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Sleep Disturbances: From Insomnia to Depression. From Animals to Humans

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ABSTRACT

This review presents data on the physiology of sleep, the pathophysiological basis of sleep disturbances, and the epidemiology of these disorders. Major hypotheses concerning the development of depressive disorders are discussed, including the monoamine, inflammatory, and neuroendocrine models. Current findings from clinical studies and meta-analyses are summarized, highlighting key factors by which sleep deprivation affects human somatic and mental functions. Sleep monitoring using electroencephalography has demonstrated a common pathophysiological link between rapid eye movement sleep behavior disorder in patients with depressive disorders and sleep deprivation. The role of sleep deprivation as an experimental and controversial method for treating depressive disorders is discussed.

The main preclinical models of disease in laboratory animals—total and paradoxical sleep deprivation—are presented and classified. Behavioral patterns observed in various paradigms, such as the Morris water maze and Y-maze tests, are analyzed. Changes in gene expression during disease modeling and alterations in neurometabolites following different sleep deprivation techniques are presented. The review outlines future directions in preclinical sleep disorder research, emphasizing unexplored areas, particularly the therapeutic potential of sleep deprivation in various depression models.

Keywords: sleep deprivation; depression; modeling; neuroinflammation; behavioral responses.

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Нарушение сна. От бессонницы к депрессии. От животных к человеку

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АННОТАЦИЯ

В обзоре представлены данные о физиологии сна, патофизиологических основах его нарушений и об эпидемиологии данного заболевания. Рассмотрены основные гипотезы формирования депрессивных расстройств: моноаминовая, воспалительная, нейроэндокринная. Приведены актуальные данные клинических исследований и результаты мета-анализов, установлены ключевые факторы влияния депривации сна на соматические и психические функции человека. По данным мониторинга сна с использованием электроэнцефалографии показана общая патофизиологическая связь нарушения быстрой фазы сна у пациентов с депрессивными расстройствами и нарушениями сна. Обсуждается роль депривации сна как одного из экспериментальных и неоднозначных методов терапии депрессивных расстройств. Представлены и классифицированы основные доклинические модели патологии на лабораторных животных: тотальной и парадоксальной депривации сна. Проанализированы примеры поведенческих паттернов животных в различных поведенческих установках (водный лабиринт Морриса, Y-образный лабиринт). Показаны изменения экспрессии генов на фоне моделирования заболевания и изменения нейрометаболитов после использования различных методик депривации сна. Обсуждены перспективы дальнейших доклинических исследований в области патологии сна, выявлены ещё не изученные области (в частности, терапевтическое влияние депривации сна на различные модели депрессии).

Ключевые слова: депривация сна; депрессия; моделирование; нейровоспаление; поведенческие реакции.

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INTRODUCTION

Sleep is an essential part of life in higher animals, including humans, and consists of two main phases: rapid eye movement (REM) and non-rapid eye movement (NREM) sleep. The REM sleep phase is characterized by high-amplitude theta waves on hippocampal electroencephalogram; beta waves similar to those observed during wakefulness; profound inhibition of skeletal muscle activity; intermittent, involuntary skeletal muscle contractions; body temperature fluctuations; rapid, chaotic eye movements; and increased heart and respiratory rates [1]. NREM sleep comprises three stages: N1 (light sleep), the briefest stage, during which skeletal muscle tone is preserved; N2, a deeper stage marked by sleep spindles—bursts of coherent brain activity; and N3, the deepest stage, associated with reduced muscle tone, heart rate, and respiration [2].

Sleep regulation is governed by circadian rhythms, which are controlled by the central circadian clock (the suprachiasmatic nucleus of the hypothalamus) and peripheral clocks located throughout body tissues. The suprachiasmatic nucleus is connected to the retina and receives environmental light signals, enabling it to modulate peripheral tissue metabolism according to the light–dark cycle. However, some tissues are capable of functioning autonomously, independent of the hypothalamic suprachiasmatic nucleus. Together, the circadian system ensures systemic biological rhythmicity [3].

EFFECTS OF SLEEP DEPRIVATION ON THE HUMAN BODY

Sleep deprivation refers to complete or partial loss of sleep, which may be voluntary or secondary to disease. In the United States, 30% of adults report inadequate sleep, and 40% experience unintentional daytime sleep episodes. Similar trends are observed in Europe; according to Kerkhof et al., up to 42% of survey respondents reported insufficient sleep [4].

Electroencephalography (EEG) is the primary method used to visualize sleep disturbances. Using this method, changes following several days of partial sleep deprivation have been demonstrated: the durations of N1 and N2 stages of NREM sleep were reduced, as was the duration of REM sleep, whereas the deep N3 stage remained unchanged. Notably, electroencephalogram abnormalities may persist even after 2 nights of normal sleep [5]. Alterations in sleep phase duration and/or sequence serve as therapeutic targets in various forms of insomnia.

SLEEP DEPRIVATION AND PSYCHOSOCIAL WELL-BEING

Sleep deprivation affects multiple aspects of mental and emotional functioning. A study involving medical students revealed that 37.8% reported low levels of daytime sleepiness, while 8.7% reported moderate to high levels, correlating with quality of life, academic performance, and symptoms of depression and anxiety [6]. In a meta-analysis, Seoane et al. found a correlation between academic performance and sleep quality and daytime sleepiness, but not sleep duration [7]. Furthermore, sleep disturbances are linked to emotional dysregulation. Tomaso et al. demonstrated that sleep deprivation induces negative emotions and reduces positive mood in humans [8].

RELATIONSHIP BETWEEN SLEEP DEPRIVATION AND DEPRESSIVE DISORDER

Depressive Disorder: General Overview

Depression is a common mental disorder that affects approximately 5% of the adult population. It is characterized by persistent low mood, loss of interest or pleasure in activities, and other symptoms such as poor concentration, hopelessness about the future, suicidal ideation, and sleep disturbances (both insomnia and hypersomnia). This article uses the classification of major depressive disorder (MDD) according to the United States nosological system, which corresponds to recurrent depressive disorder (F33 in ICD-10).

One hypothesis underlying MDD is the dysregulation of innate and adaptive immune responses, resulting in systemic inflammation. Increased levels of cytokines, including interleukins (IL-6, IL-10, IL-13, IL-18, IL-12), tumor necrosis factor alpha, and acute-phase proteins, have been reported in the plasma of patients with diagnosed MDD [9]. It has been proposed that proinflammatory factors exert neurotoxic effects on brain neurons, leading to emotional dysregulation, particularly in regions such as the hippocampus, amygdala, and anterior cingulate cortex [10].

Another prominent theory is the monoamine hypothesis, which suggests that MDD results from dysregulated concentrations of norepinephrine, serotonin, and dopamine in various brain regions. The monoamine theory is supported by pharmacotherapy targeting the monoaminergic system. Standard antidepressant treatment includes agents that inhibit the reuptake of serotonin and dopamine [11].

One theory posits that depression is caused dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. The HPA axis regulates several physiological processes and serves as a key link between the central nervous system and peripheral organs during stress. Corticotropin-releasing hormone initiates the cascade by acting on the anterior pituitary, which then secretes adrenocorticotropic hormone, ultimately stimulating the adrenal cortex, especially the zona fasciculata, to produce glucocorticoids, including cortisol, cortisone, and corticosterone [12]. In patients with depressive disorder, hyperactivation of the HPA axis has been observed, resulting in elevated plasma glucocorticoid

levels. However, a meta-analysis [13] found no significant differences in cortisol levels between individuals with MDD and healthy controls. Animal models support these findings. Li et al. used the chronic unpredictable mild stress model to induce depressive-like states in Wistar rats, observing increased corticosterone and adrenocorticotropic hormone levels in plasma [14]. In another study, chronic administration of corticosterone to mice induced depressive-like behaviors [15].

Sleep Deprivation and Depressive Disorder

Sleep deprivation negatively affects emotional well-being and may trigger depressive symptoms. Conversely, sleep disturbances are common in patients with depressive disorders. The pathophysiological link between sleep disturbances and depression is illustrated in Fig. 1. Among adolescents aged 11 to 17 years, sleeping less than 6 hours per night was associated with MDD and an increased risk of future depression [16]. A study investigating the relationship between sleep duration and increased risk of depression yielded interesting results. In a sample of over 25,000 individuals, a correlation was found between sleep duration and depression risk. The resulting graph displayed a U-shaped pattern, indicating that the risk of depression increases not only with sleep deprivation but also with prolonged sleep duration [17].

Despite the evidence that sleep deprivation impairs mood and is a risk factor for MDD, some therapeutic strategies incorporate sleep deprivation as treatment for depressive disorders. A hallmark of depression is disturbed REM sleep, characterized by shortened REM duration and increased density [18]. NREM abnormalities are less common. Landsness et al. conducted a study where patients with MDD were subjected to therapeutic sleep deprivation involving awakenings during NREM sleep across a single night, resulting in a statistically significant reduction in depressive symptoms [19]. Furthermore, Hu et al. found in a meta-analysis that sleep deprivation exerted a significant antidepressant effect in patients with emotional depression [20]. Another study using one-day sleep deprivation showed a negative impact on healthy volunteers, whereas 43% of participants with MDD experienced an antidepressant effect [21]. This treatment approach remains controversial and under active investigation. For example, a 2023 study by Goldschmied et al., which included full control over participant sleep deprivation, found no antidepressant effect, with only 6% of participants showing improvement after the procedure [22].

ANIMAL MODELS OF SLEEP DEPRIVATION

Various animal models, including mice, rats, and primates, are used to comprehensively investigate the effects of sleep deprivation. Currently, two principal types of sleep deprivation are common in animals: total sleep deprivation (TSD) and paradoxical sleep deprivation (PSD). Following sleep deprivation protocols, animals undergo behavioral testing to assess cognitive and locomotor deficits, overall condition, and biochemical alterations using various methods. Table 1 presents the number of experimental studies based on each modeling method, determined via the PubMed National

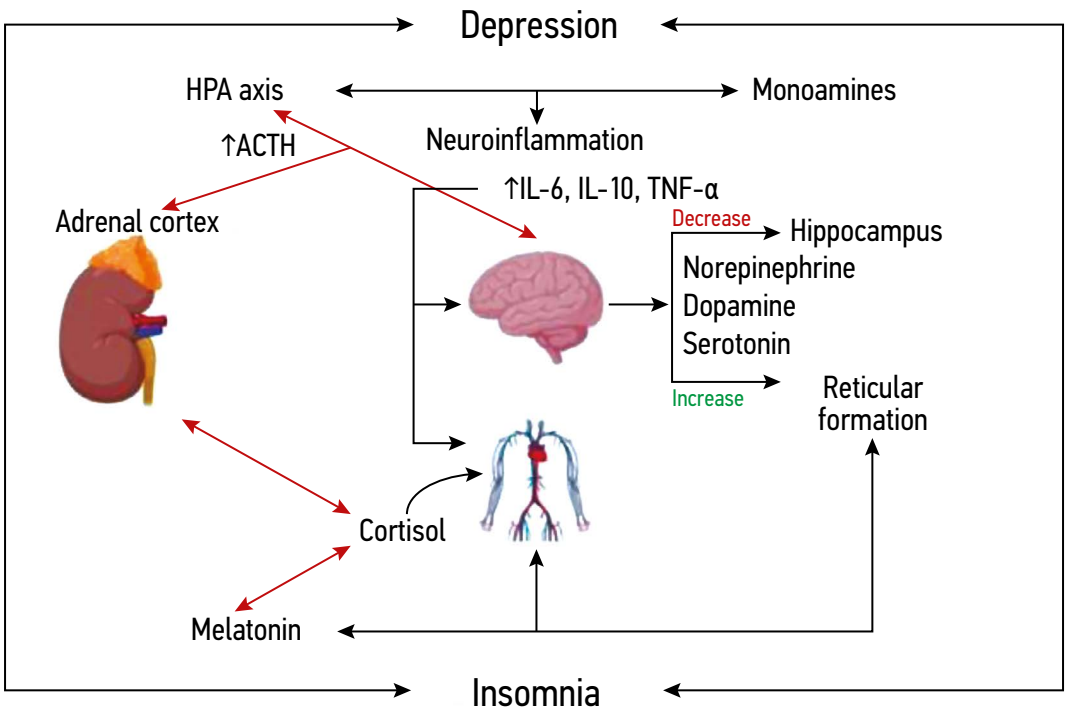

Fig. 1. Pathophysiological mechanisms linking depressive disorder and sleep deprivation. HPA, hypothalamic-pituitary-adrenal axis; ACTH, adrenocorticotropic hormone; IL, interleukin; TNF-α, tumor necrosis factor α.

Table 1. Sleep deprivation modeling

Type of sleep deprivation	Method	Year of model creation	Number of publications
Total	Handling	1987	66
	Disk-over-water	1983	—
Paradoxical	Classic platform	1965	33
	Multiple platform	2000	117
	Grid-over-water	2003	10

Library of Medicine using the following search terms: *handling method sleep deprivation*, *disc over water sleep deprivation*, *flowerpot technique sleep deprivation*, and *modified multiple platform method sleep deprivation*.

Total Sleep Deprivation

Total sleep deprivation (TSD) protocols deprive animals of both NREM and REM sleep phases [23]. Two major TSD methods are currently in use:

1. Disc-over-water method: A fiberglass disc is positioned above water in a container 2–3 cm deep and divided by a central partition. Two animals are placed on the disc and connected to an EEG monitoring device. The animals' brain bioelectrical activity is continuously monitored throughout their time in the device. When the rodents enter a sleep state, it triggers the disk rotation in a random direction. The disc stops only after 6 s of wakefulness. This method enables continuous assessment of brain bioelectrical activity throughout the modeling process and allows for precise sleep deprivation in rodents based on EEG data [24, 25].

2. Handling method: Throughout the sleep deprivation period, rodents remain in their home cages under the supervision of laboratory staff who monitor their behavior. When signs of sleep onset are observed, such as closed eyes or immobility, mild tapping on the cage or gentle touching of the animal is applied to awaken the rodent. Although the method is easy to implement, it is characterized by limited validation and reduced accuracy due to behavioral patterns that mimic sleep (e.g., freezing, stereotypy). Furthermore, the method is operator-dependent, increasing the likelihood of experimental error compared to the disc-over-water technique [23, 26].

Paradoxical Sleep Deprivation

Paradoxical sleep deprivation (PSD) involves selective deprivation of REM sleep while preserving other sleep stages. PSD techniques are now more commonly used than TSD:

1. Classic platform method: Animals are housed individually in containers with water and placed on small platforms. Upon entering REM sleep and experiencing muscle atonia, they fall into the water and awake. This technique completely eliminates REM sleep in test animals, but may also result in partial loss of NREM sleep [27]. Additionally, the solitary housing of animals contributes to increased stress, complicating validation. This method is no longer in use.

2. Multiple platform method: The principle of this method is the same as the previously described technique: animals are placed on platforms and fall into the water upon entering REM sleep, waking up as a result. However, in this modified version, the animals are housed in groups, thereby eliminating additional stress [28].

3. Grid-over-water method: The operational principle is consistent with previously described REM sleep deprivation methods; however, in this case, the animals are placed on rods with a diameter of 3 mm. These rods are arranged on a stainless-steel grid suspended within a plastic cage filled with water 1 cm below the grid. When animals fall asleep and lose balance, they contact the water and awake [29, 30].

The most frequently used method for studying sleep deprivation in animal models is the multiple platform technique. Studies have shown that sleep deprivation of up to 14 days results in elevated stress levels. The effect is markedly intensified following 21 days of REM sleep deprivation, with observed outcomes including anxiety and degenerative changes in the hippocampal region. Notably, hippocampal expression of *NR1* (Grin1) and *NR2a* (Grin2a), genes encoding subunits of the NMDA (N-methyl-D-aspartate) glutamate receptor, is downregulated [30]. PSD also impairs memory. Chen et al. [31] utilized the multiple platform method alongside the Y-maze and Morris water maze. The animals with PSD made significantly more errors in the Y-maze and took longer to locate the escape platform in the Morris water maze compared to the controls. High-performance liquid chromatography revealed reduced dopamine levels in hippocampal tissue following sleep deprivation. Another study reported significantly increased serotonin concentrations in the dorsal hippocampus, while dopamine and norepinephrine levels remained statistically unchanged [32].

DISCUSSION

As the pace of life accelerates, information overload increases, and urbanization progresses, sleep disorders in various forms are undoubtedly becoming one of the key challenges of the 21st century, affecting practitioners across multiple medical specialties. The etiology of sleep disturbances includes endocrine dysregulation, inflammatory processes, and stress-related responses. Genetic mechanisms underlying insomnia have also been identified [33]. Of particular interest is the association between depressive disorders and sleep disturbances: certain types of depression are accompanied by pathological somnolence, while others (e.g., agitated depression) are characterized by insomnia. While it is well established that sleep disturbances contribute to the development of anxiety and depressive symptoms, the precise pathological mechanisms remain unclear. The clarification of these mechanisms may yield insights into the etiology of depressive disorders. Currently, three different hypotheses explain the development of depression:

the monoamine theory, the neuroinflammatory theory, and the neuroendocrine hypothesis. Studies have shown that sleep deprivation causes a monoamine imbalance [34]. Indeed, antidepressants targeting monoamine reuptake mechanisms are commonly utilized in patients with insomnia.

Sleep restriction in humans also leads to endocrine alterations: the most well-known effect of circadian misalignment (e.g., jet lag) is decreased melatonin synthesis, heightened anxiety and stress, and elevated cortisol levels—hallmarks shared by patients with depression.

Suppressed immune responses observed in sleep-deprived individuals suggest the involvement of inflammatory pathways [35], an area which is currently under active investigation.

Conversely, therapeutic sleep deprivation has been demonstrated effective in depression. Depending on the depression subtype, sleep deprivation may restore monoamine balance or attenuate inflammatory responses.

Addressing these fundamental questions requires the use of laboratory animals, various sleep deprivation models, and classical models of depressive disorders. As shown in Table 1, paradoxical sleep deprivation models, though developed over two decades ago, remain relevant. Animals subjected to PSD consistently exhibit depression-like behaviors [36], supporting a direct etiological link to depression.

It is interesting that pharmacologic models of sleep disturbance, such as glucocorticoid- or thyrotoxicosis-induced models, are almost never used, despite their clinical relevance. While these models may be considered less refined, they can still be valuable for investigating specific mechanisms. Moreover, no studies have examined sleep deprivation as a therapeutic intervention in animal models. Such research could be highly informative, particularly the comparison of the antidepressant effects of acute sleep deprivation across different experimental models (e.g., chronic unpredictable mild stress, lipopolysaccharide-induced inflammation, learned helplessness).

There is also a pressing need to increase the use of electrophysiological tools, especially EEG monitoring, in both sleep deprivation and depression models to accurately characterize alterations in sleep phases and duration.

CONCLUSION

The findings presented in this review underscore the clinical and research relevance of studying sleep disturbances, both in human populations and in animal models. The evidence highlights a close clinical, etiological, and pathophysiological relationship between sleep disorders and depressive illnesses.

ADDITIONAL INFORMATION

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Statement of originality: Previously published data were used in this article, as it is a review of existing methods related to the subject. An original diagram illustrating the pathophysiological links between sleep disturbances and depressive disorders was developed as part of this work (Fig. 1).
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