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NEURAL PHYSIOLOGY

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SLEEP PHYSIOLOGY.

Sleep physiology refers to the basic structural organization of normal sleep. There are two types of sleep, non-rapid eye-movement (NREM) sleep and rapid eye-movement (REM) sleep. NREM sleep is divided into stages 1, 2, 3, and 4, representing a continuum of relative depth. Each has unique characteristics including variations in brain wave patterns, eye movements, and muscle tone. Sleep cycles and stages were uncovered with the use of electroencephalographic (EEG) recordings that trace the electrical patterns of brain activity.

Two Types of Sleep

Over the course of a period of sleep, NREM and REM sleep alternate cyclically. The function of alternations between these two types of sleep is not yet understood, but irregular cycling and/or absent sleep stages are associated with sleep disorders. For example, instead of entering sleep through NREM, as is typical, individuals with narcolepsy enter sleep directly into REM sleep.

NREM and REM Sleep Cycles

A sleep episode begins with a short period of NREM stage 1 progressing through stage 2, followed by stages 3 and 4 and finally to REM. However, individuals do not remain in REM sleep the remainder of the night but, rather, cycle between stages of NREM and REM throughout the night. NREM sleep constitutes about 75 to 80 percent of total time spent in sleep, and REM sleep constitutes the remaining 20 to 25 percent. The average length of the first NREM-REM sleep cycle is 70 to 100 minutes. The second, and later, cycles are longer lasting—approximately 90 to 120 minutes. In normal adults, REM sleep increases as the night progresses and is longest in the last one-third of the sleep episode. As the sleep episode progresses, stage 2 begins to account for the majority of NREM sleep, and stages 3 and 4 may sometimes altogether disappear.

Four Stages of NREM Sleep

Stage 1 Sleep

NREM stage 1 sleep serves a transitional role in sleep-stage cycling. Aside from newborns and those with narcolepsy and other specific neurological disorders, the average individual’s sleep episode begins in NREM stage 1. This stage usually lasts 1 to 7 minutes in the initial cycle, constituting 2 to 5 percent of total sleep, and is easily interrupted by a disruptive noise. Brain activity on the EEG in stage 1 transitions from wakefulness (marked by rhythmic alpha waves) to low-voltage, mixed-frequency waves. Alpha waves are associated with a wakeful relaxation state and are characterized by a frequency of 8 to 13 cycles per second.

Stage 2 Sleep

Stage 2 sleep lasts approximately 10 to 25 minutes in the initial cycle and lengthens with each successive cycle, eventually constituting between 45 to 55 percent of the total sleep episode. An individual in stage 2 sleep requires more intense stimuli than in stage 1 to awaken. Brain activity on an EEG shows relatively low-voltage, mixed-frequency activity characterized by the presence of sleep spindles and K-complexes. It is hypothesized that sleep spindles are important for memory consolidation. Individuals who learn a new task have a significantly higher density of sleep spindles than those in a control group.

Stages 3 and 4, Slow-Wave Sleep

Sleep stages 3 and 4 are collectively referred to as slow-wave sleep (SWS), most of which occurs during the first third of the night. Each has distinguishing characteristics. Stage 3 lasts only a few minutes and constitutes about 3 to 8 percent of sleep. The EEG shows increased high-voltage, slow-wave activity.

The last NREM stage is stage 4, which lasts approximately 20 to 40 minutes in the first cycle and makes up about 10 to 15 percent of sleep. The arousal threshold is highest for all NREM stages in stage 4. This stage is characterized by increased amounts of high-voltage, slow-wave activity on the EEG.

REM Sleep

REM sleep is defined by the presence of desynchronized (low-voltage, mixed-frequency) brain wave activity, muscle atonia, and bursts of rapid eye movements. “Sawtooth” wave forms, theta activity (3 to 7 counts per second), and slow alpha activity also characterize REM sleep. During the initial cycle, the REM period may last only 1 to 5 minutes; however, it becomes progressively prolonged as the sleep episode progresses. There are numerous physiological differences between NREM and REM sleep.

Physiology During Sleep

Cardiovascular: Changes in blood pressure and heart rate occur during sleep and are primarily determined by autonomic nervous system activity. For instance, brief increases in blood pressure and heart rate occur with K-complexes, arousals, and large body movements. Further, there is an increased risk of myocardial infarction in the morning due to the sharp increases in heart rate and blood pressure that accompany awakening. Sympathetic-nerve activity: Sympathetic-nerve activity decreases as NREM sleep deepens; however, there is a burst of sympathetic-nerve activity during NREM sleep due to the brief increase in blood pressure and heart rate that follows K-complexes. Compared to wakefulness, there is a rise in activity during REM sleep.

Respiratory: Ventilation and respiratory flow change during sleep and become increasingly faster and more erratic, specifically during REM sleep. Ventilation data during REM sleep are somewhat unclear, but they suggest that hypoventilation (deficient ventilation of the lungs that results in reduction in the oxygen content or increase in the carbon dioxide content of the blood or both) occurs in a similar way as during NREM sleep. Several factors contribute to hypoventilation during NREM, and possibly REM, sleep such as reduced pharyngeal muscle tone. Further, during REM sleep, there is reduced rib cage movement and increased upper airway resistance due to the loss of tone in the intercostals and upper airway muscles.More generally, ventilation and respiratory flow show less effective adaptive responses dur ing sleep. The cough reflex, which normally reacts to irritants in the airway, is suppressed during REM and NREM sleep. The hypoxic ventilatory response is also lower in NREM sleep than during wakefulness and decreases further during REM sleep. Similarly, the arousal response to respiratory resistance (for example, resistance in breathing in or out) is lowest in stage 3 and stage 4 sleep.

Cerebral blood flow: NREM sleep is associated with significant reductions in blood flow and metabolism, while total blood flow and metabolism in REM sleep is comparable to wakefulness. However, metabolism and blood flow increase in certain brain regions during REM sleep, compared to wakefulness, such as the limbic system (which is involved with emotions), and visual association areas.

Renal: There is a decreased excretion of sodium, potassium, chloride, and calcium during sleep that allows for more concentrated and reduced urine flow. The changes that occur during sleep in renal function are complex and include changes in renal blood flow, glomerular filtration, hormone secretion, and sympathetic neural stimulation.

Endocrine: Endocrine functions such as growth hormone, thyroid hormone, and melatonin secretion are influenced by sleep. Growth hormone secretion typically takes place during the first few hours after sleep onset and generally occurs during SWS, while thyroid hormone secretion takes place in the late evening. Melatonin, which induces sleepiness, likely by reducing an alerting effect from the suprachiasmatic nucleus, is influenced by the light-dark cycle and is suppressed by light.

SLEEP-WAKE REGULATION

The Two-Process Model

The sleep-wake system is thought to be regulated by the interplay of two major processes, one that promotes sleep (process S) and one that maintains wakefulness (process C). Process S is the homeostatic drive for sleep. The need for sleep (process S) accumulates across the day, peaks just before bedtime at night and dissipates throughout the night.

Process C is wake promoting and is regulated by the circadian system. Process C builds across the day, serving to counteract process S and promote wakefulness and alertness. However, this wake-promoting system begins to decline at bedtime, serving to enhance sleep consolidation as the need for sleep dissipates across the night. With an adequate night’s rest, the homeostatic drive for sleep is reduced, the circadian waking drive begins to increase, and the cycle starts over. In the absence of process C, total sleep time remains the same, but it is randomly distributed over the day and night; therefore, process C also works to consolidate sleep and wake into fairly distinct episodes. Importantly, through synchronization of the circadian system, process C assists in keeping sleep-wakefulness cycles coordinated with environmental light-dark cycles.

Sleep-Generating Systems in the Brainstem

Sleep process S is regulated by neurons that shut down the arousal systems, thus allowing the brain to fall asleep. Many of these neurons are found in the preoptic area of the hypothalamus.These neurons, containing molecules that inhibit neuronal communication, turn off the arousal systems during sleep. Loss of these nerve cells causes profound insomnia. Inputs from other regions of the brain also greatly influence the sleep system. These include inputs from the lower brainstem that relay information about the state of the body (e.g., a full stomach is conducive to falling asleep), as well as from emotional and cognitive areas of the forebrain. In addition, as described further in the next section, there are inputs from the circadian system that allow the wake-sleep system to synchronize with the external day-night cycle, but also to override this cycle when it is necessitated by environmental needs.

Wake-Generating Systems in the Brainstem

Wakefulness is generated by an ascending arousal system from the brainstem that activates forebrain structures to maintain wakefulness. This idea, originally put forward by Morruzzi and Magoun (1949), has more recently been refined. The main source for the ascending arousal influence includes two major pathways that originate in the upper brainstem. The first pathway, which takes origin from cholinergic neurons in the upper pons, activates parts of the thalamus that are responsible for maintaining transmission of sensory information to the cerebral cortex. The second pathway, which originates in cell groups in the upper brainstem that contain the monoamine neurotransmitters (norepinephrine, serotonin, dopamine, and histamine), enters the hypothalamus, rather than the thalamus, where it picks up inputs from nerve cells that contain peptides (orexin or hypocretin and melanin-concentrating hormone). These inputs then traverse the basal forebrain, where they pick up additional inputs from cells containing acetylcholine and gamma-aminobutyric acid. Ultimately, all of these inputs enter the cerebral cortex, where they diffusely activate the nerve cells and prepare them for the interpretation and analysis of incoming sensory information.

Changes in sleep with age.

Newborns and Infants

At birth, sleep timing is distributed evenly across day and night for the first few weeks, with no regular rhythm or concentration of sleeping and waking. Newborns sleep about 16 to 18 hours per day; however, it is discontinuous with the longest continuous sleep episode lasting only 2.5 to 4 hours. Newborns have three types of sleep: quiet sleep (similar to NREM), active sleep (analogous to REM), and indeterminate sleep. Sleep onset occurs through REM, not NREM, and each sleep episode consists of only one or two cycles. This distinctive sleep architecture occurs mostly because circadian rhythms have not yet been fully entrained. Circadian rhythms begin to arise around 2 to 3 months of age, leading to sleep consolidation that manifests in greater durations of wakefulness during the day and longer periods of sleep at night. Circadian rhythm development in the first 3 months includes: emergence of the 24-hour core body temperature cycle (1 month of age); progression of nocturnal sleeping (2 months of age); and cycling of melatonin and cortisol hormones in a circadian rhythm (3 months of age).

Sleep cycles also change because of the emergence of the circadian rhythm and a greater responsiveness to social cues (such as breast-feeding and bedtime routines). By 3 months of age, sleep cycles become more regular: sleep onset now begins with NREM, REM sleep decreases and shifts to the later part of the sleep cycle, and the total NREM and REM sleep cycle is typically 50 minutes. By 6 months of age, total sleep time reduces slightly and the longest continuous sleep episode lengthens to approximately 6 hours . As sleep cycles mature, the typical muscle paralysis of REM sleep replaces the propensity for movement in what was called “active sleep” as a newborn. By 12 months old, the infant typically sleeps 14 to 15 hours per day with the majority of sleep consolidated in the evening and during one to two naps during the day.

Young Children

There are a limited number of studies that address normal sleep architecture in young children; however, one trend that appears to be consistent is that sleep amounts decrease as a child gets older. The reduction cannot be attributed solely to physiologic requirements, because cultural environments and social changes also influence changing sleep characteristics in young children. Total sleep time decreases by 2 hours from age 2 to age 5 (13 hours to 11). Socially, the decrease in time asleep may be a result of decreased daytime napping, as most children discontinue napping between 3 and 5 years old. Other social and cultural factors that begin to influence sleep include how, with whom, and where children sleep and the introduction of school time routines. Physiologically, it has been suggested that by the time children enter school (typically 6 years old) they begin to manifest circadian sleep phase preferences—a tendency to be a “night owl” or “morning bird”. Older children, however, are significantly more likely to experience challenges in initiating and maintaining sleep than younger children. In addition, older children are more likely to have nightmares, which usually disrupt sleep, making it discontinuous. One study found that children appear to have longer REM sleep latencies than adolescents and consequently spend a greater percentage of sleep time in stages 3 and 4.

Adolescents

A complex and bidirectional relationship exists between pubertal development and sleep. Studies underscore the importance of using pubertal stage, rather than chronologic age as the metric in understanding sleep, as has been found for other physiologic parameters in the second decade of life. It has been determined that adolescents require 9 to 10 hours of sleep each night, though few adolescents obtain adequate sleep. In the United States, the average total sleep time in a sample of eighth-grade students was found to be 7.9 hours. Over a quarter of high school and college students were found to be sleep deprived. SWS and sleep latency time progressively declines with advancing pubertal development however, time spent in stage 2 increases. These changes are likely in part due to pubertal and hormonal changes that accompany the onset of puberty. For instance, at midpuberty, there is significantly greater daytime sleepiness than at earlier stages of puberty. Afternoon sleepiness is greater than that in late afternoon and evening in more mature adolescents than in younger subjects. With increasing age, the total time spent sleeping decreases, as does REM sleep. However, if bedtime is fixed, the duration of REM sleep remains constant.

Adults

Sleep architecture continues to change with age across adulthood. Two major attributes of age-related sleep changes are earlier wake time and reduced sleep consolidation. A hallmark change with age is a tendency toward earlier bedtimes and wake times. Older adults (approximately ages 65 to 75) typically awaken 1.33 hours earlier, and go to bed 1.07 hours earlier, than younger adults (approximately ages 20 to 30). There are no conclusive studies that demonstrate why older adults experience earlier wake times, despite decreased sleep efficiency, but one hypothesis may be an advanced circadian pacemaker that accompanies age. It is unclear if this is due to older adults experiencing an increased sensitivity to light. Nonetheless, the consequences of an advanced circadian rhythm are a 1-hour advance in body temperature increase in the early morning and misaligned melatonin and cortisol secretion rhythms with the circadian clock. Younger adults may experience brief awakenings, but they are usually minor and occur close to an REM sleep transition; thus, sleep remains relatively consolidated. Arousal occurring mostly from REM sleep in young adults suggests that there is a protective mechanism to keep from awakening during NREM sleep; however, this protective effect appears to also decline with age. As an individual ages (between the ages of 20 to 60), SWS declines at a rate of about 2 percent per decade. Because arousal thresholds are typically highest during SWS, and because SWS declines with age, older adults experience more frequent awakenings during a sleep episode. Another important variable may be an age-related reduction both in homeostatic sleep pressure and circadian pacemaker effectiveness during the night.

Elderly People

Problematic sleep has adverse effects on all individuals, regardless of age; however, older people typically show an increase in disturbed sleep that can create a negative impact on their quality of life, mood, and alertness. Elderly individuals sleep 36 percent less than children at age 5. Although the ability to sleep becomes more difficult, the need to sleep does not decrease with age. Difficulty in initiating and maintaining sleep is cited in 43 percent of the elderly, although these problems are more commonly among adults suffering from depression, respiratory symptoms, and physical disability, among others. However, declining sleep efficiency and quality has also been observed in healthy older people.

Changes in sleep patterns affect males and females differently. The progressive decrease in SWS is one of the most prominent changes with aging; however, it appears to preferentially affect men. The gender difference is unclear, but it has been suggested that older women have “better-preserved” SWS than men. Women ages 70 and older spend around 15 to 20 percent of total sleep time in stages 3 and 4; men of the same age spend only around 5 percent of total sleep time in stages 3 and 4. Another gender contrast is that older women go to bed and wake up earlier than older men, which suggests that body temperature rhythms are phase-advanced in elderly women. However, both men and women have increased stage 1 and decreased REM sleep. Older people also experience a decrease in melatonin levels, which may be due to the gradual deterioration of the hypothalamic nuclei that drive circadian rhythms. The inability to maintain long sleep episodes and bouts of wakefulness may reflect, in addition to other medical factors, a continuously decreasing sleep homeostasis. Other prominent factors are the continuous increase in sleep latency and nighttime awakenings and inconsistency of external cues such as light exposure (which tends to be low), irregular meal times, nocturia, and decreased mobility leading to a reduction in exercise.

ROLE OF BASAL GANGLIA IN CONTROLLING MOVEMENT.

Movement

The greatest source of insight into the functions of the basal ganglia has come from the study of two neurological disorders, Parkinson’s disease and Huntington’s disease. For both of these disorders, the nature of the neural damage is well-understood and can be correlated with the resulting symptoms. Parkinson’s disease involves the major loss of dopaminergic cells in the substantia nigra. Huntington’s disease involves the massive loss of medium spiny neurons in the striatum. The symptoms of the two diseases are virtually opposite: Parkinson’s disease is characterized by a gradual loss of the ability to initiate movement, whereas Huntington’s disease is characterized by an inability to prevent parts of the body from moving unintentionally. It is noteworthy that, although both diseases have cognitive symptoms, especially in their advanced stages, the most salient symptoms relate to the ability to initiate and control movement. Thus, both are classified primarily as movement disorders. A different movement disorder, called hemiballismus, may result from damage restricted to the subthalamic nucleus. Hemiballismus is characterized by violent and uncontrollable flinging movements of the arms and legs.

Function in Eye Movement

One of the most intensively studied functions of the basal ganglia is their role in controlling eye movements. Eye movement is influenced by an extensive network of brain regions that converge on a midbrain area called the superior colliculus (SC). The SC is a layered structure whose layers form two-dimensional retinotopic maps of visual space. A bump of neural activity in the deep layers of the SC drives eye movement toward the corresponding point in space.