Review Article

Sleep and Its Mechanism

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Sleep is an integral part of our daily life. We spend one third of our lives sleeping. Sleep is also an insistent drive. People will drift into sleep, even if they are in a situation (for example, driving a car) in which sleeping will mean their death.[1] It is a period of physical inactivity during which there is unconsciousness from which the person can be aroused by sensory or other stimuli. The loss of consciousness during coma, surgical anesthesia and epilepsy is not considered as sleep.[2] Sleeping people are not consciously aware of the external world but they do have inward conscious experiences such as dreams. Furthermore they can be aroused by external stimuli such as alarm of the clock or cry of a child.[3] Requirement of sleep varies with age and also in individuals. Infants sleep for more than 18 hours while young children for 12 hours. Adults require 6-8 hours sleep, while elders sleep less.[4]

Sleep is an active process consisting of alternate periods of two types of sleep. During a night, every body enjoys two types of sleep; slow wave or non-REM sleep and REM (Rapid Eye Movement) or paradoxical sleep. Depth of sleep varies from very light sleep to very deep sleep.[2]

Slow Wave or Non-REM Sleep

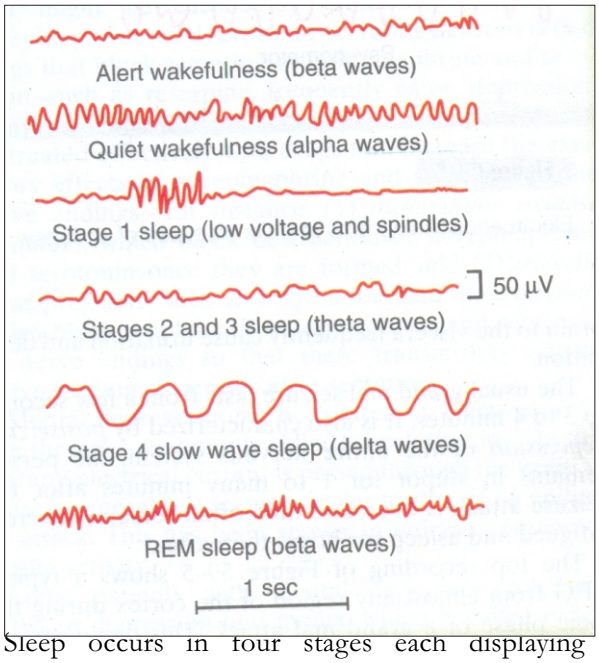
It constitutes about 75-80% of the sleep during a night. This is deep, restful sleep. A person who has been kept awake for many hours passes to the deep sleep within 1 hour after going to sleep. There is 10-30% decrease in respiratory rate and basal metabolic rate. Skeletal muscle tone also decreases slightly. This sleep is usually called "dreamless sleep". Dreams do occur but are not remembered as consolidation of dreams in memory does not occur.[2] Pulsatile growth hormone and gonadotropin secretion from the anterior pituitary occurs.[1,2] There is an overall reduction in heart rate, cardiac output and blood pressure due to general vasodilation. pCO_2 level rises while pO_2 level falls. Urine production decreases, and the concentration of urine increases. There is a decrease in the glomerular filtration rate and the renal plasma flow. Secretion of aldosterone increases, as does ADH, both of which contribute to the decreased production of urine. The motility of the gastrointestinal tract decreases during sleep. Gastric acid secretion also decreases during sleep, except in patients with duodenal ulcers, who show an increase of gastric acid secretion. The swallowing reflex normally slows down. At sleep onset, the body temperature set point is lowered and body temperature falls.[1,5]

There is a reduced discharge rate and brain metabolism. There is an increase in parasympathetic activity similar to relaxed wakefulness. Person shifts body position frequently and can be easily awakened.[3] The electroencephalogram (EEG) shows delta waves having high voltage (100uv) and slow rate (0.5-4/second). Nocturnal enuresis (bed wetting) in children, sleep talking and somnambulism (sleep walking) occurs during this sleep. The pupils react to light. Tendon reflexes are lost and planter reflex may become extensor. Sleep is facilitated by reducing the sensory input and by fatigue.[7] The secretion of melatonin does not appear to be related to sleep cycles. Melatonin, which is synthesized in the pineal gland is released at night, and is inhibited by light while exogenous administration increases total sleep time.[1]

REM (Rapid Eye Movement) or Paradoxical Sleep

It constitutes about 20-25% of the sleep during a night. It occurs in episodes each lasting for 5-30 minutes and repeated on the average every 90 minutes. There are 4-6 episodes during each night. It is associated with active dreaming which can be recalled. Humans aroused at a time when they show the EEG characteristics of REM sleep generally report that they were dreaming whereas the individuals awakened from slow wave sleep do not. Skeletal muscle tone is extremely decreased. Heart rate and respiratory rate usually become irregular. Rapid eye movements and irregular muscle twitching in other parts of the body occur. It is difficult to arouse the person during this sleep than in slow wave sleep and yet people usually wake up spontaneously in the morning during an episode of REM sleep. Duration of REM sleep is less in children and more in old people. It increases if the person has taken rest before going to sleep. When the person is much tired,

episodes of REM sleep are short or even may be absent. The electroencephalogram shows beta waves (rapid, low voltage waves) indicating that the brain is highly active; so REM sleep is also called paradoxical sleep because it is a paradox that a person can still be asleep despite marked activity in the brain. Bruxism (teeth grinding) may be present during REM sleep and it is associated with dreaming. Overall brain metabolism is also increased and secretion of adrenocortical hormones occurs. [2,6] Penile erection in males and engorgement of the clitoris in females can occur. Most REM sleep occurs towards morning; this helps to explain the erections which accompany awakening in the morning. The erections that occur during REM sleep are not necessarily related to dream content, they are just a physiological correlate of the sleep state. It does provide a useful tool for assessing impotence in males. Since erections occur involuntarily during REM sleep, it is possible to assess whether impotence is physiological or psychological. The absolute amount of REM sleep has been correlated with intellectual functioning in the elderly; REM sleep levels are shown to be diminished in Alzheimer's patients. During REM sleep, para-sympathetic activity remains about the same as during NREM sleep, but sympathetic activity decreases, resulting in an overall predominance of para-sympathetic activity.[1]



Sleep occurs in four stages each displaying progressively slower EEG waves of higher amplitude. At the onset of sleep, we move from the light sleep of stage 1 to the deep sleep of stage IV.

The hypothalamus establishes patterns of awakening and sleep that occur on a circadian (daily) schedule. Inactivation of reticular activating system produces sleep.[8] Stimulation of several specific areas of the brain produces slow wave (natural) sleep. These areas are as follows: raphe nuclei are a thin sheet of midline nuclei in lower half of the pons and in the medulla oblongata. Nerve fibers from these nuclei pass to the brain stem reticular formation, thalamus, hypo-thalamus, limbic system and spinal cord dorsal horn where these can inhibit incoming sensory signals including pain. Nerve fibers from raphe nuclei secrete serotonin at their nerve endings. Stimulation of some areas in the nucleus of the tractus solitarius can also produce sleep. Stimulation of anterior part of the hypothalamus mainly in the suprachiasmatic area and intralaminar and anterior thalamic nuclei also induces deep sleep.[2]

The thalamus, dorsal raphe, and nucleus tractus solitarius are important in NREM sleep.[1] Discrete lesions in the raphe nuclei lead to a state of high wakefulness. This is also true of bilateral lesions in the suprachiasmatic area in the anterior hypothalamus.[2] Serotonin (5-HT), found in raphe neurons of the brainstem may be involved in the sleep onset. Insomnia occurs when serotonergic cells of the dorsal raphe are lesioned. Monoamine oxidase inhibitors (specific for 5-HT) enhance sleep.[1]

Experiments have shown that the cerebrospinal fluid, blood and urine of animals that have been kept awake for several days contain a substance or substances that will cause sleep when injected into the brain ventricular system of another animal. One of the substance has been identified as muramyl peptide.[2]

The mechanism that triggers REM sleep is cholinergic neurons located in the pontine reticular formation. The noradrenergic neurons in the raphe nucleus cease their discharge when pontine cholinergic neurons discharge to initiate REM sleep. Barbiturates decrease the amount of REM sleep.[6] Acetylcholine is located within neurons in the pontine tegmentum and is involved with REM sleep generation. "REM On cells" are cholinergic cells in the lateral pontine and medial medullary reticular areas that innervate the thalamus, hippocampus and hypothalamus. These cells discharge at high rates during REM and show little or no activity during NREM sleep. Physostigmine, which inhibits catabolic enzymes, precipitates the appearance of REM sleep during NREM sleep. The injection of carbachol, a muscarinic agonist, into the pontine tegmentum induces REM sleep. Blocking muscarinic receptors

will retard the appearance of REM sleep. "REM Off cells" are noradrenergic and serotonergic cells found in the locus ceruleus and raphe nuclei. These are cells which are slow or silent during REM sleep. Affecting levels of norepinephrine or serotonin can have an effect of decreasing REM sleep, which is elevated in human endogenous depression.[1,9] During REM sleep the release of monoamine neurotransmitters such as serotonin, dopamine and histamine stops.[10]

Significance of Sleep

The principal value of the sleep is to restore natural balances among the neuronal centers in the central nervous system.[2] Sleep provides catch up time for the brain to restore biochemical or physiological processes that have progressively degraded during wakefulness. Adenosine is generated during the awake state by neurons and glial cells and its concentration in the intracellular fluid increases; it acts to inhibit the arousal center (reticular activating system) to induce sleep. Caffeine which blocks adenosine receptors in the brain revives drowsy people by removing adenosine's inhibitory influence.[8] Slow wave sleep provides time for the brain to repair damage caused by the toxic free radicals produced by metabolism during the waking state. Paradoxical sleep is necessary to allow the brain to "shift gears" to accomplish the long term structural and chemical adjustments necessary for learning and memory.[3] During Non REM sleep, there is time for neurons to repair accumulated damage from free radicals or other maintenance activity.[10]

Effects of Sleep Deprivation

Following prolonged lack of sleep, pathological changes in brain cells and psychic disturbances start. EEG shows slower pattern. There is lack of concentration & decreased intellectual performance, Progressive inability to think logically, disturbances of perception and personality changes occur.[4] Prolonged wakefulness is associated with progressive malfunction of the thought processes and sometime abnormal behavior. A person can become irritable or even psychotic after forced wakefulness.[2] Behavioral studies on humans and animals have shown that loss of REM sleep causes increased aggressiveness, heightened pain sensitivity, hypersexuality, and has a detrimental effect on memory consolidation as well as brain maturation. At the cellular level, neuronal responsiveness is known to be affected after REM sleep deprivation.[9] Sleep deprivation is associated with reduced immune system functioning and may also induce psychotic behavior if it is accompanied by stress.[11]

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