Brain, nutrition and metabolism

Studies in lean, obese and insulin resistant humans

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Nutrition in the spotlight: metabolic effects of environmental light

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Abstract

Use of artificial light resulted in relative independence from the natural light-dark cycle, allowing humans to shift the timing of food intake and work to convenient times. However, the increase in artificial light exposure parallels the increase in obesity prevalence. Light is the dominant Zeitgeber for the central circadian clock, which resides within the hypothalamic suprachiasmatic nucleus, and coordinates daily rhythm in feeding behaviour and metabolism. Eating during inappropriate light conditions may result in metabolic disease via changes in the biological clock. In this review we describe the physiological role of light in the circadian timing system and explore the interaction between the circadian timing system and metabolism. Furthermore, we discuss the acute and chronic effects of artificial light exposure on food intake and energy metabolism in animals and humans. We propose that living in synchrony with the natural daily light-dark cycle promotes metabolic health and increased exposure to artificial light at inappropriate times of day has adverse effects on metabolism, feeding behaviour and body weight regulation. Reducing the negative side effects of the extensive use of artificial light in humans might be useful in the prevention of metabolic disease.
Changes in artificial light exposure

Obesity is an increasing health problem and is associated with the development of type 2 diabetes and cardiovascular disease (1). The pathophysiology of obesity is multifactorial, with major contributions from overconsumption of high-energy highly palatable food and an inactive lifestyle (2). One modern environmental factor that contributes to changes in eating behaviour is the widespread use of artificial light. The relative independence from the natural light-dark (LD) cycle, allows people to eat and engage in activities until late in the evening and at night. Artificial light has also led to an increase in nighttime sky glow and to the transformation of nightscapes. More than ninety-nine percent of the United States (US) and European Union (EU) population, and about two-thirds of the world population lives in areas where the night sky is illuminated above the threshold for light pollution (artificial sky brightness greater than ten percent of the natural night sky brightness above 45° of elevation). Moreover, satellite data shows that seventy percent of the US population and one-half of the European population can no longer see the Milky Way, even under the best conditions (3). Cinzano et al. calculated that only forty percent of Americans live in a location where it becomes sufficiently dark at night for the human eye to make a complete transition from cone to rod vision (3). Despite the benefits for socio-economic development, changes in LD environment may have adverse effects on humans and wildlife (4). In animals, light pollution leads to behavioral and physiological adaptations, such as alterations in orientation, survivorship, reproductive success, and visual communication (5, 6).

Interestingly, in humans, the increase in artificial light exposure parallels the increase in obesity prevalence with substantial evidence for additional adverse metabolic effects of increased exposure to artificial light (7). Availability of artificial light enables people to eat at unusual feeding times, and since metabolic responses to a meal are time-of-day-dependent, this might negatively affect metabolism (8). Furthermore, light exposure at inappropriate times itself may have adverse consequences for energy metabolism via changes in the biological clock and enhance the negative effects of eating at the wrong time of day (9). In addition to greater exposure to artificial light, daytime natural light exposure is often decreased since people tend to stay inside with lower light intensities.

Light synchronizes the central circadian clock

The SCN is comprises of about 20.000 pacemaker neurons (15). The single-cell circadian oscillators are regulated by a molecular feedback mechanism that maintains a 24h rhythm. The transcription factors CLOCK and ARNTL/BMAL1 represent the positive limb of this molecular clock and induce the transcription of the factors CRY and PER, representing the negative limb of the clock by inhibiting their own transcription (16). Since the endogenous period of the SCN oscillation is not exactly 24h, it must be synchronized to the external environment. Retinal light is the dominant environmental Zeitgeber for the phase entrainment of circadian oscillators (17). In addition to rods and cones, the retina consists of intrinsically photosensitive retinal ganglion cells (ipRGCs) that contain the photopigment melanopsin (18). These ipRGCs directly innervate
the SCN via the retinohypothalamic tract (18-22). The geniculohypothalamic tract, originating in the intergeniculate leaflet (IGL), provides a second route for photic information of the SCN clock (23). ipRGCs are sensitive to a range of wavelengths, with a maximum sensitivity in the short-wavelength (blue) domain of visible light (24). Animal studies have shown that one single light pulse shifted clock gene rhythms in the SCN and induced a behavioral phase-shift (25). In humans, one single pulse of bright light induced a phase advance or a phase delay in the plasma profile of the dark hormone melatonin, depending upon the circadian phase at which the light exposure occurred (26, 27). Exposure to early morning room light results in a phase advance of the endogenous core body temperature cycle, while late evening light before bedtime has a phase-delaying effect on the circadian pacemaker (28). The relationship between light intensity and the circadian rhythm response follows a nonlinear function, with even low intensity light (100 lux) being able to phase shift the circadian clock (29). Zeitzer et al showed that exposure to a single episode of 100 lux of evening bright light generates half of the maximal phase-delaying response observed after a light stimulus of 9000 lux (29).

The SCN regulates food intake and glucose metabolism

Feeding behaviour has a clear day/night rhythm which is influenced by the LD cycle (30, 31) and disrupted in SCN-lesioned animals (32, 33). Different hypothalamic projection areas of the SCN are involved in regulating feeding behaviour, including the paraventricular nucleus of the hypothalamus (PVN), the lateral hypothalamus (LH) and the arcuate nucleus (ARC) (34). Within the ARC, Neuropeptide Y (NPY) and alpha-Melanocyte-stimulating hormone (α-MSH) neurons are known to be involved in feeding behaviour (35). In the LH, expression of the orexigenic neuropeptide orexin (also known as hypocretin) demonstrates a daily rhythm (36, 37). In addition, indirect projections from the SCN to cortico-limbic areas exist (38). Since the cortico-limbic area is important for signaling reward, the rhythmicity of the dopamine system within the cortico-limbic system points to a role for the biological clock in food reward (39).

In addition to daily rhythms in feeding behaviour, daily rhythms in glucose metabolism have also been described in both humans and rodents. Blood glucose concentrations and glucose tolerance fluctuate over the day/night cycle with a peak in circulating glucose shortly before awakening, just before the active period (40, 41). In rodents, this rhythm is independent of food intake (42, 43), depends on an intact SCN (42, 44), and has a 12h difference between nocturnal and diurnal species. Additionally, in healthy humans, glucose tolerance possesses a diurnal variation, with lower glucose tolerance in the afternoon compared to the morning (40, 45, 46). This effect has been explained by the diurnal variation in insulin sensitivity and insulin secretion (45, 47, 48) with insulin sensitivity of peripheral tissues and insulin secretion both reduced in the evening (40). To generate these daily rhythms in glucose metabolism, the SCN influences both the autonomic nervous system (ANS) and secretion of glucoregulatory
hormones. Anatomical tracing experiments revealed that there are neuronal connections between the SCN and the liver, and the SCN and the pancreas (49, 50). These connections could be involved in the rhythms of glucose metabolism by affecting, for example, hepatic glucose production and (meal-induced) insulin secretion. The involvement of liver innervation in SCN-mediated rhythms in plasma glucose concentrations was demonstrated by hepatic sympathetic denervation studies, showing that the SCN needs an intact sympathetic input to the liver to generate a daily rhythm in plasma glucose concentrations (51).

The SCN does not directly innervate autonomic motor neurons in the brainstem or spinal cord, but transmits its signal to other areas within the hypothalamus. One such example is the PVN, which receives signals from the SCN and has extensive projections to sympathetic and parasympathetic motor neurons in the spinal cord and brainstem, respectively (52). The functional importance of this SCN–PVN connection in controlling plasma glucose concentrations was revealed by administering different SCN transmitter agonists and antagonists into the vicinity of the PVN (51). Another hypothalamic area receiving input from the SCN is the LH, particularly the orexin neurons. Orexin affects both glucose production and insulin sensitivity (53, 54) and with its circadian rhythmicity could be an important mechanism for the SCN to influence glucose metabolism.

In addition to the involvement of the ANS, glucose metabolism can also be influenced by the release of hormones such as insulin, glucagon, and corticosterone. The magnitude of the endocrine response to a glucose or exercise challenge varies over the activity/inactivity cycle. For example, a marked effect of time of day on neuroendocrine responses to prolonged moderate exercise was found in healthy volunteers (55) and an oral glucose load in the early morning hours produces a higher insulin response compared to the evening or afternoon (45, 46). Similarly, in rats with meals equally distributed over the LD-cycle, the insulin responses varied based on the time of the day the meal was consumed, despite equal meal sizes (56). As locomotor activity is not affected by equally distributing meals throughout the day and maintains its rhythmicity, it can be concluded that it is not a change in activity that affects insulin sensitivity and insulin responses (56). In addition, SCN-lesion studies showed this variation in endocrine responses to be dependent on a functional SCN (41).

Although it is clear that the SCN plays a key role in the regulation of glucose metabolism, circadian oscillators are not only localized in the SCN but also in other brain regions and peripheral tissues involved in energy metabolism, including the pancreas (57), gut (58-60), liver (61-63), skeletal muscle (64), and adipose tissue (65-68). Peripheral clocks do not receive light input directly, but are synchronized by the SCN. Although the precise mechanism remains to be elucidated, there are several pathways through which light exposure (via the SCN) could entrain peripheral organs and indirectly affect energy metabolism. Light signals transmitted to the SCN might be forwarded through the ANS (49, 50, 69, 70), circulating hormones, or metabolic signals to entrain the peripheral clocks (61, 71).
The effect of light on food intake, body weight, and glucose metabolism in animals

Many studies have investigated the effect of chronically altered LD schedules on food intake, body weight, and glucose metabolism in nocturnal rodents. In mice, continuous light exposure has been shown to cause obesity and impaired glucose tolerance (72, 73). In one study, increased body weight gain under constant light conditions was partly due to increased food intake, but also due to a reduction in energy expenditure (73). Another study also showed increased body weight with constant light, but without differences in total food intake or daily locomotor activity, and energy expenditure was not measured in this study (72). Interestingly, a recent study in mice found that continuous light exposure did not affect total body weight but instead increased adiposity associated with reduced brown adipose tissue activity (74). In contrast to mice, the effect of continuous bright light on body weight in rats is moderate (75, 76) or absent (77, 78). However, in rats, continuous bright light exposure may reduce glucose-mediated pancreatic insulin secretion (79) and in diabetes-prone transgenic human islet amyloid polypeptide (HIP) rats, constant bright light causes accelerated loss of beta cell function and development of diabetes (78). Taken together, these studies suggest that disturbing the endogenous timing system by exposure to continuous bright light causes insulin resistance by inducing obesity/adiposity in mice, while in genetically susceptible rats bright light causes diabetes by reducing pancreatic insulin secretion.

Obviously, continuous bright light exposure is not frequently encountered outside the laboratory. In real life, many humans and animals are exposed to dim light at night when the natural sky is dark, either via intentional illumination or unintentional artificial light pollution. Nelson’s group reported that in Swiss Webster mice, exposure to 5 lux dim light at night caused obesity and diabetes despite similar or reduced total food intake compared to control animals (72, 80-82). This was explained by increased daytime food intake (72) and decreased whole body total energy expenditure (82). The effect of dim light at night on body weight gain increased when mice were fed a high fat diet (80) and the metabolic disruptions were reversible when the mice returned to their normal LD cycle (83). The metabolic effects of dim light at night were recently reviewed more extensively elsewhere (7).

In addition the effects of increased light exposure, repeated shifts of the LD cycle may also cause obesity (84) and diabetes (85) in mice, without significant effect on total food intake or total locomotor activity. In rats, however, effects of repeated LD shifts seem to be strain dependent; in Long Evans (86) and Sprague Dawley (78) rats, repeated shifts do not affect body weight, whereas in F344 (87) and diabetes-prone HIP rats (78), repeated shifts do cause increased body weight gain. In sheep, representing a larger diurnal mammal, repeated LD shifts did not affect body weight or glucose tolerance (88). Currently, repeated LD shifts are often used as a rodent model for shift-work in humans, a condition known to affect body weight and energy metabolism. For a systematic review on rodent
shiftwork models see (89). Finally, although few studies have investigated the acute effects of light on metabolism, it is well established that rats respond to a light pulse during the dark period by directly decreasing food intake (30). For a complete overview of the effect of light on food intake, body weight and glucose metabolism in animals see Table 1.

Among the hormones affected by light are the glucoregulatory hormones corticosterone (i.e. cortisol in humans) and melatonin. SCN output modulates the secretion of corticosterone via a neuroendocrine pathway involving the release of adrenocorticotropic hormone (ACTH) from the pituitary (i.e., the hypothalamic-pituitary-adrenal axis) and via a neural pathway involving sympathetic innervation of the adrenal gland (71). Plasma corticosterone levels have a strong diurnal rhythm, with a sharp peak near habitual wake time (90). Light stimulates the secretion of corticosterone directly via sympathetic innervation (91, 92). Another hormone involved in energy metabolism is melatonin, which is secreted by the pineal gland and has a strong diurnal rhythm with a peak during the dark period (93). Nocturnal exposure to light suppresses plasma melatonin levels (94). Daily treatment with melatonin reduces body weight increase in response to a high-fat diet, independent of total food consumption and improves plasma glucose levels, although data on energy expenditure were not reported (95-98).

A direct effect of light on glucose metabolism is to be expected, given that 1) light directly affects activity of orexin neurons (99), 2) pre-autonomic connections between the SCN and the PVN regulate hepatic glucose production and meal-induced insulin secretion through the ANS , 3) a light pulse acutely decreases efferent vagal activity to pancreas and liver in anesthetized rats (100), 4) a light pulse acutely increases the hepatic expression of PEPCK in rats (92), and 5) light directly affects glucocorticoid and melatonin secretion (as described above). However, direct effects of light exposure on glucose metabolism have never been shown.

Although nocturnal rodents display a 12h phase shift compared to humans, the function of the circadian timing system and mechanisms of the molecular clock are very similar. The daily rhythms of gene expression and electrophysiological activity as well as the substructure of the SCN are similar between nocturnal and diurnal species (101), but the downstream pathways involved in the functional output of the SCN are often reversed. For example, in nocturnal rodents, exposure to light at night reduces activity, but increases activity in diurnal species (102). At which level of the downstream pathways this 12h switch is occurring is not clear yet, although for the corticosterone rhythm this may be at the level of the subPVN and dorsomedial hypothalamic nucleus (DMH) (103).

In conclusion, animal studies emphasize the intricate relationship between acute and chronic light exposure and daily rhythms of activity, food intake, and glucose tolerance. Moreover, continuous bright light exposure (24h) and dim light at night, as well as exposure to repeated LD shifts all affect body weight and energy metabolism.

In line with the results from animal studies, there are also data from studies in humans suggesting that light exposure affects food intake, body weight and glucose metabolism which will be discussed in the next part.
The effect of light on food intake, body weight and glucose metabolism in humans

A recent report demonstrated that evening bright light exposure increases appetite (104). Studying the SCN in humans is difficult, and thus melatonin activity is studied instead, as an indirect indicator of SCN activity. Notably, chronically reduced melatonin levels are associated with obesity and type 2 diabetes (105). Little is known about the direct effects of melatonin treatment on food intake and body weight. In humans, however, one study found a negative association between melatonin supplements and BMI in obese women (106). In addition to possible effects on food intake, melatonin might play a role in the development of type 2 diabetes, since melatonin receptors are expressed on pancreatic beta cells (107) and polymorphisms in the melatonin receptor are associated with an increased risk of developing type 2 diabetes (108). To our knowledge, until now no studies have yet investigated the direct effects of acute light exposure on human glucose metabolism.

Long-term light intervention studies in humans are difficult to perform and therefore most data on the relationship between light exposure, food intake, and metabolism are derived from observational studies. In the home setting, bedroom light intensity had a positive correlation with the prevalence of obesity (109, 110) and evening artificial light intensity showed a positive correlation with the incidence of type 2 diabetes (111). Furthermore, daytime light exposure was a positively correlated with BMI (112).

Since the economic and industrial revolutions, more than 20% of the working population performs shift work in order to optimize productivity and flexibility (113) and shift workers are at increased risk of developing obesity and type 2 diabetes (114-117). Although several observational studies found an association between shift work and metabolic disease, evidence for a causal relationship between light exposure at an inappropriate time of the day and metabolic disturbances is limited. Furthermore, in shift workers, several other factors involved in metabolism might be changed, such as diet composition, timing and frequency of food intake, exercise, and sleep. For example, timing of meals rather than their total food intake was affected by shift works (118), and night shift workers reported lower meal frequency, but increased prevalence to high-energy snacks (119, 120). Furthermore, shift workers showed problems maintaining physical fitness and reported increased general fatigue as main reason (121, 122). These data fit many studies showing reduced sleep and increased sleepiness in night shift workers (123, 124). Nevertheless, data on light intensity were not reported in these studies. Since light is the dominant synchronizer for the central clock, the use of artificial light at an inappropriate time of the day could lead to chronodisruption: desynchronization of the internal circadian rhythms and the 24h environmental cycles. Chronodisruption is associated with metabolic disturbances and even permanent night workers showed only partial adaptation in their 24h rhythm of plasma levels of glucose and insulin (125). Detailed studies, however, on the effects of artificial light exposure at the home setting, or the length of artificial light exposure of shift workers have not been performed.
As changes in duration and intensity of sunlight exposure are part of the defining features of the seasons, seasonal patterns in metabolism also suggest metabolic effects of light. The incidence of type 2 diabetes has a seasonal pattern with a peak in March and a trough in August (126). Moreover, healthy subjects possess a seasonal pattern in glycemia with higher glucose levels in the winter (127-130) and patients with type 2 diabetes have a seasonal pattern of increased HbA1c levels and resulting insulin requirements in the winter (131-133). Secondary to direct effects of light exposure on glucose metabolism, these seasonal patterns may be partly explained by seasonal variations in temperature, levels of physical activity, and food intake affecting body weight.

Taken together, these observational studies suggest that increased duration (but not intensity) of daytime light exposure is associated with metabolic health, whereas increased nighttime light exposure is associated with metabolic disease. Thus, these studies are consistent with rodent studies reporting adverse metabolic effects of light at night.

Interestingly, two case reports describe patients with seasonal affective disorder and insulin dependent diabetes that showed a strong reduction in insulin requirements shortly after the initiation of light therapy (134, 135). In addition, two small studies investigated the effects of long-term light treatment on body weight, although both had methodological challenges. A randomized controlled study in 25 obese subjects investigated the effect of adding one hour of 5000 lux bright light therapy per day to a 6-week moderate exercise program. Bright light therapy did not affect body weight, but induced a slight reduction in body fat mass as measured with bioelectrical impedance analysis (136). An other randomized controlled study in 34 obese female subjects investigated the effect of three weeks of 45 minutes of 1300 lux bright light therapy every morning on body weight and fat mass. Similarly, bright light therapy did not affect body weight, but induced a small reduction in fat mass. However food intake was not recorded (137). For a complete overview of the effect of light on food intake, body weight and glucose metabolism in humans see Table 2.

In addition to the long-term metabolic effects of light, it seems likely that light also has direct metabolic effects in humans, as light intensity directly affects ANS activity in humans (138-140). Furthermore, light inhibits melatonin secretion through the ANS (141) and light has been reported to affect glucocorticoid secretion, although some studies describe increased glucocorticoid levels due to bright light (142, 143), whereas another study describes decreased glucocorticoid levels (144, 145). These inconsistent findings might be related to the duration, intensity, or timing of the light exposure.

In summary, human observational studies indicate that the duration of daytime light exposure is associated with blood glucose levels and insulin requirements, whereas exposure to light at night, as well as performing shift work, is associated with obesity and diabetes. Two small intervention studies suggest that bright light therapy may affect body composition.
### Table 1. Overview of studies on the effect of light on food intake, body weight and glucose metabolism in animals

<table>
<thead>
<tr>
<th>Author/year of publication</th>
<th>Type animal</th>
<th>n per group</th>
<th>Cohort</th>
<th>Intervention</th>
<th>Light condition</th>
<th>Outcome</th>
<th>Main study results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coomans CP, 2013</td>
<td>mice</td>
<td>8</td>
<td>male</td>
<td>exposure to normal LD, constant dark or constant light cycle for 4 wks</td>
<td>12/12 LD cycle, constant light &gt;180 lx</td>
<td>body weight, food intake and energy metabolism</td>
<td>increased food intake and body weight and decreased energy expenditure after constant light exposure compared to LD</td>
</tr>
<tr>
<td>Fonken LK, 2010</td>
<td>mice</td>
<td>10</td>
<td>male</td>
<td>exposure to normal LD, constant light or light/dLAN light cycle for 8 wks</td>
<td>16/8 LD cycle, constant light 150 lx, dLAN 5 lx</td>
<td>body weight, food intake, locomotor activity, glucose tolerance</td>
<td>increased body weight and no difference in total food intake or daily locomotor activity after constant light exposure or dLAN exposure compared to LD</td>
</tr>
<tr>
<td>Kooijman S, 2015</td>
<td>mice</td>
<td>9</td>
<td>male</td>
<td>exposure to 12, 16, or 24 hrs light for 5 wks</td>
<td>12/12, 16/8, 24/0 LD cycle</td>
<td>body weight, body composition, food intake and brown adipose tissue activity</td>
<td>increased body fat mass without affecting food intake and reduced brown adipose tissue activity after prolonged day length of 16h and 24h light, compared to 12/12 LD</td>
</tr>
<tr>
<td>Natelson BH, 1983</td>
<td>rats</td>
<td>25</td>
<td>Dahl</td>
<td>exposure to normal LD or constant light cycle for 8 mnts</td>
<td>12/12 LD cycle</td>
<td>body weight and food intake</td>
<td>no difference in body weight and food intake after 5 months, but body weight slightly higher in constant light after 8 months compared to LD</td>
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<tr>
<td>Wideman CH, 2009</td>
<td>rats</td>
<td>12</td>
<td>Long Evans</td>
<td>exposure to normal LD, constant light or constant dark cycle for 17 days</td>
<td>12/12 LD cycle, constant light 450 lx</td>
<td>body weight, food intake, locomotor activity, melatonin levels</td>
<td>decreased food intake and melatonin levels and increased adiposity in constant light compared to LD</td>
</tr>
<tr>
<td>Study</td>
<td>Species</td>
<td>n</td>
<td>Gender/Genotype</td>
<td>Light Conditions</td>
<td>Measures</td>
<td>Results/Effects</td>
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<tr>
<td>Dauchy RT, 2010</td>
<td>rats</td>
<td>6</td>
<td>male Sprague-Dawley rats</td>
<td>exposure to normal LD, constant light or light/dLAN cycle for 6 wks</td>
<td>body weight, food intake, circadian rhythms in metabolic parameters</td>
<td>no difference in body weight and food intake. Diurnal rhythms in plasma glucose, lactic acid, and corticosterone concentrations were disrupted in dim and constant light compared to LD</td>
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<td>Gale JE, 2011</td>
<td>rats</td>
<td>5</td>
<td>WT Sprague Dawley and diabetes-prone HIP rats</td>
<td>exposure to normal LD, constant light or 6h advance of the LD cycle for 10 wks</td>
<td>body weight, insulin sensitivity</td>
<td>body weight slightly increased and accelerated development of diabetes in HIP rats in constant light compared to LD. No effect of constant light in WT rats</td>
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<tr>
<td>Qian J, 2013</td>
<td>rats</td>
<td>4</td>
<td>WT and Per1:LUC rats</td>
<td>exposure to normal LD or constant light cycle for 10 wks</td>
<td>insulin secretion in vitro in islets</td>
<td>constant light diminished glucose-stimulated insulin secretion compared to LD</td>
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<tr>
<td>Aubrecht TG, 2015</td>
<td>mice</td>
<td>9</td>
<td>female Swiss Webster mice</td>
<td>exposure to normal LD or light/dLAN cycle for 6 wks</td>
<td>body weight, food intake, locomotor activity</td>
<td>increased body weight and reduced food intake after exposure to dLAN compared to LD</td>
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<tr>
<td>Borniger JC, 2014</td>
<td>mice</td>
<td>8</td>
<td>male Swiss-Webster mice</td>
<td>exposure to normal LD or light/dLAN cycle for 2 wks</td>
<td>body weight, food intake, energy expenditure, locomotor activity</td>
<td>increased body weight, reduced energy expenditure and no differences in locomotor activity and total food intake after exposure to dLAN compared to LD</td>
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</tbody>
</table>
### Table 1. Overview of studies on the effect of light on food intake, body weight and glucose metabolism in animals - Continued

<table>
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<th>Type animal</th>
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<th>Intervention</th>
<th>Light condition</th>
<th>Outcome</th>
<th>Main study results</th>
</tr>
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<tbody>
<tr>
<td>Fonken LK, 2013</td>
<td>mice</td>
<td>7</td>
<td>Swiss-Webster mice</td>
<td>exposure to normal LD or light/dLAN cycle and fed either chow or HF diet for 4 wks</td>
<td>LD: 14h light (150 lx)/10h dark (0 lx); dLAN: 14h light (150 lx)/10h dim (5 lx)</td>
<td>body weight, glucose tolerance, insulin secretion and inflammation</td>
<td>increased weight gain, reduced glucose tolerance, increased insulin levels during the light phase and inflammation in HF diet after exposure to dLAN compared to LD cycle and chow</td>
</tr>
<tr>
<td>Fonken LK, 2013</td>
<td>mice</td>
<td>-</td>
<td>male Swiss-Webster mice</td>
<td>exposure to normal LD or dLAN cycle for 8 wks or LD for 4 wks followed by 4 wks of dLAN or dLAN for 4 wks followed by 4 weeks of LD</td>
<td>LD: 14h light (150 lx)/10h dark (0 lx); dLAN: 14h light (150 lx)/10h dim (5 lx)</td>
<td>body weight and glucose tolerance</td>
<td>increased body weight and decreased glucose tolerance after dLAN compared to LD. Transferred mice to dLAN gained more body weight compared to LD</td>
</tr>
<tr>
<td>Voigt RM, 2014</td>
<td>mice</td>
<td>-</td>
<td>male C57BL/6J mice</td>
<td>weekly phase reversals of the LD cycle and fed standard chow or a HF-HS diet for 12 wks</td>
<td>12/12 LD cycle</td>
<td>body weight and microbiome</td>
<td>increased body weight in phase shifted chow group compared to controls. Altered microbiota in HF-HS diet in conjunction with phase shifts</td>
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<tr>
<td>Oike H, 2015</td>
<td>mice</td>
<td>8</td>
<td>male C57BL/6J mice</td>
<td>exposure to normal LD or shift in LD cycles with an advance of 6 hrs twice weekly and ad libitum or restricted access to food</td>
<td>12/12 LD cycle</td>
<td>body weight, food intake and glucose tolerance</td>
<td>increased body weight, reduced glucose tolerance and no effect on food intake after advances in LD cycles compared to regular LD</td>
</tr>
<tr>
<td>Author</td>
<td>Species</td>
<td>N</td>
<td>Gender</td>
<td>Description</td>
<td>LD Cycle</td>
<td>Outcome</td>
<td>Notes</td>
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<td>Bartol-Munier I, 2006</td>
<td>rats</td>
<td>6</td>
<td>male</td>
<td>Long-Evans rats</td>
<td>12/12 LD cycle</td>
<td>body weight, glucose metabolism</td>
<td>Exposure to normal LD cycle or to 10h weekly shift in LD cycle and fed either LF or HF diet for 5 mnts. Shifted rats showed disturbed locomotor activity and impaired insulin regulation compared to LD.</td>
</tr>
<tr>
<td>Tsai LL, 2005</td>
<td>rats</td>
<td>8</td>
<td>male</td>
<td>F344 rats</td>
<td>12/12 LD cycle, 300 lx light phase</td>
<td>body weight, food intake, locomotor activity</td>
<td>Increased body weight and food intake and reduced locomotor activity during LD shifts compared to normal LD.</td>
</tr>
<tr>
<td>Varcoe TJ, 2014</td>
<td>sheep</td>
<td>7</td>
<td>female</td>
<td>Border Leicester × Merino female ewes</td>
<td>12/12 LD cycle</td>
<td>body weight and glucose tolerance</td>
<td>No difference in body weight and glucose tolerance between groups.</td>
</tr>
<tr>
<td>Plata-Salaman CR, 1987</td>
<td>rats</td>
<td>10</td>
<td>male</td>
<td>Wistar rats</td>
<td>lights on during nighttime (30min from 22:30 to 23:00 or from 22:58 to 23:28), Lights off during the daytime (2hr from 10:00 to 12:00)</td>
<td>food intake</td>
<td>Decreased food intake during lights on in the dark period and increased food intake during lights off in the light period.</td>
</tr>
</tbody>
</table>

Abbreviation: LD = light/dark, LF = low fat, HF = high fat, HF-HS = high fat high sugar, dLAN = dim light at night, HIP = human isles amyloid polypeptide, lx = lux
<table>
<thead>
<tr>
<th>Author/ year of publication</th>
<th>M/F</th>
<th>Age (yr)</th>
<th>Subjects</th>
<th>Type of study</th>
<th>Intervention</th>
<th>Light condition</th>
<th>Outcome</th>
<th>Main study results</th>
</tr>
</thead>
<tbody>
<tr>
<td>AlBreiki BM, 2014</td>
<td>5/5</td>
<td>&gt;18</td>
<td>n=10 healthy subjects</td>
<td>cross-over intervention study</td>
<td>12h exposure to dim or bright light with one meal in the evening</td>
<td>dim: &lt;5 lx, bright: &gt;500 lx</td>
<td>appetite VAS scores</td>
<td>increased appetite scores after meal in bright light compared to dim light</td>
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<tr>
<td>Mantele S, 2012</td>
<td>25/0</td>
<td>&gt;18</td>
<td>n=8 lean healthy, n=10 obese non-diabetic and n=7 obese T2D subjects</td>
<td>observational</td>
<td>n.a.</td>
<td>lights on (440-825 lx) between 06:30-22:30 hrs and light off (0 lx) between 22:30-06:30 hrs</td>
<td>plasma melatonin and leptin levels</td>
<td>reduced nocturnal melatonin levels in obese-non-diabetic compared to T2D and lean subjects. 24-hr rhythm in leptin not different between groups</td>
</tr>
<tr>
<td>McFadden E, 2014</td>
<td>0/113.343</td>
<td>&gt;16</td>
<td>n=113.343 women</td>
<td>cross-sectional</td>
<td>n.a.</td>
<td>n.a.</td>
<td>body weight, LAN (questionnaire)</td>
<td>positive correlation between obesity and LAN, independent of sleep duration and physical activity</td>
</tr>
<tr>
<td>Obayashi K, 2012</td>
<td>247/281</td>
<td>&gt;60</td>
<td>n=528 elderly subjects</td>
<td>cross-sectional</td>
<td>n.a.</td>
<td>n.a.</td>
<td>light exposure, body weight and glucose metabolism</td>
<td>increased body weight and impaired lipid parameter in LAN group compared to no LAN</td>
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<tr>
<td>Obayashi K, 2014</td>
<td>238/299</td>
<td>&gt;60</td>
<td>n=537 elderly subjects</td>
<td>cross-sectional</td>
<td>n.a.</td>
<td>n.a.</td>
<td>light exposure, body weight and glucose metabolism</td>
<td>positive correlation between diabetes and evening light exposure</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Age</td>
<td>Sample Size</td>
<td>Study Design</td>
<td>Outcome Measures</td>
<td>Results/Findings</td>
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<td>Reid KJ, 2014</td>
<td>24/30</td>
<td>&gt;18</td>
<td>n=54 healthy subjects</td>
<td>cross-sectional</td>
<td>body weight, dietary intake, activity and light exposure</td>
<td>Positive correlation between BMI and daytime light exposure independent of sleep</td>
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<tr>
<td>Simon C, 2000</td>
<td>16/0</td>
<td>&gt;18</td>
<td>n=8 night workers, n=8 day-active subjects</td>
<td>intervention</td>
<td>wakefulness period: &lt;100 lx</td>
<td>Night workers only partially adapted their 24-hr rhythms of plasma glucose and insulin secretion compared to day active subjects</td>
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<tr>
<td>Doro P, 2006</td>
<td>not reported</td>
<td>n=26695 T2D subjects</td>
<td>cohort</td>
<td>n.a.</td>
<td>incidence of T2D</td>
<td>Seasonal pattern in incidence of T2D, with a peak in March and trough in August</td>
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<td>Jarrett RJ, 1984</td>
<td>not reported</td>
<td>&gt;45</td>
<td>n=3346 healthy subjects</td>
<td>cohort</td>
<td>n.a.</td>
<td>seasonal variation in blood glucose levels</td>
<td>Seasonal variation in glucose levels, with a peak in winter and trough in spring</td>
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<tr>
<td>MacDonald MJ, 1987</td>
<td>15/20</td>
<td>&gt;6</td>
<td>n=35 non diabetic children and adults</td>
<td>cohort</td>
<td>n.a.</td>
<td>seasonal variation in HbA1c levels</td>
<td>Seasonal variation in HbA1c levels, with a peak in winter and trough in summer</td>
<td></td>
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<tr>
<td>Author/year of publication</td>
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<tr>
<td>Marti-Soler H, 2014</td>
<td>117763/120216</td>
<td>&gt;18</td>
<td>n=237979 subjects</td>
<td>meta-analysis of cohort studies</td>
<td>n.a.</td>
<td>n.a.</td>
<td>seasonal variation in BMI and plasma glucose levels</td>
<td>seasonal variation in BMI and glycemia, with a peak in winter and trough in summer</td>
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<tr>
<td>Suarez L, 1982</td>
<td>not reported</td>
<td>&gt;20</td>
<td>n= 4541 subjects</td>
<td>cohort</td>
<td>n.a.</td>
<td>n.a.</td>
<td>seasonal variation in fasting plasma glucose levels</td>
<td>seasonal variation in plasma glucose levels, with a peak in winter and trough in summer</td>
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<tr>
<td>Ishii H, 2001</td>
<td>12/27</td>
<td>&gt;18</td>
<td>n= 39 T2D subjects</td>
<td>cohort</td>
<td>n.a.</td>
<td>n.a.</td>
<td>seasonal variation in HbA1c levels</td>
<td>seasonal variation in HbA1c levels, with peak in winter and trough in summer</td>
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<tr>
<td>Sohmiya M, 2004</td>
<td>11/0</td>
<td>&gt;18</td>
<td>n=11 insulin dependent T2D subjects</td>
<td>cohort</td>
<td>n.a.</td>
<td>n.a.</td>
<td>seasonal variation in HbA1c levels</td>
<td>seasonal variation in HbA1c levels, with peak in winter and trough in summer</td>
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<tr>
<td>Tseng CL, 2005</td>
<td>270.227/15.478</td>
<td>&gt;18</td>
<td>n= 285705 veterans with T2D</td>
<td>cohort</td>
<td>n.a.</td>
<td>n.a.</td>
<td>seasonal variation in HbA1c levels over 2 yrs</td>
<td>seasonal variation in HbA1c levels, with peak in March to April and trough September</td>
</tr>
<tr>
<td>Author</td>
<td>Year</td>
<td>Gender</td>
<td>Age</td>
<td>Sample Size</td>
<td>Study Design</td>
<td>Intervention Duration</td>
<td>Light Intensity</td>
<td>Outcome Measures</td>
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<tr>
<td>Allen NH, 1992</td>
<td>1/0</td>
<td>46</td>
<td></td>
<td>n=1 man</td>
<td>case report</td>
<td>1 wk of bright light phototherapy</td>
<td>not reported</td>
<td>insulin sensitivity and mental state</td>
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<tr>
<td>Nieuwenhuis RF, 2009</td>
<td>0/1</td>
<td>20</td>
<td></td>
<td>n=1 women</td>
<td>case report</td>
<td>10 sessions of bright light phototherapy</td>
<td>10.000 lx 30min/day</td>
<td>blood glucose levels and mental state</td>
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<tr>
<td>Dunai A, 2007</td>
<td>5/24</td>
<td>&gt;18</td>
<td></td>
<td>n=29 overweight or obese subjects</td>
<td>randomized controlled intervention study</td>
<td>exercise program with or without bright light phototherapy for 6 wks</td>
<td>5000 lx 60min/day</td>
<td>body weight and body composition</td>
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<tr>
<td>Danilenko KV, 2013</td>
<td>0/34</td>
<td>&gt;18</td>
<td></td>
<td>n=34 overweight women</td>
<td>randomized controlled cross-over study</td>
<td>bright light phototherapy or placebo (deactivated ion generator) for 3 wks</td>
<td>1300 lx 45min/day</td>
<td>body weight, body composition and appetite scores</td>
</tr>
</tbody>
</table>

Abbreviations: M = male, F = female, T2D = type 2 diabetes, SAD = seasonal affective disorder, VAS = visual analog scale, LAN = light at night, lx = lux
**Conclusion**

In this review we describe studies in animals and humans investigating the relationship between light, the circadian clock system, food intake, and metabolism. Taken together, the evidence, although mostly derived from rodent studies, suggests that living in synchrony with the natural daily LD cycle promotes metabolic health and that increased exposure to artificial light at unnatural times of day may have adverse metabolic effects on metabolism, feeding behavior, and body weight. So far, only two randomized controlled intervention studies in humans have investigated the effect of light therapy on body weight and found very subtle effects on body composition (136, 137). Currently, we are aware of one ongoing randomized controlled trial investigating the effects of light therapy on diabetes regulation in depressed patients with type 2 diabetes (146). It is of utmost importance to continue the effort to translate the rapidly expanding in depth knowledge of the relationship between light, circadian rhythms, and metabolism in nocturnal rodents into relevant diurnal rodent and human intervention studies. Reducing the negative side effects of the extensive use of artificial light in humans might be useful in the prevention of metabolic disease.
References


