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Sleep, Energy and Depression

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Abstract

Sleep is a universal biological behavior that to this day remains unclear. There is a lack of consensus concerning sleep's underlying function, making it a controversial matter. Throughout the years, many theories have been formulated with the purpose to uncover the reasons why we sleep. The Energy Allocation theory of sleep offers some answers concerning the function of sleep and the reason behind the constant alternation between different sleep stages. Orexins and Melanin-Concentrating Hormone (MCH) act as regulators of the sleep - wake cycle while there is evidence that they are associated with psychiatric disorders such as depression. This review covers prominent sleep theories, sleep regulators and their connection with the psychopathology of depression as well as possible novel treatments.

Keywords

sleep; depression; sleep regulators; orexins; MCH

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Introduction

Sleep is a natural state of unconsciousness based on a cyclical pattern alternating between non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. NREM sleep is characterized by high amplitude slow wave activity in the electroencephalogram (EEG), muscle immobility, normal respiration and heart rate [1]. On the contrary, REM - alternatively called paradoxical or active sleep - is distinguished by low amplitude brain activity in the EEG resembling wakefulness, generalized skeletal muscle atonia and rapid eye movements [1]. NREM is divided into 3 stages and takes up about 75-80% of total sleep, while REM accounts for the remaining 20-25% [2]. The initial cycle lasts approximately 70-100 minutes and the following ones have a duration of 90-120 minutes each. During a typical night there are 4-5 cycles in total [2]. However, the exact purpose of sleep is a matter of conflict throughout the years and several theories have been proposed in order to answer this question [2].

Sleep disturbances are a common occurrence in patients with Major Depressive Disorder (MDD), as 80% of depressed patients suffer from insomnia, while 15-35% battle with hypersomnia [3]. Sleep EEG recordings have demonstrated characteristic changes in MDD patients including impaired sleep continuity, reduced NREM sleep duration, shortened REM sleep latency and increased REM sleep density and duration [3]. Sleep abnormalities are attributed to hyperarousal that characterizes patients with MDD due to hypothalamic–pituitary–adrenal (HPA) axis hyperactivation and central nervous system activation [4]. This review covers leading sleep theories while discussing the connection between sleep modulators and MDD.

Theories of sleep

Several theories have been proposed in an attempt to identify the purpose behind sleep. From an evolutionary standpoint, the Inactivity Theory suggests that sleep is a protective mechanism that favors creatures inactive during the night. This theory is stemming from the fact that night time activity is associated with a greater risk of death due to injuries and predators [2]. From a different perspective, taking into account the evidence that growth and renewal appear to be faster during sleep, Oswald proposed the Restoration Theory of sleep. According to this theory, sleep facilitates muscle restoration, protein synthesis, tissue growth and other important physiological functions leading to compensatory restoration [5]. A more recent theory, the Brain Plasticity Theory, indicates that sleep contributes to neuronal reorganization and connectivity. It is supported by the fact that sleep duration is longer in neonatal periods than in any other period of life, indicating that sleep plays a pivotal role in the brain development [6].

The Energy Conservation Theory was formed based on the reduction of metabolic rate during sleep and suggests that sleep's main purpose is to reduce energy demand [7]. This theory was one of the most prominent ones and was considered the primary sleep function until it was proven that metabolic rate during sleep was only slightly lower than metabolic rate during quiet waking [8]. Other than that, this theory promotes a rather passive sleep model, suggesting that all biological processes are equally reduced during sleep. However, many procedures, such as immune functions, restoration, and neuronal reorganization are upregulated during sleep, proving that it is a highly active metabolic state [9]. Taking this into account, Schmidt presented the Energy Allocation Theory.

The energy allocation function of sleep

The Energy Allocation model unifies many older theories into one and proposes that sleep – wake cycle downregulates some functions during wakefulness and upregulates them during sleep [1]. Vigilance, foraging and reproduction are considered wake predominant processes, thus referred to as Waking Effort (WE). On the contrary, immune function, cellular housekeeping, neural network reorganization and processes that are responsible for maintenance and restoration are referred to as Biological Investment (BI). Schmidt proposed that in order to decrease energy demands and achieve energy conservation, WE is upregulated and BI downregulated during wakefulness, whereas the opposite occurs during sleep [1].

REM sleep is a high energy demanding sleep stage due to BI processes augmentation. The Energy Allocation model suggests that thermoregulation is suspended and muscle tone is eliminated during this sleep stage in order for energetic balance to be obtained during REM sleep. On the other hand, NREM sleep utilizes less energy for BI and therefore has the energetic capacity for thermoregulatory effort [1].

Sleep regulators

Sleep is generated by two mechanisms, the homeostatic and the circadian sleep drive. The homeostatic sleep drive increases accordingly to the time spent awake as adenosine and nitric oxide accumulate in the basal forebrain during extended periods of wakefulness [2]. The circadian sleep drive is controlled by GABAergic neurons in the suprachiasmatic nucleus (SCN) based on sensory input (light levels detected from retina) synchronizing brain activity with light-dark cycles [2]. According to the Energy Allocation model, the sleep - wake and NREM - REM sleep alternations are very important for energetic balance and require some regulators capable of combining energy levels, thermoregulatory demands and homeostatic sleep need [10]. Hypothalamus plays a pivotal role in energy allocation through modifications of behavioral states [10]. Orexin and Melanin – Concentrating Hormone (MCH) neurons are both located in the lateral hypothalamus but have opposing effects making them ideal candidates for sleep – wake cycle regulation [10].

Orexins are excitatory neuropeptides produced in the perifornical and lateral hypothalamus and are divided into two types, orexin-A (hypocretine-1) and orexin-B (hypocretine-2)

that are both synthesized by the same peptide, prepro-orexin [11]. It was revealed that fasting increased prepro-orexin peptide, proposing that orexins play an important role in feeding behavior [12]. Other than that, orexin neurons are involved in motivation, reward and addiction. Through two protein G-protein coupled receptors, orexin-1 (ORX1R) and orexin-2 (ORX2R), orexin regulates sleep – wake cycle [4]. Excitation of orexin neurons induces wakefulness, while decrease of their activity promotes sleep and loss of these neurons is linked to narcolepsy [10].

MCH is a neuropeptide located in neurons in the lateral hypothalamus and incerto – hypothalamic area. Its function is regulated by two G-protein-coupled receptors, MCH1R and MCH2R [13]. MCH neurons take part in the regulation of appetite, mood, energy homeostasis and sleep [10]. They are activated during periods of high energy levels and generate sleep for energy conservation purposes, whereas during periods of low glucose, MCH neurons have decreased excitability and promote wakefulness [2].

Orexin and MCH orchestrate the transitions from NREM sleep to REM sleep or wakefulness according to thermoregulatory needs and core body temperature (Tc). When the ambient temperature (Ta) is thermoneutral, MCH neurons promote REM sleep, whereas when the Ta is below thermoneutrality orexin neurons hinder REM sleep, as the organism needs to apply thermoregulatory defenses, such as shivering or brown adipose tissue thermogenesis [10]. As a result, REM sleep is inhibited if the Tc must be defended and REM sleep bouts' duration is short in order for Tc not to deviate from baseline [1].

MCH and Depression

MCH induces REM sleep and stimulates the HPA axis, while it is also known that patients with MDD show increased REM sleep duration and over-activation of the HPA axis, suggesting a possible relation between MCH and MDD [14].

Preclinical studies tested the effects of MCH agents in the dorsal (DR) and median (MR) raphe nuclei in rats and observed that MCH microinjections in the DR trigger a pro-depressive response as shown in the forced swim test (FST). This response was inhibited in the animals treated with antidepressants (fluoxetine or nortriptyline) [14]. Other studies proved that mice after a 5 week stress exposure showed increased MCH1R expression that was reversed by fluoxetine [15]. The hypothesis that hyperactivity of MCH neurons is associated with the pathophysiology of MDD is also supported by the finding that antidepressants suppress these neurons. It is proven that through the reduction of REM sleep rebound after sleep deprivation protocol, acute treatment with escitalopram decreases the activity of MCH neurons [16]. Other researchers have demonstrated that MCH neuronal activity is reduced after juxtacellular application of fluoxetine [17]. Schmidt and his team also established that 4 weeks of antidepressant treatment lower MCH serum levels, in agreement with the working hypothesis [18].

MCH1R is expressed in several brain regions such as amygdala, nucleus accumbens shell, dorsal raphe and locus coeruleus, indicating a relation to anxiety and mood regulation [19]. Findings from preclinical studies revealed that MCH1R antagonist hold antidepressive and anxiolytic effects in animal models [20, 21]. Furthermore, it was observed that rats that were treated with an oral dose of selective MCH1R antagonist SNAP-7941 showed a similar profile to the FST as rats treated with fluoxetine [19]. In the rat social-interaction test, rats that were administered SNAP-7941 had a similar response to those treated with chlordiazepoxide and the onset of action was more rapid than paroxetine [19]. In the light of these results, MCH1R antagonist shows potential on being a promising candidate for the treatment of depression and anxiety.

Orexins and Depression

Research has demonstrated that orexin neurons appear to be connected with brain regions responsible for cognition and mood regulation, suggesting a possible link between orexins and psychiatric disorders such as MDD. The role of the orexin system in MDD has been investigated in both animal and clinical studies. Some researchers examined the effect of orexins on animals through microinjections. It was found that orexin-A leads to depressive behavior when injected into the basolateral amygdala of mice, whereas it acts as an antidepressant when injected into the central amygdala of rats [11].

Clinical studies also showed inconsistent results. Some researchers revealed that MDD patients had decreased orexin-A levels in their cerebrospinal fluid (CSF), while others found no significant difference. On the other hand, it was found that people suffering with MDD had increased orexin-A levels in their plasma [11]. Postmortem studies also demonstrated increased orexin-A immunoreactivity in the hypothalamus of MDD patients [11]. While it is not proven that hyperactivity or hypoactivity of orexins is responsible for MDD symptoms, data from clinical studies suggest that MDD patients show dysregulation of the orexin system. The lack of consensus regarding the relationship between orexin system and MDD is attributed to the fact that orexins have the ability to act both as a pro- depressant and an anti- depressant depending on the brain region [22]. Specifically, it was proven that orexins had an anti-depressant effect in the hippocampus, ventral tegmental area, prefrontal cortex, nucleus accumbens, and dorsal raphe nucleus and a pro-depressive effect in the locus coeruleus and paraventricular nucleus of the hypothalamus. Amygdala was the region that the orexin system had both pro-depressive and antidepressive results [22].

Orexins regulate arousal and wakefulness by tempering OX1R and OX2R, receptors that are expressed in brain regions that are involved to stress and panic. OX1R and OX2R are activated by orexins during stress causing HPA axis activation [4]. Seltorexant, a selective OX2R antagonist, was tested in clinical studies as a promising treatment for both insomnia and MDD [23]. Research showed that seltorexant promoted longer sleep time, shorter latency to persistent sleep and improved sleep efficacy, solidifying it as an insomnia treatment

[24]. At the same time, it was proven that patients with MDD that were medicated with seltorexant for 10 days displayed a significant improvement in depressive symptoms compared to the group that was treated with the placebo, confirming its antidepressant activity [23]. A phase 2b study of seltorexant as an adjunctive therapy in MDD proved that patients that were treated with seltorexant showed ≥50% improvement in Montgomery-Åsberg Depression Rating Scale (MADRS) total score compared to patients that received placebo. The biggest improvement in MADRS score was observed in patients treated with seltorexant 20mg in comparison to the placebo, seltorexant 10mg and 40mg groups [25]. Furthermore, this study demonstrated that the improvement in MADRS total score at week 6 was greater in patients with sleep disturbances as opposed to patients without sleep disturbances [25]. Based on these findings, orexin appears to be the link between sleep regulation and depression, as it has effects on both insomnia and MDD and phase 3 studies of seltorexant as adjunctive therapy to antidepressants in patients suffering with MDD and insomnia are underway [25].

Conclusion

The Energy Conservation Theory has been reconsidered and The Energy Allocation model has offered an answer to why we sleep and why we alternate between sleep stages. MCH and orexins hold an important role in sleep regulation. Specifically, MCH neurons endorse REM sleep when Ta is thermoneutral and orexin neurons hinder REM sleep when the body needs thermoregulatory defenses. Research has proven that these neuropeptides are also associated with the pathophysiology of MDD. It was observed that hyperactivity of MCH neurons is correlated with MDD, supported by the findings that MCH levels decrease after antidepressive treatment. Furthermore, MCH1R antagonist appears to have antidepressive and anxiolytic effects in rats, however it would be important to determine MCH1R antagonist effects on MDD patients in the future. As for orexins, research has shown that dysregulation of the orexin system is related to MDD and that depending on the brain region orexins can act both as a pro-depressant and an anti-depressant. Lastly, seltorexant, a selective OX2R antagonist, is considered a promising candidate for treating both insomnia and MDD and is currently on phase 3 studies as an adjunctive therapy to antidepressants in MDD patients with sleep disturbances.

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