

Sleep Deprivation: A Mini Review

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Abstract

Sleep is an important process for human beings in order to keep many biological functions in a healthy recycle. However, several factors affecting sleep could induce too many sleep disorders in modern society, such as sleep deprivation.

Sleep deprivation has complex biological consequences inducing different biological effects, such as neural autonomic control changes, increased oxidative stress, altered inflammatory and coagulatory responses and accelerated atherosclerosis.

This mini review summarizes consequence of sleep deprivation and its effects on the treatment of depression in different studies in order to have a better understanding of the impact of sleep deprivation on the equilibrium at multiple levels of sleep deprivation.

Introduction

Sleep is a valuable process for the maintenance of biological functions, such as homeostasis, metabolic restoration, physiological regulation, and adaptive cognitive functions in the central nervous system [1-3]. We humans are daylight creatures. We have associated wakefulness and activity with the day/light period, and sleep and rest with the night/dark period in the course of our evolutionary adaptation. Although in modern society artificial lighting makes it possible to have light for the whole day (24 hours), body functions, such as hormonal, metabolic, digestive, cardiovascular and mental, are still mainly influenced by the natural day/night cycle, showing periodic fluctuation that have peaks during the daytime and troughs at night in general.

In fact, most of the biological functions of the body changes during sleep compared to wake, including Heart Rate (HR), Arterial Blood Pressure (ABP), temperature, as well as hormonal secretion and immune function. Cardiovascular process is mainly modified during sleep and the relationship between cardiovascular system and sleep is bidirectional. Cardiovascular diseases are associated with alterations of physiological sleep and vice versa sleep disorders can seriously affect the cardiovascular system, inducing an high risk of cardiovascular diseases [4,5]. During physiological sleep, HR and ABP is lower during non-REM sleep compared with marked increases during REM sleep [6,7]. In this interaction, a sympathetic and parasympathetic oscillation of the sympatho-vagal balance plays a vital role by the autonomic cardiovascular modulation of HR and ABP. A predominant vagal modulation and sympathetic control is observed during NREM sleep and REM sleep respectively and both are at higher levels than in wakefulness [6,7].

There might be several aspects accounting for the reasons of sleep deprivation. Firstly, our lifestyle is the most common reason for being sleep deprived, such as the use of electronic devices before going to sleep, which alter the normal physiological secretion of melatonin [8], drinking too much coffee or tea, shift work etc. Secondly, ageing is the irresistible process for being sleep deprived, which is associated with a decrease of total sleep time and a disruption of physiological sleep. Thirdly, we may suffer from Sleep Disordered Breathing (SDB), such as insomnia, Periodic Limb Movements (PLM), and Restless Leg Syndrome (RLS).

Consequence of sleep deprivation

Sleep loss stresses the organism as a whole, challenging its equilibrium at multiple levels, from the molecular and cellular domains to the complex interaction of entire systems, leading to cardiovascular diseases, performance impairment, gene regulation, metabolic disarray, inflammatory response and so on.

Cardiovascular disease: Sleep deprivation is associated with the morbidity and mortality of coronary heart disease due to pathological factors including sympathetic activation, high blood pressure, arrhythmia, neuroendocrine dysfunction, oxidative stress, endothelial malfunction, inflammatory reaction, and glycolipid metabolism disorders [9]. Increases in blood pressure, decreases in parasympathetic tone, and increases in evening cortisol are all observed after only 4 hours of sleep deprivation. Many studies have indicated that sleep duration is negatively correlated with the incidence of Coronary Heart Disease (CHD), and short sleep duration has been suggested to be

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associated with an increased risk of CHD ($P < 0.0001$) [10]. Moreover, long-term studies have indicated that Sleep Deprivation (SD) is also closely correlated with increased morbidity and mortality of myocardial infarction and heart failure, and becomes an independent predictor of cardiovascular disease risk [11-14].

Wang, J et al summarizes findings of traditional Chinese medicine tranquilization methods in different studies that indirectly treat coronary heart disease by removing the pathological factors of sleep deprivation [9]. A traditional Chinese medicine tranquilization method has been suggested to improve the pathological factors of sleep deprivation with a multiple-component, multiple-target and multiple-pathway approach that may be a treatment for coronary heart disease.

Performance impairment: Several studies on sleep deprivation have suggested that having less than 5 hours' sleep in the preceding 24 hours or less than 12 hours' sleep in the preceding 48 hours might increase the risk of significant performance impairment [15]. Moreover, on account of circadian desynchronization, and in association with sleep deprivation and increased daytime sleepiness and fatigue, performance on many psychomotor activities (e.g., reaction time, hand-eye coordination, logical reasoning, and vigilance) also shows an acute 8–10% decrement that may last for 3–5 days. While several diseases include sleep disturbances among their symptoms—including psychosis, depression, and Parkinson's and Alzheimer's disease—sleep loss per se is a risk factor for psychiatric and neurological diseases [16,17].

Gene regulation: Since the regulation of sleep-dependent gene produces long-term effects on behavior and physiology, it is important to determine how sleep deprivation affects health by the change of specific genes expression. Modifications in gene expression may be the most important effects of sleep deprivation, which can reflect the activation or suppression of cellular processes, causing changes in neuronal function and synaptic connections.

Sleep deprivation up regulates the expression of several immediate early genes, such as *c-fos*, *Arc* and *Homer1*, as well as alternative splice variants, whose protein products are involved in a regulation of several cellular processes that ultimately influence neuronal plasticity and brain function [18].

Metabolic disarray: Because of the important influence of sleep on a wide variety of metabolic process, there is no doubt that sleep deprivation induces major metabolic disarray, including changes in serum protein levels, which may reflect changes in gene expression and the release, degradation, and turnover of these proteins.

The hormones, cytokines, and other proteins whose expression levels are affected by sleep deprivation, including leptin, ghrelin, the thyroid hormones T3 and T4, Interleukin 6 (IL-6), TNF- α , and C-Reactive Protein (CRP). Combined, changes in the levels of these proteins lead to energetic imbalance, impairment of the glucose metabolism, and metabolic syndrome [19]. Increased insulin and appetite levels included by metabolic effects of short duration deprivation are possibly the results of the elevation of ghrelin, a pro-appetitive hormone, and decreased levels of leptin [20,21].

Inflammatory response: In humans, one night of sleep loss increases the levels of IL-6 and TNF- α [22]. One week of chronic sleep loss for young men and women increases the levels of IL-6, while the

increase of TNF- α can only be seen in young men [23]. Subjects with 4 h per night sleep limitation show increased levels of IL-6 compared with subjects sleeping 8 h per night, while no significant differences were found between these groups in terms of TNF- α or CRP [24]. Lymphocyte activation and up regulation of IL-1, IL-6, IL-17, and CRP can be seen when sleep restriction for 5 nights was performed [25]. A research of 70 patients have suggested that poor sleep is associated with increased concentrations of Vascular Endothelial Growth Factor (VEGF) and a decreased fatigue-related activity is associated with increased TNF- α levels [26]. Therefore, sleep deprivation is associated with a strong inflammatory response.

Sleep Deprivation and Treatment of Depression

Maintaining stable sleep-wake cycles is of central importance to the maintenance of stable mood. There is wide agreement that psychiatric illness, including depression, involves circadian disruption of body temperature, mood and sleep [27,28]. A community-based two-wave cohort study involving 3134 youths followed up a year suggested that reduced quantity of sleep increases risk for major depression, which in turn increases risk for decreased sleep [29].

Advantages

Since first being described in the 1970s, the antidepressant effect of sleep deprivation has been repeated in several studies and a great number of patients have been treated with this antidepressant technique during more than 40 years. Although antidepressant sleep deprivation is not considered as the first-line treatment like all chronobiological interventions, sleep deprivation has been widely used regarding its rapid antidepressant effect is highly repeatable and substantial [30], which makes sleep deprivation a potential first-line treatment for depression. Recently, the development of several new clinical strategies has led to the possibility of sustaining the effects of sleep deprivation and achieving long-term euthymia with the help of combining different chronobiological techniques, such as light therapy, antidepressant drugs and mood stabilizers. For example, antidepressant drugs have been successfully combined with antidepressant sleep deprivation, such as selective serotonin reuptake inhibitors, tricyclic antidepressants, and with the dopaminergic amineptine in a synergistic way [31]. Lithium salts as well have been found to sustain the antidepressant effect of SD. Benedetti et al. studied 143 in patients with a major depressive episode in the course of bipolar disorder (DSM-IV criteria). They were administered 3 consecutive total sleep deprivation cycles (each composed of a period of 36 hours awake followed by recovery sleep) combined with bright light therapy in the morning for 2 weeks and taking lithium. Among the 141 who completed the treatment, 70% achieved a 50% reduction in HDRS score in 1 week, which persisted 1 month after in 55%. This study may suggest that combination of total sleep deprivation, light therapy, and lithium is able to rapidly decrease depressive suicidality and prompt antidepressant response in drug-resistant major depression in the course of bipolar disorder [32].

Nowadays, clinicians use sleep deprivation as one of the most rapid antidepressant treatment. Moreover, acute sleep deprivation has a higher effective rate of 40% to 60% in depressed subjects improving mood within 24 to 48 hours when they are compared with antidepressant medications which typically need 2 to 8 weeks to have an effect [33].

Limitations

However, the mechanisms underlying the mood-improving effects of this sudden acute circadian "shock" are as yet unknown and it still remains unknown how many hours of sleep deprivation are needed to achieve the entire antidepressant effect. Moreover, the minimum duration of sleep restriction obtaining antidepressant effects has not been determined and the influence of sleep deprivation on mood strictly depends on the presence of a mood disorder. After recovery sleep, up to 80% of sleep deprivation responders return to the origin, only little patients maintain the achieved improvement [34]. Therefore, the clinical usefulness of this treatment has been questioned by the short duration of the antidepressant effects.

Risk

Sleep is a potential activator of interictal epileptiform discharges and sleep deprivation is a trigger of epileptic seizures. The only confirmed contraindication of sleep deprivation therapy is the presence of epilepsy [35]. The major risk using this chronotherapeutics in clinical settings comes from the possibility of depressive relapse in the first month after chronotherapeutics, which is unexpected in patients with bipolar disorder. A careful monitoring of mood in the weeks after acute response to chronotherapeutics is recommended [36].

Generally, sleep deprivation has well tolerance. But the nonspecific stress associated with staying awake all night could induce unexpected medical conditions, such as potential severe cardiovascular diseases [37,38]. Thus, regarding the fact that even low degrees of stress can worsen the potential severe diseases, a careful medical examination aiming to ruling out the unexpected medical conditions should be performed before the beginning of the treatment.

Side effects

Sleep deprivation has very few side effects and the most common and obvious adverse effect of sleep restriction is daytime sleepiness with the degree of sleepiness showing a high individual variability.

In bipolar patients, there have been occasional reports of switches into hypomania or mania. The risk of a manic switch after therapeutic Sleep deprivation seems to be low, preventable, and is usually easily treated. Current data show an approximate 5% switch rate into mania and 6% into hypomania [31]. If patients have comorbid panic disorder, they should be informed that panic attacks will be worsened during the night of Sleep deprivation and this will not reduce response to the chronobiological treatment.

Conclusion

Sleep deprivation is a growing health problem in the whole world. A better understanding of the impact of sleep deprivation on the equilibrium at multiple levels, from the molecular and cellular domains to the complex interaction of entire systems, shall provide meaningful insights into both basic and applied scientific questions. It should also help mitigate the cognitive and health problems faced by those that suffer from sleep loss due to different risk factors. An early diagnosis of subjects with sleep deprivation is essential in order to reduce the risk of cardiovascular and metabolic diseases in general population. Future large population studies are needed in order to evaluate how much benefits we can obtain from the treatment of sleep deprivation.

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