# An Overview of Sleep Physiology and Sleep Regulation

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**Abstract** Sleep is a complex behavior that cyclically alternates with wakefulness and is fundamental for both mental and physical wellness. During normal sleep the body acquires a specific posture; any active behavior is absent and mental activity typically oscillates between a state of "loss of consciousness" and the experience of dreaming.

Sleep is, by itself, a cyclical process characterized by the alternation of two phases, non-REM (NREM) sleep and "rapid eye movement" (REM) sleep, during which the typical synchronized electroencephalographic (EEG) pattern of NREM sleep is substituted by a "paradoxical" EEG desynchronization.

NREM sleep is a state of minimal energy expenditure and motor activity, during which cardiorespiratory and thermoregulatory variables are driven by the autonomic nervous system at a lower and more stable level compared to wakefulness. During REM sleep, beyond the occurrence of REMs, posture control is lost and dreams become more vivid. Furthermore, autonomic activity is highly unstable leading to centrally driven surges in heart rate and blood pressure, breathing becomes irregular, and thermoregulation is suspended or depressed, suggesting a derangement of the integrative regulation of physiological functions.

Overall sleep quality is one of the most important parameters considered for the subjective assessment of quality of life and general health status. However, although sleep function(s) is intuitively associated with some kind of rest that seems to be mostly required by the central nervous system, and many theories on sleep function have been proposed, a full comprehension of sleep function has not yet been achieved and is probably not imminent.

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# 1 Neurophysiology and Neurobiology of Sleep

## *1.1 What Is Sleep?*

Sleep is a specific behavior, common to humans and other animals, that cyclically alternates with wakefulness and is undoubtedly fundamental for both mental and physical wellness. Everyone is aware of the importance of having a good sleep and a proper daily sleep time. Sleep quality is among the most important parameters considered for the subjective assessment of quality of life and general health status.

During sleep the body needs to acquire a typical posture; any active behavior is absent and, following a normal sleep time, there is a clear perception of bodily restoration as well as that of the mind. In fact, the strong "pressure" to fall asleep after either a long period of waking or a very tiring activity is a very common subjective experience. The mental activity during sleep is also quite peculiar and after the subjective experience of the "loss of consciousness" when falling asleep, the experience of dreaming is characteristic: a mental phenomenon that, historically, represents one of the main topics in cultures and arts.

Falling asleep is a kind of progressive reduction of the awareness of self and environment; hence, in the past, sleep was considered to be a mere passive process, in which brain activity was reduced, and even absent, compared to wakefulness (Dement 2011). Some clinical observations by the neurologist Constantin von Economo in 1916, as well as experimental data obtained in the 1930s by Frédéric Bremer with his milestone experimental preparations on cats named "cerveau isolé" and "encéphale isolé", apparently supported this view. Von Economo observed that patients affected by "encephalitis lethargica" typically presented lesions localized at the boundary between the mesencephalon and the diencephalon, while Bremer, on the basis of his experimental results, postulated that sleep was the result of the reduction of afferent sensory stimuli to the forebrain.

In 1929, Hans Berger introduced electroencephalography (EEG) as a tool to record the cortical electrical activity from the scalp. The EEG was an amazing technical advancement in neuroscience and soon it was considered of primary importance for the investigation of the sleeping brain. In support of Bremer's theory, Giuseppe Moruzzi and Horace Magoun found, in the late 1940s, that the stimulation of the pontine reticular formation induced a waking EEG in the anesthetized cat. Therefore, they suggested that the "deafferentation" of the sensory signals to the telencephalon was reasonably due to a transient change in the functional activity of the reticular formation (Kumar 2010).

Although the "passive" theory of sleep was the most widely accepted, some experimental results suggested that sleep was actively induced by some neural structure. Some of the patients studied by Von Economo presented an insomnia that was associated with a lesion of the anterior hypothalamus. Moreover, in the 1940s, Rudolph Hess showed that a low frequency stimulation of the thalamus could induce sleep in the cat, while Walle Nauta proposed, on the basis of

brain-lesion studies in the rat, that the rostral part of the hypothalamus was the site for the "capacity of sleep" (Kumar 2010).

However, the definitive turning point leading to the concept that sleep is a state that is actively promoted by the brain was the discovery of an "active" sleep phase; it was in 1953 that Eugene Aserinsky and Nathaniel Kleitman described the existence of a sleep phase which cyclically interrupted the typical synchronized EEG pattern of sleep. During this phase it was possible to observe frequent eye movements under the closed eyelids and the EEG signal was desynchronized and very similar to that observed in wakefulness.

It took several years before this functional state was recognized as a distinct sleep phase. It was Michel Jouvet who, in 1959, defined this particular state as "paradoxical sleep" (Kumar 2010). Soon, sleep would be divided into two main phases: the "rapid eye movement" (REM) phase and the nonREM (NREM) phase (Dement 2011). Also, William Dement, while working with Kleitman, associated REM sleep with dream occurrence (Dement 2011). REM sleep was soon considered a very peculiar sleep phase, due to the paradoxical EEG signal and the occurrence of REMs, as well as several other physiological features, such as the paralysis of anti-gravitational muscles, the occurrence of ponto-geniculo-occipital (PGO) waves, and, as firstly assessed by Pier Luigi Parmeggiani, a dramatic functional change in physiological regulation, with a large autonomic instability.

Therefore, sleep is now considered to be a complex and active behavioral state, during which the brain works differently from normal waking. Sleep cyclically alternates with wakefulness every single day and is, by itself, a cyclical process characterized by the alternation of two phases, NREM sleep and REM sleep.

## *1.2 Sleep Architecture*

In every species studied, sleep propensity is closely related to the time of day and consequently to the circadian rest-activity cycle, and in humans, the majority of sleep time is concomitant with the nocturnal hours (Achermann and Borbély 2011).

During NREM sleep, the EEG becomes typically synchronized, i.e., rich in slow-frequency and high-voltage waves, in contrast to the fast-frequency and low-voltage waves of the typical waking EEG (Brown et al. 2012). In humans the structure of NREM sleep is further subdivided into four stages (S1–S4, Rechtschaffen and Kales classification, R&K) or three stages (N1–N3, American Academy of Sleep Medicine classification, AASM) (Carskadon and Dement 2011) based on the degree (intensity) of the EEG synchronization. During sleep occurrence, the NREM sleep stages and REM sleep appear in a precise order:

1. NREM sleep S1 (N1) represents the transition from wakefulness to sleep and is considered to be the first step of EEG synchronization; theta (4.0–7.0 Hz) activity is predominant.

2. The beginning of S2 (N2) is characterized by the appearance in the EEG of two typical signs, the "K-complex" (a single high voltage negative wave, followed by a single slow positive wave) and the "spindle" (a 12–14 Hz oscillation with an increasing and then a decreasing amplitude, lasting around 1–2 s).
3. The deeper stages of NREM sleep are S3 and S4 of the R&K classification, which essentially constitute together the N3 stage of the AASM classification. In these stages, the EEG is rich in (S3) or fully dominated by (S4) high-amplitude activity in the slow delta range (0.5–2.0 Hz). This slow-wave activity (SWA) is considered to be the macroscopic result of a cellular phenomenon, called "slow-oscillation," during which cortical neurons oscillate between two functional states, the hyperpolarized and silent "down-state" and the high-frequency (around 40 Hz) discharging "up-state" (Steriade et al. 2001). Actually, the "slow-oscillation" is a travelling wave, involving almost all the cortical areas, apparently starting from the frontal cortex and then propagating towards the posterior regions (Massimini et al. 2004).
4. During a normal NREM-REM sleep cycle, S4 is followed by a reverse progression, through S3, to light NREM sleep stages (S2–S1), until REM sleep occurs. REM sleep is followed by either an awakening or by S1–S2. In the latter case, the whole sequence to S3–S4 and back to S2–S1 and REM sleep usually starts again.

Typically, in humans, this cyclic process lasts about 90–100 min (Carskadon and Dement 2011) and during a standard night-time sleep period 4–5 cycles are completed. The deepest NREM sleep stage (S4) is usually reached only during the first part of the night. Also, late cycles are generally characterized by the occurrence of longer REM sleep phases, lasting up to 20–25 min in the very last cycle before waking (Carskadon and Dement 2011). Normally, morning awakening directly follows a completed REM sleep phase.

In the young adult the overall night sleep duration is between 7 and 8 h, and REM sleep represents 20–25 % of the total sleep amount. The daily amount of sleep and the quantity of SWA progressively decrease from childhood to old age, while the proportion of REM sleep, which is apparently almost double in the newborn compared to the young child, is then maintained at a stable level throughout the life span.

## *1.3 Sleep Mechanisms*

In recent years, great steps forward have been made in the understanding of the brain mechanisms underlying sleep and wakefulness control and regulation (cf. Brown et al. 2012). Schematically, the cyclical alternation of wakefulness and sleep is considered to be mainly due to the cyclical activation and inhibition, respectively, of a key neural structure defined as the ascending reticular activating system. This system consists of a network of fibers projecting from the brainstem to

the forebrain, via two main pathways: the dorsal and the ventral pathways. The dorsal pathway originates from the cholinergic and glutamatergic neurons within the pontine and midbrain reticular formation and within the cholinergic laterodorsal and pedunculopontine tegmental nuclei. This pathway projects to the intralaminar and midline thalamic nuclei and, consequently, widely innervates the cerebral cortex. The ventral pathway originates from the same ponto-mesencefalic structures of the dorsal pathway, but, in this case, projections are directed towards the lateral hypothalamus and the tuberomamillary nucleus, as well as to the basal forebrain. The basal forebrain also receives afferent projections from both the orexinergic neurons in the lateral hypothalamus and the histaminergic neurons in the tuberomamillary nucleus, and widely projects to the cerebral cortex. Both pathways receive important contributions from the noradrenergic locus coeruleus and the serotonergic dorsal raphe (Brown et al. 2012). Sleep neurochemistry will be addressed in more detail in Chap. "Neuronal Networks Regulating Sleep and Arousal: Effect of Drugs."

In this conceptual framework, NREM sleep is apparently induced by the inhibition of the wake-promoting neurons of the ascending reticular activating system. The mechanism that triggers this inhibitory activity is not completely known. It is possible that the inhibition of the ascending reticular activating system mainly begins with the increased GABAergic activity of the median preoptic nucleus; then, once started, sleep is maintained by the subsequently increased activity of other GABAergic neurons, in particular those located within the ventrolateral preoptic nucleus (Brown et al. 2012). At a cellular level, the increasing inhibitory activity gradually leads to the hyperpolarization of the thalamic and cortical neurons: this is the functional condition of the neural membrane that is conducive to rhythmic bursting, as described by Mircea Steriade (Steriade et al. 2001).

As stated before, NREM sleep episodes are cyclically interrupted by REM sleep. The neurophysiology of REM sleep is considered to be based on the reciprocal interaction between two main systems: the "REM-on" and the "REM-off" neurons (Saper et al. 2005). In particular, the cholinergic "REM-on" system of the laterodorsal tegmentum and pedunculo-pontine tegmentum excites the glutamatergic neurons in the sublaterodorsal nucleus, promoting REM sleep onset. These glutamatergic neurons also excite GABAergic neurons of the dorsal paragigantocellular reticular nucleus, that, in turn, inhibit adjacent REM-off neurons of the locus coeruleus (noradrenergic) and the dorsal raphe (serotonergic). In support of this mechanism is another one, based on the inhibition of the "REM-off" GABAergic activity of the ventrolateral periaqueductal gray and of the deep mesencephalic reticular nucleus; also in this case, the disinhibition of these structures activates other GABAergic "REM-on" neurons leading to the inhibition of the locus coeruleus and the dorsal raphe. In these structures, REM-off (i.e., noradrenergic and serotonergic) neurons normally inhibit the REM-on neurons in the laterodorsal tegmentum and the pedunculo-pontine tegmentum, and they can also inhibit themselves in support of the activation of other afferent inhibitory projections, thus promoting REM sleep onset (Brown et al. 2012; Luppi et al. 2013).

During REM sleep, the activation of cortical activity is mainly due to two systems: (1) the glutamatergic projection from the sublaterodorsal nucleus to the intralaminar thalamic nuclei and (2) the rostral cholinergic system in the basal forebrain (Luppi et al. 2013). From the sublaterodorsal nucleus the glutamatergic REM-on neurons also project caudally and have a key role in the activation of GABAergic and glycinergic neurons located in the alpha and ventral gigantocellular and in the lateral paragigantocellular reticular nuclei, as well as in the raphe magnus, all projecting to the spinal cord; it has been proposed that these pathways are responsible for the induction of muscle atonia during REM sleep (Luppi et al. 2013).

Recently the lateral hypothalamus has gained major attention for its involvement in both REM sleep induction and regulation. Orexinergic neurons are peculiar to this area, and are functionally involved in the maintenance of the stability of wakefulness; the lack of these neurons is associated with narcoleptic/cataleptic symptoms. Within the lateral hypothalamus, intermingled with orexinergic neurons, are also melanin concentrating hormone (MCH) REM-on neurons and GABAergic nonorexinergic/non-MCH neurons, that seem to importantly contribute to the inhibition of the REM-off neurons within the ventrolateral periaqueductal gray and the histaminergic tuberomamillary nucleus (Luppi et al. 2013), promoting REM sleep.

The lateral hypothalamus may have a pivotal role in REM sleep regulation and the REM-on cells within this area may start to inhibit REM-off areas; subsequently, other REM-on areas may be facilitated in their activity and a REM sleep episode can start and be maintained. When these REM-on areas decrease their activity, the REM-off areas may start up their activity again, allowing the reactivation of the arousal system. In fact, REM sleep episodes are very frequently terminated by an arousal (Luppi et al. 2013).

## 2 Sleep Regulation

### *2.1 Sleep Chronobiology*

In physiological conditions and in a natural environment, the distribution of sleep and wakefulness depends on the time of day, following a 24-h (nicthemeral) rhythm. In the absence of external time cues such as ambient light, this rhythm persists and becomes free running, i.e., its period deviates from its original 24 h value by 10–20 min. Synchronization (entrainment) of a near-24 h endogenous rhythm to environmental time cues is the hallmark of a circadian rhythm.

The circadian sleep rhythm is generated in the hypothalamic suprachiasmatic nucleus (SCN), which projects to the adjacent subparaventricular zone (SPZ), and thence to the dorsomedial nucleus of the hypothalamus (DMH). The DMH targets sleep-promoting neurons in the ventrolateral preoptic nucleus of the hypothalamus

(VLPO) and wake-promoting neurons in the lateral hypothalamus, such as orexinergic neurons (Chou et al. 2003). The DMH also projects to the paraventricular nucleus of the hypothalamus (PVH), which modulates the anterior hypophysis to drive the circadian rhythm of adrenal cortisol release. On the other hand, the circadian rhythms of melatonin and body temperature are mediated by neural pathways that originate upstream of the DMH. The SCN directly projects to the PVH, thereby modulating in sequence the sympathetic preganglionic neurons in the thoracic spinal cord, the sympathetic neurons in the superior cervical ganglion, and the pineal gland cells that release melatonin.

The body temperature rhythm is largely mediated by projections from the SPZ to the medial preoptic area, which is part of a thermoregulatory pathway involving the DMH and the medullary raphe pallidus. These parallel pathways, that irradiate from the SCN, ensure phase locking between the sleep rhythm and the circadian rhythms of disparate physiological variables such as cortisol, melatonin, and body temperature. These multisynaptic pathways are also flexible, allowing for differences in diurnal preference between species, the critical switch probably being located in the SPZ. Accordingly, the peak in SCN neural activity and the minimum value (nadir) of melatonin secretion invariably occur during the subjective light period, thus being associated with reduced sleep propensity in humans and with increased sleep propensity in nocturnal laboratory rodents. Both in diurnal humans and in nocturnal laboratory rodents, however, the maximal sleep propensity is associated with the nadir of body temperature, which physiologically occurs just before habitual wake time and is followed by the peak in cortisol secretion.

The circadian SCN rhythm is shifted in phase by environmental time cues (Zeitgeber) until its period achieves a precise 24-h value, as if the hands of the SCN clock were manually turned until synchronization with the environmental clock is achieved. Light is usually the most powerful Zeitgeber. The phase of the SCN circadian rhythm is delayed or anticipated by exposure to light early or late in the subjective night, respectively. Light increases the activity of SCN neurons by stimulating excitatory neurotransmitter release from terminals of the retinohypothalamic tract, which connects specialized retinal ganglion cells to the SCN. In addition to receiving information from light-sensitive rods and cones, these specialized ganglion cells express the photopigment melanopsin, which makes them intrinsically sensitive to light, particularly in the blue-green (450–500 nm) portion of the spectrum.

## *2.2 Sleep Homeostasis*

The term homeostasis was coined at the beginning of the last century by the American physiologist Walter B. Cannon to name the peculiar steady states of living organisms, characterized by slight and controlled instability rather than by fixed and rigid constancy. Some 50 years later, the term was borrowed by the sleep research community to describe rebounds in sleep duration and intensity after sleep

deprivation or reductions in sleep propensity after sleep episodes (Achermann and Borbély 2011). In this particular sense, the concept of homeostasis should be interpreted loosely, as it is still unclear which sleep-related physiological variable, if any, is kept at a steady state.

The amount of NREM sleep time gained during sleep rebound is usually lower than the loss occurred during previous sleep deprivation. However, spectral power of the EEG in the delta band also increases during rebound NREM sleep as a function of the duration of prior wakefulness, and these changes roughly parallel the increases in the arousal threshold. On these bases, it is thought that recovery of NREM sleep mainly occurs by increasing NREM sleep intensity or depth, as indexed by increased SWA. Accordingly, SWA during NREM sleep is the highest at the beginning of each sleep cycle and progressively decreases in the course of each NREM sleep episode and throughout the whole sleep period. Interestingly, NREM sleep homeostasis in terms of SWA manifests at both a local and a global brain scale. Thus, SWA during NREM sleep is higher in frontal than in posterior EEG derivations, especially at the beginning of the sleep period or after sleep deprivation, and brain regions experiencing increases in activity during wakefulness develop increases in SWA during subsequent NREM sleep. The mechanism underlying local and global NREM sleep homeostasis in terms of SWA may be that increases in cortical synaptic strength during wakefulness increase neuronal synchrony during subsequent NREM sleep, leading to more frequent and ample EEG slow waves. In turn, EEG slow waves may then contribute to downscale the strength of cortical synapses during NREM sleep (Vyazovskiy et al. 2011).

At variance with NREM sleep homeostasis, the homeostatic response to REM sleep loss is thought to occur mainly, if not solely, in terms of REM sleep amount. Selective REM sleep deprivation by cold exposure in rats is followed by an immediate and sustained rebound of REM sleep amount, which allows the animals to fully restore the previous REM sleep loss within 3 days of recovery. In humans, however, REM sleep rebound after total sleep deprivation typically occurs only after the SWA rebound in NREM sleep, if it does at all. In part, this discrepancy is because the homeostatic pressure to increase NREM sleep SWA conflicts with and prevails on REM sleep homeostasis. Moreover, allometric scaling of REM sleep rebound with body mass in different species suggests that small animals such as rats have a lower tolerance to REM sleep loss than large animals such as humans (Amici et al. 2008).

## *2.3 Interaction Between Circadian and Homeostatic Sleep Control*

Sleep and wakefulness may be viewed as the key intermediate mechanisms, through which the circadian rhythm modulates physiological functions. In this respect, an important layer of sophistication and complexity is added by the

simultaneity of circadian and homeostatic sleep control. As a result, in humans, sleep propensity is sustained by high homeostatic pressure because of previous wakefulness at the beginning of the night and by high circadian pressure at the end of the night. To some extent, circadian and homeostatic sleep control may be disentangled experimentally with the aid of appropriate study designs. Thus, continual sleep deprivation and constancy of posture, feeding, and environment in constant routine protocols allow circadian control to be singled out at least partially from the effects of sleep homeostasis. Forced desynchrony protocols force subjects to follow wake–sleep cycles with extreme periods (typically 20 h or 28 h) that make entrainment of the endogenous circadian rhythm impossible, causing sleep to occur at different circadian phases over several days. These experimental efforts have been combined with advanced mathematical modeling techniques, starting from the seminal two-process (i.e., circadian and homeostatic) model of sleep regulation in the 1980s (Achermann and Borbély 2011). Altogether, it has emerged that the interaction between circadian and homeostatic sleep control is often nonadditive and complex, and basic research has started to suggest potential mechanisms of this complexity. A simple example is that sleep is associated with eyelid closure, which decreases retinal light exposure, thus feeding back to the SCN via the retinohypothalamic tract. Furthermore, at a cellular level, sleep decreases the activity of SCN neurons, which in turn determine circadian sleep propensity via the SPZ-DMH pathway. Most importantly, circadian and homeostatic sleep controls interact at a genetic level, which will be addressed in the next section.

## *2.4 Genetics of Circadian and Homeostatic Sleep Control*

The endogenous circadian rhythm in SCN neuron activity results from sophisticated interplay between transcription, translation, and posttranslational modifications involving a relatively small set of core clock genes. At the basis of this interplay lie two linked and delayed negative feedback loops (Feng and Lazar 2012). In the first loop, homo- and heterodimers formed by CRY proteins (coded by two Cryptochrome genes, Cry1-2) and PER proteins (coded by three Period genes, Per1-3) inhibit transactivation of their own genes, which is exerted by another heterodimer between the proteins CLOCK (coded by the Clock gene, Circadian Locomotor Output Cycle Kaput) and BMAL1 (coded by the Bmal1 gene, brain and muscle ARNT-like protein). This inhibition occurs after a delay resulting from Per and Cry gene transcription, translation into proteins, and protein migration to the nucleus. Continuous and regulated degradation of PER and CRY proteins eventually disinhibits CLOCK-BMAL1 transactivation of Per and Cry genes and starts a new cycle of the molecular clock. In the second loop, CLOCK-BMAL1 heterodimers transactivate the orphan nuclear receptor gene Rev-erbα, which codes for a protein that inhibits transcription of the Bmal1 and Cry genes, thus explaining the circadian fluctuations in their mRNA. Notably, the Clock gene

transcript is not in itself rhythmical, whereas the nuclear vs. cytoplasmic localization of its protein product is.

These basic negative feedback loops are connected with other loops of gene transcription and translation and expressed ubiquitously in cells, eventually driving circadian expression of large fractions (3–20 %) of the transcriptome in different tissues (Feng and Lazar 2012). The SCN neurons collectively constitute the master circadian clock of the organism, which entrains the myriad molecular clocks in peripheral cells by means of neural, hormonal, and metabolic signals.

Recent and exciting data are unraveling links between circadian rhythms, sleep, metabolism, and the epigenome. Thus, the wake-sleep circadian rhythm causes feeding and activity cycles, which change energy balance and redox state of peripheral cells. This is reflected in changes in ATP/AMP and NADH/$NAD^+$ ratios. These ratios modulate the clock gene feedback loops either directly or indirectly through the enzymes AMP Kinase and Sirtuin (SIRT) 1, which is a $NAD^+$-dependent histone deacetylase. The CLOCK-BMAL1 heterodimers recruit other histone deacetylases as well as histone acyl-transferases. Histone acetylation remodels chromatin, leading to rhythmic epigenomic programming of gene expression that integrates information from circadian clocks, wake-sleep behavior, and energy balance (Feng and Lazar 2012).

The tight link between sleep and circadian rhythms at the genetic level is supported by the finding that mutations of core clock genes, such as Clock, Bmal1, Per, and Cry, cause not only impairments in the circadian sleep rhythm but also important alterations in sleep duration and architecture. Recent gene expression studies suggest that the Per2 gene plays a prominent role in the cross talk between circadian rhythms and sleep homeostasis. Sleep homeostasis itself is under strong genetic control. In particular, data on mice point to the short splice variant of the Homer1 gene, which codes for a protein involved in glutamatergic signaling and synaptic plasticity, as a key regulator of the rate of accumulation of NREM sleep SWA during extended wakefulness (Maret et al. 2007).

Studies performed on monozygotic and dizygotic human twins have revealed a striking heritability of some sleep traits, which approaches 100 % for REM density and EEG spectral power during NREM sleep at 8–16 Hz (De Gennaro et al. 2008). Linkage analysis in rodents has identified key genes involved in EEG delta power during NREM sleep (*Rarb1*, retinoid acid receptor beta) and EEG theta frequency in REM sleep (*Acads*, short-chain acylcoenzyme A dehydrogenase). On the other hand, genome-wide association studies (GWAS) in humans are progressively uncovering the loci that increase susceptibility to sleep disorders, such as narcolepsy and restless leg syndrome (Sehgal and Mignot 2011). However, the genetic landscape of physiological sleep traits in humans remains largely uncharted by these studies because of issues related to replicability and statistical power. Finally, microarray studies performed on rats have demonstrated that the link between sleep and gene transcription is bidirectional. In the cerebral cortex, in particular, sleep upregulates transcription of several genes coding for proteins involved in depression of synaptic plasticity, membrane trafficking, GABAergic neurotransmission, and membrane hyperpolarization. Conversely, wakefulness upregulates gene

transcripts related to acquisition of synaptic plasticity, energy metabolism, stress and unfolded protein responses, and glutamatergic neurotransmission (Cirelli et al. 2004).

## 3 Physiological Functions During Sleep

### *3.1 A Physiological View of Sleep*

The three main wake-sleep states, i.e., wakefulness, NREM sleep, and REM sleep are usually recognized on the basis of EEG rhythms and levels of muscle tone, and the presence of eye movements associated with PGO waves. However, the physiological definition and understanding of these states cannot disregard the assessment of the respiratory, cardiovascular, and metabolic parameters, which are under the integrated control of the autonomic and the endocrine system (Parmeggiani 2005). This definition surpasses the standard one, largely based on the level of brain cortical and somatomotor activity. The hypothalamus plays a key role in this complex integrative activity (Thompson and Swanson 2003), which is critical for the maintenance of body homeostasis, for body survival (fight or flight response), and for reproduction. This activity leads to the shaping of bodily functions, largely on the basis of external and internal sensory information, in accordance with the physiological meaning and goals of the different behavioral states.

During NREM sleep, physiological regulation clearly operates favoring the maintenance of body homeostasis. NREM sleep is a state of minimal energy expenditure and motor activity, during which cardiovascular, respiratory, and thermoregulatory variables are driven by the autonomic nervous system (ANS) at a lower level compared to wakefulness and are kept stable by the autonomic reflexes.

On the contrary, during REM sleep posture control is lost, ANS is highly unstable, centrally driven surges in heart rate and blood pressure occur, breathing becomes irregular, and thermoregulation is suspended or depressed. The integrative function of the hypothalamus becomes imbalanced and this modality of physiological regulation has been described as "poikilostatic," ποικιλο meaning "diverse" in Greek, (Parmeggiani 2005), because it is not apparently aimed at the maintenance of the broad stability (homeostasis) of the physicochemical properties of the extracellular compartments that underlie cellular survival.

### *3.2 Sensory and Motor Functions*

The transmission of sensory information to the central nervous system (CNS) is attenuated during sleep. Brain processing of sensory information continues across

the different sleep stages, but a thalamic gating system operates to modulate the access of sensory information to central nervous areas, even if to a different extent, during both NREM sleep and REM sleep, favoring sleep continuity (Peever and Sessler 2011). It follows that a stimulus can interrupt sleep only if it is strong enough, or coincident with sufficient levels of arousal to allow a full cortical processing of the information. Somatosensory processing, including that related to pain, is also reduced during sleep (Peever and Sessler 2011).

Somatomotor control is largely influenced by the different wake-sleep states (Chase 2013): muscle activity is high during active wakefulness, progressively decreases during quiet wakefulness and NREM sleep, and disappears during tonic REM sleep, when muscle atonia occurs due to a deep inhibition of spinal and brainstem motoneurons. During phasic REM sleep, atonia is interrupted by brief twitches and jerks of limb and eye muscles (REMs). The REM sleep pattern of somatomotor control affects all somatic muscles with the exception of pure respiratory muscles, such as the diaphragm, which is spared by REM sleep motor inhibition, and the middle ear musculature, which is activated in order to depress auditory inputs. While the progressive reduction of muscle tone from wakefulness to NREM sleep represents a continuum within a common mechanism, REM sleep atonia depends on a change to a different central control mechanism.

The degree of muscle activity during the different wake-sleep states apparently depends on changes in the balance between excitatory (glutamatergic/monoaminergic) and inhibitory (GABAergic/glycinergic) inputs to the motoneurons. As shown by experiments on intracellular recording at the level of trigeminal and spinal motoneurons, REM sleep atonia is due to a very large inhibitory input to motoneurons that overcomes any possible excitatory drive. However, during phasic REM sleep, this inhibition, which is even larger than that occurring during tonic REM sleep, can be overcome by intermittent excitatory inputs leading to the generation of twitches. The inhibitory drive to motoneurons during both tonic and phasic REM sleep seems to be glycinergic (Chase 2013).

### *3.3 Respiratory Functions*

During sleep, the regular breathing pattern of quiet wakefulness is replaced by a large respiratory variability. This is the result of the loss of voluntary control of respiratory muscles and changes in both ventilatory control and resistance of the upper airways.

At sleep onset, ventilation regularly decreases, and respiratory instability may emerge, characterized by increases and decreases in breathing amplitude; these changes may be either aperiodic or regular and periodic (Krieger 2005). Periodic breathing has been described in 40–70 % of normal subjects; its frequency increases with age and it can comprise brief apneas (central or obstructive). At sleep onset, when sleep is not stabilized, changes in the amplitude of breathing parallel changes in the level of vigilance, with an increase in ventilation occurring during

spontaneous brief arousals. Periodic breathing disappears when stable deep sleep is settled.

During stable NREM sleep, ventilation is very regular. In humans, minute ventilation and tidal volume progressively drop from wakefulness to NREM sleep stages S3 and S4. Data regarding changes in minute ventilation, tidal volume, and respiratory frequency on passing from NREM sleep to REM sleep do not follow any evident trend nor show any significant difference. During REM sleep, breathing becomes irregular, displaying phasic changes in respiratory amplitude and frequency that follow the occurrence of REMs; respiratory irregularities may comprise central apneas (Krieger 2005). Minute ventilation decreases compared to wakefulness, and it is lower in phasic REM sleep than in tonic REM sleep (Douglas 2005).

During wakefulness upper airway muscle activity is maintained by reflex-activation of dilator muscles, but at sleep onset and, principally, during REM sleep, this reflex activity is reduced. Thus, even in normal subjects, upper airway resistance increases during sleep, producing an increment in inspiratory resistance. During sleep, the cough response is suppressed, occurring only after arousal. During REM sleep, hypotonia or atonia of the upper airway muscles are accompanied by intercostal muscle atonia, greatly reducing costal breathing (Chase 2013).

## *3.4 Endocrine Functions*

The circadian system and sleep occurrence largely influence the daily profile of the basal secretion of the principal components of the endocrine system (Van Cauter and Tasali 2011). However, 24-h sleep deprivation studies or experiments in which sleep occurrence has been shifted to an unfavorable circadian phase have highlighted that the weight of the circadian and the wake-sleep ultradian modulation on hormone secretion varies for different hormones (Van Cauter and Tasali 2011).

Modulatory effects of sleep on endocrine release are not limited to the hormones belonging to the hypothalamic-pituitary axes, but also apply to hormones controlling carbohydrate metabolism, appetite regulation, and body-fluid balance. The molecules involved in energy homeostasis (glucose plasma levels) are maintained at a constant level during the night sleep period in humans despite prolonged fasting, thanks to the decrease in brain and body energy consumption during the first half of the night.

The overall framework is very complex, mostly due to the differences observed, according to gender, to age, and to the effect of lifestyle and sleep profile on basal hormonal secretion. In addition, the slow time constant of the endocrine regulation often masks the NREM sleep-REM sleep cycling ultradian influences on hormone secretion, except for cases in which secretion is strongly influenced by the activity of the ANS.

As far as the growth hormone axis is concerned, the most reproducible pulse of growth hormone occurs shortly after sleep onset of normal nighttime sleep,

concomitantly with the peak in SWA. A different regulatory modality has been shown for the hypothalamo-pituitary-adrenocortical system, in which the circadian component is largely prevalent over the sleep-related component, leading to a peak of cortisol plasma levels during the early morning hours. Daytime levels of plasma thyroid-stimulating hormone are low and relatively stable and are followed by a rapid elevation starting in the early evening and culminating in a nocturnal maximum occurring around the beginning of the sleep period. Under normal conditions, prolactin plasma levels undergo a major nocturnal elevation starting shortly after sleep onset and culminating around mid-sleep, and are maintained at lower levels during daytime (Van Cauter and Tasali 2011).

Finally, the study of mean daily profiles of both glucose levels and insulin-secretion rates (ISR) in healthy subjects, in which the normal meal schedule was replaced by intravenous glucose infusion at a constant rate, showed that sleep influence on these parameters was stronger than that of the circadian system.

## *3.5 Autonomic and Cardiovascular Functions*

The activity of the ANS greatly changes during the wake-sleep cycle (Khairandish and Shapiro 2013). In quiet wakefulness, the activity of the parasympathetic and the sympathetic branches of the ANS controls cardiovascular, respiratory, thermoregulatory, gastrointestinal, and endocrine functions, in order to maintain body homeostasis. On passing from wakefulness to NREM sleep, the contribution of the parasympathetic branch increases compared to that of the sympathetic section, according to the reduced metabolic and somatic activity of this sleep stage. During wakefulness and NREM sleep, ANS activity still works to preserve body homeostasis. During REM sleep, sympathetic activity shows a considerable variability, which is accompanied by phasic changes in parasympathetic discharge. In this state, ANS apparently works according to a "poikilostatic" modality (Parmeggiani 2005).

The regulation of cardiac and circulatory functions deeply changes across the wake-sleep cycle as a consequence of the variations in physiological regulation and autonomic outflow (Franzini 2005). The blood supply to organs must match specific metabolic requirements and it responds to the animal's behavior, through changes in blood pressure and vascular resistance. The regulation of these two variables is critically modified on the basis of autonomic activity directed to the heart and blood vessels. In turn, autonomic output to heart and blood vessels varies according to the hypothalamic integrative activity, coordinating somatic, autonomic, and endocrine functions (Silvani 2008). In NREM sleep, body temperature, metabolism, and muscle tone decrease, and both heart rate and blood pressure decrease compared to wakefulness (Silvani 2008).

The main autonomic features of REM sleep are phasic fluctuations in sympathetic and parasympathetic activity, with instability of cardiovascular and respiratory variables. In particular, it is possible to notice surges in cardiac sympathetic

and parasympathetic activity associated with bursts of phasic REMs, PGO waves, myoclonic twitches, and breathing irregularities. Phasic surges in heart rate (approximately a 35 % increase) are followed by bradycardia due to the baroreceptor response to the increase in blood pressure (Khairandish and Shapiro 2013).

In most human subjects, blood pressure shows spontaneous diurnal changes, with a decrease to its lowest levels during nighttime sleep ("dipping"), primarily related to sleep-dependent blood pressure changes, rather than to the endogenous circadian rhythm. A blunted sleep-related blood pressure reduction (non-dipping status, defined as $<10$ % decrease in blood pressure during sleep) is considered to be one of the most sensitive predictors of cardiovascular mortality.

## *3.6 Thermoregulation and Metabolism*

The wake-sleep cycle is tightly coupled to the regulation of body temperature and metabolism (Krauchi and de Boer 2011). In fact, the most opportune moment of the day for sleep occurrence is the rest period, when the circadian system drives a decrease in body temperature and energy expenditure and the probability of an active interaction with the external environment is largely reduced.

Although in the human adult the decrease in energy expenditure during sleep is apparently moderate compared to quiet wakefulness, sleep may play a more relevant role in energy conservation in animals with a less favorable surface-to-volume ratio (infants or small mammals), in which energy conservation is more pressing (Krauchi and de Boer 2011). In general, body energy expenditure decreases during sleep.

In different species, brain energy metabolism largely decreases during NREM sleep and increases during REM sleep to levels similar to, or even slightly larger than, those of wakefulness. The relationship between the different wake-sleep states and the thermoregulatory process has been widely investigated. Thermoregulatory responses may be experimentally elicited by the delivery of either external or internal thermal loads. Such responses are present in both quiet wakefulness and NREM sleep, but absent (in small mammals) or depressed (in humans) in REM sleep (Parmeggiani 2005). While the thermoregulatory differences between wakefulness and NREM sleep only depend on the different levels of energy metabolism in the two states, a deep functional change occurs during REM sleep. This change shifts the normal closed-loop homeostatic regulatory modality to an open-loop one (Parmeggiani 2005). In particular, during REM sleep episodes occurring under a positive (warm) thermal load, peripheral vasodilation and tachypnea are suppressed in animals, while sweating is abolished at the beginning of the episode and subsequently depressed in humans. Also, under a negative (cold) thermal load shivering is suppressed, and heat exchanger vasoconstriction is reduced in animals.

The involvement of central nervous structures in these processes has been confirmed by studies showing that the capacity of the preoptic-hypothalamic thermosensitive neurons to respond to a direct thermal stimulation is impaired

during REM sleep (Parmeggiani 2005). Interestingly, recent experiments in the rat have shown that this is not the case for the hypothalamic osmosensitive neurons, since the degree of the release of antidiuretic hormone (ADH) following the intracerebroventricular administration of an hyperosmotic solution does not differ across the different wake-sleep states (Amici et al. 2013).

# 4 Sleep Evolution and Sleep Functions

## *4.1 Sleep Phylogenesis*

Sleep is a kind of behavior that can be considered to be universally distributed across mammals and birds. In both classes, sleep can be unambiguously identified through both behavioral (reduced responsiveness to stimuli, homeostatic regulation) and neurophysiological (EEG activity) parameters. The commonness of sleep among the different species of the two phylogenetically most recent classes suggests that such a behavior was positively selected by natural selection and that primordial signs of it should be found in less recent classes.

Unfortunately, few studies have satisfactorily investigated the comparative physiology of sleep. Aside from behavioral traits, the neurophysiological signature of sleep appears to be drastically different in classes other than mammals and birds. In reptiles, for instance, a high-amplitude EEG is observed during periods of activity, while a low-amplitude EEG characterizes periods of rest. Indeed, the anatomical difference in the structure of the CNS throughout the animal kingdom prevents the use of the commonly used mammalian-like EEG activity as an identifier for sleep.

In general, a succession of periods of activity and rest has been described in almost every species, from insects to mammals, but whether the period of rest may be labeled as sleep is still controversial. To compensate for the unavailability of mammalian-like EEG in other species (like the Drosophila Melanogaster), the search for molecular markers of sleep have been used as a possible alternative (Zimmerman et al. 2008). This kind of approach is based on the underlying idea that sleep serves a very basic cellular function common to most of the species. While this may be true, it is worth considering that evolution may hijack older regulations to fulfill new objectives, and that, therefore, the function of sleep may differ from class to class. For instance, speculatively speaking, homeothermy made its appearance on the evolutionary scene with mammals and birds (the only two classes to present both NREM and REM sleep) and the brain of these two classes had to spend its resting period at quite a high temperature, possibly forcing a drastic change in the function and regulation of sleep. In conclusion, comparative physiology could be used as a powerful tool to investigate a possible ancestral function of sleep, while not forgetting that evolution may have redirected it towards newer needs.

## 4.2 *Effects of Sleep Deprivation*

The logic that stands behind the use of sleep deprivation in sleep research is very intuitive: in order to understand what a body function is for, such a function must be impeded. The consequences of deprivation speak about the physiological role of the function itself in two ways: (1) if a rebound in the time/intensity of the deprived function is observed during the recovery following deprivation, the conclusion is that such a function plays a critical/vital role for the organism, and (2) the adverse consequences of the deprivation on the systems physiology of the organism may suggest what that function is vital for. Sleep deprivation is therefore used as a means to try to understand the yet-to-be-understood functions of sleep.

When compared to other forms of function deprivation, like, for instance, food or water deprivation, sleep deprivation presents some peculiarities. In particular, while food and water deprivation may occur in the natural world, sleep deprivation is quite uncommon, although it has been hypothesized that migrating birds do not sleep during long flights, and also the torpor bouts in hibernators have been considered to count as a very peculiar kind of sleep deprivation. This implies that animals in a laboratory setup have to be sleep deprived by some kind of environmental interference that removes the possibility to fall asleep for the animal. Several methods of sleep deprivation have been developed in past years, among which the most relevant are: (1) forced locomotion; (2) disk over water; (3) gentle handling, while more specific for REM sleep deprivation are (4) flower pot; (5) cold exposure (see Revel et al. 2009 for review).

Independently from the methods used, a very consistent observation following sleep deprivation experiments has been that sleep loss generates a drive for a sleep rebound during the following recovery period. In other words, sleep presents the typical homeostatic kind of regulation that has been described for other behaviors such as feeding or drinking (Amici et al. 2008). As previously discussed in Sect. 2.2, the rebound response for NREM sleep occurs mostly in terms of its "intensity" (increase in SWA, Achermann and Borbély 2011), while that for REM sleep occurs mostly in terms of its "duration" (Amici et al. 2008).

The functionality of the cerebral cortex seems to be very sensitive to sleep deprivation, and such sensibility may account for the degradation of cognitive performance induced by sleep deprivation. The general excitability of cortical neurons is increased during sleep deprivation, while neighborhood neurons tend to fire synchronously, impairing the computational ability of the cortex and, therefore, the quality of tasks depending on such functionality (Vyazovskiy et al. 2013).

However, following prolonged sleep deprivation, more severe general consequences arise. In rodents, 4 weeks of sleep deprivation lead to death by a unique syndrome characterized by a set of incoherent symptoms, such as weight loss, a massive increase in food intake, and hypothermia (Rechtschaffen and Bergmann 2002). These symptoms seem to suggest that prolonged sleep deprivation causes a lethal disruption to the central control of metabolism. A disruption in metabolic

regulation was also shown to be evoked in humans by 48 h of sleep deprivation (Van Cauter et al. 2008). Such metabolic dysregulation may very well be the result of the effects of sleep deprivation on the central nervous areas controlling metabolism. It is worth noting that some neuronal populations placed within these areas (for instance, the orexinergic neurons of the lateral hypothalamus) can also modulate the activity of the cerebral cortex, therefore, possibly accounting for the effects of sleep deprivation on the cortex itself. In conclusion, the sleep rebound induced by sleep deprivation suggests that the function of sleep is very relevant; moreover, while the most visible consequences of sleep deprivation are related to an impairment in cortical functions, the central network controlling body metabolism may be a biological target of sleep deprivation.

## *4.3 Sleep and Memory*

A growing corpus of evidence has investigated the effects that sleep has over memory traces, following the hypothesis that memory traces can be strengthened or weakened by the neurophysiological events taking place in the brain during sleep. While the process of memory consolidation is not completely known in detail, it is intuitive that it requires changes in neuronal connection and metabolism, processes that, ultimately, can be identified with the expression "neuronal plasticity."

In general, the three main hypotheses on how memory may be modulated by sleep have been proposed (Peigneux and Smith 2011): (1) the first hypothesis suggests that a continuous replay of recently created engrams during sleep (both REM and NREM) promotes their consolidation; (2) an alternative proposal suggests that during NREM sleep recently acquired memories are transferred from the hippocampus to the cerebral cortex, where new engrams are stored as consolidated memories; and (3) finally, the synaptic homeostasis theory (Tononi and Cirelli 2003) suggests that synapses on local cortical circuits are downscaled in a use-dependent mode during NREM sleep, enhancing the signal-to-noise ratio of relevant memory traces compared to nonrelevant ones. Interestingly, with memory consolidation as a goal, NREM sleep seems to be more critical than REM sleep. In particular, at least according to the synaptic homeostasis theory, the electrophysiological event that signals the cortical neurons to initiate the synaptic downscaling is the slow wave. Of course, the view that NREM sleep is the only determinant of memory consolidation is an oversimplification, since several data show an effective role in memory consolidation for REM sleep as well, suggesting that the clear-cut association of memory reconsolidation processes with precise sleep states may not be so strict.

## 4.4 Theories of Sleep Functions

Sleep function is intuitively associated with some kind of rest that seems to be mostly required by the CNS. Many theories on the function of sleep have been proposed, but a theory of sleep would not just have to interpret the existing evidence but also to provide testable predictions.

One legitimate hypothesis on the function of sleep is that during sleep some sort of toxic, wake-related substance is mobilized or metabolized, especially in the brain. Such a long-existing theory was recently revived by the finding that during NREM sleep, a drastic change in the clearance of the cerebrospinal fluid takes place (Xie et al. 2013). This finding was paralleled by the observation that sleep deprivation favors the accumulation of β-amyloid. This theory provides a theoretical frame for the consideration of sleep as a general functional process, but still leaves major questions open. For instance, no hypothesis on the function of REM sleep is provided and it is unclear why a change in brain fluid clearance should require cortical synchronization and loss of consciousness.

Another claim on the function of sleep was recently suggested within the synaptic homeostasis theory frame. The synaptic homeostasis theory correlates the synaptic plasticity of the cerebral cortex with the high degree of synchronized neuronal activity that occurs during NREM sleep (Tononi and Cirelli 2003). The theory is supported by experimental data, even if alternative explanations of these findings have recently been proposed (Frank 2012). The link between SWA in the cortex and neuronal plasticity was experimentally confirmed and used as a measure of the importance of sleep for all cognitive functions that depend on a well-functioning cortex, such as memory consolidation. But, slowly, the maintenance of cerebral cortex plasticity, from being the target of the positive effects of sleep, became the main determinant of sleep (Tononi and Cirelli 2014). This subtly modified interpretation of the theory overlooks the relevance of underlying autonomic effects as the basis of sleep generation and regulation. It is hard to interpret all the autonomic changes required for sleep to occur merely as the result of a feedback signal coming from the cortex and directed to the sleep central network, which carries information regarding the state of synaptic plasticity in the cortex. In other words, if the only determinant of sleep was the state of neuronal plasticity in the cortex, sleep-related autonomic changes would appear to be meaningless. They would be an evolutionary accident conserved for no apparent reason, and cortical synchronization could occur without autonomic changes. Moreover, the synaptic homeostasis theory does not provide a clear explanation of the REM sleep function. Finally, it is interesting to underline that the synaptic homeostasis theory, as well as the "brain clearance" one, are apparently unable to predict the effects of prolonged sleep deprivation or to provide an explanation on why such a procedure is lethal.

A full comprehension of sleep functions is probably not imminent.

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