

Concepts of Neurophysiological Factors in the Central Regulatory Mechanism of Non-Rapid Eye Movement Sleep: A Review

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Received date: Nov 16, 2016 Accepted date: Jan 24, 2017 Published date: Jan 31, 2017

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Abstract

Objective: It is now fully ascertained that the generation of non-rapid eye movement sleep (NREM) involves vital brain processes achieved through complex interactions of underlying neurophysiological factors, including those of the mechanism for the production of the behavioral expressions of NREM sleep. These central processes in the mechanism of NREM sleep are still far from clear and are subject of much speculations and even controversy. It was the aim of this review to identify and assemble those factors in brain function that informed current research postulations of workers in the subject of the production of NREM sleep.

Methods: Information gathering adopted in this review included, articles and published research works, seminars and conference articles on sleep, information from current textbooks in neuroscience on sleep, lecture notes in behavioral neurophysiology and biology, and articles and reports on sleep accessed from the Internet using search engines such as Google, PubMed etc., were all sources of information consulted.

Results: The significance of specific neurotransmitter systems – Serotonin, GABA and Adenosine, in the proposed central mechanism for the production and behavioral expressions of NREM sleep have been clearly highlighted in this review. Facts noted in this review successfully sensitized the attention of research to the growing profile of the more recently identified Metabolic Energy substrates Drive in the proposed possible central mechanism for the generation of NREM sleep stage.

Conclusion: Research postulations and proposals assembled in this review appear generally to support the notion that different brain processing networks and neurochemical units are probably involved in the production of NREM sleep and other distinct states of sleep. It is therefore concluded from this review that probably different neuronal pathways and systems make up specific vital brain processes for the production and expressions of NREM sleep stage, and these central processes are still far from fully understood with certainty.

Key words:

NREM Sleep; Neurophysiological factors; Central regulatory mechanism

Introduction

Sleep as a subject, has undergone several definitions and re-definitions in the past years, with different groups of workers coming up with different approaches to the subject. Neuroscientists studied sleep as part of psychology and medicine. Meanwhile, the initial problem started with the fact that sleep was viewed and defined as a state of consciousness and not a physiological state. The problem of ascertaining a comprehensive definition of sleep became even more complicated because there was no clear demarcation or understanding of the minimum set of events that constitute sleep and distinguishes it from other states of partial or non consciousness. Nevertheless, the study of sleep appeared to receive a big boost with advances in technology from the second half of the twentieth century. The major contributors to the modern concepts of the subject of sleep and waking states evolved from the discovery of electroencephalogram in 1929 by Hans Berger, and the landmark discovery of the Ascending Reticular Activating system. Thus, sleep was then seen as a behavioral state in

the animal, and was known to be present in all species of animals including fetuses, birds, fish, reptiles and amphibians. In one earlier concept, sleep was regarded as the natural state of bodily rest during which the brain is resting, as part of the daily routine in everyone. This earlier concept gave birth to some erroneous concepts which regarded sleep as the state of natural unconsciousness from which an individual (or the animal) can be aroused. Nevertheless, among the more modern proposals was the definition which regarded sleep as the deactivation of the cerebral cortex and thalamus, expressed by the near lack of response to sensory inputs during sleep [1]. However, this definition suffered some defects of neurophysiological facts and was later invalidated because it was a known fact that both regions of the brain (cortex and thalamus) are active in some phases of sleep; in fact, only the thalamus may be assumed to be deactivated in the sense of transmission of sensory information to the cortex. The effort to ascertain a more comprehensive definition of sleep was apparently addressed through the observation method of the overall brain activity in characteristic electroencephalogram (EEG) patterns during sleep [2], and these concepts later gave way to the definition which regarded 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

[3]. This later explanation appears to be even more scientific and the more comprehensive and adequate for the purpose of the present discussion on the subject of none-rapid eye movement (NREM) sleep in this review.

It is now known that sleep is not a merely passive state in which the brain is resting or quiescent. It has become clear that cortical functions in sleep are characteristically dynamic and complicated condition during which the brain is quite active, and that certain vital processes in brain function are driven by certain stages of sleep. For example, there are observations attributed to specific stages of sleep which included: decrease of sympathetic activity and increase of parasympathetic activity in NREM sleep (3), increase in heart rate and blood pressure accompanied by decrease in homeostatic responses and muscle tone in rapid eye movement (REM) sleep [4].

Normal sleep is partitioned into the cyclic alternations of NREM sleep and REM sleep stages, clearly indicating that each sleep stage repeats itself in a characteristic pattern in the course of a night's sleep. Thus, this recurring phenomenon in which each sleep stage repeats itself in the course of the night, is clear demonstration that sleep is not merely a state of neural inactivity in which the brain is quiescent. Research findings have shown that non-rapid eye movement sleep (NREM) occupies about 75-80% of total sleep period in the human. Several studies have also shown that Slow-Wave sleep (SWS) is made up of the deepest stage of NREM sleep, and is often referred to as the deep sleep. Although muscles are not paralyzed as in REM sleep, research findings have confirmed that the highest arousal thresholds (i.e. difficulty of awakening) are generally observed in the stage 3 of the NREM sleep, and because muscles are generally not paralyzed, sleepwalking is possible in a person in NREM sleep. Reports from recent studies indicate that Slow-Wave sleep (SWS) is a highly active state of the brain, unlike the state of quiescence of the brain as previously thought. Although it has been widely reported that NREM sleep is characterized by decreased global and regional cerebral blood flow, data from brain Imaging Studies indicate that blood flow to parahippocampal gyrus increases during NREM sleep. Among several brain activities that have been studied to date, sleep spindles and K-complexes have been shown to be unique to NREM sleep, and up to date there is no reliable answer or clear understanding of what these waves activities mean. There are indications from recent study and reports which show that regional brain activities are influenced by the waking experiences of the recent past in some stages of NREM sleep [5]. It has also been observed that mental activities that take place during NREM sleep are generally thought-like. Furthermore, increased secretions of growth hormone in some parts of the brain have been demonstrated during NREM sleep, and this was shown to be indicative that there are increases in the firing rate and metabolism in these cortical cells [5]. These aforementioned facts offered the background and the basis for the follow-up working hypothesis to address the speculations that the memory encoding regions of the brain (i.e. information encoding and recall capacity of the hippocampus) are generally activated, and not functionally dormant during NREM/Slow-Wave sleep stage as previously thought [5].

Proposals and Research Hypotheses

Neurotransmitter systems implicated in NREM sleep

It has been noted that the anterior hypothalamus and adjacent forebrain areas are important in the production of NREM sleep, as are the thalamus, dorsal raphe and nucleus tractus solitarius. Serotonin

and GABA are now believed to play important roles in the regulatory mechanisms of NREM sleep, and they are known to be densely located in these regions. There is enough evidence to suggest that serotonin (5-HT) found in raphe neurons of the brainstem are involved in the central mechanism of sleep onset (Stage 1 of NREM sleep). Thus, the discharge of the serotonin secreting neurons was linked to the onset of NREM sleep. It was noted that insomnia occurred when the serotonergic cells in dorsal raphe nucleus was lesioned, while MAO Inhibitors (specific for 5-HT) enhanced NREM sleep [6]. In another report, it was noted that substances within the biosynthetic pathways of serotonin (such as tryptophan and vitamin B6) facilitated sleep onset (i.e., Stage 1 of NREM sleep) [7].

Several recent studies have shown that the inhibitory neurotransmitter, GABA, is released in highest amounts during NREM sleep [8]. GABA secreting neurons have been demonstrated throughout the basal forebrain, hypothalamus, thalamus, brainstem and cortex. Workers have shown conclusively that the ventrolateral preoptic (VLPO) cells contain GABA and Galanin, and that these transmitters play important role in the mammalian brain by attenuating the ascending monoaminergic arousal system activity during sleep [8]. Thus, it is obvious from these findings that the ventrolateral preoptic (VLPO) neurons are sleep promoting by some reciprocal inhibitory interactions and activity with the waking systems. It was then hypothesized that the reciprocal inhibitory exchanges between the major ascending monoaminergic (arousal) neuronal group and the sleep-inducing VLPO neurons act on a feedback loop model; when the monoamine nuclei discharge intensively during wakefulness, they inhibit the VLPO group, and when the VLPO neurons fire rapidly during sleep, this blocks the discharge of the monoamine cells group. Thus, the two halves of the circuit strongly inhibit each other to produce two stable discharge patterns-On or Off [8]. The research hypothesis demonstrated in this proposed sleep model may have helped to clarify why the sleep-awake transitions are relatively abrupt, and changes between sleep and arousal occur infrequently and rapidly.

There are pieces of evidence to show that hypnotics such as benzodiazepines (diazepam or triazolam) and barbiturates tend to work by potentiating GABA mediated inhibitory processes, thus, causing hyperpolarizations and reduced cell firing. These drugs shut down neurons in the reticular activating system, thereby inhibiting transmissions projected to the cortex and thalamus. In the overall, hypnotics have been noted to increase total sleep time, decrease sleep latency, decrease the duration of stages 3 and 4 of NREM sleep and decrease the number of awakenings [9]. Withdrawal from these drugs (hypnotics) resulted into insomnia and REM sleep rebound fairly quickly [9].

Brain areas implicated in the mechanism of NREM sleep

Hypothalamus: During the period of initial speculations on the actual role of the hypothalamus in the production of NREM sleep, workers proposed a Two-Process Model of sleep regulation to explain the homeostatic and circadian drives for sleep [10]. In the functional organization of this setting which is also under the control of hypothalamus (HT) and suprachiasmatic nucleus (SCN), the two process sleep model was of parallel mechanisms described as Process S (homeostatic) and Process C (circadian), respectively. The homeostatic component is believed to be driven by a substrate or protein which registers a homeostatic "need to sleep" during periods of extended wakefulness that is subsequently relieved during sleep. It was

hypothesized that the sleep model is driven by the pressure build-up of adenosine accumulation and the circadian rhythm of 24 hr cycle in the body. According to this proposal, the slow wave density of adenosine increases through the night and then drops off at the beginning of dawn, while the circadian rhythm is like a sinusoid; the pressure to sleep (towards the onset of NREM sleep) was maximum when the difference between the two was highest. However, a few years later another group of workers proposed a completely different sleep model known as Opponent Process Model [11]. In the working hypothesis of this later sleep model, these workers observed that the two parallel mechanisms as earlier described in the Borbely's Two-Process Model of sleep [10], actually opposed each other in the production of NREM sleep. Thus, according to this Opponent Process Sleep Model, the SCN enhances wakefulness and opposes the homeostatic rhythm, and the homeostatic rhythm is regulated via a complex multisynaptic pathway in the hypothalamus to shut off wakefulness system [11]. Thus, both systems mutually produce the critical effects characteristic of NREM sleep and wakefulness. However, it is noteworthy that the underlying mechanisms in these proposed sleep models are still far from clear. Nonetheless, it was suggested that both sleep models actually have some validity to them [10,11]. Meanwhile, a much later theory also maintained that the inhibition of NREM sleep by REM sleep could play significant role, hence, the two sleep processes or mechanisms add flexibility to the simple circadian rhythm and could have evolved as an adaptive measure.

Thalamus: Most of the known brain activities in sleep have been attributed to the thalamus and there appears to be pockets of evidence to suggest that a thalamic mechanism may play a critical role in Slow-Wave sleep. Pursuant to this idea, a group of workers proposed a Thalamic Pacemaker hypothesis which holds that two primary oscillations of slow spindles and delta waves are generated by both the thalamus and cortex reciprocally in NREM sleep [12]. Since sleep spindles can be generated only by the thalamus, it proves this to be very significant because inputs from the thalamus is critical in sleep onset (NREM sleep Stage 1); it was noted that when the change is from tonic to the phasic mode of the pacemaker oscillations in the neural circuit, it denotes the linking of parts of the cortex in the co-ordination of sleep onset (NREM sleep Stage 1).

Brain Stem Systems: In one of the research proposals, it was hypothesized that the reticular activating system through three groups of neuronal systems in the brainstem-pedunculopontine nucleus, locus coeruleus and raphe nucleus-act via two pathways, mainly: the cholinergic pathway which clears the system for the thalamocortical transmission [13] and, the monoaminergic pathway which by projecting to the hypothalamus and cerebral cortex, shuts down the arousal systems to activate the NREM sleep phase [14]. Considerable evidence suggest that the neural systems concerned with sleep and waking states are in the brainstem, and several studies have shown that there are neural elements in the brain stem which inhibit neuronal communications to turn off the arousal systems during sleep. A research sleep model proposal was later put forward by some workers, known as Sleep Process S [15], and this model later formed the basis for the Sleep-Generating Systems Hypothesis of the brainstem reticular formation. In this model, Sleep Process S is regulated by neurons that shut down the arousal systems of the brain stem, thus, allowing the brain to fall asleep (NREM Stage 1). There was the suggestion that many of the neurons that initiate NREM sleep by inhibiting the arousal systems are also found in the preoptic area of the hypothalamus and loss of these nerve cells lead to profound insomnia [15]. There are also proposals that provided evidence to the fact that among the

mechanisms of the sleep-generating neurons in the brainstem are: activation of inputs from the lower brainstem centers that relay information about the state of the body including emotional and cognitive areas; activation of inputs from the circadian system which allows the awake-sleep system to synchronize with the day-night cycle, but also to override this cycle when it is necessitated by the needs; activation of the cholinergic pathways to the thalamus for the characteristic EEG patterns [16]. Another group of workers also noted the possibility of the state of parasympathetic dominance during NREM sleep [17].

Energy molecules drive hypotheses

In general, sleep is considered a behavioral state in the animal, governed by some central control mechanisms. There is accumulating evidence which suggest that NREM sleep might be a fundamental property of local neuronal networks since it can be initiated at lower brain assemblies, and only later may become consolidated by general cortical mechanisms. It has been observed that in humans, NREM sleep in each local cortical column can be initiated by metabolically driven changes from manufactured molecules of sleep-regulating substances produced by neuronal activity during wakefulness-like activity. It is thought that the process may involve increased electrical activity, blood flow, extracellular levels of ATP, extra and intracellular levels of adenosine, all of which decrease the intracellular ATP level, and this may drive individual columns to enter a sleep-like activity state [7]. It was further noted that once a sleep state was reached this process would be reversed and the cortical columns become prepared for wakefulness [7]. The possible role of astrocytes as potential mediators in the adenosine sleep mechanism was also proposed [18]. It was suggested that adenosine, while acting in the basal forebrain, is a key mediator of homeostatic control of sleep expression [6]. Some of these proposals and conclusions were based on the earlier suggestion that increased adenosine release accompanies the accumulation of the need to sleep [19]. Thus, based on simple energy demand, and since the cerebral cortex-thalamus unit is a large part of the human and mammalian brain, it was considered that an awake state for long periods of time was obviously apparently very expensive, hence, energy economy by the brain during NREM sleep is one of the prevalent hypotheses to explain the pressure for going into the NREM sleep [20].

It has been observed that during periods of wakefulness, glycogen (the body's principal store of energy) becomes exhausted [21]. It was also observed that as glycogen is broken down into adenosine, extracellular levels of adenosine begin to accumulate in the basal forebrain [22], leading to the replenishment and recovered sleep [21,23]. Experimental sleep models have shown that the injection of adenosine or an adenosine A1 receptor agonist into rat's basal forebrain or cat's VLPO, respectively, promoted sleep by inhibiting multiple awake-promoting regions of the brain or by exciting sleep promoting cells groups [24,25]. Recent evidence have confirmed that the sleep-promoting effects of adenosine is further enhanced through its actions at the A1 receptors production cites [18].

Theories of NREM sleep

A number of theories were put forward by workers in the effort to conceptualize some of the central neuronal factors in NREM sleep, but with very little data. Unfortunately and surprisingly also, most of these theories failed to address the issue of ascertaining the actual mechanism involved in the generation of NREM sleep, and production of the behavioural expressions. Most of the theories were mainly

revised proposals and redefinitions expressed in the speculations that sought to explain or reposition the benefits of NREM sleep. For example, it was hypothesized that slow wave sleep has restorative effects since it appears to be a period of rest for the brain [26]. In another proposal, some workers further noted that brain areas that are very active during wakefulness show an increase in slow wave sleep with a rise in certain growth hormones that have been shown to increase during period of NREM sleep [26,27].

Conclusion

Although the processes of sleep and waking states have generally been attributed to the thalamus, hypothalamus, brainstem structures and their interaction with the cortex, advances in knowledge of the neurophysiology of distinct brain systems clearly indicate that central processes in the mechanism of various sleep stages in a subject have become even more complex than previously conceived and are still far from full understanding.

Recent insights into the neurophysiological patterns in various sleep stages indicate that different brain processing networks and neurochemical systems are probably involved in the different sleep states. Thus, it is possible that specific neuronal pathways and transmitter systems that make up the ascending arousal systems and centered in the hypothalamus, interact with sleep active neurons in the VLPO area to produce NREM sleep and other distinct sleep states with characteristic abrupt transitions.

NREM sleep is associated with synchronized EEG patterns in which unique and specific neurophysiological events take place (e.g., Sleep spindles, K complexes, Slow-wave activity etc.). It is possible that the thalamus and cerebral cortex are absolutely necessary for the expression of the most significant bioelectrical and behavioral events of NREM sleep, whilst other structures like the basal forebrain, cerebellum and brainstem, may modulate NREM sleep but are not necessary for the actual generation of the bioelectrical and behavioral events accompanying the expressions of NREM sleep.

It is the expectation that future steps in understanding the neural processes in brain circuitry underlying the production of NREM sleep may lead to less speculations on the actual mediatory roles of Serotonin, Adenosine and GABA in the production of NREM sleep, and provide greater insight into the underlying mechanisms to identify discrete neuronal substrates involved in the generation of NREM sleep. It is hoped that information assembled in this review may serve as important information source for researchers and various neuroscientists engaged in the efforts to obtain a clearer understanding of the central factors in the neuronal mechanism of NREM sleep.

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