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Sleep and sleep disturbances: biological basis and clinical implications

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Abstract. Sleep is a neurochemical process involving sleep promoting and arousal centers in the brain. Sleep performs an essential restorative function and facilitates memory consolidation in humans. The remarkably standardized bouts of consolidated sleep at night and daytime wakefulness reflect an interaction between the homeostatic sleep need that is manifested by increase in sleep propensity after sleep deprivation and decrease during sleep and the circadian pacemaker. Melatonin, the hormone produced nocturnally by the pineal gland, serves as a time cue and sleep-anticipating signal. A close interaction exists between the sleep-wake, melatonin, core temperature, blood pressure, immune and hormonal rhythms leading to optimization of the internal temporal order. With age the robustness of the circadian system decreases and the prevalence of sleep disorders, particularly insomnia, increases. Deviant sleep patterns are associated with increased risks of morbidity, poor quality of life and mortality. Current sleep pharmacotherapies treat insufficient sleep quantity, but fail to improve daytime functioning. New treatment modalities for sleep disorders that will also improve daytime functioning remain a scientific and medical challenge.

Keywords. Sleep, circadian, melatonin, rhythms, disorders, hypnotics, memory.

Sleep physiology

Sleep, a state marked by bouts of lessened consciousness, lessened movement of the skeletal muscles and slowed-down metabolism, is a ubiquitous phenomenon in the animal kingdom, including humans. Humans are unique in that they have an urge for a consolidated sleep bout of 7 – 8 h, preferably during the night, which if disturbed, results in problems during wakefulness. Sleep is associated with characteristic changes in central nervous activity as measured by polysomnography (electroencephalogram, EEG; electromyogram, EMG; electrooculogram, EOG). Ever since Aserinsky and Kleitman (1953) observed regular periods of eye movements during sleep in humans, sleep has been divided into two distinct states known as rapid eye movement (REM) and non-rapid eye movement sleep (NREM) states [1]. One defining characteristic of NREM sleep is the slow oscillation of thalamo-cortical neurons, components of which may be detected as cortical slow waves. Based on the characteristic EEG signals NREM sleep is divided into stages S1, S2, S3 and S4. The slow frequency (<4 Hz) S3/S4 cortical waves, the measure of which is often referred to as slow wave activity (SWS) or delta power, provide an indication of the intensity or depth of sleep. Human sleep alternates between NREM stages S1 – S4 and REM sleep every approximately 90 min; the 90-min cycle is repeated 5 – 6 times a night [2]. While 90-min cycle contains an NREM and REM period, the relative amount of time spent in REM/NREM sleep shifts during the course of the night from NREM sleep predominance during the first 90-min cycle, to predominance of REM sleep in the final cycle of the night.

Current concepts hold that sleep is an orchestrated neurochemical process involving sleep-promoting and arousal centers in the brain [3, 4]. From animal studies it is known that wakefulness is promoted by brainstem and hypothalamic neurons; each of these arousal

networks is capable of increasing wakefulness, but coordinated activity in all these pathways is required for complete alertness and cortical activation [3]. During SWS, the arousal systems are inhibited in part by Gamma-aminobutyric acid (GABA) ergic neurons that are co-distributed with many neurons of the arousal systems. The ventrolateral preoptic nucleus (VLPO) contains a group of sleep-active, galanin-producing neurons that appears to be a critical component of sleep circuitry across multiple species. The VLPO presumably inhibits the major ascending monoaminergic arousal systems during sleep; lesions of the VLPO cause insomnia [4]. Noradrenaline, acetylcholine and serotonin, all of which are involved in the regulation of wakefulness, inhibit the electrical activity of these VLPO neurons. Hence, the upper and lower thresholds for sleep and waking are presumed to reflect relative inactivity levels of the sleep-promoting neurons. The processing of sensory information is present during sleep; all sensory systems (visual, auditory, vestibular, somesthetic and olfactory) demonstrate some influence on sleep, and at the same time, sensory systems undergo changes that depend on the sleep or waking state of the brain [5]. Recent functional brain-imaging studies of humans during sleep revealed a number of brain areas in which activities related to sensory processing of both auditory and visual stimuli are modulated by sleep [6–8]. In sleeping and sedated infants and in spontaneously sleeping adults, visual stimulation during sleep results in robust cortical blood oxygen level-dependent (BOLD) signal intensity decreases in the rostromedial occipital cortex [6,8]. Furthermore, acoustic stimuli presentation during sleep leads to reduced auditory and visual cortex activations which suggest that there is a sleep stage-dependent cortical deactivation upon stimulation [7]. These phenomena are compatible with a lower responsiveness of the brain to sensory stimuli during sleep.

Other sleep-related changes in brain activity include a relative increase in regional metabolism in the medial temporal lobe during NREM as well as REM sleep compared with wakefulness [9]. Sleep deprivation has significant and consistent effects on activation patterns of the parietal cortex in humans [10, 11]. Human hippocampal single neurons have been reported to demonstrate greater burst firing during SWS than wakefulness [12]. The picture is yet incomplete, and direct demonstration of sleep mechanisms in humans awaits further development of imaging techniques to allow better resolution in time and space and reliable assessment of brain activity patterns at rest without stimulation.

Sleep functions

Although sleep is a fundamental physiologic process, its functions are only starting to be unraveled. The best-supported evidence of its main function suggests that sleep a) performs a restorative function for the brain and body, improving the sense of energy and 'well-being' [13], and b) has an important role in the cerebral changes that underlie learning and consolidation of memory [14]. As will be discussed below, these functions are critical for brain development, physical and mental 'well-being', and maintenance of cognitive functions, particularly at old age.

The restorative value of sleep

Fatigue (feeling of weariness, tiredness, or lack of energy) is a natural condition following a lengthy period of wakefulness and activity. The essence of restorative sleep is that a healthy person feels an absence of fatigue after becoming fully awake. Chronic sleep loss is associated with excessive sleepiness (feeling drowsy with a tendency to actually fall asleep) and decreased psychomotor performance. It may also impair mood, autonomic and immune functions [15]. Deviant sleep patterns, e.g. short or prolonged sleep duration, insomnia, delayed or advance sleep phases, are associated with increased risks of physical and mental health problems. Short (<5 h per night) and long (>8 h per night) sleep durations increase the risk of developing diabetes [16] and mortality [17]. Short sleep duration is a risk factor for hypertension [18], coronary heart disease [19] and acute myocardial infarction [20]. This association identifies the quantitative as well as qualitative aspects of sleep as being essential for the restoration of body and mind; a wide range of sleep times are reported, and time is less important than quality.

It is estimated that 10% or more of the general population experiences poor sleep quality. Of these, insomnia (a subjective complaint of difficulty falling or staying asleep or poor sleep quality) is an extremely common condition in elderly people with reported rates of 30 and 37%, respectivey, in men and women over the age of 65 years [21, 22]. Sleep apnea (a condition characterized by temporary breathing interruptions during sleep) is thought to affect approximately 6.62% of the population, 8 million people in the USA alone [23]. Insomnia and sleep apnea are associated with persisting daytime fatigue that is a primary or contributing element/symptom in the disorder. Poor sleep quality adversely affects psychosocial, physical and occupational functioning, most commonly reported as fatigue and lethargy, mood disturbance, cognitive inefficiency and motor impairment, social discomfort and non-specific physical

ailments, absenteeism, reduced productivity, and higher incidence of driving accidents, industrial accidents and falls [24]. Insomniacs averaged 5.2 lost days of work per month overall, with 7.2 in those with other medical conditions and 3.2 days per month in those with primary insomnia (i.e. insomnia not related to another medical or psychological condition or substance) [22]. Thus, in addition to detracting from good health, the phenomenon of non-restorative sleep clearly affects economic performance and competitiveness.

Average sleep quality rather than quantity appears to be better related to health and affects balance and satisfaction with life [25–28]. There is a clear relationship between sleep quality and quality of life [25]. Overall appreciation of quality of life was rated as 'bad' in 22% and 'good' in 28% of severe insomniacs, compared with 3 and 68%, respectively, in subjects with no sleep complaints [26]. However, until now, there has been little interest in the development of therapeutic approaches aimed at enhancing the restorative property of sleep. Rather, the medical field has been more oriented towards improving sleep quantity, particularly shortening the time to fall asleep; all currently available insomnia drugs are sedative hypnotics that bind to GABA-A receptors and enhance the sleep-inducing effects of GABA. These drugs promote sleep but do not improve, and even adversely affect, daytime vigilance [29]. Future approaches to the treatment of insomnia should target the restorative nature of sleep so as to improve daytime functioning. The lack of pharmacotherapies for improving sleep quality probably relates to the meager level of present knowledge of how sleep restores bodily functions; measuring sleep quality is also challenging.

The role of sleep in memory consolidation

Sleep represents a biological condition that best enables the consolidating of newly learned materials into memories [14, 30–32]. In healthy humans, following learning tasks with periods of sleep, compared with wakefulness, consistently enhanced retention of the learned material in a variety of memory tasks [14, 30–32]. However, different sleep stages seem to be implicated in the process of memory consolidation, depending on the type of memory [30, 33]. Retention of declarative memory, which includes episodic (for events) and semantic (for facts) memory, benefits specifically from early nocturnal sleep, in which SWS predominates [34, 35]. The duration of SWS during a nap/rest period may improve recognition memory performance for items studied before the nap [36]. However, REM sleep appears beneficial for declarative memory for highly emotional material l [37] and procedural (for skills) memory tasks [38,39]. EEG recordings immediately after a motor adaptation task demonstrated a local increased slow-wave activity in the parietal cortex during the first 2 h of sleep; this increase was correlated with performance improvement [39]. In addition, PET/EEG studies indicated the subset of regions that were activated during acquisition of a procedural task during wakefulness were reactivated during the subsequent REM sleep [40]. The hippocampus, activated when performing a declarative spatial memory task, was reactivated in the SWS following acquisition of the task [41]. The duration of SWS during a nap/rest period following training on an object recognition task was negatively correlated with subsequent hippocampal activity associated with correct confident object recognition [36]. Altogether these findings suggest that specific neuronal activity occurring during sleep contributes to memory consolidation. The consolidation is manifest as changes in hippocampal and cortical representation of the memory traces.

Considering the role of sleep in memory consolidation, it is not surprising that insufficient sleep can reduce cognitive ability, including attention and memory. These symptoms are of particular concern in older people, because they may be misinterpreted as symptoms of dementia/mild cognitive impairment [24]. Insomnia drugs (benzodiazepines and non-benzodiazepine hypnotics, e.g. zolpidem, zopiclone, zaleplon) enhance GABA-A receptor activity. Consequently, these drugs have a central nervous system (CNS) depressant effect which adversely affects sleep architecture and in particular may reduce SWS and REM sleep [29]. In accordance with the role of these sleep stages in memory consolidation, all benzodiazepines as well as non-benzodiazepines adversely affect cognition by disrupting both short- and long-term memory [42, 43]. New treatment paradigms for insomnia include melatonin and melatonin receptor agonists; these agents do not affect sleep architecture or REM patterns [44] and appear to be less deleterious to memory than GABA-A receptor modulators [45–47].

Homeostatic and circadian sleep regulation

Humans normally sleep at night. The current view on the physiological regulation of sleep holds that there are two components in sleep regulation: 1) a homeostatic sleep need that is manifested by increase in sleep propensity after sleep deprivation and decrease during sleep, and 2) a circadian (~24 h) pacemaker, which is basically independent of sleep and waking, that determines the times of onset and termination of sleep

by changing the threshold of sleep need that will induce sleep [48, 49]. Both the circadian pacemaker and the sleep homeostat contribute to sleep consolidation. The interaction between these processes forms the basis for a remarkably standardized bout of sleep at night and a consolidated bout of wakefulness throughout the day. Arousal levels and stress play a pivotal role in sleep induction; a higher arousal level is associated with a decrease in sleep propensity and vice versa.

Recent findings suggest that adenosine, acting via the A1 receptor, is a key factor in the homeostatic control of sleep. In brain areas that regulate cortical vigilance, particularly in the basal forebrain, high extracellular adenosine concentrations, induced by prolonged wakefulness, decrease the activity of cholinergic cells and promote sleep. These changes may at least partially mediate the long-term effects of prolonged wakefulness [50]. Yet, microdialysis studies in humans have failed to detect an increase in extracellular adenosine during sleep deprivation [51]. The role of extracellular adenosine in regulating sleep drive may be limited to specific basal forebrain areas.

The circadian component of the sleep propensity function is presumably regulated by the intrinsic body clock residing in the brain's suprachiasmatic nucleus (SCN). This endogenous cycle in humans is somewhat slower than the solar 24-h day-night cycle [52] and is normally entrained by light to match the environmental 24-h light-dark cycle [53]. In humans and animals the SCN has direct connections to the dorsomedial hypothalamic nucleus (DMH) that innervates the VLPO [54]. Animal studies indicate that his multistage processor provides the organism with flexibility so that environmental cues, such as food availability, ambient temperature and social interactions, can be integrated with the clock signal to sculpt an adaptive pattern of rhythmic daily activities [4].

In humans that are isolated from all time cues, and in totally blind individuals, the circadian rhythms tend to 'free-run' with the endogenous cycle [52], unmatched to the daily 24-h rhythm (non-24 h sleep-wake disorder). In other circadian rhythm sleep disorders the individual's circadian rhythm of sleep and wakefulness is entrained to 24 h but out of phase with the conventional environmental patterns [e.g. delayed sleep phase syndrome (DSPS), a disorder characterized by sleep-onset insomnia and difficulty in awakening at the desired time and advanced sleep phase syndrome (ASPS) characterized by early sleep onset and early awakening, mostly seen in older individuals]. The pathophysiological process of circadian rhythm sleep disorders is presumed to be associated with the pacemakers, their coupling to the external cues or their downstream synchronizing mechanisms. Disorders associated with jet lag and shift work are due to temporary misalignment of the circadian sleep-wake rhythm with environmental patterns and may resolve spontaneously or by changing lifestyle [55].

One of the most important time cues generated by the SCN is the nocturnal production of melatonin (N-acetyl-5-methoxytryptamine) in the pineal gland, which occurs during the quiescent (nocturnal) periods of SCN electrical activity. Melatonin production is inhibited by ambient light [56], and because its elimination half-life in serum is only 40–50 min [57], the circulating melatonin is diminished during the light hours. Consequently, the dim light melatonin onset (DLMO), which is the initial surge in melatonin release in the early part of the night measured under low light conditions, is a consistent and reliable measure of the intrinsic circadian phase [58].

Melatonin is an important physiological sleep regulator. The circadian rhythm in synthesis and secretion of melatonin is closely associated with the sleep rhythm in both normal and blind subjects [59, 60]. The sharp increase in sleep propensity at night usually occurs 2 h after the onset of endogenous melatonin production in humans [61]. Aging, the presence of certain diseases (e.g. primary degeneration of the autonomic nervous system and diabetic neuropathy, some types of neoplasms, Alzheimer's disease) and certain drugs (e.g. β-blockers, clonidine, naloxone and non-steroidal anti-inflammatory drugs) abolish the nocturnal production of melatonin and are associated with impaired sleep [62]. Administration of melatonin during daytime (when it is not present endogenously) results in induction of fatigue and sleepiness in humans [63]. Importantly, melatonin is not sedating: in nocturnally active animals melatonin is associated with wake, not sleep, periods [64], and in humans its sleep-promoting effects become significant about 2 h after intake similar to the physiological sequence at night [46]. Importantly, melatonin potentiates the effects of GABA-A receptor modulators (i.e. benzodiazepine and non-benzodiazepine hypnotics) [46, 65], and co-administration of melatonin during the withdrawal period is thus useful to facilitate discontinuation of hypnotic drugs [66].

Brain-imaging studies of humans indicated that melatonin attenuates activations in the rostro-medial aspect of the occipital cortex during a visual-search task and in the auditory cortex during a music task [67]. These effects correlate with subjective measurements of fatigue. In addition, melatonin enhanced the activation in the left parahippocampus in an autobiographic memory task [67]. These results demonstrate that melatonin modulates brain activity patterns in awake subjects in a manner resembling actual sleep, thus inducing a state of sleep anticipation. The effects

of melatonin on brain activity are essentially different from those seen after sleep deprivation, although both treatments result in induction of fatigue [67]. Because melatonin does not increase the amount of SWS [68], which is considered a marker of the homeostatic sleep drive [69], the sleep-promoting effects of melatonin may be mostly ascribed to the circadian component of sleep regulation.

Apart from its sleep-anticipating effect, exogenous melatonin may affect sleep through its phase-resetting action on the biological clock. Melatonin serves as a time cue (signal of darkness) to various organs, including the SCN itself, and in the absence of light, may entrain the sleep-wake and neuroendocrine rhythms to the 24-h cycle [70]. In DSPS the endogenous melatonin rhythms are delayed compared with those in normal individuals [71]. Significant association of DSPS with a mutation in arylalkylamine-N-acetyl transferase, the rate-limiting enzyme in melatonin synthesis, has been reported [72]. Melatonin administration in the evening advanced sleep in DSPS [70]. Furthermore, exogenous melatonin administration synchronized sleep and neuroendocrine rhythms to the day-night cycles in free-running totally blind subjects [73, 74]. A melatonin-induced delay in nocturnal cortisol production may explain in part some of the beneficial effects of melatonin therapy on sleep and daytime alertness in elderly patients with insomnia, in whom melatonin deficiency is frequently found [75]. Presently melatonin appears the only effective drug for treating circadian rhythm sleep-wake disorder.

Reciprocal interactions of sleep and other circadian rhythms

Body temperature

Under normal environmental conditions, the rhythms of core body temperature and sleep propensity vary inversely across the day and night in healthy young adults. However, it is still not known whether this relationship is causative or merely coincidental. The origin of the circadian rhythm of core temperature is mainly in circadian changes in the rate of heat dissipation through the extremities, which is mediated by vasodilatation of the cutaneous vasculature. Mechanisms controlling the circadian rhythm of core temperature are involved also in thermoregulation during physical activity, and there is an interaction between the circadian and activity-rest rhythms. This interaction is manifest in the initial response to spontaneous activity and to mild exercise, body temperature rising more quickly and thermoregulatory reflexes being recruited less quickly around the trough and rising phase of the resting temperature rhythm, in comparison with the peak and falling phase [76]. Furthermore, exogenous melatonin in the afternoon simulates the sleepiness and loss of heat (via increased blood flow in vasodilatated distal skin regions i.e. hands and feet) occurring naturally in the evening when endogenous melatonin levels are elevated [77]. Somnogenic brain areas contain thermosensitive cells, so it is possible that the sleep-wake cycle may be directly affected by thermoregulatory changes themselves. The crest of the circadian rhythm of REM sleep is positioned shortly after the minimum of the core body temperature rhythm [78]. Temperature changes before and after sleep onset may act in a positive feedback loop to maintain a consolidated sleep bout [79].

Respiratory function

The circadian timing system has an influence on respiration and respiratory control, even in the absence of sleep. Some measures reflecting the mechanical properties of the lungs, such as functional residual capacity, forced expiratory volumes and airway resistance, change periodically with the time of the day. Resting pulmonary ventilation, tidal volume and breathing rate also follow circadian patterns, and they respond differently to hypercapnia or hypoxia at various times of the day. Hence, a daily time window exists in which the respiratory system is less capable of responding to challenges, a factor which may contribute to the finding that some cardiorespiratory symptoms and diseases peak at particular times of the day [80]. Importantly, circadian and sleep mechanisms appear to have additive effects on breathing, suggesting that the circadian timing system can potentially amplify or suppress sleep-related breathing abnormalities, depending upon the characteristics of the circadian output and the time of day at which sleep occurs [81].

Obstructive sleep apnea (OSA) is a disorder in which the upper airway collapses despite respiratory effort, and oxygenation is impaired. Obstructive sleep apnea is most commonly seen in middle-aged and older obese men, but can be seen in others, even children. Many individuals stop breathing for brief intervals: however, when these episodes of apnea become more frequent and last longer, they can cause the body's oxygen level to decrease, which can disrupt sleep, resulting in numerous micro-arousals during the night. The patient may not fully awaken, but is aroused from the deep restful stages of sleep, and thus feels tired the next day. Obstructive sleep apnea is therefore strongly associated with excessive daytime fatigue and sleepiness. Compared with patients not diagnosed with sleep apnea, a significantly greater prevalence was

found for hypertension, renal failure, adverse cardiovascular outcomes, mood disorders, anxiety, posttraumatic stress disorder, psychosis and dementia in patients with sleep apnea [82].

Blood pressure

Blood pressure (BP) displays appreciable predictable-in-time circadian variation characterized by a nocturnal fall and a diurnal rise; systolic BP customarily falls 10–20 mmHg at night in both normotensive and hypertensive individuals. The circadian BP rhythm seems to be mediated mainly by the circadian rhythm of sympathetic tone, linked to changes in physical and mental activities, e.g. the sleep-wake cycle. Normal sleep decreases sympathetic nerve activity, BP and heart rate.

Nocturnal hypertension, which is characterized by the loss or even reversal of the expected 10–20% BP decline during sleep time, greatly increases the risk of cardiac and cerebrovascular events. Sleep apnea is a common cause of non-dipping blood pressure. The prevalence of obstructive sleep apnea among hypertensive individuals is approximately 50% [83]. Among hypertensive 'non-dippers', OSA has been reported in over 90%. Treatment of OSA with positive airway pressure (CPAP), which prevents hypoxia and lowers urinary norepinephrine levels back towards normal, has been noted to lower night time BP [84].

Diminished melatonin production at night was reported in severely hypertensive patients [85], in elderly and in patients with coronary diseases [75, 86] and in hypertensive patients with non-dipping BP profile [87, 88]. Thus, melatonin deficiency may exacerbate impaired nocturnal BP fall. Indeed, nighttime melatonin reduced BP in male patients with essential hypertension who were not treated with anti-hypertensive [89, 90] and significantly reduced nocturnal systolic BP in patients with nocturnal hypertension treated with anti-hypertensive drugs [91]. In all three studies, 'prolonged release' formulations of melatonin were used to circumvent the short half-life of melatonin. The improvement in BP control appears to be direct, unrelated to improved sleep. Thus, addition of melatonin at night to stable anti-hypertensive treatment may improve nocturnal BP control, in addition to sleep in patients with nocturnal hypertension.

Immune functions

Bidirectional communication pathways exist between the brain and the immune-endocrine systems which are able to modulate host-defense and sleep mechanisms [92–94]. Cytokines, which are mediators of immune system responses, such as tumor necrosis factor (TNF), interleukin (IL)-1, and IL-6, introduced into the brain can be retrieved in the blood. Furthermore, sympathetic nerve fibers innervate primary and secondary lymphoid organs. Circulating catecholamines and neuropeptides influence the functional capabilities of the immune system. The hypothalamic-pituitary-adrenal (HPA) axis facilitates interaction between the brain and the immune system presumably through the actions of adrenocorticotropin hormone (ACTH) and cortisol on immune cells. These pathways connecting between the brain and the lymphatic system provide a network by which the sleeping-waking brain influences immune functions.

In addition, changes in cytokine levels in the periphery modulate the CNS either directly or via the vagal nerve and influence the sleeping-waking brain. Some cytokines may either promote or inhibit sleep under physiological conditions, in the absence of infection or immune challenge. There is a significant overlap between neurohormonal systems such as the somatotropic and HPA axes and cytokines, particularly with regard to their effects on sleep-wake regulation [93]. Of cytokines studied thus far, evidence indicates that at least three, i.e. IL-1β, IL-6, and TNFX are involved in the regulation of sleep. For example, IL-1β directly alters discharge patterns of neurons in hypothalamic and brainstem circuits implicated in the regulation of sleep-wake behavior. In rats administration of IL-1β or TNFα result in increased SWS during periods of NREM sleep. In humans the circadian pattern of IL-6 coincides with sleep/sleepiness. IL-6 is elevated in disorders of excessive daytime sleepiness such as narcolepsy and OSA. Also, the secretion of this cytokine is stimulated by total acute or partial short-term sleep loss reflecting the increased sleepiness experienced by sleep-deprived individuals. It was hypothesized that IL-6 is a mediator of sleepiness, and its circadian pattern reflects the homeostatic drive for sleep [95].

Empirical data indicate that sleep is altered during sickness. These changes in physiology and behavior collectively function to support the immune system, and under normal circumstances the health of the host is restored. [92]. Because cytokines regulate/modulate sleep-wake behavior in the absence of immune challenge, and cytokine concentrations and profiles are altered during infection, it is likely that cytokines mediate infection-induced alterations in sleep [94].

A growing literature indicates that partial short-term sleep deprivation increases markers of systemic inflammation; increased plasma levels of inflammatory markers along with increased TNFα and IL-1β production by peripheral blood mononuclear cells [96]. Also, the secretion of IL-6 cytokine is stimulated by total acute or partial short-term sleep loss [95]. Insomnia is associated with nocturnal sympathetic

arousal and declines of natural immunity, which is related to decreased immune functioning [97] and appears to be a risk factor for mortality [17].

Growth hormone

Growth hormone (GH) is preferentially secreted during SWS. Because SWS is concentrated during the first sleep period, GH surge mostly appears during the beginning of sleep. This association may be due to a bidirectional interaction between sleep and GH-releasing hormone (GHRH), which regulates GH secretion [98]. Pharmacological interventions that are capable of increasing the duration and/or the intensity of SWS, such as oral administration of gamma-hydroxybutyrate (GHB), also increase the rate of GH release. Exogenous GHRH promotes NREM sleep in various species, whereas suppression of endogenous GHRH (competitive antagonist, antibodies, somatostatinergic stimulation, high doses of GH or insulin-like growth factor) results in simultaneous inhibition of NREM sleep [98]. Mutant and transgenic animals with a defect in GHRH activity display permanently reduced NREM sleep, which cannot be reversed by means of GH supplementation. GHRH contents and messenger RNA (mRNA) levels in the hypothalamus correlate with sleep-wake activity during the diurnal cycle and sleep deprivation and recovery sleep. Preliminary data from a sleep study of adult humans with GH deficiency show decreased total sleep time and increased sleep fragmentation in GH-deficient patients compared with normal controls [99]. GABAergic neurons in the anterior hypothalamus-preoptic region are believed to mediate promotion of NREM sleep by GHRH. Apparently, two populations of GHRH neurons need to be simultaneously active to stimulate, in a coordinated fashion, SWS and pituitary GH release. Simultaneous stimulation of NREM sleep and GH secretion by GHRH may promote adjustment of tissue anabolism to sleep [98]. This interrelationship may be of particular importance in children and adolescents, in whom a habitual delay in sleep hours is commonplace. The effects of this habitual sleep delay on somatic body growth and stature remains to be elucidated.

Glucocorticoids

Glucocorticoids, in particular cortisol, are essential hormones associated with waking, alertness and stress response, and are potent modulators of learning and memory functions [100, 101]. Amygdala-dependent emotional memory formation has been shown to benefit from glucocorticoid increases in humans [102–104]. However, predominant activation of glucocorticoids has generally been found to impair declarative memory acquisition during wakefulness and subsequent consolidation during sleep and formation [105]. Enhancing the plasma levels during early SWS-rich sleep completely blocked any sleep-associated declarative memory formation during this period [106].

In humans the secretion of cortisol from the adrenal gland is regulated by the HPA axis to exhibit a circadian rhythm with maximal blood levels in the early morning hours, and a decline to half of the peak value in the afternoon. The cortisol-elicited decline in plasma ACTH occurs more rapidly in the evening than in the morning. This is presumably due to the decrease in 'threshold' change in cortisol concentration necessary to initiate feedback inhibition of ACTH [107]. Studies of human subjects in isolation indicate that in most individuals, rhythms such as sleep-wakefulness, body temperature and plasma cortisol concentrations maintain a similar periodicity and stable phase relationships in the absence of external time cues [108]. Cortisol release is reduced to a minimum during early, SWS-rich sleep, whereas during late sleep, when REM sleep becomes prominent, cortisol levels distinctly increase to reach a maximum at about the time of morning awakening [109].

Cortisol impairs sleep; in healthy young and old subjects cortisol (and IL-6) plasma concentrations were positively associated with total wake time and negatively with REM sleep [110]. Insomnia is associated with an overall increase in ACTH and cortisol secretion, which, however, retains a normal circadian pattern. The increase is consistent with insomnia being primarily a disorder of hyperarousal rather than one of sleep loss, which is usually associated with no change or a decrease in cortisol secretion [111] [112]. In older subjects cortisol secretion occurs earlier during sleep than in young adults, which may cause impairment of sleep [109]. In addition, in older (>65 years old) subjects, even those who do not suffer from insomnia, the evening sensitivity to cortisol, as evidenced by the cortisol-elicited decline in plasma ACTH, is attenuated compared with healthy young (20–35 years) subjects [107]. This may explain why elevations of ACTH and cortisol resulted in significantly more wakefulness and suppression of SWS in middle-aged men but not in younger individuals [113]. Hence, middle-aged, compared with young individuals, not only have higher cortisol levels in the early portion of the night, but also an increased vulnerability of sleep to stress hormones, possibly resulting in impairment in the quality of sleep.

A temporal relationship exists between cortisol and melatonin rhythms. In young adults, the melatonin onset typically occurs during low cortisol secretion (quiescent period), with a time lag between the start of the quiescent period and the melatonin onset of about

90 min [109]. In night shift workers, whatever the timing of the melatonin surge, the start of the quiescent period of cortisol secretion remains phase locked to the melatonin onset with a similar time lag [114]. Furthermore, in normal male volunteers cortisol secretion was unaffected by sleep deprivation regardless of melatonin's presence or absence [111]. Because of the role of melatonin in circadian system functioning, the decline in melatonin with age may be causally related to low evening sensitivity to cortisol in the elderly and therefore to blunted and delayed inhibition of ACTH secretion and consequently sustained activation of the HPA axis during the early night. Such an explanation is compatible with phase delay in cortisol acrophases despite a phase advance in melatonin that is seen in older subjects with insomnia upon melatonin replacement therapy [115].

Sleep in brain development and aging

The human newborn, in the first days of life, spends approximately two-thirds of each 24 h period asleep [116]. The length of sleep decreases towards adulthood to an average 7 h asleep throughout life [117]. Both quiet (NREM) and active (REM) sleep stages are distinguishable during the last 10 weeks of gestation in humans, and REM sleep is the prevailing state even during the first postnatal months. Extensive investigations in humans have demonstrated association between the percentage of REM/NREM sleep and cerebral maturation [118]. Current results indicate that the maturation of quiet sleep not only coincides with formation of thalamo-cortical and intracortical patterns of innervation and periods of heightened synaptogenesis, but also is actually associated with important processes in synaptic remodeling [119].

Sleep begins to coalesce from a series of naps to a more prolonged night-time sleep between 8–18 weeks of age [118]. A robust melatonin rhythm appears in full-term infants at about 12 weeks of age and matures during the first 12–36 months of life [120, 121]. A further development in sleep organization characterized by increased SWS and coupling with the circadian timekeeping system takes place during the first 6 months of life in both term and preterm infants [116]. Low melatonin excretion in the first weeks of life correlates with delayed psychomotor achievements at 3 and 6 months of age [122]. Melatonin production increases at about the same time that REM abundance decreases in infants. It is, however, unclear whether deficiency in melatonin and abnormal sleep patterns only coincide or are causally related to neurodevelopmental deficits in some infants.

Aging has been associated with a significant reduction in sleep efficiency and continuity [123]. Sleep architecture changes; in particular, the deeper levels of sleep, NREM stages 3 and 4, decrease, with older adults having almost no SWS [124]. This results in more of the night spent in lighter levels of sleep, which makes it more likely that the older adult will wake up more often during the night. It remains unclear whether or how sleep impairment typically seen in older persons aged 55 years and older might underlie the increased inflammatory changes seen in these populations [125]; evidence of an association is circumstantial.

Changes in the sleep-wake cycle are likely due to changes in the core body temperature cycle, decreased light exposure and other environmental factors. In addition, the output of the circadian clock becomes less robust with age [126]. As people age, the sleep-wake circadian rhythm may become less synchronized (e.g. no longer have the same response to external cues) and may become weaker (less robust), resulting in less-consistent periods of sleep-wake across the 24-h day. More recent research suggests there may also be a genetic component to these changes [127].

The elderly are known to have a high prevalence of insomnia; insomnia is more prevalent in elderly people, with reported rates of 30 and 37% in men and women over the age of 65 years compared with the respective rates of 10 and 15% in 18 to 35 year olds [21]. Women were 1.5 times more likely than men to have a sleep problem at any age. Causes of insomnia include age-dependent disturbances in circadian rhythms, increased prevalence of breathing and other primary sleep disorders, medical and psychiatric illness, side effects of drugs/medications and psychosocial factors [128, 129]. Increase in early morning awakenings and difficulty in falling asleep are among the most frequent findings reported in the elderly [130]. However, greater quality of well-being is associated with greater sleep satisfaction, rather than with subjective nor objectively recorded sleep duration [28]], suggesting that for the elderly in particular, it may be important to improve quality and not quantity of sleep.

With age the timing of the melatonin peak is delayed into the morning hours [131, 132], and because light inhibits melatonin production, this delay may explain in part the lower amounts of the hormone present in the blood during the night. In patients with insomnia aged 55 years and older the mean melatonin production at night is about two-thirds of that in aged-matched individuals without insomnia, and about one-third of that in healthy adults aged 20–35 years [75, 131]. Taking into consideration the preeminence of the circadian clock and melatonin in timing sleep, it is

likely that insomnia is also linked to melatonin abnormalities. Beneficial effects of melatonin in improving night sleep have been reported, particularly in elderly patients with insomnia who typically produce less amounts of this hormone [75, 133, 134]. Some studies have indicated that melatonin is beneficial for improving the quality of life in the elderly [135], which agrees well with the importance of good sleep to quality of well-being [28].

Neurodegenerative disorders (e.g. Alzheimer's, AD, and Parkinson's disease, PD) are typically late-onset diseases that result from premature progressive degeneration of specific neurons, and manifest as diseases or syndromes with varied combinations of cognitive, motor, sensory and autonomic dysfunctions [136]. Sleep disorders in PD include insomnia, excessive daytime sleepiness, 'sleep attacks', nightmares, REM sleep behavior disorder, periodic limb movement in sleep, restless legs syndrome and sleep apnea syndrome [137]. Furthermore, recent data suggests that REM sleep behavior disorder and excessive daytime sleepiness are early symptoms in PD [138]. Sleep disturbances are among the more common neurobehavioral symptoms of AD. An increased tendency to fall asleep during the daytime together with increased wakefulness during the night has been demonstrated in patients with advanced but also mild/moderate AD [139, 140]. Polysomnographically, AD patients show a decrease in REM sleep as the disease progresses. Cholinesterase inhibitors, commonly used to treat cognitive loss in AD, may in principle be used to increase REM sleep, but unfortunately they also induce insomnia and vivid dreams, which add to AD burden [139].

From unknown reasons, concentrations of melatonin in the cerebrospinal fluid are diminished in AD. In particular, the decrease in melatonin is seen in subclinical stages in subjects carrying the APOE4 allele, which is a risk factor for developing AD [141]. Melatonin replacement therapy has been recently shown to increase sleep time in AD patients [142, 143], although not in all studies [144], including a large multi-center trial [145]. In parallel, the ADAS cognition and non-cognition scores significantly improved [143], although again, not in all studies [145]. Some of the effects of melatonin may pertain to the observed cognitive improvement: improving sleep quality with melatonin does not impair sleep architecture or memory, and in addition, replaces the deficiency in the endogenous hormone and may shift the cortisol peak to the morning hours so as to increase morning alertness. Whether and how these effects underlie the improved cognitive capacity in AD patients seen in a one trial remains to be explored.

Concluding remarks

Sleep is an orchestrated neurochemical process involving sleep-promoting and arousal centers in the brain. Among the major sleep functions are the restorative effect on body and mind, resulting in a sense of well-being and daytime vigilance, and facilitation of the plastic cerebral changes that underlie learning and consolidation of memory. Sleep propensity depends on the amount of sleep deprivation and on the circadian clock phase. The interaction between these processes forms the basis of a remarkably standardized bout of sleep at night and a consolidated bout of wakefulness throughout the day. Melatonin, the hormone produced by the pineal gland at night, serves as a time cue to the biological clock and promotes sleep anticipation in brain activity patterns; these effects may explain the increase in sleep propensity at night. A close interaction exists between the sleep-wake and other circadian rhythms such as body temperature, blood pressure, immune and hormonal rhythms leading to optimization of the internal temporal order. With age the robustness of the circadian system decreases, and melatonin production at night is reduced. In parallel, the prevalence of sleep disorders increases due to age-related changes in sleep patterns, increased prevalence of breathing and other primary sleep disorders, medical and psychiatric illness, side effects of drugs/medications and psychosocial factors.

Deviant sleep patterns and poor sleep quality are associated with increased risks of cardiovascular, metabolic and cognitive diseases, poor quality of life and mortality. The currently available sleep pharmacotherapies address the complaint of insufficient sleep but fail to improve its quality or daytime functioning. Treating non-restorative sleep is a prime medical need. The lack of pharmacotherapies for improving sleep quality probably relates to the meager level of present knowledge of how sleep restores bodily and cognitive functions.

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