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IMPACT OF CIRCADIAN RHYTHM AND MELATONIN PRODUCTION ON THE DEVELOPMENT OF OBESITY

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Abstract: Objective: To evaluate the interactions between the circadian rhythm, melatonin production, and the development of obesity, to understand the physiological mechanisms involved, and to explore potential therapeutic strategies. Method: A systematic search was carried out in the PubMed database, using combinations of the terms "Circadian rhythm", "Melatonin", and "Obesity". From a total of 74 articles identified in the last five years, 13 were selected for detailed analysis. Review: Studies show that melatonin has a significant role in controlling insulin secretion and action in adipose tissues, relating to obesity. Night workers, exposed to artificial light, face suppression in melatonin production, increasing the risk of obesity compared to day workers. Melatonin also has antioxidant and anti-inflammatory effects that influence energy metabolism, body mass, and immune responses. Final Considerations: Regulation of melatonin levels may be crucial to prevent obesity and improve control of circadian rhythm and lipid metabolism. However, the complexity of these interactions requires further research to develop specific treatment and prevention guidelines.
Keywords: Circadian Rhythm, Melatonin, Obesity.

INTRODUCTION

The growing global concern about obesity, exacerbated by the mismatch between natural light rhythms and contemporary lifestyle, highlights a significant disruption of the circadian cycle. This concern is alarming because more than two billion people in the world are classified as overweight or obese, which corresponds to approximately one-third of the global population (Guan et al., 2021). Therefore, it is crucial to discuss the influence of circadian rhythm and melatonin on the regulation of body weight and its direct relationship with the prevalence of obesity.

Melatonin, an endogenous hormone produced by the pineal gland, performs several essential physiological functions and is recognized for its antioxidant properties. During the night, plasma melatonin levels increase, peaking and declining to almost zero during the day (Hong et al., 2020). Recently, there has been increasing interest in the role of melatonin in regulating energy metabolism, especially glucose and lipid metabolism. Research indicates that dysregulation of the circadian rhythm can impair melatonin and cortisol levels, promoting appetite dysregulation and affecting lipid metabolism and insulin resistance (Suriagandhi, 2022).

Recent studies have also highlighted that shift work, particularly rotating night shifts, represents a significant occupational risk. Epidemiological research has revealed an association between night work and an increased risk of obesity and metabolic syndrome, conditions closely associated with chronic diseases such as coronary heart disease and diabetes (Huang et al., 2021). The inadequate production of melatonin, observed in these work patterns, may facilitate the appearance of comorbidities, such as type 2 diabetes mellitus, as melatonin is crucial for the regulation of glucose and for maintaining the function of pancreatic beta cells (Arendt & Aulinas, 2019).

Light is the main external signal that modulates the circadian rhythm, through the stimulation of light-sensitive ganglion cells in the retina, which transmit information to the suprachiasmatic nucleus (SCN). This, in turn, regulates cyclic electrical activity, directly influencing behavior and body physiology. Therefore, chronic disruption of the circadian rhythm can result in disturbances of glucose and lipid metabolism, contributing to imbalances in energy metabolism (Hong et al., 2020).

In this context, the goal of the present study was to investigate and summarize the most recent scientific evidence on the interaction between the circadian rhythm, melatonin production, and the development of obesity. This review aims to understand the physiological mechanisms involved and explore possible therapeutic strategies for the prevention and treatment of obesity, considering the potential of melatonin as a regulatory agent of the circadian rhythm and energy metabolism, and its impact on energy homeostasis and the treatment of obesity.

METHODOLOGY

This narrative literature review was conducted following the PVO strategy, which covers the Population or Research Problem, Variables involved, and Expected Outcome. The research was guided by the question: "What is the role of circadian rhythm and melatonin in regulating body weight and how does this relate to obesity?". The objective was to investigate the interaction between the circadian rhythm and melatonin secretion concerning body weight control, aiming to identify potential therapeutic strategies for the treatment and prevention of obesity.

To gather relevant data, a search was carried out in the PubMed-MEDLINE (Medical Literature Analysis and Retrieval System Online) database, using the following descriptors combined with the Boolean operators "AND" and "OR": "Circadian rhythm", "Circadian cycle", "Melatonin", "Melatonin secretion", "Body weight regulation", "Weight control", "Obesity". This initial search resulted in 74 articles.

The inclusion criteria adopted were: articles in English published between 2019 and 2024 that addressed the specified themes, including review studies, meta-analyses, and observational and experimental studies, available in full. Duplicate articles, publications available only in abstract format, articles that did not directly address the proposal studied, and those that did not meet the other established inclusion criteria were excluded.

After an initial evaluation and rigorous application of the selection criteria in the database consulted, the number of articles was reduced to 20. A detailed reading and a second round of evaluation resulted in the final selection of 13 pertinent articles that were included in this study. This meticulous selection ensured a comprehensive and up-to-date review of the impact of circadian rhythm and melatonin on body weight regulation and its implications in the context of obesity.

DISCUSSION

ROLE OF MELATONIN IN ENERGY HOMEOSTASIS AND OBESITY

Melatonin, often described as the "hormone of darkness" due to its primary synthesis by the pineal gland during the night, plays a key role in regulating lipid metabolism and circadian rhythm. This hormone interacts with melatonin receptors type 1 and 2 (MT1 and MT2), influencing not only the circadian cycle but also the synthesis, action, and secretion of insulin in tissues, as described by Li et al. (2020) and Ivanov et al. (2020). Furthermore, melatonin regulates lipolysis in adipose tissue and the expression of lipolytic genes, integrating with metabolic pathways that control the storage and breakdown of fats (Guan et al., 2021).

A study conducted by Simon et al. (2019) evaluated 31 adolescents with a body mass index (BMI) equal to or greater than the 90th percentile at a children's outpatient clinic. Participants, with a mean age of 16.0 ± 1.4 years and 77% female, had their sleep monitored by actigraphy and underwent glucose tolerance tests and salivary melatonin samples collected every 30-60 minutes from 5 pm to 12 pm the next day. The results revealed that adolescents, especially during puberty and who were overweight, were at increased risk of dysregulated sleep due to school and social demands, which was associated with reduced insulin sensitivity. This study also showed that sleep disturbances can increase ghrelin levels and decrease leptin levels, resulting in polyphagia and changes in satiety (Overberg et al., 2022).

Obesity is influenced by an imbalance between energy intake and expenditure, which results in the storage of lipids, such as fatty acids and triglycerides, in adipose tissue. The research by Li et al. (2020) highlighted how the circadian rhythm associated with lipids can be influenced by meal times, demonstrating changes in the circadian phase of triglyceride accumulation in rats subjected to nocturnal feeding. Additional studies, like Zhao et al. (2022), investigated the effects of dietary restriction on adipose tissue in obese individuals. During periods of fasting, an inhibition in the de novo synthesis of fatty acids and a stimulus to lipolysis was found, which contributed to the improvement in the function of pancreatic B cells and, consequently, in insulin sensitivity.

Recent studies, like Pivonello et al. (2022), explored the relationship between melatonin secretion, obesity, and immune regulation. Night shift workers, exposed to artificial light and with suppressed melatonin production, are at greater risk of developing obesity and immunological disorders compared to those who work during the day. This finding is corroborated by Fleury, Masís-Vargas and Kalsbeek (2020), who associated exposure to night light with significant metabolic changes, affecting glucose metabolism and increasing the incidence of conditions such as atherosclerosis and overweight.

In addition to regulating the circadian rhythm, melatonin exerts antioxidant and anti-inflammatory effects that directly influence energy metabolism, body mass, and immune responses. Guan et al. (2021) emphasized the connection between melatonin and biological processes such as oxidative stress, inflammation, sleep disorders, and the genesis of obesity, highlighting the multifunctionality of this hormone in the metabolic context.

Simon et al. (2019) carried out a cross-sectional study focused on the particularities of the circadian rhythm of melatonin in obese adolescents with and without polycystic ovary syndrome (PCOS). Their results indicated that adolescents with PCOS exhibited a pattern of melatonin secretion shifted later in the morning compared to their peers without PCOS, suggesting that PCOS may affect hormonal regulation and circadian rhythms, negatively influencing the sleep and wake cycle. The study also reported that changes in the circadian rhythm during puberty and the early start of school schedules can worsen circadian disorders in adolescents.

Studies indicate that changes in the secretion of this hormone during puberty affect these functions. A cross-sectional study by Overberg et al. (2022) with 149 obese adolescents, aged between 10 and 17 years, revealed a decrease in melatonin secretion with advancing age and Tanner stages, suggesting an association between lower melatonin secretion and increased insulin resistance.

This phenomenon is related to mechanisms such as polymorphisms in the melatonin receptor (MTNR1B) and the inhibitory effect of melatonin on insulin secretion through the cAMP and cGMP pathways, in addition to influencing the synthesis, action, and secretion of insulin through GLUT4 receptors. In addition, Ivanov et al. (2020) demonstrated that reduced melatonin levels can result in hyperinsulinemia, insulin resistance, hyperleptinemia, and, consequently, type 2 diabetes.

Other findings by Overberg et al. (2022) indicate that exposure to artificial light and the use of media after 10 pm are associated with changes in the circadian cycle and melatonin secretion, which can lead to physical, psychological, and sleep disorders. These environmental factors are crucial in regulating melatonin and can negatively influence metabolic health and overall well-being.

Furthermore, Ivanov et al. (2020) highlighted the significant influence of maternal melatonin on fetal development. Melatonin is essential for synchronizing the circadian rhythm of the trophoblast and influencing fetal gene expression related to growth and metabolic processes, especially in the early stages of pregnancy, when the transfer of melatonin receptors from mother to fetus occurs. Changes in maternal melatonin production are associated with complications such as intrauterine growth retardation and delay in the development of the fetal central nervous system, in addition to negatively impacting fetal metabolism and the development of the circadian rhythm.

REGULATION OF CIRCADIAN RHYTHM AND ENERGY METABOLISM

The study on the regulation of the circadian rhythm and its influence on energy metabolism has revealed important implications for the management of obesity. The circadian rhythm, a biological cycle of approximately 24 hours, is crucial in coordinating behavior and physiological functions, including energy balance. Disturbances in this cycle, resulting from a variety of factors such as irregular work hours, prolonged exposure to artificial light, and changes in diet, can compromise energy balance and increase the risk of obesity (Guan et al., 2021).

Guan et al. (2021) state that changes in the circadian rhythm can trigger or accelerate weight gain and the development of obesity. An example of this is exposure to blue light before the night's rest period, which can intensify circadian rhythm dysfunctions, inhibit fat oxidation, and reduce melatonin levels, factors that contribute to obesity. Furthermore, a meta-analysis by Baron et al. (2023) linked sleep deprivation with an increased risk of obesity, diabetes mellitus, and cardiovascular diseases.

Li et al. (2020) point out that sleeping less than 6-7 hours per night is associated with excessive eating behaviors, reduced leptin levels, insulin resistance, and glucose intolerance. In contrast, Baron et al. (2023) indicated that it is not only sleep duration that affects caloric intake and carbohydrate metabolism, but mainly circadian misalignment, which is associated with a higher number of meals and, in overweight individuals, insulin resistance.

These studies provide a deeper understanding of how circadian rhythm disruptions influence energy metabolism and the development of obesity, highlighting the importance of therapeutic strategies that consider circadian rhythm alignment to improve energy balance and prevent obesity.

FINAL CONSIDERATIONS

Research indicates that melatonin is essential in homeostatic regulation and predisposition to comorbidities such as obesity. It is vital in controlling circadian rhythm, lipid metabolism, and insulin sensitivity. Sleep disorders and other circadian disruptions can negatively impact melatonin secretion, leading to metabolic complications such as insulin resistance and changes in appetite, mediated by ghrelin and leptin. Furthermore, melatonin has antioxidant and anti-inflammatory effects that directly affect body mass, energy metabolism, and immune responses. Therefore, an in-depth understanding of the impact of melatonin on metabolism and the development of comorbidities is crucial for the development of effective therapeutic strategies to treat these conditions.

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