REVIEW

Investigating the Role of BDNF in Insomnia: Current Insights

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Abstract: Insomnia is a common disorder defined as frequent and persistent difficulty initiating, maintaining, or going back to sleep. A hallmark symptom of this condition is a sense of nonrestorative sleep. It is frequently associated with other psychiatric disorders, such as depression, as well as somatic ones, including immunomediated diseases. BDNF is a neurotrophin primarily responsible for synaptic plasticity and proper functioning of neurons. Due to its role in the central nervous system, it might be connected to insomnia of multiple levels, from predisposing traits (neuroticism, genetic/epigenetic factors, etc.) through its influence on different modes of neurotransmission (histaminergic and GABAergic in particular), maintenance of circadian rhythm, and sleep architecture, and changes occurring in the course of mood disturbances, substance abuse, or dementia. Extensive and interdisciplinary evaluation of the role of BDNF could aid in charting new areas for research and further elucidate the molecular background of sleep disorder. In this review, we summarize knowledge on the role of BDNF in insomnia with a focus on currently relevant studies and discuss their implications for future projects.

Keywords: sleep, insomnia, brain-derived neurotrophic factor

Introduction

Sleep is vital to cognitive performance and overall health, and sleep disturbances are known to significantly decrease life quality as well as affect the course of other diseases. For example, sleep disorders have been demonstrated to be a risk factor for disease relapse in ulcerative colitis patients.[1] In a South Korean study, patients with sleep disorders had a higher risk of developing immunomediated disorders, such as alopecia areata, Graves disease, or Hashimoto thyroiditis.[2] According to Young et al, sleeping <7 hours per night puts individuals at a higher risk of developing systemic lupus erythematosus.[3] Interestingly, Sang et al found no association between genetically determined insomnia (125 single-nucleotide polymorphisms identified by the authors) and systemic lupus erythematosus, which suggests that the relationship between the two is dynamic and could involve external factors, such as lifestyle and environment.[4] Poor sleep quality is also an important risk factor for depression relapse.[5]

The American Academy of Sleep Medicine defines insomnia disorder as frequent and persistent difficulty initiating, maintaining, or going back to sleep in spite of the right conditions, which results in nonrestorative sleep.[6] Insomnia disorder is usually associated with some level of impairment in other domains of life. The cutoff point between chronic and short-term insomnia is 3 months, and symptoms should occur at least 3 times a week.[6] Insomnia prevalence varies between studies. Depending on the population and assumed diagnostic criteria, it appears to be 10%–30%.[7] It can be a primary disease or a symptom of another condition, such as restless leg syndrome (RLS) or periodic leg movements during sleep. Insomnia also frequently accompanies psychiatric disorders and immunomediated diseases.[8–10]

The causes of insomnia remain elusive. Insomnia might have genetic predisposing factors, as familial aggregation has been observed.[11] Insomnia appears to be tightly related to stress-response and coping mechanisms. The term "sleep reactivity" describes individual propensity to sleep disruptions in response to stressful situations. This trait alongside neuroticism is a risk

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factor for insomnia development.[11,12] Currently, one of the most popular models of insomnia, developed by Spielman et al in 1987, identifies three types of factors at play: predisposing, precipitating, and perpetuating.[13]

The cornerstone of insomnia treatment is cognitive–behavioral therapy (CBT). CBT focuses on developing certain adaptive strategies, like control of stimuli, relaxation techniques, and coping with stress.[14] This approach is effective and results are sustainable over time.[14] In their guidelines, the European Sleep Research Society also approves the use of some antidepressants (eg, doxepin, mianserin, mirtazapine, trazodone), benzodiazepine-receptor agonists (Z-drugs), and benzodiazepines.[15] Commonly used antihistamines and melatonin are not recommended due to the low quality of available evidence in favor of their use.[15]

BDNF is a neurotrophin ubiquitous in the central nervous system (CNS), particularly in the prefrontal cortex and the limbic regions, with the highest levels detected in the hippocampus.[16,17] Outside the CNS it is also found in the heart, lungs, and liver.[17] As a neurotrophic factor, BDNF is responsible for growth and development of neurons, promoting neuro- and gliogenesis.[18] BDNF also has antiapoptotic properties; it stimulates the sonic hedgehog and erythropoietin and promotes the expression of Bcl-2 proteins, which together prevent cell death.[19] Neurotrophin might also exert antioxidative and antiautophagy effects through ERK1/2 and PI3K/Akt pathways, respectively.[19]

BDNF is vital for neuroplasticity: it affects the development of new synapses by modulating synaptic arborization and morphogenesis, thus promoting formation of new neuronal circuits and improving cognitive function.[20] It also controls glutamatergic transmission by regulating the activity and expression of N-methyl-ᴅ-aspartate receptors (NMDARs), associated with enhanced memory formation.[17] Therefore, it is likely to confer some of the benefits of sleep, such as memory consolidation.[18]

Disruptions in BDNF signaling have long been associated with psychiatric disorders, such as dementia or depression, which are frequently accompanied by insomnia.[21,22] Patients with Alzheimer's disease have been shown to have lower levels of this neurotrophin in brain, blood, and cerebrospinal fluid. Moreover, increased serum BDNF was associated with better cognitive faculties in this group.[23] Similar observations have been made in patients with major depressive disorders: treatment with antidepressant drugs or electroconvulsive therapy brought about significant improvements in BDNF levels.[24] BDNF might also be directly involved in the course of insomnia.[18] It shows a strong connection to sleep architecture, the sleep–wake cycle, and comorbidities of this sleep disorder.[18]

This review aims to investigate the role of BDNF in insomnia and other selected subjects related to this sleep disorder (eg, circadian rhythm, neurodenerative conditions), with a focus on currently relevant studies. We discuss the relationship between BDNF, the sleep–wake cycle, circadian rhythm, the basis of an inherent propensity to insomnia, and the interplay between stress response and the titular neurotrophin.

Neurobiology of BDNF

BDNF was discovered in 1982 by Yves Barde and Hans Thoenen.[25] It is a member of the neurotrophin family, and its structure bears a high degree of similarity to other neurotrophins, such as nerve growth factor (NGF), neurotrophin 3, and neurotrophin 4/5. The ***BDNF*** gene is located on the 11p chromosome.[18] It has five exons, with only the 3' exon coding for the BDNF protein.[18] Transcription of the remaining is tissue-dependent, with exons I–III dominating in different regions of the central nervous system, mainly the cortex and the hippocampus.[18]

BDNF's cognate receptor is tropomyosin receptor kinase B (TrkB).[18,26] Upon binding of the ligand, TrkB dimerizes and recruits other pathways, such as the MEK–MAPK pathway, ERK pathway, PLCγ pathway, and PI3K–Akt–mTOR pathway.[18] The PI3K–Akt–mTOR pathway might be of particular importance to the prosurvival effect BDNF has on neurons, as it is associated with autophagy and has been demonstrated to protect neuronal cells from hypoxic damage.[18,27] BDNF might also attenuate activation of microglia, preventing them from releasing proinflammatory cytokines and toxins that could damage neurons.[28]

BDNF is one of the major factors contributing to synaptic plasticity, which is strengthening or weakening synaptic connections, a process underlying learning or memory formation.[29] Inhibition of this pathway has been shown to reduce synaptogenic activity of the synapsin I and NMDAR pathway.[29] *BDNF*-knockout animals display decreased synaptic density to sympathetic neurons.[30] In contrast, stimulation of the BDNF pathway promotes dendrite arborization, while dendrite branching is enhanced by TrkB and MAPK pathway–mediated cypin expression.[31–35]

The BDNF pathway is strongly connected to glutamatergic neurotransmission. It has been demonstrated to regulate the amount of glutamate released to the synapse via MAPK-dependent synapsin I phosphorylation, as well as an increase in intracellular Ca^{2+} concentration.[36–38] It also interacts with the postsynaptic glutamate receptors NMDAR and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor, promoting their phosphorylation.[39–41] It might exert a protective influence against glutamate excitotoxicity via the Ras–MAPK and PI3K–Akt pathways.[42]

BDNF is also connected to γ-aminobutyric acid (GABA) signaling.[43] It controls the expression of the GABA synthetic enzyme GAD65.[43] BDNF also inhibits endocytosis of $GABA_AR$, a metabotropic GABA receptor, via PI3K, including its downstream target PP2A and PKC pathways.[43] ProBDNF has the opposite effect, promoting endocytosis of $GABA_AR$ β3 subunits through the RhoA–Rock–PTEN pathway.[43] As already mentioned, a majority of neurons in the suprachiasmatic nucleus (SCN) are GABAergic; therefore, it is possible that BDNF fulfills there a major role controlling communication between cells.

It could be suspected that orexin signaling is related to BDNF. This neuropeptide was demonstrated to prompt the expression of the neurotrophin via activation of the OX1R-related pathways: PI3K and PKC.[44] Interestingly, mice bereft of another orexin receptor, OX2R, were shown to have more depressive behavior than healthy ones. This could be caused by an in increase in BDNF expression mediated by OX2R-mediated stimulation of the CREB pathway.[44,45] Due to the importance of orexin for histaminergic signaling as well as wakefulness, future studies on the role of BDNF in the context of discussed neuropeptides are validated.

BDNF and Sleep Regulation

Sleep is a complex, involving specific brain activity, which can be shown on electroencephalography (EEG). Sleep architecture is a term describing changes in the EEG patterns seen through the night.[46] Two main stages of sleep are non–rapid eye movement (NREM) and REM phases.[46] NREM can be further divided into three stages, N1–N3: N2b and N3 are described as slow-wave sleep (SWS).[46] Apart from eye movement, those two distinctly differ in terms of muscle tone and heart and respiratory rate.[46] Slow-wave activity (SWA) is characterized by EEG power between 0.5 and 4 Hz.[46] Sleep progresses in cycles between those phases, usually four to five per night.[46]

Sleep architecture varies on an individual basis, depending on factors like age, sex or drug use.[46] Its alterations have been observed in numerous conditions, including insomnia.[46–49] Even though polysomnography is not a diagnostic method for insomnia, changes in sleep architecture might affect one's perception of sleep duration and its quality, and thus factors shaping sleep structure need to be studied.[46] Literature on the subject shows that BDNF might modulate sleep structure. Intraventricular administration of BDNF was demonstrated to increase the duration of both REM and NREM sleep in rabbits, but only NREM in rats.[50] What is interesting is that changes in sleep architecture in mice with decreased BDNF production due to heterozygosity negatively affect only REM sleep, while NREM is unaltered.[51] This includes decreased overall REM duration and number of phases and increased REM initiation.[51]

A decrease in BDNF production caused by the Val66Met BDF single-nucleotide polymorphism rs6265, present in 25%–30% of the population, is associated with prolonged initiation and termination of SWA (a type of EEG oscillation present primarily during NREM that is enhanced proportionally by the duration of wake time preceding sleep, a marker of sleep need).[52–54] Moreover, those individuals display reduced SWS duration and sleep activity (as measured by delta activity).[54] In a study on patients with major depressive disorder, it was revealed that upregulated BDNF production was linked to more intense SWA and higher NREM sleep quality; however, the level of this neurotrophin did not bear any relation to insomnia in this group.[55]

The mechanism behind BDNF's action on sleep architecture remains elusive. Some researchers maintain it has little, if any, influence on SWA.[56] The mode of BDNF administration seems to be an important modulator of the effects exerted by this protein. Intracortical administration has been shown to enhance SWA, while intraventricular BDNF injections led to SWA reduction.[50] It is plausible that the intraventricular mode of injection affect other structures controlling sleep.[57] Faraguna et al posited that BDNF is the interface between synaptic plasticity and SWA.[57] In a study on rats, animals who displayed more exploratory behavior had higher SWA than their less inquisitive counterparts.[57] Moreover, SWA, BDNF production, and exploratory behavior were positively correlated.[57]

In contrast to the aforementioned studies, Watson et al hypothesized that the BDNF pathway has a greater role in modulation of REM sleep, rather than NREM.[50] Mice lacking a form of BDNF receptor TrkB T1 (truncated isoform without the tyrosine kinase domain), did not exhibit any changes in NREM, but REM sleep in this group was profoundly distorted. The researchers noted an increase in REM duration, decrease in REM sleep latency, and sleep fragmentation.[50] Those changes resembled the ones seen in patients with depression.[50] In vivo inhibition of the BDNF pathway brought contrasting results, decreasing the number of REM duration and episodes.[58] BDNF might also be involved in regulation of REM sleep drive: mice with decreased BDNF production after selective REM sleep deprivation do not experience rebound REM sleep.[51] This is in line with other studies, which showed that receptors for BDNF can be found in GABAergic and glutamatergic neurons of the midbrain and the brain stem important for sleep regulation. The pedunculopontine tegmentum, located in the upper brain stem, in particular was demonstrated to be vital for REM drive.[51,59]

BDNF and Circadian Rhythm

Circadian rhythm is a biological clock that follows a 24-hour cycle. It regulates alertness/sleepiness, metabolism, behavior, etc.[60,61] The role of the central master clock is fulfilled by the SCN, which coordinates secondary peripheral oscillators in the tissues.[60] When endogenous circadian rhythm is altered or there occurs a misalignment between external factors and sleep–wake cycle (eg, shift work), circadian rhythm sleep disorder (CRSDs) might develop.[62] These include conditions like advanced/delayed/irregular sleep–wake phase disorder or shift-work sleep disorder. Due to similar symptomatology to insomnia, there are discussions on whether they should be classified together or regarded as a separate group of sleep disturbances. This review assumes the approach of the American Academy of Sleep Medicine, which claims that CRSDs can generate insomnia.[63] Nevertheless, thorough differential diagnosis between CRSDs and primary insomnia is necessary in order to apply proper treatment.

The pathophysiology of CRSDs is complex. Research has demonstrated that polymorphisms in clock genes like *PER3* or *CLOCK* might contribute to a susceptibility to sleep disorders.[64–66] External factors appear to play a role as well, such as with shift-work sleep disorder.[67] Due to its interactions with the circadian rhythm, BDNF might partake in the pathophysiology of CRSDs; however, the literature on this subject remains limited. It has been evidenced, that this neurotrophin and its receptor TrkB are expressed in the SCN.[68] As for BDNF, D'Agostino et al showed that it could be indispensable in the maintenance of circadian oscillators: *BDNF*-knockout zebrafish showed severe impairments in clock gene expression.[69] Studies demonstrate that this neurotrophin displays circadian rhythmicity. Piccini et al and Choi et al observed this relationship only in men.[70–72] However, in a study by Cain et al, as many as three in four women and one in two men had BDNF circadian rhythmicity.[70] The BDNF peal was unrelated to clock time in women, as opposed to men.[70] In a study on healthy male volunteers, Begliuomini et al showed that plasma levels of BDNF and cortisol are positively correlated and peak early in the day to later decrease.[73]

Melatonin is a hormone produced in the pineal gland modulating the adjustment of circadian rhythm to the photoperiod. Jang et al showed that the melatonin precursor *N*-acetylserotonin might activate TrkB receptors in a circadian-dependent manner, with peaks during the biological night.[63] This indolamine was shown to increase BDNF expression in animal models.[74] Nevertheless, a recent meta-analysis did not confirm the same effect in humans.[75] Future research on the subjects of interplay between the circadian rhythm, melatonin, and BDNF would be desirable. Organic and functional aspects of changes in the circadian rhythm occurring in the course of various CRSDs might be further studied in the context of BDNF and other neurotrophins.

BDNF and Stress

Stress can exert various effects on health, depending on its predictability, intensity, and duration. The importance of stress-induced hyperarousal (in emotional–cognitive and somatic aspects) has long been suggested to play a role in the pathophysiology of insomnia.[12] It could be hypothesized that coping strategies (cognitive and behavioral) and sleep reactivity affect the risk of developing insomnia. Studies seem to confirm this. Otsuka et al demonstrated that insomnia is more prevalent in individuals with maladaptive behavioral patterns (ie, substance use, self-blame).[76] Other researchers obtained similar results.[77,78] Insomnia is also an important diagnostic symptom in anxiety disorders: approximately 70%–

90% of these patients suffers from this sleep disorder.[79] As Neckelmann et al found, insomnia might also be a risk factor for anxiety disorder (OR 4.9, 95% CI 3.8–6.4).[80]

This system of sleep regulation might be disrupted by hyperarousal, an element strongly emphasized by insomnia models proposed in recent decades. Acute stress, a usual trigger of insomnia, was related to the increased activation of both sleep- and wake-promoting neurons, which under physiological conditions should be switched off.[81] The state of hyperarousal is difficult to exhaustively define: it might involve numerous components, like neurotransmitters, the endocrine system, and genetics.[82] Riemann et al in their work adopted a holistic view of this state, describing it as affecting cognitive–emotional, cortical, and physiological domains of functioning.[83] Even in the early studies, it was observed that insomnia individuals tend to display signs of enhanced metabolism, like increased body temperature, level of adrenaline, cortisol, and heart rate.[82] Hyperarousal in chronic insomnia might also be associated with secondary maladaptive behaviors developed in response to acute insomnia caused by a stressful life event.[83] These include rumination about adverse effects of currently experienced sleep disorder, focus on daytime insomnia symptoms, and drug/alcohol abuse, which further perpetuate the sleep disorder, creating a vicious circle.[83]

Glucocorticoids can cross the blood–brain barrier and fulfill important functions within the central nervous system.[84] Under physiological conditions, they participate in the formation and stabilization of new synapses, as well as synaptic pruning.[85] Pathological excess of glucocorticoids, like in Cushing's disease, is well known to have psychiatric consequences, such as mood disorders.[86] Individuals afflicted with this disease might also experience regressive changes in the hippocampus and the prefrontal cortex, eg, loss of synaptic density or dendrite arborization.[86] According to a recent meta-analysis, patients with insomnia also tend to have an increased level of peripheral cortisol as well as disturbed rhythm of secretion of this protein (ie, normal morning cortisol, increased during daytime and before bedtime), which demonstrated dysregulation of the HPA axis in this group.[87] Products of the HPA axis were demonstrated to alter BDNF production and pathway, which might suggest that their negative effects on neurons could be mediated by changes in activity of this neurotrophin.[84,88–90]

In a study on rats subjected to chronic stress, an increase in hippocampal, hypothalamic, and pituitary BDNF as well as plasmatic corticosterone in comparison with healthy controls was noted. Other studies with similar stress protocols showed that *BDNF* mRNA level was decreased in the hippocampal region.[91] Those results suggest that alterations in BDNF production are posttranscriptional; however, none of the BDNF precursor forms was measured.[91] The authors suggested that such alterations might aid in adaptive processes of the HPA axis due to BDNF's role in synaptic plasticity.[91] This neurotrophin could also participate in restoration of cortisol reserves, depleted during stress.[91] What is interesting is that a pattern of time-dependent changes in BDNF levels in the pituitary and hypothalamus in response to an acute stressor were similar in the study group and controls; however, in the hippocampus, an opposite dynamic was observed, with significant decreases in the study group.[91] Such an effect could explain atrophy of C3 neurons, observed in chronic stress.[91]

In a study on suicide attempters, those who had a dysregulated HPA axis (ie, did not experience suppression of cortisol production in the dexamethasone suppression test) showed a negative correlation between posttest cortisol level and plasma BDNF.[92] This association was present only in women, which might to some extend elucidate the mechanisms behind differences in suicidal behavior between sexes.[92] On the other hand, in a study on subjects with burnout, a psychosomatic disorder thought to stem from working in a high-stress environment, no significant relationship between BDNF and cortisol was noted.[93]

Another subject worth mentioning in the context of interactions between BDNF and stress is anxiety disorders. There are reports of associations between the Val66Met polymorphism in the *BDNF* gene and the conditions discussed herein; however, studies on the subject have brought conflicting results.[94] According to a meta-analysis by Suliman et al, the level of this neurotrophin on the periphery is reduced in this group of patients, but this decrease is not uniform across the spectrum of anxiety disorders. Obsessive–compulsive disorder appeared to be responsible for BDNF reduction.[94]

Next to catecholaminergic neurons and glucocorticoid axes, dopaminergic neurons are an important element of stress response.[95] The two important neuronal circuits that participate in adaptation to stress are the mesolimbic (reward) and corticolimbic (emotion) system. A10 dopamine-containing neurons are located in the ventral tegmental area (VTA), a part of the mesolimbic system that is responsible for reward, motivation, and executive and affective functions.[95]

Dopaminergic neurons from the VA project, among others, to the prefrontal cortex (PFC), amygdala, and nucleus accumbens (Nac).[88] The mesolimbic system is connected to the corticolimbic system in numerous locations, like the PFC, the hippocampus, the VTA, and the Nac, and is considered to be the major interface between the limbic system and motor regions of the cortex.[88] Proper functioning and synchrony between these two systems allows for value-based learning and selection of action based on predicted consequences.[88] Impairments of the mesocorticolimbic system have been linked to drug abuse, addiction, and depression.[88] The relationship between substance abuse and sleep disorders might be a particularly interesting subject for future research, as it appears to have a bidirectional character: sleep complaints are among the most common in subjects who have a history of addiction, and patients with sleep disorders are at a high risk of developing problems with drugs or alcohol, as they try to self-medicate insomnia.[96]

Based on studies on human brains and animal models, it appears that BDNF/TrkB expression is decreased in the corticolimbic system, inhibiting BDNF-mediated neuroplasticity in this region; the opposite occurs in the mesolimbic system.[88] Those alterations might increase the neuronal plasticity in the mesolimbic region, rendering individuals more prone to social stress or substance addiction.[88] It could be suspected that alterations in the BDNF signaling seen in insomnia could impair proper adaptive response to stress and instead facilitate the development of maladaptive habits, which would further exacerbate already existing problems with sleep, creating a vicious circle. The relationship between stress, BDNF signaling, and insomnia needs to be perceived as mutual. Disruption in one of those elements, caused by eg, trauma, could precipitate impairment of the others.

BDNF and Sleep Deficiency

Sleep deficiency might have either a chronic or acute character, which seem to have opposed effects on the organism. It might be conceptualized as a disorder in its own right, as it accompanies a vast number of conditions. Studies conducted up to this point on the subject of changes in peripheral BDNF level in insomnia consistently show BDNF reduction in individuals afflicted with this sleep disorder, regardless of sex or accompanying psychiatric conditions; findings are summarized in Table 1.[16] Among all characteristics of insomnia, ie, troubles falling asleep or maintaining this state, early-morning awakenings, etc., BDNF might be the most related to short sleep duration. According to Furihata, there were no differences between individuals with normal sleep duration (above 6 hours), regardless of the presence of insomnia.[97] However, in a group with short (<6 hours) sleep duration, BDNF levels were significantly lower only in subjects with insomnia.[97] In a study by Giese et al, BDNF concentration was negatively correlated with the severity of insomnia symptoms, as measured with the insomnia severity index (a scale based on DSM-IV criteria) and fatigue.[98] Moreover, in their study there were no differences in BDNF concentration between individuals diagnosed with RLS/periodic leg movements during sleep and those without.[98] RLS medication (ropinirole, antidepressants, etc.) did not affect the level of neurotrophin, which suggests that sleep disorders other than insomnia might not impact BDNF production.[98] There could be some variability depending on the biological material used in the study, ie, serum or plasma. About 99% of circulating BDNF is accumulated in platelets, which release it during coagulation.[99] Thus, in terms of serum, clotting time is crucial to results.[99] Trajkovska et al observed a decrease in serum BDNF in probes stored >6 months.[100] BDNF concentration might also differ on an individual basis, depending on sex, age, or physical activity.[99] In subjects with insomnia and short sleep duration (<6 hours), serum level of BDNF was positively correlated with neuropsychological faculties measured with tests on spatial span and brief visuospatial memory and the identical pair test.[101]

Acute sleep deficiency, ie, sleep deprivation, might increase BDNF both systemically in plasma/serum and locally in certain brain regions, eg, in the hippocampus.[20,107] It appears to be more related to lack of NREM sleep, as isolated REM sleep deprivation in general does not seem to strongly affect production of this neurotrophin.[107] However, there are studies showing elevated BDNF in the brain stem following REM sleep deprivation.[20,108]

A causal relationship between different types of sleep deficiency and BDNF used to be explained in the context of the biphasic model of stress, which is tightly connected to glutamate signaling in the prefrontal cortex.[109] Namely, acute stress (ie, sleep deprivation) enhances glutamatergic signaling in the PFC.[109] This process takes place thanks to genomic and nongenomic mechanisms, triggered by activation of the MR–GR pathway by corticosterone.[109] Intensification of glutamatergic transmission might promote further adaptive changes in function, morphology, and number of synapses,

Table 1 Summary of findings of studies on the subject of BDNF in insomnia

No.	Authors, year	Study population, insomnia definition	Biomaterial	Findings
1.	Sanchez-Garcia et al 2023[102]	Twenty-one insomnia patients and 22 healthy controls. Insomnia was defined as scoring at least 6 points on the AIS questionnaire.	Serum	Participants with insomnia showed decreased BDNF serum levels; BDNF serum level was negatively correlated with insomnia severity.
2.	Satyanarayanan et al 2020[103]	Sixteen patients diagnosed with primary insomnia and 10 healthy controls. Criteria for insomnia diagnosis were not included in the manuscript.	Plasma	Levels of plasma BDNF protein were lower in subjects with insomnia compared to the controls.
3.	Zhang et al 2020[104]	Twenty-seven patients with chronic insomnia disorder and 10 healthy controls. Insomnia was diagnosed according to ICSD-3 criteria.	Serum	Patients with insomnia exhibited lower serum BDNF levels than healthy controls.
4.	Furihata et al 2019[97]	Five-hundred and seventy-seven female nurses: 123 reported insomnia, 72 insomnia with short sleep duration. Sleep was assessed with a self-reported questionnaire based on DSM-IV criteria for insomnia, which included questions about sleep duration, difficulty initiating sleep (DIS), difficulty maintaining, sleep (DMS), early-morning awakening (EMA), and sleep duration. Insomnia with short sleep duration was defined as: DIS, or DMS, or EMA; and <6 hours sleep duration.	Serum	There were no differences in serum BDNF protein between participants with normal sleep time (at least 6 hours/night), regardless of the presence of insomnia. In participants with short sleep duration (<6 hours/night), those with insomnia showed decreased BDNF serum levels compared to counterparts without sleep problems.
5.	Fan et al 2019[101]	Fifty-seven patients with insomnia (30 with sleep duration <6 hours/night, 27 with normal sleep duration), and 29 healthy controls. Insomnia diagnosis was made according to DSM-V criteria.	Serum	Participants with insomnia with short sleep duration but not normal sleep duration had a lower serum BDNF protein level compared to healthy controls. In a within-group analysis, participants with insomnia with short sleep duration also exhibited a lower serum BDNF level than those with normal sleep duration.
6.	Mikoteit et al 2019[105]	Sixty patients with insomnia and 30 healthy controls. Insomnia was assessed with the ISI questionnaire, based on DSM-IV diagnostic criteria for insomnia.	Serum	Serum BDNF was decreased in the insomnia group compared to controls. Insomnia severity was predictive of lower BDNF levels.
7.	Deuschle et al 2018[106]	Thirty-five patients with insomnia and 37 healthy controls. Insomnia diagnosis was made according to the ICSD-2 criteria.	Serum	BDNF serum levels did not differ between subjects with insomnia and healthy controls.
8.	Giese et al 2014[98]	Twenty-six insomnia patients (including 19 with restless leg syndrome/periodic limb movement) and 24 healthy controls. Insomnia was defined as scoring more than 8 points on the ISI questionnaire based on the DSM-IV diagnostic criteria for insomnia.	Serum	Insomnia was associated with lower serum BDNF levels compared with healthy controls. Serum BDNF concentration was negatively correlated with insomnia severity as assessed by ISI.

Abbreviations: AIS, Athens Insomnia Scale; DSM, *Diagnostic And Statistical Manual of Mental Disorders*; ICSD, International Classification of Sleep Disorders, ISI, Insomnia Severity Index.

promoting working memory and adaptation.[109] Long-term stress (ie, insomnia) has opposite effects, producing reduction of dendritic complexity and atrophy, which might ultimately severely impair behavior.[109]

Nevertheless, this model does not fully answer the question of why chronic sleep deficiency actually leads to BDNF depletion. As shown in Figure 1, BDNF, due to a positive autoregulatory feedback loop is able to stimulate its own transcription in a CREB-mediated mechanism, as well as TrkB surface expression. Additionally, TrkB might be
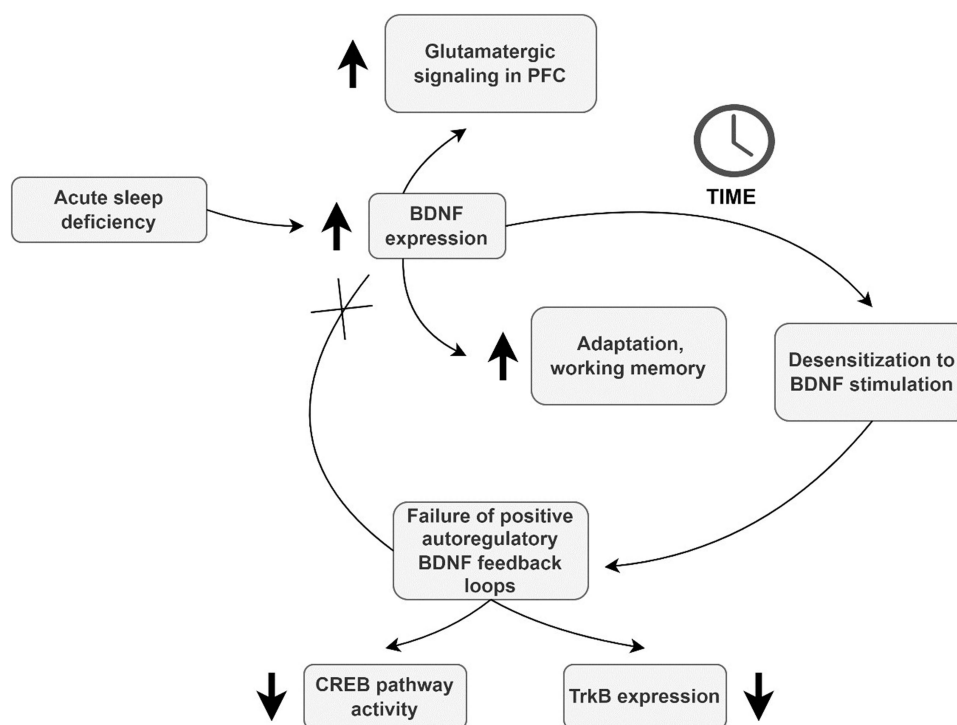
Figure 1 The possible mechanism of interactions between sleep deficiency and BDNF.
Notes: Acute sleep deficiency induces BDNF production that might promote glutamatergic signaling in the PFC, improving adaptation to a new stressor. Overtime, increased exposure to BDNF leads to desensitization and insufficiency of positive autoregulatory feedback loops, ie, decreased expression of TrkB and CREB pathway activity, which fails to maintain adequate levels of this neurotrophin.
Abbreviations: BDNF, brain-derived neurotrophic factor; CREB, cAMP response element-binding protein; prefrontal cortex, PFC; tropomyosin receptor kinase B, TrkB.

transactivated from adrenergic, dopaminergic or glucocorticoid activity in a manner similar to that caused by neurotrophins.[16] Interestingly, it appears that prolonged BDNF exposure might actually lead to a decrease in TrkB expression on the cell surface, leading to desensitization, which could ultimately reduce BDNF production.[110,111] Further studies on the BDNF pathway in insomnia would be desirable to elucidate the time point as well as exact mechanism of BDNF depletion in this sleep disorder.

BDNF is primarily produced by neurons; however, studies have shown that it can also be released by astrocytes and microglia. Zhang et al found that insomnia was associated with increased serum level of S100B, GFAP, BDNF, and GDNF, which could suggest astrocyte dysfunction.[104] In another study, both short sleep deprivation and chronic sleep restriction were shown to increase the rate of astrocytic phagocytosis involving presynaptic parts of larger synapses.[112] The pattern of changes in lipid peroxidation in synaptoneurosomes and the expression of *MERTK*, the gene responsible for astrocytic phagocytosis, was also similar, and thus authors concluded this was a cleaning of overused synaptic components during wake time.[112] However, in contrast to SD, chronic sleep restriction was associated with microglial activation and phagocytosis without other overt signs of neuroinflammation.[112] Such low-level, long-term microglial activation (microglial priming) could be associated with pathologically enhanced response to other insults, thus being detrimental to the brain.[112] Those results show that alterations in morphology and functioning of glial cells might be relevant to the pathophysiology of insomnia, and further studies on this subject would be highly desirable.

Obstructive sleep apnea (OSA) is a common disorder characterized by recurrent collapse of the upper airways during sleep, causing intermittent hypoxia.[99] This condition is associated with sleep fragmentation caused by frequent subconscious awakenings, which could be considered a form of sleep deficiency. BDNF has been quite extensively studied in the context of OSA, primarily due to its connections with cognitive decline.[99] Studies conducted to date are heterogeneous.[99] A recent meta-analysis demonstrated that peripheral levels of BDNF are unaltered by OSA or its standard treatment—continuous positive airway pressure therapy.[113]

Molecular Basis of Insomnia

Insomnia is a disorder with a complex background, involving interactions between psychological and somatic aspects of health. It frequently overlaps with disrupted BDNF production, as is the case in depression or obsessive–compulsive disorder.[94,114] Several systems have been implicated in the pathophysiology of insomnia, one of them being GABA signaling. Besides having a major role in sleep initiation and maintenance, it is also a target for insomnia medications (ie, benzodiazepines), which increase the affinity of GABA receptors.[115] According to a study by Morgan et al, individuals with primary insomnia tend to have increased levels of this neurotransmitter in the occipital region, as measured by proton magnetic resonance spectroscopy (1H-MRS); moreover, GABA was negatively correlated with a polysomnographic parameter—wake after sleep onset.[116] The authors explained this as an allogenic response to hyperarousal.[116] However, Plante et al obtained opposite results, showing stark reductions of GABA in the brain.[115] Discrepancies between studies could be attributed to, among others, timing of data acquisition, differences in sleep quality between respective control groups, as well as method of objective sleep assessment (polysomnography or actigraphy).[115] Oral administration of GABA might show benefits related to early stages of sleep, ie, increased duration of the first NREM, and decreased sleep latency, but they might be related to its stress-relieving effects.[117] Glutamatergic neurotransmission is tightly connected to GABA. Glutamate is an excitatory neurotransmitter, which might be converted into GABA by glutamate decarboxylase 1, thus supplying inhibitory synapses.[118] L-glutamate in atoxic concentrations might be also found extrasynaptically in the area surrounding neurons.[119] The relationship between insomnia and glutamatergic transmission is still under investigation. It appears to be of special importance in neurodegenerative disorders, which are linked to glutamate excitotoxicity.[120] Glutamate signaling has a major role in regulation of circadian rhythm by regulating the functioning of the SCN, the central master clock.[121] A majority of neurons in this structure are GABAergic; GABA release might be promoted by astrocytic glutamate via activation of the NR2C subunit of the glutamate NMDAR, which inhibits activation of postsynaptic neurons.[121] Selective NR2C blockade impairs the circadian variability of neuronal membrane potential as well as expression of clock genes.[121] Glutamate has two main transporters that regulate its working concentration in the brain: vesicular glutamate transporters (VGLUTs) and excitatory amino acid transporters (EAATs).[121] In animal models, alteration of EAAT1 expression changed the sleep phenotype in *Drosophila*, whereas injection of glutamate into SCN induced phase shifts.[121] Such disruptions might negatively affect the functioning of the Zeitgeber and contribute to the development of sleep disruptions associated with impaired circadian rhythm.[121] Models involving sleep deprivation give further insight into the link between sleep and mode of neurotransmission. Sleep deprivation in mice was demonstrated to increase the expression of GLT1, which removes excessive glutamate.[121] Rats subjected to this form of sleep deficiency had a higher concentration of extrasynaptic glutamate.[121] Increase in BDNF following acute sleep deprivation might be of importance here, as it was shown to protect neurons against excitotoxicity and oxidative damage.[17] Interestingly, in a study on mice subjected to chronic sleep restriction, the study group sustained less damage following the injection of NMDA (NMDAR agonist used to mimic the actions of glutamate) to the nucleus basalis magnocellularis.[122] Thus, it appears that there are mechanisms protecting the central nervous system from the damage inflicted by deregulation of the glutamatergic system associated with different forms of sleep deficiency, but this subject remains underinvestigated. More studies are validated to broaden the knowledge on the topic of interactions between glutamatergic signaling and insomnia.

Histamine is also considered to be an important neurotransmitter in the pathophysiology of insomnia. In the brain, it is produced only by the tuberomamillary nucleus (TMN); it acts as an REM suppressant and promotes wakefulness.[118] It has three main receptors: stimulatory H1, H2, and inhibitory H3. H1 and H3 appear to be of the most relevance for sleep. H1 antagonists (or rather inverse agonists, reducing the activity of constitutively active receptors) are known to cause sleepiness, such as diphenhydramine.[118] Pharmacological inhibition of H1 in rats increased NREM; animals bereft of this receptor acted in a soporific way when compared to the control group.[118] Substances that disturb H3 signaling (ie, ciprofloxacin) were shown to suppress sleep in animal studies.[118] Interestingly, other studies on animals with impaired histaminergic signaling have demonstrated that such damage might be to some extent compensated by other arousal systems, but those mechanisms fail when a higher level of arousal is required, such as in high-stress environments.[118] Studies regarding regulation feeding behavior also bring interesting results. Gotoh et al have demonstrated that food intake might be modulated by interactions between BDNF, corticotropin-releasing factor and histamine.[123] Namely,

BDNF in the ventromedial nucleus (VMH) regulates histamine production in the TMN via activation of corticotropin-releasing factor (CRF) neurons in the paraventricular nucleus (PVN).[123] The released histamine in turn inhibits different groups of feeding neurons and BDNF neurons located in the VMH and PVN via the H1 receptor.[123] Weight gain caused by the use of second-generation antipsychotic drugs was also associated with BDNF concentration in the hypothalamus and on the periphery.[124] Similar studies appear to be needed on the subject of disruptions of sleep and circadian rhythm.

Orexins are produced by neurons in the hypothalamic region.[125] They project to various locations in the brain that contain structures important for sleep regulation, such as the ventrolateral preoptic nucleus (VLPO), locus coeruleus (LC), and the TMN.[125] Orexin neurons control the release of histamine form the TMN neurons; notably, there is no feedback loop, as histamine does not influence orexin neurons.[125] Current medications targeting this mode of neurotransmission might be classified into two types: dual orexin receptor antagonist (DORA), antagonists of both orexin receptor type 1 (OX1R) and OX2R, which include relatively popular lemborexant and suvorexant, and selective orexin receptor antagonist (SORA), targeting only OX2R, such as seltorexant.[125] The latter group is still under development.[125] To date, studies report that they decrease sleep latency as well as wake after sleep onset, while increasing total sleep time.[125] Orexin might also promote BDNF production, thus exerting neuroprotective effects on neurons.[44]

Saper et al have proposed a flip-flop switch model of sleep regulation, presenting a neuronal pathway consisting of sleep-promoting GABAergic neurons in the VLPO that cooperate with neuronal pathways promoting the wakeful state, namely the orexinergic neurons in the hypothalamus, noradrenergic LC, histaminergic TMN, serotonergic dorsal raphe nuclei (DRN) as well as cholinergic neurons in the pontine laterodorsal and pedunculopontine tegmental (LDT/PPT) nuclei.[126,127] The ascending reticular system in the brain is also vital for cortical arousal.[127] Alternations between phases are controlled by the switch located in the thalamus.[127]

Insomnia is currently regarded as a polygenic disorder.[128] Genome-wide analyses as well as twin studies show that insomnia shows significant heritability and an overlap with major depression, bipolar disorder as well as schizophrenia.[128–130] The risk of insomnia increases proportionally to the number of variants, which individually have little contribution to the final outcome.[131] Van Someren has proposed that genetic alterations conditioning enhanced activity of the salience network, a circuit consisting primarily of the dorsal anterior cingulate cortex and the anterior insula, might be associated with lower amounts of SWS due to increased propensity to arousal.[131] In his review, he also stressed the importance of disturbances in REM sleep, caused by noradrenaline input from the LC, to impaired stress adaptation, restoration and synaptic plasticity in the course of insomnia.[131]

Studies have revealed that sleep–wake rhythm, sleep timing, etc. are regulated by genes responsible for stress response and circadian rhythm; specific genotypes described to date include variances of genes responsible for GABAergic signaling and clock genes, as well as polymorphism of a serotonin transporter promoter variant (5-HTTLPR), a potential mediator between stress and depression.[132,133] Individuals homozygous for the Clock gene variant 3111C/C Clock tend to suffer from insomnia more frequently than healthy controls.[130] A missense mutation GABA-A β3 subunit might be associated with chronic insomnia.[134]

Stress or trauma early in development has long been connected to sleep disorder; a possible mechanism behind this effect involves epigenetic regulations. In contrast to rather static genetic factors, they have a dynamic character and might alter in response to environmental cues, thus providing more insight into changes occurring in this sleep disorder.[83] Studies have demonstrated that stress in the prenatal period and early life development might have long-lasting consequences, increasing the reactivity of the HPA axis and impairing its negative feedback control.[130] Other studies on animals connect early-life stress to alterations in sleep architecture (eg, increased sleep fragmentation, decreasing deep SWS in relation to total sleep time).[130,135] Epigenetic regulation involves mechanisms like histone modification, regulatory noncoding RNA, as well as DNA methylation, which appears to be especially important to sleep disorders. Sammallahti et al have found that decreased methylation at cg24815001 in newborns was liked with longer sleep duration.[136] Similar change at cg02753354 resulted in longer sleep onset latency.[136] According to other studies, PPARA methylation in adolescent girls was inversely associated with sleep fragmentation.[128] Koopman-Verhoeff et al have identified that DNA methylation in the 17q21.31 region (which includes, among others, MAPT, a regulator of Tau proteins, involved in neuronal functioning) was associated with sleep duration.[137] Other authors also found associations between DNA methylation, sleep duration, and chronotype in children and adolescents.[128] Ancelin et al have revealed

that four single-nucleotide polymorphisms in the *BDNF* gene as well as higher methylation of BDNF promoter I were connected to increased wake after sleep onset (WASO), a polysomnographic parameter frequently disrupted in insomnia as well as other sleep disorders.[138] Interestingly, such a relationship was not present in psychotropic drug users, suggesting their modifying effect on BDNF production.[138] Relationships between sleep and epigenetics might have a mutual character. Lahtinen et al in their study on adult individuals with subjective sleep deficiency revealed that they tend to have altered methylation of genes associated with nervous system development, mainly hypomethylation.[139]

Sleep disturbances share a connection with neurodegenerative disorders. In a study by Elwood et al, severe excessive daytime sleepiness was a strong predictor of vascular dementia OR of 4.44 (95% CI 2.05–9.61).[140] In cases of Lewy body dementia, sleep disturbances, such as REM behavior disorder (RBD), are estimated to occur in ca. 90% of patients.[141] Prevalence of sleep disorders in patients with AD, the most common type of dementia, varies from 14% to 69%.[142] Moreover, neurodegenerative processes are associated with disruptions in circadian rhythm: in AD subjects, autopsies revealed loss of neurons expressing vasopressin, vasoactive intestinal peptide (VIP), and melatonin receptor type 1 in the SCN.[143] Melatonin level might also be increasingly reduced in the course of AD.[143] Conversely, sleep loss can further exacerbate the course of the disease, increasing Aβ content and markers of neuroinflammation in the cerebrospinal fluid[143] BDNF might also act as a link between neurodegeneration and chronic sleep deficiency. Studies have consistently shown decrease of this neurotrophin in both AD and insomnia patients. In this case, reduction of BDNF is induced by accumulation of Aβ and Tau. It is associated with apoptosis of neurons, due to lack of antiapoptotic stimulation, which in AD usually begins in the entorhinal cortex, spreading to hippocampus, amygdala and other structures (limbic system, neocortex) in a symmetrical fashion.[144] Similarly, in individuals with insomnia, hippocampal volume on magnetic resonance imaging (MRI) was reduced on both sides compared to their counterparts with no sleep problems.[130] Memory impairments, traditionally associated with insomnia, might be related to such findings; nevertheless, such studies were impossible to replicate.[130,145] People with insomnia disorder also tend to display reduced gray matter in areas like the parietal, orbitofrontal and middle cingulate cortex.[145]

The molecular background of insomnia is an interdisciplinary and active area of research. Studies on the subject of genetic overlap between this sleep disorder and other psychiatric or somatic diseases would be desirable. Projects comparing different insomnia phenotypes as well as their interactions with comorbidities would provide more insight into the pathophysiology of this sleep disorder.

Conclusion and Future Prospects

Even after years of research, numerous aspects of relationships between BDNF and insomnia remain elusive. Current studies chart a few new fields for research. First, it would be interesting to further explore the relationship between sleep regulation, architecture, and BDNF, which could in the future allow for a more personalized management of sleep disorders, especially in patients administered medications that modify the production of this neurotrophin, such as antidepressants. This topic is related to CRSD. Sudying the role of BDNF in those conditions would facilitate better understanding of differences between sleep disorders related to circadian rhythm and primary insomnia. Advancements in this field would allow for development of targeted treatment protocols for those conditions. Interactions between BDNF and stress might be an interesting field for future research in the context of both epigenetic changes regarding DNA methylation in different sleep disturbances as well as individual traits predisposing to insomnia, such as neuroticism. Another interdisciplinary field is the subject of BDNF in substance abuse, as it might involve both neuropsychological predisposing factors, neurodegeneration, as well as imbalance in certain neuronal circuits, mesolimbic and mesocortical in particular.

Expanding the knowledge about BDNF's connections to other signaling pathways appears to be particularly important due to the ongoing search for better strategies in treatment of sleep disorders. Orexin is a particularly salient subject in this regard due to its potential antidepressant effect. It would also be of interest to gain insight into the interactions between different SORAs/DORAs and BDNF. Projects aiming to investigate the exact processes behind BDNF reduction in neurodegenerative diseases as well as potential compensational mechanisms observed in certain studies (ie, increase in peripheral BDNF) might be desirable. It would also be interesting in the context of searching early biomarkers for dementia. In a 2020 study by Cechova et al, proBDNF:BDNF ratio was a more reliable marker for cognitive performance

than any of those proteins alone.[146] Another question is whether early diagnosis and proper treatment of sleep disturbances might delay the onset of dementia, decreasing the disease burden in society.

The relationship between BDNF and insomnia is multifaceted. The titular neurotrophin might have a major influence on neurotransmitters like histamine, orexin, and GABA which regulate sleep and wakefulness. Due to its neuroprotective properties, it could be involved in the pathophysiology of neurodegenerative conditions, which are frequently accompanied by various sleep disorders. BDNF might also be implicated in formation of traits predisposing to insomnia, like neuroticism, as well as other epigenetic/genetic factors. Studies have also demonstrated its importance for circadian rhythm and sleep architecture. Broadening the knowledge on insomnia will certainly improve lives of patients afflicted with insomnia as well as aid in development of new molecular targets for treatment. The present review might aid in selecting research subjects as well as offer a new perspective on BDNF's role in sleep medicine and adjacent fields.

Disclosure

The authors report no conflicts of interest in this work.

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