

Special Issue: Metabolism Through the Lens of GPCRs

Review

Sleep Control, GPCRs, and Glucose Metabolism

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Modern lifestyles prolong daily activities into the nighttime, disrupting circadian rhythms, which may cause sleep disturbances. Sleep disturbances have been implicated in the dysregulation of blood glucose levels and reported to increase the risk of type 2 diabetes (T2D) and diabetic complications. Sleep disorders are treated using anti-insomnia drugs that target ionotropic and G protein-coupled receptors (GPCRs), including γ -aminobutyric acid (GABA) agonists, melatonin agonists, and orexin receptor antagonists. A deeper understanding of the effects of these medications on glucose metabolism and their underlying mechanisms of action is crucial for the treatment of diabetic patients with sleep disorders. In this review we focus on the beneficial impact of sleep on glucose metabolism and suggest a possible strategy for therapeutic intervention against sleep-related metabolic disorders.

Sleep Disturbances and T2D

Impairments in the daily sleep/wake cycle due to sleep disturbances, including shift working, obstructive sleep apnea, and insomnia, are known to increase the risk of T2D [1,2]. Clinical studies on a large cohort of nurses showed that periods of shift work correlated with an increased risk of T2D later in life [3,4]. A subsequent study indicated that although sleep disturbances are often accompanied by depression or hypertension [5], sleep impairments themselves increase the risk of T2D [6]. Loss of sleep for one night was previously shown to induce insulin resistance in healthy human subjects [7,8], whereas restriction of sleep from 8.5 to 5.5 h for 2 weeks caused glucose intolerance without affecting insulin secretion [9]. Mechanistically, elevations in sympathetic nervous tone are a major cause of glucose intolerance in healthy human subjects [10–12]. In addition, T2D patients with short or long sleep times had elevated glucose and HbA1c levels in Japanese populations [13]. Thus, an adequate quantity of sleep is important for the maintenance of glucose homeostasis.

The quality of sleep is also known to be relevant to the regulation of energy and glucose homeostasis [1]. A previous study reported that rapid eye movement (REM) and non-REM (slow-wave sleep) sleep are functionally linked to appetite and glucose metabolism, respectively [8]. Acute suppression of slow-wave deep sleep caused insulin resistance in healthy human subjects [14]. Similarly, the amount of slow-wave sleep was shown to decrease in patients with T2D [15]. Decreases in slow-wave sleep have also been associated with thickening of the intima of the carotid arteries as an index of the progression of atherosclerosis [16]. However, it is important to note that some studies have indicated that REM sleep plays an important role in glucose metabolism. Apnea and hypopnea during REM sleep were found to be associated with insulin resistance, whereas during non-REM sleep they were associated with glucose intolerance, in a community-based sample [17]. Furthermore, chronic glycemic control has been adversely associated with obstructive sleep apnea in REM sleep but not non-REM sleep in

Trends

Sleep disturbances are associated with increased risk for type 2 diabetes (T2D). Enhanced sympathetic tone, desynchronization of tissue circadian clocks, abnormal secretion of hormones, and obesity are relevant to insulin resistance during sleep disturbances.

Melatonin regulates energy metabolism by maintaining circadian rhythms. Treatment with melatonin improves glucose metabolism by increasing insulin sensitivity in target tissues in T2D animals. Their beneficial effects in humans are controversial.

γ -Aminobutyric acid (GABA) directly modulates insulin secretion from pancreatic islet β cells. The metabolic effects of GABA agonists/benzodiazepines on glucose metabolism remain controversial.

Timely activation of the orexin system plays a crucial role in the maintenance of glucose homeostasis. Timely administration of orexin receptor antagonists might be beneficial for improving glucose intolerance in patients with sleep disorders.

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patients with T2D [18]. Impaired sleep quantity and quality are thus closely associated with the development of glucose dysregulation and progression of T2D complications [1,16].

Mechanism of Glucose Intolerance in Sleep Disturbance

The underlying mechanisms by which sleep disturbances cause glucose intolerance remain unclear and controversial [1,10]. Excessive activation of the autonomic sympathetic nervous system (SNS) is a commonly accepted crucial factor that causes glucose intolerance and insulin resistance on sleep restriction [1,10]. Inappropriate elevations in glucocorticoid and growth hormone levels also promote glucose intolerance under sleep-deprived conditions because these hormones act to elevate blood glucose levels against insulin [1,10,12]. Although a previous study reported that insulin signaling was only partially impaired in cultured adipocytes from subcutaneous fat biopsy samples from healthy subjects after four nights of sleep restriction [19], a recent *in vivo* study demonstrated that subchronic sleep restriction (five nights with 4 h of sleep) caused peripheral but not hepatic insulin resistance in healthy humans [20]. Furthermore, one night of sleep loss was found to alter the epigenetic and transcriptional profiles of core circadian clock genes in skeletal muscle and subcutaneous adipose tissue biopsy samples from healthy subjects in a tissue-specific manner [21]. Since these genes are key regulators of glucose metabolism, and because their alteration is associated with impaired glucose tolerance, the desynchronization of tissue circadian clocks following sleep restriction may underlie the associated metabolic disorders. It currently remains unclear how these factors interact with each other to cause insulin resistance on sleep deprivation. Further studies are needed to elucidate the precise mechanisms, particularly in terms of the influences of changes in sleep quantity and quality.

Sleep restriction for longer periods causes abnormal body weight gain with increases in fat mass and sleep restriction-induced increases in food consumption are considered to be key mechanisms underlying the weight gain observed [1,10,12,22]. Untimely eating and/or late-night eating have been implicated in excessive body weight gain [23,24]. However, there are conflicting findings for the effects of sleep loss on the secretion of the hunger-promoting hormone ghrelin and satiety-promoting hormone leptin [25]. Evidence for the impact of sleep restriction or circadian misalignment on daytime physical activity and energy expenditure is also inconsistent; this may be due to different protocols and/or backgrounds of subjects enrolled in each trial and the differential influences of sleep on multiple components of energy expenditure [25,26]. Sleep restriction is considered to compromise dietary interventions to reduce adiposity because 2 weeks of combined energy and sleep restriction caused a smaller loss of body fat and greater loss of fat-free body mass in overweight middle-aged adults [27]. Similarly, better sleep quantity and quality were associated with greater fat-mass loss during moderate caloric restriction in obese adults [28]. Prolonged sleep restriction with concurrent circadian disruption for 3 weeks, as a model of shift work, has been shown to decrease the resting metabolic rate and increase postprandial plasma glucose levels due to an inadequate pancreatic β cell response; however, minor weight loss was observed in this study [29]. Further studies with large cohorts are required to clarify whether the impact of sleep restriction on energy expenditure is sufficient to promote obesity and glucose intolerance. The combination of enhanced sympathetic nerve activity, increased secretion of counter-regulatory hormones, and obesity on sleep restriction may result in insulin resistance and glucose intolerance.

Improvement in Sleep with Anti-insomnia Drugs and Glucose Metabolism

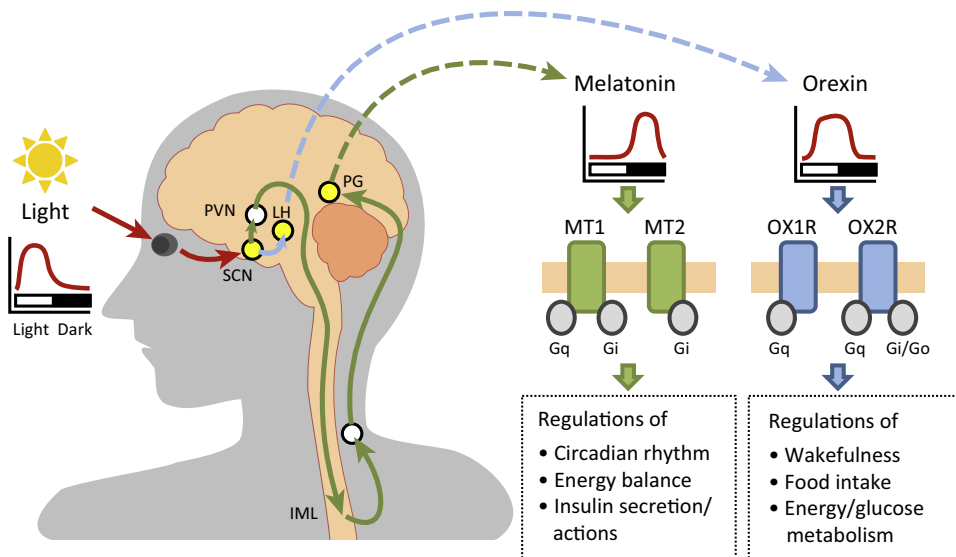
Since sleep disturbances have been strongly implicated in glucose intolerance and insulin resistance, it is important to establish whether the amelioration of sleep disturbances by anti-insomnia drugs affects glucose metabolism in diabetic patients. Melatonin agonists, a dual orexin receptor antagonist (DORA), and GABA agonists (benzodiazepines and non-benzodiazepines) are clinically used in the treatment of insomnia [30,31]. Up-to-date knowledge of their impacts on glucose metabolism is summarized below.

Melatonin and Glucose Metabolism

Melatonin Regulation of Glucose Homeostasis

The suprachiasmatic nucleus (SCN) in the hypothalamus is a master biological clock that regulates circadian periods of approximately 24 h [1,22,32]. Light is a crucial environmental factor that affects and resets clock function [1,22,32]. Various physiological functions, including the sleep/wake cycle, are synchronized with SCN oscillatory activity. Individuals with chronic circadian desynchronization (e.g., shift workers) exhibit daytime sleepiness and nighttime insomnia [1,32,33]. Melatonin is a hormone produced in the pineal gland at night according to daily signals from the SCN [34–36] (Figure 1). In mammals, melatonin is involved in the entrainment of the circadian rhythms of physiological functions such as sleep timing, blood pressure regulation, and seasonal reproduction. Melatonin acts via three GPCRs: MT1, MT2, and MT3 [37]. MT1 and MT2 (also known as melatonin receptor 1A and 1B, respectively) have been implicated in circadian rhythm-regulated sleep control [38,39]. Therefore, melatonin and its receptor agonists are utilized in the treatment of sleep disorders with rhythm disturbances [40–42].

Melatonin regulates energy homeostasis by affecting endogenous circadian rhythms [36,43]. Serum levels of melatonin were previously reported to be decreased in diabetic Goto Kakizaki rats and T2D patients with hyperinsulinemia [44]. Genome-wide association studies showed a close association between SNPs in the *MTNR1B* gene (encoding MT2) and fasting hyperglycemia and T2D [45–48]. Chronic oral administration of melatonin prevented excessive body weight gain, hyperglycemia, hyperinsulinemia, and/or hyperlipidemia in T2D rats [49–51]. Under these



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Figure 1. Melatonin and Orexin Systems for Regulating Energy and Glucose Metabolism under a 24-h Light/Dark Cycle. Circadian rhythms are produced by a central biological clock system located in the suprachiasmatic nucleus (SCN), according to the light/dark cycle. Circadian signals are transmitted to the pineal gland (PG) through the paraventricular hypothalamic nucleus (PVN), the intermedialateral nucleus (IML) in the spinal cord, and the superior cervical ganglia and, as a result, melatonin is specifically secreted in the dark phase. Melatonin activates two types of receptors, MT1 and MT2, to regulate circadian rhythms in peripheral tissues, energy balance, and the secretion and actions of insulin. For more details on the neural pathway for melatonin production, see [36]. Circadian signals are also sent to the perifornical/lateral hypothalamic area (LH), mainly through the dorsomedial hypothalamic nucleus and, as a result, orexins are secreted during active waking (i.e., the light phase for diurnal animals and dark phase for nocturnal animals). The secretion of orexin is also promoted by hypoglycemia and increased motivation. Orexin receptor 1 (OX1R) is selective for orexin A, whereas OX2R has similar affinities for orexin A and orexin B. Orexin stabilizes the wakefulness state, promotes feeding behavior, and regulates energy and glucose metabolism through the autonomic nervous system. For further details on the functions of orexin, see [70].

conditions, melatonin improved insulin sensitivity and insulin secretion [51,52]. Melatonin also increased serum levels of adiponectin, an adipose tissue-derived adipokine that has the ability to ameliorate insulin sensitivity by facilitating fatty acid oxidation and energy expenditure via the AMPK- and PPAR γ -mediated pathways [53]. Melatonin also decreased elevated serum levels of free fatty acids (FFAs), which are attributable to insulin resistance in obesity and T2D [51]. In mice fed a high-fat diet, oral treatment with melatonin for 8 weeks decreased hyperglycemia and hyperinsulinemia [54]. These effects were due to improved insulin sensitivity, at least via the restoration of the vascular action of insulin, which is responsible for glucose utilization in skeletal muscle. These findings suggest that melatonin exerts beneficial effects on impaired glucose regulation in obesity and/or T2D.

However, the beneficial effects of melatonin on glucose metabolism are controversial. A previous study reported that acute administration of melatonin in both the morning and evening impaired glucose tolerance in healthy young women [55]. Similarly, daytime administration of melatonin acutely reduced glucose tolerance and insulin sensitivity in postmenopausal women [56]. There are also negative findings from markedly longer trials, which have instead found improvements in various metabolic/cardiovascular parameters, such as blood pressure and cholesterol values, in patients with metabolic syndrome [57]. The common diabetes risk variant in *MTNR1B* (non-coding variant, rs10830963) was associated with delayed offset of melatonin synthesis and, thus, a longer duration of elevated melatonin levels in healthy humans [58]. However, melatonin has been shown to improve metabolic dysfunctions, oxidative stress, and insulin resistance in sleep-restricted rats [59], and rare coding SNP variants of the human *MTNR1B* gene that inactivate MT2 receptors are also associated with T2D [60]. Therefore, supplementation with melatonin may be beneficial, particularly for individuals with adverse baseline metabolic profiles.

Decreases and increases in insulin secretion have been reported after melatonin treatment. Previous studies have mostly shown the inhibitory effects of melatonin via MT1 and MT2 receptors expressed in pancreatic islet β cells [61]. Melatonin reduces cytosolic cAMP and/or cGMP levels and suppresses insulin secretion via these receptors [61]. An increase in the expression of the MT2 receptor found in the islets of humans with a common diabetes risk variant in *MTNR1B* (rs10830963) was found to enhance the melatonin-induced inhibition of insulin release in insulin-secreting cells [62]. By contrast, other studies demonstrated the stimulatory effects of melatonin on insulin secretion. Treatment with melatonin also induced the secretion of insulin from the pancreas in rats *in vivo* [52,63]. In addition, melatonin ameliorated hyperglycemia by increasing insulin secretion and facilitating β cell regeneration and proliferation in streptozotocin-induced diabetic rats [64]. Since melatonin and its metabolites are known to exert antioxidant and anti-inflammation effects, the protection of pancreatic β cells from dysfunction or apoptosis in alloxan- and streptozotocin-induced diabetic rats may be explained by these mechanisms [65]. The kinetics of the effects of melatonin in islets are complex because melatonin was shown to inhibit glucose-stimulated insulin secretion when used acutely in the INS-1 pancreatic β cell line [66], whereas prolonged exposure to melatonin (with a duration mimicking the period of darkness) enhanced insulin secretion from β cells [67], stressed islets from nondiabetic humans, and islets derived from T2D patients [52] by the sensitization of cAMP signaling. Although melatonin supplementation may improve metabolic function under certain conditions, it is important to note that its efficacy is strongly affected by numerous factors, including administration timing, duration, and dose and the genetic background of subjects.

Melatonin Agonists and Glucose Metabolism

Based on the beneficial effects of melatonin in animal models, melatonin agonists may also exert beneficial effects on the control of glucose metabolism. The effects of the melatonin agonist ramelteon on body weight gain and glucose metabolism were examined in 20 patients with schizophrenia. Treatment with ramelteon for 8 weeks did not affect body weight, waist

circumference, or body-fat composition. Ramelteon also did not alter blood glucose or insulin levels, whereas it decreased serum cholesterol levels [68]. The metabolic effects of another melatonin agonist, agomelatine, were examined in 40 patients with depression and poorly controlled T2D; agomelatine treatment for 4 months decreased HbA1c levels by the end of the study, whereas fasting blood levels and body weights were unaltered [69]. Studies with large cohorts are needed to more clearly understand the effects of melatonin agonists on glucose metabolism and obesity.

Orexin and Glucose Metabolism

Orexin Regulation of Glucose Homeostasis

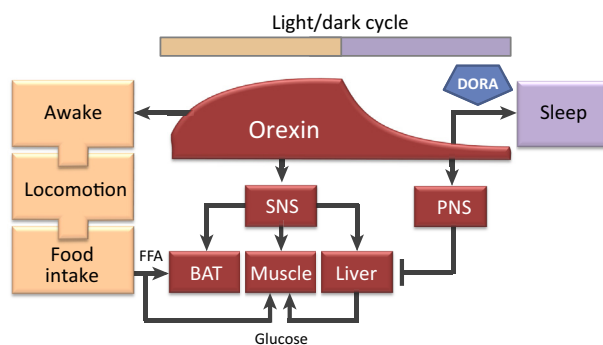
Orexins (also known as hypocretins) are hypothalamic neuropeptides and endogenous ligands for two GPCRs, orexin receptor 1 (OX1R) and 2 (OX2R) [70]. OX1R is selective for orexin A, whereas OX2R has similar affinities for orexins A and B. Although orexins regulate feeding behavior, they are mainly regarded as key modulators of the sleep/wakefulness cycle (Figure 1). OX2R plays a major role in the maintenance of a consolidated wakefulness state, whereas OX1R and OX2R both contribute to the inhibition of REM sleep. Orexin-deficient mice display a narcolepsy-like phenotype, similar to dogs that carry a mutation preventing the expression of OX2R [70].

The hypothalamic orexin system is also critically involved in the regulation of energy and glucose metabolism [22,71–73]. Narcolepsy caused by orexin deficiency was previously shown to be accompanied by obesity and glucose intolerance in humans and animals [74–76]. Orexin-deficient mice developed glucose intolerance and insulin resistance with aging and severe obesity on a high-fat diet [77]. OX2R-knockout mice also showed glucose intolerance, while transgenic mice overexpressing orexin were protected from abnormal body weight gain and glucose intolerance on a high-fat diet [73]. These findings indicate that orexin is required for the maintenance of glucose homeostasis.

Orexin levels in the cerebrospinal fluid (CSF) change daily; they increase in the awake–active phase and decrease in the sleep–resting phase [78,79]. Administration of orexin A in the awake–active phase acutely increased blood glucose levels via the OX2R–sympathetic nerve pathway and subsequently decreased blood glucose levels via the OX1R–parasympathetic nerve pathway in mice fed a normal chow diet [71]. The bidirectional regulation of hepatic gluconeogenesis by orexin explains the mechanism underlying daily glucose oscillations [71]. In T2D *db/db* mice, administration of orexin A in the awake phase, according to the daily rhythm of endogenous orexin secretion, ameliorated blood glucose levels in the subsequent resting phase by suppressing hepatic gluconeogenesis, whereas no such improvement was observed when orexin A was administered during the sleep–resting phase [71]. Thus, timely activation of the orexin system is important in ameliorating glucose metabolism. We consider elevations in orexin in the early awake phase to support locomotion with food seeking by increasing hepatic gluconeogenesis. Once a sufficient amount of food is acquired for survival, orexin suppresses hepatic gluconeogenesis to avoid postprandial hyperglycemia [71]. Orexin-induced glucose uptake in skeletal muscle and thermogenesis in brown adipose tissue [80,81] may also contribute to the regulation of daily rhythms in glucose metabolism. Overall, orexin appears to play a pivotal role in the dynamic regulation of glucose metabolism (i.e., the maintenance of ‘glucose homeodynamics’) according to the daily sleep/wake cycle (Figure 2).

Orexin Receptor Antagonists and Glucose Metabolism

Changes in orexin levels have been suggested as a cause of insomnia; however, CSF orexin levels have not yet been reported in patients with insomnia. Accordingly, transgenic mice overexpressing orexin showed reduced sleep quality [82]. mRNA expression of *preproorexin* was previously shown to be reduced due to hyperglycemia in genetically obese *ob/ob* mice [83]



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Figure 2. The Role of Orexin in the Maintenance of Energy and Glucose Homeostasis According to the Sleep/Wake Cycle. The hypothalamic orexin system is activated by the circadian system, lower energy levels, and motivation/emotion. As a result, orexin levels in the cerebrospinal fluid exhibit daily rhythms. Orexin levels are increased during the awake phase. Orexin promotes wakefulness in association with an increase in locomotor activity and food intake. It also increases glucose production in the liver, glucose utilization by skeletal muscle, and thermogenesis in brown adipose tissue (BAT) via activation of the sympathetic nervous system (SNS). All of these functions contribute to maintaining energy homeostasis. By contrast, orexin levels are decreased during the resting sleep period and, under these conditions, sleep is induced. Dual orexin receptor antagonists (DORAs) promote sleep by blocking orexin overactivation. Low levels of orexin suppress hepatic glucose production via the parasympathetic nervous system (PNS). These functions serve as a protective mechanism against insulin resistance, particularly in the liver [22,71,72]. Therefore, once the sleep/wake cycle is perturbed, daily orexin actions are disrupted leading to impaired energy and glucose metabolism. Abbreviation: FFAs, free fatty acids.

and daily rhythms in *preproorexin* gene expression were dampened in diet-induced obese mice [84]. A recent study demonstrated that CSF orexin A levels were increased in *ob/ob* and diet-induced obese mice [85]. Moreover, these obese mice exhibited impaired sleep architecture [86,87]. As described above, amplification of daily rhythms in the actions of orexin is the key to maintaining glucose homeostasis; therefore, inhibition of these actions in the sleep–resting phase may also amplify the daily orexin rhythm and improve glucose metabolism in metabolic disorders with sleep disturbances. However, this possibility has not been intensively examined.

When SB334867-A, an OX1R antagonist, was administered to *ob/ob* mice once daily for 7 days (late light phase) and then twice daily for an additional 7 days (early and late light phase), cumulative food intake and body weight gain over 14 days were reduced and fasting blood glucose levels were decreased [88]. Similarly, the administration of SB334867 (twice daily for 1 week, 4 h before lights off and lights on) reduced body weight and food intake, thereby improving hepatosteatosis without affecting sleep duration in *ob/ob* and diet-induced obese mice [85]. By contrast, the administration of another OX1R antagonist, ACT-335827 (once daily, before the onset of the dark phase), had no effect on glucose or lipid metabolism in a rat model of diet-induced obesity associated with metabolic syndrome [89]. Additional studies to clarify the appropriate timing and doses for treatment with OX1R antagonists are required to demonstrate their effects, if any, on glucose metabolism.

Suvorexant, a DORA that blocks OX1R and OX2R, has now been developed and is clinically available for the treatment of insomnia [90–92]. Suvorexant induces sleep by inhibiting the orexin-mediated awake signaling and maintaining sleep status. Randomized placebo-controlled studies have indicated that suvorexant promotes sleep in healthy humans and patients with primary insomnia, and its effects were well tolerated [93–95]. Several unique characteristics of DORA, which may be beneficial as a sleeping drug, have been reported. For example, suvorexant increased non-REM sleep and REM sleep in mice [96], whereas GABA activators, as discussed in Box 1, increased non-REM sleep but decreased REM sleep. DORA did not impair the capacity to wake up by responding to an emotionally salient acoustic stimulation, whereas it preserved sleep under conditions of an irrelevant stimulation [97]. Treatment with DORA did not

Box 1. GABA Agonists and Glucose Metabolism

Benzodiazepines and non-benzodiazepines (e.g., imidazopyridines) are allosteric positive modulators of GABA_A receptors, which are ligand-gated ion channels that are broadly expressed in the brain. These GABA-signaling activators promote sleep in patients with insomnia but also cause multiple side effects, such as amnesia, motor disturbance, and relaxation of muscle, owing to the overall suppression of neuronal activity in the central nervous system (CNS) [106,107]. Pancreatic islet β cells also express GABA_A and GABA_B receptors and the activation of GABA receptors increases insulin secretion and β cell proliferation [105]. GABA increases and suppresses insulin secretion from INS-1 cells via GABA_A receptors at low and high extracellular glucose concentrations, respectively [108]; however, the physiological significance is unclear. GABA is also converted to γ -hydroxybutyrate in β cells, which inhibits glucagon secretion from α cells [109].

Nevertheless, evidence for the metabolic effects of GABA agonists/benzodiazepines remains controversial. For example, a single administration of clonazepam, a benzodiazepine receptor ligand, reduced first-phase insulin secretion in response to a glucose challenge in healthy young male subjects in a concentration-dependent manner [110]. One-week administration of alpidem, an imidazopyridine derivative that possesses high affinity for peripheral-type benzodiazepine sites, impaired glucose tolerance in patients with anxiety [111]. Moreover, administration of brotizolam (a benzodiazepine derivative) and zolpidem (an imidazopyridine derivative) for 15 days impaired glucose tolerance in healthy subjects; impairments induced by brotizolam were greater than those by zolpidem, while insulin-induced glucose changes were not altered [112]. 4'-Chlordiazepam, which acts at peripheral benzodiazepine receptors, reduced glucose-mediated insulin secretion, whereas clonazepam did not affect insulin secretion in an isolated rat pancreas [113]. By contrast, a single administration of diazepam, a benzodiazepine derivative, increased plasma insulin levels and decreased high blood glucose levels during a glucose overload test in streptozotocin-induced diabetic rats, whereas no effects on glucose levels were observed in normal rats [114]. A recent study also demonstrated that diazepam enhanced the antidiabetic effects of metformin in T2D rats exposed to a cold-restraint stress paradigm [115]. Intraperitoneal injection of zopiclone, a non-benzodiazepine ligand, caused an acute antihyperlipidemic effect with a moderate decrease in blood glucose levels in hyperlipidemic rats [116]. These findings suggest that GABA agonists may be beneficial for glucose metabolism at least under diabetic conditions. However, further studies are required to clarify the pathophysiological relevance of GABA function/dysfunction in metabolic disorders.

impair memory-conserving functions in the brain [98]. Regarding the impact of suvorexant on metabolism, the proportions of insomnia patients who gained or lost weight during the 1-year treatment did not differ between placebo and suvorexant-treated groups [95]. However, it remains unclear whether suvorexant affects glucose metabolism by ameliorating sleep in animals and humans.

Sleep loss increases the activity of the SNS [99]. Oral administration of almorexant, a DORA, reduced blood pressure, heart rate, and sympathetic vasomotor tone in spontaneous hypertensive rats in the awake and non-REM sleep states during both the dark and light periods and these changes were associated with decreased noradrenaline levels in the CSF and plasma [100]. Intracerebroventricular injection of TCS-OX2-29, an OX2R antagonist, also reduced blood pressure and heart rates in spontaneous hypertensive rats but not normotensive rats, whereas SB-334867, an OX1R antagonist, had no effects [101]. Sympathetic nervous tone is elevated in the diabetic state [102,103] as well as under conditions of sleep restriction or circadian misalignment in humans [1,10]. As described above, elevated SNS activity is an important causal factor in glucose intolerance and insulin resistance, and the antihypertensive effects of orexin antagonists may be useful for preventing diabetic macrovascular complications.

Concluding Remarks and Future Perspectives

Sleep disturbances and glucose intolerance are highly prevalent in modern society. The exacerbating influence of sleep disturbances on the regulation of blood glucose levels and the progression of complications in diabetes have recently been demonstrated in clinical studies [3,4,6,13,16,103]. However, it remains unclear whether the amelioration of sleep itself improves glucose metabolism in the diabetic state (see Outstanding Questions). Furthermore, the relative contributions of REM versus non-REM sleep to the regulation of glucose metabolism need to be deciphered. As discussed in this review, the influences of anti-insomnia drugs on glucose metabolism in humans are largely unknown and controversial [30,31]. In brief, melatonin agonists have shown several beneficial effects on glucose and energy metabolism; however, these were mainly due to direct effects on peripheral organs or radical-scavenging effects [104]

Outstanding Questions

What are the neuroendocrine mechanisms underlying increases in food intake following sleep loss? How do melatonin and orexin cooperate to maintain energy and glucose homeostasis in diurnal and nocturnal animals? A clearer understanding of these mechanisms may open exciting new therapeutic approaches to combat sleep disorders with glucose intolerance.

Does the amelioration of sleep *per se* influence glucose metabolism in diabetic patients? What is the relative contribution of REM versus non-REM sleep in the regulation of glucose homeostasis?

Can a dual orexin receptor antagonist ameliorate glucose metabolism in diabetes and if so how? Since daily orexin actions regulating both sleep and glucose metabolism are perturbed in the obese/diabetic state, an investigation of their therapeutic potential may yield great benefits for insomnia patients with diabetes.

rather than amelioration of the sleep/wake cycle. GABA agonists not only promote sleep but also directly stimulate pancreatic insulin secretion [105]. Therefore, orexin receptor antagonists such as DORAs may be ideal pharmacological tools to evaluate the impact of natural sleep on glucose metabolism because most endogenous orexin actions occur in the CNS. In addition, DORAs increase REM and non-REM sleep, whereas GABA agonists mainly increase non-REM sleep [92,96–98]. Future large cohort clinical studies are needed to elucidate the impact of anti-insomnia drugs on glucose metabolism as well as their mechanisms of action in diabetic patients. The appropriate use of sleep therapies may assist and optimize current therapeutic approaches for the treatment of T2D.

Acknowledgments

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