Neurobiologic Mechanisms of Sleep and Wakefulness

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Defining sleep

Sleep physicians define human sleep on the basis of a person's observed behavior and accompanying physiologic changes in the brain's electrical activity as it transitions between wakefulness and sleep. Behaviorally, human sleep is characterized by reclined position, closed eyes, decreased movement, and decreased responsivity to the internal and external environment. The responsiveness to stimuli is not completely absent; a sleeper continues to process some sensory information during sleep and meaningful stimuli are more likely to produce arousals than nonmeaningful ones. For example, the sound of one's own name is more likely to arouse a sleeper than some other sound, and the cry of her baby is more likely to arouse a sleeping mother than the cry of another infant.

Constituents of sleep

Sleep consists of two strikingly different states, rapid eye movement (REM) and non-rapid eye movement (NREM). NREM sleep can be further subdivided into three stages. Polysomnography is the gold-standard technique that simultaneously records the three physiologic measures that define the main stages of sleep and wakefulness: muscle tone, recorded through electromyogram (EMG), eye movements, recorded through an electro-oculogram (EOG), and brain activity, recorded through an electroencephalogram (EEG) (1, 2). The clinical polysomnogram also monitors air flow at the nose and mouth, respiratory-effort strain via gauges placed around the chest and abdomen, and oxygen saturation via noninvasive monitors by introducing a beam of light through the skin. Other parameters include the electrocardiogram and EMG of the anterior tibialis muscles, which are intended to detect periodic leg movements. Finally, a patient's gross body movements are continuously monitored by audiovisual means.

The EEG pattern of drowsy wakefulness consists of low-voltage rhythmic alpha activity (8–13 cycles per second [Hz]). In stage 1 of NREM sleep (N1), the low-voltage mixed frequency theta waves (4–8 Hz) replace the alpha rhythm of drowsy wakefulness. Slow asynchronous eye movements are seen on the EOG in the beginning of stage N1 sleep and disappear in a few minutes. The muscle activity is highest during wakefulness and diminishes as sleep approaches. Stage N1 is viewed as a "shallow" sleep, during which an individual can be easily aroused. Individuals with behavioral characteristics of sleep and polysomnographic characteristics of stage N1 sleep may or may not perceive themselves as sleeping. With transition to stage N2, EEG patterns termed sleep spindles and K complexes appear on the EEG. Sleep spindles are 12- to 14-Hz synchronized EEG waveforms with a duration of up to 1.5 seconds. Sleep spindle waves arise as a result of synchronization of groups of thalamic neurons by a GABA-ergic thalamic spindle pacemaker. The origin of K complexes is not known. With the onset of stage N2 the arousal threshold increases, and more intense stimulus is needed to arouse a sleeper. Stage N3 of NREM sleep is defined by a synchronized high-amplitude (more than 75 mV) and slow (0.5–2 Hz) delta wave EEG pattern. Stage N3 is referred to as deep sleep, delta sleep, or slow-wave sleep (SWS). SWS is associated with a higher arousal threshold than are "lighter" stages of NREM sleep. No eye movements are detected on the EOG during stages N2 or N3 of NREM sleep. The EMG tracks continue to decline in muscle tone as NREM sleep "deepens" from stages N1 to N3.

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Table 1. Physiological Functioning During Sleep

Parameter	NREM Sleep	REM Sleep
Heart	Decreases	Irregular with increases and decreases
Blood Pressure	Unchanged, stable	Irregular with increases and decreases
Upper airway muscle tone	Decreased	Further decreased
Temperature	Preserved thermoregulation	Increased temperature and poikilothermia
Gastrointestinal	Failure of inhibition of acid secretion; prolonged acid clearance	Failure of inhibition of acid secretion
Nocturnal penile tumescence/ clitoral enlargement	Infrequent	Frequent

Data from references (9, 35)

The EEG pattern of REM sleep is characterized by low-voltage and fast frequencies (alpha or 8–13 Hz). This EEG pattern is referred to as activated or desynchronized. Activated refers to an active mind (dreams) and the EEG pattern is characteristic of wakefulness. Paradoxically, individuals in REM, while activated, are behaviorally less responsive than during the wake state (3, 4). Desynchronized refers to the random-appearing wave pattern seen on the REM sleep EEG, in contrast to the synchronized uniform wave pattern seen on the NREM sleep EEG (3, 4). To be scored as REM sleep, a polysomnographic tracing must contain an activated EEG pattern as well as muscle atonia (EMG) and the presence of rapid eye movements (EOG) (5).

Sleep architecture

Sleep typically begins with a shallow stage 1 of NREM (N1) and deepens to NREM stages 2 and 3, which are followed in approximately 90 minutes by the first brief episode of REM. After the first sleep cycle, NREM and REM sleep continue to alternate in a predictable fashion, each NREM-REM cycle lasting approximately 90 to 120 minutes (1). In the course of the night, sleep cycles recur three to seven times. Stage 1 of NREM, which lasts only a few minutes, serves as a transition from wakefulness to sleep, and later during sleep serves as a transition between REM-NREM sleep cycles. Typically, stage N1 constitutes 2%−5% of total sleep time. An increase in the amount or percentage of stage N1 sleep may be a sign of sleep disruption. The brief first period of stage 1 NREM sleep is followed by the "deeper" stage N2, which lasts for approximately 10 to 20 minutes. Stage N2 sleep normally constitutes 45%−55% of the total sleep time. Stage N2 sleep progresses to stage N3, also known as "deep sleep" or slow-wave sleep. Stage N3 constitutes 15%−20% of the total sleep time. Stage 3 of NREM sleep predominates during the first third of the night. The first REM period is brief and occurs approximately 90 minutes after sleep onset; subsequent REM cycles occur approximately 90 to 120 minutes apart. REM sleep episodes become longer as the night progresses, and the longest REM periods are found in the last third of the night (6, 7). NREM sleep accounts for 75%−80% of the total sleep time, and REM sleep accounts for 20%−25% of the total sleep time (1, 6, 8–10). These proportions commonly vary with age (see the section Effects of Age).

Control of respiration and cardiovascular function during sleep

The predominance of the parasympathetic tone and decreased energy expenditure during NREM sleep are responsible for decreased ventilation during this stage. The respiration rate in NREM sleep is regular, and cardiovascular changes are consistent with decreased energy expenditure. By contrast, breathing patterns and heart rate during REM sleep are irregular (11–13). The irregularities in cardiovascular parameters increase the risk of myocardial infarctions during REM sleep in vulnerable individuals. The changes in ventilation, respiration, and upper airway tone also make REM sleep a vulnerable period for individuals with obstructive sleep apnea (Table 1).

Effects of age

Age has a major impact on sleep continuity and the distribution of sleep stages through the night. The sleep pattern of newborn infants dramatically differs from that of adults. During the first year of life, infants sleep twice as much as adults and enter sleep through REM. During the first year of life, REM sleep constitutes as much as 50% of the total sleep time; this percentage decreases to adult levels of 20%−25% by age 3, and remains at that level until

old age. NREM-REM cycles, controlled by the ultradian process, are present at birth, but the 50- to 60-minute cycle periods in newborns are shorter than the approximately 90-minute periods in adults. SWS is not present at birth, but develops by the age of 2 to 6 months. The amount of SWS steadily declines from maximal levels in the young to almost nonexistent amounts in the elderly (6, 12, 14). In addition to loss of SWS, sleep changes in the elderly include sleep fragmentation, increased percentage of stage 1 sleep, and decreased ability to maintain continuous sleep at night and wakefulness during the day. Contrary to commonly held beliefs, the need to sleep does not decrease with advancing age; what changes in the elderly is the ability to maintain sleep (12, 14, 15).

How much sleep does one need?

One needs a sufficient amount of sleep to feel alert, refreshed, and avoid falling asleep unintendedly during the waking hours. Most young adults average between 7 and 8 hours of sleep nightly, but there is a significant individual and night-to-night variability in these figures. Genetics play a role in determining sleep length, and voluntary sleep reduction plays a significant role in determining how much sleep a person actually gets. Sleep restriction results in daytime sleepiness, and daytime sleepiness suggests that an individual's sleep needs have not been met (6).

Regulation of sleep and wakefulness

Drives. Experimental studies in humans and animals led to the development of the two-process model, which accounts for the regulation of sleep and wake time. According to the model, sleep is regulated by two basic processes: a homeostatic process, which depends on the amount of prior sleep and wakefulness, and a circadian process, which is driven by an endogenous circadian pacemaker, generating near 24-hour cycles of behavior. An ultradian process within sleep is believed to control the alternation between REM and NREM sleep every 90 to 120 minutes. It is hypothesized that the interaction of homeostatic and circadian processes is responsible for helping humans to maintain wakefulness during the day and consolidated sleep at night.

Homeostatic Regulation of Sleep. Virtually all organisms have an absolute need to sleep. Human beings cannot remain awake voluntarily for longer than 2 to 3 days (12, 16). The homeostatic factor represents an increase in the need for sleep (sleep pressure) with increasing duration of prior wakefulness. The presence of the homeostatic factor is best demonstrated through sleep-deprivation studies. When a normal amount of sleep is reduced, the homeostatic drive is increased leading to increased sleep pressure and sleepiness during the day as well as increased deep sleep at night. When normal sleep is preserved, the homeostatic factor represents a basic increase in sleep propensity during waking hours. The pull of this drive builds up during wakefulness and reaches its peak at sleep time. Its strength declines during sleep, with the lowest point (nadir) on awakening in the morning. It is also useful to differentiate sleepiness from tiredness or fatigue. A tired or fatigued individual does not necessarily have a propensity to fall asleep given an opportunity to do so. A sleepy individual is not only anergic but will fall asleep given the opportunity to do so.

Circadian Rhythms. Human beings have an endogenous circadian pacemaker with an intrinsic period of slightly longer than 24 hours (17). Virtually all living organisms exhibit metabolic, physiologic, and behavioral circadian (i.e., about 24-hour) rhythms. The most obvious circadian rhythm is the human sleep-wake cycle. Examples of other circadian rhythms include the release of cortisol, thyroid stimulating hormone, and melatonin. Most mammalian tissues and organs contain mechanisms capable of expressing their function in accordance with the circadian rhythm. The "master biological clock," which regulates sleep-wake and all other circadian rhythms, resides in the suprachiasmatic nuclei (SCN) of the hypothalamus. SCN are bilaterally paired nuclei located slightly above the optic chiasm in the anterior hypothalamus. Circadian clocks are normally synchronized to environmental cues by a process called entrainment. The process of entrainment of SCN cells is mediated through glutamate stimulating the *N*-methyl-D-aspartate (NMDA) receptor (18). Light hitting the retina activates the release of glutamate through the retinohypothalamic tract projecting to the SCN (19). In mammals, the light-dark cycle is the most potent entraining stimulus. The modulation of the SCN by both environmental cues and neurotransmitters/hormones is phase dependent. For example, when a patient is exposed to light at night it shifts the circadian clock back, whereas light exposure in the early morning shifts the clock forward (falling asleep earlier on the following night). Melatonin is effective in shifting the circadian clock only when given at dawn or at dusk but not during the daytime hours. Cholinergic activation of the muscarinic receptors affects the circadian clock only at night (20, 21).

Circadian information from the SCN is transmitted to the rest of the body after input from the hypothalamus. Thus, body-organ responses (e.g., sleep-wake cycle, core body temperature, the release of cortisol, thyroid-stimulating hormone, and

melatonin) to the circadian rhythm are controlled by the SCN and modulated by the hypothalamus. The release of melatonin from the pineal gland, signaled by the circadian rhythm, peaks at dawn and dusk. The SCN contains melatonin receptors, and the circadian clock can be reset by melatonin through a feedback mechanism (17, 20, 22). In the absence of environmental cues (e.g., under conditions of sensory deprivation), the endogenous rhythmicity of a circadian pacemaker persists independent of the light-dark cycle (20, 23). The genes of the SCN cells, through transcription/translation, are responsible for maintaining the 24-hour clock. Experimental mutation of these genes in animals produces prolonged or shortened circadian periods, whereas in humans such mutations result in abnormal circadian rhythms (20). For example, polymorphisms in the PERIOD3 (PER3) gene have been linked to specific variations in the circadian rhythm. "Morning types" were more frequently homozygous for the PER35/5 (a genetic variant found in 10% of the population where the nucleotide coding sequence is repeated five times), and they were more susceptible to decline in executive function following sleep deprivation. Individuals homozygous for the PER34/4 (a genetic variant found in 50% of the population where the nucleotide coding sequence is repeated four times) were more likely to express an evening preference and less impacted by sleep deprivation (24).

NEUROTRANSMITTERS INVOLVED IN SLEEP AND WAKEFULNESS

Adenosine, which has been identified as a possible mediator of the homeostatic sleep process (enabling the transition from prolonged wakefulness to NREM sleep), is an endogenous sleep-producing substance (12, 20, 25–27). This breakdown product of adenosine triphosphate (ATP) mediates this transition by inhibiting arousal-promoting neurons of the basal forebrain. Adenosine accumulates in certain areas of the brain when neurons consume energy in the form of ATP during prolonged wakefulness. In animal studies, adenosine levels in the brain increased during sleep deprivation and returned to baseline during sleep. Caffeine is believed to promote wakefulness by blocking adenosine receptors (16, 28, 29). Other substances hypothesized to be involved in promoting sleep and contributing to the homeostatic factor includes proinflammatory cytokines (interleukin-1) (20, 21), prostaglandin D2, and growth hormone–releasing hormone (30).

Cholinergic neurons have a dual role: some promote sleep and others promote wakefulness. The serotonergic, noradrenergic, and histaminergic wakefulness-promoting neurons have a discharge pattern nearly opposite to that of the cholinergic sleep-promoting neurons. The discharge rate of serotonergic, noradrenergic, and histaminergic neurons is fastest during wakefulness, decreases during NREM sleep, and virtually stops firing during REM sleep. In addition, newly discovered peptides called hypocretins (also known as orexins) are thought to regulate wakefulness by interacting with histaminergic, aminergic, and cholinergic systems.

Acetylcholine. Cholinergic neurons that originate in the laterodorsal and pedunculopontine tegmental nuclei (LDT/PPT) of the midbrain reticular formation reach the cortex by ascending through the thalamus and hypothalamus. These midbrain LDT and PPT areas contain two interspersed subsets of cholinergic neurons. One subset is responsible for the fast-frequency and low-voltage EEG pattern of cortical activation that appears in both REM sleep and restful wakefulness. These neurons are called wake/REM-on neurons (31). The second subset is responsible for generations of REM sleep. These latter cholinergic neurons are called REM-on cells. The three physiologic components of REM sleep (muscle atonia, rapid eye movements, EEG activation/desynchronization) are controlled by different nuclei located in the pontine reticular formation (PRF). The REM-on cholinergic neurons promote REM sleep by sending excitatory input to the PRF. This process causes the rapid firing of the PRF, which in turn produces the three cardinal physiologic components of REM sleep. The PRF is shut off during NREM sleep.

Cholinergic neurons that project from the basal forebrain to the cerebral cortex and limbic areas are part of the vigilance-waking system. The side effects produced by anticholinergic medications likely result from a disruption of both the vigilance/wake-producing cholinergic neurons and the wake/REM-on cholinergic neurons.

Serotonin and Norepinephrine. Serotonergic neurons originate in the dorsal raphe nucleus (DRN) and noradrenergic neurons originate in the locus coeruleus (LC). Both sets of neurons act as suppressants of REM sleep (REM-off cells) by inhibiting REM-promoting cholinergic neurons and by sending inhibitory input to the PRF. Serotonin and norepinephrine neurons promote cortical activation during wakefulness by rapid firing (32). Recently, the noradrenergic wake-promoting system was also found to have an important role in the cognitive function of learning during the waking state. Activity of the noradrenergic system triggers an increase in the expression of genes associated with memory formation and learning (20). The serotonergic system was not found to have this close link to cognitive function.

During the NREM sleep period, at the beginning of the first sleep cycle, the serotonergic and noradrenergic neurons significantly reduce their firing rate. This process removes the inhibition from the REM-on cholinergic neurons leading to the first REM sleep period approximately 90 minutes later.

Hypocretin. Hypocretins (also called orexins) are two neuropeptides (hypocretin 1 and hypocretin 2) with key roles in the regulation of arousal and metabolism. These compounds bind to their corresponding receptors (Hcrtr1 and Hcrtr2) throughout the brain and spinal cord. Hypocretins are produced by hypothalamic neurons that surround the fornix bilaterally and exist in the dorsolateral hypothalamus. These hypothalamic regions are implicated in the control of nutritional balance, blood pressure, and temperature regulation, as well as endocrine secretion and arousal. Hypocretins likely play a role in all these functions (33).

The hypocretin-producing neurons in the hypothalamus receive direct input from the SCN (the circadian rhythm clock) (33, 34). In accordance with circadian rhythmic control of hypocretin levels (through SCN input), their concentration is highest during the waking period. Hypocretin levels also increase during a period of forced sleep deprivation. It remains unclear whether this increase during sleep deprivation represents hypocretin actually opposing and attempting to override the sleep drive or producing a stress response to sleep deprivation. Hypocretin input to the brainstem REM-on cells controls the switch into REM by reducing the firing rate of the REM-on cells during the wake period (33, 34).

Histamine. Antihistaminergic drugs that cross the blood-brain barrier are known to produce sedation. The neurotransmitter histamine plays a key role in the maintenance of wakefulness. Histaminergic neurons originate from the tuberomammillary nucleus (TMN) of the posterior hypothalamus and project diffusely throughout the brain. In the cortex, histamine facilitates cortical arousal. Histaminergic neurons fire most rapidly during cortical activation in the wake state and turn off during REM sleep (32, 35).

Hypothalamus. The role of the hypothalamus as a key area of the brain involved in the regulation of sleep and wakefulness was recognized after the pandemic of encephalitis lethargica swept the world in the early 1900s. Thought to be a viral infection of the brain, encephalitis lethargica induced severe sleep abnormalities in affected individuals. Most patients exhibited profound and prolonged sleepiness while some suffered from a severe insomnia. Those afflicted by sleepiness were discovered to have lesions in the posterior hypothalamus; those afflicted by insomnia were found to have lesions in the anterior hypothalamus (26, 36). In accordance with these original observations, the ventrolateral preoptic nucleus (VLPO) in the anterior hypothalamus has been established as the key sleep-inducing region, with the TMN of the posterior hypothalamus being one of the important wakefulness-promoting regions of the brain.

The anterior hypothalamus contains GABA-ergic cells. Activity of GABA-ergic cells in the VLPO region is implicated in production of NREM sleep while the GABA-ergic cells in the area adjacent to the VLPO are thought to promote REM sleep by inhibiting the noradrenergic (LC) and serotonergic (DRN) REM-off nuclei of the brainstem (26). The rapid firing of the anterior hypothalamus region during sleep leads to inhibition of the LC and DRN in the brainstem, in effect, taking the "noradrenergic and serotonergic brakes" off the hypothalamic sleep generator, thus reinforcing the sleep state (36).

The posterior hypothalamus/TMN receives histaminergic input and has hypocretin receptors (hctr2). Both histamine and hypocretin produce activation of the TMN cells, which leads to sustained wakefulness (26). At the same time, hypocretin activates the noradrenergic and serotonergic cells in the brainstem, which send inhibitory signals to the anterior hypothalamus. This process in effect takes the "GABA-ergic brakes" off the hypothalamic wakefulness generator, thus reinforcing the wake state.

From the viewpoint of evolutionary advantage, it may be important for most animals to be either in the fully awake or the fully asleep state and to spend little time in the transition state between sleep and wakefulness. The anterior and posterior regions of the hypothalamus work through a system of mutual inhibition in what has been referred to as a flip-flop switch (like a light switch) (36). The hypothalamic sleep switch is quickly turned on and off, with both positions being equally stable. It is hypothesized that the circadian, homeostatic, and ultradian drives are responsible for flipping the hypothalamic switch into the sleep and wake positions. The hypocretin tone, which is also influenced by the circadian and homeostatic drives, helps to stabilize the hypothalamic switch in the wake position and prevent intrusion of REM sleep into the waking state (26, 36). When the hypocretin tone is reduced, as in narcolepsy, this stability of the wake state is impaired, resulting in abnormal shifts from wake to REM states (e.g., cataplexy, sleep paralysis).

PHARMACEUTICALS AND RECREATIONAL DRUGS

All drugs that cross the blood-brain barrier may affect sleep. Selective serotonin reuptake inhibitors, tricyclic antidepressants, serotonin norepinephrine reuptake inhibitors, and monoamine oxidase inhibitors

suppress REM sleep. Acute withdrawal from these antidepressants is likely to produce a rebound increase in REM sleep. Barbiturates increase SWS and suppress REM. Benzodiazepines suppress SWS and do not affect REM. Psychostimulants, such as amphetamines and cocaine, increase sleep latency, fragment sleep, and suppress REM sleep (6, 12, 14).

SLEEPING AND DREAMING

Several theories attempt to explain the biological function of sleep, none of which is preeminent. One such theory posits that sleep serves a restorative function for the brain and body. Normal sleep is subjectively associated with feeling refreshed on awakening. REM sleep is associated with increased CNS synthesis of proteins and is critical for the CNS development of infants/young humans/animals. Growth-hormone secretion is increased while cortisol secretion is decreased during sleep. All of these facts can be used to support the restorative theory of sleep (37). Another theory of sleep function proposes that sleep has a central role in reinforcement and consolidation of memory. Sleep-deprivation experiments have highlighted the important role of REM sleep in memory function (37). Yet another theory suggests that sleep is important for thermoregulatory function. Experiments have demonstrated that total sleep deprivation results in thermoregulatory abnormalities, NREM sleep maintains thermoregulatory function, and REM sleep is associated with impaired thermoregulatory responses (shivering, sweating, and so forth) (37).

Since the mid-1950s, when REM sleep was identified, sleep research has focused on understanding the physiology of dreams. Most dreams (about 80%) occur during REM sleep and the remainder occurs during NREM sleep. REM sleep dreams are more complex, have more emotional valence, can be bizarre, and are easier to recall. NREM sleep dreams are more logical and realistic, but more difficult to recall possibly because awakening from NREM sleep leaves a person feeling more confused and disoriented than awakening from REM sleep. During REM sleep, neuronal signals originating from the brainstem are transmitted to the cerebral hemispheres and stimulate the cortical association areas to produce images that comprise our dreams.

SUMMARY

Sleep is a vital, highly organized process regulated by complex systems of neuronal networks and neurotransmitters. Sleep plays an important role in the regulation of the CNS and body physiologic functions. Sleep architecture changes with age and is easily susceptible to external and internal disruption. The reduction or disruption of sleep can affect numerous functions varying from thermoregulation to learning and memory during the waking state.

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