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PHYSIOLOGY ASSIGNMENT

**PHYSIOLOGY OF SLEEP**

Far from a simple absence of wakefulness, sleep is an active, regulated, and metabolically distinct state, essential for health and well-being. In this article, the authors review the fundamental anatomy and physiology of sleep and its regulation, with an eye toward interactions between sleep and metabolism. Pin-pointing the essential and irreplaceable aspects of sleep remains one of the great challenges of mammalian biology. Still, much has been determined about the structures, processes, and pathways underlying the regulation of sleep and the relationship of sleep to daytime functioning and overall well-being.

Generation and Maintenance of Sleep and Wakefulness

the cortical activation necessary to maintain wakefulness is supported by an extensive network of subcortical structures and pathways. Major neurochemicals of this “ascending arousal system” include excitatory norepinephrine arising from the locus ceruleus (LC), serotonin from the midline raphe nuclei, histamine from the tuberomammillary nucleus, dopamine from the ventral periacqueductal gray matter, acetylcholine from the pedunculopontine tegmentum, and the laterodorsal tegmentum of the pons and orexin from the perifornical area. Despite their apparent redundancy, normal behavioral functioning may require all of these arousing systems. For example, it is now clear that narcolepsy results from a selective loss of orexin-releasing neurons in the forebrain, accounting for the excessive daytime sleepiness, fragmented sleep, and cataplexy (sudden muscle weakness without loss of consciousness) associated with this disorder.

Sleep itself is not a homogenous process. There exist two fundamentally distinct types of sleep: rapid eye movement (REM) sleep, which is associated with active dreaming, and non–rapid eye movement (NREM) sleep. Switches between NREM and REM sleep appear to be controlled by reciprocal inhibition between monoaminergic neurons and a specific subset of cholinergic neurons within the brainstem ([7](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4755451/#B7)). These “REM-on” cholinergic neurons exhibit reciprocal inhibitory connections to noradrenergic (LC) and serotonergic (raphe) neurons ([8](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4755451/#B8)). When REM sleep is triggered, REM-on cholinergic neurons become maximally active, while noradrenergic and serotonergic neurons become virtually silent. The switching between activity and inhibition of these neurons results in a characteristic cycling between NREM and REM during the sleep period.

## Measurement and Quantification of Sleep and Wake States

Assessment of sleep/wake states can be made by behavioral observation, physiological monitoring, or a combination of the two. Behaviorally, sleep in adults is characterized by loss of consciousness and by relative immobility in a recumbent posture with the eyes closed. During NREM sleep, there is reduced tonus of large skeletal muscles that progresses to complete or near-complete atonia with a transition to REM sleep. Throughout sleep, there is a relative sparing of activity among respiratory pump muscles. Visual, olfactory, auditory, somatosensory, and even nociceptive sensory responses all are diminished but not eliminated during sleep. Furthermore, many sensory responses exhibit differing characteristics during NREM versus REM sleep.

Physiologically, the gold standard for assessment of sleep and wake states is the laboratory polysomnogram (PSG). To conduct a PSG, numerous noninvasive sensors are attached to a subject. These sensors include multiple skin electrodes, which record brain activity (electroencephalogram [EEG]), eye movements, submental muscle tone, leg movements, and electrocardiogram (ECG). Thoracic and abdominal strain gauges, oral and nasal airflow sensors, and a finger probe to measure arterial oxygen saturation are also attached to the subject to help monitor respiration during sleep.

In addition to wakefulness and REM sleep, current clinical guidelines for scoring PSGs identify three stages of progressively deepening NREM sleep: stages N1–N3. These stages are recognized and scored based on characteristic rhythms and events observed in the PSG waveforms, but a detailed presentation of the scoring process is beyond the scope of this article. Briefly, alert wakefulness is associated with a low-amplitude mixed frequency EEG pattern. Drowsy wakefulness is associated with alpha waves seen as a rhythm with peaks in the 8- to 13-Hz range. Drowsiness also is associated with slow rolling eye movements that may persist into light sleep. The lightest stage of NREM sleep (N1) is characterized by a loss of alpha rhythm and presence of theta waves with a characteristic frequency of 4–7 Hz. Stage N2 sleep is marked by the expression of spindles (burst-like trains of waves in the 11- to 16-Hz range with a total duration ≥0.5 seconds) and K-complexes (well-defined biphasic waves lasting ≥0.5 seconds and usually maximal over the frontal cortex). Deep NREM sleep (stage N3) is associated with large (≥75 µV) slow (0.5–3 Hz) waves known as delta waves. Typically, skeletal muscle activity exhibits progressively decreasing amplitude with transitions from wakefulness to N1, N2, and N3 sleep. REM sleep is associated with the lowest skeletal muscle tone and with either sharp theta waves (sawtooth waves) or wake-like EEG patterns.

## Endocrine Manifestations of Sleep and Wake States

Plasma levels of most hormones exhibit significant 24-hour rhythms, pointing to the importance of both the circadian clock and sleep-specific influences on their release and/or metabolism. Some hormones are little influenced by sleep versus wakefulness, including adrenocortotropic hormone, cortisol, and melatonin; some are strongly influenced by sleep, such as thyroid-stimulating hormone (TSH) and prolactin; and some are affected by particular sleep stages, such as growth hormone.

Under normal conditions, prolactin levels are low during the daytime and high during sleep at night. Studies using daytime naps or sudden changes in sleep schedule have shown that sleep onset, regardless of time of day, is associated with a stimulation of prolactin release. It has been suggested that a negative association exists between EEG delta activity and pulsatile prolactin release. Growth hormone also exhibits a strong sleep-dependent rhythm, with secretion being specifically associated with stage N3 sleep. There is a strong association between the power of EEG delta activity and the rate of growth hormone secretion during sleep. Furthermore, when ritanserin (a serotonin receptor antagonist) was used to augment deep sleep, the drug-related increase in EEG delta activity was associated with a proportional increase in the rate of growth hormone secretion. These findings strongly suggest that the mechanisms regulating delta wave production and growth hormone secretion are closely coupled, but these mechanisms have not been fully defined. This is of potential relevance to the pathogenesis and management of diabetes, because the sleep-related increase in growth hormone secretion relates directly to reduced insulin sensitivity and increased plasma glucose levels during sleep. Cortisol also exhibits a significant 24-hour pattern, but, unlike growth hormone, this appears to be primarily a result of circadian influences rather than of sleep per se. Also in contrast to growth hormone, which peaks early during the sleep period, cortisol is at its nadir early during a nocturnal sleep period and peaks toward the end of sleep or in the early morning hours. There is some evidence that the sleep process does exert some inhibitory effect on cortisol release, and this may contribute to its nadir early in the sleep period. This cortisol pattern also may contribute to increased glucose levels late in the sleep period, as cortisol may inhibit insulin release. TSH exhibits low daytime values, increasing during the evening and peaking around the time of sleep onset. Sleep, and especially stage N3 sleep, appears to exert an inhibitory influence on TSH secretion. N3 sleep is consistently associated with falling TSH levels, whereas awakenings are associated with rising TSH levels. This may be significant in diabetes pathogenesis, as TSH level has been negatively associated with various measures of insulin sensitivity. However, cause-and-effect relationships remain to be determined. In summary, sleep is an actively regulated process significantly modulated by homeostatic influences that accumulate during ongoing wakefulness and dissipate during sleep and by circadian effects entrained to the 24-hour day. Sleep has a typical underlying architecture characterized by a rhythmic alternation between NREM and REM stages, and the transitions among sleep/wake states are orchestrated by a well-defined subcortical network of brain structures. Sleep and wake states also are characterized by distinct hormonal patterns that exert potential significant influences on metabolism and glucose homeostasis.

**ROLE OF BASAL GANGLIA IN COORDINATING MOVEMENT**

Basal ganglia are strongly interconnected with the cerebral cortex, thalamus, and brainstem, as well as several other brain areas. The basal ganglia are associated with a variety of functions, including control of voluntary motor movements, procedural learning, habit learning, eye movements, cognition, and emotion.

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. 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.