Review Article

Current understanding on the neurobiology of sleep and wakefulness

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Abstract

The modern concept of sleep and wakefulness has evolved from the landmark discovery of ascending reticular activating system by Moruzzi and Magoun in 1949. The other major contributions have come from the electrophysiological studies of sleep–wake states following the discovery of electroencephalogram by Hans Berger in 1929. Research studies over the past 60 years have provided us an enormous understanding on the neural basis of sleep–wake states and their regulatory mechanisms. By shuttling through the two behavioral states of sleep and wake, brain coordinates many complex functions essential for cellular homeostasis and adaptation to environment. This review briefly summarizes the current awareness on the dynamicity of brain mechanisms of sleep and wakefulness as well as the newer concepts of the biological functions of sleep.

Key words: Chemical mechanism, neural mechanism, non-rapid eye movement sleep, rapid eye movement sleep, sleep, wakefulness

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INTRODUCTION

We spend one-third of our life in sleeping. This accounts for the important role played by sleep in health and survival. Physiologically, sleep is defined as a reversible state of quiescence characterized by reduced motor activity, reduced responsiveness to sensory stimulation, and with a total lack of awareness about the outside world.[1,2] During wake, there is constant interaction between our environment and the brain activity, resulting in highly aroused, attentive, and motivated behavioral states.

Sleep has been studied over a century to understand the physiological functions it mediates. Sleep is essential for energy conservation, restoration and recovery, memory functions, brain development, brain and body homeostasis, and so forth.[1-8] From the ecological perspectives, sleep is important for adaptation to environment and hence important for health and survival.[9] Current studies provide more and more attributes and more complex concepts of brain mechanisms associated with sleep and wakefulness. The association of sleep with brain maturation during development,[10] sleep-related synaptic plasticity associated with learning and memory,[4] the impaired cognitive functions associated with sleep deprivation,[11,12] the existence of sleep rebound following sleep deprivation, and so forth, offer support to the extensive functional roles that sleep mediates. Studies have shown that sleep is essential to maintain immune, thermoregulatory, cardiovascular, and respiratory functions and hence important to maintain normal brain and body homeostasis.[6]

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NEURAL SYSTEMS OF WAKE AND SLEEP

Neural systems of wake

The history of modern scientific research studies on sleep have begun over 100 years ago. It was Pieron and Ishimori in 1900, who proposed the humoral theories of sleep; the concept that sleep is regulated by hormone-like substances was inferred from their observation that the cerebrospinal fluid from sleep-deprived dog could induce sleep when injected into a normal dog. Later, Frederick Bremer

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in 1930s[13] conducted one of the first experimental studies to identify the neural mechanisms associated with sleep–wake behavior. His experimental studies of 'encephaleisolae' and 'cerveisole' in cats had failed to demonstrate any neural structures or mechanism associated with sleep–wake and hence supported the preexisting notion of 'passive sleep theory' that sleep occurred when the sensory stimulation was insufficient to maintain the cortical activity to a waking level. It was believed that wake state was maintained by the incoming sensory inputs to cortex and sleep ensues when there is cessation of these sensory stimulations.

Moruzzi and Magoun in 1949 for the first time demonstrated successfully that electrical stimulation of the reticular formation in cats produces the behavioral signs of wakeful state.[14] The active neural mechanisms of sleep and wake emerged with the discovery of ascending reticular activating system (ARAS), the neural projection system from the brainstem to the cortex, and subcortical structures. Subsequently, the neurochemical nature of the brainstem ARAS was elucidated. The wake-promoting cell groups of ARAS[7,15-18] include the following: the lateral-dorsal and the pedunculo-pontine tegmental cholinergic cells (LDT/PPT), which provide major inputs to thalamus, lateral hypothalamus, basal forebrain, and cortex. The cholinergic neurons fire during wake state and during rapid eye movement (REM) sleep and the firing rates reduce during slow wave sleep. The monoaminergic cell groups, the noradrenergic cells in the locus coeruleus (LC), serotonergic cells in the dorsal raphe (DR) nuclei, and the histaminergic cells in the tubero-mammilary nucleus of posterior hypothalamus, all project to thalamus, basal forebrain, and cortex. The neurons of monoaminergic group fire extensively during wakefulness, reduce during slow wave sleep and are quiescent during REM sleep. The other wake-promoting cells include the glutamatergic projections from the midbrain and supramammillary regions of hypothalamus that project to cortex and the dopaminergic ventral mesencephalic neurons whose activity provides the highly motivated and positively rewarding nature of wake state.[7,15-18] Another prominent arousal-promoting neural projection includes the basal forebrain cholinergic projection to the cortex. The cholinergic neurons of the basal forebrain include the cell groups of medial septum, the vertical and horizontal diagonal bands of Broca, the magnocellular preoptic area, the substantia innominata, and the nucleus basalis of Meynert. These neurons receive input from brainstem arousal system and project widely to the cortex and limbic system. The cholinergic cells of basal forebrain system discharge extensively during waking and REM sleep and become silent during non-rapid eye movement (NREM) sleep. In addition, the wake-promoting functions of the hypothalamic orexinergic system has been studied extensively in recent years.[19,20] The orexinergic neurons activate the cortex and also provide intense excitatory inputs to the wake-promoting neurons of brainstem, hypothalamic and basal forebrain areas. They help to maintain a steady, long, consolidated, and highly stable wake state. The enhanced arousal states associated with emotion, motivation, reward, and energy homeostasis have been attributed to the orexinergic activations to limbic structures.[21] In general, the activity in the arousal-promoting neurons activate the thalamic-cortico-thalamic events leading to enhanced attention, arousal, memory, orientation, volition, sensation, perception, logical thinking, emotional stability, and motivational aspects of behaviors, energy homeostasis, and so forth. This forms the basis of an adaptive interaction with our environment essential for survival and enhances the adaptive values of consciousness. However, it is amazing to know that no single wake active system is absolutely necessary for the wake activities.

Neural systems of sleep

The control of wake and sleep has been attributed to thalamic, hypothalamic, and brainstem structures and their interaction with cortex. However, with newer discoveries of neurochemically distinct systems of hypothalamus, the brain mechanisms of sleep–wake behaviors have become much more complex. It was the Viennese neurologist von Economo[21] who for the first time predicted that anterior hypothalamic area has sleep-promoting functions and the posterior hypothalamus is involved in wake-promoting activities based on the postmortem findings that patients with lesions of the posterior hypothalamus exhibited excessive sleepiness and those with anterior hypothalamic lesions showed sleeplessness and insomnia. Almost at the same time, Walter Hess[22] provided evidences of hypothalamic role in active sleep mechanisms. Later studies have elucidated the role of preoptic and basal forebrain centers in sleep regulatory activities. Mallick and Kumar[23] have extensively studied the role of medial, lateral, and ventral preoptic areas as well as parts of basal forebrain regions in thermoregulation and found that these structures modulate the sleep mechanisms through thermoregulation. Though lesions of basal forebrain affected the sleep–wake states, the exact sleep-promoting activities of the basal forebrain regions are still obscure. Studies have shown that ventrolateral preoptic area (VLPO) and median preoptic area (MnPOA) are involved in sleep regulations.[15,16,18] It is also shown that the GABAergic and galaninergic neurons of VLPO core (VLPOc) modulate the NREM sleep and the dorsomedial extension of VLPO (eVLPO) modulate the REM sleep regulation.[24] Similarly the cell-specific lesions of VLPO have shown to reduce both NREM and REM sleep states and hence affect the total sleep. Lesions of VLPOc are associated with NREM

sleep loss and lesions of eVLPO reduces REM sleep propensity. The neurons of VLPOc project extensively to the tuberomammillary nucleus (TMN) of posterior hypothalamus and the eVLPO to the dorsal and medial raphae system and fire extensively during deep sleep. Median preoptic nucleus (MnPO) provides major inputs to VLPO, which helps to drive VLPO activity. Though VLPO express c-fos during sleep, MnPO neurons produce c-fos during sleep and during sleep deprivation.[15] Though the role of VLPO and MnPO are convincing enough in sleep regulation, further elucidation is needed with regard to the specific interactions among the sleep-promoting centers of hypothalamus in sleep–wake regulation, sleep and temperature regulation, and so forth.

The discovery REM sleep was yet another turning point in our understanding on the complex nature of brain mechanisms of sleep–wake behaviors. The REM sleep was first described by Aserinsky and Klietman more than 50 years ago.[25] Over the past few decades, studies have provided relatively clear and convincing evidences for the mechanisms associated with REM sleep and the NREM-REM alternations.[7,26,27] Earlier studies in rats have demonstrated two major groups of brain stem neurons that 'switch on' and 'switch off' the REM sleep. These include the 'REM on' pontine cholinergic neurons (LDT/PPT) and the non-cholinergic mesopontine 'REM off' neurons though these neurons are now considered as the REM modulators rather than REM on and REM off cells.[26,27] Recent studies[28] however, provided much more clear details about the existence of various non-cholinergic and non-monoaminergic 'REM on' and 'REM off' cells and their interactions in REM-NREM alternations. The newly recognized 'REM sleep generators' are situated in the mesopontine tegmentum. These include the GABAergic and glutamatergic 'REM on' neurons located in the sublaterodorsaltegmentum (SLD) and the GABAergic 'REM off' neurons of ventrolateral periaqueductal gray matter (vlPAG) and lateral pontine tegmentum (LPT). The putative 'REM on' regions such as SLD and the 'REM off' region vlPAG-LPT are having reciprocal innervations and are mutually inhibitory in nature.

THE SLEEP–WAKE DYNAMICS

The ability to fall asleep and to wake up afresh is associated with highly precise synchronized brain mechanisms among the distributed network of generators and neural pathways within the cortex, brainstem structures, hypothalamus, thalamus, basal forebrain, and other brain areas. The complex interactions among the multiple wake and sleep regulating structures together with the homeostatic and circadian regulatory system determine the various aspects of switching mechanisms; the induction, maintenance, and timing of wake, NREM and REM, NREM-REM alterations, and so forth. Only some neural systems are active at a particular state. For example, during the wake-promoting activities of brainstem and hypothalamic neurons, the brainstem and hypothalamic sleep-promoting neurons are totally inactive. Additionally, the wake activity has been strengthened and consolidated with orexinergic activations. The wake-promoting and sleep-promoting centers as well as the REM-NREM alterations occur as a result of the mutually inhibitory synaptic relations between the different centers of wake, sleep, and REM.[7,15,24] Such mutually inhibitory states together with additional arousal maintaining provisions provide the state-specific activities and prevent the state transitions. The sleep positive neurons of VLPO and the wake-promoting neurons of the basal forebrain (cholinergic), brainstem, and posterior hypothalamic TMN neurons are shown to have reciprocal inhibitory interactions with each other.[29] During wake state, both the wake active systems and the gamma-aminobutyric acid (GABA) neurons of basal forebrain inhibit the sleep-promoting VLPO. During NREM, the orexinergic and aminergic neurons are inhibited by VLPO, whereas during REM, the wake-promoting aminergic neurons are deprived of orexinergic excitation leading to their inactivation and subsequent disinhibition of the brainstem cholinergic 'REM on' neurons. Such antagonistic relations resemble the 'flip-flop switch' of the electrical circuits thereby ensuring rapid and complete state transitions between wake and sleep and between REM and NREM. According to the 'flip-flop model', the wake- and sleep-promoting regions inhibit each other and thus resemble the activity pattern of a 'flip-flop'.[28] When the VLPO neurons fire rapidly during sleep, they would inhibit the monoaminergic cell groups, reinforcing their own firing activities. Similarly when the monoamine neurons fire at a high rate during wakeful state, they would inhibit the VLPO thereby reinforcing their own firing properties. This self-reinforcing firing pattern assures stability of states. In addition, the orexinergic system stabilizes sleep and wake behaviors by activating and maintaining the activities of monoaminergic neurons. The neurons of VLPO, TMN, and LC show distinct firing properties during transitions from wake to NREM or from NREM to wake, making these transitions smooth, precise, and at the same time robust.[29]

In an REM sleep flip-flop model,[30] the activation of extended VLPO neurons during REM sleep inhibit the orexinergic neurons of lateral hypothalamus. The cessation of orexinergic neuronal activity during REM sleep in turn inactivates the 'REM off' GABAergic neurons in the vlPAG and LPT. In turn, the 'REM on' glutamatergic neuronal populations of the SLD, precoeruleus area, and parabrachial nucleus get disinhibited from the'REM off' brainstem GABAergic neurons and in turn activate the medial septum-basal forebrain cholinergic projections to

the hippocampus and cortex, leading to cortical activation and electroencephalogram (EEG) desynchrony during REM sleep. Simultaneously, the GABAergic neurons of SLD give feedback connections to the vlPAG-LPT 'REM off' neurons, inhibit their firing, and thus stabilize their own firing properties. The glutamatergic neurons of SLD project to the glycinergic/GABAergic neurons in the spinal ventral horn and in turn inhibit the motor neurons to produce atonia. The pontine glutamatergic input interacts mainly with the mesopontine cholinergic and cholinoceptive neurons to augment the REM and ponto-geniculo-occipital (PGO) activities.[7] These highly synchronized but independent mechanisms mediate the various physiological events associated with REM sleep. The mutual dopaminergic-basal forebrain cholinergic interactions and the subsequent cortical activation help to intensify the REM sleep. Supporting the concept of REM sleep generation in animals, functional neuroimaging studies in humans also found REM sleep-associated enhancement of regional brain activity in the pontine tegmentum, thalamic nuclei, subcortical and cortical limbic areas, and reduced activity in the dorsolateral prefrontal cortical regions.[31,32] The sleep–wake behaviors are the byproduct of a synchronous network event of a sleep–wake continuum. For example, during wake, the wake-active monoaminergic neurons inhibit the VLPO and 'REM on' neurons and excites the 'REM off' neurons thereby ensuring a stable wake state. The orexinergic system is associated with arousal maintenance by selectively activating the arousal-promoting neurons of brainstem, hypothalamus, and basal forebrain. Under such state, there is no chance for unwanted and abrupt transitions to take place unlike in conditions like narcolepsy, wherein the switching mechanisms become unstable due to neurodegeneration of orexinergic neurons and its receptors leading to the easy state transitions from wake to REM.[19,20] Studies from transgenic mice models support the importance of orexinergic system in sleep–wake regulations.[33] Such studies would help us to explore the physiological regulatory mechanisms associated with sleep–wake regulations and the importance of this in health and disease as well as the oscillatory network properties of the brain.

Besides the neural regulations, the circadian and homeostatic regulatory mechanisms maintain the timing, duration, and quality of sleep–wake behaviors.[34-37] The cyclical alternating pattern of REM and NREM sleep was explained by Feinberg.[38] Later, Borbély[34] proposed the separate processes underlying sleep regulation; a sleep-dependent homeostatic process, "Process S", which rises exponentially during waking and shows an exponential decline during sleep. The other process is the circadian process, "Process C", which is independent of prior sleep and waking. NREM sleep is associated with decrease in body temperature, blood pressure, heart rate, and respiratory rate. During REM sleep, the breathing becomes more rapid, irregular, and shallow, the eyes jerk rapidly in various directions, the limb muscles become temporarily paralyzed, heart rate increases, blood pressure rises, and males develop penile erections. The NREM sleep propensity is a reflection of the homeostatic process and the REM sleep propensity can be considered as a reflection of the circadian process.[34] While the homeostatic processes tracks the sleep need, the circadian regulatory mechanism of the suprachiasmatic nucleus is important for the sleep onset and sleep maintenance as well as the consolidation of wakefulness during the activity phase. Though both circadian and the homeostatic processes appear to be two independent mechanisms, any alterations in the circadian or sleep homeostatic process would affect the timing, intensity, and structure, implicating the interdependence between the two processes in sleep–wake regulations. Clock gene expression studies highlight such interdependencies between the two process, as the clock genes, besides setting the internal timing of day, are sensitive to changes in sleep homeostasis.[35] Similarly, endogenous somnogens like adenosine potentiate the dynamics of sleep by integrating various functions including circadian rhythm, though we are yet to understand the physiological mechanisms.[39]

Thalamocortical dynamics of sleep–wake states

Sleeping brain exhibits dynamics on time scales that not only ranges from several hours (circadian and homeostatic regulation of sleep) to several minutes (sleep stage transitions) but also includes time scales of seconds (typical sleep oscillations such as sleep spindles and slow waves that can be observed in EEG segments) and milliseconds (neural signaling).[40] Understanding sleep architecture at such smaller time scales has been used in laboratory-based animal studies, using electrophysiological tools. As invasive electrophysiological measurements are not always feasible in human studies, scalp EEG-derived measures are increasingly used in modern sleep research to look beyond sleep stage identification.[41-46]

Oscillatory activity in EEG is associated with neuronal synchronization and is considered as an emergent property of the thalamocortical system.[47] The patterns and the dominant frequencies of these oscillations depend on the functional state of the brain.[47] Classically, oscillatory activity during sleep is subdivided into delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-11 Hz), and spindle frequency activity (11-16 Hz). EEG delta oscillations correspond to slower < 1 Hz and faster 1-4 Hz oscillatory counterparts of local field potential recordings obtained from animal studies. These are the slow membrane potential fluctuations of cortical neurons, which alternate between depolarized up-states (neuronal activity) and

hyperpolarized down-states (neuronal silence) on a time scale between 0.5 and 2 s.[48] The <1 Hz synchronized oscillations originate mainly in the neocortex and the 1-4 Hz oscillations arise primarily from the activity of thalamocortical neurons. A finer analysis of these components from EEG delta oscillations might clarify the nature of pathophysiology in mental disorders.

These delta waves give rise to the slow waves observed in deep sleep and K-complexes in light sleep.[49] As slow waves in deep sleep are generated by a complex neural system involving anterior cortical regions and thalamus, duration of this stage and parameters of slow waves correlate with reductions in the size of frontal brain and thalamus (implied by enlarged ventricle size) seen in disorders like schizophrenia.[50] Other typical sleep oscillations exhibit frequencies between 2 and 20 Hz. Of these, the sleep spindles consist of waxing-and-waning field potentials at 7-14 Hz, which last 1-3 s and recur every 5-15 s.[48] Although spindle oscillations are generated by thalamic reticular neurons, they are synchronized and propagated by thalamothalamic and corticothalamic circuits.[51,52] Reduction in various parameters of sleep spindles, such as peak spindle frequency, spindle density, duration, and amplitude, has been reported among patients with autism, mental retardation,[53] and schizophrenia[54] and also in ageing.[55,56] At an intermediate time scale between the occurrence of sleep oscillations and sleep stage transitions, the cyclic alternating pattern is characterized by sequences of transient EEG events during NREM sleep that are distinct from background EEG activity, recurring at regular intervals.[57] Existence of such shorter time scale sleep events (microarchitecture of sleep) shows characteristic relations to the longer time scale events like sleep stages and sleep cycles.[40] Thus, exploration of sleep dynamics looking at multiple time scales would give us a better insight into the neurophysiology of sleep in health and disease.

Sleep dynamics and neural plasticity

Strategies such as exposure to enriched housing conditions, exercise, and rehabilitative programs have shown to enhance experience-dependent plasticity and better behavioral and cognitive performances.[58,59] Sleep has been reported to be an ideal behavioral state that favors synaptic plasticity events essential for memory consolidation.[4,60] Social enrichment studies in drosophila have shown that social living enhances the sleep need and sleep consolidation as an indication of enhanced restoration.[61] Such interventions perhaps may provide a window to explore the possibilities to prevent age-associated changes in sleep; the slow wave sleep is vulnerable and sensitive to aging than REM sleep and accounts for reduced sleep quality and maintenance by the fourth decade of life, whereas REM sleep changes in sleep occur later in life.[38,62] Meditative practices help man to achieve a perfect body-mind harmony, enhance the cognitive functions, and are shown to induce various aspects of neural plasticity in areas associated with self-judgment, introspection, perception, and so forth, and enhance neuroprotection of cortical tissues against aging.[63] We have reported that long-term practice of Vipassana meditation enhances the sleep quality and structure and helps to defy the age-associated changes in sleep.[64-66] Practitioners of Vipassana meditation showed enhanced slow wave sleep, REM sleep, and also number of sleep cycles. The older Vipassana meditators could defy the age-associated changes and retained a proper sleep organization with increased sleep efficiency and quality. The importance of yogic practices in improving the sleep quality and sleep efficiency in chronic insomnia patients has also been reported.[67] Similarly, long-term practice of transcendental meditation (TM) leads to experiencing 'highly restful inner wakefulness', an indication of attaining higher states of 'transcendental consciousness' as reported by Maharshi Mahesh yogi.[68] Later, Mason *et al*.[69,70] have provided electrophysiological correlates of attaining such stable higher conscious states in deep sleep states by experienced long-term TM practitioners. These studies provide ample evidences on various aspects of brain conditioning achieved through meditative practices, brain mechanisms of meditation, relation between neural plasticity and sleep quality, and a better insight into higher aspects of consciousness as important biological functions of sleep.

CONCLUSION

On the whole, this review tries to put together the current awareness on the newer dimensions in our understanding of the mechanisms of sleep–wake behavior, information on the multiple generators and neural pathways of sleep–wake systems, the flip-flop models to explain the state transitions, the circadian and homeostatic interactive mechanisms of sleep–wake regulations, and the time scale precisions of EEG dynamics associated with sleep–wake. However, we are yet to understand the fundamental issues related to sleep; that is, why no permanent loss of sleep or any absolute insomnia occurs following acute brain damage or stroke? Do these indicate the existence of additional brain regions and the brain mechanisms governing the sleep–wake states? Or are these behaviors the outcome of network properties of the brain? Understanding the brain mechanisms associated with sleep–wake behavior will be central to the overall functioning of the brain itself. The physiology of 'dream' still remains an enigma, though imaging studies provide some interesting evidences of brain activations and deactivations. Could sleep be neither a passive nor

an active phenomenon but an autoregulatory global phenomenon as pointed out by Kumar?[71] Or, could it be an emergent property of local networks linked to metabolic activities?[72] Further, systematic studies are warranted to understand the effects of yoga on sleep quality and behavior. Till we undertake sleep studies on a broader perspective, the evolution, complexities, and the many possible functions of sleep (and the functions of brain itself) remain still a mystery.

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