The Effects of the Pineal Gland and Melatonin on Sleep Disorders

Akhil Anandan[1] and Dr. Prahlad Parajuli[#]

[1]Academy of Allied Health and Science, Neptune, NJ, USA
[#]Advisor, Gifted Gabber

ABSTRACT

Sleep disorders are prevalent and impactful conditions significantly affect individuals' health and well-being. This research paper provides an in-depth exploration of the effects and roles the pineal gland and melatonin play in regulating sleep patterns and their relations to various sleep disorders, including insomnia, hypersomnolence, and circadian rhythm sleep-wake disorders. Furthermore, the paper examines the genetic factors related to melatonin and their influence on sleep disturbances. Ongoing clinical trials are also evaluated to study the effectiveness of melatonin combined with Cognitive Behavioral Therapy for Insomnia (CBT-I) and how CBT is used to reduce parasomnias. While significant progress has been made in understanding the pineal gland, melatonin, and sleep disorders, there are still many unanswered questions and opportunities for further research. Through advanced research and studies, we can continue to deepen our understanding of sleep disorders and develop personalized treatments to address individuals' unique needs.

Introduction

Sleep is a fundamental necessity that plays a crucial role in maintaining one's overall health and well-being. Adequate amounts of sleep are essential for various bodily functions, including cognitive function, immune system regulation, and even emotional well-being. Without enough sleep, individuals may experience a range of adverse consequences, including impaired cognitive abilities, decreased immune function, severe mood swings and disturbances, and increased risk of chronic health conditions such as obesity, diabetes, and cardiovascular disease. The pineal gland plays a key role in the regulation of sleep.

The pineal gland, a relatively undersized neuroendocrine structure, primarily secretes melatonin, a hormone produced in response to darkness, during the nighttime. "In lower vertebrates, the pineal gland is directly photosensitive," meaning it directly reacts to light. Conversely, in higher vertebrates, its direct light sensitivity is diminished. Instead, it acts as a conduit between environmental light and bodily functions by receiving light cues via one's retina. In humans, the functions of the pineal gland largely coincide with those of melatonin in that they both play significant roles involving cell protection as well as sleep and immunity regulation. Unfortunately, melatonin's significance has been on the rise due to heightened cancer risks among individuals and disrupted melatonin rhythms in patients with "neurodegenerative diseases, autism, or depression" (Sapedé et al., 2013).

Melatonin, a hormone secreted by the pineal gland, is critically involved in the control of the sleep-wake cycle. Many researchers have even established melatonin as a form of treatment for insomnia, a disorder that stems from disruptions in melatonin secretion, due to its synthesis and easy oral administration. Moreover, since the production of melatonin declines with age, potentially contributing to poor sleep quality, correcting this deficit is a natural and effective way to enhance sleep as an individual ages. Despite this, there is only limited scientific evidence supporting the effectiveness of melatonin replacement therapy for insomnia. Furthermore, the optimal dosage ranges regarding melatonin administration remain uncertain (Poza et al., 2018).

Together, the pineal gland and melatonin work to regulate an individual's sleep-wake cycle. The pineal gland produces melatonin during the dark hours, with its secretion diminished by light exposure. Through its secretion, melatonin conveys the message to the body that it is time to sleep. Once this message is conveyed, melatonin levels rise, promoting a sense of sleepiness and leading to the onset of sleep. This hormone's secretion follows a circadian rhythm, with a high peak at night and a decline towards morning time, thus synchronizing bodily functions with the "day-night cycle." Additionally, melatonin assists in the synchronization of body clocks, ensuring coordination between both physiological processes and external environmental signals. In all, the interaction between the pineal gland and melatonin is crucial for maintaining a healthy sleep pattern and one's overall well-being.

This research will provide a general overview of the different types of sleep disorders and then dive deep into underlying mechanisms involving melatonin in individuals with certain sleep disorders. While research supports that melatonin plays a crucial role in regulating the sleep-wake cycle, individuals with sleep disorders may show signs of reduced responsiveness to melatonin. Investigating the factors contributing to this reduced responsiveness can answer many questions relating to the pathophysiology of various sleep disorders. It even has the potential to lead to the development of more targeted and effective treatment approaches from healthcare providers. This research will also expand on studying different genes related to melatonin and how alterations in these genes could lead to certain sleep disorders and mental illnesses.

The Different Types of Sleep Disorders and Treatment

Insomnia

There are two major types of insomnia: short-term and long-term. Short-term insomnia, generally prevailing for just a few days to weeks, often stems from stress and tends to resolve with the mitigation of the particular stressor. Chronic insomnia, on the other hand, lasts for at least 3 nights per week over at least 3 months. It can even be worsened by behaviors such as spending excessive time in bed or daytime napping. Many risk factors also play a role in the development of insomnia, including age, gender, mental health conditions, certain medical issues, and medication usage. When it comes to treatment, for short-term cases, consultation with a physician about the stressor causing sleep difficulty may help resolve the problem. However, chronic insomnia is often managed with cognitive behavior therapy for insomnia (CBTI), "which aims to reduce fear and anxiety about sleeping and provide bedtime relaxation strategies." If CBTI proves ineffective, medications such as nonbenzodiazepine hypnotics, benzodiazepines, or melatonin receptor agonists may be prescribed, taking into account their timing and potential side effects. As of right now, there are no existing FDA-approved drugs for treating pediatric insomnia, although melatonin may be considered for children with neurodevelopmental disorders experiencing sleep-onset difficulties (Krystal et al., 2021).

Narcolepsy

Narcolepsy is a sleep disorder "characterized by excessive daytime sleepiness (EDS), frequent uncontrollable sleep attacks as well as sleep fragmentation and can be associated with cataplexy, sleep paralysis, and hypnagogic hallucinations." Similar to insomnia, there are two main types of narcolepsy as well: narcolepsy type 1, which includes cataplexy, and narcolepsy type 2, which lacks cataplexy. The loss of most orexin-containing neurons characterizes narcolepsy type 1. This might occur due to an autoimmune process triggered by infection. "HLA haplotype DQB1*0602 is present in 95% of narcolepsy type 1 patients, but [it] is also present in about 20% of the general population without narcolepsy as well. While the specific cause of Narcolepsy type 2 may not be clear, research suggests it involves "less severe loss of orexin neurons or impaired orexin receptor signaling." In some cases, narcolepsy type 2 patients may progress to develop cataplexy, the sudden loss of muscular tension while one is awake. In all, narcolepsy "is a rare sleep disorder that has no cure and is difficult to manage." Nevertheless, the effects of this disorder can be mitigated through various medications and modifications to healthcare and lifestyle (Slowik et al., 2023).

Sleep Apnea

Sleep apnea is a common sleep disorder distinguished by frequent pauses in breathing during sleep. This often leads to loud snoring and daytime sleepiness. The two main types of sleep apnea are obstructive sleep apnea (OSA) and central sleep apnea (CSA). OSA occurs when the airway becomes blocked during sleep, causing excess snoring and sudden and sharp gasps for breath. It affects approximately 10% to 30% of adults in the United States, while many other cases go undiagnosed. CSA, on the other hand, involves "disruption in the communication between the brain and the muscles that control breathing," resulting in shallower breathing and pauses. It is less common, only affecting less than 1% of people. Treatment for OSA often involves positive airway pressure (PAP) therapy, which keeps the airway open during sleep. Other options include mouthpieces and surgical procedures. For CSA, treatment focuses on addressing underlying medical issues or oxygen therapy to promote steady breathing during one's sleep (Suni et al., 2024).

Sleep Paralysis

Only prevalent in 1.7% of the population, sleep paralysis is defined as "a temporary sense of paralysis that occurs between stages of wakefulness and sleep." One main difference between sleep paralysis and dreams and nightmares is that one is awake during an episode of sleep paralysis. Like most of the other main sleep disorders, sleep paralysis also has two different types: isolated sleep paralysis and recurrent sleep paralysis. "Sleep paralysis is isolated when it appears without any other signs of narcolepsy or other sleep disorders," whereas recurrent sleep paralysis is characterized by multiple episodes over time. In relation to sleep paralysis, there are also two other types, including hypnagogic and hypnopompic sleep paralysis. These hallucinations are fairly simple: hypnagogic hallucinations occur as one is falling asleep, and hypnopompic hallucinations take place as one is waking up from sleep. An episode of sleep paralysis can last from as short as a few seconds to as long as a few minutes. During these episodes, one might experience a sense of evil or a disturbing presence in the room, chest pressure, or even a feeling of movement or flying (Restivo, 2023).

Effects of Melatonin on Different Sleep-Related Disorders

Insomnia

Insomnia, while characterized by persistent difficulty with sleep initiation, sleep consolidation, and staying asleep," often co-occurs with psychiatric disorders and has a strong association with age-related declines in melatonin levels. Melatonin supplementation has shown promise in treating insomnia, with effectiveness demonstrated across populations, including "children with autism spectrum disorders, adolescents with depression, women with premenstrual dysphoric disorder, hypertensive patients taking beta-blockers, and children with attention-deficit/hyperactivity disorder." Melatonin's actions on MT1 and MT2 receptors play crucial roles in regulating sleep, with numerous studies suggesting differential effects on non-rapid eye movement sleep duration. Selective agonists targeting these receptors offer the potential to enhance sleep quality, duration, and efficiency in insomnia (Xie et al., 2017).

Hypersomnolence

Hypersomnolence is the "inability to stay awake and alert during major waking episodes, resulting in periods of irrepressible need for sleep or unintended lapses [into drowsiness or sleep]" (Bollu et al., 2018). Hypersomnolence branches into other sleep-related disorders as well, including "narcolepsy type 1, narcolepsy type 2, and idiopathic hypersomnia. While current treatment for this disorder primarily revolves around medications like methylphenidate

and modafinil to alleviate daytime sleepiness, recent research suggests melatonin as a promising treatment alternative to hypersomnolence. Furthermore, studies have proven that “doses of melatonin significantly increase REM sleep time in both normal cohorts, as well as patients with central disorder of hypersomnolence.” Thus, by managing central disorders of hypersomnolence and providing neuroprotective effects, doses of melatonin have been proven to offer benefits to individuals with altered sleep patterns and disorders (Xie et al., 2017).

Circadian Rhythm Sleep-Wake Disorders

Circadian rhythm Sleep-Wake disorders (CRSWD), or sleep-wake cycle disorders, are disorders “that occur when your body's internal clock, which tells you when it's time to sleep or wake, is out of sync with your environment” (Khullar, 2022). Common CRSWDs include “delayed sleep-wake phase disorder, advanced sleep-wake phase disorder, irregular sleep-wake rhythm disorder, and non-24-hour sleep-wake rhythm disorder.” Melatonin plays a crucial role in regulating the sleep-wake cycle, both internally (circadian) and externally (sleep propensity). This is accomplished through the suprachiasmatic nucleus (SCN) in the brain, which interacts and sends excitatory signals, suppressing melatonin during the day and releasing it during nighttime. (Khullar, 2022).

Genes and Proteins Related to Melatonin

PER1 and PER2 Gene (Period Circadian Clock Genes)

The PER1 and PER2 genes play key roles in circadian rhythms and the regulation of sleep-wake cycles by regulating the synthesis and release of melatonin. These two genes are crucial for one’s sleep-wake cycles as they enforce the “molecular clock machinery” and influence the actual production of melatonin by the pineal gland. PER1 and PER2 gene form complexes with other “clock” proteins, “creating transcriptional feedback loops that drive the oscillatory expression of genes involved in melatonin synthesis.” Disturbance in the PER1 and PER2 genes, however, can disrupt the timing of the release of melatonin, ultimately leading to disturbances in an individual's sleep patterns and circadian rhythms. As they work together, the PER1 and PER2 genes and melatonin are paramount in controlling the sleep-wake cycle of humans and in providing new research and studies to address sleep-related disorders (Rodríguez-Santa et al., 2023).

CRY1 Gene (Circadian Cryptochrome Gene)

The relationship between melatonin and the CRY1 gene emphasizes the complex relation between molecular clock machinery and the regulation of circadian rhythm. The CRY1 gene, along with its counterpart CRY2, plays the crucial role of forming a critical part of the negative feedback loop within the circadian clock. These proteins interact with other clock proteins, like the Per1 and Per2 genes, to inhibit their activity and regulate the timing of expression. Significantly, the expression of CRY1 exhibits a rhythmic pattern that coincides with the synthesis and release of melatonin. Numerous studies have shown that disruptions in the CRY1 gene can lead to an alteration in the timing of melatonin production. This, in turn, will result in a disturbance in one's sleep-wake cycle and circadian rhythms. Without a doubt, the CRY1 gene is a crucial gene in the body that optimizes circadian health and helps manage sleep disorders (Patke et al., 2021).

Bmal1 Protein (Brain and Muscle Arnt-like protein-1)

The Bmal1 protein is a major part of the molecular circadian clock. Bmal1 forms a heterodimeric transcription factor complex with the Clock, which in turn induces the expression of numerous clock-controlled genes. Additionally, the

Bmal1 protein acts as a regulator for the transcription of genes involved in melatonin synthesis, including the key enzyme serotonin-N-acetyltransferase (SNAT). As the name suggests, SNAT catalyzes the conversion of serotonin to N-acetylserotonin, which is a precursor of melatonin. Thus, SNAT is the molecular clock to melatonin production. Moreover, melatonin itself may exert feedback effects on the circadian clock by modulating the expression and activity of Bmal1, thus influencing the timing and amplitude of circadian rhythms. This relationship between melatonin and the Bmal1 protein underscores the important roles they play in the regulation of the body's internal clock and also highlights their significance in maintaining “rhythmic physiological processes” (C. Becker et al., 2019).

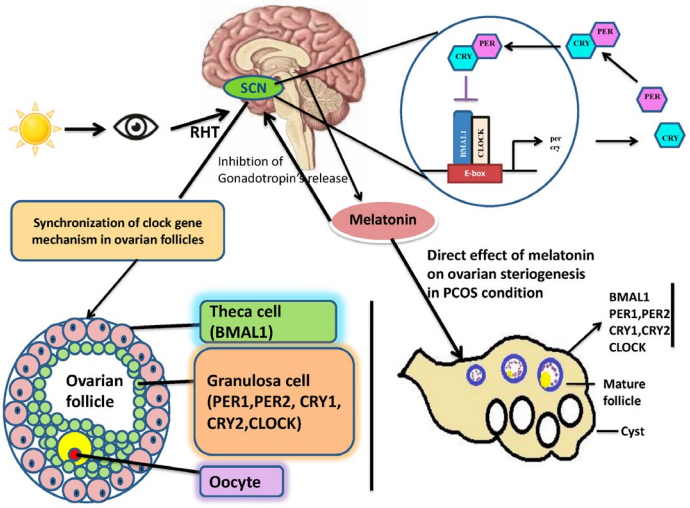

Figure 1: The different factors that play into factor when regulating one's circadian rhythm and sleeping better with light. Source: Brzezinski, 2021

Melatonin and clock genes impact reproductive performance. They follow rhythms controlled by the suprachiasmatic nucleus (SCN) in the hypothalamus, synced with light/dark cycles. These genes are found in ovarian granulosa cells. Disrupted rhythms affect ovarian steroidogenesis and reproduction.

Ongoing Clinical Trials and Future

A clinical study titled, “The Effects of Sesame Extract on the Quality of Life and Antioxidative Status in Sleeping Disorder Patients” is being conducted at Taipei Medical University. This study goes in-depth on the effects of sesame extract on sleep quality, life quality, and anti-oxidative functions in individuals with obstructive sleep apnea (OSA) or low arousal threshold OSA. The study, which started in November of 2023, involves 30-50 subjects, aged from 20 to 80 years, without sleep apnea or with low arousal threshold OSA.a During the treatment period, which lasts the first 8 weeks, the subjects will receive either 2 placebo capsules or 2 capsules that contain sesame complex (37-56 mg sesamin per capsule). Weeks 9 to 11 will comprise the washout period, “the period of time between treatment periods that is intended to prevent misinterpreting observations about [the] study.” After this, both the control and sesamin groups will cross over. Sleep quality, life quality, and anti-oxidative functions will be assessed throughout the study. Anthropometric examinations will be conducted at various intervals, and routine laboratory parameters, including liver and kidney function, blood sugar, lipid profile, and anti-oxidative status, will be measured. Questionnaire evaluations will also be administered and reviewed as well (clinicaltrials.gov, 2023).

Another national clinical trial, conducted by the Ache Laboratorios Farmaceuticos S.A. in two stages, aims to evaluate the effectiveness of melatonin combined with Cognitive Behavioral Therapy for Insomnia (CBT-I) in participants aged 55 years and older. In the first stage, 307 participants will be randomly assigned to one of three treatment groups: Melatonin 3mg plus CBT-I, Melatonin 5mg plus CBT-I, or CBT-I plus placebo. An interim analysis

will also take place to determine whether or not to proceed with the study and select doses for the second stage. Then, the final analysis will compare the selected dose of melatonin plus CBT-I with CBT-I alone and placebo, incorporating participants from both stages. Melatonin, in this study, is expected to enhance the therapeutic effects of CBT-I in treating insomnia disorders (Ache Laboratorios Farmaceuticos S.A., 2020).

Finally, a University of Manitoba clinical trial research titled, "Impact of Cognitive Behavioral Therapy on Parasomnias (parasomnia)" seeks to determine the effectiveness of cognitive behavioral therapy (CBT) in reducing parasomnias in "a sample of 20 adult outpatients with Non-REM and REM parasomnias." The study was also focused on evaluating whether CBT improves daytime energy, mood, anxiety symptoms, and functional impairment. Parasomnias, a disorder correlated to "unwanted physical or mental events that occur during sleep or during arousal from sleep," can have significant impacts on mental health and overall well-being. This study seeks to develop and test the incorporation of CBT as the primary intervention. Participants in this study will go through a 6-week CBT program and be compared to those engaging in self-monitoring of sleep disturbances. The hypotheses suggest that CBT participants will report fewer parasomnia episodes and demonstrate relatively better sleep outcomes, measured at one-week and two-month follow-ups post-treatment (Vincent, 2022).

Study Site	Start Year	Disease type	Intervention	Reference
University of Taipei	2023	Low arousal threshold obstructive sleep apnea (OSA)	Sesame seed extract	Taipei Medical University. (2024). Effects of Sesamin on Sleep Quality and Antioxidative Status. National Library of Medicine, https://clinicaltrials.gov/study/NCT05678439?cond=Sleep%20Disorder&rank=1
Ache Laboratorios Farmaceuticos S.A.	2020	Non-REM and REM parasomnias	Cognitive behavioral therapy	Ache Laboratorios Farmaceuticos S.A. (2020). Melatonin 3mg and 5mg Compared to Cognitive Behavioral Therapy for Insomnia (CBT-I) in the Treatment of Insomnia (Morfeu). National Library of Medicine, https://clinicaltrials.gov/study/NCT02798367?cond=Insomnia&term=Melatonin&rank=1
University of Manitoba	2022	Insomnia	Cognitive Behavioral Therapy for Insomnia	Vincent, N. (2022). Impact of Cognitive Behavioral Therapy on Parasomnias (parasomnia). National Library of Medicine, https://clinicaltrials.gov/study/NCT04633668?cond=Sleep%20Disorder&rank=3

Collectively, these clinical studies suggest promising future treatments for sleep disorders, whether it is through natural supplements or different types of therapies. The Taipei Medical University study, for example, suggests sesame extract has the potential to greatly enhance one's sleep quality and antioxidative status in individuals with obstructive sleep apnea (OSA). Ache Laboratorios Farmaceuticos S.A., on the other hand, studies the combination of melatonin with Cognitive Behavioral Therapy for Insomnia (CBT-I) in older adults, which could offer a more effective and comprehensive treatment for insomnia by addressing both the biological and psychological aspects. Finally, The University of Manitoba's research on CBT for parasomnias emphasizes its potential as a viable treatment with the aims of reducing parasomnia episodes and improving corresponding daytime functioning. Together, these studies are the starting points in order to find ways sleep disorders can be managed in the future - through a holistic approach and emphasis on patient outcomes and overall well-being.

Conclusion

In conclusion, the relationship between the pineal gland, melatonin, and sleep disorders emphasizes the connection among various medical specializations like neurobiology, genetics, and clinical medicine. This relationship underscores the impact of medical research on the health and well-being of humans, which extends beyond physiological processes to encompass emotional factors and overall quality of life. Recognizing the intricate connections between sleep, mental health, and other medical conditions underscores the importance of comprehensive treatment plans. While significant progress has been made in understanding the pineal gland, melatonin, and sleep disorders, there is still much more to uncover.

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