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The Regulatory Role of Sleep Hormones, Neurotransmitters, and Gene Expression in Rapid Eye Movement Sleep

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Abstract:

Rapid Eye Movement (REM) sleep typically initiates approximately 90 minutes following the onset of sleep. REM sleep is crucial for memory consolidation and learning. It also supports physical recovery and promotes cell regeneration, neurotransmitter transmission, and immune function. The regulating function of REM sleep remains ambiguous despite numerous advancements in its investigation. The absence of neurotransmitter receptors reduces REM sleep, and altered environmental conditions have a corresponding effect on REM sleep. This study summarized how REM sleep interacts with hormones, neurotransmitters, and gene expression. The study found novel properties of REM sleep, explored the connection between cognitive and emotional functions with REM sleep. REM sleep is a stage of increased brain activity, and the study of REM sleep helps us to better understand brain function and neural activity. Examining REM sleep allows for a thorough exploration of the brain's operational processes, offering valuable insights for neuroscience research. Further study on REM sleep in the future could focus on impact of sleep on body and brain processes, leading to a better comprehension of treating sleep disorders and advancing cognitive neuroscience.

Keywords: REM sleep; hormones; neurotransmitters; gene expression.

1. Introduction

Rapid Eye Movement (REM) sleep is a phase in the sleep cycle that involves rapid eye movement. Sleep is often categorized into four Non-Rapid Eye Movement (NREM) stages and one REM stage. Initially, deep sleep is predominant when you initially fall asleep, but as time passes, the amount of deep sleep reduces while the amount of REM sleep grows. During this stage, a person has REM, high brain activity, and frequent dreaming. REM sleep typically begins approximately 90 minutes after falling asleep, and individuals go through many REM sleep cycles per night. During the 1960s, a widely accepted definition of REM sleep was established through research mostly involving adults and several other mammals. The consensus was established using three methodological foundations: electrocardiograph (EMG) for muscular dystonia, electrooculograph (EOG) for rapid eye movements, and electroencephalography (EEG) for brain activity [1].

The study of REM sleep has consistently been a significant subject in the realm of sleep science. Recent research has progressed in the fields of REM sleep related to inflammatory illnesses, microbiological systems, emotion control, and mental health. The discoveries offer novel insights into the impact of REM sleep on the human body and the potential for creating medications and treatment strategies based on this knowledge. To elucidate the mechanisms of action between REM and hormones, neurotransmitters, and gene expression, the authors reviewed the hormones, neurotransmitters, and gene expression associated with rapid eye movement as follows.

2.1 Hormone

2.1.1 Melanin-concentrating hormone

The Melanin-Concentrating Hormone System comprises Melanin-Concentrating Hormone (MCH) and its receptors. The group of neurons in the hypothalamus of the brain plays a crucial role in regulating sleep. The study examined the relationship between the melanin-concentrating hormone system and REM sleep by utilizing a transgenic mouse model [2]. The study investigated the effect of ambient temperature on REM sleep in mice by observing their sleep-wake cycle and electrophysiological activity. Higher ambient temperatures were found to stimulate activity in the MCH system, hence boosting REM sleep. A decrease in ambient temperature results in reduced activity of the MCH system, which suppresses REM sleep. Changes in ambient temperature can influence the MCH system, which in turn affects REM sleep. The study used optogenetic techniques to investigate the impact of the melanin-concentrating hormone system on

sleep by stimulating specific neuronal groups with light. Light stimulation of MCH neurons in mice increased both NREM sleep and REM sleep.

2.1.2 Corticotropin-releasing hormone (CRH)

CRH is a neuropeptide released by the hypothalamus that triggers the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland in reaction to stress. Studies have demonstrated that neurons in the hypothalamus known as CRH neurons regulate REM sleep in response to threat by releasing CRH, which stimulates REM sleep [3]. Stimulating these neurons increased the duration of REM sleep, whereas suppressing them decreased REM sleep. Hypothalamic neurons that secrete CRH have a vital role in regulating adaptive REM sleep and response to danger. Stimulation of these neurons causes animals to wake up from REM sleep when faced with potential dangers. The release of CRH may play a crucial role in facilitating this alertness response.

On another study, researchers studied the impact of increased levels of CRH in the forebrain of mice by analyzing blood samples to observe its impacts on sleep. They also conducted sleep recordings and data analysis to evaluate its effects on REM sleep. The study demonstrated that elevated levels of CRH led to an increase in the length of REM sleep in mice. The researchers employed a genetic engineering technique to consistently and permanently increase the expression of CRH in the brains of mice, replicating certain characteristics seen in clinical settings. While the mice displayed typical HPA axis activity at rest, they exhibited higher levels of spontaneous REM sleep. This trait can also be found in other animal models of depression. The excess of CRH expression could be responsible for the rise in REM sleep, which might be a natural characteristic of the changed REM sleep patterns observed in depressed patients. This discovery indicates that an increase in CRH levels in the brain could be linked to changes in REM sleep in those with depression. The researchers found that the activation of CRH receptor 1 (CRHR1) is the mechanism responsible for this facilitation CRHR1 antagonists could potentially help in treating sleep disorders related to stress and disturbed sleep. This study proposes that changes in REM sleep could indicate excessive production of central CRH and potentially be used as a biomarker to predict future health issues. These disorders could potentially be averted by using CRHR1 antagonists [4].

2.1.3 Growth Hormone Releasing Hormone (GHRH)

Prior research has shown that GHRH induces both REM and NREM sleep in animals, although there is limited direct proof of the hypnotic impact of GHRH in people. Researchers examined the impact of increased growth hormone (GH) release on sleep duration and quality induced by GHRH at varying doses [5]. They studied eight men in each scenario with different experimental interventions, such as early sleep, deep sleep, and early sleep after sleep deprivation. Along with intravenous injections of GHRH or saline. They not only assessed the effect of injections of GHRH on ghrelin secretion by monitoring ghrelin levels in the blood, but also analyzed changes in sleep duration and quality in several experimental situations. This study showed that injecting GHRH during the initial slow-wave sleep phase did not affect slow-wave sleep but did enhance REM sleep. Injecting GHRH during the third REM state greatly decreases alertness and boosts slow-wave sleep by nearly ten times. Injecting GHRH during the initial slow-wave sleep phase following sleep deprivation decreases the length of time spent awake. Hence, GHRH may promote sleep in healthy young men, especially if the propensity to sleep is diminished.

2.2 Neurotransmitter

2.2.1 Acetylcholine

Acetylcholine is a vital neurotransmitter that controls sleep in mammals. Meanwhile,Acetylcholine is crucial for REM sleep, and its release is strongly linked to the incidence of REM sleep. Acetylcholine is released more often during REM sleep. Acetylcholine enhances the excitability of the cerebral cortex and boosts neuronal activity, hence facilitating the onset of REM sleep. More specifically, acetylcholine receptors are categorized into neuronal-type nicotinic acetycholine receptors and muscarinic acetylcholine receptors. The study examined the effects of Chrm1 and Chrm3 gene deletion on mouse brain activity [6]. Yasutaka Niwa utilized knockout techniques to delete these genes and employed electrophysiological recordings and fluorescence imaging to assess and analyze sleep patterns. The study discovered that the simultaneous removal of Chrm1 and Chrm3 greatly decreased the amount of REM sleep to the extent that REM sleep was hardly noticeable [6]. Fluorescence analysis revealed that removing Chrm1 and Chrm3 led to changes in activity patterns in some brain areas. Thus, regulation of acetylcholine binding to the receptor influences REM.

2.2.2 5-Hydroxytryptamine (5-HT)

Studies have demonstrated that manipulating the 5-HT receptor can impact an organism's control of wakefulness, slow-wave sleep, and REM sleep by modifying the degree of 5HT binding to the receptor. Research indicates that various serotonin receptor subtypes have distinct functions in enhancing alertness and inhibiting REMS. Studies have shown that serotonin receptor antagonists can enhance slow-wave sleep (SWS) and/or REMS, suggesting potential new approaches for treating insomnia. The study

delved into the mechanism of action of several serotonin receptor subtypes, focusing on 5-HT's involvement in regulating sleep-wake behavior. This study discovered that various 5-HT receptors had distinct functions in regulating the sleep-wakefulness cycle [7]. Activation of 5-HT1A receptors can promote alertness and disrupt REM sleep. Activation of 5-HT1B receptors can promote alertness and disrupt REM sleep [7]. The lack of 5-HT2A receptors leads to heightened alertness and reduced deep sleep stages [7]. Stimulation of 5-HT2A receptors promotes alertness and reduces the duration of sleep [7]. Absence of 5-HT2C receptors leads to heightened alertness and less deep sleep [7]. Stimulation of 5-HT2C receptors promotes alertness and reduces the duration of sleep [7].

2.2.3 Dopamine

Sleep deprivation has been demonstrated as a risk factor for relapse in substance dependence, according to past research. The current work aimed to investigate the effect of sleep deprivation on the extinction and recovery of methylamphetamine (METH) reward memories. It also includes analyzing the involvement of dopamine receptors in this process. The study was separated into two parts: REM sleep deprivation (RSD) before and after resolution. The researchers studied the decline and restoration of reward memories during REM sleep deprivation by restricting rats' sleep time on a narrow platform and by evaluating their preference for METH-related surroundings in the Conditioned Place Preference (CPP) test. The study demonstrated that RSD elevated D1-like dopamine receptor activity, leading to an increase in METH-induced conditioned preferences [8]. Administering RSD before the extinction or recovery of METH reward memory impacts the time it takes for reward memory to extinguish and the animals' locomotor activity. Antagonists of D1-like dopamine receptors can influence these effects. RSD did not have a substantial impact on the recovery of METH reward memory. RSD prior to extinction increased the locomotor activity of the animals, and D1-like dopamine receptor antagonists reduced this effect.

Another study investigated how dopamine affects sleep, both experimentally and observations, by manipulating dopamine release and inhibiting dopamine receptors in the cortex using optogenetic methods [9]. It causes muscular weakening episodes known as cataplexy. The release of dopamine in the nucleus accumbens has been linked to the promotion of REM sleep and sudden seizures. Continuous exposure to dopamine leads to elevated basal dopamine levels instead of temporary spikes. The results indicated that dopamine is crucial in controlling both sleep and abrupt seizure occurrences.

2.2.4 Gamma-aminobutyric acid (GABA)

This study utilized mice as a model to investigate the impact of GABA neurons and glutamate in the anterior hypothalamus on various sleep stages and sleep regulation [10]. The researchers monitored body temperature, locomotor activity, sleep status, tissue sections and immunohistochemical analyses in mice by selectively activating or inhibiting GABA and glutamatergic neurons using viral vectors and optogenetic techniques. The findings indicated that activating MnPOVgat neurons led to an increase in NREM sleep and a decrease in REM sleep, implying that GABA neuron activation suppresses REM sleep production. Furthermore, these neurons have varying responses to both sleep deprivation and stress. The research had uncovered the distinct functions of GABA and glutamatergic neurons in controlling sleep in the anterior hypothalamus.

On the other study, researchers Nitz and Douglas implanted electrodes and catheters in one-year-old cats to investigate the role of gamma-aminobutyric acid (GABA) release in the dorsal nucleus of the spinal cord (DR) in regulating REM sleep. Nitz and Douglas utilized in vivo microdialysis to measure GABA release, which was analyzed using high performance liquid chromatography (HPLC) along with glutamate and glycine concentrations. This study discovered that during REM sleep, there was a notable increase in GABA release from the DR, but the release of glutamate and glycine remained rather stable [11]. Additionally, injecting the GABA agonist muscimol into the DR improved the duration of REM sleep, while injecting the GABA antagonist picrotoxin inhibited the development of REM sleep. Thus, GABA release is crucial for inducing the REM sleep state and regulating the firing of 5-hydroxytryptaminergic neurons in the dorsal nucleus of the spinal cord.

2.2.5 GABA, glutamate

GABA and glutamate neurons in the ventral tegmental area (VTA)play a crucial role in regulating sleep and wakefulness. The VTA, a significant brain area, gets glutamate and GABA inputs from nearly all brain regions. Activating GABA neurons in the VTA was shown to suppress REM sleep and promote wakefulness, as per the study [12]. Inhibiting glutamate neurons in the VTA enhances REM sleep. Glutamatergic neurons in the VTA are crucial for controlling the sleep-wakefulness state, especially REM sleep.

2.3 Genetic transcription

2.3.1 Hypothalamic gene

Aiming to explore the impact of sleep loss on hypothalamic gene expression and its correlation with validation responses. This study utilized C57BL/6 mice as experimental participants, who were randomly allocated into sleep deprivation and control groups. The study analyzed

Interleukin-1β (IL-1β) immunoreactivity in the hypothalamus by immunohistochemical methods and measured it by determining the percentage of threshold area. This study discovered that lack of sleep resulted in higher expression of inflammation-related genes in the hypothalamus, along with enhanced immunohistochemistry reactions to the inflammatory cytokine IL1β [13]. Sleep deprivation may trigger an inflammatory response in the hypothalamus, as indicated by these findings.

2.3.2 Glutamic acid

Metabotropic glutamate receptor 1 (mGluR1) is a protein that plays a role in transmitting signals related to the neurotransmitter glutamate. The study found that mutations in the mGluR1 gene lead to changes in the brain signalling system, resulting in a reduction in the duration of REM sleep in mice, through protein extraction and immunoblotting analysis of mouse brain tissue and HEK293 cells [14]. These results indicate a connection between mGluR1 and REM sleep, and mutations in mGluR1 could impact REM sleep. Further studies are required to uncover the particular mechanisms and specifics.

3. Conclusion

This paper summarizes and describes the effects of different hormone, neurotransmitter, and gene expression on sleep or REM. It is shown that hormone, neurotransmitter and gene expression have different degrees of influence on REM. Based on the above experiments, it is suggested that hormone, neurotransmitter and gene expression have a potential relationship with REM sleep, and this relationship needs to be studied in depth. REM sleep is essential for regulating hormones, neurotransmitters, and gene expression. REM sleep is strongly linked to alterations in the external environment and internal factors. This study examined the advancements in studies concerning REM sleep and its relationship with hormones, neurotransmitters, gene expression, and other associated factors. REM sleep is crucial for brain function and behavior, aiding in memory consolidation, enhancing learning ability, and promoting emotional stability. In the future, advanced researches in sleep science could be anticipated to offer more effective methods to enhance sleep quality, support health, and address sleep-related conditions by furthering the understanding of REM sleep.

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