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COMMENTARY

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Melatonin multifaceted pharmacological actions on melatonin receptors converging to abrogate COVID-19

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Abstract

Data indicate that controlling inflammatory responses to COVID-19 may be as important as antiviral therapies or could be an important adjunctive approach. Melatonin possesses anti-inflammation, antioxidation, and immune-enhancing features directly and/or indirectly through its own receptor signaling and is therefore well suited to reduce the severity of COVID-19. Studies have proposed that melatonin regulates COVID-19–associated proteins directly through regulation of molecules such as calmodulin (CALM) 1 and CALM 2, calreticulin (CalR), or myeloperoxidase (MPO) and/or indirectly through actions on GPCR (eg, MTNR1A, MTNR1B) and nuclear (eg, RORα, RORβ) melatonin receptor signaling. However, the exact mechanism(s) and doses by which melatonin reduces the severity of COVID-19 is still open for debate, warranting the need for further testing of melatonin in placebo-controlled randomized clinical trials for COVID-19.

KEYWORDS

COVID-19, cytokines, melatonin, melatonin receptors, outpatient

1 | INTRODUCTION

As of March 2021, globally more than 110 million people have been infected with SARS-CoV-2, the virus that causes COVID-19 (see COVID-19 Dashboard for real-time cases: https://coronavirus.jhu.edu/map.html). Since the beginning of the pandemic, scientists have been repurposing molecules to treat, prevent, or reduce the severity of COVID-19. Melatonin is one such molecule under investigation.[1,2] Melatonin, synthesized in several tissues including the retina and immune cells, is released into the circulation primarily from the pineal gland following a circadian rhythm.[3-5] Melatonin at 0.1-10 mg promotes the onset of sleep and synchronizes circadian rhythms and related physiological functions through the activation of G protein–coupled receptors (ie, the MT_1 and MT_2).[4-9] Melatonin also has anti-inflammatory, antioxidant, analgesic, anti-anxiety, and immune-regulating properties.[3,10] Melatonin is safe, has low toxicity,[11] is readily available and inexpensive, and is amenable for the treatment of a large number of people, making it an exceptional candidate for the treatment of COVID-19.

2 | MELATONIN'S EFFECTS ON COVID-19

In an open-label uncontrolled study, high-dose melatonin (36-72 mg/d), given as adjuvant therapy to 10 patients admitted with COVID-19 pneumonia, induced clinical stabilization within 4-5 days[12] with no significant side effects except for sleepiness, which is expected as melatonin is known to promote the onset of sleep. Interestingly, a network-based drug repurposing in silico modeling platform using existing drug-target networks and the global map of the SARS-CoV-2 interactome identified COVID-19–associated proteins targeted by melatonin directly through signaling molecules (eg, calmodulin [CALM] 1 and CALM 2; calreticulin [CalR], myeloperoxidase [MPO]) or indirectly through GPCR (eg, MTNR1A, MTNR1B) and/or nuclear (eg, RORα, RORβ) receptor signaling.[1,2] Similarly, Artigas et al (2020)[13] using a systems biology and artificial intelligence–based approach identified melatonin and pirfenidone combination as modulators of COVID-19 protein targets. Findings from this study suggest that melatonin through its receptor signaling pathways inhibits immunomodulatory molecules induced in the COVID-19 cytokine storm.[13] Further, melatonin usage was associated with a 28% reduction in infection with SARS-CoV-2 and a 53% reduction in infection in the black population.[1,2] Together, evidence suggests that melatonin is a unique molecule with multifaceted pharmacological actions, targeting directly or indirectly via its GPCR and/or nuclear receptors SARS-CoV-2 associate proteins.[1,13]

2.1 | Melatonin receptors as potential targets for the treatment of COVID-19

The mechanism(s), that is, receptor vs. non–receptor-mediated, by which melatonin may modulate the immune system response to SARS-CoV-2 is still open for debate. Both membrane (MT_1 and MT_2) and nuclear (RORα/RORβ) melatonin receptors identified in target immune tissues (eg, spleen, thymus) and cells (eg, monocytes, lymphocytes, macrophages) are known to modulate immune system responses[3,10] and MT_1-mediated mitochondrial dysfunction.[14] Melatonin has been shown to suppress TLR9-triggered pro-inflammatory cytokine production in macrophages independent of melatonin receptors likely by inhibiting ERK1/2 and AKT activation[15] and by downregulating iNOS via modulation of NF-κB.[16] Melatonin at 0.25-1 mM has been shown to decrease mitochondrial dysfunction, oxidative stress, and cytokine response in human blood cells and respiratory bursts in mitochondria,[3,17] which would have a dramatic effect on its own receptor expression (ie, desensitization, internalization, supersensitization). Melatonin differentially regulates MT_1 and MT_2 melatonin receptor density and functional sensitivity depending on the cellular milieu, time of exposure, time of day, and concentration. Melatonin desensitizes and internalizes recombinant human and rodent MT_2 melatonin receptors expressed in neuronal (eg, SCN2.2) or non-neuronal (eg, CHO) cells following exposure to both physiological (3-300 pM) and supraphysiological (10 nM) concentrations of melatonin in a time-, concentration-, and protein synthesis–dependent manner.[6] Desensitization is reversible depending on exposure concentration and length of time.[6] Melatonin is also known to increase MT_1 and MT_2 receptor expression and signaling through supersensization. Prolonged exposure (eg, 8-16 hrs) of MT_1 receptors (but not MT_2) to physiological nocturnal concentrations (up to 300 pM) of melatonin increases signaling responses (eg, receptor density, forskolin-stimulated cAMP and CREB phosphorylation) only upon withdrawal, promoting gene expression (eg, per1—pars tuberalis; insulin—pancreatic β-cells).[18] MT_1 and MT_2 mRNA and protein expression in the liver is pineal-dependent and rhythmic with maximal levels at night.[19] By contrast, the expression of endogenous mRNA, protein, and/or cytoplasmic ROR/RZR nuclear melatonin receptors is low during the night, rhythmic and pineal-dependent in the liver.[19] Interestingly, melatonin (40 and 200 mg/kg) significantly enhances membrane melatonin receptor expression, with no effect on the ROR/RZR nuclear receptors.[19] Taken together, it is conceivable that the multifaceted pharmacological actions of melatonin on membrane MT_1 and MT_2 receptors, both by inhibiting and by supersensitizing signaling after exposures to either physiological or pharmacological doses of melatonin, modulate the receptor sensitivity and cellular milieu on target tissues.[5,6,18,19] We propose that at either low or high concentrations melatonin desensitizes MT_2 receptors rendering them inactive, and supersensitizes MT_1 receptors increasing signaling responses, thus generating opposite and complementary signaling.[5,6,9,18,19] The proposed mechanism(s) for melatonin-mediated signaling at MT_1 and MT_2 receptors may provide the model by which melatonin at physiological or pharmacological levels modulates a multiplicity of functions including chronobiological responses when given at specific periods of sensitivity.[10] In conclusion, melatonin through plastic changes in melatonin receptors and associated proteins may optimally shape the cellular milieu to modulate the immune response and lessen the course and severity of COVID-19.

3 | CLINICAL TRIALS USING MELATONIN FOR THE TREATMENT OF COVID-19

Currently, there are 9 clinical trial studies reported in Clinicaltrials.gov database (see https://www.clinicaltrials.gov/ for current studies), proposing melatonin (8) or a

melatonin agonist (1) for COVID-19 treatment in mild-to-moderate (4), or severe hospitalized (4), or as a prophylactic indication (1). With the exception of our two randomized, double-blind, placebo-controlled studies using melatonin in COVID-19 outpatients at the University at Buffalo, all the clinical trials listed above are testing combination drug therapy (eg, estrogen, vitamin C, pentoxifylline). It is therefore imperative to design well-controlled and powered clinical trials to test the hypothesis that melatonin is safe and efficacious to treat COVID-19. In fact, our study, currently enrolling, assesses the safety and efficacy of melatonin (9, 30, and 90 mg/day in 3 divided doses) in mitigating the COVID-19. Melatonin, if proven effective in this double-blind randomized study, could be tested in children and the elderly, as well as under-represented minorities that are disproportionately affected by COVID-19, and provide an inexpensive therapy with minimal side effects.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

JLR and MLD contributed equally to the writing and preparation of the manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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REFERENCES

1. Zhou Y, Hou Y, Shen J, Huang Y, Martin W, Cheng F. Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. *Cell Discov*. 2020;6:14.
2. Zhou Y, Hou Y, Shen J, et al. A network medicine approach to investigation and population-based validation of disease manifestations and drug repurposing for COVID-19. *PLoS Biol*. 2020;18(11):e3000970.
3. Carrillo-Vico A, Guerrero JM, Lardone PJ, Reiter RJ. A review of the multiple actions of melatonin on the immune system. *Endocrine*. 2005;27(2):189-200.
4. Arendt J, Skene DJ. Melatonin as a chronobiotic. *Sleep Med Rev*. 2005;9(1):25-39.
5. Liu J, Clough SJ, Hutchinson AJ, Adamah-Biassi EB, Popovska-Gorevski M, Dubocovich ML. MT1 and MT2 melatonin receptors: a therapeutic perspective. *Annu Rev Pharmacol Toxicol*. 2016;56:361-383.
6. Dubocovich ML. Melatonin receptors: role on sleep and circadian rhythm regulation. *Sleep Med*. 2007;8(suppl 3):34-42.
7. Dollins AB, Zhdanova IV, Wurtman RJ, Lynch HJ, Deng MH. Effect of inducing nocturnal serum melatonin concentrations in daytime on sleep, mood, body temperature, and performance. *Proc Natl Acad Sci U S A*. 1994;91(5):1824-1828.
8. Zhdanova IV, Wurtman RJ, Lynch HJ, et al. Sleep-inducing effects of low doses of melatonin ingested in the evening. *Clin Pharmacol Ther*. 1995;57(5):552-558.
9. Gobbi G, Comai S. Differential function of melatonin MT1 and MT2 receptors in REM and NREM sleep. *Front Endocrinol (Lausanne)*. 2019;10:87.
10. Cardinali DP, Brown GM, Pandi-Perumal SR. Can melatonin be a potential "Silver Bullet" in treating COVID-19 patients? *Diseases*. 2020;8(4):44.
11. Andersen LP, Gogenur I, Rosenberg J, Reiter RJ. The safety of melatonin in humans. *Clin Drug Investig*. 2016;36(3):169-175.
12. Castillo RR, Quizon GR, Juco MJM, et al. Melatonin as adjuvant treatment for coronavirus disease 2019 pneumonia patients requiring hospitalization (MAC-19 PRO): a case series. *Melatonin Res*. 2020;3(3):297-310.
13. Artigas L, Coma M, Matos-Filipe P, et al. In-silico drug repurposing study predicts the combination of pirfenidone and melatonin as a promising candidate therapy to reduce SARS-CoV-2 infection progression and respiratory distress caused by cytokine storm. *PLoS One*. 2020;15(10):e0240149.
14. Suofu Y, Li W, Jean-Alphonse FG, et al. Dual role of mitochondria in producing melatonin and driving GPCR signaling to block cytochrome c release. *Proc Natl Acad Sci U S A*. 2017;114(38):E7997-E8006.
15. Xu X, Wang G, Ai L, Shi J, Zhang J, Chen Y-X. Melatonin suppresses TLR9-triggered proinflammatory cytokine production in macrophages by inhibiting ERK1/2 and AKT activation. *Sci Rep*. 2018;8(1):15579.
16. Gilad E, Wong HR, Zingarelli B, et al. Melatonin inhibits expression of the inducible isoform of nitric oxide synthase in murine macrophages: role of inhibition of NFkappaB activation. *FASEB J*. 1998;12(9):685-693.
17. Galley HF, Lowes D, Allen L, Cameron G, Aucott LS, Webster NR. Melatonin as a potential therapy for sepsis: a phase I dose escalation study and an ex vivo whole blood model under conditions of sepsis. *J Pineal Res*. 2014;56(4):427-438.
18. Masana MI, Witt-Enderby PA, Dubocovich ML. Melatonin differentially modulates the expression and function of the hMT1 and hMT2 melatonin receptors upon prolonged withdrawal. *Biochem Pharmacol*. 2003;65(5):731-739.
19. Venegas C, Garcia JA, Doerrier C, et al. Analysis of the daily changes of melatonin receptors in the rat liver. *J Pineal Res*. 2013;54(3):313-321.

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