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Neurobiology of sleep

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Abstract

The central nervous system undergoes several dynamic changes during sleep, which are coordinated by the pons, basal forebrain areas, and other subcortical structures and are mediated by three major neurotransmitters—norepinephrine, serotonin, and acetylcholine. The neuronal populations that produce these neuromodulators constitute the central representation of the sympathetic and parasympathetic subdivisions of the autonomic nervous system. The locus coeruleus (noradrenergic) and the raphe nucleus (serotoninergic) are most active during waking and become progressively less active in the transition from non-rapid eye movement (non-REM) to rapid eye movement (REM) sleep. On the other hand, the cholinergic neurons in the dorsolateral tegmental and pedunculopontine nuclei area are active both during waking and REM sleep. Over the past decade, a number of studies have provided interesting new evidence supporting the role of sleep in sleep-dependent memory processing. These studies have been directed specifically towards the role of sleep in memory encoding, memory consolidation, brain plasticity and memory reconsolidation, and have confirmed the hypothesis that sleep contributes importantly to processes of memory and brain plasticity. It has been shown in humans that sleep triggers overnight learning on a motor-sequence memory task, while equivalent waking periods produce no such improvement. These findings have important implications for acquiring real-life skills and in clinical rehabilitation following brain trauma and sroke.

1. Normal sleep in humans

"Sleep is a reversible behavioral state of perception disengagement from and unresponsiveness to the environment" [1]. Sleep involves a number of complex physiologic and behavioral processes and is usually accompanied by closed eyes, postural recumbence, and behavioral quiescence [1]. Within sleep, 2 separate states have been identified, non–rapid eye movement (non-REM) and rapid eye movement (REM) sleep. Non-REM sleep is conventionally subdivided into 4 stages based on the electroencephalogram (EEG), and is described as "synchronous," with characteristic wave forms such as "sleep spindles," K complexes, and high-voltage slow waves. The 4 stages of REM sleep (stages 1-4) roughly correspond with the depth of sleep, with stage 1 having the lowest arousal threshold and stage 4 the highest [1]. Non-REM sleep is associated with a "movable body," an active regulating brain, and minimal mental activity. Rapid eye movement sleep by contrast, as defined by EEG parameters, closely resembles wakefulness (high-frequency, low-amplitude waves) and is associated with muscle atonia, intermittently interrupted by muscle twitching, and episodic bursts of REMs (saccades of quick conjugate eye movements, that is, REMs), a highly active mental state that is associated with dreaming, based on vivid dream recall after approximately 80% of arousals from this state of sleep [2]. In addition, REM sleep is associated with suspended thermoregulation and autonomic irregularities such as irregular respiration and irregular heart beats. Another characteristic of REM sleep is the presence of spike EEG waves that arise in the pons and are transmitted to the lateral geniculate nucleus and the visual cortex (these waves are called the pons–lateral geniculate nucleus–occipital cortex waves).

In the past, the goal of sleep was thought to reduce the metabolic rate below that obtained by rest alone [3]. Attention was drawn to similarities between the slow waves of sleep and the EEG during entry into hibernation and

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shallow torpor. However, sleep has a relatively small metabolic savings (between 5% and 10%) [4,5].

2. A historical perspective

It has been said that "...more has been learned about sleep in the past 60 years than in the preceding 6,000" [6]. Sleep is a dynamic behavior (not simply the absence of waking), during which special activity of the brain occurs that is controlled by elaborate and precise mechanisms. Electrical activity of the human brain (EEG) was first recorded in 1928 and this measurement clearly demonstrated differences in electrical rhythms when subjects were awake and asleep [7]. The role of the brain stem reticular formation in the transition from sleep (or even drowsiness) to wakefulness (or alertness and attention) was studied in 1949 and showed the association between synchronization and desynchronization of the EEG (ie, replacement of the high-voltage slow wave activity with low-voltage fast activity) [8]. Ascending connections between the brain stem reticular formation and the intrathalamic nuclei (the ascending reticular activating system [RAS]) have been shown to activate the brain and produce the de-synchronized low-voltage fast waves in the EEG that indicate wakefulness.

Psychoanalytic theories of dreams [9] created widespread interest in sleep because this state is an essential concomitant of dreams. With the neurophysiologic concept of the RAS and the discovery of REM sleep and its association with dreams, the interpretation of dreams has remained one of the cornerstones of psychoanalysis.

Sleep medicine was established once polysomnography began to be used as a research tool for studying overnight and long-term sleep. This approach replaced the existing sleep research, which had been focusing on studies of dreaming, REM sleep, mental illness, and psychoanalysis. Dreaming had been strongly implicated in psychosis. After sufficient numbers of all-night studies with polysomnography had been completed, the different phases of "normal" sleep became apparent. Polysomnographic studies on depressed patients showed a significant reduction in the duration of REM latent periods demonstrating an association between REM sleep and endogenous depression [10]. Some significant precursors of modern sleep medicine have been the introduction of benzodiazepines and the use of sleep laboratory studies to study the efficacy of hypnotic therapy and studies examining the relationship between sleep, epilepsy, and abnormal movements, and the clinical relationship between sleep-onset REM periods and narcolepsy.

The discovery of sleep apnea in 1965 [11,12] has been described as "one of the most important events in the history of sleep disorders medicine..." [13]. Although this phenomenon was recognized much earlier, these studies provided the first clear-cut recognition and description of sleep apnea, generating observations that are directly related to present-day sleep disorders medicine. Before 1980, the only effective treatment of obstructive sleep apnea syndrome was long-term tracheostomy. This was been replaced by 2 new types of procedures—surgical [14] (eg, uvulopalatopharyngoplasty) and nonsurgical [15] (continuous positive nasal airway pressure).

3. The basic sleep cycle and REM sleep

Several compensatory regulatory mechanisms are observed in most mammals after sleep deprivation (changes in heart rate, sleep continuity, arousal threshold, and motor activity). Such changes indicate that a need for sleep has evolved. This need is increased as waking is prolonged and is dissipated when sleep occurs. Sleep, therefore, has an adaptive value that overrides the constraints of the circadian rhythm. Even lower vertebrates (fish and reptiles) and invertebrates (bees, cockroaches, and even *Drosophilia*) compensate for lack of sleep.

Although there is general agreement that chronobiology (the study of biologic rhythms) and sleep medicine are closely linked; research in these 2 fields has developed independently. As a consequence, sleep research has often ignored important information regarding the biologic clock, such as phase response curves, entrainment, and internal desynchronization. In addition, long-term studies with continuous recordings (which are an essential part of chronobiology research) were not done in sleep research before 1957 [16]. These long-term sleep studies showed a predictable sequence of patterns over the course of the night. The sequence most consistently seen after the onset of sleep EEG shows a quite rapid progression to stage 4, which persists for about 30 minutes [16,17]. This is followed by an abrupt "lightening" of sleep, which coincides with body movements, during which EEG shows short periods of stages 2 and 3, giving way to stage 1 and REMs. This sequence repeats cyclically throughout the night at intervals of 90 to 100 minutes (from one REM period to the other). Rapid eye movement sleep occupies between 20% and 25% of total sleep time (these periods are shorter in the early cycles of the night). An important advance in sleep research took place when it was realized that REM sleep was qualitatively different from non-REM sleep [18] and that these 2 types of sleep consisted of 2 different physiologic states. Jouvet [18] showed in 1960 that the pontine brain stem system is the primary anatomical site for REM sleep, during which muscle tone is completely suppressed. Atonia is a fundamental characteristic of REM sleep, which originates by activity in the pontine reticular formation and exerts its effect on spinal γ motoneurons through the reticular spinal tract. In addition to increased activity in the brain stem reticular formation during REM sleep, several other brain regions (visual cortex) show a marked increase in blood flow [19] leading to the important conclusion that REM sleep is an active process. In addition, the association of REM sleep with dreaming is now well established.

4. The neurophysiology of sleep

4.1. Essential brain regions for sleep

4.1.1. Hypothalamus

4.1.1.1. Suprachiasmatic nucleus. Two basic mechanisms have been recognized—a homeostatic mechanism and a circadian mechanism. The homeostatic mechanism dictates that a given quota of sleep duration and intensity needs to be obtained over a short term and that current needs depend on the individual's immediate history of sleep/wakefulness. Sleep deprivation causes a "rebound" effect where, at the nearest available opportunity, an individual will sleep with an increased duration and intensity (increased cortical slow waves) to compensate for lost sleep [20-22]. The circadian mechanism, located in the suprachiasmatic nucleus (SCN) of the hypothalamus, sets the time frame for sleep during each day [23]. The SCN promotes arousal during the day. Loss of input from the SCN causes a loss of sleep consolidation [24,25]. Most of SCN neurons project to the dorsomedial hypothalamus, which in turn projects to the ventrolateral preoptic area; to a collection of hypothalamic endocrine cells that secrete hypocretin, corticotrophin-releasing hormone, thyrotropin-releasing hormone, and gonadotrophin-releasing hormone; and to autonomic neurons that project to the brain stem and spinal cord autonomic (sympathetic and parasympathetic) nuclei. In addition, the SCN drives neurons in the locus coeruleus and independently influences melatonin and body temperature cycles directly.

4.1.1.2. Lateral hypothalamus. The lateral hypothalamus, located in the posterior hypothalamus, is the exclusive source of arousal-promoting peptides hypocretins I and II. Lateral hypothalamic neurons start firing before the transition from sleep to wakefulness [26]. This suggests a direct role of the hypocretins in sleep-wake transitions. Hypocretin-producing lateral hypothalamic neurons send numerous excitatory projections to wake-promoting adrenergic, histaminergic, dopaminergic, and cholinergic nuclei, and are involved in regulating these centers [27]. The adrenergic and serotoninergic neurons, in turn, inhibit hypocretin production by a negative feedback loop. The cholinergic neurons, on the other hand, excite hypocretinergic neurons by a positive feedback loop. In this way the role of hypocretins is "to facilitate motor activity in association with motivated behaviors and coordinate this with activation of attentional and sensory systems [27]."

4.1.1.3. Ventrolateral preoptic nucleus. This nucleus located in preoptic area of the anterior hypothalamus is a "sleep-generating" center, which opposes the arousing effect of the posterior hypothalamus. Two major nuclei have been identified—one located in the ventrolateral preoptic nucleus (VLPO) associated with non-REM sleep and the other located dorsal and medial to the VLPO (the extended VLPO) that is closely linked to REM sleep [28,29]. Ventrolateral preoptic nucleus neurons are activated by sleep-inducing factors such as adenosine and prostaglandin D_2. They are also temperature (warm)-sensitive. These neurons in the VLPO contain inhibitory transmitters γ-aminobutyric acid (GABA) and galanin and project to "arousal neurons" in the hypothalamus and brain stem. The GABA release into the arousal areas increases during REM sleep and the VLPO regulates the amount of delta wave activity. Because the activation of the VLPO is required for normal regulation of sleep, it is an essential element of the sleep-wake central circuitry.

4.1.1.4. Tuberomammillary nucleus. It has long been recognized that antihistamines have a powerful sedative action. However, histaminergic neurons in the brain have been identified only recently [30,31]. So far, histaminergic neurons have been identified in the posterior hypothalamus in the region of the tuberomammillary nucleus. These neurons project throughout the CNS, with the heaviest projections going to the cerebral cortex, the amygdala, and the substantia nigra. The tuberomammillary nucleus receives input from hypocretinergic neurons in the lateral hypothalamus as well as from GABAergic neurons in the VLPO, which contribute strongly to the firing rate of these histaminergic neurons in relation to sleep and other behavioral activities.

4.1.1.5. Pineal gland. The highly vascularized pineal gland is located on the posterodorsal aspect of the third ventricle. It secretes melatonin into the surrounding cerebral sinuses in response to photic information received primarily by the eyes. Upon exposure to light, retinal ganglion cells release melanopsin into the SCN [32], which in turn activates the sympathetic intermediolateral cell column in the thoracic spinal cord, which has a negative feedback loop with the pineal gland, resulting in inhibition of melatonin release. The relationship between the pineal gland, melatonin, and sleep has not been clearly established. It has been suggested that the concept of a "biological night" for humans involves melatonin, cortisol, body temperature, and sleep propensity fluctuations [33].

4.1.2. Brain stem

Regions in the rostral reticular formation, that is, the RAS, send projections to the forebrain through 2 main pathways critical for regulation of sleep-wake cycles. One pathway ascends dorsally through the lateral hypothalamus to the basal forebrain. The dorsal ascending pathway projects to multiple thalamic nuclei, which in turn have widespread projections to the cortex [34,35] Neurons in the rostral pons and caudal midbrain are the primary source of ascending projections to the dorsal thalamic nuclei. These neurons fire rapidly during wakefulness, but slow down during slow-wave sleep and resume rapid firing again during REM (active) sleep. Acetylcholine release in the thalamus increases during wakefulness and REM sleep, and is primarily excitatory. The ventral ascending pathways of

the brain stem RAS project rostrally through the lateral hypothalamus, terminating on magnocellular neurons in the substantia innominata, medial septum, and the diagonal band [34,35]. These are regions that contain cortically projecting neurons. This pathway originates in the noradrenergic nucleus, the locus coeruleus, and in the serotoninergic dorsal and median raphe nuclei. These cells fire actively during wakefulness and become inactive during REM sleep. Regions caudal to the pons also contribute to the regular cycling between sleep and wakefulness.

5. The function of sleep

5.1. New evidence of sleep-dependent memory processing and sleep-dependent motor learning

Over the past decade, a number of studies have provided exciting evidence supporting the role of sleep in "sleep-dependent memory processing" [36]. These studies have been directed specifically toward the role of sleep in memory encoding, memory consolidation, brain plasticity, and memory reconsolidation, and have confirmed the new hypothesis that sleep contributes importantly to processes of memory and brain plasticity.

Sleep-dependent memory consolidation [37] relates the concept of "sleeping on a problem" (which is familiar to most people) to the myriad stages of sleep with forms of memory and processes of memory encoding and consolidation. Although the sorting out of data regarding how sleep contributes to memory has been cumbersome and complex, new evidence from molecular to phenomenological has been very convincing, leaving little doubt that off-line memory reprocessing during sleep is an important component of how our memories are formed and ultimately shaped [1]. Memory consolidation and reconsolidation reflect molecular, cellular, and systems-level processes that convert labile memory representations into more permanent ones available for continued reactivation and recall over extended periods. These processes (which are optimally engaged during sleep) are a continuing series of biologic adjustments that enhance the efficiency and utility of stored memories over time, the rescue of memories of intentional and unintentional skills, and in response to changing needs of the organism. These findings are of fundamental importance of sleep in real-life skill learning [37].

Sleep duration and intensity are finely regulated through a phenomenon known as sleep homeostasis [38]. The best index of the intensity of sleep is slow wave activity, containing sleep spindles, K complexes, and delta waves, in the EEG with frequencies between 0.5 and 4 Hz, which are seen in non-REM sleep. It has been shown that in early nocturnal sleep when SWS is predominant, hippocampus-dependent declarative memory is enhanced. This is associated with low cortisol levels [39], low muscle tone, and minimal psychological activity. Late sleep, when REM sleep predominates, has been found to be associated with amygdala-dependent emotional memory [39]. Recently, functional nuclear magnetic resonance imaging [40] has been used to assess how system-level "consolidation" affects the neural correlates of memory retrieval. System-level consolidation is the process by which recently acquired memories (stored in the hippocampus), with time, are taken over by the neocortex. It has been shown that the natural cortisol rise during late sleep (REM sleep) protects from overshooting emotional memory formation.

There is a growing body of evidence regarding the role of sleep in off-line motor learning, specifically in posttraining consolidation [41]. It has been shown that in humans, sleep triggers overnight learning on a motor-sequence memory task, whereas equivalent waking periods produce no such improvement. Using functional nuclear magnetic resonance, after a night of sleep after a period of appropriate training, one can demonstrate an improvement in motor memory. This is reflected in increased activation of the right primary motor cortex, medial prefrontal lobe, hippocampus, and left cerebellum. These changes support faster motor output and more precise mapping of key-press movements. On the other hand, there is a decrease in activity in the parietal cortex, the left insular cortex, the temporal pole, and the frontal region, reflecting a reduced need for conscious spatial monitoring and a decreased emotional task burden. These findings have important implications for acquiring real-life skills and in clinical rehabilitation after brain trauma and stroke [42].

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