Sleep and the Endocrine System

Dionne Morgan, MBBS[a], Sheila C. Tsai, MD[a,b,*]

KEYWORDS

• Circadian rhythms • Sleep apnea • Endocrine abnormalities • Hormonal regulation
• Sleep disorders • Sleep deprivation • Critical illness • Critical care

KEY POINTS

- The endocrine system is influenced by both circadian rhythms and sleep-wake state.
- Hormonal abnormalities can contribute to sleep disruption and disorders.
- Sleep disorders can lead to hormonal dysregulation, resulting in endocrine abnormalities.
- Sleep fragmentation and deprivation are common in critically ill patients and may be associated with various hormonal disturbances.

INTRODUCTION

The endocrine system is a group of specialized organs or glands that secrete hormones directly into the circulation. These hormones are instrumental in growth, metabolism, and maintaining homeostasis. Similarly, sleep plays an important role in human homeostasis. Some hormonal secretion patterns are controlled mainly by the body's internal circadian pacemaker, located in the hypothalamus within the suprachiasmatic nucleus (SCN), whereas other hormones are primarily affected by the sleep-wake state. Sleep and the endocrine system are closely intertwined, with many hormonal secretions influenced by sleep. In addition, sleep quality and duration affect hormonal function such that sleep disorders and sleep fragmentation can contribute to endocrine abnormalities. Conversely, endocrine dysfunction can significantly affect sleep. In this article, the effect of sleep and sleep disorders on endocrine function and the influence of endocrine abnormalities on sleep are discussed. Sleep disruption and its associated endocrine consequences in the critically ill patient are also reviewed.

CIRCADIAN RHYTHM AND SLEEP-WAKE STATE CONTROL OF HORMONAL SECRETION

The primarily circadian-regulated hormones include those produced by the hypothalamic-pituitary axis, such as adrenocorticotropic hormone (ACTH) and cortisol, thyroid stimulating hormone, and melatonin. Growth hormone (GH), prolactin (PRL), and renin secretion are sleep related. Sleep, especially slow wave sleep (SWS), is associated with increased GH, growth hormone–releasing hormone (GHRH), and ghrelin levels.

Adrenocorticotropic Hormone and Cortisol

The hypothalamic-pituitary-adrenal axis (HPA) is primarily under circadian rhythm control. Cortisol and ACTH levels peak in the early morning and decline during the day. The primary circadian

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[a] Department of Medicine, National Jewish Health, 1400 Jackson Street, A02, Denver, CO 80206, USA; [b] University of Colorado Denver, Aurora, CO 80045, USA
* Corresponding author.
E-mail address: tsais@njhealth.org

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control is evidenced by the fact that daytime sleep does not significantly inhibit cortisol secretion. This diurnal variation in cortisol secretion persists even when sleep is altered and is not significantly affected by the absence of sleep or by sleep at an unusual time of day. The 24-hour periodicity of corticotropic activity is therefore primarily controlled by circadian rhythmicity.

However, secretion is also weakly modulated by the sleep-wake state. Sleep onset is normally associated with a decrease in cortisol secretion and nadir levels of cortisol and ACTH levels occur during the first part of sleep. Cortisol secretion is already low in the late evening, and sleep initiation results in prolongation of the low secretory state. At the end of sleep, morning awakening is associated with a burst of cortisol secretion. In sleep deprivation, the cortisol secretion pattern seems to be dampened such that the nadir of cortisol secretion is higher and the maximum morning cortisol level is lower than during nocturnal sleep.[1]

Melatonin

Melatonin release is controlled by the light-dark cycle and SCN through a series of complex polysynaptic pathways. It is produced and released from the pineal gland directly into the blood and cerebrospinal fluid. Melatonin levels start to increase in the evening and peak in the early morning. Melatonin is postulated to promote sleep by decreasing the firing rate of SCN neurons. Its production is suppressed by exposure to bright light.

Thyroid-Stimulating Hormone

Thyroid-stimulating hormone (TSH) is primarily under circadian control but is significantly influenced by the sleep-wake state. During daylight, TSH levels are low and stable. Starting in the early evening, TSH levels increase quickly and peak shortly before sleep onset. Sleep inhibits TSH levels from increasing further. Therefore, sleep has an inhibitory effect on TSH secretion, most notable during SWS. During the latter part of the sleep period, there is a progressive decline in TSH levels. The circadian effect on TSH secretion is predominant with some influence from sleep. For example, sleep deprivation results in higher TSH levels during the night because of the lack of sleep's inhibitory effect. But this inhibitory effect of sleep on TSH secretion seems to depend on time of day because daytime sleep does not seem to have this same suppressive effect on daytime TSH secretion.

Growth Hormone

GH secretion is largely influenced by sleep. The release of GH from the anterior pituitary gland is stimulated by hypothalamic GHRH and inhibited by somatostatin. In addition, ghrelin, a peptide produced by the stomach, acts as a potent endogenous stimulus for GH secretion by binding to the GH secretagogue receptor. GH secretion increases during sleep with less influence by the time of day. The sleep-onset GH pulse is the largest in men. Most GH secretion is associated with SWS (stage N3), although GH secretion also occurs in the absence of SWS. The amount of GH secretion closely correlates with the duration of stage N3 sleep. In older age, both N3 sleep and GH release decrease.

Prolactin

PRL secretion is strongly linked to sleep. Levels increase shortly after sleep, regardless of the time of day, although this stimulatory effect is greatest at night. During nocturnal sleep, the PRL levels peak around the middle of the sleep period. Awakenings associated with sleep disruption inhibit nocturnal PRL release. Therefore, the secretion of PRL is mainly sleep dependent.

In addition, a potential role of PRL in regulating rapid eye movement (REM) or SWS has been suggested because of a close temporal relationship between increased PRL secretion and SWS. However, this correlation is not as close as that seen with GH, and the normal secretory pattern of PRL does not decline with age despite a decline in SWS.

Gonadotropic Hormones

Gonadotropic hormone secretion seems to have both circadian rhythmicity and sleep influences. Gonadotropin-releasing hormone from the hypothalamus controls the secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by the anterior pituitary. In men, LH is responsible for testosterone secretion, whereas FSH stimulates spermatogenesis. In women, the gonadotropins regulate the release of estrogen and progesterone and control the menstrual cycle.

The 24-hour patterns of gonadotropin release and gonadal steroid levels vary according to gender and the stage of life. There is a pulsatile increase in LH and FSH levels at sleep onset in children. As the child approaches puberty, the amplitude of the nocturnal pulses increases, which is one marker of puberty.

Testosterone production varies diurnally, but its production depends directly on sleep, with testosterone levels normally increasing at sleep onset. In young adult men, a notable diurnal rhythm in circulating testosterone levels exists, with minimal levels in the late evening and a clear nocturnal

increase leading to maximal levels in the early morning. Approximately 3 hours of SWS is required, irrespective of whether it occurs during the day or at night, for peak testosterone production to occur, and levels remain stable thereafter while sleep is maintained. After waking, the plasma concentration of testosterone declines in proportion to the duration of time awake.[2] With sleep fragmentation experiments, the nocturnal increase in testosterone is attenuated, especially if no REM sleep is achieved.[3]

Renin-Angiotensin-Aldosterone System

Some circadian rhythmicity occurs in the renin-angiotensin-aldosterone system, with more urine flow and increased electrolyte excretion occurring during the day. Increased renin and aldosterone levels during sleep decrease urine output. In addition, plasma renin activity is synchronized with non-rapid eye movement (NREM)-REM cycles: higher levels occur during NREM sleep, and the lowest levels occur during REM sleep. Therefore, decreased urine flow and increased urine osmolality occurs during REM sleep. However, sleep deprivation decreases the usual elevation in aldosterone levels occurring during sleep, which results in increased sodium excretion.

Leptin and Ghrelin

Sleep plays an important role in energy balance. Both sleep and circadian rhythms control leptin secretion. Leptin is a hormone primarily secreted by adipocytes that promotes satiety and increases metabolism. Higher levels are noted in obese versus lean individuals suggesting possible leptin resistance. Levels fluctuate in response to caloric balance and increase at night. Leptin levels peak at night (around 2:30 AM) and nadir in the early afternoon (around 1 PM).[4] This nocturnal elevation of leptin level is thought to suppress hunger during sleep and may increase SWS.[5] When controlling for nutrition and activity, a shift in nighttime to daytime sleep results in leptin peaks during both day and night.[5,6]

Ghrelin is released primarily from the stomach, stimulates appetite, and promotes weight gain. Its release is controlled more by sleep-wake state than by circadian influences.[7] Ghrelin levels typically increase during the first half of the night and decrease in the second half, even when fasting. Ghrelin also enhances GH secretion and may stimulate SWS.[8]

Insulin and Glucose

A complex relationship between sleep, insulin, and glucose control also exists. Decreased glucose tolerance is noted during sleep, whether sleep occurs during the daytime or nighttime. This occurrence is thought to be related to decreased brain glucose use, decreased muscle use and tone, and anti-insulin effects of GH. Although decreased glucose metabolism occurs during NREM sleep, increased glucose metabolism occurs during REM sleep and wakefulness.[9]

Improved insulin sensitivity seems to occur at the end of sleep.[10] The improved glucose control at the end of the night is thought to be due to multiple factors, including increased metabolism during REM and wake time, greater body activity, augmented noninsulin-mediated glucose removal, and action by previously secreted insulin.[11,12]

EFFECTS OF ENDOCRINE ABNORMALITIES ON SLEEP

The previous section discussed normal hormonal secretion and the influence of sleep on hormonal balance. This section discusses endocrine disorders and their effect on sleep.

Acromegaly and Sleep Apnea

Acromegaly results from excessive GH production. In addition to notable physical findings, such as elongated digits and coarsening of features, several of other morphologic abnormalities can predispose to sleep apnea. These features include soft-tissue changes such as macroglossia, elongation and thickening of the soft palate, swelling and thickening of the pharyngeal walls, and thickening of the true and false vocal cords, which result in pharyngeal airway narrowing and an increased tendency of the airway to collapse.[13] Bony changes also contribute to this increased risk of obstructive sleep apnea (OSA): more vertical bony growth of the face results in posterior placement of the tongue, thus narrowing of the pharyngeal airspace. In addition, a more inferior position of the hyoid bone may contribute to upper airway instability.[14]

The relationship between sleep-disordered breathing and excessive GH production dates back to the late 1800s when Roxburgh and Collis linked acromegaly, snoring, and excessive daytime sleepiness.[15] More recent studies have demonstrated a high prevalence of sleep-disordered breathing in patients with acromegaly. An Australian study found a high prevalence of sleep apnea in acromegalic patients with approximately 60% of the patients with acromegaly having sleep apnea.[16] The same research group found that 33% of patients with acromegaly had central sleep apnea possibly due to increased hypercapnic ventilatory response.[17]

The prevalence of sleep apnea in those already treated for their acromegaly has been investigated. Although this percentage is lower than in untreated acromegalic patients, the prevalence remains high at more than 20%.[18] Surgical treatment of acromegaly may improve sleep-disordered breathing. Improvement in obstructive sleep apnea syndrome (OSAS) has been noted after transphenoidal hypophysectomy alone or transphenoidal hypophysectomy and radiation. However, uvulopalatopharyngoplasty has not been shown to improve OSA in these patients.[19] Treatment with octreotide has also been demonstrated to improve sleep-disordered breathing in patients with acromegaly. After 6 months of octreotide treatment, up to a 50% decline in respiratory events has been reported.[20,21] However, other studies have found that treatment of acromegaly does not result in resolution of the sleep-disordered breathing.[22,23] Furthermore, central sleep apnea seems to persist despite intracranial resection with or without radiation therapy.[23]

Thyroid Hormone and Sleep Disorders

Both hypothyroidism and hyperthyroidism can cause or exacerbate sleep disorders, such as OSAS, insomnia, and hypersomnia.

Symptoms of hypothyroidism overlap with those of OSA and may be difficult to distinguish. OSA may be a consequence of hypothyroidism. Up to 50% of hypothyroid patients have some degree of sleep-disordered breathing compared with 29% in the euthyroid control group.[24] Hypothyroidism can potentially cause or exacerbate OSAS for several reasons, including excess weight gain, reduction in ventilatory drive, thyroid myopathy, and abnormal mucopolysaccharide content in upper airway tissue. In addition, the presence of a goiter, independent of any concurrent hypothyroidism or hyperthyroidism, has occasionally been reported as a cause of OSAS due to mechanical constriction of the upper airway.

Evidence varies and is conflicting as to whether thyroid hormone supplementation improves sleep-disordered breathing. In some studies, thyroid hormone replacement has been shown to improve sleep-disordered breathing in hypothyroid patients with OSA.[25] In patients with sleep apnea and hypothyroidism, treatment of sleep apnea is recommended until thyroid replacement has been achieved because of reports of angina in patients initiated on thyroid replacement before management of sleep apnea. This angina resolves with initiation of continuous positive airway pressure (CPAP) therapy.[26] Fatigue and lack of energy are prominent features of hypothyroidism. In addition, the symptom of sleepiness has been noted quite commonly.[27]

Sleep propensity is increased even in patients with subclinical hypothyroidism.[28] Thyroid replacement therapy has been used with success in the management of sleepiness in patients diagnosed with idiopathic hypersomnia who were treated for subclinical hypothyroidism.[29] As such, patients with symptoms of hypersomnia should be evaluated for thyroid abnormalities.

Both hyperthyroidism and overdose of thyroid supplements have been associated with insomnia complaints.[30] Hyperthyroidism has been more typically associated with difficulty falling asleep rather than maintenance insomnia.[31] Thyroid excess may also contribute to restlessness with a higher prevalence of restless legs syndrome,[32] which in turn may exacerbate insomnia complaints.

Hypothalamic-Pituitary-Adrenal-Cortisol Axis Disorders and Sleep

Adrenal insufficiency, primarily due to deficient cortisol secretion, results in severe fatigue, sleepiness, and poor-quality sleep. These symptoms may persist even in patients who are on treatment.[33] Sleep-wake disorders have also been attributed to elevated cortisol levels. Furthermore, there has been a link between cortisol levels and chronic insomnia: higher nighttime levels are noted in patients with insomnia.[34,35] This relationship may be bidirectional but suggests that elevated cortisol levels may contribute to chronic insomnia.

There is limited information concerning a possible link between Cushing syndrome and an increased risk of OSAS. One study found that 18% of 22 subjects demonstrated an Respiratory Disturbance Index (RDI) of greater than or equal to 17.5.[36] In addition, there has been a link between exogenous corticosteroid therapy and sleep apnea.[37] Furthermore, well-known complications of corticosteroid therapy include issues with insomnia, in addition to other neuropsychiatric issues.[38]

Sex Hormones and Sleep Disturbances

Testosterone

Patients with low testosterone levels often note a lack of energy or fatigue. There is also a decline in sleep quality after middle age and with increasing age in men. This decline may be due in part to reduced testosterone levels in aging men.[39] Decreased testosterone may lead to increased fat mass, and there may be poorer sleep quality associated with obesity.[40,41] Weight loss

may improve plasma testosterone levels in obese men.[42]

Although based largely on anecdotal evidence, exogenous testosterone has been considered to have a deleterious effect in OSA. Current guidelines suggest that it is contraindicated in the presence of untreated OSA.[43] In one study involving obese men with severe OSA and low plasma testosterone levels, testosterone supplementation, irrespective of baseline testosterone level, resulted in worsening of the oxygen desaturation index and nocturnal hypoxemia at 7 weeks but not at 18 weeks.[44] Testosterone supplementation may affect sleep in other ways. In one study of young men engaging in resistance exercises and taking anabolic steroids, there was a reduction in sleep efficiency and alteration of sleep architecture.[45]

Estrogen and progesterone

Several issues can potentially affect sleep in postmenopausal women such as alterations in mood, hot flashes, insomnia, and an increased prevalence of upper airway instability. The Wisconsin Sleep Cohort Study demonstrated that postmenopausal women are more frequently affected by respiratory instability. Postmenopausal women were more likely to manifest OSAS, even when corrected for body mass index (BMI) and age.[46] Hormonal therapy is often used to assist with insomnia associated with hot flashes in perimenopausal and postmenopausal women. Evidence suggests that administration of hormones can improve sleep quality in women. In one study, women who did not use hormone therapy reported more sleep difficulties than those on hormonal therapy.[47] The Sleep Heart Health Study examined the prevalence of an RDI greater or equal to 15 in women without and with hormonal therapy and found that there was 50% reduction in the elevated RDI rate in the hormone users.[48] Overall, these data suggest that hormonal therapy may be a useful adjunct, although not a replacement for therapies such as CPAP, in treating OSAS in postmenopausal women.

Melatonin Effects on Sleep

Melatonin plays a role in the regulation of human sleep. In addition to its direct sleep-facilitating effect, melatonin may improve sleep through a chronobiotic effect by entraining the circadian system to a desired sleep-wake cycle.[49,50] Exogenous melatonin decreases sleep latency, and the sustained release and transdermal formulations can increase total sleep time and sleep maintenance.[51–53] Exogenous melatonin, in 0.3-mg up to 5-mg doses, has also been shown to improve sleep efficiency in healthy people during the daytime when endogenous melatonin production is absent.[54] These results are consistent with the hypothesis that both exogenous and endogenous melatonin promote sleep by opposing the wake-promoting signal from the circadian clock. The intake of either low-dose (0.3 mg) or high-dose (5 mg) melatonin has a similar effect on sleep efficiency, indicating no additional benefit of exogenous melatonin concentrations more than the endogenous nighttime levels.[55] These findings also suggest that daytime melatonin intake may be useful for individuals, such as rotating shift workers, who need to obtain sleep during the daytime.

THE EFFECT OF SLEEP DISORDERS ON HORMONAL REGULATION

Sleep Deprivation

Sleep deprivation is common in industrialized countries. Insufficient sleep may occur as a result of voluntary sleep restriction, insomnia, or shift work. Decreased sleep is associated with increased risk for obesity, diabetes, and hypertension.

Adrenocorticotropic hormone and cortisol

Studies have shown that partial or complete sleep deprivation results in elevations of evening cortisol levels.[56] Conversely, sleep deprivation also results in a significant reduction of cortisol secretion the next day. This reduction in cortisol secretion seems to be related to an increase in SWS during the recovery night, which exerts an inhibitory effect on the HPA axis.[57] The impact of restricted sleep on the HPA axis seems to depend on the time of day. In addition, the amplitude of normal circadian rhythm decline in cortisol levels is reduced with insufficient sleep.[58]

Insulin and glucose metabolism

The interactions between sleep, circadian function, and glucose metabolism have also been evaluated.[59] Both sleep insufficiency and sleep fragmentation have been linked to abnormal glucose metabolism. It has been shown that sleep restriction affects glucose tolerance through a direct effect on insulin sensitivity. There is decreased insulin sensitivity associated with loss of sleep that is not compensated for by an increase in insulin release.[60] Subsequent studies in healthy human subjects involving sleep restriction and assessments of glucose metabolism have confirmed an approximately 20% reduction in insulin sensitivity without simultaneous increases in insulin levels, resulting in reduced glucose tolerance and, subsequently, an increased risk of diabetes.[61] In

addition, the association of short sleep duration, usually less than 6 hours per night, with an increased risk of diabetes has been shown in multiple cross-sectional epidemiologic studies.[62]

Leptin, ghrelin, and appetite regulation

The duration of sleep plays an important role in the regulation of leptin and ghrelin levels in humans. Sleep loss may affect energy expenditure due its impact on the levels of leptin and ghrelin. Leptin and ghrelin exert opposing effects on appetite: leptin promotes satiety, whereas ghrelin promotes increased food intake and reduced fat metabolism. Several studies have shown that partial sleep deprivation is associated with significant decreases in leptin levels and conversely increases in levels of ghrelin. Although there is an increase in ghrelin levels after partial sleep restriction, the nocturnal increase in ghrelin levels is modestly reduced during acute total sleep deprivation.[7] Leptin levels decline with sleep restriction, although the nocturnal peak in leptin persists.[63] In a study of sleep deprivation in healthy adult men, while rigorously controlling diet and activity, the decline in leptin levels was observed.[64] This decline in leptin levels correlates with increases in sympathetic nervous system activity, which suggests that increased autonomic activity might reduce leptin secretion. The association between sleep duration and leptin and ghrelin levels was observed in the Wisconsin Sleep Cohort Study. Limited total sleep time was associated with higher ghrelin and reduced leptin levels.[65] These findings would support the postulate that sleep deprivation may alter the ability of leptin and ghrelin to accurately signal caloric need and so lead to increased food intake due to an internal misperception of insufficient energy availability.

It is likely that the increased hunger and food intake are potential mechanisms by which sleep deprivation contributes to weight gain and obesity. In a study of healthy young male subjects, limiting sleep opportunity to only 4 hours versus 10 hours resulted in elevated daytime ghrelin and decreased daytime leptin levels. These changes were associated with both increased hunger and appetite.[64] In another trial, when subjects underwent 5 nights of insufficient sleep of only 5 hours per night, they had increased food intake and total daily energy expenditure. The increased food intake during the insufficient sleep schedule exceeded energy expenditure and so contributed to weight gain.[66]

Insomnia

Adrenocorticotropic hormone and cortisol

Investigators have studied the effect of chronic insomnia on the HPA axis and associated clinical consequences. In insomnia, higher nighttime cortisol levels have been noted. With chronic insomnia, there is an overall and sustained increase in ACTH and cortisol secretion, although maintaining the normal circadian pattern. It is possible that the chronic activation of the HPA axis places patients with insomnia at risk of significant medical morbidity.[67] Therapy for patients with insomnia may include sleep restriction combined with cognitive behavioral therapy. Lower cortisol levels occur during treatment, which confirms part of the proposed physiologic mechanisms behind insomnia. These data support the benefit of sleep restriction in contributing to a decrease in hyperarousal insomnia.[68]

Insulin and glucose metabolism

Studies in healthy volunteers have demonstrated that sleep fragmentation results in abnormal glucose metabolism, especially if there is associated suppression of SWS.[69] In addition, prospective population-based studies have linked poor sleep quality to incident diabetes. In one study, the risk of type 2 diabetes was found to be almost 3 times higher in subjects with insomnia, defined by a sleep duration less than 5 hours versus those with a longer sleep duration.[70,71]

Obstructive Sleep Apnea

Sleep-disordered breathing may have several adverse effects on the endocrine hormonal axes, especially with regard to glucose metabolism and insulin resistance.[72,73]

Insulin and glucose metabolism

The link between OSA and impaired glucose metabolism due to insulin resistance seems to occur independently of obesity. Patients with OSA have been shown to have higher fasting serum glucose and insulin resistance index, independent of adiposity. The severity of OSA is associated with increased insulin resistance.[74] Similarly, an increased apnea-hypopnea index has been associated with worsened glucose tolerance and insulin resistance independent of obesity.[75] It is postulated that the primary mechanism linking OSA to impaired glucose metabolism and diabetes may be a consequence of sleep fragmentation with diminished SWS. Sleep fragmentation is associated with elevated sympathetic nervous activity, which could lead to alterations in glucose metabolism.[69] It is possible that through mechanisms such as enhanced sympathetic activity, endothelial dysfunction, and impairment of peripheral vasodilation, insulin resistance may contribute to the metabolic syndrome.

The metabolic syndrome

The metabolic syndrome is a complex of metabolic disturbances diagnosed when 3 of the following 5 characteristics are present: abdominal obesity, increased serum triglyceride levels, low high-density lipoprotein (HDL) levels, elevated blood pressure, and elevated plasma glucose levels. Patients with OSA seem to be at higher risk of developing certain features of metabolic syndrome, specifically hypertension, insulin resistance, and type 2 diabetes. OSA has been independently associated with an increased prevalence of the metabolic syndrome.[76]

Even after adjusting for obesity, OSA has been associated with increased systolic and diastolic blood pressure, higher fasting insulin and triglyceride concentrations, decreased levels of HDL cholesterol, and increased cholesterol to HDL ratio. Therefore, it has been concluded that metabolic syndrome is more likely to be present in patients with OSA.[77] It is also likely that OSA and metabolic syndrome share similar pathophysiologic mechanisms. Patients with sleep apnea are often obese and have a heightened sympathetic drive, endothelial dysfunction, systemic inflammation, insulin resistance, hypercoagulability, and high plasma leptin levels, which are also secondary factors associated with metabolic syndrome.

Circadian Rhythm Disorders

Circadian misalignment occurs when the internal circadian clock is not properly aligned with the external environment, including light-dark, sleep-wake, and fasting-feeding cycles. This condition can occur acutely with jet lag or on a chronic basis with shift work, delayed sleep phase, or advanced sleep phase disorders. With nearly 20% of the working population in industrialized countries being shift workers,[78] the impact of shift work disorder can be quite significant. Night-shift work is an example of severe circadian misalignment, as workers are awake, active, and eating during their biological night and trying to sleep and fast during their biological day. Several studies have examined the effects of circadian misalignment on sleep and related hormones.

Adrenocorticotropic hormone, cortisol, and thyroid-stimulating hormone

The impact of delayed sleep phase syndrome (DSPS) on cortisol and TSH release has been investigated. One study showed that the hormonal rhythms were delayed in patients with DSPS, although there was no difference in total 24-hour secretions of TSH and cortisol when compared with controls. Based on these results, it would seem that the hormonal delay in DSPS is due more to the phase delay of the circadian clock rather than any overt hormonal dysfunction.[79]

Abnormally high cortisol levels have also been noted at the end of wake and start of sleep. Therefore, it has been postulated that the high cortisol secretion seen in circadian misalignment could contribute to insulin resistance and hyperglycemia.[80]

Insulin, glucose metabolism, and appetite regulation

Investigators have tested the different effects of phase advance and phase delay, compared with a daily 24-hour cycle, on sleep, energy expenditure, substrate oxidation, appetite, and related hormones in energy balance. They found that the primary effect of a phase shift, whether phase advanced or phase delayed, was a combined disturbance of glucose-insulin metabolism. Glucose concentrations were higher without any concomitant change in insulin concentrations.[81]

Acute circadian misalignment results in an increase in postprandial glucose and insulin levels with a concurrent decline in leptin levels. Similarly, low leptin levels are associated with appetite stimulation. An increase in appetite coupled with decreased energy expenditure could account for the increased risk of obesity noted in shift workers.[80]

There is considerable epidemiologic evidence that shift work is associated with increased risk for obesity, diabetes, and cardiovascular disease. Shift workers suffering from chronic sleep deprivation and circadian rhythm misalignment seem to be at an increased risk of type 2 diabetes.[82,83] Prospective studies have demonstrated this association. For example, in the Nurses' Health Study, researchers found that subjects who worked rotating night shifts had an increased risk for diabetes, even after adjusting for traditional diabetic risk factors, including BMI.[82] The risk was also noted to be higher in those with longer duration of shift work as compared with no shift work.

Evidence suggests that increased insulin resistance may be an intrinsic adverse effect of circadian rhythm misalignment on glucose metabolism, independent of sleep loss.[84] However, further prospective and interventional studies are needed to evaluate the role of circadian rhythm misalignment in the development and severity of type 2 diabetes.

Melatonin, gonadotropin, and oncogenic effect

Melatonin rhythms are also delayed in patients with DSPS, although the total 24-hour secretion of melatonin is similar to controls.[79] Shift workers may exhibit altered nighttime melatonin secretion

and reproductive hormone profiles that could increase their risk of hormone-dependent cancers. Several studies have been conducted to investigate the effect of circadian rhythm disruption on reproductive hormone production and nocturnal production of melatonin as a possible cause for breast cancer.[85] Melatonin is known to affect regulation of gonadal function because decreased concentrations, as seen in circadian rhythm misalignment, result in increased pituitary gonadotropin release, leading to testosterone or estrogen production.

Melatonin also has been found to have tumor suppressive properties. For example, in rodent models, pinealectomy was found to enhance tumor growth,[86] whereas exogenous melatonin administration has demonstrated anticancer activity.[87] Overall, the antitumor effect of melatonin may be due to its direct effect on hormone-dependent proliferation through interaction with nuclear receptors, an effect on cell cycle control, and possible increase in p53 tumor-suppressor gene expression.[85]

Disorders of Hypersomnia

Limited data exist regarding hypersomnia disorders and associated endocrine abnormalities. However, patients with narcolepsy are often obese and have been reported to be at increased risk of diabetes. Yet, there is a paucity of studies looking at the endocrine consequences of narcolepsy. In a case-control study, investigators studied glucose metabolism using the oral glucose tolerance test and assessed dynamic function of the HPA axis with the dexamethasone suppression test in narcoleptic patients.[88] The study showed that, independent of obesity, narcolepsy is not associated with impaired glucose metabolism. In addition, there was no alteration in dynamic HPA function, although the negative feedback response to dexamethasone was mildly enhanced in narcolepsy cases. Similarly, other studies using BMI-matched controls have not shown any increased risk of type 2 diabetes or impaired glucose metabolism, independent of BMI, in narcoleptic patients.[89,90]

SLEEP AND ENDOCRINE ABNORMALITIES IN CRITICALLY ILL PATIENTS

Sleep fragmentation and deprivation are common in critically ill patients and may be associated with various hormonal disturbances. Patients experience poor sleep quality characterized by frequent disruptions and loss of circadian rhythms because of factors such as environmental noise; light; patient care activities, such as vital signs checks, drug administration, and diagnostic testing; patient-ventilator dyssynchrony; and pain or discomfort. Although the total number of hours of sleep in a 24-hour period may be normal (7–9 hours), approximately 50% of the sleep time occurs as short periods of light sleep during the day.[91] In patients in the intensive care unit (ICU), there is an increased percentage of wakefulness and stage N1 sleep (40%–60%) with decreased amounts of N2 (20%–40%), N3 (10%), and REM sleep (10%).[92] Thus, there is a significant reduction in the total time spent in restorative N3 and REM sleep stages.

It has been shown that there is loss of the normal circadian secretion of melatonin in critical illness, especially in sepsis, which seems to occur independently of light exposure.[93,94] In one study of patients with sepsis, investigators found that despite the exclusion of exposure to ambient light in the ICU, there was loss of periodic excretion of the melatonin urinary metabolite 6-sulfatoxymelatonin.[95] In addition, this noncircadian release of melatonin seems to persist for several weeks after recovery from sepsis that may contribute to continued sleep disturbances after ICU discharge.

The disruption of sleep, particularly restriction of SWS, as is seen in critically ill patients, negatively affects glucose metabolism and results in blunted insulin secretion with decreased insulin sensitivity.[60,69] ICU-related sleep disruption could therefore contribute to and exacerbate glucose abnormalities in critical illness; this is of particular importance in the critically ill patient, who is susceptible to episodes of hyperglycemia and the adverse outcomes associated with inadequate glucose control.

Exogenous corticosteroid administration may exacerbate the poor sleep and sleep disruption that is seen in these critically ill patients. Similarly, cortisol and catecholamine levels along with indices of energy expenditure, such as oxygen consumption (V_{O_2}) and carbon dioxide production (V_{CO_2}), tend to increase in sleep deprivation. The persistent sleep disruption that occurs in the critically ill patient, especially in the setting of sepsis, intensifies this stress response.[56,60]

Furthermore, in the acute phase of critical illness, increased levels of GH and PRL are initially noted. This increase seems to occur regardless of sleep onset and is likely due to increased pituitary activity.[96] However, with prolonged critical illness, the normal pulsatile secretion of GH and PRL is impaired, which may be a consequence of the potent inhibitory effect of sleep deprivation on GH and PRL release.[96,97] This decrease in GH and PRL levels may play a role in critical illness muscle wasting and impaired immunity.

SUMMARY

This article discusses the interactions between sleep and endocrine function. The authors have demonstrated the importance of sleep quality and quantity on maintaining hormonal balance. Disrupting this balance can have significant health consequences. Abnormalities in the endocrine system, such as excess GH secretion or thyroid hormone production, can lead to significant sleep disruption, such as sleep apnea and insomnia, respectively. Treating these hormonal abnormalities can improve sleep. Similarly, poor-quality or insufficient sleep can have a major impact on hormonal balance. Considerable research supports the effect of poor sleep on insulin and glucose metabolism, as well as on appetite regulation. Growing evidence supports the adverse consequences of sleep restriction, insomnia, and circadian rhythm abnormalities on endocrine balance and overall health. Restoring sleep quantity and improving sleep quality may assist in hormonal regulation, which is of particular importance in the critically ill patient who experiences sleep fragmentation and deprivation with loss of circadian rhythms. Understanding the sleep disruption and endocrine imbalances that occur in critically ill patients supports the importance of sleep and the need to optimize sleep in this patient population.

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