

Sleep Deprivation and Related Disorders

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Sleep is essential for humans to continue their daily life. It is also a key function for the life span of humans and their cognitive behaviors.^[1] Therefore, having no or too little sleep can have great effects on us. It is regulated by our biological rhythm called the circadian rhythm which swings in 24-hour periods and the homeostatic system which ensures that the body had a sufficient amount of sleep.^[2] Studies show that neurotransmitters such as melatonin play an important role in sleep regulation.^[3,4] Melatonin is released in darkness, and it has an effect on the initiation of sleep rather than the total amount of sleep. When melatonin is released, it decreases the body temperature and in this way creates sleepiness. This mechanism specifies that it has no direct hypnotic effect on the body.^[5] Experiments also show that brain regions such as the thalamus, cerebral cortex, brain stem, basal forebrain are involved in the regulation of sleep-wakefulness states.^[3,5] According to experiments, electrical stimuli in the basal forebrain of cats induce sleep.^[3]

Sleep deprivation is defined as the disruption of the normal circadian rhythm also, it has many physiological and psychological effects. There are different types of sleep disorders such as insomnia

ABSTRACT

Sleep disruption and related disorders are very common among humans. However, this situation is mostly underestimated. Aside from its contribution to daily life functions, sleep quality is also important as a risk factor for a variety of diseases, including neurodegenerative disorders, metabolic diseases, and cardiovascular diseases. The diagnosis and treatment of such diseases may be difficult, but once they are treated, the patients' quality of life will greatly improve. This review aimed to compile and represent information on sleep deprivation, as well as the relationship between sleep and the immune system.

Keywords: Alzheimer's disease, immune system, insomnia, sleep, sleep deprivation

and sleep apnea. Furthermore, it is known that these disorders trigger some cardiovascular and metabolic diseases.^[6] Sleep disorders are defined by behavioral changes in organisms and electrophysiological activity of the brain. Electroencephalogram (EEG) is used for investigating the electrophysiological activity of the brain. For better understanding, the working mechanism of EEG, the pathophysiology of insomnia, neurophysiology of sleep, and sleep disorders were discussed in this review.

The term "electroencephalogram" was first introduced by Hans Berger in the 19th century.^[5] He used EEG to determine the alterations in the electrical potential of the brain. It is measured by scalp electrodes on the unopened skull or electrodes inside or outside the brain. With these records, abnormal patterns and normal patterns of sleep can be compared, so the individual with abnormal sleep patterns is referred to as a professional. The concept of sleep consisting of organized cycles going through diverse stages is understood with the help of EEG. Studies for the characterization of normal sleep patterns started with Loomes and his colleagues. Seventeen years later, Aserinsky defined rapid eye movement (REM) sleep, which led to studies about

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sleep stages. Mainly, sleep has two stages: REM sleep and non-rapid eye movement (NREM) (also referred to as slow-wave sleep).^[7] NREM is also divided into four substages and an individual who falls asleep first enters stage 1. Electroencephalogram starts with low-frequency waves in this stage, which is called the theta rhythm. In stage 2, high amplitude K-complexes and sleep spindles appear. In stage 3, high amplitude delta waves appear, and the waves start to slow down even more in stage 4.^[5] There are diverse multiple cycles of NREM and REM sleep. In healthy individuals, each cycle takes 90-120 minutes, and 4-5 cycles occur in an eight-hour night of sleep. The first period of sleep mostly consists of NREM sleep, and the second period mostly consists of REM sleep, which has low amplitude high-frequency waves.^[5,7]

As stated before, melatonin plays a role in the regulation of sleep and circadian rhythm. According to studies, it also has an effect on alterations of EEG swings such as slow waves and sleep spindles.^[8] The effects of melatonin on REM sleep and slow-wave sleep are investigated in a study for better understanding. In the study, the effect of melatonin in daytime sleep in men is examined. 5 mg dose of melatonin is applied to eight men prior to 4-hour daytime sleep. Results of the study showed that melatonin improved the power density in the sleep spindles in NREM sleep and suppressed the low-frequency activity in EEG. So, it proves the regulatory effect of melatonin on the EEG of sleep. Also, this study indicates that melatonin may play a role in the circadian alteration of the spectral composition of EEG during sleep.^[9]

INSOMNIA

As stated before, sleep has very important effects on our bodies and life. Therefore, it is a very essential function for humans, and they need to fulfill the function completely. To have a better idea about healthy sleep, let's examine the studies about the requirements of it. Sleep time less than seven hours has been related to some cardiovascular diseases, obesity, diabetes.^[10] It is now understood that sleep disorders, including insomnia, also affect cognitive functions.^[10,11] More than seven hours of sleep duration is recommended for adults between the 18-60 age gap. There is a study about the prevalence of healthy sleep time in the southeastern United States and according to its results, geographies that have less prevalence of healthy sleep have a higher prevalence of diabetes and obesity. Again, the effects of sleep deprivation on these diseases are clearly seen. Also in the same study, it is shown that employment and

higher education may be the factors in healthy sleep. Other factors that influence sleep duration badly are smoking, physical inactivity, and dietary habits.^[12,13] On the other hand, sleeping more than nine-hour and excessive sleep time may cause negative effects on individuals' life.^[10,14]

Diagnosis of insomnia mostly consists of subjective complaints of the patient. These complaints are generally having a hard time falling asleep, can't maintain sleep, waking up early, and having a hard time doing daytime functions.^[15] In some research centers, the polysomnographic test results are also being used in the diagnosis of insomnia.^[16] However, there is no significant objective diagnosis of insomnia. So, recent studies are trying to find some ways to use quantitative measurements of sleep in the diagnosis of this disorder. According to the research, the most reliable way to do that is by measuring sleep onset latency and vigilance after 30 minutes of sleep onset.^[15] In the manuals for diagnosis of insomnia, the duration and frequency of complaints are considered, but there is no information about severity.^[17]

To understand the pathophysiology of insomnia, *Drosophila* flies, which are known as fruit flies, are used in studies as model organisms because their insomnia characteristics are similar to insomnia in humans. From these studies, insomnia-related genes are found as apolipoprotein (apo) E4, circadian locomotor output cycles kaput (CLOCK), period circadian regulator 3 (PER3), and serotonin-transporter-linked polymorphic region (5-HTTLPR).^[18] Recent studies bring to light the information that polymorphism in the PER3 gene may define the variances in vulnerability to insomnia.^[19]

There are wake-promoting neurotransmitters that play a role in sleep-wake regulation such as norepinephrine, histamine, and orexin. Orexin works by increasing the firing of neurons in wake-promoting regions of the brain. It is believed that sleep-inhibition mechanisms and the working mechanism of orexin contribute to insomnia. This possible mechanism of insomnia is called the switch model.^[18]

Insomnia is a risk factor for many diseases, which means individuals with insomnia usually have other comorbid diseases. These associated diseases are hypertension, cardiovascular diseases^[20], asthma, gastroesophageal reflux, and type 2 diabetes.^[18] In accordance with estimations, it is said that insomnia increases the risk of type 2 diabetes mellitus by 16% in adult patients. Furthermore, studies about type 2 diabetes onset in humans indicated that sleep pattern affects the onset of disease.^[21] In another study, the

relation between insomnia duration and risk of type 2 diabetes is examined by observing patients who have insomnia for less than four years, between four and eight years, and more than eight years. It is found that the risk of type 2 diabetes is increased by 14% (for patients with insomnia <4 years), 38% (for patients with insomnia 4-8 years), and 51% (for patients with insomnia >8 years).^[22] The relationship between these two diseases actually arises from the sleep immune crosstalk, which will be explained next.

SLEEP AND IMMUNITY

Sleep and the immune system are linked bidirectionally. Immune system stimulation by foreign substances such as microbes, harmful bacteria, etc. initiates an inflammatory response. This response in turn may increase the duration and intensity of sleep, whereas it may create disruptions in sleep. Even when there is no infectious challenge, sleep advances inflammatory homeostasis by affecting inflammatory mediators like cytokines.^[23] Studies showed that cytokines are regulators of both infections associated with sleep and natural sleep. Decreased time spent in REM sleep and increased time spent in slow-wave sleep (SWS) are found in infection by viruses that infect the nerve cells.^[24] Researchers in the 19th century found that sleep deprivation is lethal in dogs after several days.^[25] Also, later studies showed that sleep deprivation in rats leads to death after two to three weeks, furthermore, destruction of the immune system of the host by a systemic bacterial infection is reported.^[26-28] The idea of sleep deprivation lowering the body's defense system is supported by these studies. Also, these relations between sleep and the immune system showed the association of sleep deprivation with diseases that have inflammatory elements, such as diabetes^[29,30] and neurodegenerative diseases.^[31]

For optimizing the defense mechanism, the central nervous system creates changes in functions and behaviors of the body such changes are called sickness behavior, and it is determined by inactivity, sleep alterations, fever, social withdrawal, increased sensitivity to pain, fatigue.^[32,33] Sleepiness and fatigue preserve energy; therefore, they facilitate the recovery from infection.^[23] In the last 30 years of research, it is very well explained that sickness behavior is mediated by inflammatory mediators such as cytokines.^[34] Some products of bacterial cell walls which are lipopolysaccharide and peptidoglycan, and also double-stranded RNA of viruses have the ability to increase cytokine production.^[35] Some of

these cytokines such as interleukin-1 (IL-1), tumor necrosis factor (TNF)^[36] induce sleep. They change the production of neuroendocrine and neurotransmitters, for example, growth hormone-releasing hormone (GHRH) and nitric oxide which are involved in sleep-wakefulness regulation. Thus, the microbial infection affects sleep regulatory mechanisms.

IMPORTANCE OF SLEEP IN MEMORY: ASSOCIATION WITH ALZHEIMER'S DISEASE

Initial theories of sleep and memory were about sleep having a passive role in memory, as enhancing memories by shielding them from intervening stimuli. However, current theories highlight the active role of sleep as memories go into system consolidation during sleep. In this consolidation event, new memories are strengthened and adapted to long-term memories.^[37] The assumption of the one study says that memories are first encoded in a fast learning store which is specifically the hippocampus in the declarative memory system, then transposed to long-term storage.^[38] It is thought that SWS is the main sleep stage for hippocampus-dependent declarative memory, whereas REM sleep is important for nondeclarative memory.^[39]

There is another hypothesis called the sequential hypothesis, which points out the importance of cyclic succession between SWS and REM sleep stages for memory.^[40] This hypothesis assumes that in the SWS stage adaptive memories are strengthened and stored, whereas in the REM stage non-adaptive memories are strengthened and stored in long-term memory. This hypothesis of the importance of cycling of SWS and REM is proved by studies on rats. In these studies on rats, it is seen that awakening after the SWS stage affected the memory performance negatively but when SWS followed by REM sleep no such effect is observed.^[41,42]

When memory could not be encoded distinctly, false memory formation occurs.^[43] Recent studies show that voluntary sleep restriction plays an important role in this false memory formation. In the result of a particular study, one night of sleep deprivation led to false memory formation in young adults.^[44] In these studies, the misinformation paradigm is used for the determination of false memory.^[43] First, a photo is shown to the subjects for giving information. Then false information about the photo is given for creating misinformation. Finally, a test is done after sleep deprivation to see if false memory formation

has occurred.

Sleep deprivation is found very commonly in patients with Alzheimer's disease.^[45] Alzheimer's disease is caused by dementia, which means the corruption of cognitive functions that affect daily life.^[46,47] In these patients, decreased time spent in SWS and REM sleep and increasing frequency of awakening are found.^[45] It is thought that this relation between sleep and Alzheimer's disease came from the damage to neuronal pathways that are involved in sleep regulation.^[48] One example of these changes is alterations in the suprachiasmatic nucleus (SCN)^[49] of the hypothalamus which includes the circadian pacemaker, and it also involves the regulation of the production of melatonin.^[50] The suprachiasmatic nucleus may go under neurodegenerative changes in Alzheimer's disease, so that is how sleep is altered in patients with Alzheimer's disease. Another change may occur in the cortical region which creates EEG slow-wave activity in sleep. Clinical studies found evidence about the corruption of the circadian system related to these regions in patients with Alzheimer's disease.^[45]

TREATMENTS FOR INSOMNIA

The goal of treatment for insomnia is to increase sleep quality and time spent in sleep, reducing stress and anxiety which causes sleep deprivation and enhancing daytime functions.^[51] There are two broad categories in the treatment as medication treatments and cognitive-behavioral treatments.^[52,33] Patients also may try to treat themselves by considering sleep hygiene, reading, and relaxation.

Cognitive-behavioral treatment is a commonly used non-medication treatment. Targets for this treatment of insomnia are sleep hygiene, Maladaptive behaviors, beliefs, and thoughts about sleep. In this treatment, usually patients are told to use diaries to observe changes in sleep. Specific techniques for cognitive-behavioral treatment of insomnia (CBT-I) are sleep education, sleep construction techniques, cognitive therapy techniques, and relaxation training. This treatment is frequently effective on primary and comorbid insomnia patients.^[52] Efficacy studies of CBT-I showed that treatment over six to 10 weeks is comparable or even better to hypnotic medications and maintained up to three years.^[52,53] Behavioral treatment is effective on patients who use hypnotic medications and may even reduce the necessity of medication.^[54] This treatment when initially combined with pharmacotherapy and then followed by CBT-I alone gives the best long-term results. Typically CBT-I

is completed in six to eight individual sessions. In medication treatment, hypnotics that are approved by Food and Drug Administration (FDA) such as antihistamine drugs (i.e., hydroxyzine), melatonin receptor agonist (ramelteon), benzodiazepine receptor agonists (BzRAs) are used.^[52] Physicians may also prescribe some sedating antidepressants and antipsychotic drugs without FDA indication. In fact, particular research shows that most prescribed drugs for insomnia treatments are not FDA approved.^[55] Also, BzRA drugs are the most prescribed drugs annually in the United States. These drugs work by binding specific recognition sites of gamma-aminobutyric acid type A (GABA-A) receptors.^[52] Activation of these GABA-A receptors favors sleep in turn.^[56] The effectiveness of BzRA drugs in the short term is well-defined in studies. Also, significant improvements in sleep time, sleep quality, and sleep latency are indicated with the duration of drug action.^[57]

In conclusion, all the studies stated in this paper collectively show that sleep has an effect on every side of human life. If the quality of sleep is bad, it brings bad effects to life, but if its quality is good, it makes life easier. Also, studies prove that sleep is specifically important in patients with diabetes, Alzheimer's disease, and inflammatory diseases. These patients must be very careful with their sleep quality and try to make it better. Also, patients with sleep deprivation disorders such as insomnia must see a physician to treat their disorder. Otherwise, their sleep deprivation will be a risk factor for other diseases. There are efficient treatments for insomnia. Efficacy and the preservation duration of treatment of medications used in the treatment are proved by studies. So, sleep deprivation is not impossible to treat, people should be aware of it. If the patients do not want to use medication, they can still get cognitive-behavioral treatment. There are studies about the efficacy of this treatment, and they indicate that it is very effective. This treatment even reduces the need for medication. In conclusion, there are effective treatments for sleep deprivation illnesses and since it is a very important risk factor for other diseases, they must be treated.

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