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The Effect of Melatonin on Metabolism and the Sleep-Wake Cycle

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ABSTRACT

The aim of this study was to investigate the influence of melatonin on metabolism and the implementation of the sleep-wake cycle. Methodology. Publications for this review were collected from PubMed, MedLine, and Google Scholar databases. Results. Melatonin is the main hormone that communicates the main circadian clock, located in the suprachiasmatic nucleus of the hypothalamus, and the peripheral biological clock located in brain cells and other organs. Melatonin production is related to day and night cycles, with peak production of the hormone occurring at night. Considering the pathophysiological mechanisms triggered by melatonin deficiency, the question reasonably arises about the possibilities of treating metabolic disorders (including type 2 diabetes), cardiovascular pathology and sleep disorders with melatonin preparations. Domestic and foreign publications provide reports of the clinically successful use of such drugs to improve sleep quality, increase sensitivity to glucose, lower blood pressure, reduce myocardial ischemia, and improve anthropometric parameters. All this makes melatonin a promising drug for managing cardiovascular risks against the background of metabolic disorders.

KEYWORDS: Melatonin, diabetes, insomnia, cardiovascular, Endocrinology.

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El efecto de la melatonina sobre el metabolismo y el ciclo sueño-vigilia

RESUMEN

El objetivo de este estudio fue investigar la influencia de la melatonina en el metabolismo y la implementación del ciclo sueño-vigilia. Metodología. Las publicaciones para esta revisión se obtuvieron de las bases de datos PubMed, MedLine y Google Scholar. Resultados. La melatonina es la principal hormona que comunica el reloj circadiano principal, ubicado en el núcleo supraquiasmático del hipotálamo, y el reloj biológico periférico ubicado en las células cerebrales y otros órganos. La producción de melatonina está relacionada con los ciclos de día y noche, y la producción máxima de la hormona se produce durante la noche. Teniendo en cuenta los mecanismos fisiopatológicos desencadenados por la deficiencia de melatonina, surge razonablemente la pregunta sobre las posibilidades de tratar los trastornos metabólicos (incluida la diabetes tipo 2), la patología cardiovascular y los trastornos del sueño con preparados de melatonina. Las publicaciones nacionales y extranjeras informan sobre el uso clínicamente exitoso de dichos medicamentos para mejorar la calidad del sueño, aumentar la sensibilidad a la glucosa, reducir la presión arterial, reducir la isquemia miocárdica y mejorar los parámetros antropométricos. Todo esto hace de la melatonina un fármaco prometedor para controlar los riesgos cardiovasculares en el contexto de trastornos metabólicos.

PALABRAS CLAVE: Melatonina, diabetes, insomnio, cardiovascular, Endocrinología.

Introduction

Melatonin is a hormone secreted by the pineal gland, and its primary function is directed towards synchronizing the circadian rhythms of the organism and aligning them with environmental signals such as sunlight, daily rhythms, and food intake. The peak secretion of melatonin occurs during the nighttime. In addition to the pineal gland, melatonin is synthesized in the retina, the gastrointestinal tract, and cells of the natural immune system. Melatonin possesses pronounced antioxidant properties. Its action is mediated through the MT1 and MT2 receptors belonging to the G protein-coupled receptor (GPCR) superfamily. Upon binding to the MT1 and MT2 receptors, its α and β/γ subunits initiate downstream signaling pathways, including adenylyl cyclase, phospholipase C, and phospholipase A2. Sensitization of adenylyl cyclase by melatonin enhances cyclic adenosine monophosphate (cAMP) signaling when melatonin levels decrease at dawn. This amplifies the rhythmic expression of genes in the tuberal part of the pituitary gland (including the clock gene mPER1) and provides a mechanism for enhancing rhythmicity in peripheral tissues, which themselves are capable of sustaining auto-oscillations [*Shen et al., 2022*].

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Urbanization processes and scientific-technical advancements have led to an extension of the photoperiod through the use of artificial lighting, predominantly emitting blue light. This results in a reduction of the peak synthesis of melatonin with an overall decline in its secretion. Hypomelatoninemia is accompanied by disturbances in the normal sleep-wake cycle, contributes to disruptions in eating behavior, metabolic disorders, increased daytime insulin resistance, and triggers constitutional obesity [*Czvetkova et al., 2021; Jockers et al., 2016*]. Melatonin-regulated insulin resistance is a key factor underpinning numerous metabolic dysregulations, including type 2 diabetes and sleep disturbances.

The aim of this study was to investigate the influence of melatonin on metabolism and the implementation of the sleep-wake cycle.

1. Materials and Methods

Data collection for this article was conducted in the PubMed, MedLine, and Google Scholar databases. The search depth covered a span of 10 years. Exploration was carried out using a series of key phrases: melatonin; insulin resistance; insomnia; diabetes mellitus; melatonin and diabetes mellitus; circadian rhythms. Duplicate, low-informative, and off-topic sources were excluded. In total, 41 references were included in the bibliography.

2. Regulation of melatonin synthesis

The synthesis of melatonin by the pineal gland is regulated by the suprachiasmatic nucleus (SCN) of the medulla oblongata. In turn, the activity of the SCN is controlled by the day-night cycle. Sunlight, upon reaching the retina through the retinohypothalamic tract, influences the SCN, which releases norepinephrine into the synaptic cleft connecting the SCN to the pineal gland. This leads to the cessation of melatonin formation from tryptophan. Thus, under conditions of significant illumination, melatonin production ceases, and conversely, it resumes during the dark period [*Czvetkova et al., 2021*].

3. Control of eating behavior

Melatonin influences the secretion of leptin and ghrelin hormones, exhibiting anorexigenic and orexigenic effects, respectively. In the hypothalamus, leptin regulates energy homeostasis by interacting with leptin receptors, subsequently activating JAK2 and STAT3 complexes [*Shen et al., 2022*]. In experiments, the removal of the pineal gland in rats

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led to increased expression of agouti-related peptide (Agrp), neuropeptide Y, and orexin, which enhance appetite. Conversely, the addition of melatonin to the nighttime water intake reduced the expression of Agrp and orexin. Moreover, rats with pinealectomy exhibited impaired thermogenic response in brown adipose tissue to cold exposure [*Buonfiglio et al., 2018*]. Mice lacking the melatonin receptor MT1 consumed more food after a fasting episode and gained more weight than wild-type mice. Leptin injections led to a reduction in appetite and body weight. In MT1 knockout mice, leptin administration did not result in STAT3 phosphorylation, and leptin receptor mRNA levels were reduced compared to the wild type. Thus, MT1 signaling appears to be a crucial modulator of leptin's impact on its receptor and subsequent signal transmission [*Buonfiglio et al., 2019*]. It can be concluded that the anorexigenic action of melatonin is, at least partially, realized through the secretion of leptin.

Ghrelin determines orexigenic behavior, with its levels rising before each meal, during nocturnal fasting, and decreasing postprandially. Ghrelin, alongside glucocorticoids and preprandial glucagon, is classified as a preprandial timer, while leptin and insulin function as postprandial timers. Ghrelin enhances growth hormone secretion, ultimately leading to the activation of adenosine monophosphate-activated protein kinase (AMPK), inducing an energy-conserving state [*Shen et al., 2022; Challet, 2015*]. The interactions between melatonin and ghrelin are not entirely clear. In a recent study by D. Sobko et al., a positive correlation was established between ghrelin and melatonin concentrations ($r = +0.72$, $p < 0.001$) in hypertensive patients [*Sobko et al., 2021*]. However, earlier studies demonstrated the absence of ghrelin in the hypothalamus (arcuate nucleus) of pinealectomized rats. In rats with intact pineal glands treated with melatonin, ghrelin levels in the hypothalamus were elevated. This led the authors to suggest that the preserved pineal gland is necessary for the exogenous melatonin's action on ghrelin [*Canpolat et al., 2006*]. Perhaps, the interaction between ghrelin and melatonin occurs indirectly, such as through serotonin, a precursor of melatonin.

4. Circadian cycles

The mammalian circadian system consists of central clocks represented by the suprachiasmatic nucleus of the hypothalamus (SCN) and peripheral clocks distributed in the brain and other organs, including the liver, muscles, adipose tissue, and pancreas.

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Circadian clocks (both central and peripheral) are composed of intracellular mechanisms capable of generating self-sustaining oscillations lasting approximately 24 hours, facilitated by a set of proteins known as clock proteins, acting through feedback loops of autoregulation. The circadian cycle can encode a series of biological, metabolic, and behavioral processes occurring throughout the day to anticipate and adapt to daily rhythmic changes. Central and peripheral oscillators generate circadian rhythms that are self-supporting and autonomous [*Queiroz et al., 2021*]. The molecular clocks of mammals consist of transcription and translation feedback loops oscillating with an almost 24-hour cycle. The positive loop involves the heterodimerization of either the CLOCK protein or the Neuronal PAS domain-containing protein 2 (NPAS2) with the Brain and Muscle ARNT-like 1 (BMAL1) protein in the nucleus. Formed dimers bind to enhancer blocks (E-boxes) in the promoters of clock-regulated genes, activating the transcription of clock-controlled genes, including those encoding Period (PER) and Cryptochrome (CRY) proteins. PER and CRY proteins accumulate in the cytoplasm during the circadian cycle, eventually forming dimers that translocate to the nucleus, where they inhibit their own transcription, closing the feedback loop. An auxiliary feedback loop includes orphan receptors associated with the retinoic acid receptor (RORα and RORβ) and REV-ERB (REV-ERBα and REV-ERBβ), which are also regulated by CLOCK and BMAL1 heterodimers. REV-ERBα and RORα, respectively, suppress and activate the transcription of BMAL1 by inhibiting and activating ROR response elements and REV-ERB [*Logan, McClung, 2019*].

4.1. Circadian regulation of metabolism

The circadian system plays a crucial role in the regulation of lipid metabolism, and disruptions in the normal sleep-wake cycle (coupled with associated disturbances in dietary patterns) can lead to pathological changes in metabolism. Triglyceride and LDL cholesterol levels exhibit significant variations throughout the day, surpassing interindividualvariabilities [*Logan, McClung, 2019*]. In a recent systematic review by M. Bonham et al., postprandial elevation of triacylglycerol was more pronounced during nighttime meals compared to daytime meals. The authors emphasized the importance of considering this factor in the treatment of cardiovascular diseases [*Bonham et al., 2021*].

Circadian regulation is associated with the production of melatonin by the pineal gland under light control, implemented through the structure of the SCN. Melatonin

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production is linked not only to daylight but also to the timing of food intake. Some studies report a significant decrease in melatonin levels ($p < 0.05$) during the month of Ramadan (meal consumption after sunset), while cortisol changes were inconclusive [*Chawla et al., 2021*]. This suggests that untimely food intake may influence the functioning of circadian rhythms.

Central clocks regulate food intake, energy expenditure, and the body's cellular sensitivity to insulin. Peripheral clocks in the intestines control glucose absorption. Peripheral clocks in muscles, adipose tissue, liver regulate local insulin sensitivity, and in the pancreas, they regulate insulin secretion. Inconsistency among different components of the circadian system and daily rhythms of sleep-wake cycles and food intake due to genetic, environmental, and behavioral factors can be a significant contributor to insulin resistance. Mutations in clock genes, exposure to artificial light-dark cycles, sleep disruption, shift work, and changes in time zones can be particularly influential factors. The endogenous circadian system's time period does not align with the 24-hour rhythm of the external world, necessitating a daily reset. Light (day-night transitions) serves as a crucial cue for resetting the central pacemaker, reaching the SCN through a direct connection with light-sensitive cells of the retinal ganglion via the retinohypothalamic tract. Peripheral circadian clocks depend on the SCN, and thus, the entire system is calibrated by light. Signals from the SCN to the periphery travel through various pathways, including the autonomic nervous system, hormones (melatonin, cortisol), modulation of body temperature, behavior, physical activity, and food intake. Peripheral clocks (liver, muscles, pancreas, brown and white adipose tissue) utilize metabolic signals arising from food intake [*Stenvers et al., 2019*]. In healthy individuals, glucose tolerance is higher in the morning than in the evening, partly associated with the circadian rhythm of cell sensitivity to insulin. Additionally, the mediated rhythm of β-cell sensitivity to glucose influences this pattern. In the study conducted by C. Morris et al., postprandial glucose levels were investigated at different times of the day. The authors demonstrated that the circadian system and circadian misalignment (night shifts, etc.) significantly impact glucose tolerance independently of the behavioral cycle. Postprandial glucose levels were 17% higher (indicating lower glucose tolerance) in the evening (20:00) compared to the morning (8:00). The circadian misalignment alone increased postprandial glucose levels by 6%. The authors explained the

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differences in glucose tolerance by a decrease in β-cell function in the evening (insulin concentration 27% lower in the early phase) and reduced insulin sensitivity (elevated postprandial glucose levels despite a 14% increase in insulin in the late phase without changes in the early phase). Thus, the circadian system makes a significant contribution to the decreased glucose tolerance in the evening, explaining the elevated risk of diabetes development in night shift workers [*Morris et al., 2015*].

Circadian control of food intake may occur through direct anatomical connections between the SCN and the hypothalamic nucleus involved in the regulation of feeding. Additionally, the SCN regulates the secretion of melatonin and cortisol. The circadian rhythm of cortisol secretion is orchestrated by the hypothalamo-pituitary-adrenal axis through signals from the SCN to the paraventricular nucleus. Cortisol influences insulin signal transduction and reduces its secretion. The circadian rhythm of melatonin also impacts fluctuations in insulin resistance throughout the day, altering insulin secretion. Furthermore, the SCN influences growth hormone production by controlling sleep-wake cycles. In addition to central clocks, several peripheral clocks affect carbohydrate metabolism: intestinal clocks (expression of glucose membrane transporters); muscle clocks (changes in insulin sensitivity); adipose tissue clocks (circadian rhythm in glucose uptake); liver clocks (a combination of autonomic and endocrine signals). The liver maintains euglycemic states through glycogen stores by accumulating or breaking down glucagon. Pancreatic clocks are synchronized with light and darkness through SCN signals transmitted via autonomic neurons, melatonin release, glucocorticoid release, and changes in body temperature [Stenvers et al., *2019*].

5. The role of melatonin in metabolic disorders

The circadian rhythm, in which melatonin plays a crucial role, closely interacts with endocrine metabolism. Sleep disturbances are comorbidly associated with type 2 diabetes and obesity [*Berger et al., 2022*]. Several studies confirm the favorable impact of melatonin on carbohydrate metabolism. Hyperglycemia associated with diabetes leads to mitochondrial chain dysfunction, consequently increasing reactive oxygen species (ROS) levels. Mitochondrial stress contributes to diabetic retinopathy. Autophagy is enhanced in the retinas of diabetic patients due to oxidative stress and inflammation. Melatonin and its metabolites reduce retinal oxidative stress through direct antioxidant action and by

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stimulating glutathione reductase, glutathione peroxidase, superoxide dismutase, and catalase. Melatonin also modulates autophagy by reducing oxidative stress and inflammation. Melatonin reduces cardiac dysfunction by preventing mitochondrial fission through the expression of SIRT1-PGC 1α, decreasing cardiomyocyte apoptosis, and suppressing the development of retinopathy [Dehdashtianet al., 2018; Ding et al., 2018]. Treatment with melatonin (3 mg) in four patients led to increased volume and activity of brown adipose tissue, normalization of blood cholesterol and triglyceride levels without affecting body mass, decreased fasting insulin, and HOMA insulin resistance index in all cases [*Halpern et al., 2019*].

Melatonin can be used to treat exogenous-constitutional obesity, which is one manifestation of metabolic syndrome. In this context, the action of melatonin is directed towards most mechanisms contributing to obesity: eating behavior, circadian desynchronization, insomnia, and adipokine production. In metabolic syndrome combined with type 2 diabetes (T2D), melatonin's effect is likely associated with its antioxidant and anti-inflammatory actions, as well as chronobiological mechanisms [*Czvetkova et al., 2021*].

In cases of diabetes with high hyperglycemia, self-oxidation of glucose occurs, leading to oxidative stress against a backdrop of already reduced antioxidant system activity. Melaxen (melatonin) therapy contributes to the normalization of carbohydrate and lipid metabolism, as well as improves the synthetic function of the liver in patients with T2D complicated by non-alcoholic steatohepatitis. In the study by S.S. Popov et al., the inclusion of melaxen in the treatment regimen (in addition to antidiabetic, hepatoprotective, and antihypertensive drugs) led to a 1.8-fold reduction in beta-lipoprotein levels and a 1.5-fold reduction in cholesterol within 10 days of treatment, significantly higher than in the control group (baseline therapy). Fasting glucose concentration decreased by 1.8 times (vs 1.5), postprandial glucose by 1.7 times (vs 1.4), insulin levels increased by 43% (vs 27%), and C-peptide by 38% (vs 29%). Cholinesterase activity at the beginning of the study was, on average, 2.2 times higher than the upper normal level. After treatment, including melaxen, it decreased by 1.7 times (vs 1.3), and the atherogenic index decreased by 2.1 times (vs 1.4). Moreover, the level of low-density lipoprotein (LDL) significantly decreased, and the content of high-density lipoprotein (HDL) increased more significantly than with basic therapy. The study demonstrated that

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melaxen significantly and reliably enhances the therapeutic effect, explained by the authors' antioxidant activity of melatonin [*Popov et al., 2015*].

The association of type 2 diabetes (T2D) with oxidative stress lies in the increase of free radicals in T2D, which is linked to a decrease in the levels of antioxidants such as superoxide dismutase, glutathione peroxidase, and catalase [*Kandimalla et al., 2017*]. There is a genetic basis for the action of melatonin and the development of T2D. In a review study by A. Karamitri et al., attention was drawn to 14 rare mutations of the melatonin receptor MT2 with loss of protein Gi activation, which was associated with an increased risk of developing T2D [*Karamitri et al., 2013*].

Experiments on animal models with T2D and obesity have demonstrated that melatonin injections provide antiapoptotic protection to the liver parenchyma, manifested by the improvement of the ultrastructural state of liver cells and their mitochondrial apparatus [*Vasendin et al., 2023*]. Additionally, the degradation of small lipid droplets in hepatocytes was noted, indicating the hepatoprotective action of melatonin [*Vasendin et al. 2023*].

In a randomized placebo-controlled study by H. Bazyar et al., the effect of melatonin supplements on certain cardiovascular risk factors and anthropometric indices in patients with type 2 diabetes (n=50) was investigated. Melatonin intake for 8 weeks significantly reduced systolic, diastolic, and pulse blood pressure levels, as well as decreased body mass index, waist circumference, body obesity index, volume index, conicity index, and waist-to-height ratio ($p<0.05$) [*Bazyar et al., 2021*]. Thus, melatonin supplementation proves to be effective in controlling blood pressure and anthropometric indicators (predictors of obesity) in type 2 diabetes.

The prospects of melatonin in the treatment of type 2 diabetes are explained by the association of this condition with circadian rhythm disruption. Strong genetic associations between type 2 diabetes (T2D) and mutations in the MTNB1B alleles (melatonin receptor gene) serve as evidence for this connection. Alterations in the normal functioning of melatonin increase the risk of developing type 2 diabetes [*Zhu et al., 2023*].

Melatonin holds clinical potential in T2D and other disorders by resynchronizing disrupted circadian rhythms, consequently leading to the gradual normalization of metabolic deviations. Acting as a chronobiotic, melatonin addresses sleep disturbances

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induced by night shifts or changes in time zones, improves glucose hemostasis, energy balance, and overall health in T2D. The cytoprotective role of melatonin, acting as an antioxidant, proves beneficial in combating oxidative stress and helps preserve the functions of pancreatic β-cells, thereby reducing the risks of further T2D development [*Wajid et al., 2020*].

6. The impact of melatonin on insomnia

Deviation of melatonin levels from the physiological circadian curve is often associated with insomnia, affecting 2.3% to 25.5% of the global population. Melatonin levels tend to decrease with age, likely contributing to sleep disturbances in the elderly, with 30-48% of this population experiencing insomnia. Traumatic brain injuries are linked to disrupted melatonin production and frequently accompany insomnia [*Pizova et al., 2022*]. While the specific role of melatonin in each nosological case is not described, its deficiency is assumed to play a critical role in conditions and states where sleep disturbances are symptomatic. Sleep can be considered a modifiable risk factor for cardiovascular diseases (CVD), metabolic disorders, including diabetes. Short sleep duration is associated with coronary heart disease (CHD), arrhythmias, and arterial hypertension. The pathogenetic mechanisms of these diseases involve autonomic nervous system dysfunction, endothelial function alteration, metabolic dysregulation, heightened inflammation, and blood clotting system changes [*Tobaldini et al., 2019*]. In a study assessing sleep efficiency in 2148 patients, a 10% increase in the sleep fragmentation index was shown to correlate with a 5.2% increase in hypertension prevalence (p=0.0071), while frequent daytime sleep was associated with an 11.6% increase in hypertension prevalence (p=0.0002). However, sleep duration (p=0.2) and insomnia (p=0.17) were not linked to hypertension. These findings were obtained after excluding individuals with an apnea/hypopnea index exceeding 15/hour [*Ramos et al., 2018*]. Thus, sleep quality and the disruption of its normal periodicity posed a greater risk than insomnia itself. Sleep deficiency was associated with poorer prognoses in CVD, cerebrovascular disorders, cancer, arterial hypertension (AH), and diabetes [*Pizova et al., 2022*].

Diabetes mellitus may indirectly impact brain functions and possibly melatonin production. Metabolic disorders associated with melatonin imbalance, including type 2

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diabetes (T2D) and the related insulin resistance, trigger stroke, cerebrovascular, and neurodegenerative diseases. Insulin resistance in brain tissues leads to the disruption of insulin response, ultimately resulting in disturbances in metabolic and immune functions. The insulin receptor is responsible for enhancing glucose uptake by cells, normal functioning and replacement of mitochondria, anti-apoptosis, autophagy through MAPK, AKT signaling pathways, and activation of the Nrf2 factor, providing antioxidant protection. Besides glucose homeostasis, insulin plays a crucial role in the generation, restoration, and maintenance of neuronal function [*Shen et al., 2022*].

In metabolic disorders, including T2D, adipose tissue-resident macrophages polarize toward the pro-inflammatory M1-polarized phenotype, leading to increased expression of inflammatory mediators such as IL-6, tumor necrosis factor-alpha (TNF-α), IL-1β. These cytokines, among other effects, penetrate the blood-brain barrier, increasing brain cell resistance to insulin, inducing hypothalamic dysfunction, inhibiting insulin receptor substrate 1 signaling by amyloid beta oligomers (through TNF-α/JNK activation), and disrupting insulin signaling in the brain [*Shen et al., 2022*]. Additionally, advanced glycation end products accumulated in T2D activate GSK-3β and NF-kB signaling pathways, leading to increased levels of reactive oxygen species and pro-inflammatory cytokines, contributing to cellular dysfunction [*Kandimalla et al., 2017*].

The work of nurses during the night shift is associated with an increased risk of developing cardiometabolic syndrome. However, it is essential to consider not only potential disruptions in melatonin production rhythm but also nocturnal eating habits, leading to dyslipidemia [*Molzof et al., 2017*]. The risk of developing metabolic syndrome in shift workers was found to be 1.7 times higher than that of their counterparts working during the day shift [*Lin et al., 2015*].

Melatonin is one of the ancient antioxidants, localized in various concentrations within mitochondria, cell membranes, the nucleus, and cytosol of brain cells. Melatonin is effective in reducing overall oxidative stress, serving as a mitochondria-targeted antioxidant. In addition to neutralizing free radicals, melatonin acts as an immunomodulator and neuroprotector. Melatonin therapy alleviates insomnia in neurodegenerative diseases by activating the Ntf2 factor and inhibiting proinflammatory cytokines in nervous tissue [*Balmik, Chinnathambi, 2018; Das et al., 2020*].

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Despite attempts to use melatonin in the treatment of insomnia, it does not demonstrate a significant effect in real clinical practice. In a meta-analytical review encompassing 170 studies and 47,950 adult participants, benzodiazepines, eszopiclone, zolpidem, and zopiclone were found to be more effective in treating insomnia compared to melatonin [*De Crescenzo et al., 2022*]. Nevertheless, melatonin has the ability to improve cognitive functions in Alzheimer's disease [*Sumsuzzman et al., 2021*]. In children with autism spectrum disorder, long-term melatonin treatment led to improved sleep quality. After 52 weeks of continuous treatment, children slept 62 minutes longer ($p=0.007$), fell asleep 48.6 minutes faster ($p<0.001$), had episodes of continuous sleep 89.1 minutes longer ($p=0.001$), experienced 0.41 fewer nighttime awakenings ($p=0.001$), and exhibited better sleep quality ($p<0.001$) compared to baseline. Additionally, melatonin demonstrated its effectiveness when compared to a placebo group [*Maras et al., 2018*]. An integrative review, summarizing data from 25 articles, indicates that melatonin application reduces sleep latency, facilitating falling asleep in children and adolescents, with minimal side effects, making it a safe option for both children and adults [*Bueno et al., 2021*].

7. Melatonin and the Cardiovascular system

The normal physiological activity of the cardiovascular system (CVS) is regulated according to circadian rhythms controlled by melatonin. In arterial hypertension complicated by metabolic syndrome, circadian amplitude-frequency parameters are substantially altered, sometimes leading to inversion, disrupting the coordination of different body rhythms. The increased sympathetic activation during the night in individuals with metabolic syndrome alters the dynamics of the blood pressure graph, often accompanied by nocturnal hypertension. Another characteristic of such patients is endothelial dysfunction, characterized by reduced nitric oxide (NO) production by endotheliocytes. Melatonin has demonstrated anti-atherogenic effects, suppressing the expression of adhesion molecules in endotheliocytes, reducing their lipid infiltration, neutralizing free radicals, improving cholesterol clearance, and inhibiting lipid peroxidation [*Nedogoda et al., 2017*].

Melatonin exerts indirect influence on the cardiovascular system through lipid and carbohydrate metabolism, blood pressure, and the sleep-wake cycle. Circadian fluctuations occur in arterial pressure, catecholamine levels, heart rate, and pulse wave velocity.

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Exogenous melatonin administration leads to a reduction in blood pressure, while endogenous melatonin levels negatively correlate with pulse wave velocity [*Ozkalayci et al., 2021*]. Melatonin administration reduces nocturnal systolic and diastolic blood pressure [*Borghi, Cicero, 2017*]. The favorable impact of melatonin on the cardiovascular system is attributed to the improvement of the lipid profile, including decreased levels of cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglycerides. Melatonin's anti-inflammatory and antioxidant actions also contribute to its effects. Melatonin enhances the conversion of endogenous cholesterol to bile acids, suppresses cholesterol synthesis, and inhibits cholesterol accumulation [*Ozkalayci et al., 2021*].

In a study by S.V. Nedogoda et al., the influence of melatonin on patients with sleep disorders, hypertension, and metabolic syndrome was investigated. It was found that the addition of melatonin to the treatment regimen (in addition to metformin) significantly increased the circadian index, improved vascular elasticity (reducing central systolic blood pressure and augmentation index), enhanced endothelial function (increasing flow-dependent vasodilation), normalized daily blood pressure and lipid profiles. In the melatonin group, the vascular age index decreased more significantly than in the control groups. Thus, the inclusion of melatonin in therapy led to improvements in endothelial function, vascular stiffness, blood pressure control, and sleep quality [*Nedogoda et al., 2017*].

The nocturnal secretion of melatonin is reduced in patients with ischemic heart disease (IHD) and microvascular angina (syndrome X). In the case of syndrome X, baroreceptor sensitivity is impaired, and sympathetic nervous system predominance reduces sensitivity to adrenergic stimuli, affecting the pineal gland and contributing to a decrease in melatonin levels [*Ozkalayci et al., 2021*].

Endogenous melatonin has the capacity to limit ischemic damage and enhance the efficacy of mechanical reperfusion with primary percutaneous coronary intervention (pPCI) in ST-segment elevation myocardial infarction (STEMI). In cases where the procedure was rapidly conducted (on average 136 minutes from symptom onset), infarct size was approximately 40% smaller in patients receiving intravenous and intracoronary melatonin compared to the placebo group (p=0.003) [*Dominguez-Rodriguez et al., 2017*]. In the early stages of ischemia oxidative effects are still latent, and melatonin effectively reduces the affected area.

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Conclusion

Melatonin is a crucial hormone that performs the function of synchronizing the central body clocks located in the suprachiasmatic nucleus with numerous peripheral clocks. This synchronization is necessary to prepare metabolic cycles for the normal sleep-wake cycle, activity, and food intake. The presented publications have demonstrated that glucose tolerance and lipid components vary throughout the day, with significantly lower levels in the evening than in the morning, in accordance with these cycles. This difference is attributed to changing insulin resistance and β-cell activity. Any disruptions in the physiological rhythm of life can lead to desynchronization of circadian processes and disturbance in melatonin synthesis, contributing to increased insulin resistance during daylight hours and disruptions in normal eating behavior. Accumulating metabolic disorders can form the basis for the development of cardiovascular pathology.

The action of melatonin on the cardiovascular system is mainly associated with its influence on lipid and carbohydrate metabolism, as well as on blood pressure and sympathetic nervous system function. Prolonged therapy with melatonin preparations has demonstrated effectiveness in improving hemodynamic, metabolic, and anthropometric parameters related to modifiable cardiovascular risk factors. The antioxidant and anti-inflammatory properties of melatonin play a significant role in enhancing the condition of cardiomyocytes. Therefore, melatonin should be considered as a promising therapeutic agent for long-term treatment aimed at gradual elimination of cardiovascular disease risk factors.

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