Current Concepts in the Neurophysiologic Basis of Sleep; a Review

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Abstract

Background: Sleep is a very vital physiological mechanism, which involves complex interactions in the nervous system. These interactions are not well understood and have been a subject of controversy in contemporary medical practice.
Objectives: To review of the neurophysiological factors in the subject of sleep, and recent research findings that forms the basis for the current knowledge on sleep.
Methods: Information sources consulted included, published works of past researchers, current articles on sleep in conference papers, recent editions of textbooks on neuroscience, articles in seminar papers, reports extracted from newspaper and magazine articles on sleep, reports accessed from the Internet using Google Search Engines and lecture notes.
Results: It was noted that emphasis has now shifted from the concept that sleep was predominantly the product of activities in the neural systems in phylogenetically old reticular core of the brain through withdrawal of sensory input, to emphasis on the role of neurotransmitter systems, especially - Ach, serotonin and GABA. This review also noted that, among others, emphasis is further shifting to the PGO waves which is fast gaining prominence as the mechanism involved in the production of REM sleep and dreams in particular.
Conclusion: It became obvious from this review, that full knowledge of the neurophysiological processes involved in sleep production appear generally to still be more of speculative, and are yet far from full understanding.
Key Words: Current concepts; neurophysiological basis, sleep

Ann Med Health Sci Res Jul.-Dec., 2011; 1(2) 173- 180 received 11/06/11; accepted 26/09/11/published 22/12/11

Introduction

Essentially, sleep is a behavioral state. It is estimated that an individual spends approximately, one third of his lifetime in sleep. We have knowledge that sleep is part of the daily routine in everyone, even when the normal sleep and wake cycle (or pattern) is disrupted by outside factors. Sleep may be defined as a state of natural unconsciousness from which an individual can be aroused. However, in this review paper on the subject of sleep, another definition regards sleep as a naturally recurring state of relatively suspended sensory and motor activity in the animal, characterized by total or partial unconsciousness and nearly complete inactivity of voluntary muscles. This later explanation or definition appears to be even more scientific.

Sleep is observed in all species of animals, including reptiles, amphibians, fish and birds. In humans, it is commonly regarded as a natural state of bodily rest. For example, a recent report observed that regular sleep is essential for survival.[1] In one earlier report, it was similarly noted that sleep is a condition specifically required by the body as part of its homeostatic regulatory and repair mechanism. [2]

Researchers have put in much effort in the quest for a better understanding of the neurophysiologic mechanisms of sleep. Factors in the mechanisms of the transitions between sleep stages and even dreams, are subjects that have attracted intense research over the years.

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A number of earlier workers believe that sleep is purely a passive state in which the brain is resting. With advances in scientific research however, workers have come to learn that, on the contrary, sleep is not merely a passive or static state in which the brain is resting. It is now known that sleep is a dynamic and complicated condition during which the brain is quite active. It is also now known that normal sleep is made up of complex series of stages that repeat itself in a characteristic pattern, and this aspect has helped to further establish the fact that sleep is not simply a state of neural inactivity. For example, not long ago a group of workers were surprised to learn that regions of the frontal cortex display more activity in direct correlation with a person's sleepiness; the sleepier the person, the more active the frontal cortex.[3]

Many workers have speculated on the adverse effects of lack of sleep on the brain and behavior, and this is what is often forgotten as society and employers push workers to perform even when they are functioning with lack of sleep. A recent report cited a number of the detrimental effects of lack of sleep to both the brain and immune system. [4] In that same report, it was noted that after periods of extended reduced sleep, neurons begin to malfunction as sleep is needed to regenerate certain parts of the body, especially the brain. Also in an earlier report, it was noted that brain activity is visibly altered following sleep deprivation in that certain patterns of electrical and chemical activity that occur during sleep are interrupted, impeding the brain's ability to function normally.[3] Thus, it is obvious that lack of sleep affects both physical and mental health. Lack of adequate sleep is fast becoming one of the commonest problems in our society today. For example, a recent study carried out in some tertiary institutions in Nigeria revealed that sleep deprivation is a significant pattern among medical students. [5]

There is no doubt that lack of adequate sleep can account for poor performance at work or study; there are obvious life threatening problems associated with human errors of judgment such as traffic accidents. Sleep deprivation obviously account for many of the fatigue related decision making errors that have been responsible for several deaths. One obvious consequence of lack of sleep is that it renders the body and mental faculties less than intact and functional. On the other hand, it has been noted that the quality of sleep is as important as its duration.[4] In addition, sleep is undeniably one of the greatest healing therapies with many benefits; the effects of good and adequate sleep can be seen in improved mental clarity, boosted overall efficiency at work, training and academic exercise, etc.

Methods: A thorough search was conducted on pub med and Google using some of the following key words; sleep; neurophysiology of sleep; current concepts in sleep physiology; sleep and the hypothalamus; sleep and neurotransmitters,*e.t.c.* Information sources consulted included, published works of past researchers, current articles on sleep in conference papers, recent editions of textbooks on neuroscience, articles in seminar papers, reports extracted from newspaper and magazine articles on sleep, reports accessed from the Internet using Search Engines, lecture notes, *e.t.c.*

Concepts

Originally, sleep was regarded simply, as the product of activities in the neural systems in phylogenetically old reticular core of the brain. In those earlier concepts also it was concluded that the preoptic and posterior hypothalamic areas are deeply involved in the central regulatory mechanisms of sleep. In fact, the earlier proposals on sleep referred to the posterior hypothalamus as the 'waking' area in the brain. The lateral hypothalamus and the mammillary bodies were also linked with sleep regulatory functions. In the wake of these earlier concepts, the proposal that sleep was a passive state initiated mainly through withdrawal of sensory input was advocated by earlier workers.

Presently, withdrawal of sensory awareness is similarly believed to be a factor in sleep, but an active initiation mechanism that facilitates brain withdrawal has also been recognized. Thus, both homeostatic factors (factor S) and circadian factors (factor C) are now believed to interact to determine the timing and quality of sleep. [6]

In the sleep model as proposed by another group of workers, the 'switch' factor for sleep is considered to be located in ventrolateral preoptic nucleus (VLPO) of anterior hypothalamus. [7] This area is said to become active during sleep and uses the inhibitory neurotransmitter Gamma Amino Butyric Acid (GABA) and galanin to initiate sleep by inhibiting the arousal regions of the brain. The VLPO is also known to innervate, and can inhibit the awake-promoting regions of the brain, including the tuberomammillary nucleus, lateral hypothalamus, locus coeruleus, dorsal raphe, the laterodorsal tegmental, and pendunculopontine tegmental nuclei. Thus, in the sleep model proposed by this later group of workers, hypocretin (orexin) neurons in the lateral hypothalamus are believed to help to stabilize the 'switch'; when the hypocretin neurons are lost, narcolepsy can result. [7]

Circadian Sleep Rhythm

Among several intrinsic body rhythms modulated by the hypothalamus, is the circadian sleep rhythm. It has been observed that the suprachiasmatic nucleus sets the body's 'clock' to approximately 24.2 hours, with both light exposure and schedule clues entraining to the 24 hours cycle, measured from awakening after one sleep period. According to report by a group of workers, the physiologic mechanism of the circadian rhythm begins when light strikes special cells within the retina of the eye which, in turn, causes the cells to secrete a special hormone that causes the suprachiasmatic nucleus to signal the pineal body to stop secreting melatonin.[8] These workers also noted that melatonin reaches its highest level during sleep, and as the day progresses adenosine accumulates within the brain as the level of melatonin falls. At night fall the inhibitory effects of the retinal secretions on the pineal body are removed, allowing the pineal to begin secreting melatonin once more. [8] Much later, another worker noted that it is the presence of higher melatonin levels within the thalamus and hypothalamus that controls the urge to sleep. [2]

Most workers believe that the nadir of the sleep rhythm is in the early morning. The downswing in circadian rhythm prior to the nadir is thought to assist the brain to remain asleep overnight for full restoration by preventing premature awakening. The morning upswing then facilitates awakening and through the day, acts as a counterbalance to the progressive discharge of the awake neuronal activity. In another observation, it was noted that after the circadian climax in the early evening, the downswing aids sleep initiation.[8] It should be noted that the circadian rhythm of day and night cycle can also serve as a model that can be employed to explore brain chemistry. It is a model that can explain the relatively steady cognitive function throughout wakefulness.

Neurotransmitter Systems

Most of the characteristics of sleep are functions of different brain activities and circuits. For example, the extremely complex interconnecting neurons within the brain stem and the reticular formation provoke EEG desynchronization and arousal when stimulated. Further, there is experimental evidence which show that cells from the reticular formation project to the cortex, but indirectly. Thus, it should be recognized that one of the functions of the cells of reticular formation is to maintain the state of wakefulness in the animal.

The first stage upon falling asleep is the non-rapid-eye movement sleep (NREM), and is thought to be produced by the absence of desynchronizing activity in the ascending reticular activating system. It has been noted that serotonin is involved in the production of NREM sleep; the discharge of the serotonin secreting neurons was linked with the onset of NREM. This observation was supported by the report that drugs that deplete brain serotonin level, such as parachloro-phenylalanine caused insomnia in cats, while administration of 5-hydroxytryptophan which restores the serotonin content of the brain abolishes the effect.[9]

The mechanism that trigger rapid-eye movement sleep (REM) is believed to be located in the pontine reticular formation, but the neurotransmitter substance involved in the production of this sleep is still far from clear. However, it is thought that the locus coeruleus and the norepinephrine-secreting neurons emanating from it play important role in the phenomenon of REM sleep. In an earlier effort to try to explain the production of REM sleep, a group of workers postulated the existence of two neuronal systems that control sleep in the brain stem, each using a different chemical to communicate: one of the neuronal systems use acetylcholine and they are "on" during REM sleep, while the other system uses norepinephrine and serotonin and they are "off" when the acetylcholine neurons turn on. [10]. In that proposal, these workers maintained that acetylcholine neurons send rapid bursts of electrical signals to the cortex, the seat of higher thought and vision, and suggested that acetylcholine may be the very stuff that the REM sleep is made of.[10]

More recently, a study by a group of researchers identified specific clusters of cholinergic neurons in the pons believed to play important role in the activation of REM sleep. These workers called this region in the pons the peribrachial area, and argued that acetylcholine cells in the peribrachial area are quite active during REM sleep.[11] In that report, they maintained that the acetylcholine cells start firing 80 seconds before the onset of REM sleep, and noted further that lesions in the peribrachial area greatly reduced REM sleep.[11]

Neurons in the peribrachial area are known to project directly to the brain stem regions that control eye movements. This obviously suggests that Ach cells in the peribrachial area might play a part in the mechanism responsible for the initiation of the fast scanning eye movements' characteristic of REM sleep. It is also suggestive that cells of the peribrachial area might be a part of the neural network in the mechanism responsible for the emotional aspect in dreams, characteristic of REM sleep stage.

From these accounts above, it is obvious that the subject of the mechanism involved in the production of REM sleep is still far from clear, as no neurotransmitter agent has been earmarked with certainty.

The Ponto-Geniculo-Occipital (PGO) Waves

Very recently a group of workers noted that the first sign of REM sleep is the presence of ponto-geniculo-occipital (PGO) waves, which are bursts of phasic electrical activity that originate in the pons, runs through the lateral geniculate nucleus, and ending in the occipital primary visual cortex. That report noted that the PGO waves occur shortly before the onset of REM sleep, and they argued that it is indicative that the PGO areas might be responsible for the roving eye movements in REM sleep. [11] They further concluded that the PGO wave's areas are probably involved in the mechanism for the visual processing of information in dreams, at least, as by-product of the PGO waves. [11]

One fascinating aspect of REM sleep is the fact that we often experience dreams during this stage of sleep. It is possible that the roving eye movements during REM sleep are related to the scanning of the visual scene of a dream. In other words, we are looking at the surroundings in the dream the same way we do to the surroundings when we are awake. Furthermore, it is possible that activation of the brain areas involved in the control of eye movements, signal whatever mechanisms that are responsible for the visual scenery (visual information) during REM sleep, created by the occipital lobe and the lateral geniculate nucleus when a person is undergoing PGO waves. One very interesting observation recently was suggestive that the brain areas in charge of controlling and planning of body movements, and the areas that receive sensory information (motor and somatosensory cortices) are both active during REM sleep. [11 This observation can also be taken as indicative that the PGO waves probably play major role in the mechanism for the rapid roving eye movements, and the vivid visual experiences (in dreams) characteristic of REM sleep stage. Finally, the report also noted that in REM sleep deprived individuals, the PGO activity take place in the earlier stages of sleep, and this was further proof that the PGO waves have physiological relevance in sleep. [11]

Theories

A number of theories were put forward by workers, mostly in the recent past. Surprisingly the proposals on the subject of sleep by these workers were not necessarily in any effort to explain or examine such issues as neural processes involved in the production of sleep. Instead, the bulk of proposals put forward by these workers were more of speculations on the benefits of sleep; they were more concerned about the vital role of sleep to our daily lives, speculations on the possible risks in sleep, and how the benefits outweigh the risks, etc. Only three of these theories are here mentioned in this review:

Restorative Theory

The Restorative Theory was put forward in 2006, during which a group of workers argued that sleep served as a behavioral state of the body to save energy by lowering our body metabolism. [2] The workers sought to explain that the purpose of sleep was to reorganize and store information, arguing that the cortical neurons that are involved in memory and attentive learning needed to rest in sleep, especially during REM sleep. The workers noted that this probably explains why we feel mentally sharper after a good night's sleep, as compared to how we feel after staying awake all night long. Thus, in Restorative Theory it was hypothesized that REM sleep plays a vital role in memory retention and consolidation, removal of trivial or unwanted information, and storage of important data from memory, all taking place during REM sleep stage. The theory predicts that sleep helps replenish our stores of neurotransmitters, arguing that this is because most cortical neurons decrease their activity during sleep.

Another group of workers hypothesized that slow wave sleep also has some restorative effect, since it appears to be a period of rest for the brain. They noted that the brain areas that are very active during wakefulness show an increase in slow wave sleep. [14] As it has been stated that sleep is generally a time of growth and repair, these workers also noted that there is a rise in certain growth hormones that have been shown to increase during period of slow wave sleep. [14]

Developmental Theory

Some group of workers proposed the **Developmental Theory**, during which they put forward the idea that sleep, especially the REM sleep, play important role in the development of the brain. [15] In support of this proposal, the workers further observed that REM sleep is a major component of sleep for babies in utero and infants.

It was hypothesized that REM sleep activates the visual, motor and sensory areas of the brain. In the brain of babies, it is believed that REM sleep increases the ability of neurons to function properly and to make the correct connections. Observation from lamb fetuses through Plexiglas windows implanted on the uterine walls, showed that during REM sleep fetuses, as a result of not having air to breathe, nevertheless move their chest as if they were breathing. According to these workers, this suggests that REM sleep plays a role in preparing the infant on how to behave in the natural function even before they come out into the world. [16]

Preservation Theory

In an overview, sleep was noted to be so essential that long periods of sleep deprivation eventually results in stress- related deaths. In the Preservation Theory it was stated that sleep (and the desire to sleep at night or under conditions resembling night) are the result of the evolutionary process to keep us away from trouble. Thus, the theory proposes that sleep is an adaptive behavior to keep us away from night and darkness when predator species enjoy advantage in vision and stealth. Workers further argued that over time, the "sleep when it is dark" and "work in the day light" behaviors were amplified by natural selection and are present in the brain neurochemistry. [17]

Since the classical hypnotoxin experiments of Legendre and Pieron in 1910, the existence of some sleep-regulating substances was proposed, and a number of endogenous factors were actually listed. [12] Most of the listed substances were prostaglandins or their synthesis inhibitors, and these factors were believed to be present in the cerebrospinal fluid. It was believed that these multiple endogenous factors are functionally linked, such that sleep regulation involves a complicated mutual interference mechanism among them. The time of that report heralded the period of more intense efforts in the search for a better understanding of the neurophysiologic factors in sleep.

In view of the growing number of proposed and suspected neurotransmitter agents in the mechanism of sleep regulation, it has become obvious that full knowledge of the neural processes in the mechanism of sleep is still far from clear. Recent reports in the proposed neural mechanisms of sleep appear to speculate more on the possible roles of the PGO waves in REM sleep. On the whole, the actual neural processes involved in the production of REM sleep appear to be still far from very clear. Thus, it can be stated that the actual factors in the neurophysiologic mechanisms of sleep (and dreams) are yet far from full understanding.

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