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REVIEW ARTICLE

The Role of Sleep Deprivation in Arrhythmias

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Abstract

Sleep is essential to the normal psychological and physiological activities of the human body. Increasing evidence indicates that sleep deprivation is associated with the occurrence, development, and poor treatment effects of various arrhythmias. Sleep deprivation affects not only the peripheral nervous system but also the central nervous system, which regulates the occurrence of arrhythmias. In addition, sleep deprivation is associated with apoptotic pathways, mitochondrial energy metabolism disorders, and immune system dysfunction. Although studies increasingly suggest that pathological sleep patterns are associated with various atrial and ventricular arrhythmias, further research is needed to identify specific mechanisms and recommend therapeutic interventions. This review summarizes the findings of sleep deprivation in animal experiments and clinical studies, current challenges, and future research directions in the field of arrhythmias.

Keywords: Sleep deprivation; Heart-brain interaction; Arrhythmias

Introduction

Sleep is defined as a natural and reversible state of diminished response to external stimuli, relative inactivity, and loss of consciousness. Sleep occurs at regular intervals and is dynamically regulated; that is, the loss or delay of sleep leads to subsequent prolonged sleep [1]. The term "sleep deprivation" originated from the description of sleep loss caused by continuous work, and gradually developed into an independent concept specifically referring to a process and state in which the required amount of sleep is not obtained for environmental or personal reasons. With societal changes, the acceleration of the pace of life, and increases in life pressure, people continually face various stressful events that cause sleep disorders and significantly increase the incidence of sleep deprivation, thereby affecting the physiological functions of various body systems and causing circadian rhythm disorders [2]. Therefore, the pathophysiological changes caused by sleep deprivation are gradually becoming a major public health and safety issue with high economic and social costs [3].

Among the various effects of sleep deprivation on psychophysiological activities, effects on brain function are the earliest and clearest manifestations. Therefore, current research on sleep deprivation in China and other countries focuses primarily on neurological and cognitive function. However, with advances in sleep deprivation research, clinical and

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basic science studies increasingly confirm that sleep deprivation can also affect the normal physiological function of the cardiovascular system. Studies have shown that sleep deprivation activates an immune response that promotes the development of atherosclerosis [4]. In addition, women who sleep for less than 5 hours have clear cardiac ischemic changes [5]. Joukar et al. [6], in experiments in rats, have found that 72 hours of complete sleep deprivation significantly increases the incidence of preventricular contractions. This review discusses the mechanisms of sleep deprivation-induced arrhythmia (see Figure 1).

Sleep Deprivation and Neuromodulation Networks

The central nervous system regulates the electrophysiological substrate of arrhythmia through mediating autonomic nerve activity, and the regulation of autonomic nerves has been used as a target for prevention and treatment of arrhythmia with modalities such as beta-blockers, cardiac sympathetic denervation, renal sympathetic denervation, and spinal cord stimulation. The paraventricular nucleus of the hypothalamus (PVN) plays a key role in maintaining cardiovascular activity, which can directly innervate sympathetic preganglionic neurons and participate in the regulation of peripheral sympathetic nerve activity; sensory afferent fibers are also integrated at the PVN level and affect sympathetic output [7, 8]. The neuronal firing activity in the PVN significantly increases for 24 hours after 6 hours of sleep deprivation in rats [9]. Perry et al. [10] have found that the levels of γ-aminobutyric acid receptors in the PVN are down-regulated, the renal sympathetic nerve activity increases, and the plasma cortisol concentration increases after 20 hours of sleep deprivation, thus suggesting that γ-aminobutyric acid in the PVN inhibits sleep deprivation-induced sympathetic excitation. Therefore, under the influence of sleep deprivation, the cardiac autonomic nervous system may be regulated by neurons in the PVN, thus resulting in the excitation of sympathetic nerve activity and the weakening of vagal nerve activity, and subsequently affecting changes in heart rate variability (HRV). Bourdillon et al. [11], in a sleep deprivation study in 15 participants, have confirmed that the continuous difference root mean square and high frequency band power of HRV indicators during sleep deprivation decrease while the normalized power increases; photoelectric plethysmogram parameters indicate decreased amplitude and duration of systolic and diastolic waveforms, in agreement with increased sympathetic nerve activity and vascular tone. These findings suggest that cardiovascular function is destroyed if changes are observed in those two markers. In fact, HRV analysis is recognized as

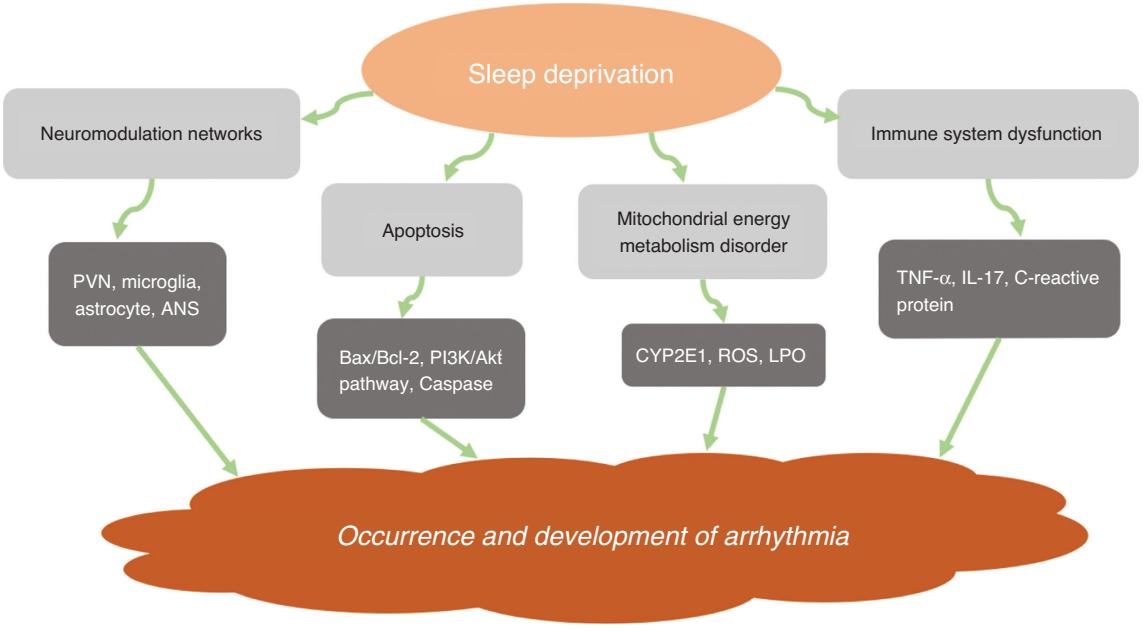

Figure 1: Mechanisms of Sleep Deprivation-Induced Arrhythmia.

an effective indicator for quantitative assessment of autonomic nerve activity. Over-activation of the sympathetic or vagus nerve in the cardiac autonomic nervous system can lead to arrhythmias and even sudden cardiac death.

In addition, a recent study has shown that microglia regulate neuronal plasticity by directly upregulating the expression of neuronal glutamate receptors [12]. Many articles have confirmed that sleep deprivation significantly increases the activity of microglia in the brain, thus resulting in changes in mood and cognitive function. However, studies on cardiovascular disease, particularly cardiac arrhythmias, are extremely rare and may become a new direction for future research on sleep deprivation-induced arrhythmias.

Sleep Deprivation and Apoptosis

Apoptosis, an active cell death process modulated by genes in multicellular organisms, regulates the development of the body and maintains the stability of the internal environment. Recent studies have shown that cardiomyocyte apoptosis is a major pathogenic mechanism underlying various cardiac diseases including arrhythmia. Aime et al. have found cardiomyocyte apoptosis in most of 50 examined right atrial myocardium samples from patients with atrial fibrillation and atrial hypertrophy, and observed that apoptosis contributes to the remodeling of cardiomyocytes. Santos et al. [13], in autopsies of two brothers with a family history of arrhythmia who experienced sudden cardiac death, have observed apoptosis in the sinoatrial node, atrioventricular node, and internode. In an autopsy study of 20 patients with arrhythmogenic right ventricular cardiomyopathy, Fornes et al. have found that the occurrence and development of the disease is a degenerative process involving apoptosis.

In recent years, studies have confirmed that apoptosis indices (such as Bax/Bcl-2) are significantly increased in sleep deprivation rat models [14]. Yuan et al. [15] have also found elevation of the apoptosis-associated protein caspase-3 in sleep-deprived rats. In addition, Chen et al. [16] have confirmed that sleep deprivation causes overexpression of apoptosis-associated proteins, and the PI3K/Akt pathway plays a key role in maintaining apoptosis. The mechanisms of apoptosis are highly complex, involving a variety of signaling molecules. According to the different triggering mechanisms, related signal transduction pathways can be divided into extrinsic pathways, mediated by death receptors triggered by death ligands of the tumor necrosis factor (TNF) superfamily, and intrinsic apoptotic pathways, mediated by mitochondria [17, 18]. The morphological and biochemical changes in apoptotic cells are caused mainly by the activation of the cysteine proteolytic enzyme (caspase) family. In healthy cells, caspase family members usually exist in the form of inactive zymogens, which initiate apoptosis when activated. According to their roles in apoptosis, the known caspase family members can be divided into initiator caspases (including Caspase-2, Caspase-8, Caspase-9, and Caspase-10) and effector caspases (including Caspase-3, Caspase-6, and Caspase-7). Initiator caspases activate effector caspases, thus resulting in protein hydrolysis and DNase activation in apoptosis [19]. The Bcl-2 family includes the anti-apoptotic factor Bcl-2 and the pro-apoptotic factor Bax. The binding of Bax to the mitochondrial membrane channel directly alters membrane permeability and causes the release of cytochrome C (Cyt C) [20], thus leading to cell apoptosis; in contrast, Bcl-2 prevents the release of Cyt C and inhibits apoptosis. With changes in mitochondrial membrane permeability, cell apoptosis is irreversible [21]. Cyt C released into the cytoplasm can form apoptotic bodies with apoptotic protease activating factor-1 (Apaf-1) and Caspase-9 precursor, thus resulting in Caspase-9 activation [22]. A key molecule of the caspase family, Caspase-3, is positively correlated with apoptosis and is currently considered an effector of the final pathway of various apoptotic pathways. The involvement of PI3K/Akt in various anti-apoptotic effects in cells has been confirmed by many studies. The activation of Akt is triggered by many cytokines and growth factors, thereby protecting cells against apoptosis. For example, Cheng et al. [23] have found that Akt inhibitors decrease the activation of Akt and extracellular regulated protein kinases, thereby regulating the apoptosis program and the lifespan of Drosophila. For example, Wei et al. [24] have found that ELF4 overexpression activates the Akt signaling pathway, and consequently promotes the proliferation of insulinoma cells and inhibits their apoptosis. Therefore, sleep deprivation participates in the apoptosis pathway

through various modes of action, thereby forming a potential structural basis for the development of arrhythmias, and inducing the occurrence of various types of arrhythmias including atrial fibrillation and ventricular arrhythmia.

Sleep Deprivation and Mitochondrial Energy Metabolism Disorder

Cardiomyocyte electrical remodeling is the electrical basis for arrhythmia. Myocardial cell energy metabolism disorders can directly or indirectly affect the function of ion channels, induce electrical remodeling, and cause arrhythmia [25]. Shao et al. [26] have indicated that mitochondria regulate the calcium cycle process in cells, and play an important role in cardiomyocyte energy metabolism and dynamics. In animal studies, Liguo et al. [27] have found that mitochondria in cardiomyocytes in a diseased state participate in the regulation and transport of sodium ions in the cytoplasm, thus decreasing the concentrations of sodium ions in mitochondria and resulting in metabolic dysfunction. In addition, ventricular muscle I_{K1} channels are regulated by mitochondrial adenosine triphosphate-sensitive potassium (K_{ATP}) channels. The density of mitochondrial K_{ATP} channels is very high, so they are very sensitive to changes in intracellular ATP, ADP, and pH. Therefore, when the oxidative respiratory chain in mitochondria is destroyed by pathological conditions, the production of ATP decreases, K_{ATP} channels are activated, and electrical changes in cardiomyocytes and arrhythmia subsequently result. Therefore, identifying pathological stress factors affecting mitochondrial metabolism is critical.

Sleep deprivation is one of many factors affecting mitochondrial function. Many studies have confirmed a causal relationship between sleep disorders and energy metabolism disorders. Epidemiological studies have indicated that night shift workers whose circadian rhythm is reversed because of their work have poor sleep quality and a significantly higher incidence of metabolic disorders [28]. Saner et al. [29] have found that sleep deprivation affects circadian clock gene expression, damages mitochondrial structure, and affects cellular energy metabolism, such as through decreasing insulin sensitivity. In the brain, sleep deprivation decreases mitochondrial membrane excitability and promotes the release of Cyt C, thus resulting in neuronal apoptosis [30]. In addition, Rodrigues et al. [31], in an experimental model of Drosophila, have found that sleep deprivation leads to changes in mitochondrial enzymes, decreases mitochondrial bioenergy efficiency, and increases susceptibility to arrhythmias. Lindsay et al. [32] have recently reported that sufficient evidence from population studies and animal model studies indicates that mitochondria are involved in energy metabolism disorders caused by sleep deprivation through oxidative phosphorylation dysregulation. Kyoji et al. [33] have found that when rats with sleep disorder have metabolic disorders, their adrenal glands show changes in the expression of cytochrome P450 metabolism-associated genes. Cytochrome P450 2E1 (CYP2E1) is a member of the cytochrome oxidase P450 superfamily. CYP2E1 is distributed mainly in the liver, and it is also highly expressed in the heart, brain, lung, and stomach. CYP2E1 localizes in the endoplasmic reticulum and additionally has a targeting mechanism that localizes in the mitochondria [34]. Numerous studies have shown that CYP2E1 produces reactive oxygen species (ROS) in the metabolic process. ROS transfer electrons that oxidize macromolecules and damage target organs. During this process, ROS further generate lipid peroxides, which in turn interact with ROS in a vicious cycle aggravating mitochondrial damage [35]. Under pathological conditions such as stress, CYP2E1 is overexpressed in the liver, thus generating ROS and damaging liver tissue. Little research has examined the mechanisms of CYP2E1 damage to myocardial mitochondria under pathological conditions, such as sleep disorders; this area may be a new direction for future research. In conclusion, sleep deprivation participates in the mitochondrial energy metabolism pathway through oxidative stress reactions such as ROS production, which in turn regulates ion channels in cardiomyocytes, induces electrical remodeling of cardiomyocytes, and increases the incidence of arrhythmias.

Sleep Deprivation and Immune System Dysfunction

Studies have confirmed that circulating white blood cells, such as neutrophils, NK cells, and monocytes, are affected by circadian rhythms. When sleep

deprivation occurs, the level of immune cells in the body also fluctuates significantly [36]. Moreover, the levels of inflammatory response markers (such as C-reactive protein and interleukins) increase during sleep deprivation [37]. Thus, sleep deprivation may affect natural killer cells, lymphocytes, cytokines, and the production of immunoglobulin and complement, thereby causing immune system dysfunction and immune system-associated diseases.

The effects of sleep deprivation on the levels of immune system-associated factors have been extensively studied in recent years. Most circulating immune factors are secreted by monocytes and neutrophils. Sleep deprivation causes changes in the number and function of these cytokines, including tumor necrosis factor-α (TNF-α), the interleukin family (such as IL-1β, IL-6, IL-8, IL-17, and IL-18) and related acute phase reactive protein (e.g., C reactive protein). No significant change in TNF-α levels has been observed after 24 h of acute sleep deprivation in rats, but changes have been observed after 20 and 30 days of chronic sleep deprivation [38]. In a group-controlled study of sleep deprivation in 13 healthy young adults, Wessel et al. [39] have found that five nights of sleep deprivation increases lymphocyte activation and pro-inflammatory cytokine production, including IL-17 mRNA levels. Another study has confirmed that abnormal secretion of IL-17 may persist for more than 1 week [40]. The interleukin 17 family is a class of interleukin molecules secreted by T helper 17 cells. IL-17 is a pro-inflammatory cytokine demonstrated by numerous studies to be involved in innate and adaptive immune responses, and to be associated with autoimmune diseases, heart disease, and cancer. Nikoo et al. [41] have reported that elevated IL-17 levels are associated with the pathology of atrial fibrillation mediated by neutrophils and monocytes. Li et al. [42] have further demonstrated that IL-17 increases susceptibility to ventricular arrhythmias through NF-κB-mediated electrical remodeling, a process potentially associated with diminished cardiac conduction velocity and prolonged action potential duration. Current understanding of sleep deprivation and IL-17 is focused on the relationship between brain cognitive function and neuron-associated functions. However, few reports have described the molecular mechanism of IL-17 in the myocardium in sleep deprivation, particularly in arrhythmia; this topic may be a new area for further research on the mechanisms underlying sleep deprivation-induced arrhythmias.

Conclusions

Although most cardiovascular effects of short-term sleep deprivation recover after sleep compensation, long-term chronic sleep deprivation may result in irreversible changes in body function and permanent damage to the body [43]. Increasing awareness of the effects of sleep deprivation on population health is essential to improve quality of life and safeguard life and health. However, systematic studies on the exact relationships and underlying mechanisms between sleep deprivation and changes in cardiac structure and function are lacking. Therefore, in-depth studies are much needed to elucidate the effects of different degrees of sleep deprivation on cardiac structure and function, particularly cardiac electrophysiology; to study the possible underlying mechanisms; and to further identify relevant protective measures against sleep deprivation.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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