CIRCADIAN RHYTHMS IN ENDOCRINOLOGY AND METABOLISM

Circadian clocks and insulin resistance

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Abstract | Insulin resistance is a main determinant in the development of type 2 diabetes mellitus and a major cause of morbidity and mortality. The circadian timing system consists of a central brain clock in the hypothalamic suprachiasmatic nucleus and various peripheral tissue clocks. The circadian timing system is responsible for the coordination of many daily processes, including the daily rhythm in human glucose metabolism. The central clock regulates food intake, energy expenditure and whole-body insulin sensitivity, and these actions are further fine-tuned by local peripheral clocks. For instance, the peripheral clock in the gut regulates glucose absorption, peripheral clocks in muscle, adipose tissue and liver regulate local insulin sensitivity, and the peripheral clock in the pancreas regulates insulin secretion. Misalignment between different components of the circadian timing system and daily rhythms of sleep–wake behaviour or food intake as a result of genetic, environmental or behavioural factors might be an important contributor to the development of insulin resistance. Specifically, clock gene mutations, exposure to artificial light–dark cycles, disturbed sleep, shift work and social jet lag are factors that might contribute to circadian disruption. Here, we review the physiological links between circadian clocks, glucose metabolism and insulin sensitivity, and present current evidence for a relationship between circadian disruption and insulin resistance. We conclude by proposing several strategies that aim to use chronobiological knowledge to improve human metabolic health.

Insulin resistance in liver, muscle and adipose tissue is a pivotal pathophysiological process in the development of type 2 diabetes mellitus (T2DM), which has been designated as one of the four priority noncommunicable diseases by the WHO[1]. Major complications of T2DM are retinopathy, chronic kidney disease, neuropathy, peripheral vascular disease, myocardial infarction and stroke. The central approach in the prevention and treatment of insulin resistance is lifestyle modification. The second step is medication, with metformin being the cornerstone of the oral glucose-lowering drugs. If necessary, glycaemic control can be further improved with additional medication, including oral sulphonylureas, oral sodium–glucose cotransporter 2 (SGLT2) inhibitors, injectable glucagon-like peptide 1 (GLP1) receptor agonists or injectable insulin[2]. Traditionally, research has focused on the quantity and quality of physical activity, food intake and medication; however, circadian factors including the timing of light exposure, physical activity, food intake, medication and sleep–wake behaviour might also prove important for the prevention and treatment of insulin resistance.

The mammalian circadian timing system consists of a central brain clock in the hypothalamic suprachiasmatic nucleus (SCN), and peripheral clocks in other brain regions and tissues throughout the body, including muscle, adipose tissue and liver. The SCN receives a direct projection from the retina, via which environmental light synchronizes the approximately 24 h rhythm of the SCN with the exact 24 h rhythm of the environment (FIG. 1). The entrained timing signal from the SCN is forwarded via neural and hormonal signals and body temperature to the peripheral clocks. The molecular mechanism of the central and peripheral clocks is based on transcriptional-translational feedback loops, which are present in almost every cell of the human body.

In this Review, we describe the physiological links between circadian clocks, glucose metabolism and insulin sensitivity. We also present current evidence for the relationship between circadian disruption and insulin resistance, with a focus on human studies. Finally, we propose several strategies to implement chronobiological knowledge with the aim to improve human metabolic health. The chronobiology terms and metabolic terms we use are defined in BOX 1 and BOX 2, respectively.

Circadian control of insulin sensitivity

The circadian timing system

The mammalian circadian timing system is composed of a central pacemaker in the bilateral SCN of the anterior hypothalamus and a multitude of peripheral clocks in other brain areas and peripheral tissues (FIG. 2). The

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Key points

- The circadian timing system consists of a central brain clock in the hypothalamic suprachiasmatic nucleus and peripheral clocks in tissues, including the liver, muscle, adipose tissue and pancreas.
- Misalignment between different components of the circadian timing system and daily rhythms of sleep–wake behaviour and food intake might contribute to the development of insulin resistance.
- Strategies to improve metabolic health by circadian synchrony include modulating light exposure, modulating rhythmic behaviour and chronotherapy.
- Circadian molecules are a promising new treatment option for insulin resistance.

Period
The time difference between two consecutive peaks or troughs, or any other fixed point in the rhythm. In the case of daily or circadian rhythms, this period is exactly or approximately 24 h, respectively. The period of the rhythm in constant conditions is called the free-running period and is denoted by the Greek letter τ.

circadian timing system serves to prepare an organism for the alternating opportunities and challenges that go along with the rhythmic changes of the daily light–dark cycle. This concept is illustrated by the evolutionary advantage of an internal clock that matches the period duration of the environment, as demonstrated in cyanobacteria[3,4].

The discovery of the molecular mechanism that keeps these clocks functioning was awarded the 2017 Nobel Prize in Physiology or Medicine. The central feature of this molecular mechanism is the transcriptional–translational feedback loop (TTFL) involving the core clock genes: the period genes (*PER1*, *PER2* and *PER3*), cryptochrome genes (*CRY1* and *CRY2*), *ARNTL* (also known as *BMAL1*), *CLOCK* (or its orthologue *NPAS2*) and the genes encoding the nuclear receptors REV-ERB (*NR1D1* and *NR1D2*) and ROR (*RORA*, *RORB* and *RORC*). The rhythmic signal produced by this molecular clock has a period of approximately 24 h, which is a circadian period.

The period of the endogenous circadian timing system does not match the exact 24 h rhythm of the outside world and, therefore, has to be reset every day. Environmental light is the most important Zeitgeber for resetting the central pacemaker, reaching the SCN through a direct connection from intrinsically photosensitive retinal ganglion cells through the retinohypothalamic tract. The remaining clocks in the circadian timing system therefore depend predominantly on the SCN for entrainment to the light–dark cycle of the outside world.

The SCN sends its entrained timing signal to the peripheral tissue clocks through the autonomic nervous system, hormonal signals (including melatonin and cortisol), modulation of body temperature, and behavioural signals, such as physical activity and food intake. As most peripheral clocks do not receive direct light information, they are also sensitive to these other Zeitgebers. This scenario is especially true for peripheral clocks in metabolic tissues such as liver, white adipose tissue (WAT), brown adipose tissue (BAT), pancreas and muscle, which use the metabolic signals resulting from food intake for their entrainment[5–8] (FIG. 1).

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Circadian rhythm in glucose metabolism

In healthy humans, plasma glucose tolerance depends on the time of day of glucose ingestion, with glucose tolerance being higher in the morning than in the evening[9,10]. This diurnal rhythm in glucose tolerance is partly mediated by the diurnal rhythm in whole-body insulin sensitivity[11]. Moreover, the time-dependent glucose tolerance in healthy individuals is strongly mediated by the rhythm in pancreatic β-cell glucose sensitivity (that is, pancreatic glucose-induced insulin secretion), as demonstrated by studies that use hyperglycaemic clamping[12] and a triple-tracer mixed-meal technique[13]. However, because participants in these studies were sleeping at night and were awake during the day, it remains unclear to what extent these morning–evening differences are the result of behavioural and environmental differences or are caused by a direct influence of the circadian system. A 2015 study using a circadian misalignment protocol demonstrated that the diurnal rhythm in glucose tolerance is robustly regulated by the circadian timing system, separate from influences of behavioural and environmental changes[14]. Consistent with the results from diurnal studies, the endogenous circadian influence on glucose tolerance results from a stronger β-cell response in the circadian morning[14].

Clock control of insulin sensitivity

In this section, we discuss the clocks in the different tissues and organs that are involved in the control of glucose metabolism and explain their role in the regulation of insulin sensitivity and insulin secretion.

The central clock. The central clock in the SCN not only synchronizes the peripheral clocks described in the sections below, but also affects multiple processes that influence the diurnal rhythm in glucose metabolism, including the physiological daily rhythms in sleep–wake behaviour, food intake, hormone secretion, insulin sensitivity and energy expenditure (FIG. 3).

The SCN controls the daily rhythm in sleep–wake behaviour[15,16] via its connections with hypothalamic areas such as the subparaventricular zone, the ventrolateral preoptic area and the dorsomedial hypothalamus[17]. The SCN presumably also has a direct role in the control of food intake[18,19], which is enhanced via the regulation of the sleep–wake cycle since food intake requires a waking state. The circadian control of food intake might be mediated via direct neuroanatomical connections between the SCN and the hypothalamic arcuate nucleus, which is involved in the regulation of food intake[20], but indirect connections between the SCN and areas involved in the rewarding aspects of food could also have a role[21].

In addition to the aforementioned roles, the SCN controls the daily rhythm of release of several hormones

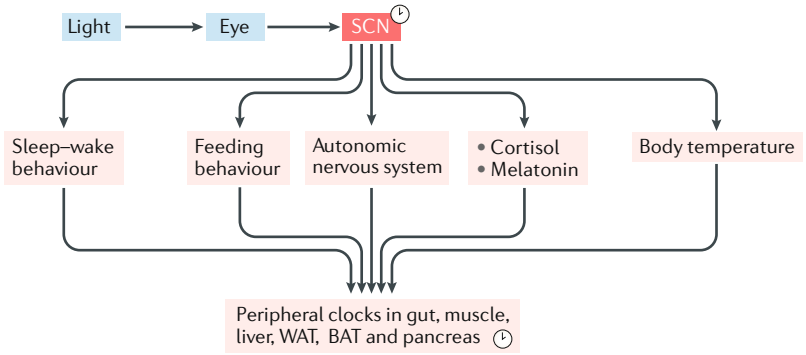

Fig. 1 | **The circadian timing system.** The circadian timing system is composed of a central clock in the suprachiasmatic nucleus (SCN) located in the hypothalamus of the brain and peripheral clocks in other brain areas and peripheral tissues. The circadian rhythms in these clocks are generated by a molecular transcriptional-translational feedback loop. The light signal, reaching the SCN via the retina and the retinohypothalamic tract, is the most important Zeitgeber for the SCN. The SCN synchronizes peripheral clocks through neural, endocrine, temperature and behavioural signals. BAT, brown adipose tissue; WAT, white adipose tissue.

affecting glucose tolerance. Firstly, the activity of the hypothalamic–pituitary–adrenal axis is regulated via connections from the SCN to the paraventricular nucleus, resulting in a diurnal rhythm of cortisol secretion, with a peak before the onset of the active period[22]. The glucocorticoid cortisol affects insulin signalling and reduces insulin secretion[23]. Secondly, the circadian rhythm of melatonin (also known as the hormone of darkness, as it is exclusively released during the dark phase in diurnal and nocturnal species alike), which affects insulin secretion[24,25], is orchestrated by output from the SCN, via the paraventricular nucleus and the intermediolateral column to the pineal gland[26]. Thirdly, the diurnal rhythm in growth hormone, which antagonizes insulin action in liver and muscle[27], is partly regulated by the SCN via its control of the sleep–wake cycle[27–29].

Furthermore, SCN lesion studies in rodents demonstrated that the SCN controls the diurnal rhythm in whole-body insulin sensitivity[30] and reported that within 8 weeks of an SCN lesion being created, rodents are insulin resistant[31]. In humans, a role for the SCN in the control of insulin sensitivity is suggested by misalignment protocols demonstrating the endogenous circadian control of glucose tolerance, independent of behavioural rhythms[14,32].

Finally, the central clock is responsible for the circadian regulation of multiple components of energy expenditure, such as the sleep–wake cycle[15,16], diet-induced thermogenesis[33], resting energy expenditure[34] and (at least in rodents) BAT activity[35–37].

The gut clock. Glucose enters the body via the gastrointestinal tract. Intestinal cells throughout the intestinal tract contain a molecular clock[38,39] and this gut clock is synchronized by signals resulting from food intake[38]. The gut clock regulates intestinal motility[40] and nutrient absorption (FIG. 4). ARNTL regulates the expression of membrane glucose transporters and thus matches the timing of maximal monosaccharide uptake to the habitual feeding period[41]. Brush border disaccharidases, including sucrase, display a circadian rhythm in activity[42,43], but the mechanism regulating this circadian activity remains to be elucidated (FIG. 4).

The muscle clock. Human skeletal muscle has an autonomous molecular clock[44,45] (FIG. 5). Rodent data showed that the SCN synchronizes the skeletal muscle clock[46,47], but signals resulting from physical exercise[48,49] and food intake have also been shown to be involved in synchronization[49–51].

Cultured rodent myotubes express circadian rhythmicity in insulin sensitivity[52]. CLOCK and ARNTL regulate muscle insulin sensitivity via changes in protein levels and membrane translocation of the insulin-sensitive glucose transporter GLUT4 (REF.[53]), as well as through the modulation of the insulin signalling pathway via expression of the deacetylase SIRT1 (REF.[54]). Furthermore, a 2017 study showed that the muscle clock regulates muscle insulin sensitivity via histone deacetylation of metabolic genes by HDAC3 (REF.[55]) (FIG. 5). Consistently, human muscle tissue shows a diurnal rhythm in insulin sensitivity with higher insulin sensitivity in the morning than in the evening[56], as well as a diurnal rhythm in mitochondrial oxidative capacity, which peaks in the evening[57].

Box 1 | **Concepts in circadian studies**

Chronobiology
The study of biological rhythms such as daily, tidal, weekly, monthly and seasonal rhythms.

Chronotype
Humans can be characterized according to their preferred sleep times; late chronotypes (owls) prefer to sleep later than early chronotypes (larks).

Circadian rhythm
A rhythm with a period of ~24 h that persists in constant conditions. Circadian comes from the Latin words *circa*, which means around, and *dies*, which means one day.

Daily (diurnal) rhythm
Physiological, hormonal and behavioural rhythms that are measured under regular light–dark and sleep–wake cycles, and therefore should be described as daily rhythms, instead of circadian rhythms.

Entrainment and Zeitgeber
The non-24 h period of the endogenous circadian rhythm can be adjusted, aligned or synchronized to the exact 24 h period of the outside world by a process called entrainment. The external stimulus responsible for this entrainment is called a Zeitgeber. In mammals the strongest Zeitgeber for the endogenous central brain clock is environmental light, but food intake, locomotor activity and temperature can also serve as Zeitgebers.

Nocturnal species
Species that are mainly awake and active during the dark period, such as most rodents.

Diurnal species
Species that are mostly awake and active during the light period, such as humans.

Chronotherapy
The specific timing of administration of drug classes based on the diurnal rhythms in pharmacodynamics and pharmacokinetics of therapeutic drugs.

Suprachiasmatic nucleus lesion
In rodents, a thermal or electrolytic complete lesion of the suprachiasmatic nucleus neurons causes a loss of all circadian rhythmicity (that is, the absence of daily rhythms in locomotor activity and food intake, but also in hormone release, body temperature and metabolic fluxes).

Misalignment protocol
An experimental protocol using a recurring non-24 h behavioural cycle (for example, a 28 h cycle). This protocol can be used to investigate the relative contributions of the endogenous circadian cycle and the behavioural cycle to a particular physiological rhythm.

Box 2 | **Metabolic definitions**

Insulin resistance[240]
Resistance to the physiological effects of insulin at the tissue level. The gold standard to measure insulin sensitivity is the hyperinsulinaemic euglycaemic clamp.

HOMA-IR[241]
Homeostatic model assessment of insulin resistance, based on a single combination of fasting glucose and insulin levels.

Glucose tolerance
Plasma glucose excursion after a fixed oral or intravenous glucose load, with higher glucose excursions being indicative of reduced glucose tolerance.

Prediabetes[2]
Fasting plasma glucose 5.6–6.9 mmol/l (100–125 mg/dl), 2 h plasma glucose after oral glucose tolerance test (75 g glucose) 7.8–11.0 mmol/l (140–199 mg/dl) or HbA_{1c} 39–47 mmol/mol (5.7-6.4%).

Diabetes mellitus[2]
Fasting plasma glucose ≥7 mmol/l (126 mg/dl), 2 h plasma glucose after oral glucose tolerance test (75 g glucose) ≥11.1 mmol/l (200 mg/dl) or HbA_{1c} ≥48 mmol/mol (≥6.5%) or random plasma glucose ≥11.1 mmol/l (200 mg/dl) with hyperglycaemic symptoms.

Type 2 diabetes mellitus[2]
Diabetes mellitus due to peripheral insulin resistance, combined with relative insulin deficiency.

The metabolic syndrome[242]
Three or more of the following:

- Waist circumference >102 cm in men or >88 cm in women
- Triglycerides ≥1.69 mmol/l (150 mg/dl)
- HDL-cholesterol <1.04 mmol/l (40 mg/dl) in men or <1.30 mmol/l (50 mg/dl) in women
- Blood pressure ≥130/85 mmHg
- Fasting plasma glucose ≥5.6 mmol/l (100 mg/dl)

The adipose tissue clock. WAT contains an autonomous circadian clock as shown in both rodent[58,59] and human[60,61] in vitro models (FIG. 6). Similar to the muscle clock, the WAT clock is synchronized by the SCN[62] and by signals resulting from food intake[63,64].

Adipocytes from rodents have circadian rhythmicity in glucose uptake[52]. In line with this observation, in human WAT ~25% of the transcriptome shows diurnal variation, including pathways involved in the regulation of glucose uptake[65]. Subcutaneous WAT explants from humans who are obese show an intrinsic diurnal rhythm in insulin signalling as determined by AKT phosphorylation, with peak insulin sensitivity at noon[66]. Rodent data indicated that this diurnal rhythm in adipose tissue insulin sensitivity could be the result of circadian regulation of the retinol-binding protein receptor STRA6 (REF.[67]). In addition, CLOCK and ARNTL regulate the expression of key enzymes in the regulation of lipolysis such as adipose triglyceride lipase (ATGL), lipoprotein lipase (LPL) and hormone-sensitive lipase (HSL)[68,69] (FIG. 6).

BAT from mice also shows a diurnal rhythm in glucose uptake[70]. A 2016 human study confirmed circadian rhythmicity of glucose uptake in BAT, with peak activity just before waking up[71].

The liver clock. The liver contains an autonomous clock that is synchronized by the SCN[72,73] via a combination of autonomic signals and endocrine signals[64] (FIG. 7). The liver clock also responds strongly to the timing of food intake, as the liver clock can be uncoupled from the SCN clock by inverting the daily feeding rhythm[74]. The liver clock regulates several pathways involved in the control of glucose and lipid metabolism, as indicated by microarray[73,75,76], proteomic[77,78] and metabolomic[79–81] studies.

By synchronizing the diurnal rhythms in gluconeogenesis and glucose export to the habitual fasting period, the liver clock in rodents is essential to maintain euglycaemia[82,83]. The repression of gluconeogenesis during the feeding period is mediated by the interaction of CRY (which has its diurnal peak of expression during the feeding period) with the glucocorticoid receptor[84] and with G protein-coupled receptor signalling[85]. The overall result of these interactions is the repression of the expression of rate-limiting gluconeogenetic genes. In addition, insulin-mediated suppression of gluconeogenesis is partly dependent upon CRY-mediated FOXO1 degradation[86,87] (FIG. 7). In view of this information, it is tempting to speculate that the liver clock contributes to the diurnal rhythms in hepatic glycogen content[88] and in hepatic insulin sensitivity[13] that are observed in healthy individuals.

In addition to the regulation of gluconeogenesis, the liver clock regulates the diurnal rhythm in mitochondrial dynamics (FIG. 7). Therefore, the liver clock is involved in regulating mitochondrial glucose oxidation and fatty acid oxidation[89,90], which protects the liver against oxidative stress during fasting[91].

The pancreatic clock. The presence of an autonomous circadian pancreatic clock[92] has been demonstrated not only in rodents[93–95], but also in human islets and dispersed human islet cells (that is, the cells were cultured as seperate or single cells, not as an intact islet)[96,97]. The pancreatic clock is synchronized to the light–dark cycle[95] via signals derived from the central brain clock in the SCN that include autonomic neuronal signals[98], melatonin release[93], glucocorticoid release[96] and changes in body temperature[96]. The amplitude of oscillations in the expression of clock genes in cultured rat islets is dependent on the glucose concentration in the culture medium[95].

Pancreatic islets isolated from rats show a circadian rhythm in insulin secretion[93]. CLOCK and BMAL1 activate the transcription of genes involved in insulin biosynthesis, insulin transport and glucose-stimulated insulin secretion[99] (FIG. 8). In line with this observation, disruption of the pancreatic clock causes defective insulin secretion[94,100,101]. Similarly, in human pancreatic islets one group has confirmed that the pancreatic clock controls insulin secretion[97].

Circadian disruption

Insulin resistance

Insulin resistance of liver, muscle and adipose tissue, which is initially compensated for by increased insulin secretion, is an early characteristic in the development of T2DM. Of note, in addition to insulin resistance, β-cell failure contributes to the development of T2DM[102].

Insulin resistance in skeletal muscle is characterized by a reduced insulin-stimulated glucose uptake as a result of reduced insulin signalling and GLUT4 translocation[103]. As skeletal muscle is responsible for the

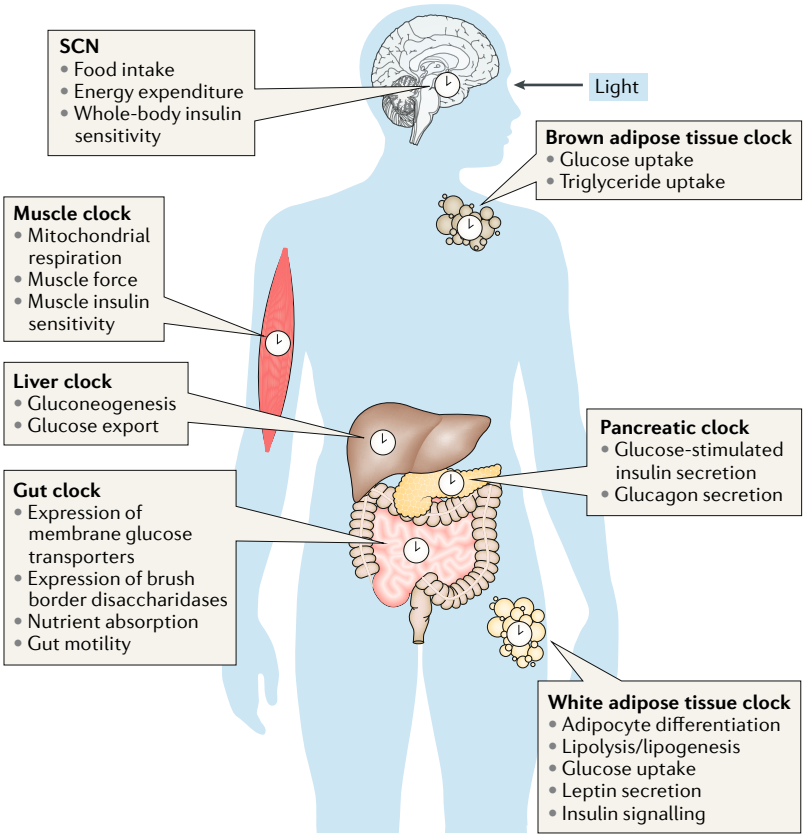

Fig. 2 | **Circadian clocks regulate glucose metabolism, insulin sensitivity and insulin secretion.** The molecular clock consists of a transcriptional translational feedback loop involving the clock proteins CLOCK, ARNTL, PER and CRY and the nuclear receptors NR1D1, NR1D2 and ROR. The central and peripheral clocks are responsible for a variety of functions. SCN, suprachiasmatic nucleus.

majority of glucose uptake in the postprandial state[104], skeletal muscle insulin resistance contributes to elevated postprandial glucose levels and reduced glucose tolerance.

The main role of the liver in the maintenance of glucose homeostasis is to release glucose — that is, endogenous glucose production — when plasma glucose and insulin levels are low. Under normal conditions, endogenous glucose production is strongly suppressed by insulin. Following hepatic insulin resistance, endogenous glucose production remains unsuppressed despite high plasma insulin levels, thereby contributing to elevated glucose levels via enhanced gluconeogenesis and reduced glucose uptake[105]. Insulin also suppresses de novo lipogenesis and VLDL production in the liver, and therefore hepatic insulin resistance is also characterized by elevated VLDL secretion[106].

The role of adipose tissue insulin resistance in the development of T2DM is more indirect than that of muscle and hepatic insulin resistance. Insulin suppresses adipose tissue lipolysis; therefore, patients with T2DM are characterized by having elevated levels of plasma free fatty acids[107]. Tissues such as liver and muscle take up the additional circulating plasma free fatty acids, which contributes to ectopic lipid accumulation. This ectopic fat accumulation in itself strongly contributes to the development of liver and muscle insulin resistance[108].

Amplitude
On a line graph, the amplitude is half the distance between the peak and trough of a daily or circadian rhythm.

Circadian disruption and insulin resistance

The first clue that the circadian timing system might be involved in the pathophysiology of insulin resistance was the observation in the 1960s of an altered daily rhythm in glucose tolerance in patients with T2DM[109]. Later, observations including the development of metabolic syndrome in the *Clock* mutant mouse[110], the discovery that food intake at the wrong circadian phase (the habitual sleeping phase) causes obesity in mice[111] and the observation that circadian misalignment results in decreased glucose tolerance in humans[112] led to the proposal of the circadian disruption hypothesis[113]. Sophisticated tissue-specific pancreatic[94,99,100,114], hepatic[82,91], muscle[53,115] and adipose[116] transgenic and knockout models gave further support for this hypothesis. On the other hand, several studies, including transgenic mouse models[117–119] and studies with desynchronized food intake[120–122], have not been able to confirm the circadian disruption hypothesis, as they reported no negative metabolic effects of circadian disruption. An overview of the metabolic phenotypes of published transgenic animal models is outside the scope of the present Review, but can be found in several previous papers[123–125].

According to the circadian disruption hypothesis, metabolic health is optimal when the different daily rhythms, including the behavioural fasting–feeding and sleep–wake rhythms, hormonal and autonomic nervous system rhythms and central and peripheral clock rhythms, oscillate in synchrony with each other. By contrast, misalignment between certain components of this system, such as between behavioural and tissue clock rhythms, can result in circadian disruption and the development of insulin resistance and T2DM. In the sections below, we discuss epidemiological and experimental human studies that investigated the association between insulin resistance and several forms of circadian disruption (BOX 3).

Clock genes in humans. In line with the rodent clock gene mutation studies, human mutations in several clock genes were shown to contribute to the genetic susceptibility to obesity, insulin resistance and T2DM. Observational studies have shown associations between single nucleotide polymorphisms in *ARNTL*[126] and T2DM, between specific haplotypes of *CLOCK* and obesity[127,128], between polymorphisms in *CRY2* and elevated fasting glucose[129,130] and between polymorphisms in the circadian clock gene *NR1D1* and obesity[131]. Inspired by these findings, several investigators explored gene–behaviour interactions and showed that interactions between diet and clock gene mutations affect fasting glucose[132], insulin resistance[133,134], body weight[135,136] and T2DM[137].

We only identified three studies that investigated tissue clock gene expression rhythms in patients with T2DM. One study described a reduced amplitude of the daily rhythm in leukocyte clock gene expression in patients with T2DM[138]. Another study investigated the diurnal rhythm in clock gene expression in gluteal subcutaneous adipose tissue and surprisingly found no differences between lean participants, participants

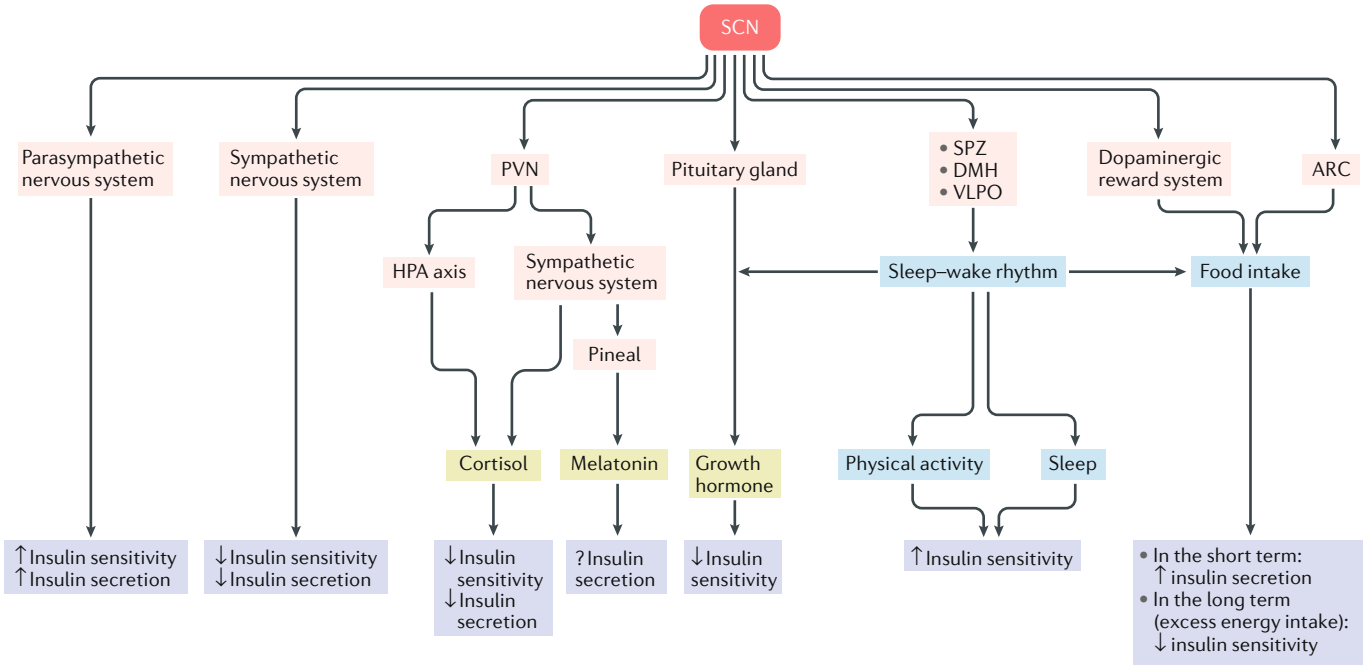

Fig. 3 | **The central clock.** The suprachiasmatic nucleus (SCN), which contains the central clock, controls the daily rhythms of sleep–wake behaviour and food intake via hypothalamic connections. The central clock controls the circadian rhythm in the secretion of hormones affecting glucose tolerance, including cortisol, melatonin and growth hormone. ARC, arcuate nucleus; DMH, dorsomedial hypothalamus; HPA axis, hypothalamus–pituitary–adrenal axis; PVN, paraventricular nucleus; SPZ, subparaventricular zone; VLPO, ventrolateral preoptic nucleus.

with obesity and patients with T2DM[139]. A study in circadian myotube explants described unaltered clock gene expression rhythms, but a decreased amplitude in *NR1D1* expression in patients with T2DM[44]. In sum, indications of altered tissue clock rhythms in patients with T2DM are very limited.

Effects of light. Daylight is the main synchronizer of the central clock. Our modern lifestyle, however, is characterized by reduced light exposure during the day and increased light exposure during the night. These lifestyle changes have a substantial effect on the alignment of our circadian timing system to the solar day, as illustrated by an elegant study that investigated the effects of camping in natural light–dark conditions on human daily sleep–wake behaviour[140].

In several animal models, investigators have shown that dim light at night disturbs diurnal rhythms of food intake and locomotor behaviour[120,125,141], causing obesity and reduced glucose tolerance in mice[125,141] but not in rats[120]. In line with these findings, observational studies in humans have shown correlations of exposure to light at night with obesity[142,143] and T2DM[144].

Under conditions of controlled food intake and physical activity, bright ambient light directly reduces insulin sensitivity in a time-dependent manner in healthy individuals[145]. When healthy participants are kept awake during the night, bright light causes increased levels of glucose in plasma[146]. In patients with T2DM, bright morning light increases fasting and postprandial levels of glucose[147]. A 2017 study in rats reported wavelength-dependent effects of ambient light on glucose tolerance, with white and green light but not blue and red light reducing glucose tolerance[148], but whether these observations translate to humans remains to be determined.

Melatonin. Melatonin is secreted by the pineal gland and shows a pronounced diurnal rhythm. During the dark period, plasma levels of melatonin are high[149], and melatonin secretion is acutely suppressed by light exposure[26]. Melatonin acutely increases insulin secretion in cultured human islets[24]. By contrast, melatonin administration in healthy women acutely decreases glucose tolerance[150,151], an effect that is dependent on a common gain-of-function variant of the melatonin receptor gene *MTNR1B*[152].

The role of melatonin signalling in the pathophysiology of T2DM remains a topic of lively debate[153]. On the one hand an association exists between reduced melatonin levels and the incidence of T2DM[154], and rare loss-of-function mutations in *MTNR1B* are associated with an increase in the risk of T2DM[155]. On the other hand, one publication suggests that increased pancreatic β-cell melatonin signalling might reduce insulin secretion in humans[25].

Sleep–wake rhythms. Accumulating evidence from both epidemiological and experimental studies shows that behavioural sleep–wake rhythms affect the risk of developing insulin resistance. A 2015 meta-analysis of prospective studies showed that both individuals who sleep for short periods and those who sleep for long periods are at increased risk of developing T2DM,

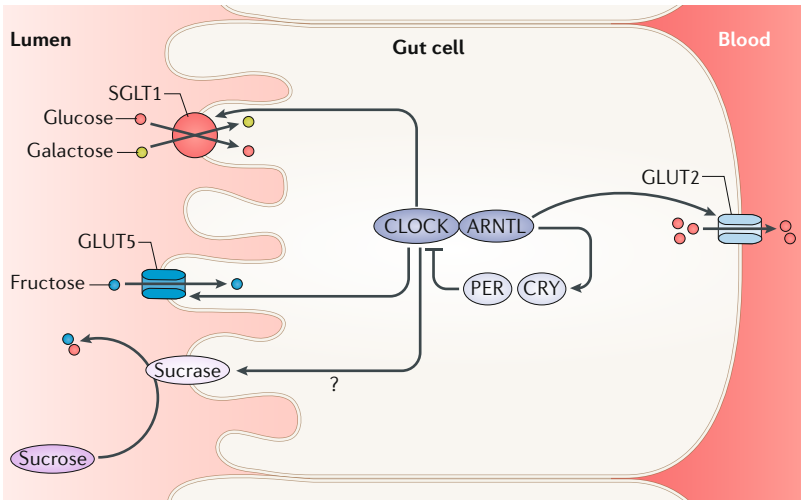

Fig. 4 | **The gut clock.** The molecular clock consists of a transcriptional–translational feedback loop involving the clock proteins CLOCK, ARNTL, PER and CRY and the nuclear receptors NR1D1, NR1D2 and ROR. The gut clock regulates the expression of membrane glucose transporters and brush border disaccharidases. GLUT, glucose transporter; SGLT1, sodium–glucose cotransporter 1.

with a proposed 'optimal' sleep duration of 7–8 h per night[156].

The interpretation of epidemiological studies, however, should be made with caution. It has been suggested that the relationship between long sleep duration and adverse health could be the result of reversed causality, undiagnosed disease, residual confounding and the subjective reporting on sleep duration possibly representing time in bed[157]. On the other hand, investigators are in general agreement that poor sleep quality increases the risk of obesity and T2DM. A meta-analysis showed that people with reduced subjective sleep quality are at increased risk of developing T2DM[158]. In line with this finding, patients with obstructive sleep apnoea are at increased risk of developing T2DM, which could be mediated by increased food intake and/or decreased physical activity[159,160], among other mechanisms, owing to disturbed sleep[161].

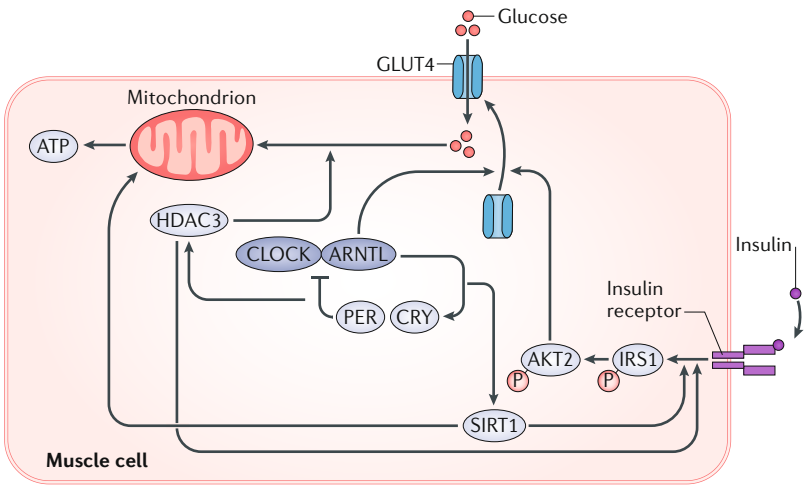

Fig. 5 | **The muscle clock.** In muscle, the muscle clock regulates muscle insulin sensitivity via protein levels and membrane translocation of the insulin-sensitive glucose transporter 4 (GLUT4) and through modulation of the insulin signalling pathway via expression of the deacetylase sirtuin 1 (SIRT1). In addition, the muscle clock regulates muscle insulin sensitivity via histone deacetylation of metabolic genes by histone deacetylase 3 (HDAC3). IRS1, insulin receptor substrate; P, phosphate.

Several well-controlled human experimental studies shed further light on the relationship between sleep deprivation and insulin sensitivity. The seminal experimental study showed reduced glucose tolerance after five nights of chronic partial sleep loss (4 h per night) compared with five well-rested nights (12 h per night) in healthy human participants, under conditions of controlled food intake and physical activity[162]. Subsequent experimental studies under controlled conditions confirmed reduced liver[163], adipose[164] and whole-body[163–168] insulin sensitivity as a result of sleep restriction to 4–6 h per night for 1–14 nights in healthy individuals. By contrast, other studies under controlled conditions found only short-term effects[169] or no effect[170] of sleep restriction on insulin sensitivity, which could be the result of milder sleep restriction[169] or a mitigating effect of the negative energy balance owing to the experimental design[170]. Further to these observations, studies have shown that experimental slow-wave sleep suppression resulted in reduced whole-body insulin sensitivity in healthy individuals[171–173].

The proposed mechanisms for the effects of sleep restriction and sleep disturbance on insulin sensitivity include an altered sympatho–vagal balance[162,171,172] and increased circulating levels of catecholamines[167] or cortisol[167,172]. In conditions of ad libitum food intake, increased food intake as a result of sleep restriction or disturbance probably contributes to decreased insulin sensitivity[159,160].

A systematic review and meta-analysis showed that in patients with established T2DM, individuals who sleep for a short duration or a long duration and individuals with lower sleep quality have reduced glycaemic control compared with individuals who get adequate sleep[174]. Although several of the studies included in the systematic review and meta-analysis corrected for physical activity, the meta-analysis did not correct for food intake or physical activity, so it is possible that these correlations are partly confounded by increased food intake or decreased physical activity[174].

The incidence of obstructive sleep apnoea is high in patients with T2DM. Furthermore, in patients with comorbid obstructive sleep apnoea and T2DM, poor glycaemic control correlates with the severity of obstructive sleep apnoea, a finding that could again be partly confounded by increased food intake and/or decreased physical activity[161].

Chronotype and social jet lag. An individual's chronotype could also be a risk factor for insulin resistance. Observational studies show that evening chronotypes are at increased risk of developing T2DM compared with morning chronotypes[175], even when results are corrected for sleep duration and physical activity (food intake was not corrected for in this study)[176]. Some evidence suggests that this increased risk could be the result of increased social jet lag — the discrepancy between the social (behavioural) and endogenous (circadian) time. Individuals with an evening chronotype who are

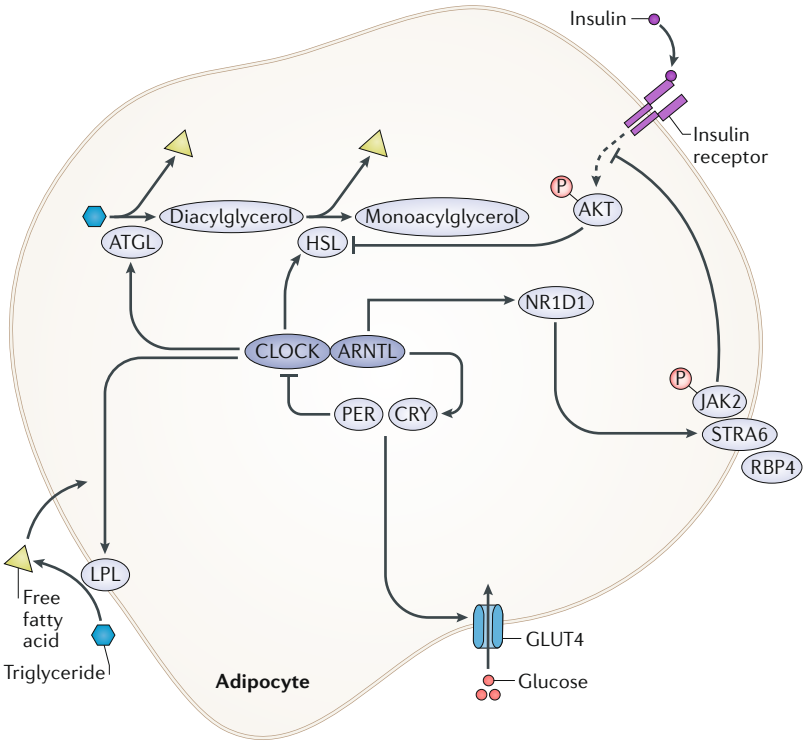

Fig. 6 | **The white adipose tissue clock.** In white adipose tissue, the circadian clock probably regulates the diurnal rhythm in insulin sensitivity via the circadian regulation of the retinol-binding protein receptor stimulated by retinoic acid 6 (STRA6). CLOCK and ARNTL regulate the expression of key enzymes in the regulation of lipolysis. ATGL, adipose triglyceride lipase; GLUT, glucose transporter; HSL, hormone-sensitive lipase; JAK2, Janus kinase 2; LPL, lipoprotein lipase; P, phosphate; RBP4, retinol–binding protein 4.

working regular daytime hours are at increased risk of social jet lag.

Social jet lag is associated with the development of T2DM, independently of sleep duration[177–179], even when results are corrected for food intake and physical activity[177]. Patients with T2DM who are evening chronotypes show worse glycaemic control compared with patients who are morning chronotypes, a finding that might, in part, be mediated by an increase in evening food intake[180]; however, an association between poor glycaemic control and chronotype, independent of sleep duration, total food intake and physical activity, does also exist[180,181].

Shift work and jet lag. Shift workers are at increased risk of developing T2DM, as shown by a 2015 meta-analysis of observational studies[182]; the degree of increased risk relates to the number of night shifts per month[183]. This increased risk of T2DM might be mediated by a combination of acute and chronic effects.

Experimental circadian misalignment under strictly controlled conditions acutely decreases glucose tolerance and insulin sensitivity both in non-shift workers and in chronic shift workers[14,32,112,184–186]. To our knowledge, the chronic effects of repeated phase shifts on food intake, physical activity and insulin sensitivity have not been studied experimentally in humans, but several animal studies show that repeated phase shifts cause increased food intake, increased body weight and disturbed glucose metabolism[187]. A 2014 translational study showed that repeated jet lag in mice causes reduced glucose tolerance via disturbance of the intestinal microbiome. Fascinatingly, faecal transfer from jet-lagged humans into germ-free mice also reduced glucose tolerance in mice, suggesting that the microbiome clock might have an important role in the development of insulin resistance owing to repeated phase shifts[188].

Does circadian disruption contribute to insulin resistance? Taken together, the hypothesis that circadian disruption contributes to the development of insulin resistance in humans is supported by the following findings: decreased glucose tolerance caused by experimental circadian misalignment in humans; the association between human clock gene polymorphisms and insulin resistance; the experimentally observed effects of night-time light exposure and sleep disturbance on glucose metabolism; and the association of short sleep duration, long sleep duration, low sleep quality, late chronotype, social jet lag and shift work with insulin resistance. Therefore, it seems probable that disturbance of the central and/or tissue clock rhythms (FIG. 9) contributes to the pathophysiology of insulin resistance at the tissue level. Furthermore, circadian disruption might cause misalignment of nutrient fluxes. For instance, a mismatch between hepatic glucose production, muscle glucose uptake and carbohydrate intake could contribute to elevated levels of glucose and an imbalance between lipid storage in WAT, lipid oxidation in BAT and hepatic lipid production might contribute to ectopic lipid accumulation.

Circadian synchrony and metabolic health

Modulating light exposure

Light provides the main input for the SCN, and optimization of daily light exposure can therefore increase circadian synchrony[140]. To our knowledge, however, no published randomized controlled trials (RCTs) have investigated the effects of long-term natural light exposure on insulin sensitivity or glycaemia.

One potential strategy is the adaptation of architecture and/or indoor lighting conditions. For example, one RCT showed that supplementing daytime indoor light conditions with bright artificial light in homes for the elderly improves cognitive functioning, sleep quality and the diurnal rhythm of locomotor activity[189,190]. Another study found that increasing blue light intensity in the morning with a system of wavelength-controlled light bulbs and LEDs at home improved subjective sleep quality in elderly women compared with low morning blue light intensity[191].

A second potential strategy is to limit the use of screens from computers, tablets and smartphones in the evening, or to use blue light filters with these devices. An experimental study showed that reading a paper book in the evening reduced sleep-onset latency and improved daytime alertness the next day compared with reading a book on a light-emitting tablet[192].

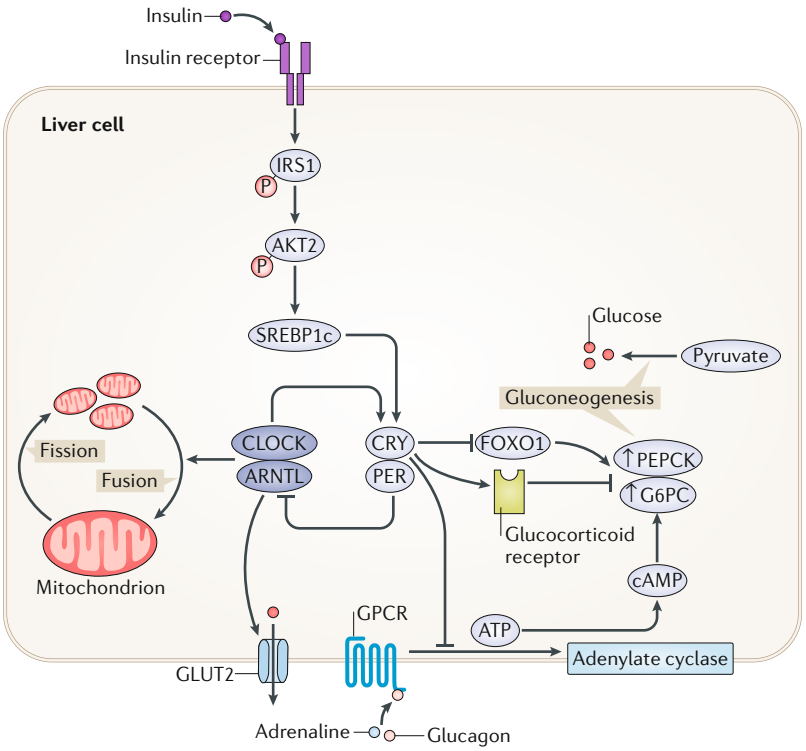

Fig. 7 | **The liver clock.** In the liver, the circadian repression of gluconeogenesis during the habitual feeding period is mediated by the interaction of CRY with the glucocorticoid receptor, G protein-coupled receptor (GPCR) signalling and FOXO1 degradation. The liver clock also regulates the diurnal rhythm in mitochondrial dynamics. FOXO1, forkhead box protein O1; G6PC, glucose 6 phosphatase; GLUT, glucose transporter; IRS1, insulin receptor substrate 1; P, phosphate; SREBP1c, sterol regulatory element-binding protein 1c.

Modulating rhythmic behaviour

Sleep–wake behaviour. In view of the strong association between disturbed sleep and impaired insulin sensitivity, sleep improvement could be a sensible approach in the prevention and treatment of insulin resistance[193,194], but high-quality intervention studies are currently lacking (FIG. 9). One study in chronically sleep-restricted healthy individuals showed a correlation between improved indices of insulin sensitivity and increased sleep duration after 40 days of sleep extension (~45 min extra each night)[195]. A study on the metabolic effects of sleep extension in sleep-restricted individuals who are obese is ongoing[196].

Evidence-based strategies to treat insomnia include cognitive behavioural therapy (high-quality evidence according to the GRADE criteria), light therapy (low-quality evidence) and exercise (low-quality evidence)[197]. A short course (<4 weeks) of benzodiazepines or benzodiazepine receptor agonists can be considered if these strategies are not successful[197], but concerns exist of negative effects of these hypnotic drugs on glucose tolerance, possibly owing to a reduction in slow-wave sleep after hypnotic drug use[193].

Individuals with obstructive sleep apnoea represent a unique population regarding sleep–wake behaviour. A 2017 meta-analysis of four RCTs assessed the effect of continuous positive airway pressure (CPAP) treatment on insulin resistance in patients with obstructive sleep apnoea who had either normal glucose values or prediabetes. The authors found no effect on HOMA-IR, but reported a small reduction of fasting insulin[198]. A 2017 meta-analysis showed that treatment of obstructive sleep apnoea with CPAP does not improve levels of haemoglobin A_{1c} (HbA_{1c}) or fasting levels of glucose in patients with obstructive sleep apnoea who have established T2DM, despite reduced daytime sleepiness[199]. The surprising lack of effect of CPAP treatment on glycaemia in patients with obstructive sleep apnoea could be related to treatment adherence[199], as two studies with good adherence did show a decrease in HbA_{1c} (REF.[200]) or mean 24 h glucose concentrations[201].

Physical activity. Regular physical activity is one of the cornerstones of the lifestyle changes prescribed to patients with T2DM (FIG. 9). Regular physical exercise decreases insulin resistance and reduces HbA_{1c} (REF.[202]). As physical activity also shifts the central circadian pacemaker in humans[203], improves sleep duration and quality[204] and affects the muscle clock[48,49], it is possible that some of the beneficial metabolic effects of (daytime) physical activity are mediated through the circadian timing system. To our knowledge, however, no studies have proved this idea. We are also not aware of any studies investigating the optimal timing of physical exercise for the reduction of body weight and insulin resistance.

Feeding behaviour. Individualized nutrition therapy is another core intervention in the prevention and treatment of insulin resistance and T2DM[2]. Classically, the main focus points for feeding behaviour are calorie reduction and healthy macronutrient distribution. An approach with a focus on the timing of food intake can also be of great value for people with insulin resistance[205]. A 2017 systematic review on meal timing and frequency in the prevention of cardiovascular disease proposed an approach to eating that included the recommendations to eat a greater share of calories early in the day and to use consistent overnight fast periods[206] (FIG. 9).

The advice to consume a greater share of calories early in the day mainly results from RCTs showing that breakfast consumption (compared with breakfast skipping) improves insulin sensitivity[207–210], although not all studies agree[211,212]. A hallmark study on the overnight fast in 156 North American individuals showed that most people do not consume the 'normal' three meals per day within 12 h, but instead showed an irregular eating pattern spread over a >15 hr period. In that same study it was reported that a small group of eight people classed as obese who were treated with 'time-restricted feeding' (that is, they were asked to restrict eating to a 10 h period for 16 weeks) lost 3 kg in weight, which persisted over 1 year[213]. In line with this finding, a 2018 randomized crossover trial in eight individuals with prediabetes showed that isocaloric early time-restricted feeding (that is, a 6 h feeding period with dinner before 15:00 h) reduces insulin resistance compared with a 12 h feeding period[214].

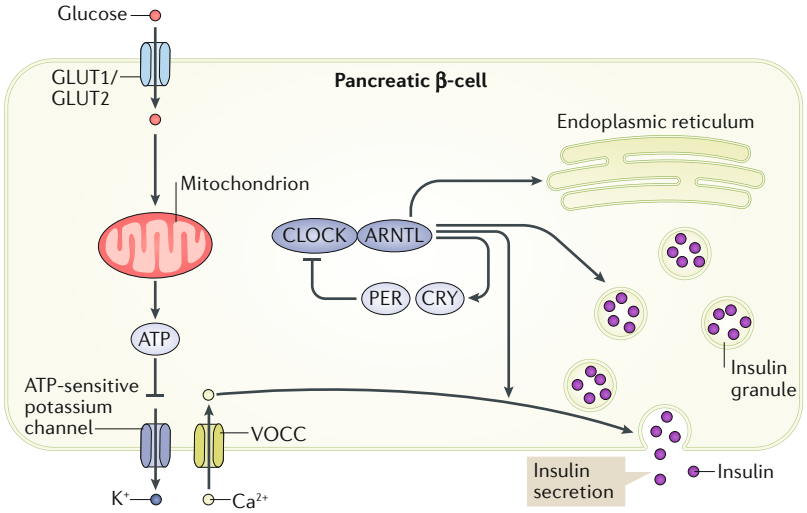

Fig. 8 | **The pancreas clock.** In the pancreas, CLOCK and BMAL1 activate the transcription of genes involved in insulin biosynthesis, insulin transport and glucose-stimulated insulin secretion. All depicted processes show circadian rhythmicity. GLUT, glucose transporter; VOCC, voltage-dependent calcium channel.

Chronotherapy in patients with T2DM

In patients with T2DM, glycaemic control with oral glucose-lowering drugs and/or insulin reduces microvascular and cardiovascular complications[2,215]. To our knowledge and despite preclinical observations on the effects of metformin on the molecular clock[216,217], the time-dependent effects of metformin on blood levels of glucose[218] and the time-dependent effects of the sulphonylurea tolbutamide on insulin secretion[219], no trials have assessed the chronotherapeutic effects of these frequently prescribed glucose-lowering drugs on clinically relevant outcomes.

The only potential example of evidence-based chronotherapy in T2DM is the dopamine agonist bromocriptine (FIG. 9). Dopaminergic activity shows a diurnal rhythm[220] and dopamine signalling increases insulin sensitvity[221]. When administered in the morning, a quick-release bromocriptine formulation reduces HbA_{1c} and fasting levels of glucose in patients with T2DM[2,222]. To our knowledge, however, no human trials have compared the effects of different administration times, which would be the ultimate proof that bromocriptine treatment is actually a chronotherapy.

The effects of timed melatonin administration in patients with T2DM have been investigated in one small RCT with 36 participants, which compared 3 weeks of melatonin administration with placebo[223]. The investigators reported no convincing evidence of beneficial metabolic effects of melatonin.

The insulin requirements of patients on insulin therapy vary over the diurnal cycle owing to the diurnal rhythms of sleep–wake behaviour, physical activity, food intake and insulin sensitivity. The research community has made tremendous efforts to improve insulin pharmacokinetics with the aim of matching them to the individual patient's diurnal pattern in insulin requirements[224,225]. The question of whether the beneficial effects of insulin are (partly) mediated through central or peripheral clock modulation, however, remains to be resolved.

The artificial pancreas — which consists of an insulin pump controlled by a control algorithm coupled to a continuous glucose sensor[226] — was in 2016 shown to increase the length of time spent in target glucose ranges in patients with T2DM who had been admitted to hospital[227]. One possible approach to further improve the algorithm controlling the artificial pancreas for patients with T2DM would be to incorporate information on the diurnal rhythm of insulin sensitivity.

The administration of exogenous glucocorticoids causes insulin resistance[23]. Data from a subgroup analysis of a small open-label randomized trial[228] and two prospective cohort studies[229,230] suggest once-daily modified-release hydrocortisone formulations might be beneficial for metabolic health compared with thrice-daily immediate-release hydrocortisone. Analysis of the small subgroup of patients with comorbid adrenal insufficiency and diabetes mellitus showed that replacement therapy with once-daily modified-release hydrocortisone formulations (which mimic the physiological diurnal rhythm of cortisol levels) might lead to improvements in body weight and HbA_{1c} compared with thrice-daily immediate-release hydrocortisone.

Circadian molecules

New circadian therapies might arise from large-scale chemical screens looking for clock-improving molecules[231–233] (FIG. 9). Promising candidates include the REV-ERBα agonist SR9011 and the REV-ERBβ agonist SR9009, both of which directly target the molecular clock and were shown to decrease obesity and hyperglycaemia in diet-induced obese mice. Timed twice-daily administration of these REV-ERB agonists alters metabolic gene expression patterns in muscle and WAT, leading to increased muscle glucose and fatty acid oxidation (increased energy expenditure), in combination with decreased WAT triglyceride synthesis[234].

Another promising candidate is the natural citrus compound nobiletin, which has been shown to reduce body weight and improve insulin sensitivity

Box 3 | Circadian disruption and insulin resistance

Epidemiological studies in humans

- Clock gene polymorphisms (*ARNTL*[126], *CLOCK*[127,128], *CRY2* (REFS[129,130]), *NR1D1* (REF.[131])
- Light at night[125,142,143]
- Reduced or increased melatonin signalling[25,153,154,155]
- Short or long sleep (optimal: 7–8 h)[156,158]
- Reduced sleep quality[158]
- Evening chronotype[175,176,181]
- Social jet lag[177–179]
- Shift work[182,183]

Experimental studies in humans

- Diet-clock gene mutation interactions[132–137]
- Ambient light[145–147]
- Melatonin[150–152]
- Sleep restriction[162–170] and sleep disruption[171–173]
- Circadian misalignment[14,32,112,184–186]

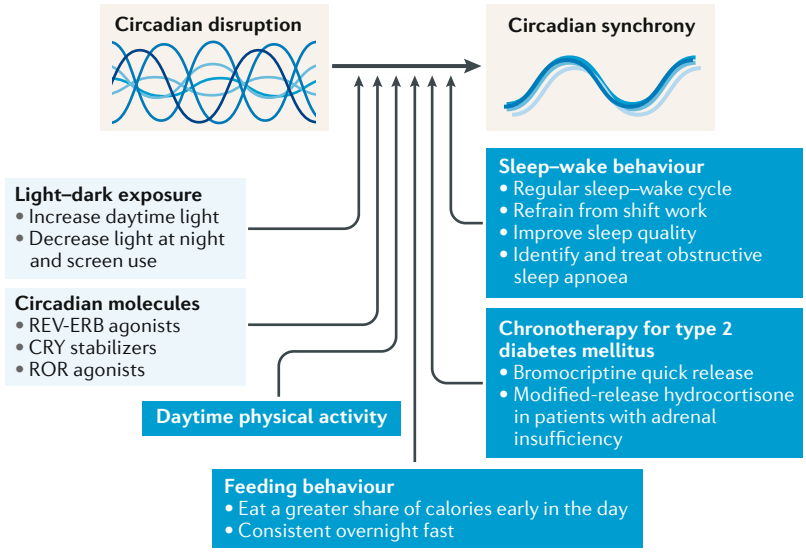

Fig. 9 | **Potential interventions promoting metabolic health through circadian synchrony.** Improving the synchrony between behavioural fasting–feeding and sleep–wake rhythms, hormonal and autonomic nervous system rhythms, and central and peripheral clock rhythms, might prove a valuable approach to prevent and/or treat insulin resistance and type 2 diabetes mellitus. Therapeutic interventions to improve circadian synchrony are possible at several levels: the light input to the circadian timing system; the behavioural level (sleep–wake behaviour, physical activity and food intake), directly targeting the molecular clock and the timing of medication (chronotherapy). Dark blue boxes show information that has some clinical human evidence supporting an effect on insulin sensitivity. Light blue boxes show information that has no clinical evidence supporting an effect on insulin sensitivity.

in two different mouse models of the metabolic syndrome (diet-induced obese mice and *db*/*db* mice). Nobiletin directly targets the molecular clock by activating RORα and RORγ, thus increasing the amplitude of circadian locomotor behaviour, the rhythm of tissue clock gene expression and the rhythm of hepatic metabolic gene expression. As a result, energy expenditure increases, adiposity decreases and hepatic steatosis decreases[235]. Finally, in preliminary reports, two different CRY stabilizers were shown to improve glucose tolerance in diet-induced obese mice[236] and *db*/*db* mice[237]. The exact mechanism responsible for these metabolic benefits, however, remains to be elucidated.

In conclusion, REV-ERB agonists, ROR agonists and CRY stabilizers are promising circadian molecules for the treatment of T2DM, and human phase I studies of these compounds are to be expected.

Conclusions

Despite the large body of evidence from animal studies, the exact mechanisms mediating the metabolic derangements resulting from circadian disruption remain to be resolved. For example, does circadian misalignment cause a mismatch of glucose and lipid fluxes between the various organs or do disrupted tissue clocks cause insulin resistance at the tissue level, or are both mechanisms involved?

Currently, the clinical utility of the knowledge on circadian clock regulation of insulin sensitivity is only beginning to be explored. A clear need exists for RCTs that investigate the metabolic effects of natural light–dark exposure, sleep improvement, time-restricted feeding and the daily timing of exercise. Clinical trials are needed that investigate methods to prevent metabolic complications in shift workers. With regard to biomarkers, evidence suggests that circadian phase biomarkers can help to optimally synchronize the circadian timing of behavioural or pharmacological interventions[238]. We are in no doubt that new circadian molecules targeting the molecular clock will be identified within the next 10 years. Furthermore, mathematical models could be an important aid to predict the effects of timed administration of clock agonists[239]. We expect the further development of promising candidate circadian molecules, including nobiletin, in phase I human trials in the coming years.

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Author contributions
D.J.S. researched data for article, all authors provided a substantial contribution to discussion of content and wrote the article, F.A.J.L.S., P.S., S.E.L.F. and A.K. reviewed and edited the manuscript before submission.

Competing interests
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