REVIEW DERLEME

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Obstructive Sleep Apnea and Circadian Rhythms

Obstrüktif Uyku Apnesi ve Sirkadiyen Ritimler

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ABSTRACT Obstructive sleep apnea (OSA) is a sleep disorder characterized by recurrent episodes of partial or complete obstruction of the upper airway during sleep. Circadian rhythms are natural biological rhythms that follow a 24-hour cycle and are synchronized with external cues, primarily the alternating patterns of light and darkness. The relationship between sleep apnea and circadian rhythms is complex and multifaceted. Disruptions in circadian rhythms can impact sleep quality and overall sleep-wake regulation. In the case of sleep apnea, the recurrent episodes of partial or complete obstruction of the upper airway during sleep can lead to disruptions in the normal sleep pattern. Sleep fragmentation and sleep apnea-related factors, such as intermittent hypoxia and oxidative stress, can directly affect the molecular and cellular mechanisms underlying circadian rhythms. Clinical and basic research studies have provided further evidence of the relationship between circadian rhythm and OSA. These studies highlight the importance of the circadian clock in regulating breathing, metabolism, and hormone secretion, the impact of OSA on melatonin secretion, blood pressure, and glucose metabolism, and propose it as a potential therapeutic target for sleep apnea and associated metabolic disorders. Understanding the relationship between OSA and circadian rhythms is important for managing and treating sleep apnea and its associated comorbidities. This review paper explores the molecular and systemic aspects of the circadian rhythm, their relationship with OSA, and the potential implications for disease development and treatment in literature highlights.

Keywords: Obstructive sleep apnea; sleep disorders; circadian rhythm

ÖZET Obstrüktif uyku apnesi [obstructive sleep apnea (OSA)], uyku sırasında üst solunum yollarının kısmi veya tam tıkanıklığına bağlı olarak tekrarlayan epizodlardan oluşan bir uyku bozukluğudur. Sirkadiyen ritimler, doğal biyolojik ritimlerdir ve 24 saatlik bir döngüyü takip ederler. Bu ritimler, dış çevre faktörleri ile özellikle ışık ve karanlık arasındaki değişimlerle senkronize olurlar. OSA ve sirkadiyen ritimler arasındaki ilişki karmaşık ve çok yönlüdür. Sirkadiyen ritimlerin bozulması, uyku kalitesini ve genel uyku-uyanıklık düzenini etkileyebilir. Uyku apnesi durumunda, uyku sırasında üst solunum yollarının tekrarlayan tıkanma epizodları normal uyku düzenini bozabilir. Uyku parçalanması ve uyku apnesine bağlı faktörler, örneğin aralıklı hipoksi durumu ve altta yatan oksidatif stres, sirkadiyen ritimlerin temeldeki moleküler ve hücresel mekanizmalarını doğrudan etkileyebilir. Klinik ve temel araştırmalar, sirkadiyen ritim ile OSA arasındaki ilişki hakkında çeşitli bulgular ortaya koymuştur. Bu çalışmalar; solunum, metabolizma ve hormon salgısı düzenlemesinde sirkadiyen ritmin önemini, OSA'nın melatonin salgısı, kan basıncı ve glukoz metabolizması üzerindeki etkisini vurgulamaktadır. Ayrıca bu çalışmalar, sirkadiyen ritmi, uyku apnesi ve ilişkili metabolik bozukluklar için potansiyel bir terapötik hedef olarak önermektedir. OSA ve sirkadiyen ritimler arasındaki ilişkinin anlaşılması, uyku apnesi ve ilişkili komorbiditelerin yönetimi ve tedavisi açısından önemlidir. Bu derleme makalesi, sirkadiyen ritmin moleküler ve sistemik yönlerini, OSA ile ilişkisini, hastalık gelişimi ve tedavisi açısından potansiyel sonuçları literatür eşliğinde araştırmaktadır.

Anahtar Kelimeler: Obstrüktif uyku apnesi; uyku bozuklukları; sirkadiyen ritim

Circadian rhythms are inherent biological rhythms that occur in a 24-hour cycle and are synchronized with external factors, particularly the alternation between light and darkness. The suprachiasmatic nucleus (SCN) in the hypothalamus is the central clock, coordinating various physiological and behavioral processes such as sleep, feeding, and hormone release. These rhythms are regulated by a complex molecular mechanism involving clock genes and their protein products, which control the expression of downstream clock-controlled genes (CCGs) in specific tissues (Figure 1).[1]

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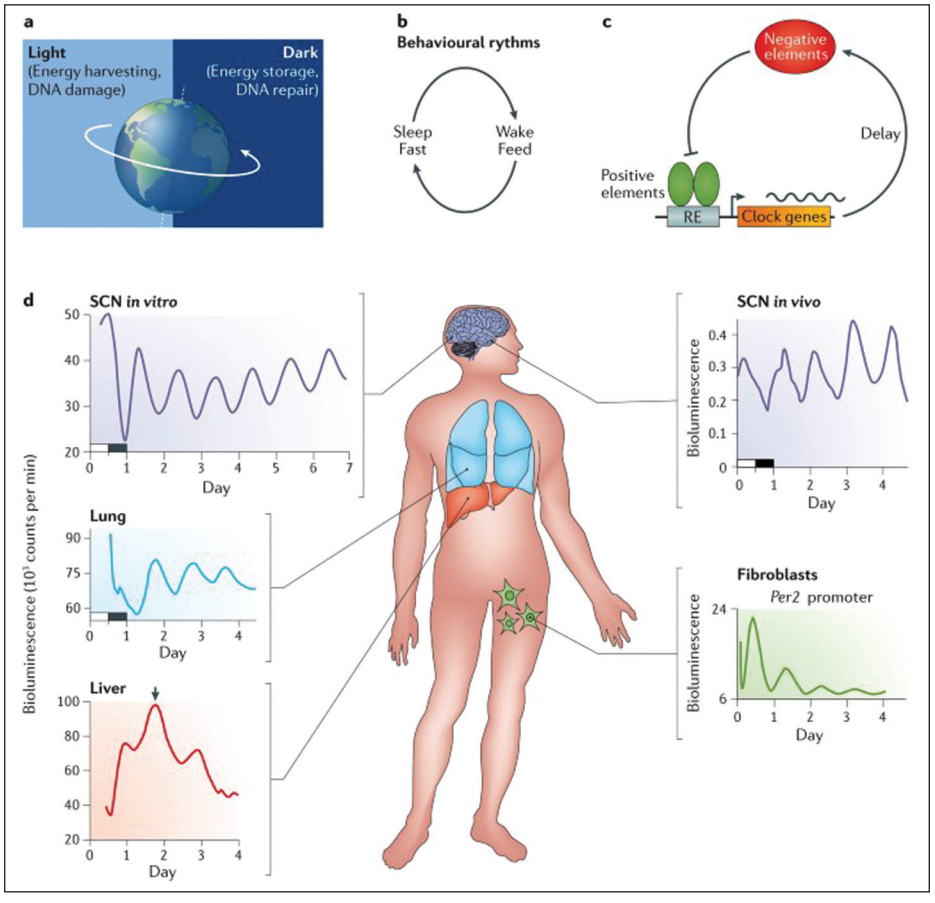

FIGURE 1: Circadian adaptation to the solar cycle.

The 4 parts of the figure provide insight into the adaptation of organismal physiology to align with the 24-hour solar energetic cycle on Earth.

Part a illustrates how the Earth's 24-hour rotation results in a diurnal cycle of light and darkness, which in turn drives an energy harvesting and storage daily rhythm. Furthermore, solar irradiation imposes a cycle of DNA damage and recovery.

Part b highlights the behavioral rhythms observed in animals, such as sleep-wake cycles and feeding-fasting cycles, which occur on a 24-hour basis in synchrony with the solar day.

Part c describes the conserved network motif of circadian clocks, which is based on a transcription-translation negative-feedback loop with a delay.

Part d explains that in mammals, circadian clocks are cell autonomous and are present in all major organ systems and tissues of the body. The hypothalamic SCN acts as a master pacemaker, establishing a hierarchical organization that synchronizes behavioral and physiological rhythms throughout the body. RE are also involved.

Parts a and b of the figure are reproduced from Ref.66 by Nature Publishing Group, while part d is adapted from Ref. 67 by Nature Publishing Group. Total idea from Ref.1.

SCN: suprachiasmatic nucleus; RE: Regulatory elements.

Obstructive sleep apnea (OSA) is a prevalent sleep disorder that affects approximately 10% of adults. It is characterized by recurrent obstruction of the upper airway during sleep, resulting in episodes of reduced oxygen levels, increased carbon dioxide levels, and frequent awakenings from sleep.[2] OSA has been linked to various coexisting conditions, including hypertension, cardiovascular disease, metabolic syndrome, and cognitive impairment.[3] Emerging evidence suggests a potential association between circadian rhythms and OSA.[4]

MOLECULAR POINTS OF THE CIRCADIAN RHYTHM

The circadian rhythm's molecular basis is governed by a transcription-translation feedback loop that involves a specific group of clock genes and their corresponding proteins. This intricate mechanism includes key clock genes such as PER1, PER2, CLOCK, BMAL1, CRY1, and CRY2. These genes form heterodimers and initiate the transcription of downstream CCGs by binding to E-box elements within their promoters (Figure 2).[5]

The molecular process of the circadian rhythm encompasses a sophisticated network of transcriptional and post-transcriptional feedback loops that regulate the expression of clock genes and their protein products. The fundamental molecular clock in mammals comprises two transcriptional activators, CLOCK and BMAL1. These activators form a heterodimer and bind to E-box elements located in the promoter regions of clock genes, such as Period (Per) and Cryptochrome (Cry) (Figure 2).[5] Consequently, the transcription of Per and Cry genes is activated. The protein products PER and CRY combine to form a complex that inhibits the activity of CLOCK-BMAL1, establishing a negative feedback loop. Ultimately, the PER-CRY complex undergoes degradation, allowing the CLOCK-BMAL1 heterodimer to bind to the E-box elements and initiate a fresh cycle of transcriptional activation. Epigenetic

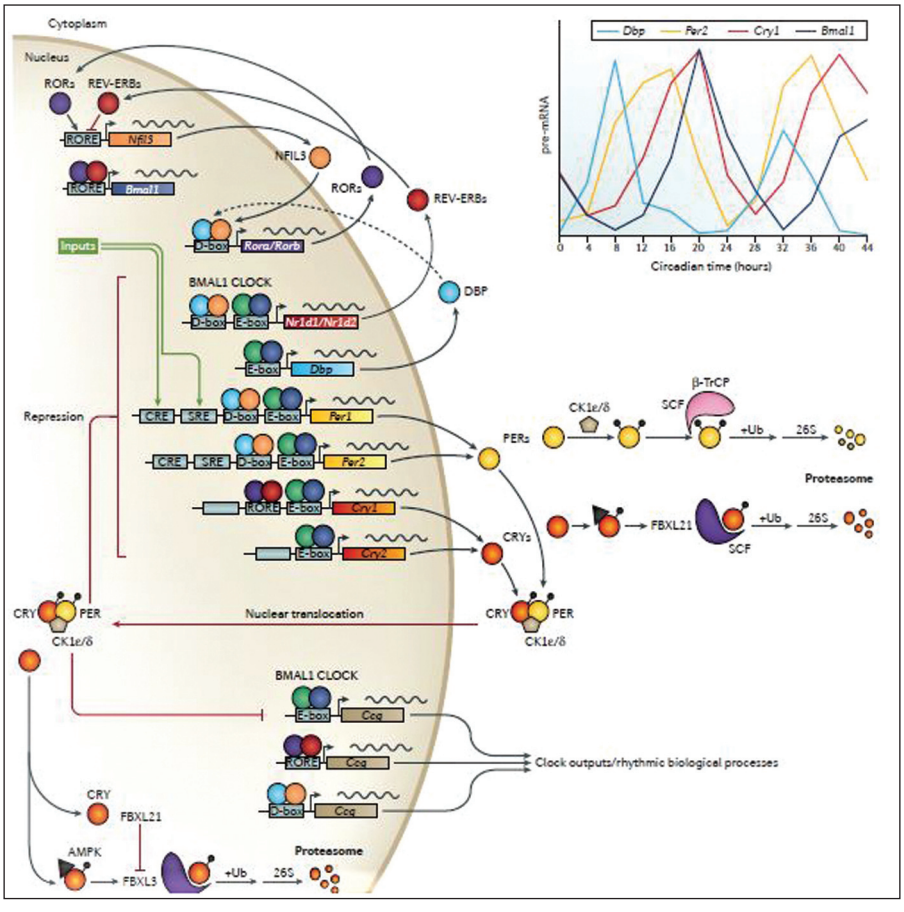

FIGURE 2: Circadian gene network in mammals.

Basic helix-loop-helix (bHLH)-PER-ARNT-SIM (PAS) transcription factors CLOCK and BMAL1. These factors activate the transcription of Per1, Per2, Cry1, and Cry2 genes, whose protein products interact to repress their own transcription. The stability of the PER and CRY proteins is regulated by parallel E3 ubiquitin ligase pathways. CLOCK and BMAL1 also regulate the nuclear receptors REV-ERBα and REV-ERBβ, which rhythmically repress the transcription of Bmal1 and Nfil3 (which encodes nuclear factor, interleukin-3 regulated) that is driven by the activators retinoic acid-related orphan receptor-α (RORα) and RORβ. NFIL3 then represses the PAR-bZip factor DBP (D-box binding protein) to establish a rhythm in the ROR nuclear receptors. These three interlocked transcriptional feedback loops represent the primary transcriptional regulators of most cycling genes.

Different combinations of these factors generate different phases of transcriptional rhythms, as shown in the graph (top right) displaying the RNA profiles of Dbp, Per2, Cry1, and Bmal1 in the mouse liver. The three loops regulate additional rhythmic output genes, known as CCGs, by acting on E-boxes, RevDR2 and ROR-binding elements (ROREs), and D-boxes in the regulatory regions of target genes. The figure also includes information about various molecular components involved in the circadian gene network, such as AMPK, CK1, CRE, FBX, SKP1-cullin-F-box protein (SCF), SRE, and ubiquitin (Ub).(Ref.1)

CCGs: Clock-controlled genes; AMPK: AMP-activated protein kinase; CK1: Casein kinase 1; CRE: cAMP response element; FBX: F-box protein; SRE: Serum response element.

modifications, including DNA methylation, histone modifications, and non-coding RNAs, regulate the expression of clock genes and CCGs.[6]

Dysfunction within the molecular clock machinery has been associated with a broad spectrum of disorders, such as cancer, metabolic disorders, and neurodegenerative diseases.[7] The molecular mechanism of the circadian rhythm operates as a complex network of transcriptional and post-transcriptional feedback loops tightly regulated by diverse epigenetic and post-translational modifications (Figure 3).

CIRCADIAN RHYTHM AND OSA

OSA has been demonstrated to disrupt the molecular and cellular circadian rhythms in various tissues, including the brain, liver, and skeletal muscle.[8] Exposure to intermittent hypoxia (IH) as a result of OSA alters the expression and activity of clock genes and CCGs, leading to the dysregulation of downstream pathways involved in metabolism, inflammation, and oxidative stres.[9]

Research conducted at the University of Chicago investigated the impact of OSA on circadian rhythms in blood glucose levels and insulin sensitivity among patients.[10] The findings revealed disrupted circadian patterns in blood glucose levels and reduced insulin sensitivity in individuals with OSA. The researchers proposed that the hypoxia and oxidative stress induced by intermittent hypoxia may disrupt the molecular clock machinery, resulting in altered glucose metabolism and insulin sensitivity.

Another study conducted by Drager et al. observed that patients with severe OSA exhibited elevated levels of the pro-inflammatory cytokine interleukin-6 (IL-6) and disrupted circadian rhythms in the expression of IL-6 and its receptors.[11] The researchers suggested that inflammation and oxidative stress caused by OSA could potentially contribute to developing comorbidities associated with OSA, such as cardiovascular disease and metabolic syndrome.

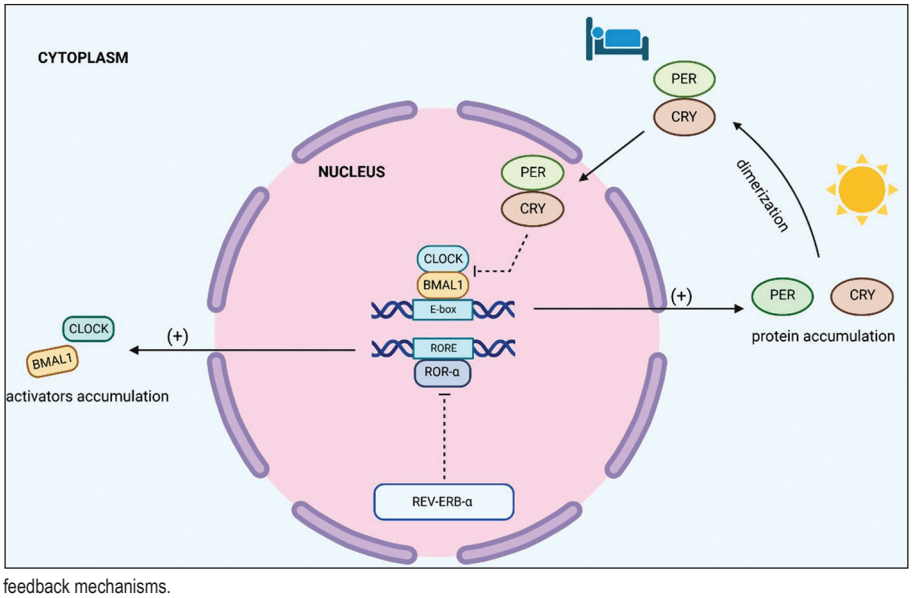

FIGURE 3: Circadian feedback mechanisms.

The core circadian clock mechanism utilizes 2 primary feedback loops. Firstly, CLOCK and BMAL1 are transcription factors that function as activators by forming heterodimers and binding to E-box sequences in DNA, resulting in the transcription of various genes, such as PER, CRY, and REV-ERB-α. During the daily cycle, PER and CRY proteins accumulate within the cytoplasm of cells, with the highest levels occurring before sleep. They then form a dimer that is transported to the nucleus, where they exhibit repressor activity by inhibiting CLOCK-BMAL1, thus establishing a fundamental negative feedback loop that regulates the circadian clock. The second feedback mechanism of the core clock involves ROR-α and REV-ERB-α proteins. ROR-α binds to RORE sequences in DNA and promotes the transcription of activators such as CLOCK and BMAL1, while REV-ERB-α serves as a repressor by inhibiting ROR-α activity. The essential molecular components of the core clock include BMAL1 (brain and muscle ARNT-like 1), CLOCK (clock circadian regulator/circadian locomotor output cycles protein kaput), CRY (cryptochrome), E-box (enhancer box), PER (period protein), REV-ERB-α (nuclear receptor subfamily 1 group D member 1), RORE (ROR response elements), and ROR-α (nuclear retinoid-related orphan receptors α).(Ref.41).

SYSTEMIC HYPOXIA AND THE CELLULAR CIRCADIAN RHYTHM

The molecular clock machinery is present in almost all body cells, and its disruption by systemic hypoxia can have widespread effects on cellular physiology. IH has been shown to disrupt the molecular and cellular circadian rhythms in various tissues, including the brain, liver, and skeletal muscle.[8] The underlying mechanisms of this disruption involve both transcriptional and post-transcriptional regulation of clock genes and their protein products. IH exposure alters the expression and activity of clock genes and CCGs, leading to dysregulation of downstream pathways involved in metabolism, inflammation, and oxidative stress.[9]

In the brain, IH-induced hypoxia has been shown to disrupt the expression of clock genes and their protein products in the SCN, leading to altered sleep-wake cycles and impaired circadian regulation of hormone secretion.[12] In the liver, IH exposure disrupts the circadian rhythms of clock genes and CCGs involved in glucose and lipid metabolism, leading to impaired glucose tolerance and dyslipidemia.[13] In skeletal muscle, IH-induced hypoxia alters the expression of clock genes and CCGs involved in mitochondrial function and energy metabolism, leading to muscle fatigue and impaired exercise capacity.[14]

Research studies have demonstrated acute and chronic OSA significantly impacts the circadian rhythm. Acute OSA can lead to disturbances in sleep-wake cycles, which can cause alterations in the timing of the circadian rhythm. Chronic OSA can disrupt the molecular and cellular circadian rhythms in various tissues, including the brain, liver, and skeletal muscle, leading to the dysregulation of downstream pathways involved in metabolism, inflammation, and oxidative stress. A study by Lo Martire et al. investigated the effects of acute OSA on the circadian rhythm of cortisol, an important hormone involved in regulating the circadian rhythm. The study found that acute OSA led to a delay in the peak cortisol secretion, indicating a disruption in the timing of the circadian rhythm.[15] Another study by Joo et al. investigated chronic OSA's effects on the circadian rhythm in patients with metabolic syndrome. The study found that chronic OSA disrupted the circadian rhythm of blood pressure, heart rate, and melatonin secretion. The study also found that the severity of OSA was correlated with the degree of circadian disruption.[16] These studies suggest that OSA can have significant effects on the circadian rhythm, which may contribute to the development of OSA-related comorbidities. Therefore, it is important to consider the circadian rhythm in managing and treating OSA.

DISEASE RELATIONSHIP BETWEEN CIRCADIAN RHYTHM AND SLEEP APNEA

In the case of OSA, the associated hypoxia and oxidative stress can lead to DNA damage and mutations, potentially promoting the onset of cancer.[17,18] Zhang et al. conducted a study that demonstrated how chronic intermittent hypoxia (CIH), a model of OSA, promoted lung cancer growth and metastasis in mice by upregulating hypoxia-inducible factor-1α and vascular endothelial growth factor.[19]

Furthermore, OSA has been linked to the development of metabolic disorders, such as obesity and Type 2 diabetes. Buxton et al. discovered that sleep restriction and circadian misalignment disrupted glucose metabolism and insulin sensitivity in healthy adults, mimicking the effects observed in individuals with OSA.[20] Additionally, Peschke et al. observed disrupted circadian rhythms in cortisol secretion among OSA patients, potentially contributing to the development of metabolic disorders like obesity and insulin resistance.[21] The disruption of the circadian rhythm associated with OSA has also been implicated in cardiovascular disease. The study by Yang et al. revealed disrupted circadian rhythms in blood pressure and heart rate variability among OSA patients, potentially contributing to hypertension and cardiovascular disease.[22]

CLINICAL RESEARCH STUDIES

Recent clinical research has provided additional evidence regarding the association between circadian rhythm and OSA, shedding light on its implications for disease development and treatment. One study conducted by Cajochen et al. examined the impact of OSA on the circadian rhythm of melatonin. The study

revealed disrupted melatonin secretion patterns in patients with severe OSA, characterized by a delayed peak and reduced amplitude of melatonin secretion compared to controls. The authors propose that this disruption in melatonin secretion may contribute to the sleep fragmentation and daytime sleepiness experienced by individuals with OSA.[23]

Another study by Huang et al. explored the effects of OSA on circadian blood pressure rhythms. The findings demonstrated disrupted circadian rhythms in blood pressure among patients with OSA, including a blunted nocturnal dip in blood pressure and an increased morning surge. The authors suggest that these disruptions in blood pressure circadian rhythms may contribute to the heightened risk of cardiovascular disease observed in individuals with OSA.[24]

A systematic review and meta-analysis conducted by Benjafield et al. investigated the relationship between sleep apnea and cardiovascular disease. The review revealed an increased risk of cardiovascular disease, encompassing hypertension, arrhythmias, coronary artery disease, heart failure, and stroke, in individuals with sleep apnea. The authors propose that the disruption of circadian rhythms, particularly those involved in blood pressure regulation, may play a role in the development of cardiovascular disease among sleep apnea patients.[25]

Feng et al. conducted a study investigating the impact of continuous positive airway pressure (CPAP) therapy on the circadian rhythm of blood pressure in individuals with sleep apnea. The study demonstrated that CPAP therapy significantly improved circadian blood pressure rhythms, leading to a greater reduction in nighttime blood pressure and an increase in the nocturnal dip. The authors suggest that improving circadian blood pressure rhythms may contribute to the observed cardiovascular benefits associated with CPAP therapy.[26]

In addition, a systematic review and meta-analysis by Zhang et al. focused on the effects of CPAP therapy on circadian blood pressure rhythms in OSA patients. The review found significant improvements in circadian blood pressure rhythms following CPAP therapy, including a greater reduction in nighttime blood pressure and an increase in the nocturnal dip. The authors propose that the enhancement of circadian blood pressure rhythms may contribute to the cardiovascular benefits observed with CPAP therapy.[25-27]

Wang et al. conducted a study to examine the impact of CPAP therapy on circadian blood glucose rhythms in individuals with OSA and Type 2 diabetes. The findings demonstrated that CPAP therapy significantly improved circadian blood glucose rhythms in OSA patients with Type 2 diabetes, resulting in reduced nighttime blood glucose levels and an increased nocturnal dip. The authors suggest that the improvement in circadian blood glucose rhythms may contribute to the metabolic benefits observed with CPAP therapy in individuals with OSA and Type 2 diabetes.[28]

Moreover, Borregán et al. investigated the impact of CPAP therapy on the incidence of major adverse cardiovascular events (MACE) in patients with sleep apnea and established cardiovascular disease. The study revealed a significant reduction in the risk of MACE, including cardiovascular death, myocardial infarction, and stroke, associated with CPAP therapy. The authors propose that the improvement of circadian rhythms, particularly those involved in blood pressure regulation, may contribute to the cardiovascular benefits observed with CPAP therapy.[29]

These recent clinical studies provide further evidence regarding the relationship between circadian rhythm and OSA, highlighting potential therapeutic implications for managing and treating OSA-related comorbidities. Further research is needed to gain a comprehensive understanding of the underlying mechanisms connecting circadian rhythm and OSA and to explore the potential of circadian-based interventions in effectively managing comorbid

BASIC SCIENCE RESEARCH STUDIES

The manuscript delves into various basic science research studies exploring the intricate mechanisms that connect animal models, circadian rhythm, and sleep apnea. These studies, conducted by Zhang et al. in 2017 and 2018, Schmid et al. in 2019, and Han et al. in 2020, provide valuable insights into the molecular and systemic aspects of circadian rhythm and its relationship with sleep apnea, elucidating how disrup-

tions in circadian rhythms, particularly in animal models of sleep apnea, can contribute to the development of diverse comorbidities.[30-33]

These studies emphasize the significance of the circadian clock in regulating crucial processes like breathing, metabolism, and hormone secretion. Furthermore, they propose the circadian clock as a potential therapeutic target for managing sleep apnea and associated metabolic disorders. However, additional research is essential to fully comprehend the precise mechanisms that interconnect animal models, circadian rhythms, and sleep apnea. Furthermore, it is necessary to explore the potential of circadian-based interventions for effectively managing the comorbidities associated with sleep apnea.[30-32]

The study by Zhang et al. focuses on investigating the role of the circadian clock in sleep apnea development using a mouse model. The authors conducted experiments to examine the impact of disrupted circadian rhythms on respiratory function. The findings reveal that mice with mutations in circadian clock genes were more susceptible to sleep apnea compared to wild-type mice. This study underscores the critical role of the circadian clock in regulating respiratory function and suggests that circadian-based interventions may hold promise as a potential therapeutic strategy for sleep apnea.[30] Another manuscript by Zhang et al. explores the influence of sleep apnea on the circadian rhythm of gene expression in mice. The study involved subjecting mice to intermittent hypoxia, a common characteristic of sleep apnea. The researchers analyzed the expression of various clock genes and their downstream targets in different tissues of the mice. The study's results demonstrate that sleep apnea disrupts the circadian rhythm of gene expression in multiple tissues, including the brain, liver, and skeletal muscle. These findings offer significant insights into the molecular mechanisms underlying the relationship between sleep apnea and the circadian clock.[31-33]

CIRCADIAN RHYTHMS AND OSA FROM THE TREATMENT STRATEGY POINT

Research has demonstrated that disruptions in the molecular clock machinery caused by OSA-related hypoxia and oxidative stress can lead to dysregulation of pathways involved in metabolism, inflammation, and oxidative stres.[5-8,9-15]

The circadian rhythm plays a crucial role in the treatment of various diseases as it regulates essential physiological and behavioral processes, including sleep, metabolism, hormone secretion, and immune function. Disruptions in the circadian rhythm have been associated with sleep disorders, metabolic disorders, cardiovascular disease, and cancer.[34] In the context of OSA, disruptions in the circadian rhythm resulting from OSA-related hypoxia and oxidative stress can lead to dysregulation of metabolism, inflammation, and oxidative stress pathways.[34,35]

Melatonin, a hormone involved in regulating the sleep-wake cycle, has shown potential benefits in the treatment of sleep apnea. A randomized controlled trial conducted by Ramar et al. demonstrated that melatonin administration improved sleep quality and reduced the severity of sleep apnea in patients with moderate to severe OSA.[36]

Other drugs targeting the circadian rhythm, including tasimelteon and suvorexant, have been investigated for their potential in sleep apnea treatment. Tasimelteon, a melatonin agonist, has been found to improve sleep quality and reduce the severity of sleep apnea in patients with chronic obstructive pulmonary disease (COPD).[37,38] Suvorexant, an orexin receptor antagonist, has shown efficacy in improving sleep quality and decreasing the frequency of apneic events in patients with sleep apnea.[39] However, further research is needed to fully understand the effectiveness and safety of these drugs, particularly in different patient populations and in combination with other treatments such as CPAP therapy.[39,40] Individual variations in circadian rhythm function should also be considered when evaluating the potential of circadian-based interventions for sleep apnea treatment.

Disruptions to these rhythms can have profound effects OSAS and also hearing and balance disorders. This part of discussion aims to explore the literature surrounding the relationship between circadian rhythms, OSAS, and their association with hearing and balance disorders.[41-51]

CIRCADIAN RHYTHMS, OSAS, AND HEARING DISORDERS

Emerging evidence suggests a potential association between circadian rhythm disruptions, OSAS, and hearing disorders.[41,42-45] CIH a hallmark of OSAS, has been shown to induce oxidative stress and inflammation, which can damage cochlear tissues. Ohinmaa et al. study explored the role of oxidative stress in the association between intermittent hypoxia and hearing loss.[46] The study involved animal models subjected to intermittent hypoxia to simulate the effects of sleep apnea. The researchers measured hearing thresholds and assessed markers of oxidative stress in the auditory system. They found that exposure to intermittent hypoxia led to a significant increase in oxidative stress markers in the cochlear tissues. Furthermore, the study demonstrated a correlation between the levels of oxidative stress and the severity of hearing loss. Animals with higher oxidative stress levels exhibited more significant hearing impairment. These findings suggest that oxidative stress plays a crucial role in the association between intermittent hypoxia and hearing loss. The study highlights the potential mechanisms through which intermittent hypoxia may induce damage to the auditory system, emphasizing the importance of oxidative stress in this process.

Understanding the role of oxidative stress in the context of intermittent hypoxia and hearing loss can contribute to developing targeted therapeutic approaches aimed at mitigating the detrimental effects of sleep apnea and other conditions characterized by intermittent hypoxia on auditory function. Animal studies have demonstrated that CIH leads to hearing loss, cochlear degeneration, and disruption of the inner ear's antioxidant defense system.[47-49] In human studies, individuals with OSAS have shown increased prevalence of hearing loss, especially in the high-frequency range.[43-51] The study by Fettweis et al. investigated the relationship between sleep apnea syndrome and auditory evoked potentials. The researchers determine if sleep apnea has an impact on the auditory system by assessing the changes in auditory evoked potentials.[43] The study involved measuring the auditory brainstem response (ABR) in individuals with sleep apnea syndrome and comparing it to a control group. The results indicated that individuals with sleep apnea had prolonged ABR wave latencies, suggesting impaired auditory function. These findings contribute to our understanding of the potential effects of sleep apnea on the auditory system.

The study conducted by Wang et al. aimed to examine the effect of sleep apnea on hearing function.[44] The researchers evaluated the hearing thresholds of individuals with sleep apnea and compared them to a control group. The results demonstrated that individuals with sleep apnea had significantly higher hearing thresholds, particularly in the high-frequency range. This suggests that sleep apnea may have a detrimental effect on hearing, specifically affecting the ability to hear high-frequency sounds. These findings contribute to our understanding of the potential impact of sleep apnea on auditory function and highlight the importance of considering hearing evaluations in individuals with sleep apnea. These all clinical study findings highlight the potential impact of circadian rhythm disruptions associated with OSAS on hearing function.

CIRCADIAN RHYTHMS, OSAS, AND BALANCE DISORDERS

In addition to hearing disorders, circadian rhythm disturbances and OSAS have been implicated in balance disorders. The vestibular system, responsible for maintaining postural control and balance, is closely linked to circadian rhythmicity. Studies have shown that sleep disorders, including OSAS, can affect vestibular function and postural stability.[52-54] Etemadifar et al. study aimed to investigate the impact of OSA on balance in individuals with this sleep disorder.[54] The study included a group of individuals diagnosed with moderate to severe OSA and a control group without sleep apnea. Balance assessment was performed using a computerized dynamic posturography system, which measures various parameters related to postural stability and balance control. The participants underwent tests under different sensory conditions, including eyes open, eyes closed, and on foam. The findings of the study revealed that individuals with OSA exhibited significantly poorer balance compared to the control group. The OSA group

demonstrated increased postural sway and instability during all sensory conditions tested. These results suggest that OSA may contribute to balance impairment and affect postural control. The study also highlighted a correlation between the severity of OSA and the degree of balance impairment. Individuals with more severe OSA showed greater balance deficits compared to those with milder forms of the disorder. The findings of this study have important clinical implications. They emphasize the potential impact of OSA on balance and postural control, which may increase the risk of falls and related injuries in individuals with this sleep disorder. Therefore, incorporating balance assessments and implementing appropriate interventions targeting balance and postural control may be beneficial in the management of individuals with OSA. Further research is necessary to investigate the underlying mechanisms by which OSA affects balance and to explore potential interventions aimed at improving balance outcomes in individuals with this sleep disorder. The intermittent hypoxia and autonomic dysregulation associated with OSAS may disrupt the vestibular system, leading to impairments in balance control. This link between circadian rhythms, OSAS, and balance disorders warrants further investigation to elucidate the underlying mechanisms and clinical implications.[52-54]

FUTURE ASPECTS

Sleep apnea is a prevalent sleep disorder that affects a significant portion of the global population. Recent studies have highlighted the importance of circadian rhythm in developing and managing sleep apnea, regulating the sleep-wake cycle, and other physiological functions. As research in this field continues to evolve, there is a growing need to explore the complex interactions between sleep apnea and circadian rhythm and develop effective interventions that target circadian disruption in sleep apnea patients. Future research in this area may promise to improve sleep apnea's diagnosis, treatment, management, and associated with hearing and balance disorders.[55-59]

Further research is needed to understand the mechanisms underlying the relationship between sleep apnea and circadian rhythm. While recent studies have shed light on the role of circadian rhythm in the development of sleep apnea, the specific molecular and cellular pathways involved are not yet fully understood. Identifying these mechanisms could lead to new sleep apnea therapies targeting the circadian clock.[60-63] There is a need to explore the potential of circadian-based interventions for the management of sleep apnea and its associated comorbidities. Studies have shown that CPAP therapy, a common treatment for sleep apnea, can improve circadian rhythm disruption in sleep apnea patients. However, more research is needed to determine the optimal timing and duration of CPAP therapy to maximize its circadian benefits.[26,39,64-67] Some studies have suggested that individual variations in circadian rhythm function may contribute to sleep apnea severity and treatment response differences. Developing personalized approaches to managing sleep apnea that considers individual differences in circadian rhythm function could improve treatment outcomes.[68,69]

As research in sleep apnea and circadian rhythm continues to advance, several future aspects must be considered. Understanding the mechanisms underlying the relationship between sleep apnea and circadian rhythm, exploring the potential of circadian-based interventions, and developing personalized approaches to managing sleep apnea are all important areas for future research. By addressing these aspects, we may be able to improve the management and treatment of sleep apnea and its associated comorbidities.[70-74]

Research investigating the relationship between circadian rhythm and OSA has highlighted the potential of circadian-based interventions as a treatment strategy for OSA-related comorbidities. Chronotherapy, the administration of medication or other interventions at specific times of the day based on the individual's circadian rhythm, has been suggested as a promising approach for the management of OSA and related metabolic disorders.[75-81]

SUMMARY

Emerging evidence suggests a link between circadian rhythms and OSA. The impact of OSA-related hypoxia and oxidative stress on different tissues' molecular and cellular circadian rhythms can lead

to disturbances in downstream pathways involved in metabolism, inflammation, and oxidative stress. These disruptions in the circadian rhythm have been implicated in the development of various diseases, including metabolic disorders, neurodegenerative diseases, and cancer. However, further research is needed to fully comprehend the mechanisms underlying the relationship between circadian rhythm, sleep apnea, and cardiovascular disease. Additionally, exploring the potential of circadian-based interventions is crucial for preventing and managing cardiovascular disease in individuals with sleep apnea.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

This study is entirely author's own work and no other author contribution.

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