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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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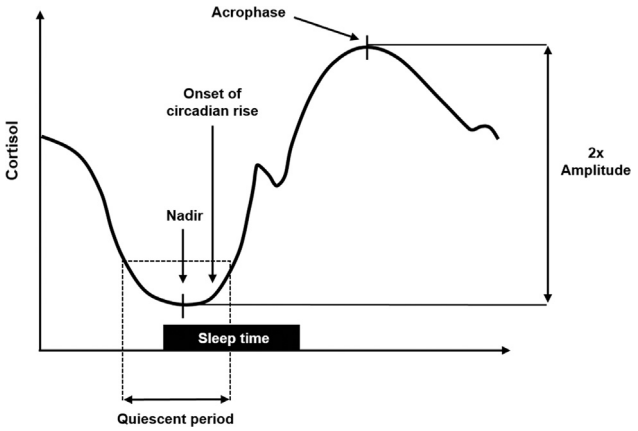

Fig. 1 – 24-h individual cortisol profile showing the minimum (nadir), the maximum (acrophase), the onset of the circadian rise, and the amplitude of the cortisol profile. After a nadir during the early night, there is an important rise in ACTH and cortisol in the late night, reaching a peak near the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