World Journal of Advanced Research and Reviews
eISSN: 2581-9615 CODEN (USA): WJARAI
Cross Ref DOI: 10.30574/wjarr
Journal homepage: https://wjarr.com/

(REVIEW ARTICLE)

The role of sleep deprivation in physiological system dysfunctions

Hamit Uslu and Gözde Atila Uslu *

Department of Physiology, Faculty of Medicine, Erzincan Binali Yıldırım University, Erzincan, Türkiye.

World Journal of Advanced Research and Reviews, 2023, 20(03), 1155–1165

Publication history: Received on 20 October 2023; revised on 28 November 2023; accepted on 01 December 2023

Article DOI: https://doi.org/10.30574/wjarr.2023.20.3.2412

Abstract

Night shifts, long working hours of healthcare professionals, irregular lifestyles, due to increasing economic difficulties and decreasing purchasing power, people have to accept difficult working conditions, resulting in inadequate and/or poor quality sleep problems. Sleep is a physiological need and the emergence of sleep problems not only negatively affects the performance and quality of life of the person during the day, but also causes various changes in the physiological systems and functions of these systems. Sleep problems are often ignored by people in spite of the fact that it is generally a health problem that can be treated by doctors. In this review, as a result of the current literature review, the nervous, cardiovascular and gastrointestinal systems are the most affected systems by sleep deprivation, and the effects of sleep deprivation on these systems and the mechanisms underlying these effects are summarized. It is an undeniable fact that sleep is a physiological need, and that insufficient and/or poor quality sleep will adversely affect physiological functions. However, the existence of conflicting studies and the fact that the physiological and pathological mechanisms in this process have not been elucidated indicate that long-term and more comprehensive studies are needed.

Keywords: Sleep Deficiency; Nervous System; Gastrointestinal System; Cardiovascular System

1. Introduction

Sleep is an essential process that is necessary for emotional, physical and cognitive health [1], and it is a very important physiological process in which the human body tries to recover from the exhausting effects of intense activity, stress and fatigue. Basically, when the sleep types are considered, we come across with rapid eye movements (REM) and non-rapid eye movements (NREM) sleep. The use of electroencephalographic (EEG) recordings allowed the identification of sleep cycles and stages. It was found that NREM or slow-wave sleep (SWS) is divided into four stages, whereas in REM sleep, fast, low-voltage waves occur periodically. This wave type seen during REM is also called paradoxical sleep because it resembles the waves seen during wakefulness and sleep stage 1 [2,3]. It has been shown that in the NREM period, low amplitude theta rhythm is observed in stage 1, high voltage waves called sleep spines and K complex occur in stage 2, high amplitude delta rhythm is observed in stage 3, and slow wave sleep accompanied by large waves is observed in stage 4 [2,4]. It has been reported that brain activity is dynamically modulated even during the sleep phase, with increases in activity in the pontine, amygdala and anterior cingulate gyrus and decreases in activity in the prefrontal and parietal cortex during REM [2]. Moreover, basal brain activity and connectivity in the default mode network increased during NREM periods and reduced throughout REM periods, while in the somatosensory network, there had a significant decreased in all regions and in the connectivity of all regions during NREM periods. It has been also found that in all resting state networks, activity changes during NREM periods were negatively correlated with those during REM periods [5].

It is an inevitable conclusion that sleep is of vital importance, sleep and sleep regulation is a complex physiological process, and disruptions in this process will cause sleep deficiency. It has begun to be revealed that sleep deficiency can

* Corresponding author: Gözde Atila Uslu.

cause disruptions in body homeostasis, trigger disorders in the cardiovascular system, endocrine system and immune system, especially the nervous system, and lead to serious problems that cannot be ignored on various systems in the body. The purpose of this review was to demonstrate how sleep deprivation can impair the neurological system's, cardiovascular system's, and gastrointestinal system's physiological functions.

2. Sleep Deprivation and The Nervous System

Mammals spend about 1/3 of their lives sleeping [6]. However, this period is gradually shortening due to physical and psychological reasons, such as increased television viewing and internet use due to today's lifestyle, leading to sleep deprivation and a decrease in sleep quality [7]. Nearly 40 years ago, studies showed that the tissue most affected by total sleep deprivation is the brain, which exhibits both psychological and neurological declines. Studies in humans and experimental animals deprived of REM or subjected to total sleep deficiency have shown that the central nervous system is profoundly affected. This can lead to behavioral and psychological deviations, mood swings, concentration disorders and perceptual distortions [8]. There is now growing evidence that both acute and chronic sleep deficiency is related with distraction, impaired arousal and impaired memory and neurobehavioral functioning. In contrast, lifestyles that contribute to sleep deprivation are on the rise [9,10].

Numerous genes have been shown to have their expression upregulated in the cerebral cortex and other brain regions after spontaneous wakefulness or sleep deprivation. Three groups of genes have been identified as found to be elevated after short-term sleep deprivation in fruit flies, just like they are in mammals [11]. Yoo et al. [12] reported that amygdala reactivity to unpleasant emotional stimuli in sleep deprived individuals showed an enhanced hyper-limbic response, and that increased limbic activity caused a loss of amygdala medial prefrontal cortex (mPFC) connectivity. Due to these central alterations, sleep deprived individuals were observed to be unable to register the emotional facial expressions shown to them and consequently unable to accurately imitate the same expressions. Similarly, Chee and Tan [13] reported that sleep deprivation caused attention delays and difficulties in visual perception with decreases in fronto-parietal signals, extrastriate cortex and thalamus activation due to decreased cerebral blood oxygenation levels.

Sleep oscillations are mainly generated by the corticothalamic system. This system is composed of cortical neurons, reticular nuclei of the thalamus and dorsal thalamic nuclei. Sleep oscillations are suppressed during wakefulness by signals from various increased monoaminergic, cholinergic and glutaminergic systems [14]. Kotagal and Yardi [15] reported that sleep disorders are effective in the control of epileptic seizures and that treatment of sleep disorders may be beneficial in the control of epileptic seizures. Indeed, it has been discovered that interictal epileptiform discharges can be triggered by both sleep deprivation and sleep, and some epilepsies are nearly only observed when sleeping. Méndez et al. [16] claim that interictal discharges are seen throughout sleep, particularly during NREM sleep, and that epileptic seizures are triggered by falling asleep or waking up after a nap. However, they also noted that sleep increases the frequency of epileptiform abnormalities, modifies their morphology, and affects their distribution, whereas sleep deprivation makes epileptiform abnormalities and seizures more likely, i.e., both circumstances have an interdependent relationship. Foldvary-Schaefer and Grigg-Damberger [17] reported that sleep impotence can promote epileptic seizures and sleep deficiency causes seizures and epileptiform discharges in some epileptic individuals. They also stated that NREM sleep facilitates seizures while REM sleep prevents seizures. Effective treatment of obstructive sleep apnea and sleep deprivation, which worsen the epileptic condition, can reduce the frequency of epileptic seizures [17,18].

One of the main characteristics of many neurodegenerative illnesses, including Parkinson's disease, is the cellular buildup of misfolded neurotoxic proteins such amyloid-β, α-synuclein, and tau. Lack of sleep inhibits the glymphatic system's ability to operate properly, disturbs the removal of these proteins from the body, and causes them to accumulate in the areas where they cause cognitive impairment [19]. Parkinson's patients also often complain of insomnia. This complaint often takes the form of problems maintaining sleep, but can also be manifested as disturbed sleep onset and waking up in the morning. Although the diagnosis of insomnia is dependent on subjective observations, patients report difficulty falling asleep, remaining asleep, waking up early, having restless sleep, experiencing worry, and having trouble functioning during the day [20-22]. In addition to insomnia, excessive sleepiness, restless leg syndrome, REM sleep behavior disorders are also observed in these patients [23].

In individuals with sleep apnea, sleep is interrupted at irregular intervals and these individuals cannot get enough sleep, which can lead to memory impairment and other higher cognitive function deficits. Similarly, the findings in studies using experimental animal models [24] and in humans [25] with lower than required sleep length or poor quality sleep are similar.

As with many other neurodegenerative disorders, sleep deprivation and insufficient sleep are known to raise the chance of acquiring Alzheimer's disease. The mechanisms through which sleep deficiency affects Alzheimer's disease

pathogenesis are still not completely understood. However, it has been reported that the most significant mediating factors between the two conditions are risk factors like apolipoprotein E risk alleles, dysregulation of kinases and phosphatases, reactive oxygen species, endoplasmic reticulum damages, glymphatic system dysfunctions, and orexinergic system deficiency [26]. Increased levels of Tau protein, which has a role in microtubule regulation [27], and increased levels of β-Amyloid (Aβ) [28] are prominent features of Alzheimer's disease. In case of sleep deficiency and circadian rhythm disturbance, the increase in Aβ and microtubule-associated protein Tau levels may lead to impaired glymphatic-vascular-lymphatic clearance and consequently increased oxidative stress in the brain and decreased levels of circulating melatonin hormone [29].

Zhao et al. [30] showed that acute sleep deprivation with physiological stimuli significantly increased serotonin 2A receptor (5-HT2AR) levels in the frontal cortex of mice in as little as 6 hours for mRNA and 8 hours for protein via the immediate early gene Egr3. The majority of examinations of brain tissues from post-mortem schizophrenia patients showed a decrease in 5-HT2AR expression [31-34] in cortical areas and this decrease was reported to be most pronounced in the frontal cortex. Similarly, it was revealed that 5-HT2AR expression in these patients was considerably lower than in healthy people [35,36]. However, the mechanisms regulating this have not yet been elucidated. Sleep deprivation increases the severity of schizophrenia and worsens the clinical picture. Although the use of new medications such as CBT-I and suvorexant are promising, prevention of insomnia is still an important therapeutic goal in these patients [37].

Although severe insomnia causes hallucinations, it has been reported that it may progress towards psychosis as the duration of insomnia increases. It has been stated that insomnia lasting 24-48 hours causes perceptual distortions, anxiety, depersonalization, irritability, depersonalization and disruption of the concept of time, insomnia lasting 48-90 hours causes hallucinations and disordered thinking, delusions occur after 72 hours of insomnia and at the end of this period, the clinical condition of the person is similar to acute psychosis or toxic delirium. It was reported that the psychotic states listed in the majority of these cases resolved after a period of normal sleep [38].

In a meta-analysis study involving 15892 individuals with depression, addiction, obsessive-compulsive disorder, schizophrenia, bipolar disorder and anxiety disorders, it was emphasized that gray matter loss in the brain was combined in 3 regions: dorsal anterior cingulate, right and left insula [39]. In women, sleep deprivation causes a decrease in amount of gray matter in the anterior insula and lateral orbitofrontal cortex, and thus an anxiogenic effect. In contrast, sleep deprivation may cause gray matter deficiency and anxiogenic state in the ventromedial prefrontal cortex in both males and females [40]. According to studies, those who don't get enough sleep experience much higher levels of anxiety [41,42]. Sleep deficiency has also been reported to cause more anxiety in women than in men [40]. However, animal experiments (mice, rats and zebrafish) have demonstrated that sleep deficiency causes a reduction in anxiety-like behaviors, so it has been argued that the results of these studies cannot be extrapolated to humans and therefore new experimental tools are needed [42,43]. On the contrary, there is an undeniable number of studies showing that sleep deprivation has anxiety-like effects in experimental animals as well as in humans [44-47].

Table 1 Various effects of sleep deprivation on the nervous system and the pathways of these effects.

Investigators	**The System it Affects - the Situation**	**Pathway - Mechanism of Action**
Thomas et al. 2000 Thomas et al. 2003	Distraction, impaired arousal and disruption of memory and neurobehavioral functions.	Decreases in metabolic rate in thalamic, parietal and prefrontal regions during prolonged sleep deprivation.
Chee and Tan 2010	Decreased visual perception and attention.	Reductions in fronto-parietal signal and extrastriate cortex and thalamus activation according to cerebral blood oxygenation level-dependent fMRI technique.
Yoo et al. 2007	Sleep deprivation leads to impaired expression of emotions and inability to imitate facial expressions shown to them.	This is caused by negative emotional stimuli causing an amygdala response, which triggers increased hyper-limbic reactivity and loss of amygdala-mPFC connectivity with increased limbic activity.
Kotagal and Yardi 2008 Méndez et al. 2001	Interictal epileptiform discharges can be activated	-

	by both sleep deprivation and sleep. Discharges are more frequent during NREM sleep.	
Foldvary-Schaefer and Grigg-Damberger 2009	NREM sleep facilitates seizures, whereas REM sleep prevents them. Treatment of obstructive sleep apnea and sleep deprivation reduces the frequency of epileptic seizures.	-
Bishir et al. 2020	Lack of sleep inhibits the development of cognitive and mental abilities in Parkinson's patients.	In sleep deprivation, the cellular accumulation of misfolded neurotoxin proteins such as amyloid-β, α-synuclein and tau and the interruption of their clearance by the glymphatic system lead to suppression of cognitive abilities in Parkinson's disease.
Yaffe et al. 2011 Kwon et al. 2015	Sleep apnea can lead to memory impairment and other higher cognitive function deficits.	By causing hypoxia.
Ahmadian et al. 2018	Sleep deprivation affects Alzheimer's pathology.	It shows these effects through pathways such as Apolipoprotein E risk alleles, dysregulation of kinases and phosphatases, reactive oxygen species, endoplasmic reticulum damage, glymphatic system dysfunction and orexinergic system deficiency.
Wu et al. 2019	Sleep deprivation affects Alzheimer's pathology.	β-Increased levels of Tau protein, which is involved in the regulation of amyloid and microtubules, impair glymphatic-vascular-lymphatic clearance and increase oxidative stress in the brain, leading to a decrease in circulating melatonin.
Zhao et al. 2022 Selvaraj et al. 2014 Kang et al. 2009 Matsumoto et al. 2005 Pralong et al. 2000	Sleep deprivation increases the severity of schizophrenia and worsens the clinical condition of the patient.	Both EGR3 and 5-HT2AR mRNA levels were found to be decreased in the frontal cortex of postmortem schizophrenia patients. However, the mechanism has not been fully elucidated.
Goldstein-Piekarski et al. 2018	Sleep deprivation can cause anxiety by affecting gray matter volume in various parts of the brain.	Causes this effect by affecting gray matter volume. For example; decreased gray matter volume in the anterior insula and lateral orbitofrontal cortex may indicate an anxiogenic effect of sleep loss in women. In contrast, decreased gray matter volume in the ventromedial prefrontal cortex may indicate an anxiogenic effect of sleep loss in both men and women.

3. Sleep Deprivation and The Cardiovascular System

According to reports, lack of sleep increases blood pressure, one of the major risk factors for cardiovascular diseases, and one of the reasons for this is the resetting of arterial baroreflex mechanisms to a higher blood pressure level [48]. According to Lusardi et al. [49] loss of sleep at night in hypertension patients may enhance sympathetic nerve activity, raising blood pressure and heart rate as well as increasing norepinephrine excretion in the urine. Another study found that lack of sleep raises systolic and diastolic blood pressure, which may increase the risk of hypertension. It was thought that this increase in blood pressure may be due to sympathetic arousal after sleep deprivation and increased vascular response due to increased adrenergic stimulation [50]. According to Kato et al. [51] inadequate sleep resulted in a rise in blood pressure, a decrease in the activity of the muscular sympathetic nerve, and no change in heart rate

compared to regular sleep. It has been stated that the reason for this may be that the suppressive response to sleep deficiency is not mediated by muscle sympathetic vasoconstriction or tachycardia. Zhong et al. [52] found that acute sleep deprivation increased sympathetic activity, decreased parasympathetic activity and decreased baroreceptor sensitivity on the cardiovascular system. It has been reported that similar findings such as increased sympathetic activation, high systolic or diastolic pressures are also observed in children with obstructive sleep apnea [53]. Systolic blood pressure increased in both men and women in a different study that looked at the effects of 24 hours of total sleep deficiency on volunteers aged 55 to 75. However, there was no visible difference between the sexes. Sympathoexcitation has been found to occur only in postmenopausal women, although an acute increase in blood pressure has been observed [54]. Neglected sleep disorders in women have been reported to be associated with increased blood pressure and vascular inflammation [55]. It has been discovered that short-term sleep loss in healthy people causes an increase in heart rate, systolic and diastolic blood pressure, but not noradrenaline levels [56]. Sauvet et al. [57] 24 hours of sleep deficiency caused a transient rise in blood pressure and pulse rate in rats and suggested that this was due to a decrease in endothelium-dependent vasodilatation independent of sympathetic stimulation. These findings are supported by the findings of another study, which showed that healthy men's blood pressure rose during sleep deprivation and remained elevated for the whole period of the condition. This increase may be caused by a dysregulated vascular endothelial system, according to reports [58]. It was stated that systolic blood pressure risen in rats with REM sleep deprivation and the reason for this may be endothelial damage due to lipid peroxidation [59].

There are studies that emphasize that sleep deprivation causes stress, that this stress situation may cause an increase in systolic blood pressure while trying to be regulated by physiological mechanisms, therefore it may increase cardiovascular risk [60,61]. In contrast to previous results, Vaara et al. [62] have demonstrated that a 60-hour sleep deficiency reduces heart rate due to an increase in vagal impulses. Another study indicated that in healthy, normal-weight people, short-term lack of sleep had no effect on resting blood pressure [63]. Dettoni et al. [64] determined that there was no alteration in pulse, systolic and diastolic blood pressure levels due to sleep deprivation in volunteers in partial sleep deprivation was induced for five nights. Nevertheless, it was noted that there had been a considerable rise in plasma norepinephrine levels, which was correlated with an increase in sympathetic modulation and a decline in parasympathetic modulation of cardiac autonomic balance.

According to Kamperis et al. [65] acute sleep deficiency in young healthy volunteers had a blunting effect on the decrease in expected blood pressure at night, due to the renin-angiotensin-aldosterone system. In a study conducted in healthy children, it was stated that acute sleep deficiency had a blunting effect on the decrease in nighttime blood pressure, and this was due to the suppression of the normal increase in sodium-sparing hormones. The renin-angiotensin-aldosterone system is one of the physiologically most powerful mechanisms involved in this process, and it has been suggested that sleep deficiency may cause levels of this system to drop [66].

Acute sleep deprivation has also been linked to structural and functional alterations in mouse with heart failure, and inflammatory cytokines are thought to play a role in these process [67]. According to a different study, persons who get little sleep are more likely to develop coronary heart disease and cardiovascular disease [68]. In another study, it was emphasized that optimal sleep duration is important in reducing the risk of cardiovascular disease [69]. As a result of a long-term study, Bertisch et al. [70] discovered that there was a significant relationship between insomnia or short sleep and insufficient sleep and cardiovascular diseases, and a 29 percent higher risk of CVD in the group with sleep problems compared to the reference group. Another large-scale investigation demonstrated an association between the risk of coronary heart disease and short sleep duration and/or poor sleep quality [71].

On the other hand, a different study contends that acute sleep deprivation has a cardioprotective impact by reducing the extent of myocardial infarction [72]. Shah et al. [73] also observed less severe cardiac injury during acute myocardial infarction in patients with obstructive sleep apnea and claimed that sleep apnea may have a cardioprotective effect through ischaemic preconditioning. Parsa et al. [74] suggested that sleep deprivation induced before ischaemia and reperfusion in rats showed cardioprotective effect by suppressing inflammatory responses. Summerer et al. [75] reported that obstructive sleep apnea causes more extensive coronary collateralization in patients with acute myocardial infarction and therefore shows cardioprotective effects.

Table 2 Various effects of sleep deprivation on the cardiovascular system and the pathways of these effects

Investigators	The System it Affects - the Situation	Pathway - Mechanism of Action
Ogawa et al. 2003	Sleep deprivation caused an increase in blood pressure.	Resetting or decreased of arterial baroreflex.
Lusardi et al. 1999 Robillard et al. 2011	-	Sympathetic arousal and increased adrenergic stimulation.
Sauvet et al. 2013 Słomko et al. 2018 Nawi et al. 2020	Sleep deprivation causes a transient increase in blood pressure and heart rate.	Decrease in endothelium-dependent vasodilatation which independent of sympathetic stimulation due to decreased NOS and COX-1 activity. Elevation in blood pressure may be due to dysregulated vascular endothelial function. The reason for this may be endothelial damage due to lipid peroxidation.
Carter et al. 2019	Sleep deficiency increased blood pressure.	Sympathoexcitation was found to occur only in postmenopausal women.
Vaara et al. 2009	Reducing effect on heart rate	Increased vagal outflow
Keeffe et al. 2013	Short-term sleep deprivation does not cause changes in resting blood pressure.	-
Dettoni et al. 2012	Partial sleep deprivation does not cause changes in resting systolic and diastolic blood pressure and pulse rate levels.	-
Kamperis et al. 2010 Mahler et al. 2012	Sleep deprivation prevents a drop in blood pressure at night.	A decrease in renin-angiotensin-aldosterone levels may occur.
Summerer et al. 2021	Obstructive sleep apnea may have cardioprotective effects in patients with acute myocardial infarction.	Obstructive sleep apnea causes more extensive coronary collateralization.

4. Sleep Deprivation and The Gastrointestinal System

Another system affected by sleep quality and sleep disorders is the gastrointestinal system. Sleep is largely regulated by circadian rhythms associated with the light-dark cycle system. It has been stated that any irregularity in this rhythm may affect the symptoms and pathogenesis of gastrointestinal diseases [76]. It has been shown that laryngopharyngeal reflux occurs in rats with chronic sleep deprivation and the reason for this is the occurrence of dysfunction in the central nervous system due to sleep deprivation and consequently, impairment in the control of gastrointestinal system motility [77]. It has even been reported that sleep deprivation may affect intestinal dysbiosis, which is one of the most important underlying causes of digestive system diseases, and may increase colitogenic microbiota [78]. It has been reported that in mice exposed to sleep deprivation, plasma norepinephrine levels are significantly increased, melatonin levels are decreased, the expression of anti-inflammatory cytokines is decreased and the expression of pro-inflammatory cytokines is increased, resulting in the development of intestinal barrier dysfunction [79]. In another study reported that intermittent sleep deprivation increased the gastrointestinal transit rate and visceral pain symptoms, and the hypofunction of the peripheral alpha 2A adrenoceptor played a role in this scene [80]. It has been suggested that oxidative stress induced by sleep deficiency leads to the development of inflammation by inducing the NF-κB pathway, resulting in damage to the intestinal mucosa and disruption of absorption mechanisms from the intestines [81]. In another study supporting this study, it was determined that oxidative stress due to sleep deprivation causes inflammation, which leads to small intestinal microbiota disorders [82]. Short-term sleep deprivation (5 hours) was found to have no effect on the overall gut microbiota of male C57Bl6/J mice, however Clostridiaceae and Lachnospiraceae increased relatively [83]. In a study conducted in China on nurses working in shifts and experiencing sleep disorders, it was found that the rate of irritable bowel syndrome and constipation was higher [84]. Chung et al.

[85] also found that intestinal inflammation was triggered by an increase in proinflammatory cytokine levels in mice with sleep deprivation and that there was a decrease in gene expressions effective in the connections between the brain and the intestine, and as a result of these effects, intestinal permeability decreased. It has been found that the oxidative stress resulting from the disruption of oxidant/antioxidant balance in rats with paradoxical sleep deprivation leads to salivary secretion disorders [86]. According to Shigiyama et al. [87], mice subjected to a 6-hour sleep deficiency period may develop hepatic steatosis and hepatic insulin resistance, with an increase in the levels of hepatic lipogenic enzymes perhaps acting as the underlying mechanism. Sleep disorders not only trigger gastrointestinal diseases, but also exacerbate existing diseases and complaints. Patel et al. [88] found that sleep disorders increased the reporting of abdominal and somatic pain in patients with irritable bowel syndrome. In mice exposed to 24 to 72 hours of sleep deprivation, it was determined that mild to moderate damage may develop in the organs of the cardiovascular and gastrointestinal systems due to inflammation triggered by sleep deprivation [89]. Benedict et al. [90] found that Coriobacteriaceae and Erysipelotrichaceae were higher and Tenericutes were lower in individuals subjected to two days of normal sleep after two days of partial sleep deprivation. It has been suggested that acutely impaired glucose metabolism in response to partial sleep deficiency may be effective in this change.

Table 3 Various effects of sleep deprivation on the gastrointestinal system and the pathways of these effects

Investigators	The System it Affects - the Situation	Pathway - Mechanism of Action
Zhang et al. 2021	Chronic sleep deprivation may cause laryngopharyngeal reflux.	Chronic sleep deprivation causes central nervous system dysfunction, resulting in deterioration in the control of gastrointestinal system motility.
Park et al. 2020	Sleep deprivation affects intestinal dysbiosis.	Increases colitogenic microbiota.
Benedict et al. 2016	Repeated partial sleep deprivation causes changes in the intestinal microbiota.	This may be due to acute disturbances in glucose metabolism due to partial sleep deprivation.
Chung et al. 2023	Sleep deprivation affects intestinal permeability.	Sleep deprivation triggered gut inflammation (increased levels of TNF-α and IL-1β) and decreased expression of genes involved in connections between the brain and gut (OCLN, CLDN1, TJP1 and TJP2).
Lasisi et al. 2021	Sleep deprivation leads to impaired salivary secretion in the submandibular glands.	Oxidative stress is the cause of salivary secretion disorders due to paradoxical sleep deprivation.
Shigiyama et al 2018	Partial sleep deprivation triggers the development of hepatic steatosis and hepatic insulin resistance.	Increased levels of lipogenic enzymes in the liver may trigger this condition.

5. Conclusion

Challenging working conditions, night shifts and irregular lifestyles may cause sleep disorders and deficiencies. Inadequate and/or poor quality sleep may cause various problems affecting many systems. As a result of the screening performed in this review, it was determined that the most affected systems are the nervous, cardiovascular and gastrointestinal systems. In this review, the effects of sleep deprivation on these systems and the mechanisms underlying these effects are summarized. However, it is an undeniable fact that there are contradictory studies and physiological and pathological mechanisms that are still not elucidated.

Compliance with ethical standards

Disclosure of conflict of interest

Authors declare no conflict of interest.

References

[1] Hirshkowitz M, Whiton K, Albert SM, Alessi C, Bruni O, DonCarlos L, et al. National Sleep Foundation's sleep time duration recommendations: methodology and results summar. Sleep health. 2015;1:40-3.

[2] Barrett KE, Barman SM, Boitano S, Brooks HL. Ganong's Review of Medical Physiology. 23rd ed. McGraw-Hill Companies, Incorporated; 2010. P. 234-236.

[3] Dement W, Kleitman N. Cyclic variations in EEG during sleep and their relation to eye movements, body motility, and dreaming. Electroencephalogr clin neurophysiol 1957;9(4):673-90.

[4] Harris CD. Neurophysiology of sleep and wakefulness. Respir Care Clin N Am 2005;11(4):567-86.

[5] Watanabe T, Kan S, Koike T, Misaki M, Konishi S, Miyauchi S, et al. Network-dependent modulation of brain activity during sleep. Neuroimage 2014;98:1-10.

[6] Tobaldini E, Costantino G, Solbiati M, Cogliati C, Kara T, Nobili L, et al. Sleep, sleep deprivation, autonomic nervous system and cardiovascular diseases. Neurosci Biobehav Rev 2017;74:321-29.

[7] Van Cauter E, Spiegel K, Tasali E, Leproult R. Metabolic consequences of sleep and sleep loss. Sleep med 2008;9:S23-8.

[8] Horne JA. Sleep function, with particular reference to sleep deprivation. Ann Med Res 1985;17(5):199-08.

[9] Thomas M, Sing H, Belenky G, Holcomb H, Mayberg H, Dannals R. Neural basis of alertness and cognitive performance impairments during sleepiness. I. Effects of 24 h of sleep deprivation on waking human regional brain activity. J Sleep Res 2000;9(4):335-52.

[10] Thomas ML, Sing HC, Belenky G, Holcomb HH, Mayberg HS, Dannals RF. Neural basis of alertness and cognitive performance impairments during sleepiness II. Effects of 48 and 72 h of sleep deprivation on waking human regional brain activity. Thalamus & related systems 2003;2(3):199-29.

[11] Cirelli C. Cellular consequences of sleep deprivation in the brain. Sleep med rev 2006;10(5):307-21.

[12] Yoo SS, Gujar N, Hu P, Jolesz FA, Walker MP. The human emotional brain without sleep a prefrontal amygdala disconnect. Curr Biol 2007;17:R877-78.

[13] Chee MW, Tan JC. Lapsing when sleep deprived: neural activation characteristics of resistant and vulnerable individuals. Neuroimage 2010;51(2):835-43.

[14] Steriade MM, McCarley RW. Brainstem control of wakefulness and sleep. In: Amzica, F., & Steriade, M, editors. Electrophysiology of sleep. In Epilepsy and Sleep, New York: Academic Press. Springer Science & Business Media; 2001. p. 19-41.

[15] Kotagal P, Yardi N. The relationship between sleep and epilepsy. Semin Pediatr Neurol 2008;15(2):42-9.

[16] Méndez M, Radtke RA. Interactions between sleep and epilepsy. J Clin Neurophysiol 2001;18(2):106-27.

[17] Foldvary-Schaefer N, Grigg-Damberger M. Sleep and epilepsy. Semin Neurol 2009;29(04):419-28.

[18] Carreño M, Fernández S. Sleep-related epilepsy. Curr Treat Options Neurol 2016;18:1-17.

[19] Bishir M, Bhat A, Essa MM, Ekpo O, Ihunwo AO, Veeraraghavan VP. et al. Sleep deprivation and neurological disorders. Biomed Res Int 2020:Id:5764017.

[20] Pont-Sunyer C, Iranzo A, Gaig C, Ana Fernández-Arcos, Vilas D, Valldeoriola F. Sleep disorders in Parkinsonian and nonParkinsonian LRRK2 mutation carriers. PLoS ONE 2015;10:e0132368.

[21] Videnovic A, Comella CL. Sleep disorders in Parkinson's disease. Handb Clin Neurol 2011;99:997-10.

[22] Stefani A, Högl B. Sleep in Parkinson's disease. Neuropsychopharmacology 2020;45(1): 121-28.

[23] Bollu PC, Sahota P. Sleep and Parkinson disease. Mo Med 2017;114(5):381.

[24] Kwon KJ, Lee EJ, Kim MK, Jeon SJ, Choi YY, Shin CY. The potential role of melatonin on sleep deprivation-induced cognitive impairments: implication of FMRP on cognitive function. Neuroscience 2015;301:403-14.

[25] Yaffe K, Laffan AM, Harrison SL, Redline S, Spira AP, Ensrud KE. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. Jama 2011;306(6):613-9.

[26] Ahmadian N, Hejazi S, Mahmoudi J, Telebi M. Tau pathology of Alzheimer disease: Possible role of sleep deprivation. Basic Clin Neurosci 2018;9(5):307.

[27] Bloom GS. Amyloid-β and tau: the trigger and bullet in Alzheimer disease pathogenesis. JAMA Neurol 2014;71(4):505-08.

[28] Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. EMBO Mol Med 2016;8(6):595-08.

[29] Wu H, Dunnett S, Ho YS, Chang RCC. The role of sleep deprivation and circadian rhythm disruption as risk factors of Alzheimer's disease. FIN 2019;54:100764.

[30] Zhao X, Ozols AB, Meyers KT, Campbell J, McBride A, Marballi KK. Acute sleep deprivation upregulates serotonin 2A receptors in the frontal cortex of mice via the immediate early gene Egr3. Mol Psychiatry 2022;27(3):1599-610.

[31] Selvaraj S, Arnone D, Cappai A, Hoves O. Alterations in the serotonin system in schizophrenia: a systematic review and meta-analysis of postmortem and molecular imaging studies. Neurosci Biobehav Rev 2014;45:233-45.

[32] Kang K, Huang XF, Wang Q, Deng C. Decreased density of serotonin 2A receptors in the superior temporal gyrus in schizophrenia-a postmortem study. Prog Neuropsychopharmacol Biol Psychiatry 2009;33:867-71.

[33] Matsumoto I, Inoue Y, Iwazaki T. 5-HT2A and muscarinic receptors in schizophrenia: a postmortem study. Neurosci Lett 2005;379:164-8.

[34] Pralong D, Tomaskovic-Crook E, Opeskin K. Serotonin (2A) receptors are reduced in the planum temporale from subjects with schizophrenia. Schizophr Res 2000;44:35-45.

[35] Hernandez I, Sokolov BP. Abnormalities in 5-HT2A receptor mRNA expression in frontal cortex of chronic elderly schizophrenics with varying histories of neuroleptic treatment. J Neurosci Res 2000;59:218-25.

[36] Ebdrup BH, Rasmussen H, Arnt J, Glenthøj B. Serotonin 2A receptor antagonists for treatment of schizophrenia. Expert Opin Investig Drugs 2011;20(9):1211-23.

[37] Robertson I, Cheung A, Fan X. Insomnia in patients with schizophrenia: current understanding and treatment options. Prog Neuropsychopharmacol Biol Psychiatry 2019;92:235-42.

[38] Waters F, Chiu V, Atkinson A, Blom JD. Severe sleep deprivation causes hallucinations and a gradual progression toward psychosis with increasing time awake. Front Psychiatry 2018;9:303.

[39] Goodkind M, Eickhoff SB, Oathes DJ, Jiang Y, Chang A, Jones-Hagata L. Identification of a common neurobiological substrate for mental illness. JAMA psychiatry 2015;72(4):305-15.

[40] Goldstein-Piekarski AN, Greer SM, Saletin JM, Harvey AG, Williams LM, Walker MP. Sex, sleep deprivation, and the anxious brain. J Cogn Neurosci 2018;30(4):565-78.

[41] Chellappa SL, Aeschbach D. Sleep and anxiety: From mechanisms to interventions. Sleep Med Rev 2022;61:101583.

[42] Pires GN, Bezerra AG, Tufik S, Andersen ML. Effects of experimental sleep deprivation on anxiety-like behavior in animal research: systematic review and meta-analysis. Neurosci Biobehav Rev 2016;68:575-89.

[43] Pires GN, Tufik S, Andersen ML. Sleep deprivation and anxiety in humans and rodents-Translational considerations and hypotheses. Behav Neurosci 2015;129(5):621.

[44] Yin M, Chen Y, Zheng H, Pu T, Marshall C, Wu T. et al. Assessment of mouse cognitive and anxiety-like behaviors and hippocampal inflammation following a repeated and intermittent paradoxical sleep deprivation procedure. Behav Brain Res 2017;321:69-8.

[45] Manchanda S, Singh H, Kaur T, Kaur G. Low-grade neuroinflammation due to chronic sleep deprivation results in anxiety and learning and memory impairments. Mol Cell Biochem 2018;449:63-2.

[46] Xie JF, Shao YF, Wang HL, Wang C, Cui GF, Kong XP. Neuropeptide S counteracts paradoxical sleep deprivation-induced anxiety-like behavior and sleep disturbances. Front Cell Neurosci 2018;12:64.

[47] Da Silva Rocha-Lopes J, Machado RB, Suchecki D. Chronic REM sleep restriction in juvenile male rats induces anxiety-like behavior and alters monoamine systems in the amygdala and hippocampus. Mol Neurobiol2018;55:2884-96.

[48] Ogawa Y, Kanbayashi T, Saito Y, Takahashi Y, Kitajima T, Takahashi K, et al. Total sleep deprivation elevates blood pressure through arterial baroreflex resetting: a study with microneurographic technique. Sleep 2003;26(8):986-9.

[49] Lusardi P, Zoppi A, Preti P, Pesce RM, Piazza E, Fogari R. Effects of insufficient sleep on blood pressure in hypertensive patients: a 24-h study. Am J Hypertens 1999;12(1):63-8.

[50] Robillard R, Lanfranchi PA, Prince F, Filipini D, Carrier J. Sleep deprivation increases blood pressure in healthy normotensive elderly and attenuates the blood pressure response to orthostatic challenge. Sleep 2011;34(3):335.

[51] Kato M, Phillips BG, Sigurdsson G, Narkiewicz K, Pesek CA, Somers VK. Effects of sleep deprivation on neural circulatory control. Hypertension 2000;35(5):1173-5.

[52] Zhong X, Hilton HJ, Gates GJ, Jelic S, Stern Y, Bartels MN, et al. Increased sympathetic and decreased parasympathetic cardiovascular modulation in normal humans with acute sleep deprivation. J Appl Physiol 2005;98(6):2024-32.

[53] DelRosso LM, Mogavero MP, Ferri R. Effect of sleep disorders on blood pressure and hypertension in children. Curr Hypertens 2020;22:1-7.

[54] Carter JR, Fonkoue IT, Greenlund IM, Schwartz CE, Mokhlesi B, Smoot CA. Sympathetic neural responsiveness to sleep deprivation in older adults: sex differences. Am J Physiol Heart Circ 2019;317(2):H315-22.

[55] Aggarwal B, Makarem N, Shah R, Emin M, Wei Y, St-Onge MP. Effects of inadequate sleep on blood pressure and endothelial inflammation in women: findings from the American Heart Association go red for women strategically focused research network. JAHA 2018;7(12):e008590.

[56] Kuetting DL, Feisst A, Sprinkart AM, Hosmi R, Luetkens J, Thomas D. Effects of a 24-hr-shift-related short-term sleep deprivation on cardiac function: A cardiac magnetic resonance-based study. J Sleep Res 2019;28(3):e12665.

[57] Sauvet F, Florence G, Van Beers P, Drogou C, Lagrume C, Chaumes C. Total sleep deprivation alters endothelial function in rats: a nonsympathetic mechanism. Sleep 2014;37(3):465-3.

[58] Słomko J, Zawadka-Kunikowska M, Kozakiewicz M, Klawe JJ, Tafil-Klawe M, Newton JL, et al. Hemodynamic, autonomic, and vascular function changes after sleep deprivation for 24, 28, and 32 hours in healthy men. YMJ 2018;59(9):1138-42.

[59] Nawi A, Eu KL, Faris ANA, Wan Ahmad WAN, Noordin L. Lipid peroxidation in the descending thoracic aorta of rats deprived of REM sleep using the inverted flowerpot technique. Exp Physiol 2020;105(8):1223-31.

[60] Franzen PL, Gianaros PJ, Marsland AL, Hall MH, Siegle GJ, Dahl RE, et al. Cardiovascular reactivity to acute psychological stress following sleep deprivation. Psychosom Med 2011;73(8): 679.

[61] Cabeza de Baca T, Chayama KL, Redline S, Slopen N, Matsushida F, Prather AA, et al. Sleep debt: the impact of weekday sleep deprivation on cardiovascular health in older women. Sleep 2019;42(10):zsz149.

[62] Vaara J, Kyröläinen H, Koivu M, Tulppo M, Finni T. The effect of 60-h sleep deprivation on cardiovascular regulation and body temperature. Eur J Appl Physiol 2009;105:439-44.

[63] O'Keeffe M, Roberts AL, Kelleman M, RoyChoudhury A, St-Onge MP. No effects of short-term sleep restriction, in a controlled feeding setting, on lipid profiles in normal-weight adults. J Sleep Res 2013;22(6):717-20.

[64] Dettoni JL, Consolim-Colombo FM, Drager LF, Rubira MC, De Souza SBPC, Irigoyen MC. Cardiovascular effects of partial sleep deprivation in healthy volunteers. J Appl Physiol 2012;113(2):232-36.

[65] Kamperis K, Hagstroem S, Radvanska E, Rittig S, Djurhuus JC. Excess diuresis and natriuresis during acute sleep deprivation in healthy adults. Am J Physiol Renal Physiol 2010;299(2):F404-11.

[66] Mahler B, Kamperis K, Schroeder M, Frøkiær J, Djurhuus J, Rittig S. Sleep deprivation induces excess diuresis and natriuresis in healthy children. Am J Physiol Renal Physiol 2012;302(2):F236-43.

[67] Zhu Y, Chen X, Guo L, Wang L, Chen N, Xiao Y, et al. Acute sleep deprivation increases inflammation and aggravates heart failure after myocardial infarction. J Sleep Res 2022;31(6):e13679.

[68] Yazdanpanah MH, Homayounfar R, Khademi A, Zarei F, Shahidi A, Farjam M. Short sleep is associated with higher prevalence and increased predicted risk of cardiovascular diseases in an Iranian population: Fasa PERSIAN Cohort Study. Sci Rep 2020;10(1):1-13.

[69] Kario K, Hoshide S, Nagai M, Okawara Y, Kanegae H. Sleep and cardiovascular outcomes in relation to nocturnal hypertension: the J-HOP Nocturnal Blood Pressure Study. Hypertens Res 2021;44(12):1589-96.

[70] Bertisch SM, Pollock BD, Mittleman MA, Buysse DJ, Bazzano LA, Gottlieb DJ, et al. Insomnia with objective short sleep duration and risk of incident cardiovascular disease and all-cause mortality: Sleep Heart Health Study. Sleep 2018;41(6):zsy047.

[71] Lao XQ, Liu X, Deng HB, Chan TC, Ho KF, Wang F, et al. Sleep quality, sleep duration, and the risk of coronary heart disease: a prospective cohort study with 60,586 adults. J Clin Sleep Med 2018;14(1):109-17.

[72] Edalatyzadeh Z, Aghajani M, Imani A, Faghihi M, Sadeghniiat-Haghighi K, Askari S, et al. Cardioprotective effects of acute sleep deprivation on ischemia/reperfusion injury. Auton Neurosci 2021;230:102761.

[73] Shah N, Redline S, Yaggi HK, Wu R, Zhao CG, Ostfeld R, et al. Obstructive sleep apnea and acute myocardial infarction severity: ischemic preconditioning? Sleep and Breathing 2013;17:819-26.

[74] Parsa H, Faghihi M, Kardar GA, Imani A. Acute sleep deprivation induces cardioprotection against ischemia/reperfusion injury through reducing inflammatory responses: the role of central GABA-A receptors. Gen Physiol Biophys 2018;37(3):345-52.

[75] Summerer V, Arzt M, Fox H, Oldenburg O, Zeman F, Debl K, et al. Occurrence of coronary collaterals in acute myocardial infarction and sleep apnea. JAHA 2021;10(15):e020340.

[76] Orr WC, Fass R, Sundaram SS, Scheimann AO. The effect of sleep on gastrointestinal functioning in common digestive diseases. Lancet Gastroenterol 2020;5(6):616-24.

[77] Zhang Y, Jiang X, Chen H, Li H, Wang Z, Chen Y, et al. Chronic REM-sleep deprivation induced laryngopharyngeal reflux in rats: a preliminary study. Auris Nasus Larynx 2021;48(4):683-689.

[78] Park YS, Kim SH, Park JW, Kho Y, Seok PR, Shin J, et al. Melatonin in the colon modulates intestinal microbiota in response to stress and sleep deprivation. Intestinal research 2020;18(3):325.

[79] Gao T, Wang Z, Dong Y, Cao J, Lin R, Wang X, et al. Role of melatonin in sleep deprivation-induced intestinal barrier dysfunction in mice. J Pineal Res 2019;67(1):e12574.

[80] Yaoita F, Muto M, Murakami H, Endo S, Kozawa M, Tsuchia M, et al. Involvement of peripheral alpha2A adrenoceptor in the acceleration of gastrointestinal transit and abdominal visceral pain induced by intermittent deprivation of REM sleep. Physiol Behav 2018;186:52-1.

[81] Gao T, Wang Z, Cao J, Dong Y, Chen Y. Melatonin alleviates oxidative stress in sleep deprived mice: Involvement of small intestinal mucosa injury. Int immunopharmacol 2020;78:106041.

[82] Gao T, Wang Z, Cao J, Dong Y, Chen Y. Melatonin attenuates microbiota dysbiosis of jejunum in short-term sleep deprived mice. J Microbiol 2020;58:588-97.

[83] El Aidy S, Bolsius YG, Raven F, Havekes R. A brief period of sleep deprivation leads to subtle changes in mouse gut microbiota. J Sleep Res 2020;29(6):e12920.

[84] Zhou HQ, Yao M, Chen YW, Huang JY, Chen GY. Functional gastrointestinal disorders common among nurses with poor sleep quality in Shanghai, China: a pilot study. Gastroenterol Nurs 2017;40(4):312-19.

[85] Chung Y, Wu JL, Huang WC. Effects of prebiotics on intestinal physiology, neuropsychological function, and exercise capacity of mice with sleep deprivation. Food Res Int 2023;165:112568.

[86] Lasisi TJ, Shittu STT, Abeje JI, Ogunremi KJ, Shittu SA. Paradoxical sleep deprivation induces oxidative stress in the submandibular glands of Wistar rats. JBCPP 2021;33(4):399-08.

[87] Shigiyama F, Kumashiro N, Tsuneoka Y, Igarashi H, Yoshikawa F, Kakehi S, et al. Mechanisms of sleep deprivation-induced hepatic steatosis and insulin resistance in mice. Am J Physiol Endocrinol Metab 2018;315(5):E848-58.

[88] Patel A, Hasak S, Cassell B, Ciorba MA, Vivio EE, Kumar M, et al. Effects of disturbed sleep on gastrointestinal and somatic pain symptoms in irritable bowel syndrome. AP&T 2016;44(3):246-58.

[89] Periasamy S, Hsu DZ, Fu YH, Liu MY. Sleep deprivation-induced multi-organ injury: role of oxidative stress and inflammation. Excli Journal 2015;14:672.

[90] Benedict C, Vogel H, Jonas W, Woting A, Blaut M, Schürmann A, et al. Gut microbiota and glucometabolic alterations in response to recurrent partial sleep deprivation in normal-weight young individuals. Mol Metab 2016;5(12):1175-86.