EXOGENOUS MELATONIN AND ITS METABOLIC EFFECTS: A LITERATURE REVIEW

MELATONINA EXÓGENA E SEUS EFEITOS METABÓLICOS: REVISÃO DA LITERATURA

Paulo Roberto da Silva Júnior[1], Hianny Ribeiro Cabral[1], André Luis Oliveira Ramos Gomes[1], Pedro Bruno Estevam Teófilo[1], Thárcia Kiara Beserra de Oliveira[2]

[1] Medical student at Centro Universitário Unifacisa, Paraíba, Brazil; [2] PhD, Professor at Centro Universitário Unifacisa and Faculdade de Medicina de Olinda, Paraíba, Brazil.

ABSTRACT

Introduction: Melatonin is a hormone produced mainly by the pineal gland, playing a key role in the regulation of physiological processes, particularly the circadian rhythm. **Objectives:** To discuss the diverse effects of exogenous melatonin administration. **Methods:** This descriptive and exploratory study summarized recent publications in English or Portuguese. Twenty-four studies indexed in Scielo, PubMed, Science Direct, and Cochrane databases were included and analyzed. **Results:** Melatonin regulates the circadian rhythm, modulates the immune and cardiovascular systems, and promotes protection to oxidant stimuli while inducing antioxidant activities. It also exerts gastroprotective, neuroprotective and neuromodulatory effects. **Conclusion:** Melatonin induces beneficial effects across different physiological processes in humans. It is considered a safe and well-tolerated pharmacological agent, associated with minimal side effects and no withdrawal symptoms.

Keywords: Effects; Melatonin; Physiological regulation

RESUMO

Introdução: A melatonina é um hormônio produzido majoritariamente pela glândula pineal e que tem ação direta sobre a regulação de processos fisiológicos, especialmente o ritmo circadiano. ***Objetivo:*** Demonstrar através da literatura, os diferentes efeitos fisiológicos relacionados à administração da melatonina exógena. ***Métodos:*** Trata-se de um estudo descritivo e exploratório, baseado na sumarização de trabalhos recentes publicados em inglês ou português. Foram analisados e incluídos 25 artigos indexados nas bases de dados Scielo, Pubmed, ScienceDirect e Cochrane. **Resultados:** Este hormônio está diretamente envolvido na regulação de processos fisiológicos, como o ciclo circadiano, regulação imune e cardiovascular, atividade pró-oxidante e antioxidante e gastroproteção, além de possuir efeito neuroprotetor e neuromodulador. ***Conclusão:*** A melatonina está diretamente ligada a efeitos positivos em processos dos mais diversos sistemas corporais. Trata-se de uma molécula de uso terapêutico seguro e de boa tolerância, estando relacionada a poucos efeitos colaterais e não ocasionando sintomas de retirada.

Palavras-chave: Efeitos; Melatonina; Regulação fisiológica

INTRODUCTION

Insomnia is the most common sleep disorder, with a prevalence ranging from 10% to 25%. Individuals with insomnia experience reduced work productivity and increased healthcare utilization. Despite the availability of numerous medications, no pharmacological strategy has yet been firmly established for its management[1].

Melatonin (N-acetyl-5-methoxytryptamine) is a hormone primarily produced by the pineal gland that affects the secretion of several endogenous substances (e.g., cortisol, adrenaline, etc.). Consequently, melatonin also plays a key role in regulating activity-rest and sleep-wake rhythms[2].

The synthesis of melatonin begins with the conversion of the amino acid tryptophan into 5-hydroxytryptophan (5-HTP) by tryptophan hydroxylase 1 enzyme. Next, 5-HTP is decarboxylated by 5-HTP decarboxylase into serotonin, which is subsequently acetylated to N-acetylserotonin. Last, melatonin is formed from N-acetylserotonin and released into the bloodstream[3].

Owing to its high lipophilicity and ability to easily cross the blood-brain barrier, melatonin has been extensively investigated in clinical and experimental studies. Beneficial effects on the central nervous system have been reported, with high safety and tolerability even at elevated doses[4].

Moreover, melatonin exerts diverse physiological effects, including regulation of the circadian rhythm, modulation of the immune and cardiovascular systems, reduction of pro-oxidant activity with concomitant enhancement of antioxidant activities, gastroprotection, and neuroprotective and neuromodulatory actions[5].

Based on the extensive evidence supporting its effects, the present study aimed to discuss the clinical use of exogenous melatonin.

METHODS

This descriptive and exploratory study summarized recent publications in English or Portuguese. A total of 24 articles indexed in Scielo, PubMed, ScienceDirect, and Cochrane databases were included and analyzed. The search strategy employed the following DeCS/MeSH descriptors: “melatonin”, “physiology”, and “drug effects”. Grey literature was excluded.

DISCUSSION

Light stimuli regulate melatonin synthesis: darkness increases production, whereas light exposure inhibits it. Sleep propensity is associated with the daily rise in melatonin secretion, with serum levels starting to increase approximately two hours before usual bedtime[6].

Clinical studies with middle-aged and older adults showed improvements in primary insomnia symptoms following daily administration of 2 mg of slow-release melatonin. The largest trial, involving more than 500 patients, demonstrated particularly favorable outcomes in individuals aged 55 years or older, with efficacy sustained for over six months[7].

Exogenous melatonin combined with antidepressants has been shown to improve depressive symptoms; however, no significant effect was observed when administered as monotherapy[8].

In addition to its role in regulating the circadian rhythm, melatonin also modulates immunobiological processes by influencing key cellular components of the innate immune response. In rats, multiple daily injections of melatonin into the pineal gland and adjacent brain regions significantly increased phagocytic microglia cellularity[9].

Moreover, melatonin administration significantly increased the chemotaxis index[10], enhanced the concentration of natural killer cells and monocytes in the bone marrow of healthy young mice, and attenuated the excessive production of pro-inflammatory mediators, particularly cytokines, in several in vitro inflammation models[11].

Recent evidence also suggests that melatonin exerts relevant antiviral, antibacterial, and antiparasitic effects[12, 13]. In immunocompetent mice, melatonin reduced viral levels in the brain, whereas such effects were absent in immunosuppressed mice, indicating that its antiviral action requires an intact immune system.

Several studies using experimental models of endotoxin-induced and polymicrobial sepsis have demonstrated the protective role of melatonin[15, 16]. This protective effect has been attributed to its pleiotropic action, including the inhibition of pro-inflammatory cytokine production, especially tumor necrosis factor alpha (TNF-α), and increased levels of the anti-inflammatory interleukin-10 (IL-10)[15, 17].

Exogenous melatonin also has also shown benefits in gastrointestinal diseases. In experimental colitis models, melatonin has been shown to reduce visceral hyperalgesia and attenuate disease severity[18, 19]. Clinical studies have further reported improvements in irritable bowel syndrome, suggesting a close relationship between this condition and circadian rhythm regulation[20].

In the cardiovascular system, melatonin administration combined with conventional treatment for acute myocardial infarction induced significant protective effects against ischemia-reperfusion injury in clinical trials[21]. Additional studies have described improvements in macrovascular and microvascular diseases. In mice exposed to a hyperlipidemic diet and an experimental model of streptozotocin-induced diabetes mellitus, melatonin restored endothelial function and improved microvascular responses.

The expression of melatonin membrane receptors (MT1 and MT2) in pancreatic islets of Langerhans and diffusely in the human pancreas was confirmed immunohistochemically. In pancreatic β-cells, these receptors play in three parallel signaling pathways that distinctly modulate insulin secretion[23].

Chronic oral administration of melatonin in mice for three months significantly reduced total cholesterol and low-density lipoprotein levels, while increasing serum high-density lipoprotein levels. Serum triglyceride levels were decreased by 39%, and insulinemia was reduced by 33%[24].

Furthermore, oral administration of melatonin reduced hepatic steatosis and liver inflammation, as evidenced by decreased serum aspartate aminotransferase (AST) levels. In hepatocytes, melatonin also downregulated pro-inflammatory cytokines levels and inhibited apoptosis[25].

Table 1. Main physiological effects related to exogenous melatonin administration.

Effects of Exogenous Melatonin		
Author	**Objective**	**Results**
Wade et al., 2011	To analyze the effect of melatonin on sleep regulation in individuals with insomnia.	Insomnia was significantly improved, especially in patients over 55 years of age.
Srinivasan et al., 2006	To evaluate the use of melatonin in the treatment of mood disorders.	Patients with depression presented improved symptoms when treated with antidepressants combined with exogenous melatonin compared with antidepressants alone.
Tang et al., 2009	To analyze the effect of sleep on colitis and irritable bowel syndrome.	Melatonin induced antinociceptive effects in colitis. Improved sleep was associated with reduced severity of irritable bowel syndrome symptoms.
Hussein et al., 2007	To evaluate the effects of melatonin on lipid metabolism.	Reduced serum total cholesterol, LDL, and triglycerides levels, and increased HDL levels after treatment with melatonin.
Tahan et al., 2009	To analyze the use of melatonin in the treatment of hepatic steatosis.	Reduced hepatic steatosis, liver tissue inflammatory status, and decreased hepatocyte apoptosis.

CONCLUSION

Melatonin is widely regarded as a safe and well-tolerated compound, characterized by minimal side effects and the absence of withdrawal symptoms. Beyond its regulatory function in circadian rhythm, melatonin exerts anti-inflammatory effects and modulates the immune, cardiovascular, and gastrointestinal systems. Additionally, it enhances the efficacy of other pharmacological agents by synergistically attenuating infectious processes.

REFERENCES

1. Heather EG, Joshua TMA, Daniel JB. Brief Behavioral Treatment of Insomnia. Sleep Medicine Clinics, 2019; 14 (2): 235-243.
2. MAGANHIN, Carla C. et al. Efeitos da melatonina no sistema genital feminino: breve revisão. Rev. Assoc. Med. Bras. 2008, 54(3): 267-271.
3. Al-Omary, F.A.M. in: H.G. Brittain (Ed.), Profiles of drug substances, excipients and related methodology, Academic Press, San Diego, 2013,159-226.
4. Marra, Annachiara et al. CriticalCareClinics. Melatonin in CriticalCare. 2017; 35(2), 329 - 340.
5. Bellapart J, Boots R. Potential use of melatonin in sleep and delirium in the critically ill. Br J Anaesth 2012; 108(4): 572–80.
6. Brzezinski, A. Melatonin in humans. N. Engl. J. Med. 1997, 336, 186–195.
7. Wade AG, Crawford G, Ford I, et al. Prolonged release melatonin in the treatment of primary insomnia: evaluation of the age cut-off for short- and long-term response. CurrMed Res Opin. 2011;27:87-98.
8. Srinivasan V, Smits M, Spence W, et al. Melatonin in mood disorders. World J BiolPsychiatry. 2006;7:138-151.
9. Kaur C., Ling E.A. Effects of melatonin on macrophages/ microglia in postnatal rat brain. J. Pineal Res. 1999;26:158– 168.
10. Currier N.L., Sun L.Z., Miller S.C. Exogenous melatonin: Quantitative enhancement in vivo of cells mediating nonspecific immunity. J. Neuroimmunol. 2000;104:101–108.
11. Xia M.Z., Liang Y.L., Wang H., Chen X., Huang Y.Y., Zhang Z.H., Chen Y.H., Zhang C., Zhao M., Xu D.X., et al. Melatonin modulates tlr4-mediated inflammatory genes through myd88- and trif-dependent signaling pathways in lipopolysaccharide-stimulated raw264.7 cells. J. Pineal Res. 2012; 53: 325–334.
12. Srinivasan V., Mohamed M., Kato H. Melatonin in bacterial and viral infections with focus on sepsis: A review. Recent Pat. Endocr. Metab. Immune Drug Discov. 2012; 6: 30–39.
13. Bagnaresi P., Nakabashi M., Thomas A.P., Reiter R.J., Garcia C.R. The role of melatonin in parasite biology.

Mol. Biochem. Parasitol. 2012; 181: 1–6.

14. Bonilla E., Rodon C., Valero N., Pons H., Chacin-Bonilla L., Garcia Tamayo J., Rodriguez Z., Medina-Leendertz S., Anez F. Melatonin prolongs survival of immunodepressed mice infected with the venezuelan equine encephalomyelitis virus. Trans. R. Soc. Trop Med. Hyg. 2001; 95: 207–210.
15. Carrillo-Vico A., Lardone P.J., Naji L., Fernandez-Santos J.M., Martin-Lacave I., Guerrero J.M., Calvo J.R. Beneficial pleiotropic actions of melatonin in an experimental model of septic shock in mice: Regulation of pro-/anti-inflammatory cytokine network, protection against oxidative damage and anti-apoptotic effects. J. Pineal Res. 2005; 39: 400–408.
16. Escames G., Acuna-Castroviejo D., Lopez L.C., Tan D.X., Maldonado M.D., Sanchez-Hidalgo M., Leon J., Reiter R.J. Pharmacological utility of melatonin in the treatment of septic shock: Experimental and clinical evidence. J. Pharm. Pharmacol. 2006; 58: 1153–1165.
17. Lowes D.A., Webster N.R., Murphy M.P., Galley H.F. Antioxidants that protect mitochondria reduce interleukin-6 and oxidative stress, improve mitochondrial function, and reduce biochemical markers of organ dysfunction in a rat model of acute sepsis. Br. J. Anaesth. 2013; 110: 472–480.
18. Mickle A., Sood M., Zhang Z., Shahmohammadi G., Sengupta J.N., Miranda A. Antinociceptive effects of melatonin in a rat model of post-inflammatory visceral hyperalgesia: A centrally mediated process. Pain. 2010; 149: 555–564.
19. Pentney P.T., Bubenik G.A. Melatonin reduces the severity of dextran-induced colitis in mice. J. Pineal Res. 1995; 19: 31–39.
20. Tang Y., Preuss F., Turek F.W., Jakate S., Keshavarzian A. Sleep deprivation worsens inflammation and delays recovery in a mouse model of colitis. Sleep Med. 2009; 10: 597–603.
21. Yang Y, Sun Y, Yi W, et al. A review of melatonin as a suitable antioxidant against myocardial ischemia-reperfusion injury and clinical heart diseases. J Pineal Res 2014; 57: 357–366.
22. Salmanoglu DS, Gurpinar T, Vural K, et al. Melatonin and L-carnitin improves endothelial disfunction and oxidative stress in Type 2 diabetic rats. Redox Biol 2016; 8: 199–204.
23. Kemp DM, Ubeda M, Habener JF. Identification and functional characterization of melatonin Mel 1a receptors in pancreatic beta cells: potential role in incretin-mediated cell function by sensitization of cAMP signaling. Mol Cell Endocrinol. 2002; 191(2): 157–66.
24. Hussein MR, Ahmed OG, Hassan AF, Ahmed MA. Intake of melatonin is associated with amelioration of physiological changes, both metabolic and morphological pathologies associated with obesity: an animal model. Int J Exp Pathol. 2007; 88(1): 19–29.
25. Tahan V, Atug O, Akin H, Eren F, Tahan G, Tarcin O, et al. Melatonin ameliorates methionine - and choline-deficient diet-induced nonalcoholic steatohepatitis in rats. J Pineal Res. 2009; 46 (4):401–7