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Symposium 2: Metabolic and endocrine mechanisms

Nutrition in the spotlight: metabolic effects of environmental light

Ruth I. Versteeg[1], Dirk J. Stenvers[1], Andries Kalsbeek[1,2], Peter H. Bisschop[1], Mireille J. Serlie[1] and Susanne E. la Fleur[1]*

[1]*Department of Endocrinology & Metabolism, Academic Medical Center, University of Amsterdam, Meibergdreef 9, F2-154, 1105 AZ Amsterdam-Zuidoost, The Netherlands*
[2]*Hypothalamic Integration Mechanisms, Netherlands Institute for Neuroscience, Royal Netherlands Academy of Arts and Sciences, Amsterdam, The Netherlands*

Use of artificial light resulted in relative independence from the natural light–dark (LD) cycle, allowing human subjects 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 human subjects. We propose that living in synchrony with the natural daily LD 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 human subjects might be useful in the prevention of metabolic disease.

Artificial light: Circadian: Glucose metabolism: Obesity

Changes in artificial light exposure

Obesity is an increasing health problem and is associated with the development of type 2 diabetes and CVD[1]. The pathophysiology of obesity is multifactorial, with the 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 99% of the US and 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 10% of the natural night sky brightness above 45° elevation). Moreover, satellite data show that 70% of the US population and 50% of the European population can no longer see the Milky Way, even under the best conditions[3]. Cinzano *et al.*[3] calculated that only 40% 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. Despite the benefits for

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socio-economic development, changes in LD environment may have adverse effects on human subjects and wildlife[4]. In animals, light pollution leads to behavioural and physiological adaptations, such as alterations in orientation, survivorship, reproductive success and visual communication[5,6].

Interestingly, in human subjects, 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 synchronises the central circadian clock

For most organisms, a day is characterised by two distinct behavioural phases: one phase with activity and feeding behaviour and one phase with resting/sleeping and fasting behaviour. During the active period, ingested nutrients provide fuel for energy production and excess energy is stored. During the resting period, energy stores are mobilised to sustain metabolic homeostasis. The hypothalamus controls a vast array of the behavioural and physiological processes that alternate between the behavioural phases, including feeding, but also sleep and arousal, thermoregulation and energy expenditure[10,11]. These activity/feeding and resting/fasting periods are defined by a molecular mechanism in the central clock that is located in the suprachiasmatic nuclei (SCN) of the hypothalamus[12]. This central clock generates a biological rhythm of approximately 24 h (hence 'circadian' from 'circa diem', approximately 1 d) and lesions of the SCN result in loss of all circadian rhythms, including those in locomotor activity, food intake and drinking activity[13,14].

The SCN comprises about 20 000 pacemaker neurons[15]. The single-cell circadian oscillators are regulated by a molecular feedback mechanism that maintains a 24 h 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 24 h, it must be synchronised 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 that contain the photopigment melanopsin[18]. These intrinsically photosensitive retinal ganglion cells directly

innervate the SCN via the retinohypothalamic tract[18–22]. The geniculohypothalamic tract, originating in the intergeniculate leaflet, provides a second route for photic information of the SCN clock[23]. Intrinsically photosensitive retinal ganglion cells 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 behavioural phase shift[25]. In human subjects, 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.*[29] 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.

Suprachiasmatic nuclei 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 and the arcuate nucleus[34]. Within the arcuate nucleus, neuropeptide Y and α-melanocyte-stimulating hormone neurons are known to be involved in feeding behaviour[35]. In the lateral hypothalamus, 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 signalling 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 human subjects 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 12 h difference between nocturnal and diurnal species. In addition, in healthy human subjects, glucose tolerance possesses a diurnal variation, with lower glucose tolerance in the afternoon compared with 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 lateral hypothalamus, 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 with 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 localised 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 synchronised 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].

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 rats, constant bright light causes accelerated loss of β 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 human subjects 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 with 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 to 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, the 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 human islet amyloid polypeptide 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 human subjects, 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 human subjects) and melatonin. SCN output modulates the secretion of corticosterone via a neuroendocrine pathway involving the release of adrenocorticotropic hormone 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 the 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 anaesthetised rats[100]; (4) a light pulse acutely decreases the hepatic expression of phosphoenolpyruvate carboxykinase in rats[92]; and (5) light directly affects glucocorticoid and melatonin secretion (as described earlier). However, the direct effects of light exposure on glucose metabolism have never been shown.

Although nocturnal rodents display a 12 h phase shift compared with human subjects, 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 12 h 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[103].

In conclusion, animal studies emphasise the intricate relationship between acute and chronic light exposures and daily rhythms of activity, food intake and glucose tolerance. Moreover, continuous bright light exposure (24 h) 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 human subjects suggesting that light exposure affects food intake, body weight and glucose metabolism which will be discussed in the following section.

Effect of light on food intake, body weight and glucose metabolism in human subjects

A recent report demonstrated that evening bright light exposure increases appetite[104]. Studying the SCN in human subjects 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 human subjects, 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 β 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 human subjects 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 positively correlated with BMI[112].

Since the economic and industrial revolutions, more than 20 % of the working population performs shift work in order to optimise 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

Table 1. Overview of studies on the effect of light on food intake, body weight and glucose metabolism in animals

Reference	Type animal	n per group	Cohort	Intervention	Light condition	Outcome	Main study results
Coomans et al.[73]	Mice	8	Male C57Bl/6J mice	Exposure to normal LD, constant dark or constant light cycle for 4 weeks	12/12 LD cycle, constant light >180 lx	Body weight, food intake and energy metabolism	Increased food intake and body weight and decreased energy expenditure after constant light exposure compared with LD
Fonken et al.[72]	Mice	10	Male Swiss–Webster mice	Exposure to normal LD, constant light or light/dLAN light cycle for 8 weeks	16/8 LD cycle, constant light 150 lx, dLAN 5 lx	Body weight, food intake, locomotor activity and glucose tolerance	Increased body weight and no difference in total food intake or daily locomotor activity after constant light exposure or dLAN exposure compared with LD
Kooijman et al.[74]	Mice	9	Male C57BL/6J mice	Exposure to 12, 16 or 24 h light for 5 weeks	12/12, 16/8, 24/0 LD cycle	Body weight, body composition, food intake and brown adipose tissue activity	Increased body fat mass without affecting food intake and reduced brown adipose tissue activity after prolonged day length of 16 and 24 h light, compared with 12/12 LD
Natelson et al.[75]	Rats	25	Dahl rats	Exposure to normal LD or constant light cycle for 8 min	12/12 LD cycle	Body weight and food intake	No difference in body weight and food intake after 5 months, but body weight slightly higher in constant light after 8 months compared with LD
Wideman & Murphy[76]	Rats	12	Long Evans rats	Exposure to normal LD, constant light or constant dark cycle for 17 d	12/12 LD cycle, constant light 450 lx	Body weight, food intake, locomotor activity and melatonin levels	Decreased food intake and melatonin levels and increased adiposity in constant light compared with LD
Dauchy et al.[77]	Rats	6	Male Sprague Dawley rats	Exposure to normal LD, constant light or light/dLAN cycle for 6 weeks	12/12 LD cycle, constant light 300 lx, dLAN max 0·2 lx	Body weight, food intake and circadian rhythms in metabolic parameters	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 with LD
Gale et al.[78]	Rats	5	WT Sprague Dawley and diabetes-prone rats	Exposure to normal LD, constant light or 6 h advance of the LD cycle for 10 weeks	12/12 LD cycle, constant light >100 lx	Body weight and insulin sensitivity	Body weight slightly increased and accelerated development of diabetes in HIP rats in constant light compared with LD. No effect of constant light in WT rats
Qian et al.[79]	Rats	4	WT and Per-1:LUC rats	Exposure to normal LD or constant light cycle for 10 weeks	12/12 LD cycle	Insulin secretion in vitro in islets	Constant light diminished glucose-stimulated insulin secretion compared with LD
Aubrecht et al.[81]	Mice	9	Female Swiss Webster mice	Exposure to normal LD or light/dLAN cycle for 6 weeks	LD: 16 h light 150 lx/8 h dark 0 lx; dLAN: 16 h light 150 lx/8 h dim light 5 lx	Body weight, food intake and locomotor activity	Increased body weight and reduced food intake after exposure to dLAN compared with LD
Borniger et al.[82]	Mice	8	Male Swiss-Webster mice	Exposure to normal LD or light/dLAN cycle for 2 weeks	LD: 14 h light (150 lx)/10 h dark (0 lx); dLAN: 14 h light (150 lx/10 h dim light (5 lx)	Body weight, food intake, energy expenditure and locomotor activity	Increased body weight, reduced energy expenditure and no differences in locomotor activity and total food intake after exposure to dLAN compared with LD
Fonken et al.[80]	Mice	7	Swiss-Webster mice	Exposure to normal LD or light/dLAN cycle and fed either chow or HF diet for 4 weeks	LD: 14 h light (150 lx)/10 h dark (0 lx); dLAN: 14 h light (150 lx)/10 h dim (5 lx)	Body weight, glucose tolerance, insulin secretion and inflammation	Increased weight gain, reduced glucose tolerance, increased insulin levels during the light phase and inflammation in HF diet after exposure to dLAN compared with LD cycle and chow

Table 1. (*Cont*.)

Reference	Type animal	*n* per group	Cohort	Intervention	Light condition	Outcome	Main study results
Fonken et al.[83]	Mice	–	Male Swiss-Webster mice	Exposure to normal LD or dLAN cycle for 8 weeks or LD for 4 weeks followed by 4 weeks dLAN or dLAN for 4 weeks followed by 4 weeks LD	LD: 14 h light (150 lx)/10 h dark (0 lx); dLAN: 14 h light (150 lx)/10 h dim (5 lx)	Body weight and glucose tolerance	Increased body weight and decreased glucose tolerance after dLAN compared with LD. Transferred mice to dLAN gained more body weight compared with LD
Voigt et al.[84]	Mice	–	Male C57BL/6J mice	Weekly phase reversals of the LD cycle and fed standard chow or a HF–HS diet for 12 weeks	12/12 LD cycle	Body weight and microbiome	Increased body weight in phase shifted chow group compared with controls. Altered microbioma in HF–HS diet in conjunction with phase shifts
Oike et al.[85]	Mice	8	Male C57BL/6J mice	Exposure to normal LD or shift in LD cycles with an advance of 6 h twice weekly and *ad libitum* or restricted access to food	12/12 LD cycle	Body weight, food intake and glucose tolerance	Increased body weight, reduced glucose tolerance and no effect on food intake after advances in LD cycles compared with regular LD
Bartol-Munier et al.[86]	Rats	6	Male Long-Evans rats	Exposure to normal LD cycle or to 10 h weekly shift in LD cycle and fed either LF or HF diet for 5 min	12/12 LD cycle	Body weight, glucose metabolism	No difference in body weight. Shifted rats showed disturbed locomotor activity and impaired insulin regulation compared with LD
Tsai et al.[87]	Rats	8	Male F344 rats	Exposure to normal LD cycle or 12 h shift twice weekly for 13 weeks	12/12 LD cycle, 300 lx light phase	Body weight, food intake and locomotor activity	Increased body weight and food intake and reduced locomotor activity during LD shifts compared with normal LD
Varcoe et al.[88]	Sheep	7	Border Leicester × Merino female ewes	Exposure to normal LD cycle or 12 h shift twice weekly for 4 weeks	12/12 LD cycle	Body weight and glucose tolerance	No difference in body weight and glucose tolerance between groups
Plata-Salaman & Oomura[30]	Rats	10	Male Wistar rats	Exposure to normal LD or short-time lights on during dark period or short-time lights off during light period	Lights on during nighttime (30 min from 22:30 to 23:00 or from 22:58 to 23:28). Lights off during the daytime (2 h from 10:00 to 12:00	Food intake	Decreased food intake during lights on in the dark period and increased food intake during lights off in the light period

LD, light/dark; HF, high fat; LF, low fat; HF–HS, high fat/high sugar; dLAN, dim light at night; HIP, human isles amyloid polypeptide; lx, lux.

Table 2. Overview of studies on the effect of light on food intake, body weight and glucose metabolism in human subjects

Reference	M/F	Age (year)	Subjects	Type of study	Intervention	Light condition	Outcome	Main study results
AlBreiki et al.[104]	5/5	>18	n 10 healthy subjects	Cross-over intervention study	12 h exposure to dim or bright light with one meal in the evening	Dim: <5 lx, bright: >500 lx	Appetite VAS scores	Increased appetite scores after meal in bright light compared with dim light
Mantele et al.[105]	25/0	>18	n 8 lean healthy, n 10 obese non-diabetic and n 7 obese T2D subjects	Observational	n.a.	Lights on (440–825 lx) between 06:30 and 22:30 h and light off (0 lx) between 22:30 and 06:30 h	Plasma melatonin and leptin levels	Reduced nocturnal melatonin levels in obese-non-diabetic compared with T2D and lean subjects. 24-h rhythm in leptin not different between groups
McFadden et al.[109]	0/113·343	>16	n 113·343 women	Cross-sectional	n.a.	n.a.	Body weight, LAN (questionnaire)	Positive correlation between obesity and LAN, independent of sleep duration and physical activity
Obayashi et al.[110]	247/281	>60	n 528 elderly subjects	Cross-sectional	n.a.	n.a.	Light exposure, body weight and glucose metabolism	Increased body weight and impaired lipid parameter in LAN group compared with no LAN
Obayashi et al.[111]	238/299	>60	n 537 elderly subjects	Cross-sectional	n.a.	n.a.	Light exposure, body weight and glucose metabolism	Positive correlation between diabetes and evening light exposure
Reid et al.[112]	24/30	>18	n 54 healthy subjects	Cross-sectional	n.a.	n.a.	Body weight, dietary intake, activity and light exposure	Positive correlation between BMI and daytime light exposure independent of sleep
Simon et al.[126]	16/0	>18	n 8 night workers, n 8 day-active subjects	Intervention	Night workers were 24 h studied during their normal cycle and compared with day-active subjects studied once with nocturnal sleep and once with an 8 h-shifted-sleep	Wakefulness period: <100 lx	Plasma glucose and insulin levels	Night workers only partially adapted their 24-h rhythms of plasma glucose and insulin secretion compared with day active subjects
Doro et al.[127]	Not reported	Not reported	n 26 695 T2D subjects	Cohort	n.a.	n.a.	Incidence of T2D	Seasonal pattern in incidence of T2D, with a peak in March and trough in August
Jarrett et al.[129]	Not reported	>45	n 3346 healthy subjects	Cohort	n.a.	n.a.	Seasonal variation in blood glucose levels	Seasonal variation in glucose levels, with a peak in winter and trough in spring

Table 2. (*Cont.*)

Reference	M/F	Age (year)	Subjects	Type of study	Intervention	Light condition	Outcome	Main study results
MacDonald et al.[131]	15/20	>6	n 35 non diabetic children and adults	Cohort	n.a.	n.a.	Seasonal variation in HbA1c levels	Seasonal variation in HbA1c levels, with a peak in winter and trough in summer
Marti-Soler et al.[130]	117763/ 120216	>18	n 237 979 subjects	Meta-analysis of cohort studies	n.a.	n.a.	Seasonal variation in BMI and plasma glucose levels	Seasonal variation in BMI and glycaemia, with a peak winter and trough in summer
Suarez & Barrett-Connor[128]	Not reported	>20	n 4541 subjects	Cohort	n.a.	n.a.	Seasonal variation in fasting plasma glucose levels	Seasonal variation in plasma glucose levels, with a peak in winter and trough in summer
Ishii et al.[133]	12/27	>18	n 39 T2D subjects	Cohort	n.a.	n.a.	Seasonal variation in HbA1c levels	Seasonal variation in HbA1c levels, with peak in winter and trough in summer
Sohmiya et al.[134]	11/0	>18	n 11 insulin dependent T2D subjects	Cohort	n.a.	n.a.	Seasonal variation in HbA1c levels	Seasonal variation in HbA1c levels, with peak in winter and trough in summer
Tseng et al.[132]	270·227/ 15·478	>18	n 285 705 veterans with T2D	Cohort	n.a.	n.a.	Seasonal variation in HbA1c levels over 2 years	Seasonal variation in HbA1c levels, with peak in March to April and through September
Allen et al.[136]	1/0	46	n 1 man with insulin dependent T2D and SAD depression for 3 consecutive years	Case report	1 week of bright light phototherapy	Not reported	Insulin sensitivity and mental state	Improvement in insulin sensitivity and affective state after phototherapy
Nieuwenhuis et al.[135]	0/1	20	n 1 women with insulin dependent T2D and SAD	Case report	Ten sessions of bright light phototherapy	10 000 lx 30 min/d	Blood glucose levels and mental state	Decreased glucose levels, reduction in insulin requirement and improvement of affective state after phototherapy
Dunai et al.[137]	5/24	>18	n 29 overweight or obese subjects	Randomised controlled intervention study	Exercise program with or without bright light phototherapy for 6 weeks	5000 lx 60 min/d	Body weight and body composition	No difference in body weight and body fat mass slightly reduced after phototherapy compared with control
Danilenko et al.[138]	0/34	>18	n 34 overweight women	Randomised controlled cross-over study	Bright light phototherapy or placebo (deactivated ion generator) for 3 weeks	1300 lx 45 min/d	Body weight, body composition and appetite scores	Reduced body fat and appetite scores after phototherapy compared with placebo

M, male; F, female; T2D, type 2 diabetes; SAD, seasonal affective disorder; VAS, visual analogue scale; LAN, light at night; lx, lux.

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 the main reason[122,123]. These data fit many studies showing reduced sleep and increased sleepiness in night shift workers[124,125]. Nevertheless, data on light intensity were not reported in these studies. Since light is the dominant synchroniser for the central clock, the use of artificial light at an inappropriate time of the day could lead to chronodisruption: desynchronisation of the internal circadian rhythms and the 24 h environmental cycles. Chronodisruption is associated with metabolic disturbances and even permanent night workers showed only partial adaptation in their 24 h rhythm of plasma levels of glucose and insulin[126]. 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[127]. Moreover, healthy subjects possess a seasonal pattern in glycaemia with higher glucose levels in the winter[128–131] and patients with type 2 diabetes have a seasonal pattern of increased HbA1c levels and resulting insulin requirements in the winter[132–134]. 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[135,136]. In addition, two small studies investigated the effects of long-term light treatment on body weight, although both had methodological challenges. A randomised controlled study in twenty-five obese subjects investigated the effect of adding 1 h of 5000 lux bright light therapy daily to a 6-week moderate exercise programme. Bright light therapy did not affect body weight, but induced a slight reduction in body fat mass as measured by bioelectrical impedance analysis[137]. Another randomised controlled study in thirty-four obese female subjects investigated the effect of 3 weeks of 45 min 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[138]. For a complete overview of the effect of light on food intake, body weight and glucose metabolism in human subjects see Table 2.

In addition to the long-term metabolic effects of light, it seems likely that light also has direct metabolic effects in human subjects, as light intensity directly affects ANS activity in human subjects[139–141]. Furthermore, light inhibits melatonin secretion through the ANS[142] and light has been reported to affect glucocorticoid secretion, although some studies describe increased glucocorticoid levels due to bright light[143,144], whereas another study describes decreased glucocorticoid levels[145,146]. 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.

Conclusion

In this review, we describe studies in animals and human subjects 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 behaviour and body weight. So far, only two randomised controlled intervention studies in human subjects have investigated the effect of light therapy on body weight and found very subtle effects on body composition[137,138]. Currently, we are aware of one ongoing randomised controlled trial investigating the effects of light therapy on diabetes regulation in depressed patients with type 2 diabetes[147]. 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 human subjects might be useful in the prevention of metabolic disease.

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Conflict of interest

None.

Authorship

R. I. V. and D. J. S. wrote the manuscript. A. K., P. H. B., M. J. S. and S. E. F. reviewed the manuscript.

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