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Review article

Interactions between sleep, stress, and metabolism: From physiological to pathological conditions

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ABSTRACT

Poor sleep quality due to sleep disorders and sleep loss is highly prevalent in the modern society. Underlying mechanisms show that stress is involved in the relationship between sleep and metabolism through hypothalamic–pituitary–adrenal (HPA) axis activation. Sleep deprivation and sleep disorders are associated with maladaptive changes in the HPA axis, leading to neuroendocrine dysregulation. Excess of glucocorticoids increase glucose and insulin and decrease adiponectin levels. Thus, this review provides overall view of the relationship between sleep, stress, and metabolism from basic physiology to pathological conditions, highlighting effective treatments for metabolic disturbances.

1. Introduction

Sleep and stress interact in a bidirectional fashion, sharing multiple pathways that affect the central nervous system (CNS) and metabolism, and may constitute underlying mechanisms responsible in part for the increasing prevalence of metabolic disorders such as obesity and diabetes [1]. Hormones like melatonin and others from the hypothalamic–pituitary–adrenal (HPA) axis modulate the sleep–wake cycle, while its dysfunction can disrupt sleep. In turn, sleep loss influence the HPA axis, leading to hyperactivation [2]. In the first part of this paper, we focus on the definitions of sleep and the HPA axis, and the relationship between sleep and stress. In the second part, we review the effects of sleep and stress on the metabolism, addressing mainly sleep deprivation, circadian alterations, and key sleep and stress disorders. Finally, we connected these topics to provide a better understanding of the intrinsic relationship between sleep, stress and metabolism, and suggest possible targets for future intervention.

The secretory activity of the HPA axis follows a distinct 24 h pattern. CRH is released in a circadian-dependent and pulsatile manner from the parvocellular cells of the PVN [3]. In fact, the circadian rhythm of cortisol secretion derives from the connection between the PVN and the central pacemaker, the suprachiasmatic nucleus (SCN) [4]. The close

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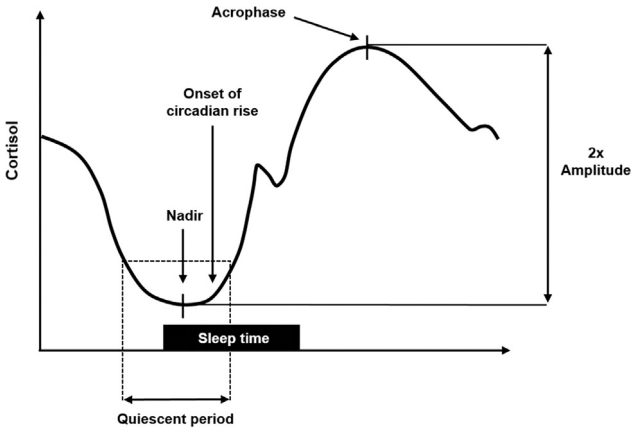

Fig. 1 – 24-h individual cortisol profile showing the minimum (nadir), the maximum (acrophase), the onset of the circadian rise, and the amplitude of the cortisol profile. After a nadir during the early night, there is an important rise in ACTH and cortisol in the late night, reaching a peak near the awakening time, driven by circadian oscillators, such as sleep.

proximity of AVP-containing SCN nerve endings near CRH-containing neurons in the PVN suggests that via this projection circadian information is imprinted onto the HPA-axis [5]. Typically, the nadir (time point with the lowest concentration) for cortisol occurs near midnight. Then, cortisol levels increase 2–3 h after sleep onset, and keep rising into to the waking hours. The peak happens in the morning at about 9 a.m. [4]. Along the day, there is a progressive decline that is potentiated by sleep, until it reaches the nadir and the quiescent period (Fig. 1). In general, 3 main pathways are essential for biological clock function: the input (*zeitgebers*, retina) → SCN circadian pacemaker (as clock genes, neurotransmitters, peptides) → output (pineal melatonin synthesis, thermoregulation, hormones). Then, these factors interact with the sleep–wake cycle to modulate, for example, sleep propensity and sleep architecture, and influence behavior, performance or hormonal output such as cortisol [4].

2. Disturbed or shifted sleep, sleep loss and HPA axis

Many stressful situations, such as low socioeconomic status and chronic work overload, have been associated with a deficit in sleep duration and several neuroendocrine effects (for review, see [6]). Indeed, there is long-standing evidence of reciprocal interactions between the HPA axis and sleep regulation [7], which will be discussed below.

Circadian misalignment affects sleep architecture and may also reduce total sleep time. Both advanced and delayed phases result in disruption of the normal phase relationship between SWS and REM sleep [8]. During the first day of an 8 h phase delay, profound disruptions in the 24 h cortisol rhythm were found, with a higher nadir value mediated by the lack of the inhibitory effects caused by sleep onset, and lower acrophase values due to the lack of the stimulatory effects of awakening, resulting in an overall 40% reduction in the rhythm [9]. Five days after the shift, the cortisol profile had adapted to the new schedule [9]. On the other hand, an advanced phase of 8 h had advanced the timing of the cortisol nadir by about 3 h and 20 min, with marked reduction in the quiescent period, and increased the rising phase of cortisol secretion by 3 h [10]. In this last case, no adaptation of the timing of the acrophase to the new schedule was observed. In summary, these studies confirm that the misalignment of the sleep–wake cycle has a negative impact on the stress system. Although it seems to be a short-term effect probably due to a biphasic pattern of the cortisol rise after the shift, it may also contribute to metabolic changes. Alterations of the HPA axis may play a causative role in sleep disorders such as insomnia. HPA axis dysfunction may be secondary to a clinical sleep disorder, such as obstructive sleep apnea (OSA), leading to other complications.

Insomnia is a sleep disorder characterized by difficulties in falling or staying asleep or having restorative sleep, associated with daytime impairment or distress [11]. Despite the relationship between sleep and the HPA axis, little is known about the neurobiological basis of this sleep disorder and its link with HPA axis activation. One study did not show any significant differences in urinary cortisol between control and poor sleepers [12]. However, another study presented a positive correlation between polysomnographic indices of sleep disturbance and urinary free cortisol in adults with insomnia [13]. Patients with insomnia without depression do present high levels of cortisol, mainly in the evening and at sleep onset, suggesting that, rather than the primary cause of insomnia, the increase in cortisol may be a marker of CRH and norepinephrine activity during the night [14]. Preceding evening cortisol levels are correlated with the number of the following night's nocturnal awakenings, independent of insomnia [15]. However, excessive activation of the HPA axis induces sleep fragmentation [16], while the sleep fragmentation increases cortisol levels [15], suggesting that the HPA axis may contribute to the initiation as well as the perpetuation of chronic insomnia [15]. There is still debate whether the activation of the HPA axis found in insomnia is secondary to sleep loss or a marker of CRH activity.

OSA is a common sleep disordered breathing, characterized by recurrent apneas (complete breathing cessation) or hypopneas (shallow breathing), upper airway constriction, hypoxemia, hypercapnia, autonomic activation, and EEG arousal and sleep fragmentation, leading to daytime fatigue and sleepiness [17]. As nocturnal awakening is associated with pulsatile cortisol release and autonomic activation, we can expect OSA to lead to HPA axis activation through the same mechanisms involved in arousal and sleep fragmentation [4]. However, the studies to date are contradictory. Some have shown that continuous positive airway pressure (CPAP) therapy for OSA does not lower cortisol while the acute withdrawal of CPAP does not change cortisol levels [18]. On the other hand, other authors have demonstrated that CPAP does reverse hypercortisolemia [19]. A systematic review revealed that only 2 studies showed statistically significant differences in cortisol levels after CPAP treatment [20].

Elevated cortisol levels were reported in patients with OSA by some studies [21], but not in others [22]. Responsiveness of ACTH to CRH administration was much higher in obese

patients with OSA, possibly due to alterations in the central control of ACTH secretion and impairment in the negative feedback of glucocorticoids [23]. A recent study showed that serum basal and peak cortisol levels were lower in OSA patients when compared to the control group during 1 μg ACTH and glucagon stimulation tests, showing an association between OSA and hypocortisolemia in the morning with reduced responses to ACTH and glucagon stimulation tests [24]. Many of the discrepancies observed in the literature are reflective of methodological differences. The majority of studies are limited by assessment of cortisol at a single time point. The available studies do not provide clear evidence regarding whether OSA is associated with alterations in cortisol levels or that treatment with CPAP changes cortisol levels. Methodological concerns such as infrequent sampling, failure to match comparison groups on demographic factors known to impact cortisol levels (age, body mass index etc.), and inconsistent control of confounding factors may have limited the findings. However, there is evidence that excessive HPA axis activation may be a result from sleep loss, hypoxemia, and autonomic activation, playing an important role in the metabolic alterations arising from OSA [17].

Many studies have shown increase in cortisol levels during the nighttime period of total sleep deprivation and in the prolonged wakefulness of the following day. This is likely a result of stress due to the effort of maintaining wakefulness, as high frequency EEG activity is correlated with indices of arousal and cortisol release [25,26]. However, some authors also reported no change [27,28] or a decrease in cortisol levels [29,30] after 1 or more nights of sleep deprivation. These discrepancies seem to be influenced by insufficient frequency of blood sampling, small sample size, and by fatigue and sleepiness. In animals, however, the results are more consistent. Adult rats subject to paradoxical sleep deprivation during 96 h show increased levels of corticosterone, which are normalized after 48 h of sleep rebound [31]. Notwithstanding, it is important to consider that animal models do not accurately reflect human physiology; and thus, it is difficult to compare these results.

Studies using chronic protocols of sleep restriction, which model a widespread condition in modern society, have also addressed the role of HPA axis. The first study assessed the effect of 6 consecutive nights of 4 h in bed in young men, showing increased levels of cortisol in the afternoon and early evening, and a shorter quiescent period, with onset delayed by 1.5 h [16]. The rate of decrease of free cortisol in saliva was nearly 6 times slower in sleep restricted volunteers compared to fully rested condition. Notably, chronic short sleepers do present higher levels of cortisol compared to chronic long sleepers [32].

Sleep deprivation seems to be related to the elevation of cortisol, reflecting impairment of HPA axis regulation, and resulting in glucocorticoid overload, which can lead to large deleterious effects on the body. Moreover, there is an association between short sleep duration and higher risk of developing obesity and type II diabetes, suggesting the HPA axis hyperactivation as one of the mechanism involved in the metabolic consequences of sleep loss [33,34].

3. Effects of glucocorticoids on sleep and metabolism

Classic studies in rats and humans have demonstrated that exogenous CRH is able to modulate sleep by increasing EEG frequency and wakefulness and decreasing SWS [35,36]. However, studies focused on the direct effects of glucocorticoids have shown that they increase time spent awake at the expense of REM sleep [37]. Other studies show that cortisol decreases SWS when MRs are activated, while dexamethasone increases awakening after activation of GRs [38]. The effects of both exogenous and endogenous glucocorticoids on sleep EEG depend on the type and location of the receptors activated (MR *vs.* GR), the dose of cortisol/corticosterone used, and the optimal cortisol levels to effect maximal nocturnal CRH suppression [4,39]. Studies that have demonstrated decreases in SWS with elevated cortisol levels and total occupation of GR may be due to excessive GR activation in the amygdala. The effects are opposite to the known inhibitory action found in PVN and anterior pituitary, leading to positive feedback [39,40]. However, the effects of glucocorticoids as well as CRH on REM are not well understood and most of them are contradictory [4].

Chronic exposure to excess glucocorticoids, such as occurs during diseases like Cushing's syndrome, can offer insight into the role of these hormones in sleep. For example, consistent alterations in polysomnographic recordings are reported in Cushing's syndrome, such as reduction of SWS, increased sleep latency, enhanced wake time, shortened REM latency, and elevated REM density, among others [17], reflecting the deleterious effects of glucocorticoid excess. Bierwolf and colleagues [41] have demonstrated that adrenal secretory activity starts predominantly during periods of NREM in both Cushing's and healthy patients, showing a link between pituitary–adrenal activity and the ultradian rhythmicity of NREM and REM sleep.

Reductions in sleep duration have become common due to the socioeconomic demands and opportunities in modern society [42]. In average, self-reported sleep time has decreased 1.5–2 h in the USA [43]. Quantitative alterations in sleep duration may impact the metabolic balance of the body, including control of body mass and food intake, glucose metabolism, and adipokine levels (for review, see [44]). In addition to the neurocognitive consequences of sleep loss, recent studies have been focused on the role of sleep in areas outside the brain, including other organs and physiological systems, such as the metabolism [45].

Many studies have shown an association between sleep duration and obesity both in adults and children, suggesting that short sleep duration may be a predictor of weight gain [46–48] and an important risk factor for development of insulin resistance, diabetes, and cardiovascular disease [16,49,50]. A meta-analysis revealed that each reduction of 1 h of sleep per day is associated with an increase of 0.35 kg m^{-2} in body mass index (BMI) [51]. These observed changes due to sleep loss indicate a probable imbalance between food intake and energy expenditure caused by neuroendocrine alterations.

Naturally, sleep is a period of fasting. Glucose utilization by the brain is increased during REM sleep at the end of the night [52], leading to a negative energy balance in the body. However, sleep "resets" the metabolism and energy expenditure rates in the brain, giving effective and flexible control of energy expenditure under changing environmental pressures [53]. Much like sleep, hypothalamic control of metabolism is comprised by mutually inhibiting networks. The appetite-promoting neuropeptide Y (NPY) and agouti-related protein (AGRP) neurons mutually inhibit the appetite-suppressing pro-opiomelanocortin (POMC) and amphetamine-related transcript (CART) neurons. Both sets of neurons work as sensors of the circulating hormones leptin and ghrelin. Leptin is produced by adipose tissues and promotes satiety through inhibition of NPY/AGRP neurons and activation of POMC/CART neurons, with higher levels during sleep compared to awake states, independent of food intake [54]. Recent animal studies have also suggested that leptin participates in sleep regulation, reducing REM sleep and modulating SWS [55]. In turn, ghrelin is an appetite-stimulating hormone produced in the gut, which acts by inhibiting POMC/CART and activating NPY/AGRP. Like leptin, ghrelin has higher levels during sleep, which are followed by a decrease in the morning before the breakfast [56]. Current evidence indicates that ghrelin is also a sleep-promoting factor, able to induce SWS and stimulates GH secretion during the night [57,58].

Sleep curtailment is able to change food intake as a result of decreased secretion of leptin [59–61] and increased secretion of ghrelin [49,59,62], which leads to increased food intake [49]. Two consecutive nights of sleep restriction (4 h of time in bed) in young men were associated with a 28% increase in ghrelin and 18% reduction in leptin during the day, leading to increased hunger (24%) and appetite (23%), mostly for energy-rich foods with high carbohydrate content and low nutritional quality, such as sweets, salty snacks and starchy foods [49]. Six consecutive nights of sleep restriction (4 h of time in bed) increased sympathetic nervous system activity, evening cortisol level and growth hormone, in addition to decreasing glucose effectiveness and the acute insulin response by 30% each, much like is found in non-insulin-dependent diabetes [16]. Buxton and colleagues [63] found that sleep restriction (5 h/night) for 1 week significantly reduced insulin sensitivity, although no correlation was observed with cortisol levels. In a protocol of 14 consecutive days of sleep restriction (5.5 h of time in bed) with *ad libitum* food intake, caloric consumption was increased during the night, when the individual would generally be sleeping, explaining in part the increased vulnerability for weight gain induced by sleep loss [64]. On the other hand, another study did not find differences in hunger ratings after 1 night of total sleep deprivation compared to 1 night of sleep recovery (8 h time in bed) both in men and women [65]. However, actual food intake was not measured in this study, and therefore it is unknown whether participants would or would not have actually increased their food intake during the day of total sleep deprivation compared to the day of sleep rebound [66]. Gonnissen and colleagues [67] evaluated the effect of sleep fragmentation during 8 h on subjective feelings of appetite in men. They did not find a significant reduction in total sleep duration, but rather a reduction in REM sleep and an increase in N2 sleep stage. The volunteers reported a greater desire to eat after the night of sleep fragmentation, suggesting that sleep quality may be more important than sleep duration for appetite regulation, although they did not measure food intake in this study [67].

Increasing specific clinical evidence has shown that sleep quality and metabolic-related systems are connected. For instance, 50–98% of patients with OSA are morbidly obese [6]. There is an association between OSA and type 2 diabetes [68]. Cross-sectional studies indicate that up to 30% of patients with OSA also present type 2 diabetes, while up to 86% of obese patients with type 2 diabetes have OSA [69,70]. Strong evidence suggests that OSA may increase the risk of developing insulin resistance, glucose intolerance and diabetes [71]. Metabolic disorders and OSA share common pathogenic pathways, such as alterations in autonomic nervous system regulation, increased inflammatory activity, alterations in adipokine levels and endothelial dysfunction, which may be involved in the interplay between these conditions [71]. However, it is not well understood whether these effects are likely due to obesity. In this sense, a systematic review showed that the current literature does not support the hypothesis that OSA independently influences glucose metabolism [72]. The methodological quality varied a lot within the included studies, pointing to a need for more powerful, long-term randomized controlled trials defining changes of insulin resistance as primary endpoint [72].

Obesity is commonly associated with narcolepsy, a sleep disorder characterized by hypocretin (also called orexin) deficiency, excessive daytime sleepiness, and frequent sleep attacks during the day [73]. Narcoleptic patients often present an excess of fat storage in abdominal depots, metabolic alterations, and craving for food with a binge eating pattern [74,75]. The responsiveness of orexin neurons to peripheral metabolic cues, such as leptin and glucose, and the dopaminergic reward system response suggest that both of these 2 neurons are related to the regulation of energy homeostasis and vigilance states [76]. The studies are limited and it is not clear if narcolepsy independently affects glucose metabolism. A recent case-control study showed no clinically relevant pathologic findings in the glucose metabolism of narcoleptic patients compared to weight matched controls [77]. On the other hand, Poli and colleagues showed that narcoleptic patients have higher BMIs and BMI-independent metabolic alterations, such as higher waist circumference, high-density lipoprotein cholesterol, and insulin resistance, compared to idiopathic hypersomnia patients [78]. Evidence has shown that continuous disruption of circadian rhythm in human shift workers is associated with weight gain, metabolic disturbances, type 2 diabetes, and cardiovascular diseases due to increases in postprandial glucose, insulin, cortisol, and mean arterial pressure and decreased 24 h leptin levels [45,79,80].

Another relevant factor that contributes to the development of metabolic disturbances associated with sleep restriction is energy expenditure. Individuals who sleep less are more likely to experience fatigue and sleepiness during the day, which may discourage them from daytime physical activity and promote sedentary behaviors [81,82]. However, the literature presents varied results, in part due to differences in sleep protocols, either total sleep deprivation [83,84]

or partial sleep restriction [85,86], and measurement type (doubly-labeled water [86,87], indirect calorimetry [84], metabolic chamber [83,88], or actigraphy [85,86]). The majority of studies have enrolled small samples with only young, normal-weight men [83,84,88]. Thus, more studies are necessary to determine if sleep duration does affect total energy expenditure and if there is difference between men and women, normal weight and overweight/obese, and young and older individuals. It is possible that improving physical activity could improve sleep, which in turn would impact other components of energy balance, since individual variability in sleep onset latency is reduced by regular physical activity [89].

Not only can sleep affect metabolism, but metabolic changes also can affect sleep architecture [73]. There is an association between late-night-snack intake and sleep patterns [56]. Rodents adjust their sleep onset to match food availability during their sleep–wake cycle [90]. Inversely, food restriction can increase sleep onset latency and reduce total SWS [91]. The common behavior of overeating during a period of sleep deprivation may be a physiological attempt to restore sleep, as it is known that higher food intake promotes sleep [92]. The impact of sleep duration on energy expenditure is less clear due to the multiple factors involved, such as sleeping metabolic rate, thermic effect of food, physical activity, non-exercise activity thermogenesis, etc. [66]. In summary, current literature shows a pattern of increased food intake during periods of sleep loss, mostly in lean and normal sleepers. To date, studies looking for the influence of sleep duration on energy expenditure have produced disparate results due to methodological issues. Due to individual variability, future research assessing whether improving physical activity would improve sleep is also desired for a better understanding.

4. Stress and metabolism

Similarly to sleep, stress is also connected to metabolism. Basal HPA axis activity seems to be dysregulated and overactive both in humans with diabetes and in animal models of type 1 and type 2 diabetes, underlining the neuroendocrine abnormalities common to diabetes-related risk factors such as depression, obesity, hypertension, and cardiovascular diseases [93,94]. Exposure to stressful events leads to increased release of glucocorticoids by activation of the HPA axis [95]. Prolonged activation of the HPA axis may result in maladaptive changes [96], affecting puberty, stature, body composition, as well as leading to obesity, metabolic syndrome, and type 2 diabetes mellitus [97]. Excesses in glucocorticoids increase glucose and insulin and decrease adiponectin levels [98]. Stress exposure alters food intake [99], increasing or decreasing it, depending upon the type of stress [100]. For instance, Ely and colleagues [99] showed that rats subjected to repeated stress by restraint presented increased ingestion of sweet food, while models of chronic variable stress demonstrated a decrease in appetite for sweet food or palatable solutions [101]. There is evidence that glucocorticoids stimulate appetite [102] and increase body weight through the orexigenic effect of NPY [103], an effect that is inhibited by leptin and insulin [103]. Clinical studies also reveal high food consumption, specifically of palatable food, during periods of psychological stress [104]. The increase in palatable food intake is induced by glucocorticoids [105] and is associated with reward-based eating, as a way to reduce the stress response [106].

Although it appears that hypercortisolemia may contribute to the development of different features of metabolic syndrome, it is not clear in the literature whether glucocorticoids play a role in the pathogenesis of obesity. Some studies show that cortisol levels are not higher in obese subjects, and sometimes they are even lower than in lean subjects [107,108]. This may be, at least in part, a consequence of enhanced cortisol clearance that is thought to accompany obesity, for instance, through increased activity of 5α-reductase in the liver [108]. Mean 24 h plasmatic ACTH levels were positively correlated with body mass index, reflecting increased hypothalamic drive and reduced negative feedback of cortisol in obesity [109].

Other factors related to cortisol action are also determinants. In this sense, the local expression of 11β-hydroxysteroid dehydrogenase 1 (11β-HSD1) plays a role in the relationship between cortisol, adiposity, and metabolic disease [110]. The enzyme 11β-HSD1, expressed in several peripheral tissues, such as liver ad adipose tissue, can modulate HPA axis activity, regenerating active cortisol from its inactive form intracellularly [111]. In humans, 11β-HSD1 expression is increased in subcutaneous adipose tissue from obese subjects compared to lean subjects [112], being stimulated by TNFα, leptin and adipokines [113,114].

In the presence of insulin, cortisol promotes triglyceride accumulation, mainly in visceral adipocytes, thus leading to increased central adiposity. Masuzaki and colleagues have also demonstrated that overexpression of 11β-HSD1 in adipose tissue resulted in visceral obesity and metabolic syndrome in mice fed with a high-fat diet [115]. Adipose tissue that overexpressed 11β-HSD2, the enzyme that inactivates cortisol, protected mice from high-fat diet-induced obesity [116]. The modulation of 11β-HSD1 might be a promising therapeutic target for obesity and metabolic disturbances. Studies focusing the inhibition of 11β-HSD1 in animal models of diabetes and obesity have shown improvement of insulin resistance and glucose levels, beyond weight loss [117,118].

Dysregulation of the HPA axis has been associated with some eating disorders [119,120], mainly due to changes in insulin, NPY levels, and other peptides implicated in food intake regulation that can be modulated by cortisol metabolism [112]. Food intake is stimulated by administration of glucocorticoid prednisone in healthy men [121], while diet influences cortisol metabolism, affecting the HPA axis and the reward circuitry for palatable foods [112,122]. Important effects of altered cortisol levels on weight gain are also reported in Cushing's syndrome and Addison's disease, which are both associated with effects such as central obesity/hypercortisolism and weight loss/hypocortisolism, respectively [123].

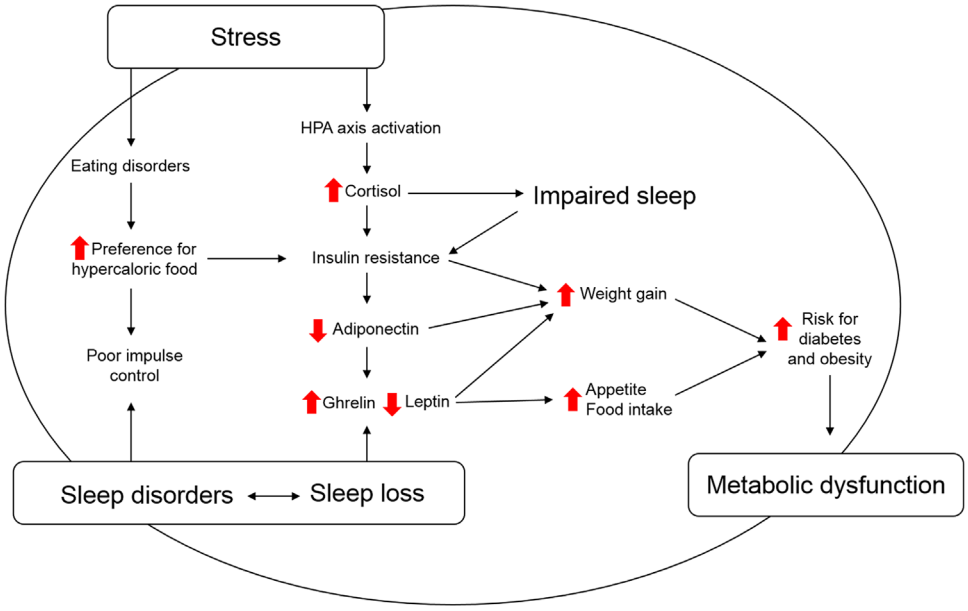

Fig. 2 – Schematic of the main interactions between sleep, stress and metabolism. Sleep disorders which can lead to sleep loss share common pathways with stress system via HPA axis activation on the metabolic dysfunction, contributing to increased risk of developing obesity and diabetes.

5. Sleep, stress, and metabolism

Because of the new lifestyle imposed by work and family, physical and psychological problems, and social changes due to internet and television, stress and sleep restriction have become endemic, with a major impact on the metabolic process. Importantly, stress hormone levels correlate positively with decreased sleep duration, while both are associated with obesity, metabolic syndrome, and eating disorders [73]. A study by Galvao and colleagues [124] showed that rats subjected to 96 h of paradoxical sleep deprivation present increased immunoreactivity for CRH and orexin as well as higher levels of ACTH and corticosterone, in addition to increased diurnal food intake, but without changes in global food intake. A negative correlation was found between corticosterone and body weight gain throughout paradoxical sleep deprivation [124].

Stress is known to reduce SWS, REM sleep, and delta power, as well as to affect metabolism in rodents, with the magnitude varying according to the type and duration of stress exposure [73]. Sleep deprivation, in turn, activates many stress-related pathways including the HPA axis and sympathetic nervous system, which indirectly modulate arousal and affect the metabolism [26,125]. It has been proposed that the bidirectional relationship between sleep and stress and its impact on metabolism are, in part, mediated by hypocretin circuitry. Hypocretinergic cells project to several CRH-responsive regions in the central nervous system, including *locus coeruleus*, the PVN, the bed nucleus of the *stria terminalis* and the central amygdala [126].

Sleep deprivation *per se* is associated with HPA axis hyperactivity and negatively affects glucose tolerance [16]. The mechanism involved in impaired glucose metabolism following changes in the sleep–wake cycle seems to be the decreased efficacy of the negative feedback regulation of the HPA axis [42]. Activation of HPA axis may be a risk factor in the development of metabolic syndrome in OSA, via increased visceral obesity, insulin resistance, and sympathetic activity as well as changes in leptin levels [4,127]. However, HPA axis hyperactivity must be only one among several factors that mediate metabolic syndrome in OSA. On the other hand, a recent study in healthy women with clinically diagnosed primary chronic insomnia has demonstrated a dysregulation of circadian cortisol secretion despite normal sleep architecture. Although the limitation of a small number of participants, the authors found that increased midnight cortisol levels were not associated with impaired metabolism of glucose and lipids [128].

The bidirectional interaction between sleep and the HPA axis is complex. Current studies suggest that HPA hyperactivity, sleep loss, and sleep disturbances are closely linked in a vicious circle and play a role in the pathogenesis of metabolic disorders. Understanding sleep and stress system physiology is essential for elucidating the physiopathology of these syndromes and revealing new ways of prevention and treatment.

6. Summary and conclusions

The current review provides evidence for overlap between sleep, stress, and metabolism, which can explain, at least in part, the outcomes observed in the modern society, where sleep deprivation, overnutrition, and chronic exposure to stress potentially lead to the increased incidence and prevalence of metabolic disorders such as obesity and type 2 diabetes. Through hyperactivation of the HPA axis and changes in the neuroendocrine response, sleep loss and chronic stress can lead to metabolic dysfunction. The HPA

axis dysregulation is commonly seen in obesity, sleep deprivation, and sleep disorders such as OSA and insomnia. Conversely, sleep architecture and metabolism are impaired in hypercortisolism conditions such as Cushing's disease, confirming the close relationship between sleep, stress and metabolism, which is summarized in Fig. 2. We conclude that good sleep quality achieved through sleep hygiene and treatment of sleep disorders, in addition to nutritional education with regular meal frequency and circadian alignment of food intake, would be interesting strategies for preventing metabolic disorders. Targeting 11β-HSD1, a key enzyme in cortisol metabolism in peripheral tissues, and the hypocretin system, which actively and partially regulates the interconnection between sleep, stress and metabolism, might represent a promising therapeutic option for obesity, insulin resistance, and other consequences of excess glucocorticoids which arise from interactions between sleep and stress.

Review criteria

A search for original and review articles that focus on sleep, stress, and metabolism was performed in PubMed. The search terms used were “sleep”, “sleep disorders”, “sleep loss”, “sleep deprivation”, “stress”, “HPA axis”, “cortisol”, “corticosterone”, “metabolism”, “diabetes”, “obesity”, “glucose”, “insulin”, “metabolic”, “endocrine”. We also searched the reference lists of identified articles for further papers. Articles were restricted to human studies. In order to limit the number of references, we selected, whenever possible, a recent review complemented by original papers published after the review.

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