

REVIEW ARTICLE

SLEEP MEDICINE: AN OVERVIEW

By

Alaa El-Gendy

Pulmonary and Critical Care Medicine, Allegheny Medical School, Philadelphia, USA

Sleep is defined as the state of natural rest observed throughout the animal kingdom, in all mammals and birds, and in many reptiles, amphibians, and fish.⁽¹⁾ Regular sleep is necessary for survival as well as arousal from sleep.

CLASSIFICATION

According to the American Academy of Sleep Medicine (AASM) *International Classification of Sleep Disorders: Diagnostic and Coding Manual, Second Edition*, there have been more than 70 sleep disorders, that can be managed effectively once they are correctly diagnosed.⁽²⁾ Primary sleep disorders are presumed to be due to disturbance in sleep-wake generating or timing mechanisms. They are further subdivided into parasomnias and dyssomnias. Parasomnias are characterized by abnormal behavioral or physiological events in association with sleep, sleep stages, or sleep-wake transitions, rather than increased or decreased sleep. Parasomnias include nightmare disorder, sleep terror disorder, and sleepwalking disorder. Dyssomnias are characterized by abnormalities in the amount, quality, or timing of sleep. These include primary insomnia and hypersomnia, narcolepsy, breathing-related sleep disorder (i.e., sleep apnea), and circadian rhythm sleep disorder.

This article provides an overview of relationship of sleep and body systems.

CONTROL OF SLEEP

During the past decade, there has been tremendous progress in our understanding of the neural regulation of wakefulness and sleep. They are generated by a complex interaction of endogenous circadian and sleep homeostatic processes, as well as social and environmental factors.⁽³⁻⁴⁾ In mammals, the suprachiasmatic nuclei in the hypothalamus are the site of a master circadian clock.⁽⁵⁻⁸⁾ The suprachiasmatic nuclei generate circadian rhythms and maintain the temporal organization of circadian rhythms to the external physical, social, and work schedules. In humans, light is the strongest synchronizing agent for the circadian clock,⁽⁹⁾ and its ability to advance or delay circadian rhythms depends on the time of light exposure. In addition to light, nonphotic agents, such as melatonin or physical and social activity, also play a role in entrainment of human circadian rhythms.⁽¹⁰⁻¹¹⁾ The phase shifting responses to melatonin are generally in the opposite direction of light exposure.⁽¹²⁻¹⁴⁾ The primary role of the circadian pacemaker is to promote wakefulness during the day, and facilitate the consolidation of sleep during the nighttime hours. The interaction between

circadian and homeostatic processes typically allows for approximately 16 h of wakefulness and 8 h of sleep.⁽¹⁵⁻¹⁹⁾

GENETICS AND SLEEP

There has been interesting and exciting advancements observed in identification of genetic predispositions to a variety of sleep disorders in the past several years.⁽²⁰⁾ One of the interesting discoveries is the role of hypocretin/orexin deficiency in narcolepsy. The most prominent allele associated with the development of narcolepsy is DQB1*0602.^(21,22) Several studies have looked at the genetic influences on Obstructive Sleep Apnea Syndrome. Clinically, there appear to be numerous familial forms of sleep apnea. It would be unlikely a single genetic predisposition could be found. However, these studies have been hindered by the fact that many of the risk factors are also familial or genetically determined, such as obesity and craniofacial abnormalities. No monozygotic twin studies have been successfully completed in the OSA syndrome.^(23,24) There is an intriguing association between the risk for cardiovascular disease and OSA appears to be associated with the haptoglobin polymorphism. The study showed that patients with OSA and cardiovascular disease had a different pattern of haptoglobin phenotype than patients with OSA but without cardiovascular disease. This suggests that haptoglobin genotype may play a role in determining risk for cardiovascular disease and sleep apnea syndrome.⁽²⁵⁾ A strong genetic predisposition of restless leg syndrome has been suggested by Winkelmann et al, therefore, attention has been paid to genes that code for CNS dopamine transmission. However, an exact gene that has a high correlation with restless leg syndrome has not been identified.⁽²⁶⁻²⁸⁾

IMMUNE SYSTEM AND SLEEP

It has been observed for many years that patients with acute viral or bacterial infections feel excessively sleepy. The most widely studied inflammatory parameters associated with sleep and sleep deprivation are IL-1 β and TNF- α .

However, other work has identified possible roles of other cytokines in sleep. For example, increased levels of IL-6 are associated with increased sleep, IL-4 tend to suppress sleep, and IL-10 appears to inhibit IL-1 β and TNF- α .⁽²⁹⁻³⁴⁾ The mechanism of sleep enhancement from viral and bacterial infections is different. In viral infections, it seems to be related to viral induction of cytokines such as IL-1 and interferon. Gram-positive bacteria are associated with enhanced production of muramyl peptides, probably through a mechanism of promoting IL-1 and TNF. Gram-negative bacteria are associated with production of endotoxin and lipopolysaccharide.⁽³⁵⁻³⁶⁾ CRP has been linked as a risk factor for cardiovascular disease. CRP has been shown to be increased in OSA in several studies. However, CRP is also increased in obesity, and it is not clear whether obesity or sleep-disordered breathing is the predominant factor in producing increases in inflammatory markers. IL-6 and TNF- α have been increased in patients with OSA. This could be related to the cellular injury from hypoxia and reoxygenation. Several studies have shown that treatment of patients with OSA resulted in a reduction in these inflammatory markers. These are preliminary data at this point in time.⁽³⁷⁻⁴⁰⁾

ENDOCRINE SYSTEM AND SLEEP

Changes in hormone levels throughout the 24-h day are related either to circadian rhythms, sleep itself, or both. Takahashi and colleagues determined that an obvious peak level of GH occurred about 70 min after the initiation of sleep. This increase in GH lasted from 1.5 to 3.5 h. They also stated that delay in sleep was linked to a delay in GH peak. Subsequent work reveals that there are sex differences in the sleep-related secretion of GH. Van Cauter and colleagues noted that between 60 and 70% of GH secretion occurs at sleep initiation in men. They stated that more numerous daytime pulses of GH occur in women and that, perhaps, less than 50% of GH secretion occurs at the beginning of sleep. Recent studies in elderly men and women demonstrate that, with age, there are changes in the relationship of GH and sleep. Latta and colleagues determined that elderly women (but not men) manifested a

presleep increase in GH that correlated, not only with subsequent attenuation of sleep-related GH, but also with increased sleep fragmentation.⁽⁴¹⁻⁴⁵⁾ Roxburgh and Collis, in late 1800, linked the relationship between sleep-disordered breathing and excessive GH. More recent studies demonstrate a high prevalence of sleep-disordered breathing, snoring, and excessive daytime sleepiness in acromegaly.^(46,47) Several studies demonstrated that the highest TSH levels occurred between 9 pm and 6 am and the lowest between 10 am and 7 pm. Interestingly, level of TSH did not associate with T4 or T3 levels.^(48,49) Both hypothyroidism and hyperthyroidism can cause or exacerbate sleep disorders, such as OSAS, insomnia, excessive daytime sleepiness and restless legs syndrome (RLS). Two situations would strongly suggest the performance of thyroid testing: (1) patients manifesting symptoms and/or signs of hypothyroidism and (2) women over age 60 years.⁽⁵⁰⁾ The peak levels of cortisol secretion occur at approximately 9 am. A slow decline in cortisol levels ensues with a nadir during sleep. The lowest levels for cortisol levels are noted at approximately 12 am. Cortisol levels begin to rise prior to awakening.^(51,52) Both mineralocorticoid and glucocorticoid receptors exist. Stimulation of these receptors has different sleep results. Low-dose steroids would be more apt to stimulate mineralocorticoid, with increases in SWS. Higher doses of glucocorticoids produce a glucocorticoid effect, with increases in wake time and light sleep.⁽⁵¹⁾ Altered Luteinizing hormone (LH) and testosterone lead to altered sexual function. Luboshitzky and colleagues compared both patients with OSAS and healthy men to measure night LH and testosterone. Patients with OSAS showed a significant reduction in nocturnal (LH) and testosterone.⁽⁵³⁾ The degree of OSAS confers risk of erectile dysfunction. In one study, a total of 15% of those with an RDI of 29.5, and 40% of those with RDI of 67, had the diagnosis of erectile dysfunction. It was also found that approximately 75% of the patients had improved sexual function with nasal CPAP treatment.⁽⁵⁴⁾ Patients with OSAS develop increased atrial natriuretic peptide (ANP) levels. Krieger and colleagues measured ANP and noted elevated

sleep ANP and reduction in response to application of nasal CPAP.⁽⁵⁵⁾ A recent study of elderly men and women again revealed elevated ANP and increased nocturnal urine volume.⁽⁵⁶⁾ More severe RDI associated with greater nighttime urine volumes. There are number of studies implicate changes in the leptin, ghrelin, and insulin hormones and the OSAS. However, there is much less data linking them narcolepsy or RLS.⁽⁵⁷⁻⁶²⁾

CARDIOVASCULAR SYSTEM AND SLEEP

During sleep, there are changes in autonomic nervous system that play a pivotal role in the control of cardiovascular system functions. During non-REM sleep, there is a drop in sympathetic nervous activity and an increase in parasympathetic activity. During REM sleep, parasympathetic activity decreases and sympathetic activity may increase. There are several cardiovascular conditions suggesting that they may be caused by a sleep breathing disorder. Pregnancy induced hypertension, or preeclampsia, has been linked to snoring and possibly to OSA.⁽⁶³⁻⁶⁵⁾ Pregnant women with preeclampsia (i.e., hypertension and proteinuria) should be evaluated for the possibility that they may have a sleep breathing disorder. Arterial hypertension that is resistant to therapy has been linked to untreated OSA.⁽⁶⁶⁾ These patients should be evaluated for the possibility of a sleep breathing disorder. About 50% of people who have had a stroke have sleep apnea.⁽⁶⁷⁾ In some patients, nocturnal ischemia is related to OSA.⁽⁶⁸⁾ Right and left cardiac failure and bradyarrhythmias may be manifestations of sleep breathing disorders.⁽⁶⁹⁾ Patients with heart failure (with or without OSA) may not manifest the degree of sleepiness and generally have a lower Epworth sleepiness scale score compared to that is seen in typical OSA. Therefore, the absence of subjective sleepiness cannot exclude sleep apnea in patients with heart failure.⁽⁷⁰⁾ The unexpected results of the CANPAP study reinforce the fact that well-designed clinical trials need to be performed to evaluate the effects of treatment of sleep breathing disorders in heart failure patients.⁽⁷¹⁾

ELDERLY AND SLEEP

Sleep deteriorates with age.⁽⁷²⁾ The Sleep Heart Health Study (SHHS) investigators analyzed sleep staging from 2,685 individuals aged 37 to 92 years who did not use psychotropic drugs or large amounts of alcohol, and who did not have restless legs syndrome (RLS) or systemic pain. However, some of the included individuals did have cardiovascular disease, sleep apnea, or chronic pulmonary conditions. The data is remarkable for the sex differences in the deterioration of sleep. The percentage of SWS fell from 11.2% to 5.5% for men as they went from the 37-54 age group to the over-70 age group. The percentage of SWS for women increased from 14.2% to 17.2%. The authors did not find much change in REM sleep for either sex, with the percentage of REM in men falling from 19.5% in those aged 13 to 54 years old, to 17.8% in those over 70 years. For women, the REM falling from 20.9% to 18.8% in those from the lower to the higher age group. This study confirmed a decline in sleep efficiency for both sexes (from 85.7 to 79.2%) when comparing the youngest and oldest groups. There was an increase in the number of arousals, decreased K complex and decreased spindle density with aging. In addition, they found that the Respiratory Disturbance Index was a better predictor of arousals than was age or sex. The Respiratory Disturbance Index was associated with reduced REM sleep in both sexes, and with reduced SWS in men. It should be noted that the investigators used a 75 micro-volt amplitude criterion for SWS. Although women are more likely to complain of sleep difficulty than are men, their sleep quality in general is better preserved than that of men.⁽⁷³⁾ Both sleep apnea and RLS increase in prevalence with age.^(74,75)

THE FUTURE

Sleep medicine is expanding and attracting more and more attention from physicians and scientists. We now know that sleep is an active and dynamic state that greatly influences our waking hours, and we realize that we must understand sleep to fully understand the brain. Innovative techniques such as actigraphy and polysomnography are helping

us to diagnose and manage different sleep disorders. Understanding the factors that affect sleep in health and disease are assisting us to develop new therapies for different sleep disorders and to overcome jet lag, shift work, and insomnia associated problems. We can expect many benefits from research that will allow us to understand sleep's impact on our lives.

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