Current Concepts of Neurophysiological Factors in Central Regulatory Mechanism of Rapid Eye Movement Sleep: A Review

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ABSTRACT

Rapid eye movement (REM) sleep is physiologically different from the other phases of sleep. Most of the postulations by researchers have speculated on the role or significance of the REM sleep stage. Most of the proposed roles that are attributed to REM sleep in vital brain functions are still mere speculations. For example, there is no clear evidence to suggest that REM sleep may play a particular role or may mediate a proposed mechanism for a specific brain function. The aim of this review is to identify those vital processes in brain function believed to be REM sleep driven, and which have featured prominently in the works of researchers in the past. The method adopted in this review was that of information gathering from sources which included published works of past and present researchers, articles on sleep presented in seminars and conferences, published articles on sleep, lecture notes on sleep physiology, textbooks of current editions in neuroscience, reports and published works accessed from the Internet using search engines such as Google, Mamma, PubMed etc. The postulations and hypothesized roles of REM sleep in vital brain function have been clearly highlighted in this review. It is concluded from this review that neural factors involved in the central mechanisms of REM sleep are not fully understood. Nevertheless, information noted in this review lends further credence to the notion that REM sleep is crucial and probably the most important sleep phase. It is hoped that facts in the proposals and postulations chronicled in this review will serve as important information source for neuroscientists and different researchers engaged in the subject of sleep.

Keywords: Central regulation, crucial phase, REM sleep, vital brain functions

Conceptos actuales de los factores neurofisiológicos en el mecanismo central de regulación del sueño de movimiento ocular rápido: una revisión

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RESUMEN

El sueño de movimiento ocular rápido (MOR) es fisiológicamente diferente de las otras fases del sueño. La mayoría de los postulados por los investigadores ha especulado sobre el papel o la importancia de la etapa de sueño REM. La mayoría de los roles propuestos que se atribuyen al sueño MOR en las funciones cerebrales vitales son todavía meras especulaciones. Por ejemplo, no hay ninguna evidencia clara para sugerir que el sueño MOR puede desempeñar un papel particular o puede mediar un mecanismo propuesto para una función cerebral específica. El objetivo de esta revisión es identificar los procesos vitales en la función del cerebro que se cree que son impulsados por el sueño MOR, y que han ocupados lugares destacados en los trabajos de los investigadores en el pasado. El método adoptado en esta revisión fue la compilación de información de fuentes que incluyen obras publicadas de investigadores del pasado y presente, artículos sobre el sueño presentados en seminarios y conferencias, publicaciones de artículos sobre el sueño, notas de conferencias sobre la fisiología del sueño, libros de texto de ediciones actuales en neurociencias, reportes y publicaciones accedidos a través de la Internet utilizando dispositivos de búsqueda tales como Google, Mamma, PubMed. etc. Los postulados y papeles hipotéticos del sueño MOR en la función

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DOI: 10.7727/wimj.2014.215

vital del cerebro se han destacado claramente en este informe. A partir de este estudio, se concluye que los factores neurales que intervienen en los mecanismos centrales del sueño MOR no se entienden cabalmente. Sin embargo, la información destacada en este estudio da mayor credibilidad a la idea de que el sueño MOR es crucial y probablemente la fase más importante del sueño. Se espera que los hechos en las propuestas y postulados relatados en esta revisión, servirán como fuente de información importante para los neurocientíficos y diferentes investigadores en el tema del sueño.

Palabras claves: regulación central, fase crucial, sueño MOR, funciones cerebrales vitales

West Indian Med J 2016; 65 (2): 346

INTRODUCTION

One of the earliest definitions of sleep stated that it was a state of natural unconsciousness from which a person can be aroused. One other earlier definition designated sleep as purely a passive state in which the brain is resting. A much later definition offered that sleep may be regarded as a naturally recurring state of relatively suspended sensory and motor activity in animals, characterized by total or partial unconsciousness and the nearly complete inactivity of voluntary muscles. This later definition or explanation may be regarded as more scientific and appears to be the more adequate explanation of the subject of sleep.

Essentially, sleep is a behavioural state, and is believed to be present in all species of animals including fetuses, reptiles, amphibians, fish, birds *etc*. Normal sleep is distinguishable from quiet wakefulness by a decreased ability to react to stimuli. It is common knowledge that normal sleep is generally more easily reversible than coma and as pointed out by some authors, regular sleep is essential for survival (1). Others have also noted that sleep is a state, specifically required by the body as part of homeostatic regulatory and repair mechanism, (2, 3). In another observation, it was noted that sleep affects both mental and physical health, hence, it is essential for the normal functioning of all the systems of the body (4). In humans, it was estimated that an individual spends approximately one-third of his lifetime in sleep. At present, frequent complaints of inability falling asleep, inability staying asleep, lack of adequate sleep, total lack of sleep *etc* are fast becoming some of the greatest problems and sleep disorders in our modern society.

For many years, sleep was believed to be purely a passive state of the body in which the brain was resting. However, it is now known that sleep is a dynamic and complicated condition during which the brain is quite active. A few questions seeking adequate explanations have for years remained the subject of intensive research. For example, among the queries that have for some time occupied the attention of researchers are: Why do we sleep? Why do we spend so much time sleeping than any other single activity? Why do we abandon vigilance and render ourselves vulnerable during sleep? How do the benefits of sleep outweigh the risks *etc*. The pondering on these questions and related issues have led to the proposition of a number of theories. Some of these theories are here briefly presented.

The phenomenon of rapid eye movement (REM) sleep and its association with dreaming was discovered in 1953 at the University of Chicago by a medical student, with the assistance of the work previously done by another student in 1952 (5). At present, REM sleep is still considered the deepest stage of sleep, and it is well documented that the relative amount of REM sleep in the individual varies considerably with age (6, 7).

CONCEPTS

Sleep cycle

The predictable cycling of sleep and the reversal of relative external unresponsiveness are features that assist in distinguishing sleep from other states of unconsciousness. The brain gradually becomes less responsive to visual, auditory and other environmental stimuli during the transition from awake to sleep, and which is considered by some authors to be stage 1 sleep.

Advances in electrophysiology have made possible the mapping of normal sleep into five distinct stages. One important discovery followed the realization that it is the firing of cortical neurons at different intervals, at different times and at different strengths that provide the defining features of the different stages of sleep from other intrinsic brain activities. Thus, it was hypothesized that sleep is not a random process; that marked the beginning when it was noted that sleep is a well organized cyclical process of stages 1–4 of sleep, followed by the REM sleep episode. In the cyclic phenomena of these organized stages, once the REM sleep is achieved, the cycle repeat itself (8). It was observed that REM sleep typically occupies about 20–25% of total sleep time in the human (this is very prolonged in the very young: the newborn and infants) and accounts for up to 90–120 minutes of a total night's sleep (8). It is noteworthy that a single REM sleep cycle lasts about 20–30 minutes and occurs at about ninety-minute intervals in a healthy adult person. This means that in an eight-hour sleep, we might experience four or five REM sleep episodes or stages.

Factors in neuronal mechanisms of rapid eye movement sleep

Rapid eye movement sleep is named for the rapid movement of the eyeballs that occur in this sleep stage. About ninety minutes after the onset of sleep, and following stage 4 of non-REM sleep, the synchrony of the brain waves is suddenly interrupted by desynchronized activity, similar to what obtains when we are awake (alpha and beta waves activity). The (EEG) patterns of REM eye movement sleep (waves of faster frequency and lower amplitudes than of the non-NREM stages 2 and 3) are superficially similar to those of drowsiness (stage 1 of non-REM sleep). Thus, whereas the non-REM sleep model is divided into four stages, REM sleep is usually referred to as a single phase despite the fact that very complex sets of fluctuating neural processes of activation take place in this sleep stage. Therefore REM sleep is physiologically different from the other phases of sleep collectively referred to as non-REM sleep. It is believed that the central mechanisms involved in REM sleep are linked to a parasympathetically mediated tonic component and a sympathetically mediated phasic component. According to the sleep model proposed by Stevens (9), the phasic portion of REM sleep is characterized by skeletal muscle twitches, increased heart rate variability, pupillary dilatation and increased respiratory rate.

One other neural process displayed in REM sleep is the phasic pontine-geniculo-occipital (PGO) spikes. Several studies show that the PGO spikes are projected to the lateral geniculate and other thalamic nuclei, and to the occipital cortex. It was noted that bursts of PGO spikes precede rapid eye movements by several seconds, suggesting that dreaming is caused by PGO waves. A further support for this is the activation of the occipital lobe and lateral geniculate nucleus, areas that process (create, or fill-in) visual information. In this regard, it is possible that the activation of these areas involved in the control of eye movements also translate to the responses to visual scenery created by the occipital lobe and lateral geniculate nucleus. This means that the person undergoing PGO waves could be having visual experiences that are visually scanned. It is therefore also possible that the PGO waves are the very stuff generating the vivid visual experiences of dreams and the rapid eyeball movements typical of REM sleep stage.

A number of studies compared the eye movements while awake with the eye movements in REM sleep and found that there was almost no disparity between the two. In his scanning hypothesis of REM sleep proposal, Hobson and his team of workers hypothesized that the eye movements during REM sleep are related to the scanning of the visual scenery of the dream, similar to the way we look at the surroundings when awake (6). Research findings have confirmed that the brain areas that control the planning of body movements and the areas that receive sensory information (motor and somatesthetic cortex) are both active during REM sleep, thus, the vivid sensation of movements and the feelings in dreams indicate that we actually feel the dream as though it is real (1).

Essentially, activity in cortical neurons during REM sleep is quite similar to that in the waking state and for this reason, the REM sleep stage was described as paradoxical sleep; the electrooculogram (EOG), which picks up muscular activity of the eyes, senses that the eyeballs of the sleeper are moving rapidly, and at the same time, the electromyogram (EMG) senses no activity in the rest of the body muscles (atonia). Data from a number of studies have confirmed a state of greatly decreased muscle tone in the entire body muscles (except for the diaphragm, a key muscle for maintaining breathing) during REM sleep. This decrease in muscle tone and subsequent suppression of spinal reflexes are indicative of heightened motor neuron inhibition during REM sleep. From the results of a number of animal model studies, the locus coeruleus in the brainstem appears to be the source of this motor neuron inhibition. Thus, REM sleep is a state of diffused bodily activation; in mammals, REM sleep stage can be mapped out from the concurrence of three events: low-voltage mixed-frequency EEG, intermittent REM dreams sleep and suppressed muscle tone.

The sleeper in REM sleep is believed to be mostly disconnected from the outside world; there is a complete shutdown in the release of certain neurotransmitters, mainly the monoamine transmitters-norepinephrine, serotonin and histamine. The resultant rapid depletion of the monoamine transmitters is believed to be the main trigger in the associational signals for the onset of rapid low-voltage EEG activity and the low muscle tone (atonia) in the entire body muscles (6, 10, 11). It was suggested in one earlier report that the loss of muscle tone in REM sleep was to prevent the animal from fully awakening unnecessarily, thus, allowing it to return easily to deeper sleep (12). However, it has also been proposed that loss of muscle tone in REM sleep is in place to prevent us from acting out our dreams, and keep us away from trouble (13).

Researchers have successfully demonstrated that blood flow to the brain is generally increased during REM sleep (14) and polysomnographic records of REM sleep revealed some measureable genital activities (ie in males, full or partial penile erection and in females, vaginal secretion). However, research findings have confirmed that genital activity in REM sleep may not necessarily mean that the sleeper is experiencing a dream of sexual content.

Centres in the mechanism of rapid eye movement sleep

There is considerable evidence which shows that neural processes in brain activation during the REM sleep are localized to several areas of the brainstem and thalamus, and the structures involved in the regulation of emotions (the limbic structures). Specific clusters of cholinergic neurons located in the pons were shown to play an important role in the activation of REM sleep. Notably, the peribrachial area (a region in the pons) is believed to be the actual site for the activation of REM sleep because cells in this region are known to be very active during REM sleep. Specifically, acetylcholine cells (located in pontine tegmentum) are at present referred to as 'the REM-on cells' because they are believed to be an integral part of the neuronal mechanism in the activation of REM sleep stage. Acetylcholine is released in high levels as a result of wakefulness and alertness, but it is also found in high levels during REM sleep. These findings appear to strongly support the report which noted that people exposed to organophosphate insecticides (*ie* acetylcholine agonists) spend more time in REM sleep than individuals who are not exposed to these toxins (1). These observations and similar reports finally led to the conclusion that acetylcholine is probably the neurotransmitter agent mediating REM sleep as well as arousal mechanism.

One impressive demonstration of REM sleep activation was carried out using the firing rates of individual cerebral neurons in experimental animals. This study revealed that during REM sleep, the firing rates of brain cells exceed the firing rates in non-REM sleep, and often equals or surpasses those of wakefulness (1). The authors also demonstrated that REM sleep displays some localized areas of neuronal deactivation, particularly in the frontal (anterior) and parietal (posterior and lateral) regions of the cerebral cortex. The reasons for the disparity in the distribution patterns of activations and deactivations remain hypothetical, but it has been suggested that these responses in the brain cells may represent the processes involved in the generation of REM sleep and production of dreams.

Proposals of function

Knowledge about the central processes involved in the production of REM sleep are still very hazy and far from clear. In spite of several studies to date, very little data are available on the actual neural mechanism of REM sleep and the mechanism governing the transition between one sleep stage and another. A number of theories have been put forward in the quest for a clearer knowledge of the brain processes in the production of REM sleep, thus, to ascertain the possible, actual or potential benefits of REM sleep. Some of these theory proposals are presented here.

Theories related to memory

One of the earliest reports noted that REM sleep is important for consolidation of procedural memory and spatial memory (12). Another study also noted that certain memories are consolidated during REM sleep (15). These views on REM sleep functions in memory consolidation appear to be consistent with most reports and research postulations. In one of these proposals, the authors hypothesized that by virtue of its inherent spontaneous activity, one function of REM sleep "is to remove certain undesirable modes of interaction in the networks of cells in the cerebral cortex", a process characterized as "unlearning" (12). These authors further explained that as a result of the "unlearning" process, memories which are considered relevant (*ie* whose underlying neuronal substrates are strong enough to withstand spontaneous, chaotic activation) are further strengthened in the brain, whilst weaker, transient or "noise" memory traces disintegrate. These views emphasizing the importance of REM sleep, in memory consolidation were further supported by reports which noted that REM sleep through its processes, adds creativity by allowing neocortical structures to reorganize associative hierarchies in which information from the hippocampus may be reinterpreted (16).

Theories related to brain development

A number of proposals were generally held as views representing the primary function of REM sleep. One of these theory proposals put forward was the ontogenetic hypothesis of REM sleep. According to this theory, the REM sleep stage can also be called the active sleep stage in neonates, and is particularly important to the developing brain as it provides the neural stimulation that newborns need to form mature neural connections for proper nervous system development (17). A number of studies also investigated the effect of active sleep (REM sleep) deprivation in the early life. Resulting from this study, it was hypothesized that sleep deprivation can result in behavioural problems, permanent sleep disruption, decreased brain mass and an abnormal amount of neuronal cell death (18). This theory was further supported by facts noted in humans which showed that the amount of REM sleep decreases progressively with age (the development of the central nervous system being completed in the mature adult brain), and these data were also demonstrated in other species of animals. However, the significance of the ontogenetic hypothesis of REM sleep in the function of the mature adult brain is yet to be fully ascertained. Meanwhile, it was suggested that REM sleep may provide the vital source of sustained spontaneous stimulation in neurogenesis of the fully matured adult brain (11).

Defensive immobilization theory

According to Synder in 1966, REM sleep is an evolutionary transformation of the tonic immobility reflex, a well documented defensive mechanism (19). This reflex is also known as animal hypnosis or death feigning hypothesis, and it functions as the last line of defence against an attacking predator. The death feigning reaction consists of the total immobilization of the animal, hence, it actually appears to be dead. After a number of intensive studies, a group of authors came up with another proposal which also was largely in agreement with the animal hypnosis hypothesis. In their observations, these authors hypothesized that the neurophysiologic basis of animal hypnosis (death feigning) reactions share strong affinity to REM sleep, both reactions being essentially precursors of dreams, exhibiting brainstem control, paralysis, sympathetic activation and thermoregulatory changes (20).

Claims of the benefits of REM sleep

It has been observed that if REM sleep is repeatedly interrupted in a person, the individual will compensate for it with longer REM sleep at the next opportunity (the "rebound sleep" effect). Indeed, a number of researchers have argued that the perpetuation of complex brain process such as REM sleep indicate that it serves to fulfill important physiological needs vital for the survival of the animal. Within the period of these observations, a number of unsubstantiated claims were put forward along with other proposals. Some of the unsubstantiated observations were claims that prolonged REM sleep deprivation led to death in experimental animals; claims that several behavioural and physiological abnormalities were seen in both humans and experimental animals due to loss of REM sleep; claims of loss of REM sleep which resulted from various natural and experimental infections; claims that the survivability of experimental animals decreased when REM sleep was totally attenuated during infections (this was considered as proof that the quality and quantity of REM sleep is essential for normal body physiology). Thus, it can be argued that these observations (despitebeing mostly unsubstantiated claims) have further re-emphasized the possible or potential benefits of REM sleep.

According to Snyder's hypothesis put forward in 1966, Rapid eye movement sleep activates an animal periodically so it can scan the environment for possible predators size (19). However, authors were later to identify the flaws in this hypothesis, noting that it failed to account for the muscle paralysis (or muscle atonia) in REM sleep. Other researchers also ascribed some benefits to REM sleep with their observations that it lubricates the cornea, warms the brain, stimulates and stabilizes neural circuits that have not been activated during waking state and creates internal stimulation to aid development of the central nervous system (21). The authors also noted that most autonomic variables (*eg* heart and respiratory rates) exhibit relatively high rates of activity and variability during REM sleep (21). Interestingly, one positive consequence of lack of REM sleep was recorded when it was successfully demonstrated that some symptoms of depression could be suppressed in humans through REM sleep deprivation (22).

CONCLUSION

Research findings and a number of reports from polysomnographic studies show that REM sleep is a complex brain process. These research accounts, proposals and postulations brought into focus in this review have further highlighted the importance of REM sleep in relation to brain function. There is no doubt from the indications in this review that many vital brain functions and processes are probably REM sleep driven. For example, the hypothesized role of REM sleep in the neuronal creativity of memory function (*eg* stimulation of hippocampal neurogenesis), learning, emotions *etc*, point to the fact that this sleep stage is crucial and of great survival value to the animal. In fact, in view of its hypothesized roles and importance in vital brain function, researchers now believe that REM sleep is an evolutionary adaptation. These facts highlighted and assembled in this review have significantly demonstrated the crucial nature of REM sleep stage, and these are consistent with the notion that REM sleep is probably the most important sleep stage.

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