behav Physiol*. 2006;192(7):769–775.
151. **Kennaway DJ, Owens JA, Voultsios A, Boden MJ, Varcoe TJ.** Metabolic homeostasis in mice with disrupted Clock gene expression in peripheral tissues. *Am J Physiol Regul Integr Comp Physiol*. 2007;293(4):R1528–R1537.
152. **Sadacca LA, Lamia KA, deLemos AS, Blum B, Weitz CJ.** An intrinsic circadian clock of the pancreas is required for normal insulin release and glucose homeostasis in mice. *Diabetologia*. 2011;54(1):120–124.
153. **Lamia KA, Storch KF, Weitz CJ.** Physiological significance of a peripheral tissue circadian clock. *Proc Natl Acad Sci U S A*. 2008;105(39):15172–15177.
154. **Kornmann B, Schaad O, Bujard H, Takahashi JS, Schibler U.** System-driven and oscillator-dependent circadian transcription in mice with a conditionally active liver clock. *PLoS Biol*. 2007;5(2):e34.
155. **Paschos GK, Ibrahim S, Song WL, et al.** Obesity in mice with adipocyte-specific deletion of clock component Arntl. *Nat Med*. 2012;18(12):1768–1777.
156. **Mieda M, Sakurai T.** Bmal1 in the nervous system is essential for normal adaptation of circadian locomotor activity and food intake to periodic feeding. *J Neurosci*. 2011;31(43):15391–15396.
157. **Reppert SM, Weaver DR.** Molecular analysis of mammalian circadian rhythms. *Annu Rev Physiol*. 2001;63:647–676.
158. **Bechtold DA, Brown TM, Luckman SM, Piggins HD.** Metabolic rhythm abnormalities in mice lacking VIP-VPAC2 signaling. *Am J Physiol Regul Integr Comp Physiol*. 2008;294(2):R344–R351.
159. **Baggs JE, Green CB.** Nocturnin, a deadenylase in *Xenopus laevis* retina: a mechanism for posttranscriptional control of circadian-related mRNA. *Curr Biol*. 2003;13(3):189–198.
160. **Green CB, Douris N, Kojima S, et al.** Loss of nocturnin, a circadian deadenylase, confers resistance to hepatic steatosis and diet-induced obesity. *Proc Natl Acad Sci U S A*. 2007;104(23):9888–9893.
161. **Douris N, Kojima S, Pan X, et al.** Nocturnin regulates circadian trafficking of dietary lipid in intestinal enterocytes. *Curr Biol*. 2011;21(16):1347–1355.
162. **Yin L, Wu N, Curtin JC, et al.** Rev-erbα, a heme sensor that coordinates metabolic and circadian pathways. *Science*. 2007;318(5857):1786–1789.
163. **Feng D, Liu T, Sun Z, et al.** A circadian rhythm orchestrated by histone deacetylase 3 controls hepatic lipid metabolism. *Science*. 2011;331(6022):1315–1319.
164. **Solt LA, Wang Y, Banerjee S, et al.** Regulation of circadian behaviour and metabolism by synthetic REV-ERB agonists. *Nature*. 2012;485(7396):62–68.
165. **Reutrakul S, Hood MM, Crowley SJ, et al.** Chronotype is independently associated with glycemic control in type 2 diabetes. *Diabetes Care*. 2013;36(9):2523–2529.
166. **Zanquetta MM, Correa-Giannella ML, Giannella-Neto D, et al.** Expression of clock genes in human subcutaneous and visceral adipose tissues. *Chronobiol Int*. 2012;29(3):252–260.
167. **Gomez-Abellan P, Hernandez-Morante JJ, Lujan JA, Madrid JA, Garaulet M.** Clock genes are implicated in the human metabolic syndrome. *Int J Obes (Lond)*. 2008;32(1):121–128.
168. **Milagro FI, Gómez-Abellán P, Campión J, Martínez JA, Ordovás JM, Garaulet M.** CLOCK, PER2 and BMAL1 DNA methylation: association with obesity and metabolic syndrome characteristics and monounsaturated fat intake. *Chronobiol Int*. 2012;29(9):1180–1194.
169. **Scott EM, Carter AM, Grant PJ.** Association between polymorphisms in the Clock gene, obesity and the metabolic syndrome in man. *Int J Obes (Lond)*. 2008;32(4):658–662.
170. **Ferrari E, Fraschini F, Brambilla F.** Hormonal circadian rhythms in eating disorders. *Biol Psychiatry*. 1990;27(9):1007–1020.
171. **Lee A, Ader M, Bray GA, Bergman RN.** Diurnal variation in glucose tolerance. Cyclic suppression of insulin action and insulin secretion in normal-weight, but not obese, subjects. *Diabetes*. 1992;41(6):750–759.
172. **Corbalán-Tutau MD, Madrid JA, Ordovás JM, Smith CE, Nicolás F, Garaulet M.** Differences in daily rhythms of wrist temperature between obese and normal-weight women: associations with metabolic syndrome features. *Chronobiol Int*. 2011;28(5):425–433.
173. **Kohsaka A, Laposky AD, Ramsey KM, et al.** High-fat diet

disrupts behavioral and molecular circadian rhythms in mice. *Cell Metab*. 2007;6(5):414–421.
174. **Stucchi P, Gil-Ortega M, Merino B, et al.** Circadian feeding drive of metabolic activity in adipose tissue and not hyperphagia triggers overweight in mice: is there a role of the pentose-phosphate pathway? *Endocrinology*. 2012; 153(2):690–699.
175. **Pendergast JS, Branecky KL, Yang W, Ellacott KL, Niswender KD, Yamazaki S.** High-fat diet acutely affects circadian organisation and eating behavior. *Eur J Neurosci*. 2013;37(8):1350–1356.
176. **Mendoza J, Pevet P, Challet E.** High-fat feeding alters the clock synchronization to light. *J Physiol*. 2008;586(Pt 24): 5901–5910.
177. **Phillips MS, Liu Q, Hammond HA, et al.** Leptin receptor missense mutation in the fatty Zucker rat. *Nat Genet*. 1996;13(1):18–19.
178. **Murakami DM, Horwitz BA, Fuller CA.** Circadian rhythms of temperature and activity in obese and lean Zucker rats. *Am J Physiol*. 1995;269(5 Pt 2):R1038–R1043.
179. **Mistlberger RE, Lukman H, Nadeau BG.** Circadian rhythms in the Zucker obese rat: assessment and intervention. *Appetite*. 1998;30(3):255–267.
180. **Becker EE, Grinker JA.** Meal patterns in the genetically obese Zucker rat. *Physiol Behav*. 1977;18(4):685–692.
181. **Wangsness PJ, Dilettuso BA, Martin RJ.** Dietary effects on body weight, feed intake and diurnal feeding behavior of genetically obese rats. *J Nutr*. 1978;108(2):256–264.
182. **Roesler WJ, Helgason C, Gulka M, Khandelwal RL.** Aberrations in the diurnal rhythms of plasma glucose, plasma insulin, liver glycogen, and hepatic glycogen synthase and phosphorylase activities in genetically diabetic (db/db) mice. *Horm Metab Res*. 1985;17(11):572–575.
183. **Su W, Xie Z, Guo Z, Duncan MJ, Lutshumba J, Gong MC.** Altered clock gene expression and vascular smooth muscle diurnal contractile variations in type 2 diabetic db/db mice. *Am J Physiol Heart Circ Physiol*. 2012;302(3):H621–H633.
184. **Dauncey MJ.** Activity-induced thermogenesis in lean and genetically obese (ob/ob) mice. *Experientia*. 1986;42(5): 547–549.
185. **Ando H, Kumazaki M, Motosugi Y, et al.** Impairment of peripheral circadian clocks precedes metabolic abnormalities in ob/ob mice. *Endocrinology*. 2011;152(4):1347–1354.
186. **Balagura S, Devenport LD.** Feeding patterns of normal and ventromedial hypothalamic lesioned male and female rats. *J Comp Physiol Psychol*. 1970;71(3):357–364.
187. **Ando H, Yanagihara H, Hayashi Y, et al.** Rhythmic messenger ribonucleic acid expression of clock genes and adipocytokines in mouse visceral adipose tissue. *Endocrinology*. 2005;146(12): 5631–5636.
188. **Hashinaga T, Wada N, Otabe S, et al.** Modulation by adiponectin of circadian clock rhythmicity in model mice for metabolic syndrome. *Endocr J*. 2013;60(4):483–492.
189. **Carmona-Alcocer V, Fuentes-Granados C, Carmona-Castro A, Aguilar-González I, Cárdenas-Vázquez R, Miranda-Anaya M.** Obesity alters circadian behavior and metabolism in sex dependent manner in the volcano mouse *Neotomodon alstoni*. *Physiol Behav*. 2012;105(3):727–733.
190. **Krieger DT.** Food and water restriction shifts corticosterone, temperature, activity and brain amine periodicity. *Endocrinology*. 1974;95(5):1195–1201.
191. **Gooley JJ, Schomer A, Saper CB.** The dorsomedial hypothalamic nucleus is critical for the expression of food-entrainable circadian rhythms. *Nat Neurosci*. 2006;9(3): 398–407.
192. **Stokkan KA, Yamazaki S, Tei H, Sakaki Y, Menaker M.** Entrainment of the circadian clock in the liver by feeding. *Science*. 2001;291(5503):490–493.
193. **Lamont EW, Diaz LR, Barry-Shaw J, Stewart J, Amir S.** Daily restricted feeding rescues a rhythm of period2 expression in the arrhythmic suprachiasmatic nucleus. *Neuroscience*. 2005;132(2):245–248.
194. **Marchant EG, Mistlberger RE.** Anticipation and entrainment to feeding time in intact and SCN-ablated C57BL/6j mice. *Brain Res*. 1997;765(2):273–282.
195. **Arble DM, Bass J, Laposky AD, Vitaterna MH, Turek FW.** Circadian timing of food intake contributes to weight gain. *Obesity*. 2009;17(11):2100–2102.
196. **Arble DM, Vitaterna MH, Turek FW.** Rhythmic leptin is required for weight gain from circadian desynchronized feeding in the mouse. *PLoS One*. 2011;6(9):e25079.
197. **Bray MS, Ratcliffe WF, Grenett MH, Brewer RA, Gamble KL, Young ME.** Quantitative analysis of light-phase restricted feeding reveals metabolic dyssynchrony in mice. *Int J Obes (Lond)*. 2013;37(6):843–852.
198. **Salgado-Delgado RC, Saderi N, Basualdo Mdel C, Guerrero-Vargas NN, Escobar C, Buijs RM.** Shift work or food intake during the rest phase promotes metabolic disruption and desynchrony of liver genes in male rats. *PLoS One*. 2013;8(4):e60052.
199. **Bray MS, Tsai JY, Villegas-Montoya C, et al.** Time-of-day-dependent dietary fat consumption influences multiple cardiometabolic syndrome parameters in mice. *Int J Obes (Lond)*. 2010;34(11):1589–1598.
200. **Sherman H, Genzer Y, Cohen R, Chapnik N, Madar Z, Froy O.** Timed high-fat diet resets circadian metabolism and prevents obesity. *FASEB J*. 2012;26(8):3493–3502.
201. **Hatori M, Vollmers C, Zarrinpar A, et al.** Time-restricted feeding without reducing caloric intake prevents metabolic diseases in mice fed a high-fat diet. *Cell Metab*. 2012;15(6): 848–860.
202. **Baron KG, Reid KJ, Kern AS, Zee PC.** Role of sleep timing in caloric intake and BMI. *Obesity*. 2011;19(7):1374–1381.
203. **Baron KG, Reid KJ, Horn LV, Zee PC.** Contribution of evening macronutrient intake to total caloric intake and body mass index. *Appetite*. 2013;60(1):246–251.
204. **Garaulet M, Gomez-Abellan P, Alburquerque-Bejar JJ, Lee YC, Ordovas JM, Scheer FA.** Timing of food intake predicts weight loss effectiveness. *Int J Obes (Lond)*. 2013; 37(4):604–611.
205. **Jakubowicz D, Barnea M, Wainstein J, Froy O.** High caloric intake at breakfast vs. dinner differentially influences weight loss of overweight and obese women. *Obesity (Silver Spring)*. 2013;21(12):2504–2512.
206. **Hibi M, Masumoto A, Naito Y, et al.** Nighttime snacking reduces whole body fat oxidation and increases LDL cho-

lesterol in healthy young women. *Am J Physiol Regul Integr Comp Physiol*. 2013;304(2):R94–R101.
207. **Weiss A, Xu F, Storfer-Isser A, Thomas A, Ievers-Landis CE, Redline S.** The association of sleep duration with adolescents' fat and carbohydrate consumption. *Sleep*. 2010; 33(9):1201–1209.
208. **Nishiura C, Noguchi J, Hashimoto H.** Dietary patterns only partially explain the effect of short sleep duration on the incidence of obesity. *Sleep*. 2010;33(6):753–757.
209. **Allison KC, Lundgren JD, O'Reardon JP, et al.** Proposed diagnostic criteria for night eating syndrome. *Int J Eat Disord*. 2010;43(3):241–247.
210. **Goel N, Stunkard AJ, Rogers NL, et al.** Circadian rhythm profiles in women with night eating syndrome. *J Biol Rhythms*. 2009;24(1):85–94.
211. **Birketvedt GS, Florholmen J, Sundsfjord J, et al.** Behavioral and neuroendocrine characteristics of the night-eating syndrome. *JAMA*. 1999;282(7):657–663.
212. **Wideman CH, Murphy HM.** Constant light induces alterations in melatonin levels, food intake, feed efficiency, visceral adiposity, and circadian rhythms in rats. *Nutr Neurosci*. 2009;12(5):233–240.
213. **Fonken LK, Weil ZM, Nelson RJ.** Dark nights reverse metabolic disruption caused by dim light at night. *Obesity*. 2013;21(6):1159–1164.
214. **Fonken LK, Lieberman RA, Weil ZM, Nelson RJ.** Dim light at night exaggerates weight gain and inflammation associated with a high-fat diet in male mice. *Endocrinology*. 2013;154(10): 3817–3825.
215. **Fonken LK, Melendez-Fernandez OH, Weil ZM, Nelson RJ.** Exercise attenuates the metabolic effects of dim light at night. *Physiol Behav*. 2014;124:33–36.
216. **Karatsoreos IN, Bhagat S, Bloss EB, Morrison JH, McEwen BS.** Disruption of circadian clocks has ramifications for metabolism, brain, and behavior. *Proc Natl Acad Sci U S A*. 2011;108(4):1657–1662.
217. **Barclay JL, Husse J, Bode B, et al.** Circadian desynchrony promotes metabolic disruption in a mouse model of shiftwork. *PLoS One*. 2012;7(5):e37150.
218. **Preuss F, Tang Y, Laposky AD, Arble D, Keshavarzian A, Turek FW.** Adverse effects of chronic circadian desynchronization in animals in a "challenging" environment. *Am J Physiol Regul Integr Comp Physiol*. 2008;295(6):R2034–R2040.
219. **Brainard GC, Lewy AJ, Menaker M, et al.** Dose-response relationship between light irradiance and the suppression of plasma melatonin in human volunteers. *Brain Res*. 1988;454(1–2):212–218.
220. **Wang XS, Armstrong ME, Cairns BJ, Key TJ, Travis RC.** Shift work and chronic disease: the epidemiological evidence. *Occup Med*. 2011;61(2):78–89.
221. **Pietroiusti A, Neri A, Somma G, et al.** Incidence of metabolic syndrome among night-shift healthcare workers. *Occup Environ Med*. 2010;67(1):54–57.
222. **Ha M, Park J.** Shiftwork and metabolic risk factors of cardiovascular disease. *J Occup Health*. 2005;47(2): 89–95.
223. **Sookoian S, Gemma C, Fernández Gianotti T, et al.** Effects of rotating shift work on biomarkers of metabolic syndrome and inflammation. *J Intern Med*. 2007;261(3):285–292.
224. **Esquirol Y, Bongard V, Mabile L, Jonnier B, Soulat JM, Perret B.** Shift work and metabolic syndrome: respective impacts of job strain, physical activity, and dietary rhythms. *Chronobiol Int*. 2009;26(3):544–559.
225. **De Bacquer D, Van Risseghem M, Clays E, Kittel F, De Backer G, Braeckman L.** Rotating shift work and the metabolic syndrome: a prospective study. *Int J Epidemiol*. 2009;38(3):848–854.
226. **Lin YC, Hsiao TJ, Chen PC.** Persistent rotating shift-work exposure accelerates development of metabolic syndrome among middle-aged female employees: a five-year follow-up. *Chronobiol Int*. 2009;26(4):740–755.
227. **Lin YC, Hsiao TJ, Chen PC.** Shift work aggravates metabolic syndrome development among early-middle-aged males with elevated ALT. *World J Gastroenterol*. 2009; 15(45):5654–5661.
228. **Scheer FA, Hilton MF, Mantzoros CS, Shea SA.** Adverse metabolic and cardiovascular consequences of circadian misalignment. *Proc Natl Acad Sci U S A*. 2009;106(11): 4453–4458.
229. **Monk TH.** Shift work. In: Kryger MH, Roth T, Dement WC, eds. *Principles and Practice of Sleep Medicine*. Philadelphia, PA: WB Saunders; 2000:471–476.
230. **Rajaratnam SM, Arendt J.** Health in a 24-h society. *Lancet*. 2001;358(9286):999–1005.
231. **Cinzano P, Falchi F, Elvidge CD.** The first World Atlas of the artificial night sky brightness. *Monthly Notices Royal Astronom Soc*. 2001;328(3):689–707.
232. **Roenneberg T, Allebrandt KV, Merrow M, Vetter C.** Social jetlag and obesity. *Curr Biol*. 2012;22(10):939–943.
233. **Cho JR, Joo EY, Koo DL, Hong SB.** Let there be no light: the effect of bedside light on sleep quality and background electroencephalographic rhythms. *Sleep Med*. 2013.
234. **Scott S, Pellman K.** *Living Without Electricity (People's Place Book No. 9)*. Intercourse, PA: Good Books; 1990.
235. **Tremblay MS, Esliger DW, Copeland JL, Barnes JD, Bassett DR.** Moving forward by looking back: lessons learned from long-lost lifestyles. *Appl Physiol Nutr Metab*. 2008; 33(4):836–842.
236. **Esliger DW, Tremblay MS, Copeland JL, Barnes JD, Huntington GE, Bassett DR Jr.** Physical activity profile of Old Order Amish, Mennonite, and contemporary children. *Med Sci Sports Exerc*. 2010;42(2):296–303.
237. **Westman JA, Ferketich AK, Kauffman RM, et al.** Low cancer incidence rates in Ohio Amish. *Cancer Causes Control*. 2010;21(1):69–75.
238. **Kloog I, Haim A, Stevens RG, Barachana M, Portnov BA.** Light at night co-distributes with incident breast but not lung cancer in the female population of israel. *Chronobiol Int*. 2008;25(1):65–81.
239. **Kloog I, Haim A, Stevens RG, Portnov BA.** Global co-distribution of light at night (LAN) and cancers of prostate, colon, and lung in men. *Chronobiol Int*. 2009;26(1):108–125.
240. **Reiter RJ.** Melatonin: the chemical expression of darkness. *Mol Cell Endocrinol*. 1991;79(1–3):C153–C158.
241. **Brainard GC, Rollag MD, Hanifin JP.** Photic regulation of melatonin in humans: ocular and neural signal transduction. *J Biol Rhythms*. 1997;12(6):537–546.
242. **Blask DE.** Melatonin, sleep disturbance and cancer risk. *Sleep Med Rev*. 2009;13(4):257–264.

243. **Blask DE, Brainard GC, Dauchy RT, et al.** Melatonin-depleted blood from premenopausal women exposed to light at night stimulates growth of human breast cancer xenografts in nude rats. *Cancer Res*. 2005;65(23):11174–11184.
244. **Tan DX, Manchester LC, Fuentes-Broto L, Paredes SD, Reiter RJ.** Significance and application of melatonin in the regulation of brown adipose tissue metabolism: relation to human obesity. *Obes Rev*. 2011;12(3):167–188.
245. **Mantele S, Otway DT, Middleton B, et al.** Daily rhythms of plasma melatonin, but not plasma leptin or leptin mRNA, vary between lean, obese and type 2 diabetic men. *PLoS One*. 2012;7(5):e37123.
246. **Srinivasan V, De Berardis D, Shillcutt SD, Brzezinski A.** Role of melatonin in mood disorders and the antidepressant effects of agomelatine. *Expert Opin Investig Drugs*. 2012;21(10):1503–1522.
247. **Walton JC, Weil ZM, Nelson RJ.** Influence of photoperiod on hormones, behavior, and immune function. *Front Neuroendocrinol*. 2011;32(3):303–319.
248. **Hoffmann K.** The influence of photoperiod and melatonin on testis size, body weight, and pelage colour in Djungarian hamster (*Phodopus sungorus*). *J Comp Physiol*. 1973;85(3):267–282.
249. **Bartness TJ, Demas GE, Song CK.** Seasonal changes in adiposity: the roles of the photoperiod, melatonin and other hormones, and sympathetic nervous system. *Exp Biol Med (Maywood)*. 2002;227(6):363–376.
250. **Fenn AM, Fonken LK, Nelson RJ.** Sustained melatonin treatment blocks body mass, pelage, reproductive, and fever responses to short day lengths in female Siberian hamsters. *J Pineal Res*. 2011;51(2):180–186.
251. **Terrón MP, Delgado-Adámez J, Pariente JA, Barriga C, Paredes SD, Rodríguez AB.** Melatonin reduces body weight gain and increases nocturnal activity in male Wistar rats. *Physiol Behav*. 2013;118:8–13.
252. **Agil A, Rosado I, Ruiz R, Figueroa A, Zen N, Fernández-Vázquez G.** Melatonin improves glucose homeostasis in young Zucker diabetic fatty rats. *J Pineal Res*. 2012;52(2):203–210.
253. **Ríos-Lugo MJ, Cano P, Jiménez-Ortega V, et al.** Melatonin effect on plasma adiponectin, leptin, insulin, glucose, triglycerides and cholesterol in normal and high fat-fed rats. *J Pineal Res*. 2010;49(4):342–348.
254. **Sartori C, Dessen P, Mathieu C, et al.** Melatonin improves glucose homeostasis and endothelial vascular function in high-fat diet-fed insulin-resistant mice. *Endocrinology*. 2009;150(12):5311–5317.
255. **Park JH, Shim HM, Na AY, Bae KC, Bae JH, Im SS, Cho HC, Song DK.** Melatonin prevents pancreatic beta-cell loss due to glucotoxicity: the relationship between oxidative stress and endoplasmic reticulum stress. *J Pineal Res*. 2014;56:143–153.
256. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet*. 1998;352(9131):854–865.
257. **Nduhirabandi F, du Toit EF, Lochner A.** Melatonin and the metabolic syndrome: a tool for effective therapy in obesity-associated abnormalities? *Acta Physiol*. 2012;205(2):209–223.
258. **Cardinali DP, Pagano ES, Scacchi Bernasconi PA, Reynoso R, Scacchi P.** Disrupted chronobiology of sleep and cytoprotection in obesity: possible therapeutic value of melatonin. *Neuroendocrinol Lett*. 2011;32(5):588–606.
259. **Cardinali DP, Cano P, Jiménez-Ortega V, Esquifino AI.** Melatonin and the metabolic syndrome: physiopathologic and therapeutical implications. *Neuroendocrinology*. 2011;93(3):133–142.
260. **Rastmanesh R, de Bruin PF.** Potential of melatonin for the treatment or prevention of obesity: an urgent need to include weight reduction as a secondary outcome in clinical trials of melatonin in obese patients with sleep disorders. *Contemp Clin Trials*. 2012;33(4):574–575.
261. **Reiter RJ, Tan DX, Korkmaz A, Ma S.** Obesity and metabolic syndrome: association with chronodisruption, sleep deprivation, and melatonin suppression. *Ann Med*. 2012;44(6):564–577.
262. **Nachtigal MC, Patterson RE, Stratton KL, Adams LA, Shattuck AL, White E.** Dietary supplements and weight control in a middle-age population. *J Altern Complement Med*. 2005;11(5):909–915.
263. **McMullan CJ, Schernhammer ES, Rimm EB, Hu FB, Forman JP.** Melatonin secretion and the incidence of type 2 diabetes. *JAMA*. 2013;309(13):1388–1396.
264. **Bouatia-Naji N, Bonnefond A, Cavalcanti-Proença C, et al.** A variant near MTNR1B is associated with increased fasting plasma glucose levels and type 2 diabetes risk. *Nat Genet*. 2009;41(1):89–94.
265. **Bonnefond A, Clément N, Fawcett K, et al.** Rare MTNR1B variants impairing melatonin receptor 1B function contribute to type 2 diabetes. *Nat Genet*. 2012;44(3):297–301.
266. **Prokopenko I, Langenberg C, Florez JC, et al.** Variants in MTNR1B influence fasting glucose levels. *Nat Genet*. 2009;41(1):77–81.
267. **Ramracheya RD, Muller DS, Squires PE, et al.** Function and expression of melatonin receptors on human pancreatic islets. *J Pineal Res*. 2008;44(3):273–279.
268. **Kemp DM, Ubeda M, Habener JF.** Identification and functional characterization of melatonin Mel 1a receptors in pancreatic beta cells: potential role in incretin-mediated cell function by sensitization of cAMP signaling. *Mol Cell Endocrinol*. 2002;191(2):157–166.
269. **Ma WP, Cao J, Tian M, et al.** Exposure to chronic constant light impairs spatial memory and influences long-term depression in rats. *Neurosci Res*. 2007;59(2):224–230.
270. **Abílio VC, Freitas FM, Dolnikoff MS, Castrucci AM, Frussa-Filho R.** Effects of continuous exposure to light on behavioral dopaminergic supersensitivity. *Biol Psychiatry*. 1999;45(12):1622–1629.
271. **Kiessling S, Eichele G, Oster H.** Adrenal glucocorticoids have a key role in circadian resynchronization in a mouse model of jet lag. *J Clin Invest*. 2010;120(7):2600–2609.
272. **Sage D, Ganem J, Guillaumond F, et al.** Influence of the corticosterone rhythm on photic entrainment of locomotor activity in rats. *J Biol Rhythms*. 2004;19(2):144–156.
273. **Tataranni PA, Larson DE, Snitker S, Young JB, Flatt JP, Ravussin E.** Effects of glucocorticoids on energy metabolism and food intake in humans. *Am J Physiol*. 1996;271(2 Pt 1):E317–E325.
274. **Rosmond R, Dallman MF, Björntorp P.** Stress-related cor-

tisol secretion in men: relationships with abdominal obesity and endocrine, metabolic and hemodynamic abnormalities. *J Clin Endocrinol Metab*. 1998;83(6):1853–1859.
275. **Valassi E, Crespo I, Santos A, Webb SM.** Clinical consequences of Cushing's syndrome. *Pituitary*. 2012;15(3):319–329.
276. **Betterle C, Zanchetta R, Presotto F.** Addison's Disease. *Contemp Endocrinol S*. 2008:303–329.
277. **Dallman MF, Pecoraro N, Akana SF, et al.** Chronic stress and obesity: a new view of "comfort food." *Proc Natl Acad Sci U S A*. 2003;100(20):11696–11701.
278. **Fonken LK, Haim A, Nelson RJ.** Dim light at night increases immune function in Nile grass rats, a diurnal rodent. *Chronobiol Int*. 2012;29(1):26–34.
279. **Fonken LK, Finy MS, Walton JC, et al.** Influence of light at night on murine anxiety- and depressive-like responses. *Behav Brain Res*. 2009;205(2):349–354.
280. **Weitzman ED, Zimmerman JC, Czeisler CA, Ronda J.** Cortisol secretion is inhibited during sleep in normal man. *J Clin Endocrinol Metab*. 1983;56(2):352–358.
281. **Weibel L, Spiegel K, Follenius M, Ehrhart J, Brandenberger G.** Internal dissociation of the circadian markers of the cortisol rhythm in night workers. *Am J Physiol*. 1996;270(4 Pt 1):E608–E613.
282. **Scheer FA, Buijs RM.** Light affects morning salivary cortisol in humans. *J Clin Endocrinol Metab*. 1999;84(9):3395–3398.
283. **Griefahn B, Kuenemund C, Robens S.** Shifts of the hormonal rhythms of melatonin and cortisol after a 4 h bright-light pulse in different diurnal types. *Chronobiol Int*. 2006;23(3):659–673.
284. **Leproult R, Colecchia EF, L'Hermite-Balériaux M, Van Cauter E.** Transition from dim to bright light in the morning induces an immediate elevation of cortisol levels. *J Clin Endocrinol Metab*. 2001;86(1):151–157.
285. **Kostoglou-Athanassiou I, Treacher DF, Wheeler MJ, Forsling ML.** Bright light exposure and pituitary hormone secretion. *Clin Endocrinol (Oxf)*. 1998;48(1):73–79.
286. **Jung CM, Khalsa SB, Scheer FA, et al.** Acute effects of bright light exposure on cortisol levels. *J Biol Rhythms*. 2010;25(3):208–216.
287. **Beck-Friis J, von Rosen D, Kjellman BF, Ljunggren JG, Wetterberg L.** Melatonin in relation to body measures, sex, age, season and the use of drugs in patients with major affective disorders and healthy subjects. *Psychoneuroendocrinology*. 1984;9(3):261–277.
288. **Fonken LK, Nelson RJ.** Dim light at night increases depressive-like responses in male C3H/HeNHsd mice. *Behav Brain Res*. 2013;243:74–78.
289. **Spiegel K, Tasali E, Leproult R, Van Cauter E.** Effects of poor and short sleep on glucose metabolism and obesity risk. *Nat Rev Endocrinol*. 2009;5(5):253–261.
290. **Mullington JM, Haack M, Toth M, Serrador JM, Meier-Ewert HK.** Cardiovascular, inflammatory, and metabolic consequences of sleep deprivation. *Prog Cardiovasc Dis*. 2009;51(4):294–302.
291. **Di Milia L, Vandelanotte C, Duncan MJ.** The association between short sleep and obesity after controlling for demographic, lifestyle, work and health related factors. *Sleep Med*. 2013;14(4):319–323.
292. **Reilly JJ, Armstrong J, Dorosty AR, et al; Longitudinal Study of Parents and Children Study Team.** Early life risk factors for obesity in childhood: cohort study. *BMJ*. 2005;330(7504):1357.
293. **Mitchell JA, Rodriguez D, Schmitz KH, Audrain-McGovern J.** Sleep duration and adolescent obesity. *Pediatrics*. 2013;131(5):e1428–e1434.
294. **Seegers V, Petit D, Falissard B, et al.** Short sleep duration and body mass index: a prospective longitudinal study in preadolescence. *Am J Epidemiol*. 2011;173(6):621–629.
295. **Markwald RR, Melanson EL, Smith MR, et al.** Impact of insufficient sleep on total daily energy expenditure, food intake, and weight gain. *Proc Natl Acad Sci U S A*. 2013;110(14):5695–5700.
296. **Akerstedt T.** Shift work and disturbed sleep/wakefulness. *Occup Med*. 2003;53(2):89–94.
297. **Borniger JC, Weil ZM, Zhang N, Nelson RJ.** Dim light at night does not disrupt timing or quality of sleep in mice. *Chronobiol Int*. 2013;30(8):1016–1023.
298. **Kempenaers B, Borgström P, Loës P, Schlicht E, Valcu M.** Artificial night lighting affects dawn song, extra-pair siring success, and lay date in songbirds. *Curr Biol*. 2010;20(19):1735–1739.
299. **Brainard GC, Hanifin JP, Greeson JM, et al.** Action spectrum for melatonin regulation in humans: evidence for a novel circadian photoreceptor. *J Neurosci*. 2001;21(16):6405–6412.
300. **Kayumov L, Casper RF, Hawa RJ, et al.** Blocking low-wavelength light prevents nocturnal melatonin suppression with no adverse effect on performance during simulated shift work. *J Clin Endocrinol Metab*. 2005;90(5):2755–2761.
301. **Boivin DB, Boudreau P, James FO, Kin NM.** Photic resetting in night-shift work: impact on nurses' sleep. *Chronobiol Int*. 2012;29(5):619–628.