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Dark matters: effects of light at night on metabolism

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Abstract

Life on earth has evolved during the past several billion years under relatively bright days and dark night conditions. The wide-spread adoption of electric lights during the past century exposed animals, both human and non-human, to significant light at night for the first time in their evolutionary history. Endogenous circadian clocks depend on light to entrain to the external daily environment and seasonal rhythms depend on clear nightly melatonin signals to assess time of year. Thus, light at night can derange temporal adaptations. Indeed, disruption of naturally evolved light-dark cycles results in several physiological and behavioural changes with potentially serious implications for physiology, behaviour and mood. In this review, data from night-shift workers on their elevated risk for metabolic disorders, as well as data from animal studies will be discussed. Night-shift workers are predisposed to obesity and dysregulated metabolism that may result from disrupted circadian rhythms. Although studies in human subjects are correlative, animal studies have revealed several mechanisms through which light at night may exert its effects on metabolism by disrupting circadian rhythms that are associated with inflammation, both in the brain and in the periphery. Disruption of the typical timing of food intake is a key effect of light at night and subsequent metabolic dysregulation. Strategies to avoid the effects of light at night on body mass dysregulation should be pursued.

Keywords

Circadian disruption; Circadian rhythms; Food intake; Light at night; Metabolism; Shift work

Life on earth evolved to internalise the daily rotation of our planet; that is, for the past 3–4 billion years life evolved under conditions of dark nights and bright days. Biological functions are exquisitely timed for optimal functioning: some processes occur at night and others during the day. For non-human animals, restricting activities to the appropriate temporal niche is crucial for optimal fitness and survival. For human animals, temporal organization of physiology is equally important for health and wellness. Over the past century, however, the boundaries between day and night have been blurred by the

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Conflicts of Interest

None.

widespread adoption of electric lighting devices at night. Disruption of our internal daily rhythms has become quite common in all developed countries. For human animals, the health consequences of chronic temporal disruption by night-time light exposure are becoming increasingly apparent[1,2].

Circadian rhythms are approximately, but not exactly 24 h in duration. Although these internal rhythms are reliable, they require external light input to align with the external light-dark conditions. Light during the night can wreak havoc with the process of precise entraining of internal circadian rhythms with the 24-h solar day. This review will examine the role of circadian rhythms in metabolic function, and how misaligned circadian rhythms can derange metabolism. Epidemiological studies, as well as studies of night-shift workers, will be reviewed. Also, experimental evidence from non-human animal studies will be summarised in order to understand the underlying mechanisms of disrupted metabolic rhythms and body mass regulation.

Circadian rhythms

Circadian rhythms are endogenously-driven functional cycles that are generated from biological clocks. Circadian rhythms are self-sustaining and have periods of approximately 24 h. The mammalian master circadian clock is located in a hypothalamic cluster of neurons within the suprachiasmatic nuclei (SCN) at the base of the brain. The SCN generates daily transcription–translation rhythms comprising feedback loops of gene transcription and translation in the SCN that approximates the daily rotation of the planet. These endogenous circadian rhythms are synchronised (entrained) to the 24-h external light–dark environment primarily using light information transmitted from specialised retinal non-visual photoreceptors directly to the SCN; the gene and protein components of this cycle are modulated by light to maintain tight synchronisation with the environment. Without light and dark cues, the endogenous clock runs out of phase with the external environment. Thus, the properly timed light input is critical to maintain the internal biological clocks because physiological and behavioral processes have evolved to function optimally in 24 h rhythms.

Briefly, Circadian Locomotor Output Cycles Kaput (CLOCK) and Brain and muscle Arnt-like protein-1 (BMAL1) proteins form a heterodimer at the onset of the circadian day; this heterodimer acts as a transcription factor to induce expression of Period, Cryptochrome, and other clock genes and so-called clock-controlled genes. Period and Cryptochrome proteins accumulate throughout the day; when the accumulation reaches a specific threshold, these proteins form hetero or homodimers, enter the nucleus, where they repress transcription of *CLOCK* and *BMAL1* genes[3]. The feedback cycle takes approximately 24 h, thus driving the circadian cycle of gene transcription. In addition to this primary feedback loop, several other regulatory loops are involved in the precise generation of circadian rhythms including kinases (e.g. casein kinase 1-ε) and phosphatases. Transcriptional loops may not be the only factor driving the circadian pacemaker. Other mechanisms, including posttranslational modifications, appear to be essential for molecular clock function; phosphorylation, sumoylation, methylation and other modifications determine the activity, degradation and localisation of components essential to the molecular timing loop[4]. The molecular clocks (the different components of the circadian rhythm or the different circadian genes) are

expressed as changes in the daily amplitudes of various clock proteins in cells, with peaks and nadirs linked to particular times of the day. As noted, endogenous circadian rhythms are nearly, but rarely, precisely 24 h. Environmental input, typically light, adjusts the endogenous rhythms to exactly 24 h.

The retina is the sole mechanism of light detection among mammals[5], comprising image-forming photoreceptors, rods and cones, and non-image-forming photoreceptors called intrinsically photosensitive retinal ganglion cells (ipRGC). In contrast to rods and cones, ipRGC are depolarised in response to light and are generally responsible for circadian photoentrainment[6]. Light detected by ipRGC activates a unique photopigment called melanopsin, which is maximally sensitive to blue wavelengths (about 480 nm) and minimally sensitive to longer, red wavelengths (about 600 nm)[7]. This means that blue wavelengths exert a more potent influence on the circadian system than other longer wavelength lights. Notably, in Europe and the US incandescent bulbs, which produce light in the longer wavelengths of the visible electromagnetic spectrum (i.e. yellowish), are being replaced by compact fluorescent light bulbs, which generate the short wavelengths (bluish) that maximally activate ipRGC[8]. Activated ipRGC project to the SCN directly through the retinohypothalamic tract and indirectly via the intergeniculate leaflet. Information sent via the retinohypothalamic tract reaches the SCN through a single glutamatergic synapse. An indirect pathway from the intergeniculate leaflet of the thalamus, the geniculohy-pothalamic tract, also carries photic information to the SCN[9]. Although most of the fundamental discoveries about the input to and processing of the SCN was made in nocturnal rodents, the processes are similar in both nocturnal and diurnal species. Importantly, the circadian system is entrained primarily by light, however, other *zeitgebers* (time givers), such as feeding and social cues, can also entrain biological rhythms.

Because lesions of the SCN eliminate all circadian rhythms, it was generally assumed that the SCN was the only locus capable of sustained rhythmicity and thus, rhythms in other systems or in behaviour were driven by broad communication of timing throughout the brain and body by this central pacemaker. However, the observation that cultured fibroblasts displayed circadian rhythms in gene expression[10] led to the hypothesis that the ability to oscillate was a general property of tissues throughout the central nervous system and periphery[11–13]. The circadian system is now known to comprise multiple, individual cellular oscillators located throughout the body and most of its organs and glands. Nonetheless, the SCN remains unique in three respects: (1) the network of connectivity among cells within the SCN allows for the synchronisation of independent cellular oscillators required for coherent tissue-level clock functioning, (2) the SCN is the only clock with access to environmental light information, allowing internal time to be properly synchronised to environmental time, and (3) through neural and hormonal communication, the SCN synchronises independent cellular oscillators within a system (e.g. adipose tissue, fiver) and sets their phase relative to external time. Without the SCN or its outputs, subordinate oscillators within a system lose coherence, leading to tissue-level arrhythmicity, despite the observation that individual cells continue to exhibit daily rhythms[14,15].

Metabolism

Metabolism is a major physiological process under circadian control[16]. Thus, disruption of circadian rhythms such as exposure to light at night might be expected to affect metabolism. Indeed, studies of night-shift workers and other epidemiological studies, as well as laboratory studies of non-human animals have established strong relationships between exposure to light during the night and dysregulated glucose, increased prevalence of metabolic syndrome, and obesity[17]. These studies will be reviewed later.

Night-shift workers

Night-shift workers might be considered as the ‘canaries in the coal mine’ in terms of night-light exposure effects on health. The first large group to be affected by repeatedly working in light at night, night-shift workers warn of the health problems the rest of us could face. Research on men and women working night shifts has suggested that night-shift workers are more likely to be overweight or obese than people performing the same jobs during the day[18]. This research suggests that working the night shift, and being exposed to light at night, may disrupt circadian signals, which can dysregulate metabolism and lead to obesity.

For example, more offshore oil-rig workers who go to the North Sea become obese than those who stay local. It was initially attributed to the difference in oil-rig workers eating high-energy foods and not exercising[19]. However, follow-up studies indicated that how much time spent on night shifts was most highly correlated with increases in body mass; indeed, working nights was even more influential than age, even though age was strongly associated with weight gain among the day-shift rig workers[19]. Researchers in Japan reported a similar relationship; male night-shift workers at a steel factory, as well as at a sash and zipper factory were at increased risk for obesity[20,21]. Both current and cumulative night-shift work was associated with obesity in a recent study of Polish nurses who worked eight or more night shifts per month[22]. Similar results have been reported for long-term night-shift nurses in Brazil[23,24]. The effects of night-shift work on metabolism seem to persist because former night-shift workers retained a higher risk of obesity after they switched to day shifts. Indeed, a meta-analysis of all the longitudinal data published on night-shift work and body weight revealed a strong relationship between working night shifts and being overweight or obese[25].

A more recent meta-analysis of thirty-nine papers describing twenty-two longitudinal studies was conducted[26]. This analysis found a strong relationship between working night shifts and body mass gain, the risk for becoming overweight and impaired glucose tolerance. The authors concluded that the strong methodological quality did not allow assessment of the relationship between night-shift work and other metabolic risk factors[26].

Nonetheless, some studies have a sufficiently strong methodology to support the relationship between night-shift work and other metabolic risks. For example, a positive relationship between working night shifts and elevated risk for type 2 diabetes has been reported as part of the Nurses’ Health Studies. Nearly 70 000 adults aged 42–67 years were monitored from 1998 to 2008, and the second group of about 108 000 adults aged 25–47 years from 1989 to 2007. Women who worked night shifts not only had a higher risk for type 2 diabetes but the

risk was also proportionally finked to how many years they worked night-shifts[27]. Of course, night-shift workers also face risks other than night light, including social jet lag[28] and disrupted sleep[29,30] which makes it difficult to isolate its influence on body mass.

Epidemiological studies

Given the limitations of night-shift studies, studies have also examined the role of exposure to light at night in people not working night shifts. Body mass also increases from exposure to light at night in typical home settings. For example, participants who were exposed to night-light levels higher than just three lux gained significantly more weight, increased their waist circumference, and developed higher TAG and higher LDL-cholesterol[31]. A study of 100 000 women in the UK reported that the chances of obesity increased in fine with increased exposure to light at night[32].

Late-night eating is associated with a perturbed daily cortisol rhythm, reduced glucose tolerance, increased insulin resistance and less physical activity[33]. People with the night-eating syndrome[34] often wake up and eat most of their day's energy food late at night. Night-eating syndrome is associated with elevated body mass[35].

The timing of food composition consumption is also important for body mass regulation. For example, one epidemiological study of several thousand UK men and women born in 1946 reported that those who ate the majority of their daily carbohydrates during breakfast or mid-morning had less abdominal obesity and metabolic syndrome than people who ate carbohydrates at night[36]. This relationship was maintained even when factors, such as socioeconomic status, tobacco use, alcohol use and exercise levels were considered.

In another study on the effects of mealtimes on health, nearly 2000 Italian men and women were studied. Study participants documented when and what they ate and researchers recorded their health parameters over 3 d. Six years later, the researchers re-examined them and discovered that eating the majority of energy foods at dinner was associated with an increased risk of obesity, metabolic syndrome and non-alcoholic fatty fiver disease[37]. A recent meta-analysis of several studies on evening eating habits and obesity in many different countries and cultures also reported a strong fink between eating at night and obesity[38].

Cross-sectional analyses of the timing of food intake were performed using data from the University of California, Los Angeles Energetics Study[39]. Obesity was associated with mealtime in participants who consumed >33 % of their energy foods at dinner, not among those who consumed >33 % of their daily energy food at breakfast or lunch.

The timing of food intake on dieters affects outcomes. In one study of 420 people on a 5-month diet, 51 % were early eaters (lunch before 15.00 hours) and 49% were late eaters (lunch after 15.00 hours). Even though both had similar diets, sleep, exercise and leptin levels, the late eaters had a slower weight-loss rate and lost less weight than the early eaters[40].

Laboratory studies: human animals

In one laboratory study that simulated night-shift work, ten people lived in a controlled setting with recurring 28-h days, so they ate and slept in all phases of their normal 24-h circadian cycle[41]. Participants ate four isoenergetic meals daily. When the participants ate and slept during the opposite 12 h from their normal routine (i.e. living the night shift), their blood glucose levels increased as leptin concentrations decreased. Three of the ten study participants developed a pre-diabetic state during this brief 8-week experiment. These three individuals decreased their RMR and displayed increased postprandial glucose levels. After reestablishing stable sleep and circadian schedules for only 9 d, however, their metabolic rate and insulin production returned to normal. Thus, even a short period of being awake and exposed to light at night can disrupt circadian rhythms, which can cause dramatic changes in metabolism that lead to a rapid deterioration in health status[41].

Laboratory studies: rodents

Many of the metabolic effects of night shift workers or individuals exposed to light at night have been attributed to sleep disruption. To rule out this hypothesis, studies of nocturnal rodents, that typically sleep during the light portion of the day and are typically active at night, have been conducted. These studies demonstrate that exposure to light at night affects metabolism without affecting sleep[42]. Studies of the effects of light at night on rodents demonstrate that light at night deranges circadian rhythms, which disrupts metabolism and contributes to weight gain, as well as potentially sleep in people[18]. Again, it is difficult to distinguish between disrupted circadian rhythms or disrupted sleep in studies of people. That is, to determine whether people gain weight from light at night because it disrupts their circadian rhythms or their sleep. Sleep confounds light at night research for several reasons: (1) sleep is also regulated by the circadian system, (2) insufficient sleep is also associated with obesity and metabolic disorders and (3) people with sleep problems also often expose themselves to more light at night. To parse out the causative effects of sleep or circadian rhythms disruption on metabolism, most non-human animal studies have been conducted on nocturnal rodents that generally sleep mainly during the light of day; any changes in their body mass and metabolic functions in response to light exposure at night, when they are typically awake, can be attributed to light at night disrupting their circadian rhythms, rather than their sleep.

Approximately 10 % of the mammalian transcriptome display circadian rhythms in expression[43–45]. Many of the identified genes are key components of metabofism[18,44,46]. Indeed, several studies have linked components of the molecular circadian clock and metabolism[18,47]. *CLOCK* is a gene that encodes for a helix-loop-helix-PAS transcription factor (CLOCK) that appears to affect both the persistence and period of circadian rhythms. Mice with mutant *CLOCK* gene develop obesity and metabolic syndrome[48]. *CLOCK* mutants display dramatic changes in circadian rhythmicity, as well as disrupted rhythms of food intake and elevated body mass. Serum leptin, glucose, cholesterol and TAG concentrations also are increased in *CLOCK* mutants compared with wild-type mice[48,49]. Mice with mutant *BMAL1* genes also have impaired glucose tolerance, hypoinsulinemia, as well defective proliferation and size of pancreatic islets[49].

High-fat diet alters circadian rhythmicity and the cycling of circadian clock genes in mice potentially resulting in a 'feed-forward' elevation of body mass[50,51]. For example, mice fed a high-fat diet display alternations in daily rhythms of food intake, as well as in clock gene expression[51,52]. Altered clock gene expression occurs rapidly after the onset of high-fat diet; for example, fiver clock rhythms are phase-advanced by 5 h after only 1 week[53].

Several rodent models of obesity have reported attenuated amplitude of circadian clock gene expression, and changes in the phase and daily rhythm of clock genes may cause obesity[54]. The reciprocal relation between internal clocks and dysregulated metabolism led one team of investigators to attempt to overcome high-fat diet induced obesity by increasing the amplitude of clock gene expression[55]. Using a chemical screen in fibroblasts expressing Period 2:Luciferase, they identified Nobiletin, a naturally occurring polymethoxylated flavonoid, as a clock amplitude-enhancing small molecule. When administered to diet-induced obese mice, Nobiletin blocked the onset of metabolic syndrome and augmented energy expenditure and locomotor activity in a *CLOCK* gene-dependent manner. In *db/db* mutant obese mice, the *CLOCK* gene is also required for the mitigating effects of Nobiletin on metabolic disorders. This important work suggests a pharmacological intervention that enhances circadian rhythms to combat metabolic disease via the circadian gene network[55].

One common approach to test the effects of disruption of circadian clocks is to subject animals to rapid phase shift in their light–dark cycles. These types of experiment are commonly called jet-lag studies. For example, housing mice in 20-h light–dark cycles cause disruption with the standard entrainment of endogenous approximate 24-h circadian rhythms, as well as elevated body mass gain and obesity in concert with changes in metabolic hormones[56]. Chronic jet lag is also sufficient to induce central leptin resistance in wild-type mice, as well as disrupt endogenous clocks in adipose tissue[57]. BMAL1/CLOCK dimers promote circadian rhythms of C/EBPα-mediated leptin transcription in adipose tissue. The coupling of the central and peripheral clocks controls leptin homeostasis and disruption may play a role in circadian dysfunction-induced obesity and metabolic syndrome[57,58]. Indeed, combining short sleep with circadian disruption in human animals for 3 weeks reduced participants' RMR, increased post-prandial plasma glucose concentrations and decreased pancreatic insulin secretion[59].

Although jet-lag studies can provide insights into the mechanisms underlying circadian disruption on metabolism, another type of circadian disruption, namely, light at night, may provide additional face validity as a disrupter of circadian rhythms. For example, one study reported that after just 2 months, mice maintained in dim light at night (5 lux) increased their body mass about 15 % compared with mice housed in dark nights despite consuming equivalent energy foods and expending equivalent locomotor activities[60]. In a related study, mice were maintained in 12 h light followed by either 12 h dim light (5 lux) or 12 h darkness. None of the animals displayed disrupted circadian rhythms in locomotor activity levels or glucocorticoid secretion. After only 2 months, however, the mice exposed to dim light at night displayed impaired glucose processing, more fat (white adipose tissue) and weighed more than mice maintained in dark nights, even though both groups ate equivalent energy foods and produced equivalent locomotor activity[60].

In a follow-up study, researchers examined how dim light at night *v.* complete darkness affects young male mice with unlimited access to two different diets: standard mouse chow or a high-fat diet developed to be similar to diets in developed countries (approximately 45 % energy from fat and 55 % from carbohydrates and proteins)[61]. Their original study was replicated: in only 3 weeks, the mice housed under dim light at night and eating standard mouse chow gained about 50 % more weight than the mice fed the same diet under dark nights. Indeed, mice exposed to the dim light at night on either diet gained weight faster than their counterparts consuming the high-fat diets. With unlimited access to high-fat food, mice exposed to dark nights increased their body mass by 30 %, whereas the mice exposed to dim light at night increased their body mass by about 40%[61]. Additionally, mice fed the high-fat diet and exposed to dim light at night developed a prediabetic phenotype displaying elevated blood glucose and insulin concentrations. These differences are remarkable, particularly given that all four groups displayed equivalent locomotor activity[61].

How did dim light at night cause the mice to gain so much weight so quickly? In short, it changed the time of their food intake. Nocturnal mice are usually active and eat at night and they typically rest and do not eat during the day. However, mice exposed to light at night changed some of their activities, namely, they consumed the majority of their energy foods during the day instead of at night, which was the wrong time because it is out of synch with their circadian system; this might correspond to the human animals' situation of eating more food at night. Indeed, there is a medical syndrome called night eating syndrome which is characterised by night-time hyperphagia, altered metabolic hormones and obesity[62,63]. Meal timing seems to affect metabolism in significant ways. In a ground-breaking study, male mice were housed on a 12:12 light-dark schedule; half the mice received high-fat food only at night, whereas the other half received their food only during the day. The mice fed during the day gained significantly more weight than the mice fed at night[64]. A number of other researchers have reported similar findings: eating outside the typical active period leads to more weight gain, primarily from increased body fat.

Why does eating outside the active period cause weight gain? The mice exposed to dim light at night displayed changes in their circadian clock rhythms at both the genetic and protein levels[65]. At the protein level, exposure to dim light at night suppressed the amplitude of fundamental CLOCK protein production (e.g. Period 1 and Period 2). At the level of gene expression, exposure to dim light at night slowed the rhythmic expression of virtually all the core circadian clock genes in the mice's fat and fiver tissue, both critical for proper metabofism[65].

Conclusions

We mentioned that night-shift workers are the 'canaries in the coal mine' regarding the effects of light at night on metabolism in human animals; however, the use of electronics and lights at night has likely caused most of us to have disrupted circadian rhythms. Can we offset the changes that light at night exposure causes to our biological clocks? Mouse research suggests that we can. For example, reverting to dark nights reversed the weight mice gained from night-light exposure and exercise eliminated the fat they gained from it[66]. Exercise tends to strengthen circadian rhythms and generally prevents weight gain.

Therefore, it was hypothesised that providing mice a running wheel for voluntary exercise would buffer against the effects of light at night on weight gain. Mice were maintained in either dark or dimly illuminated nights and provided either a functional running wheel or a locked wheel. Again, mice exposed to dim light at night instead of dark nights increased weight gain. However, access to a functional running wheel prevented body mass gain in mice exposed to dim light at night[67]. Voluntary exercise appeared to limit weight gain independently of rescuing changes to the circadian system caused by dim light at night; that is, increased daytime food intake provoked by dim light at night was not affected by increased voluntary exercise suggesting that voluntary exercise can prevent weight gain induced by dim light at night without rescuing circadian rhythm disruptions. If these techniques work for people, then we should start thinking about managing our exposure to light at night the same way we try to manage everything else in our fives: work and social time, diet, sleep and exercise.

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Abbreviations:

BMAL1	brain and muscle Arnt-like protein-1
CLOCK	Circadian Locomotor Output Cycles Kauput
ipRGC	intrinsically photosensitive retinal ganglion cells
SCN	suprachiasmatic nuclei

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