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**IN BRIEF** 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.

1 PHYSIOLOGY OF SLEEP

Initiation and maintenance of sleep require suppression of activity in the ascending arousal systems. This is accomplished by inhibitory neurons of the ventrolateral pre-optic area, which remain active throughout sleep. The molecular “triggers” that activate the VLPO and initiate sleep onset have not been fully defined, but a substantial body of evidence points to extracellular adenosine as a candidate. Adenosine accumulates in basal forebrain during wakefulness and diminishes with ongoing sleep. Adenosine receptors are expressed in the VLPO and adenosine activates VLPO neurons in vivo, making it a reasonable candidate for the “sleep switch.” Caffeine and theophylline are potent adenosine receptor antagonists, which may form the basis for their well-known alerting effects. Despite this evidence, it is almost certain that other molecules also play important signaling roles controlling the initiation and maintenance of sleep. The monoaminergic arousal centers project to the VLPO and may serve to inhibit its activity. This creates the concept of “flip-flop” control of behavioral state, in which, at any given time, activity of either arousal-producing or sleep-producing neurons dominates and suppresses the other. In addition, the VLPO receives important circadian modulation from the suprachiasmatic nucleus—the central circadian clock .

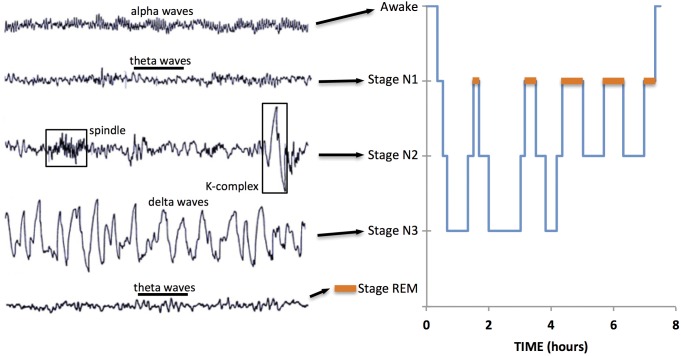
Sleep itself is not a homogenous process. There exist two fundamentally distinct types of sleep: rapid eye movement (REM) sleep, which is associated with active dreaming, and non–rapid eye movement (NREM) sleep. Switches between NREM and REM sleep appear to be controlled by reciprocal inhibition between monoaminergic neurons and a specific subset of cholinergic neurons within the brainstem. These “REM-on” cholinergic neurons exhibit reciprocal inhibitory connections to noradrenergic (LC) and serotonergic (raphe) neurons. 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. As illustrated in [Figure 2](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4755451/figure/F2/), 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.

[](https://www.ncbi.nlm.nih.gov/core/lw/2.0/html/tileshop_pmc/tileshop_pmc_inline.html?title=Click%20on%20image%20to%20zoom&p=PMC3&id=4755451_5fig2.jpg)

[FIGURE 2.](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4755451/figure/F2/)

EEG features of sleep/wake stages (left) and typical temporal organization of healthy nocturnal sleep in an adult (right).

Conclusion

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.

**2 BASAL GANGLIA**

The basal ganglia, or basal nuclei, are a group of [subcortical structures](https://www.kenhub.com/en/library/anatomy/subcortical-structures-anatomy) found deep within the white matter of the [brain](https://www.kenhub.com/en/library/anatomy/cerebral-cortex). They form a part of the [extrapyramidal motor system](https://www.kenhub.com/en/library/anatomy/extrapyramidal-system) and work in tandem with the pyramidal and [limbic systems](https://www.kenhub.com/en/library/anatomy/limbic-system).

The basal ganglia consist of five pairs of nuclei: caudate nucleus, putamen, globus pallidus, subthalamic nucleus, and substantia nigra. These nuclei are grouped into broader clusters;

* Striatum, which further consists of the:
  + Dorsal striatum, made by the caudate nucleus and putamen
  + Ventral striatum, composed of nucleus accumbens and olfactory tubercle (this part of the striatum is considered part of the limbic system)
* Globus pallidus, that consists of an internal segment (GPi) and an external segment (GPe)
* Subthalamic nucleus
* Substantia nigra

The function of the basal ganglia is to fine-tune the voluntary [movements](https://www.kenhub.com/en/library/anatomy/types-of-movements-in-the-human-body). They do so by receiving the impulses for the upcoming movement from the [cerebral cortex](https://www.kenhub.com/en/library/anatomy/cortical-cytoarchitecture), which they process and adjust. They convey their instructions to the [thalamus](https://www.kenhub.com/en/library/anatomy/thalamus), which then relays this information back to the cortex. Ultimately, the fine-tuned movement instruction is sent to the [skeletal muscles](https://www.kenhub.com/en/library/anatomy/histology-of-skeletal-muscle) through the tracts of the pyramidal motor system. Basal ganglia mediate some and other higher cortical functions as well, such as planning and modulation of movement, memory, [eye](https://www.kenhub.com/en/library/anatomy/eye-anatomy) movements, reward processing, and motivation.

Connections

The major efferents (outputs) of the basal ganglia consist of the [neurons](https://www.kenhub.com/en/library/anatomy/histology-of-neurons) that project towards the thalamus and brainstem from the internal part of globus pallidus and the reticular part of the substantia nigra. These are ansa lenticularis and lenticular fasciculus.  
Afferents (inputs) to the basal ganglia include the following:

* From the entire cerebral cortex - through the corticostriatal pathway, which is the largest afferent connection of the basal ganglia. The fibers are glutamatergic – releasing the neurotransmitter glutamate to excite the striatal neurons.
* From the substantia nigra - fibers arising in the pars compacta of the substantia nigra reach the striatum, forming the nigrostriatal connections. This very important connection of the basal ganglia ensures a continuous supply of dopamine to the striatum, which promotes the regulation of direct, indirect and hyperdirect pathways.
* From the thalamus - fibers from the thalamus to the basal ganglia form the thalamostriatal connections or the thalamostriatal afferents. Those connections or pathways are glutamatergic and responsible for excitatory effects on the cerebral cortex and brainstem.
* From the reticular formation of the brainstem (specifically from the midbrain) - afferents from the reticular formation are noradrenergic and responsible, besides vital functions, for modulation and regulation of flexor and extensor muscles tonus in voluntary movements.

In summary, the basal nuclei can be grouped functionally into four categories:

1. Input nuclei: striatum and subthalamic nucleus, which receive cortical inputs
2. Output nuclei: internal part of globus pallidus and reticular part of substantia nigra, which project outside the basal ganglia to the thalamus and brainstem
3. Connecting nucleus: external part of globus pallidus, which connects the input nuclei to the output nuclei.
4. Modulatory nucleus: compact part of substantia nigra, which modulates the activity of the basal ganglia.

## Pathways

The basal nuclei modulate **motor function**through various [pathways](https://www.kenhub.com/en/library/anatomy/direct-and-indirect-pathways-of-the-basal-ganglia) in order to initiate, terminate, or modulate the extent of the movement.

These are the following:

**Direct pathway**: which is responsible for the initiation of the movement. In order to make this happen, the direct pathway funnels the information from the striatum to GPi/SNr via GABAergic inhibitory projections. This inhibition releases the firing from the thalamocortical neurons to initiate the movement

**Indirect pathway**:which has a net excitatory effect on the same structures. The neurons from the external part of globus pallidus send inhibitory fibers to the subthalamic nucleus instead of sending directly to the thalamus (hence its name “indirect”). From the subthalamic nucleus, neurons send their axons to the internal part of the globus pallidus and reticular part of the substantia nigra and then continue as the direct pathway with GABAergic inhibitory neurons to the thalamus and glutamate excitatory efferents to the cortex. So, functionally, the striatum inhibits the external globus pallidus, and that causes disinhibition of the subthalamus..

**Hyperdirect pathway**: via which the internal part of globus pallidus and reticular part of the substantia nigra receive strong excitatory signals from the cortex directly through STN and has a shorter conduction time compared to the direct and indirect pathways. The hyperdirect pathway consists of neurons projecting from the cortex directly to the subthalamic nucleus (STN), skipping the striatum. Therefore, the glutamatergic excitatory neurons of the STN can then excite the GPi/SNr thus suppressing thalamic activity on the cerebral cortex and increasing inhibitory influences on the upper motor neurons. Considering the conduction path and time, we can say that the **hyperdirect**and **indirect pathways**make clear initiation and termination of the selected motor program, while at the same time canceling other competing motor programs.