The impact of sleep disorders on glucose metabolism: endocrine and molecular mechanisms

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Abstract

Modern lifestyle has profoundly modified human sleep habits. Sleep duration has shortened over recent decades from 8 to 6.5 hours resulting in chronic sleep deprivation. Additionally, irregular sleep, shift work and travelling across time zones lead to disruption of circadian rhythms and asynchrony between the master hypothalamic clock and pacemakers in peripheral tissues. Furthermore, obstructive sleep apnea syndrome (OSA), which affects 4 - 15% of the population, is not only characterized by impaired sleep architecture but also by repetitive hemoglobin desaturations during sleep. Epidemiological studies have identified impaired sleep as an independent risk factor for all cause of-, as well as for cardiovascular, mortality/morbidity. More recently, sleep abnormalities were causally linked to impairments in glucose homeostasis, metabolic syndrome and Type 2 Diabetes Mellitus (T2DM). This review summarized current knowledge on the metabolic alterations associated with the most prevalent sleep disturbances, i.e. short sleep duration, shift work and OSA. We have focused on various endocrine and molecular mechanisms underlying the associations between inadequate sleep quality, quantity and timing with impaired glucose tolerance, insulin resistance and pancreatic β-cell dysfunction. Of these mechanisms, the role of the hypothalamic-pituitary-adrenal axis, circadian pacemakers in peripheral tissues, adipose tissue metabolism, sympathetic nervous system activation, oxidative stress and whole-body inflammation are discussed. Additionally, the impact of intermittent hypoxia and sleep fragmentation (key components of OSA) on intracellular signaling and metabolism in muscle, liver, fat and pancreas are also examined. In summary, this review provides endocrine and molecular explanations for the associations between common sleep disturbances and the pathogenesis of T2DM.

Keywords: Sleep, Obstructive sleep apnea, Shift working, Intermittent hypoxia, Metabolic syndrome, Diabetes, Obesity, Insulin resistance

Introduction

Modern society, characterized by widespread use of electricity, demand for high performance at work, shift work, prolonged commute times and multiple leisure time activities, has significantly changed human sleep patterns. The average self-reported sleep duration has decreased from over 8 hours in the 1960’s to ≈ 6.5 hours in 2012, with 20–30% of middle aged Americans reporting sleep duration of less than 6 hours [1-7]. Similar patterns have been reported in other populations [8,9] and confirmed in studies employing actigraphy to objectively quantify sleep duration [10,11]. In addition to voluntary and work-related sleep restrictions, a variety of common sleep disorders such as insomnia and obstructive sleep apnea syndrome (OSA) contribute to impaired sleep in over 30% of adults [12].

Over the past decade, substantial evidence has accumulated showing that sleep disorders negatively impact not only cognitive functions and performance [13,14], but also cardiovascular morbidity and mortality [15-18]. More recently, it has been recognized that sleep is also causally related to the regulation of glucose homeostasis and appetite control and that impaired sleep contributes...
to the rising prevalence of obesity and Type 2 diabetes mellitus (T2DM) across the globe. In the following review our goal is to discuss possible mechanisms behind the epidemiological and experimental findings that document an independent role for sleep disturbances (including short sleep, shift work and OSA) in the development of glucose intolerance, insulin resistance and pancreatic endocrine dysfunction – impairments ultimately leading to T2DM. Although some epidemiological data suggest that excessively prolonged sleep might also be associated with metabolic impairments, we have chosen not to cover this topic here due to the lack of experimental tools, poor understanding of this association and the possible confounding effect of other chronic diseases.

**Review**

**Physiological sleep**

Sleep is an actively regulated, periodically occurring state of reduced consciousness, muscle relaxation and altered responsiveness to stimuli occurring in mammals, birds, reptiles, amphibians, fish and even in flies and worms. Based on patterns of brain electric activity, eye movements and skeletal muscle tone, human sleep is separated into distinct stages: non-rapid eye movement (NREM) sleep, which is further divided into stages according to sleep depth (stage 1, stage 2 and stage 3 also referred to as slow-wave sleep), and rapid eye movement (REM) sleep occurring every 60–90 minutes initially as short episodes, but which progressively increase in duration during the night.

Sleep onset and periodicity are precisely controlled processes determined by three major factors: a) circadian rhythms, b) homeostatic drive and c) emotional/cognitive inputs. Circadian rhythmicity of sleep onset is secured through the master pacemaker located in the hypothalamic suprachiasmatic nucleus (SCN) with projections into various regions in the brain participating in the regulation of sleep timing, behavioral and endocrine processes, food intake, physical activity and substrate metabolism. The intrinsic rhythm of these cells is independent of exogenous stimuli and is mediated by cell-autonomous periodic changes in gene expression and protein levels of transcriptional factors, such as Clock/Bmal (with a complex network of transcriptional-translational negative feedback loops). Adequate entrainment of SCN intrinsic oscillations with environmental light/dark cycles is mediated by direct projections from retina to the SCN. In contrast, homeostatic drive represents a sleep promoting mechanism with molecular actors which remain to be identified; its magnitude and thus the tendency to fall asleep increases with the duration of wakefulness and diminishes during sleep [19].

**Whole body metabolism during sleep**

Contrasting physiological purposes of sleep and wakefulness are mirrored in substrate utilization and energy expenditure differences. During physiological sleep, which is harmonically entrained to environmental and behavioral zeitgebers (time cues), whole body energy expenditure drops by 15 - 35% with the lowest expenditure during slow-wave sleep and slightly higher during REM sleep [20]. Furthermore, glucose, lipid and protein turnover exhibits significant variability during the natural sleep/wake cycle that is independent of metabolic changes induced by food intake. For example, plasma glucose levels strongly follow the circadian pattern and progressively increase during sleep with the highest levels in the early morning [21-23]. Diurnal variations in glucose metabolism are mediated primarily through direct autonomic innervation of target organs from the SCN [21] and are independent of circulating insulin or glucagon levels [24,25]. In fact, SCN-driven autonomic output has been shown to regulate hepatic glucose output [21,26,27] and is most likely also involved in the reduction of skeletal muscle blood flow and decreased muscle glucose uptake during sleep [26-28]. In the anticipation of awakening, hepatic glucose output increases and contributes to the “dawn phenomenon” in healthy as well as diabetic subjects [28,29]. Additionally, decreased neuron activity during slow-wave sleep contributes to decreased glucose utilization by the brain during sleep [30]. Similar circadian sleep/wake oscillations have been described in lipid metabolism. Plasma triglycerides and fatty acids demonstrate strong circadian oscillations with progressively decreasing levels during sleep [31] when lipoprotein lipase (LPL) activity and fatty acid synthesis in adipose tissue are at their highest [28,32,33]. Some authors have reported a slight increase in plasma free fatty acids (FFA) and glycerol in the late stages of sleep, which has been attributed to central pacemaker activity as well as to the adipose tissue lipolysis promoting effects of growth hormone [28,34,35].

**Metabolic abnormalities in sleep disorders**

Inadequate sleep duration together with misaligned or irregular sleep (e.g. during shift work) not only impairs cognitive performance [13,14,28] but are also associated with increased mortality and morbidity [15-18]. More recently, epidemiological and experimental studies have demonstrated that sleep quality and quantity are important determinants of whole-body metabolism. It has been suggested that impaired sleep might causally contribute to the T2DM and obesity epidemic via mechanisms depicted in Figure 1 and described further below.

**Short sleep duration**

**Models**

The detrimental impact of short sleep duration on human health has been demonstrated in multiple studies
including: a) cross-sectional studies, b) longitudinal epidemiological studies and c) experimental studies using variable severity and duration of sleep deprivation in human volunteers. Even though the physiological need for sleep significantly varies between individuals and is dependent on other factors such as age, epidemiological studies in adults typically consider 7–8 hours of sleep as “normal” sleep. In contrast, the definition of “short sleep” across studies is quite heterogeneous (from subjectively reported insufficient sleep to cut-off values for sleep duration set at < 5, < 6 or < 7 hours).

Evidence

Large-scale cross-sectional epidemiological studies conducted in various populations including adolescents, middle-aged and elderly subjects, hypertensive patients and pregnant women have convincingly and repeatedly demonstrated that self-reported sleep duration is associated with approximately doubled prevalence of T2DM or impaired glucose tolerance, particularly in women [36-47]. Importantly, cross-sectional associations between T2DM and short sleep are independent of other traditional risk factors for diabetes. Furthermore, subjectively perceived insufficient, poor or short sleep is associated with several pre-diabetic features such as fasting hyperglycemia, elevated postprandial glucose and insulin levels or indices of whole-body insulin resistance [39,46,48-56]. Finally, inadequate sleep has also been shown to be detrimental in patients who have already developed diabetes, since it negatively impacts glycemic control [45,47].

Interpretation of cross-sectional studies is inherently limited due to the uncertainty of causality and its eventual direction. In fact, several reports suggest that hyperglycemia, hyperinsulinemia and endocrine changes associated with T2DM can significantly influence sleep quality and quantity [57-59]. To better understand possible impact of sleep duration on metabolic homeostasis, observations based on prospective studies have proven to be very informative. In these studies, subjects with variable sleep habits and sleep duration, but free of diabetes, were followed for an extended period of time while newly diagnosed cases of T2DM were recorded. Results of these studies, which followed from 661 to 70,026 adults over 4 to 32 years [60-71] plus meta-analyses [2,72] fully support the relationship suggested in cross-sectional studies. After adjustments for known risk factors, subjects with short sleep duration have a higher relative risk (RR = 1.28 [1.03-1.60]) of developing T2DM compared to those with normal sleep times.

Additional support for the epidemiological evidence has been provided by experimental studies demonstrating that healthy human volunteers exposed to a rather severe paradigm of total sleep deprivation lasting from one to five days develop insulin resistance [73,74] and β-cell dysfunction [75]. As a consequence of insulin resistance combined with defects in insulin secretion, fasting and postprandial glucose levels were increased following sleep deprivation [75-79]. Although total sleep deprivation studies have provided important insights into the role of sleep in metabolic regulations, studies using milder paradigms, restricting sleep to 4–5 hours/night for several consecutive nights more closely mimic chronic sleep loss present in today’s lifestyles. Despite the heterogeneity of study designs, partially sleep-deprived subjects also exhibited impairments in numerous parameters of glucose tolerance and insulin sensitivity [80-87]. Interestingly, the metabolic profile observed after sleep restriction shared several similarities with T2DM, including

![Metabolic pathways linking sleep disorders with the development of Type 2 diabetes. HPA (hypothalamic-pituitary-adrenal axis), ROS (reactive oxygen species), IL-6 (Interleukin-6), TNF-α (tumor necrosis factor-α).](image-url)
decreased muscle glucose uptake, increased liver glucose output and pancreatic β-cell dysfunction [80,83,84,88].

**Mechanisms**

**Endocrine** Despite the clear association between short sleep and metabolic impairments, the underlying endocrine and molecular mechanisms remain only partially elucidated. Among the suggested mechanisms, the causal role of the hypothalamo-pituitary-adrenal (HPA) axis and sympathetic activation are supported by the largest body of literature. Circulating cortisol, assessed either by 24 h profiles or by single measurements of evening cortisol levels, were elevated together with markers of sympathetic activation [81] and circulating catecholamines [86] after total or partial sleep deprivation [79-81,83,89,90] as well as in short sleepers [91]. In contrast, some studies reported impairments in glucose homeostasis in sleep restricted individuals along with unchanged cortisol and catecholamine levels [82-84,88]. The complexity of associated endocrine mechanisms can be further demonstrated by observations of elevated levels of pro-inflammatory cytokines, lower circulating testosterone, decreased thyroid stimulating hormone levels, impaired pulsatility of growth hormone secretion [81,92,93] and changes in adipokines secreted from adipose tissue [94-96] in short sleepers [97-103] as well as after sleep deprivation [104-107] (also reviewed in [108]).

**Appetite regulation** Prospective and cross-sectional studies have also identified short sleep duration as an independent risk factor for weight gain and abdominal fat accumulation (as reviewed in [109,110]). Experimental evidence supports this association, since sleep-restricted subjects express a preference for fat and carbohydrate rich foods [111,112] and increase their daily caloric intake by ≈ 20% [112-116]. It is therefore reasonable to suggest that insufficient sleep stimulates food intake [117] and contributes to the development of obesity and metabolic syndrome. Furthermore, short sleep duration decreased the amount of fat overweight subjects lost during caloric restriction [118]. Within the complex network of factors regulating food intake [119], increased drive to eat in subjects exposed to sleep deprivation [81,111,118,120-122] or in patients with short sleep duration [39,123] has been linked to decreased leptin (limits food intake, secreted from adipose tissue) and elevated ghrelin (increases food intake, secreted mainly from the stomach) plasma levels. However, opposite or conflicting results have also been published [79,85,90,114,116,118,124,125] pointing to the role of other factors, e.g. decreased levels of anorexigenic peptide YY (PYY) [126]. In summary, it is safe to conclude that development of obesity, due to neuroendocrine changes, induced by inadequate sleep represents an additional independent risk factor for the development of metabolic abnormalities.

**Circadian misalignment and shift working**

**Peripheral tissue pacemakers**

Non-traditional work schedules (including shift and night work) together with travel across time zones represent typical examples of circadian disruption. Under these circumstances, behavioral cues such as physical activity, food intake and sleep/wake cycling are misaligned with the autonomous timing of the central pacemaker located in the hypothalamic suprachiasmatic nucleus (SCN). Furthermore, cells of peripheral organs involved in metabolic control including the liver, adipose tissue and muscle express a functional network of pacemaker genes and exhibit circadian cycling in expression of these genes, similar to the autonomous circadian rhythmicity observed in the SCN. As a result, expression of hundreds of tissue-specific genes undergo circadian variation in peripheral tissues [127-130].

Because pacemakers in peripheral tissues do not get any direct information about the day/night cycle, other mechanisms have developed to secure harmonious synchronization of metabolic functions in peripheral tissues with the SCN (which receives information about light intensity through direct retinal projections). At the transcriptional level, entrainment of metabolic function in peripheral tissues could be mediated by glucocorticoids. Plasma levels of cortisol (or corticosterone in mice) exhibit a rigid circadian variability persisting even under conditions of experimental forced desynchronization [22]. Glucocorticoid synthesis and release is controlled by a peripheral clock-oscillator [131] entrained to the SCN via direct sympathetic innervation of the adrenals [132-134]. The resulting circadian oscillations in plasma glucocorticoid levels induce oscillations in gene expression in target tissues (e.g. the liver) by binding to the promoter region of the *Per* gene, which represents a key component of the peripheral pacemaker network in the liver, adipose tissue and skeletal muscle [135-140]. The unique feature of peripheral oscillators is that they can be entrained by external cues. For example, nutrition has been identified as a potent zeitgeber for peripheral pacemakers even when clock genes were deleted or the SCN damaged [141,142]. Similarly, physical activity and exercise have been shown to entrain peripheral oscillators especially in skeletal muscle [140].

Together with the transcriptional regulation of genes participating in peripheral pacemaker activity, metabolism in peripheral tissues can be synchronized with SCN via endocrine mechanisms. For example, metabolic responses to oscillations in plasma levels of melatonin (a hormone released from the pineal gland under direct SCN control) were documented in fat [143], muscle [144-146], the liver [147,148] and the pancreas [149]. Studies revealed that melatonin (or
melatonin receptor agonist) administration improved glucose homeostasis through various mechanisms including enhanced glucose uptake, increased glucose-induced insulin secretion, improved insulin sensitivity or decreased liver gluconeogenesis in various animal models [144,145,147,148, 150-159]. Melatonin or melatonin receptor agonists also increased glycerone synthesis in hepatocytes [147], limited fat accumulation in adipocytes [160] and even decreased adiposity in humans [161] and rats [162]. Additionally, growth hormone [163], thyroid stimulating hormone [164] and direct sympathetic innervation of peripheral tissues [165] also exhibits strong circadian rhythmicity and contributes to entrainment of peripheral pacemakers to the SCN and the metabolic needs of the whole organism.

**Metabolic impact of shift working**

The harmony between pacemakers located in the SCN and peripheral tissues and their synchronization with environmental and behavioral cycles such as light/dark cycle, sleep/wake cycle, food intake and physical activity is challenged by shift work and long-distance travel. Complete re-setting of the central biological pacemaker to a night shift work is extremely rare in humans, especially under rotating shift schedules [166-170]. Incomplete adaptation to irregular sleep patterns results in a significant misalignment between biological pacemakers and the living environment. Metabolically active tissues obtain environmental cues (e.g. nutrition and physical activity) at inappropriate “central” times or at an inappropriate times of their own pacemaker cycle. Alignment of central and peripheral pacemakers is important for survival and overall needs of the organism [171], while dysynchrony results in serious consequences including increased cardiovascular mortality and morbidity [172-178] and higher risk of cancer (reviewed in [179,180]).

Shift work and circadian misalignment profoundly impair metabolic function and glucose homeostasis. Cross sectional and retrospective studies have found a higher prevalence of T2DM [181-183], glucose intolerance [183], insulin resistance [184,185] and metabolic syndrome in shift workers [186-188]. Furthermore, a meta-analysis of observational studies confirmed higher risk of T2DM in shift workers, particularly men, in all shift-working schedules except evening and mixed shifts [189]. Shift workers also gained more weight over time [190,191]. Causal effect of shift work in the development of metabolic abnormalities has been corroborated in several prospective studies conducted in men and women who engaged in shift work. The studies found a higher risk of developing metabolic syndrome [192-196] and T2DM [176,197-201], although some of these findings lost significance after being adjusted for changes in body weight. All of the above effects seem to resonate in patients who have already developed diabetes and seem to be especially affected by the negative consequences of shift work. Elevated HBA1C levels were reported in diabetics engaged in shift work and insufficient diabetes control was linked to the duration of shift work employment and the number of hours worked per shift [177,182,192,193,201].

**Mechanisms**

Studies using mice with whole-body or organ-selective mutations in pacemaker genes have demonstrated the crucial role of central and peripheral pacemakers in the regulation of glucose levels, glucose tolerance, insulin sensitivity, insulin secretion and food intake [202-208]. For example, liver-specific loss of the *Bmal* gene induces hypoglycemia and altered expression of genes involved in glucose metabolism [209], while the β-cell-specific *Bmal* gene deletion results in hyperglycemia and impaired glucose-induced insulin secretion [205] caused by excessive production of reactive oxygen species [203]. Similarly, mice fed under conditions of central and peripheral pacemaker misalignment gained more weight and developed insulin resistance [210]. Additionally, healthy human volunteers subjected to circadian misalignment exhibited decreased insulin sensitivity, impaired compensatory insulin secretion and increased CRP (C-reactive protein) despite preserved total sleep time [211]. These regulations were also observed in shift work subjects, where plasma glucose and insulin responses to a test meal were significantly higher when identical food was administered during the night as opposed to during the day [212]. In parallel, insulin resistance and hyperinsulinemia were observed in shift work individuals [212,213].

Prolonging the natural 24-hour day to 28 hours (or more) for several consecutive days provides an experimental tool to investigate the metabolic impact of circadian misalignment and shift work independently of the possible influence of circadian oscillations in metabolic and endocrine pathways. Using such an experimental paradigm of forced dysynchrony in human volunteers resulted in elevated glucose and insulin levels along with impaired glucose tolerance and pancreatic β-cell dysfunction [22,84]. Additionally, circadian disruption accelerated diabetes development in diabetes-prone rats due to apoptosis of insulin secreting β-cells [214].

Recent studies have identified elevated FFA levels, decreased leptin levels and a disrupted cortisol rhythm as possible endocrine mechanisms contributing to the development of insulin resistance and β-cell dysfunction in shift workers and/or after circadian disruption. Furthermore, increased secretion of pro-inflammatory cytokines by macrophages has been reported after circadian disruption in mice [203,215], suggesting a putative mechanism for the overall pro-inflammatory activation typical of T2DM [216].
Obstructive sleep apnea syndrome (OSA)

Metabolic impact of OSA

Obstructive Sleep Apnea Syndrome (OSA) is a common sleep disorder with a recognized prevalence of 3 - 7% in the general population. Its prevalence is actually increasing along with the prevalence of obesity, which represents the most important risk factor for OSA [217]. OSA is about twice as common in men than in women [218,219]. OSA is characterized by repeated obstructions of the upper airways during sleep, causing intermittent oxygen desaturations and arousals during sleep. OSA is widely recognized as an independent risk factor for cardiovascular diseases [220-222]. Moreover, a growing body of evidence suggests that OSA is also associated with a number of metabolic alterations such as dyslipidemia, insulin resistance, glucose intolerance and T2DM. This has been reviewed extensively in the last few years [223-226]. Several cross-sectional studies have shown that obstructive sleep apnea impaired glucose tolerance and/or insulin sensitivity, as measured by HOMA-IR, even after adjusting for BMI [227-230]. Overall, it has been reported that the prevalence of prediabetes, assessed by insulin resistance and glucose intolerance, was higher in OSA patients than in controls with estimates varying from 20 to 67% [231]. More importantly, the severity of nocturnal hypoxia in non-obese OSA patients was associated with insulin resistance [232], suggesting that the OSA-related hypoxia-reoxygenation sequences play a major role in this metabolic dysfunction.

In large longitudinal studies, such as the Wisconsin cohort or the Busselton Health Study, the authors were able to demonstrate that OSA was associated with a higher prevalence of T2DM over 2 to 11 year follow-up periods [233-236]. Meta-analysis of prospective studies confirmed that moderate to severe OSA increases the risk of development of T2DM by approx 60% [237]. Finally, based on the hypothesis that OSA can cause insulin resistance and diabetes, several studies have investigated whether OSA treatment by CPAP could reverse these deleterious effects. Uncontrolled studies examining the effect of CPAP on glucose tolerance and insulin sensitivity in OSA patients with or without diabetes have yielded mixed results, leading to no clear conclusion [231]. Of the nine randomized controlled trials that have examined the effect of CPAP (compared with sham-CPAP) on glucose metabolism, only four studies demonstrated beneficial effects for therapeutic CPAP [231]. However, it should be emphasized that overall compliance with CPAP therapy has been demonstrated to be rather limited [238] and could influence outcomes of published studies. Recent study showed that CPAP use limited to 4 hours/night (traditionally considered as the lower limit of “compliant” CPAP use) would not sufficiently treat REM-associated apneas and hypopneas, which are closely associated with HBA1c levels [239]. Only minor improvements in glucose control can thus be expected with 4 hours/night CPAP use and prolonged CPAP therapy (i.e. 7 hours/night) was calculated as necessary to achieve clinically significant improvements in HBA1c levels [239]. Similarly, changes in HBA1c levels were associated with CPAP use only in those T2DM patients, who used CPAP for more than 4 hours/night [240].

Non-Alcoholic Fatty Liver Disease (NAFLD), a prevalent liver disease in which fat excessively deposits in the liver, has been recently associated with OSA [241]. NAFLD is related to insulin resistance and is included among the clinical conditions associated with metabolic syndrome. Interestingly, it was suggested that OSA-induced intermittent hypoxia was associated with hepatic fibrosis and inflammation in both obese or non-obese patients [242-245]. Minville et al. further suggested that the severity of nocturnal hypoxia was independently associated with steatosis, and that pre-existing obesity exacerbated this effect [246]. These results were confirmed in pediatric OSA patients [247].

Mechanisms

Intermittent hypoxia

Whole-body effects of intermittent hypoxia

Numerous studies have investigated the link between intermittent hypoxia, as a component of OSA, and insulin resistance. In several rodent models, chronic exposure to IH induced impaired glucose tolerance (GTT) [248-250], increased HOMA index [251-253] and impaired glucose clearance [254]. Moreover, acute IH exposure of healthy human volunteers resulted in a decrease in insulin sensitivity and glucose effectiveness (the ability of glucose itself to stimulate glucose uptake and suppress hepatic glucose production) [255].

Overall, CIH appears to be responsible for carbohydrate dysregulation, nonetheless, the mechanisms involved remain unclear. In the following sections, we will review the consequences of IH on insulin target tissues, namely the liver, skeletal muscle, the pancreas and adipose tissue (summarized in Figure 2), with special emphasis on the molecular mechanisms involved, such as impaired lipid metabolism, inflammation, oxidative stress and sympathetic nervous system activation.

Impact of IH on the liver

Structural damage. Studies have demonstrated that CIH can induce liver damage and increase serum levels and activity of key liver enzymes such as serum aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase in both mice and humans [251,256-258]. Several weeks of IH exposure resulted in liver steatosis, necrosis, inflammation with neutrophil accumulation and collagen deposits [256,257,259]. While triglyceride content is increased by CIH in lean and obese mice [251,257], hepatic cholesterol content appears to be depleted
after 12 weeks of IH but was, by contrast, increased after 6 months in another study [257,258].

Exposure to IH led to increases in key lipid biosynthesis enzymes in the liver (SREBP-1, SCD-1 or HDL receptor) [260,261], at least partly mediated by HIF-1 transcription factor [262]. Glucose production is upregulated by IH, as supported by the observation of higher glycogen content [257,258], increased gene expression and protein levels of key gluconeogenic enzymes [250] and increased glucose output from isolated hepatocytes [250].

Oxidative stress and inflammation. Nitric oxide metabolites as well as liver iNOS levels have been shown to be increased by CIH along with reduced activity of liver antioxidant enzymes and DNA damage and apoptosis. Intermittent hypoxia effects may be direct and/or mediated through the activation of the sympathetic nervous system. HIF-1α (hypoxia inducible factor 1-alpha), NF-κB (nuclear factor-κB), GLUT4 (glucose transporter type 4).

Overall, experimental evidence suggests that IH promotes liver injury and increases hepatocyte glucose output through several mechanisms. It should be noted that structural and functional lesions observed in IH-exposed livers resemble those of non-alcoholic fatty liver disease (NAFLD), a prevalent liver disease associated with OSA [246,265]. Therefore, apnea-related intermittent hypoxia appears to play a major role in OSA-related liver injury.

Impact of IH on skeletal muscle As the principal insulin-sensitive organ, skeletal muscle is responsible for 80 to 90% of insulin-induced glucose uptake. However, probably because of the lack of consensus about the time-course of insulin resistance development, very few studies have focused on skeletal muscle metabolism in response to IH. It was suggested that IH-induced modifications of muscle metabolism were characterized by a decrease in creatine phosphate, citrate, alpha-ketoglutarate and glutamate content and by alterations in the anaerobic glycolytic pathway [266]. More recently, Liyori et al. observed a decrease in glucose metabolism in the soleus, a mostly oxidative muscle, using a mice model of CIH [252]. Finally, an alteration of the cytosolic-to-membrane translocation of GLUT4 that could provide an explanation for the development of IR in mice exposed to CIH [267].
Impact of IH on the pancreas Insight into the effects of IH on pancreatic function is of great importance for understanding mechanisms leading to impaired glucose homeostasis. Although many hypotheses have been proposed, only a few have been confirmed [268]. In severely obese adults, OSA was independently associated with an increase in basal pancreatic beta-cell function although glucose metabolism remained normal [269]. On the other hand, pancreatic insulin secretion was not affected in healthy volunteers exposed to IH, although insulin sensitivity and glucose effectiveness were diminished [255]. In mice exposed to CIH, beta-cell death as well as proliferation were observed [270,271]. Due to down-regulation of the enzyme prohormone convertase 1 (converting proinsulin to insulin), insulin content was decreased in islets from CIH-treated mice [272]. In-vitro cellular experiments have also suggested that IH exposure diminished glucose-induced insulin secretion due to down-regulation of CD38 gene transcription, which is involved in Ca2+ mobilization and thus insulin secretion [273]. Finally, studies in mice models using antioxidant strategies suggested that ROS are involved in IH-induced pancreatic damages [271,272].

Impact of IH on adipose tissue Adipose tissue is generally recognized as a key player in insulin resistance. Free fatty acids (FFA) released by lipolysis of adipose tissue are able to induce insulin resistance through their effects on muscle, liver and adipose tissue itself (see [274] for review).

Results from several studies showed that IH can cause dyslipidemia through an increased FFA release [275-277] than can be normalized by oxygen supplementation in humans [276] and is accompanied with morphological and functional remodeling of the adipose tissue in mice [277]. Moreover, IH-induced dyslipidemia can also be related to decreased lipoprotein clearance due to the inhibition of lipoprotein lipase (LPL) mediated by HIF-1 and Angiopoietin-Like 4 (Angptl4) [249,277,278]. Finally, Intermittent hypoxia down-regulates adiponectin in 3 T3-L1 adipocytes [279], which is a potent insulin-sensitizing hormone and increases adipose tissue production of resistin that can contribute to the development of insulin resistance through pro-inflammatory processes involving TNFα and IL-6 production [280].

Sympathetic nervous system activation Healthy adults display lower sympathetic nervous system (SNS) activity during sleep than during wake-time. In contrast, OSA patients exhibit high level of sympathetic nervous system activity during both wake-time and sleep, accompanied by higher levels of circulating catecholamines [281,282]. Both human and animal models of IH reproduce this phenotype. Indeed, IH exposure has been shown to increase sympathetic nervous system activity in healthy humans [283] and in rodents [284,285]. Oxidative stress, increased HIF-1α signaling and decreased HIF-2 signaling as well as endothelin-1 have been proposed as key mechanisms in IH-induced SNS activation [286].

Increased sympathetic tone strongly impacts lipid and glucose metabolism, through circulating factors as well as neural innervation of the liver, pancreas, skeletal muscle and white adipose tissue [287-289], depicted in Figure 2. Adrenal epinephrine released during sympathetic activation triggers glucose production and impairs insulin secretion, thereby promoting insulin resistance [290]. Consistently, sympathetic nervous system inhibition by carotid body denervation abolished insulin resistance in a rat model of diet induced obesity [291] and abolished IH-induced fasting hyperglycemia and HOMA-IR elevation [292]. Moreover, epinephrine, and to a lesser degree norepinephrine, have been largely studied and acknowledged as crucial mediators of adipose tissue lipolysis [293,294] acting through several β-adrenoceptor subtypes [295,296]. It is therefore tempting to postulate that IH-induced lipolysis and insulin resistance might be mediated through sympathetic nervous system activation. Finally, sympathetic innervations could be involved in hepatic glucose release [297] and in muscle insulin resistance [298]. In human volunteers, a 5 hour IH exposure induces a decrease in insulin sensitivity along with an increase in sympathetic nervous system activity but to date no causal link has been demonstrated [255]. Even though using α-blockers or inhibiting epinephrine release by adrenal medullectomy improved glucose tolerance [299,300] and phentolamine treatment additionally prevented impairments in insulin secretion induced in mice by IH [299], the impact of IH on insulin sensitivity seems to be independent of autonomic activity as neither medullectomy, phentolamine treatment or administration of SNS blocking agent hexamethonium improved IH-induced insulin resistance in mice [252,299,300]. More studies are therefore needed to clarify the involvement of SNS activation in IH-induced metabolic dysregulation.

Sleep fragmentation Apneic episodes, a cornerstone of OSA, are associated with bouts of increased brain activity (arousals) leading to repetitive partial or full awakenings and thus, sleep fragmentation [301]. Taking into consideration the multiple detrimental metabolic consequences of intermittent hypoxic exposure, the obvious question with important clinical and therapeutic implications has been asked: does sleep fragmentation per se, without concomitant hypoxemia contribute to the development of metabolic impairments observed in OSA?

Sleep fragmentation represents a situation where total sleep duration is preserved, but continuous sleep and its architecture is interrupted by internal (e.g. arousals in OSA) or external (e.g. auditory stimuli in experiments) factors.
Experimental studies using sleep fragmentation paradigm showed, that disruption of sleep by auditory and mechanical stimuli for two to three nights decreased insulin sensitivity [302-304], which was not compensated by increased insulin secretion [303], suggesting that such exposures compromise fundamentals of glucose homeostasis and induce impairments typical for pathogenesis of T2DM.

Epidemiological studies support the experimental evidence. Number of arousals was closely associated with fasting insulin levels and insulin resistance even after adjustments for age and severity of adiposity in young adults [301] and EEG cues of wake/sleep transitions were associated with decreased insulin sensitivity and impaired insulin secretion independently of age, sex, body mass index, sleep stages, the arousal index, and the apnea-hypopnea index [305]. Importantly, it was observed that sleep fragmentation exerts a negative impact in subjects with clinically manifested diabetes, as suggested by a community-based study investigating middle-age adults assessing sleep using wrist actigraphy which demonstrated that sleep fragmentation was associated with higher fasting glucose and insulin levels as well as with reduced insulin sensitivity in patients with T2DM, but not in non-diabetics [56]. Additionally, sleep of patients with T2DM is characterized by higher sleep fragmentation scores detected by wrist actigraphy [306].

Mechanisms linking sleep fragmentation to altered metabolic control probably include elevated night and morning cortisol levels [302,307] as well as sympathetic activation [302]. Additionally, sleep fragmentation is independently associated with increased adiposity [308] and less weight reduction during weight loss program [309]. Experiments performed in rodent models of acute and prolonged (2 weeks) sleep fragmentation confirmed increased adiposity, insulin resistance, hyperglycemia and impaired insulin secretion [310-312]. Additionally, animal demonstrated increased markers of inflammation and oxidative stress in adipose tissue, in parallel to elevated corticosterone levels [310,313]. Sleep fragmentation in mice also induced changes in visceral adipose tissue transcriptome with modifications in signaling and metabolic pathways including glucose metabolism [314] and adipocyte differentiation [315], however it is not known, whether these changes happen also in humans. Besides endocrine effects, sleep fragmentation seems to also have epigenetic effects demonstrated by insulin resistance and increased body weight of offspring of pregnant dams exposed to sleep fragmentation [316].

Sleep fragmentation is typically accompanied by a reduction in slow-wave sleep duration, which represents another mechanism for impaired glucose metabolism. It has been proposed that slow-wave sleep is particularly important for metabolic homeostasis as selective suppression of slow-wave sleep (SWS), without perturbation of total sleep time, resulted in glucose intolerance, insulin resistance and impaired β-cell function [303]. Selective SWS suppression (but not REM sleep suppression) also elevated morning glucose and insulin levels and impaired post-prandial glucose homeostasis in healthy men [317]. Furthermore, sleep fragmentation impaired satiety perception, impaired insulin and glucagon-like peptide 1 response to meals [304] and reduced fat oxidation [318], making subjects prone to adipose tissue accumulation, especially under conditions of reduced satiety perception [304]. The importance of SWS in glucose homeostasis is further supported by cross-sectional studies documenting that SWS duration is strongly predicting glucose-induced insulin secretion in obese individuals [43] as well as by studies reporting shorter SWS in T2DM compared to nondiabetic subjects [58]. Importantly, duration of SWS was negatively associated with HbA1c levels also in T1DM patients [319], suggesting a global position of SWS in the regulation of glucose metabolism, independently of obesity or pathogenesis of T2DM. In contrast, REM sleep duration seems to be more related to energy homeostasis, as reduction in REM sleep is associated with obesity in children and adults [320-322], which could be at least partly explained by increased metabolic rate during REM sleep, which is lost with REM time reduction [323].

Conclusions

In this review, we summarized the current knowledge of molecular and endocrine mechanisms underlying independent and possibly causal associations between short sleep, circadian rhythm disruption (as observed with shift working) and OSA with glucose intolerance, insulin resistance, impaired insulin secretion and ultimately T2DM. Based on the literature, it can be concluded that hypothalamic-pituitary-adrenal axis activation with increased circulating cortisol levels, misalignment between central and peripheral pacemakers, enhanced lipolysis and modified adipokine release in adipose tissue and intermittent hypoxia-induced sympathetic nervous system activation, generation of reactive oxygen species and the induction of a whole-body pro-inflammatory state are the most likely mediators. Several of these mechanisms represent potential drug targets, however future research is warranted to determine, whether targeting the above mentioned molecular regulations would provide metabolic benefit in patients with inappropriate sleep.

Competing interests

The authors declare that they have no competing interests.

Authors’ contributions

JP, MW: Wrote sections on physiological sleep, sleep fragmentation and shift working. AB, MH: Wrote sections on the metabolic consequences of obstructive sleep apnea in-vivo and in-vitro, contributed to sections on the effect of intermittent hypoxia on liver and muscle. AT, DG: Wrote section on the effects of intermittent hypoxic exposure on adipose tissue and pancreas and the development of insulin resistance. All authors read and approved the final manuscript.
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