

NEUROBIOLOGY OF SLEEP

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ABSTRACT

Sleep is an essential physiological phenomenon of our lives. It is a highly organized and complicated process, hidden behind its apparent simple nature. The complexity and organization is maintained by several coordinated neurochemical systems, acting in concert with each other and the environment, e.g. sunlight. This review focuses on sleep organization, mechanisms underlying various sleep stages and sleep control.

Sleep is a fascinating physiological phenomenon of daily life which is defined as a reversible behavioral state of perceptual disengagement from, and unresponsiveness to, the environment.¹ We live about a third of our lives in sleep. Is it a waste of time? The answer is no. But the answer to "Why do we sleep?" is not very clear. Possible roles include replenishment of energy, thermoregulation, learning, memory and cognition.^{2,5} Sleep used to be considered as a passive phenomenon until the twentieth century when observations of Von Economo, and classical experiments by Moruzzi and his colleagues made it clear that sleep is not a passive phenomenon but different brain regions, especially diencephalon and brain stem actively control sleep and arousal.^{6,7} Later Kleitman and his colleagues recognized two phases of sleep — rapid eye movement sleep (REM sleep) and non-rapid eye movement sleep (NREM sleep), which alternate in highly organized pattern through out the sleep.⁷ This review is focused on the organization and control of sleep.

ORGANIZATION OF SLEEP

Sleep is a highly organized and structured physiological process, composed of two distinct phases i.e. NREM sleep, comprising approximately 75-80%, and REM sleep comprising about 15-20% of total sleep time (TST).¹ Both phases alter cyclically and REM sleep recurs approximately after every 90 minutes. This NREM-REM sleep cycle

recurs 4-6 times per night and time spent in REM sleep increases in successive cycles.² The NREM sleep is further subdivide in to four phases — stages I through IV.

Stage I

This stage comprises about 2-5% of TST and is characterized by several EEG findings, i.e. slow roving eye movements and waxing and waning of alpha rhythm followed by constant mildly slow background^{1,2} (figure 1). This represents the transition from awake state to sleep onset.

Stage II

This stage comprises 45-55% of TST. Sleep spindles and K complexes are EEG hallmarks of this stage, which crop up episodically against a background of low voltage mixed frequency EEG activity^{1,2} (figure 1).

Stages III and IV

Both stages are collectively called slow wave sleep (SWS). SWS comprises of about 13-23% of TST and is characterized by high voltage slow activity in delta range (0.5-2Hz). The amount of slow wave activity determines either of the two sleep stages^{1,2} (figure 1). Throughout the NREM sleep some skeletal activity persists but no rapid eye movements occur during this phase. After sleep

onset, sleep progresses from stage I to stage IV and then briefly drifts back to stage III or II before entering to REM sleep.²

REM sleep

REM sleep is characterized by rapid eye movements, as indicated by its name. Other important features include low amplitude mixed frequency EEG activity, resembling stage I or awake EEG, atonia (of all skeletal muscles with notable exception of muscles controlling eye movements, diaphragm and movements of middle ear ossicles)² (figure 1).

In addition many other physiological changes also occur during REM sleep including penile erection in men and clitoral engorgement in women, attenuation of homeostatic mechanisms, i.e. response to change in environmental temperature and response of respiration to change in blood CO₂.² Dreams, which we can recall, usually occur during this stage of sleep.²

CHEMISTRY AND CIRCUITRY

The control of sleep and arousal is mediated through different neural systems, and several neurotransmitter systems have been recognized to control sleep and arousal. A complex and coordinated interaction between these systems exists to control and regulate different sleep phases and arousal. Broadly, anterior hypothalamus

promotes sleep and posterior hypothalamus and rostral brain stem promotes arousal.

Arousal or wakefulness

The most important neurotransmitters promoting arousal are acetylcholine, norepinephrine, histamine, serotonin, dopamine and hypocretin/orexin.^{2,8,9}

Acetylcholine

Cholinergic neurons are abundant in pedunculopontine and laterodorsal tegmental areas of rostral brain stem, and these heavily innervate medial and intralaminar thalamic nuclei, lateral hypothalamus and basal forebrain. Activation of thalamic nuclei leads to cortical stimulation and generation of fast cortical rhythms, characteristics of REM sleep and wakefulness. Pharmacological correlate of this system is sleep induction secondary to anticholinergic effects of tricyclic antidepressants.

Norepinephrine

Locus coeruleus (LC), a pontine nucleus, is a major area where norepinephrine containing neurons reside. The neurons extend to cortex, hippocampus and diencephalon. This system is most active during wakefulness followed by NREM. The LC neurons are almost silent during REM sleep. This transmitter promotes arousal/wakefulness, especially under stressful situations.

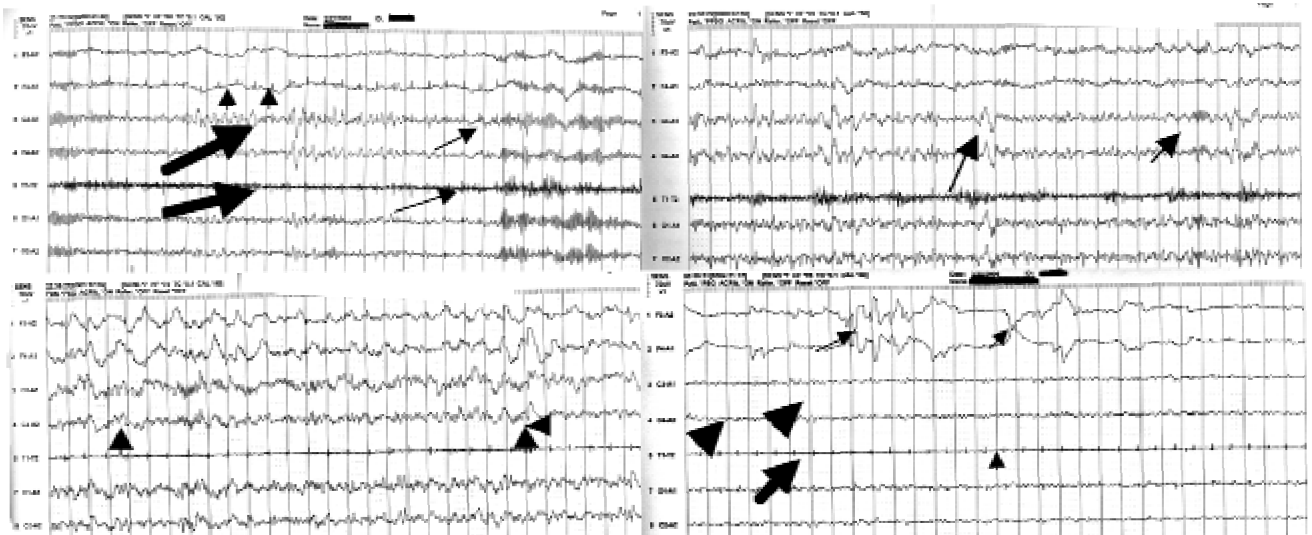


Figure 1

Right top: Stage I sleep (Vertical arrows; slow roving eye movements, thick oblique arrow; mixed frequency relatively low voltage EEG activity, thin oblique arrows; alpha rhythm). Left top: Stage II sleep (Large arrow; K complex, small arrow; sleep spindles). Right bottom: Slow wave sleep (Arrows; delta activity). Left Bottom: REM sleep (Thin oblique arrows; rapid eye movements, thick oblique arrows; low voltage EEG, vertical arrow; paucity of EMG activity). In each portion 1st two channels represent eye movements, 3rd, 4th, 6th and 7th channels represent EEG activity and 5th channel represent chin EMG.

Histamine

Within posterior hypothalamus, tuberomammillary nucleus (TMN) contains histaminergic neurons, which project to the whole neuraxis. These neurons also lead to cortical activation and promote wakefulness, especially at the onset of waking, and conditions require high behavioral arousal. These are less active during NREM sleep and are least active during REM sleep. Pharmacological correlate of this system is somnolence as a result of antihistamines (H1 blockers).

Serotonin

Major source of serotonergic fibers are dorsal raphe nuclei, located in pons. These project to whole CNS and promote wakefulness. Pharmacological correlate of this system is insomnia secondary to selective serotonin re uptake inhibitors.

Hypocretin/Orexin

Orexin-producing neurons are populated in lateral and posterior hypothalamus and they heavily innervate and stimulate the aforementioned cholinergic, histaminergic, adrenergic and serotonergic systems. This system is most active during the awake periods, especially during periods of locomotor activity and latter half of the day.

Dopamine

Dopaminergic neurons are plentiful in substantia nigra, ventral tegmental area and posterior hypothalamus. They probably have wake-promoting effect as evidenced by pharmacological effect of dopamine agonists and antagonists, i.e. insomnia and somnolence, respectively.

NREM sleep

The most important neurotransmitters promoting sleep are - aminobutyric acid (GABA) and galanin.⁸ Both of these are inhibitory neurons, populated in preoptic area of anterior hypothalamus. Most of these cells reside in a cluster, known as ventrolateral preoptic area (VLPO) and project to wake-promoting areas (*vide supra*). Hence these VLPO neurons, promote sleep by inhibiting the wake promoting regions.⁸ These GABA-ergic inhibitory cells are also called NREM-on cells, and many of these cells are activated by heat, thus may be responsible for sleep inducing effect of raised temperature.² Rhythmic firing of thalamic relay neurons is responsible for sleep spindles and slow waves of NREM sleep. This is mediated through GABA-ergic inhibitory input of thalamic relay cells from nucleus reticularis.²

REM sleep

REM sleep is controlled by interaction of cholinergic and aminergic systems.^{2,8} Near the LDT/PDT nuclei there is a distinct cell population, REM-active cholinergic cells, the key to low voltage mixed frequency EEG activity. These cells project to thalamus and secrete acetylcholine. During NREM and awake state these cells are inhibited by aminergic systems (NE, HA and 5-HT), but during REM, aminergic activity vanishes leading to disinhibition of REM-on cells, which in turn activate thalamus, and thalamic activation leads to cortical desynchrony. This desynchrony manifests electrophysiologically as low amplitude mixed frequency EEG activity, an important feature of REM sleep.

Another unique feature of REM sleep is atonia. The atonia is mediated through multisynaptic descending pathways through medial medulla. The dorsal pontine nuclei (nucleus reticularis pontis oralis) contain two different populations of neurons, i.e. REM-on cells and REM-waking-on cells. The REM-on cells are active exclusively during REM sleep, and they inhibit aminergic system through GABAergic activity, and activate atonia producing medial medullary neurons through histaminergic outflow. Atonia-producing medial medullary neurons project to motor neurons of the brain-stem and spinal cord and secrete glycine, an inhibitory neurotransmitter. The medullary neurons also inhibit excitation from LC and red nucleus. The REM-waking-on cells fire during awake state and REM sleep. Some of these neurons project to motor neurons destined to supply extraocular muscles. These neurons fire in a burst pattern and are responsible for rapid eye movements, characteristic of REM sleep.

Overall sleep control

Arousal state is maintained actively by many neuronal systems (*vide supra*). Sleep wake cycle is controlled by two different, albeit, interacting mechanisms, i.e. homeostatic and circadian.

The first process is based on endogenous factor (somnogen), which accumulates during wakefulness and declines during sleep. The best candidate somnogen is adenosine which disinhibits sleep-promoting neurons in diencephalon e.g. VLPO, and inhibits wake-promoting neurons. Adenosine concentration is increased after sustained wakefulness, seizures, hypoglycemia and ischemia.⁸

The second process helps in time wakefulness. The chief player in controlling circadian rhythms is suprachiasmatic nucleus (SCN).¹⁰ The SCN receives information from retinal ganglion cells, and then the efferent flow goes to dorsomedial hypothalamus through the ventral

subparaventricular region. Dorsomedial hypothalamic nucleus than inhibit sleep promoting regions and activates wake-promoting regions ¹¹ (figure 2).

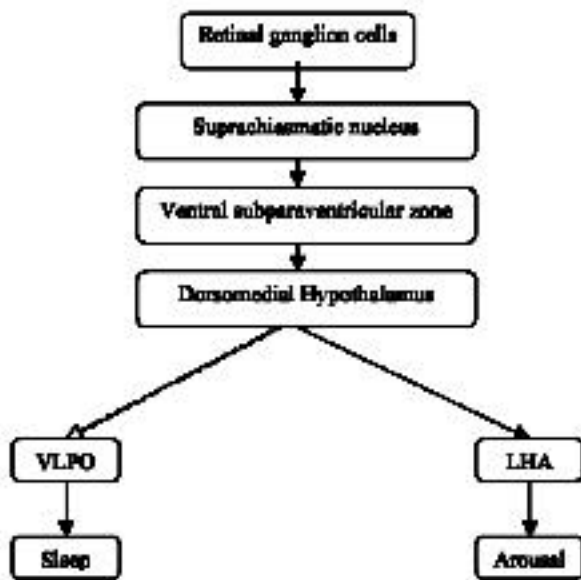


Figure 2

Simplified diagram of circadian of sleep. Dashed arrow indicates inhibition; solid arrow indicates activation/stimulation; VLPO=Ventrolateral preoptic area; LHA=Lateral hypothalamus.

SUMMARY

Sleep is a complicated, yet very organized phenomenon. The sleep-wake cycle is controlled by integrated mechanisms regulated through circadian rhythm and endogenous somnogens. Major arousal mechanisms are localized to the rostral brain stem and posterior hypothalamus, while sleep promoting systems are located in the anterior hypothalamus. In addition, characteristic features of REM sleep are mediated through multisynaptic ascending and descending pathways across the neuraxis.

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