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SLEEP DISTURBANCES AND DEPRESSION: DIRECTIONS AND MECHANISAMS OF INTERACTION

POREMEĆAJI SPAVANJA I DEPRESIJA: POVEZANOST I MEHANIZMI INTERAKCIJE

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Abstract

Sleep represents physiological process which effects are crucial to maintain homeostasis. Sleep disturbances are widely spread within the population worldwide. The loss in quantity or quality of sleep is associated with numerous diseases. Also, sleep disturbances are highly connected to depressive disorders, but exact mechanism of this interaction still remains unknown. Understanding the underlying mechanisms could be the key for treatment of both disorders especially in patients with psychosomatic and psychiatric comorbidities. Therefore, in this article, we will summarize the most recent findings on the connection between sleep disturbances and depressive disorders, including the mechanisms of this interaction.

Keywords:
sleep,
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sleep disturbances,
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Sažetak

Spavanje predstavlja fiziološki proces čiji efekti su presudni za održavanje organizma u homeostazi. Poremećaji spavanja su široko rasprostranjeni. Poremećaj u kvantitetu ili kvalitetu spavanja usko je povezan sa brojnim poremećajima. Već je dokazana veza između poremećaja spavanja i depresije, ali mehanizmi njihove interakcije su još uvek nedovoljno razjašnjeni. Razumevanje etiologije poremećaja i mehanizama interakcije može biti od presudnog značaja za adekvatno lečenje oba poremećaja, naročito kod pacijenata sa poremećajem spavanja koji imaju psihijatrijske i psihosomatske manifestacije. U ovom preglednom radu biće sabrana najnovija saznanja o povezanosti između poremećaja spavanja i depresije, uključujući i potencijalne mehanizme njihove interakcije.

Ključne reči:
spavanje,
depresija,
poremećaj spavanja,
BDNF

Introduction

Sleep disturbances are widely spread within the community. It has been well determined that adolescents require at least 9 to 10 hours of sleep per day. However, in the United States, an average teenager experiences only about 7.9 hours of sleep and over 25% of college and high school students have been found to be sleep deprived (1,2). Inadequacy of quantity and quality of sleep are associated with numerous diseases, but in this paper, we will focus our attention to its relationship with psychiatric disorders, i.e. depression at the forefront (3-5).

There are two major types of sleep pattern alteration: sleep deprivation (SD) and sleep fragmentation (SF). Sleep deprivation is characterized by prolonged time since the last sleep period (in total sleep deprivation), chronically restricted sleep duration (in chronic partial sleep deprivation) or exclusively REM sleep deprivation, in a model of paradoxical SD. It is well known that sleep deprivation has numerous negative effects on our health, such as excessive daytime sleepiness (EDS), clumsiness and weight deregulation. However, in some cases, it can also lead to increased alertness and heighten energy. Therefore, it was used for the treatment of depression (6). Total sleep time is insignificantly diminished in SF. Instead, it consists of frequent, brief arousals, followed by a rapid sleep onset, thereby modulating regular sleep architecture (7,8). Interruption of REM, as well as NREM sleep phase, are included (8). Sleep fragmentation is a primary psychological disorder, and may occur in patients with various psychiatric, medical and respiratory problems including patients who suffer from obstructive sleep apnea (OSA) (9). It usually results with daily somnolence, lack of attention and reduced cognitive abilities (10-12).

Sleep is a major part of our everyday life, and some of its effects are crucial to maintain physiological function throughout the day (13). Most common symptom that occurs in people suffering from the lack of sleep, regardless of sex or age, is EDS (14), along with the reduced reaction time (15), shortened anaerobic performance (16), decline in cognitive processes (such as visual tracking, focus, determination, mood) (17,18) and emotional breakdown in adolescents (19). Also, we need to mention a bidirectional relationship between sleep and mental health (20), focusing majorly on depression as the proven consequence of chronic sleep disorders. However, some of the researchers argued that sleep disturbance cannot be a cause of depression but merely a contributing factor (21). As a connection between the lack of sleep and depression has always been suspected, a strong etiologic correspondence has always been a tricky subject to study.

In this article, we will review the recent findings about connection between sleep disturbances and depressive disorders. Also, we will address the mechanisms included in this interaction, so that hopefully we could understand the cause and the consequence of this relationship.

Sleep Deprivation and Depression

Sleep deprivation could be partial and total sleep deprivation, which differ depending on the length of the deprivation. However, from the clinical point of view, their effects have been demonstrated to be qualitatively similar (22). It has been established that 90% of depressed patients have sleep disorders (22). Ford and Kamerow were first who proposed insomnia as an independent risk factor for depression in 1989. Since then, several studies have been carried out, in order to investigate this correlation. Authors like Riemann and Voderholzer, after reviewing the literature from 1966 - 2000, established a strong evidence that insomnia can be considered an independent risk factor for depression (23). Giedke and Schwaerzler were first to propose an unconventional treatment for depression, suggesting that sleep deprivation, whether total or partial, leads to improvements in the symptoms of depression, including a decrease of suicidal tendency (24). Few differences have been noticed between total sleep deprivation and partial sleep deprivation, with the first one being the most relevant for clinical improvement of patients treated for depression (25).

Furthermore, it should be noticed that depressed patients have an increase in the REM latency, which is the reason they spend more time in the REM phase than healthy sleepers. From the clinical and therapeutic point of view, evidences show that a selective REM partial sleep deprivation can be performed on these patients with a positive outcome. However, it is slightly less effective when compared to total sleep deprivation (26). The main

indication for the therapeutic use of sleep deprivation is primary depression. The use on secondary forms is still under investigated, however, it has been shown that sleep deprivation has a positive effect on depressive episodes secondary to schizophrenia and schizoaffective disorder (27). Despite all the research, results on anti-depressive effect of sleep deprivation are contradictory at best. Babson et al. showed that deprived sleep in healthy subjects highly increases stress levels and strongly potentiates intensive symptoms of both anxiety and depression (28).

Considering potential beneficial effects, sleep deprivation is still used as a treatment, but with strict indication range. Around 60% of patients with major depressive disorder showed clinical improvement after one night of SD (29). Improvement has been noticed even in patients in suicidal intent, but it had the strongest effect on patients with severe diurnal mood alterations (30). Unfortunately, therapeutic effect can disappear as quickly as it came. In some, it lasts for a few hours, and in others the whole day, rarely for a few days. Around 50 - 80% of these patients have a recurrence of symptoms, while 20 - 50% do not, mostly the ones poly-treated with antidepressants and sleep deprivation (31) (**Figure 1**).

Sleep Fragmentation and Depression

Obstructive sleep apnea (OSA) is classified as the sleep-related breathing disorder, associated with impaired ventilation and fragmentation of sleep. It is estimated that OSA is highly prevalent in the population, reaching the prevalence of 3% to 7%, with certain subgroups of the population bearing higher risk (32). It is classified within the sleep-related breathing disorders. Although there is a critical gap in the diagnoses of OSA in patients with severe mental illnesses (33), a correlation between OSA and depression has been noticed. Since the first studies, in which 25% (34) and 40% (35) of OSA patients also met diagnostic criteria for depressive disorders, a link has been highlighted. A cohort study published in 2013 described almost doubled incidence of depressive disorders, in patients with OSA (36). There is a strong prevalence of depression among OSA patients, both in community and in specialized clinics for sleep-disorders. Moreover, an improvement of psychiatric symptoms was noticed in these subjects when treated with continuous positive airway pressure (CPAP). Yet, there was no strong evidence on etiologic origin of depression

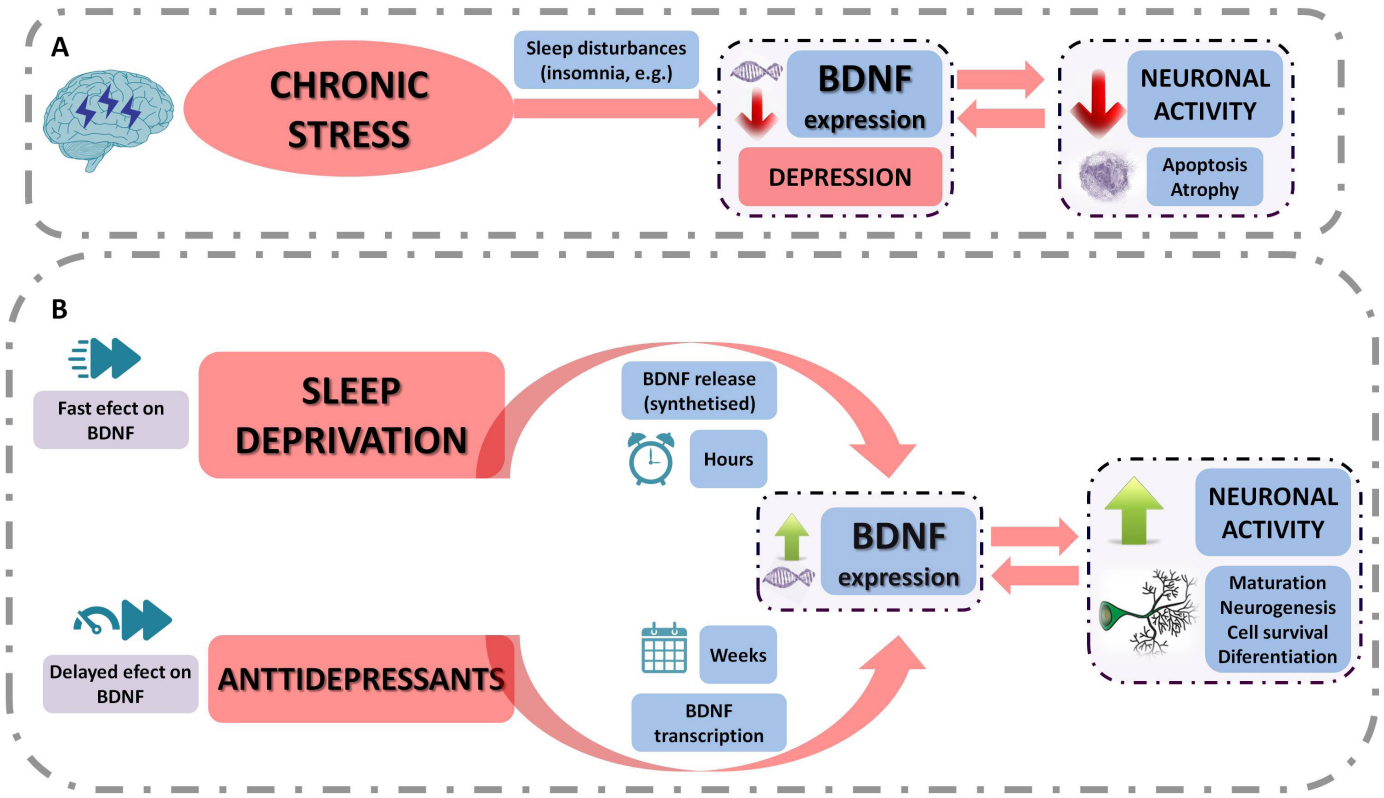

Figure 1. The effects of chronic stress, sleep deprivation and antidepressive treatment on depressive disorder.
A. Chronic stress (sleep deprivation or fragmentation, insomnia, etc.) lower the level of BDNF expression thereby causing depressive episodes by attenuating neuronal activity.
B. Sleep deprivation only acutely have beneficial role in depressive disorder, however, chronically without antidepressive treatment there is no effect, moreover clinical image of depression could be worsened by repeated deprivation if left untreated. Combined with antidepressants, sleep deprivation chronically cause rise in neuronal activity potentiating maturation of synapses, neurogenesis and differentiation of stem cells.

in OSA patients (37). Many plausible explanations have been proposed. Intermittent hypoxemia during sleep may influence mood and promote EDS. As demonstrated by a randomized controlled trial patients may benefit from both therapeutic CPAP (correcting both desaturation and sleep fragmentation) and O_2 supplementation (only correcting hypoxemia), with the latter having a greater therapeutic impact on depression (38). In contrast, other authors, concluded that psychological symptoms are mostly correlated with sleep fragmentation and not with oxygen desaturation. According to them, OSA patients had an increase in time spent in NREM phase 1 of sleep and wakefulness, and a decrease in slow wave sleep. This correlates with several symptoms being mostly somatization, obsession-compulsion, depression, anxiety and hostility. Also, the severity of these symptoms is inversely related to the total sleep time, sleep in stage 1, and latency to NREM sleep. On the other hand, it is directly related to the percentage of wake time after sleep, and the percentage of stage 2 of NREM sleep. The psychological symptoms didn't correlate with oxygen saturation in this study (39).

No study has given a definitive answer about the etiology and the correlation between sleep apnea and depressive states yet. It should also be noticed, that it is quite difficult to totally distinguish between endogenous depression, mood changes and daytime sleepiness, caused by OSA. There is indeed a profound overlap of symptoms; for instance, fatigue, poor concentration, loss of interest, insomnia, and decreased libido are shared between the two conditions, as well as with other more generalized clinical situations such as obesity, diabetes, metabolic syndromes, and systemic inflammation.

Many scales and questionnaires exist for the evaluation of depression, each of them giving slightly different results. However, none of these scales has been validated in OSA patients (37). As a consequence, several biases and confounders may lie within experimental results. For example, the results are strongly dependent on the sample size, sex and age distribution, and on the method used for the evaluation of the psychological status. It should be also mentioned that some subjects tend to adapt to their diseases and upgrade their performances if needed. Thus, opposite results may be expected from different studies (39).

BDNF in Sleep Disturbances and Depression

Synaptic remodeling and synaptogenesis are greatly dependent on neurotrophic factors, mainly neural growth factor (NGF), neurotrophins 3 and 4 (NT-3, NT-4), glial cell-line derived neurotrophic factor (GDNF) and brain derived neurotrophic factor (BDNF) (40). The BDNF is a neurotrophin essential for neuronal development and survival, synaptic plasticity and cognitive function (41).

Previous research showed a decrease of BDNF serum levels in untreated depressed patients when compared to those who received adequate therapy, which brought BDNF in focus of research for mechanisms of depression (42). Moreover, positive correlation between levels of BDNF and severity of clinical image in depressed patients has been found (43). Postmortem hippocampal samples of depressed patients confirmed significantly lover BDNF concentrations in untreated patients compared to treated, along with smaller volume of the hippocampal tissue in all depressed patients (44). However, results on effect of BDNF in depression are not consistent enough, and this matter is still under researched. In animal models of depression, chronic stress and maternal deprivation led to decrease in BDNF mRNK levels in the hippocampus (45). Also, infusion of tyrosine-kinase inhibitors block an anti-depressive effect of BDNF, which emphasize important role of tyrosine kinase B receptor (TrkB) cascade in anti-depressive mechanism of BDNF (45). Considering all mentioned, it is probable that the lack of BDNF is instrumental in pathogenesis of major depressive disorder and activation of BDNF-TrkB cascade is necessary for therapeutic effect of anti-depressives.

The procedure of sleep deprivation has proven its efficacy for alleviating depression (46) with multiple neurobiological mechanisms involved in the therapeutic effects acutely, and pathophysiologic processes chronically (47). The BDNF gene transcription, inducing long-term potentiation (LTP), seems to play a role for neuroprotection and neurogenesis, and TrkB (activated by BDNF) has a role in the modulation and mediation of circadian rhythms, that appears to be disturbed in mood disorders (47,48). The BDNF is thought to increase intracellular calcium, by activation of tyrosine kinase B receptor/phospholipase Cγ (TrkB/PLCγ) pathway, thus promoting phosphorylation of CaMKII (49). The CaMKII is a key mediator which can readily enter potentiated synapses and act as a molecular switch to mediate long-term information storage. This phase of LTP leads to long lasting enhancements in synaptic efficacy, enhanced pre-synaptic neurotransmitter release and phosphorylation and trafficking of AMPA receptors (49). The negative effect of sleep deprivation on LTP and synaptic plasticity is thought to be a product of the underlying alterations in intracellular signaling molecules such as CaMKII, calcineurin, and BDNF. The decrease in basal BDNF levels may directly affect the reduction of P-CaMKII basal levels (49). Conversely, while short-term total sleep deprivation appears to up-regulate the expression of BDNF in various regions of the brain, selective deprivation like REM or paradoxical SD in rats showed no alterations of BDNF expression (50). Acute, therapeutic effects of SD or partial SD may stem from fast release of BDNF, thus normalizing BDNF levels, in contrast to prolonged latency of classic antidepressants. Particularly, it has been shown that REM-SD in major depressive disorder (MDD) leads to a gradual improvement, suggesting that the antidepressant effects of both selective REM-SD and total SD are based on the suppression of slow wave activity (SWA). In addition, it is known that BDNF production is stimulated by serotonin and conversely, BDNF increases serotonergic signaling. Chronically, there are suggestions that prolonged stress in form of

inadequate sleep might induce a deregulation of the hypothalamic-pituitary-adrenal system. In the long-term, it leads to exacerbated sleep disturbance, decreased BDNF levels, which in turn may impair the individual's ability to adapt to crisis situations, as well as depression (47) (**Figure 1**).

Acute sleep deprivation leads to higher levels of pCREB (active form of transcriptive factor) and increase in levels of BDNF receptor TrkB (51). As a result, we also have an increase in molecules involved in brain plasticity, which expression is also heightened during chronic anti-depressive treatment. However, as we can conclude from previous text, the effect of sleep deprivation is acute and cannot sustain for a longer period without proper anti-depressive treatment. In their meta-analysis, Brunoni et al. are also in agreement with neurotrophin theory of depression, suggesting that improvement in major depressive disorder is correlated with neuroplasticity and different type of anti-depressive treatments all lead to incensement in BDNF levels (52). The effect of sleep fragmentation on BDNF levels in depressive disorder still remains to be determined.

Other Mechanisams Potentially Involved in Interaction Between Depression and Sleep Disturbances

Beside mechanisms related to BDNF, described in the previous section, a number of other mechanisms could be potentially involved in the relationship between sleep disturbances and depression. These mechanisms include serotonergic and dopaminergic neurotransmission, as well as the oxidative stress.

Serotonin has a prominent role in the regulation of sleep–wake circadian cycles, as well as in the modulation of mood states in humans (53-55). Decreased function of serotoninergic neurotransmission in sleep disturbances is proven to be associated with depression, mainly because of gradual alterations of HPA axis and limbic functions (53,54). The reason could be found in the tight connections of *ncc. raphe* with areas responsible for stress and emotion management (54,56). In chronic sleep restriction, gradual reduction of 5-HT_{1A} postsynaptic receptor sensitivity was observed in rats, that led to the lack of exploratory capacity and frequent mood alterations, as well as the further incapability to maintain the sleeping continuity (53).

Dopamine (DA) is a neurotransmitter that helps control the brain's reward and pleasure centers. Dopamine also helps regulate movement and emotional responses, and it enables us not only to see rewards, but to take action to move toward them. There are suggestions that dopamine plays a central role in behavioral alterations in sleep disturbances. Studies showed that rats with posttraumatic stress disorder (PSD) had increased postsynaptic responsiveness of D2 receptors (e.g. in striatum, *nc. accumbens*), with DA-agonist induced stereotypy and aggression (55). Additive effects have the down-regulation of brain's α1- and β-adrenergic receptors, while α2 were up-regulated (55-58). This can further explain the reduction of the exploratory behavior in rat model of SF.

Disturbances of monoaminergic neurotransmitter systems have been well observed, specifically cholinergic and noradrenergic. There is a strong evidence that pontine cholinergic and cholinoceptive neurons, interacting in coordination, trigger and maintain REM sleep (59). Onset of mood disorders is suggested to be a consequence of imbalance of cholinergic and noradrenergic regulatory systems that occur during REM sleep phase (59). In neuroendocrine mouse model of depression, it is considered that the main mechanisms underlying sleep and behavioral alteration are probably a consequence of chronic corticosterone treatment that triggers a negative feedback control on the HPA axis. Moreover, patients with depression are resistant to suppression of cortisol secretion after dexamethasone administration and, therefore, dexamethasone suppression test has been used as a biological marker for depression (58). These claims correlate with findings in a subpopulation of depressed patients, which had a decrease in HPA axis activity, corticotrophin-releasing hormone (CRH) secretion and hypo activity of the waking systems and, consequentially, increased concentration of glucocorticoid receptors in the CNS. Loop, altered this way, could affect NREM sleep. By increasing its share in total sleeping time by activation of mineralocorticoid receptor dependent mechanism, it could cause a decrease in REM length and incidence, by glucocorticoid receptor mediated mechanism. Since neurons in suprachiasmatic nucleus (SCN) do not express either mineral- or glucocorticoid receptors, this center could only be affected by corticosterone indirectly, through projections from other areas expressing them and reach SCN (59).

In addition to all described mechanisms that could play major roles in SD or SF induced depression, it should be mentioned that reactive oxygen species (ROS) could also have, at least minor impact on psychological stress, since reduced glutathione (GSH) levels are reported in some brain regions of rats, particularly hypothalamus and thalamus, although findings suggest that the oxidative stress in the brains of rats following PSD does not result in cell loss (60). There are evidences that suggest possible role of increased brain NADPH oxidase level in sleep fragmentation-induced oxidative stress, too. This enzyme has emerged as a major source of ROS generation in most mammalian cells, including neurons and synapses, either as a by-product of normal catalytic activity or as the result of aberrant function in disease. In an experiment that involved mice with knock out mutation of NADPH oxidase, and adequate controls, after 15 days of SF, experimental group displayed normal learning and was protected from the spatial learning deficits observed in controls exposed to SF, with significantly elevated NADPH oxidase gene expression and activity. Most importantly, neither sleep duration, sleep state distribution nor sleep latency were affected in both experimental, as well as control group (61). Results vary among studies, with some suggesting increased affection of the hippocampus and hypothalamus, while

others report reduced susceptibility to ROS in cortex and brainstem in response to SD.

Conclusion

Sleep disturbances are highly connected to depressive disorders but exact mechanism of this interaction still remains unknown. There are probably at least several mechanisms fortifying this relationship. It is important to mention that not all sleep disturbances have the same effect on depressive disorder. On the one side, we have a sleep deprivation (total or partial), which is proven to have beneficial effect on depressed patients in acute treatment, and on the other patients with OSA (sleep fragmentation), which symptoms of depression only get more severe as the disease progresses. The reason for this difference is still to be found, but the possible cause could be different duration of sleep between SD and SF. In SD, as previously mentioned, we have a shorter sleep period in one faze or in all, depending on the type of deprivation. However, in sleep fragmentation sleep duration is insignificantly changed or unchanged, since the main problem is architectural disturbance in sleep fazes and in the way they intertwine with one another.

Understanding the underlying mechanisms could be the key for treatment of both disorders especially in patients with psychosomatic and psychiatric comorbidities. The BDNF has significant role in both sleep disturbances and depression and should be included in diagnostic criteria for prediction of this diseases, especially with patients in suicidal tendencies. There is also a possibility of gene related deficiency of BDNF, so supplementation could represent a possible model of treatment, and BDNF could be used as a screening target.

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