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La melatonina como tratamiento alternativo en tiempos de pandemia por COVID-19

Melatonin as an alternative treatment in time of COVID-19 pandemy

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RESUMEN

La melatonina o N-acetil-5-metoxiptriptamina es una hormona sintetizada a partir del aminoácido esencial triptófano fundamentalmente por las células de la glándula pineal. Las funciones de la melatonina son muy variadas y muchas de ellas todavía poco conocidas. Se ha estudiado ampliamente su efecto antioxidante, antiinflamatorio y antiviral en diferentes modelos biológicos tanto in vitro como en modelos animales. En esta mini revisión se dan a conocer las experiencias con el uso de la melatonina y se destaca s potencial uso terapeutico durante la pandemia de COVID-19 y el tratamiento de las secuelas ya ampliamente descritas.

Palabras clave: N-acetil-5-metoxiptriptamina, efecto antiviral, antiinflamación, antioxidants, COVID-19.

ABSTRACT

Melatonin or N-acetyl-5-methoxyptryptamine is a hormone synthesized from the essential amino acid tryptophan mainly by the cell of the pineal gland. The functions of melatonin are very varied and many of them are still poorly understood. Its antioxidant, anti-inflammatory and antiviral effect has been extensively studied in different biological models, both in vitro and in animal models. In this mini-review, the experiences with the use of melatonin are reported and its potential therapeutic use during the COVID-19 pandemic and the treatment of the sequelae already widely described are highlighted.

Keywords: N-acetyl-5-methoxyptryptamine, antiviral effect, anti-inflammation, antioxidants, COVID-19.

ectamente, estos mecanismos pueden re- Because SARS-CoV-2 is a new pathogen, people of all ages have no immunity to it and are generally susceptible to infection. In about 3 years, COVID-19 has spread quickly to over the world countries, infected more than 547.415.112 people of all ages, and killed at least 6.335.724 patients, mostly in The United States, Germany, France, Brazil and Italy (1). The emergence of this disease has been explained by the presence of an unknown human coronavirus (CoV) with increased virulence factors. The exponentially increasing number of cases in the world reflects in part the rapid transmission of COVID-19, which translates into a severe test for the health systems of the most affected countries. Since no specific anti-virus drugs or vaccines are available to treat this sudden and lethal disease, many drugs have been used as therapy (2).

Li et al. (3) discussed the neuroinvasive potential of SARS-CoV-2 and suggested that it may play a role in the respiratory failure of COVID-19 patients. The most characteristic symptom of patients with COVID-19 is respiratory distress, and most of the patients admitted to intensive care units could not breathe spontaneously. Additionally, some patients with COVID-19 have also shown neurologic signs, such as headaches, nausea, and vomiting. Increasing evidence shows that coronaviruses are not always confined to the respiratory tract and that they may also invade the central nervous system inducing neurological diseases. Moreover, Yang and Shen (4) discussed the importance of the endocytic pathway as well as the autophagy process in viral infection of several pathogenic CoVs inclusive of SARS-CoV, MERS-CoV and the new SARS-CoV-2, and how novel therapeutic approaches could be developed by targeting these processes to treat COVID-19.

Ben-Nathan et al. (5) showed the protective effects of melatonin in mice infected with encephalitis viruses; Then, Bonilla et al. (6) studied the mechanisms involved in this protection in animal models infected with Venezuelan equine encephalitis (VEE) virus and in vitro assays, having increased the survival rate of the mice. Melatonin has been shown to decrease brain apoptosis, oxidative stress, viral titers and CD200 expression, alone and in combination with minocycline and ascorbic acid treatment evidencing an antiviral effect involving their anti-oxidant properties (7). This protective effect seems to be due to the increase in the production of interleukin-1β (IL-1β), as 100% of the infected mice treated with melatonin die when IL-1β is blocked with antimurine IL-1β antibodies. Although melatonin administration raises serum levels of tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ), the mortality observed in neutralization experiments with the corresponding anticytokine antibodies, suggests that neither TNF-α nor IFN-γ are essential for the protective effect of melatonin on murine VEE virus infection. Melatonin treatment also enhances the efficiency of immunization against the VEE virus. Reactive oxygen species have been implicated in the dissemination of this virus, and their deleterious effects may be diminished by melatonin. This indole inhibits nitric oxide synthetase activity and it is a potent scavenger of nitric oxide, which also plays an important role in the spread of the VEE virus (8, 9).

The immunomodulatory, antioxidant, and neuroprotective effects of melatonin suggest that this indole must be considered as an additional therapeutic alternative to fight viral diseases. The potential use of melatonin has been demonstrated in respiratory syncytial virus as well (10) and its use has been proposed in humans infected with Ebola virus (11), however, Paemanee et al. (12) showed a slight proviral effect of melatonin upon dengue 2 virus infection in HEK293T/17 cells under conditions of the lowest MOI used, and the highest concentration of melatonin, but no effect was seen in HepG2 cell.

Zhang et al. (15) said that there is significant data showing that melatonin limits virus-related diseases and would also likely be beneficial in COVID-19 patients, but additional experiments and clinical studies are required to confirm this speculation.

Melatonin (N-acetyl-5-methoxytryptamine) is an endogenous indoleamine widely distributed. In vertebrates, circulating melatonin is largely derived from the pineal gland, although there are other organs such as gastrointestinal tract, epithelial hair follicles, skin, retina, salivary glands, platelets, and lymphocytes that produce melatonin (9). The maximal melatonin plasma concentration occurs usually 3–5 hours after darkness onset, and its level during the daily light period is low or even undetectable (16). Throughout life, melatonin levels are significantly reduced as well; in young children, nocturnal melatonin levels are highest (17). During aging, the amplitude of the melatonin peak and total melatonin production is significantly reduced, although there is a great interindividual variability regarding these mechanisms (18). It is important to underline that higher melatonin levels likely have important and positive roles in healthy aging and longevity. In fact, a reduction in endogenous melatonin levels throughout life seems to cause greater organism detriments (19).

This could explain why the aggressiveness of the SARS-CoV-2, is many times stronger in the elderly than in children, with all its serious consequences; in fact, most studies have demonstrated involvement of multiple lung lobes and pleural effusion associated with the severity of COVID-19, and advanced age (≥75 years) was a risk factor for mortality in China and Italy (20, 21). Recently, in a study aimed to determine the effect of melatonin on thrombosis, sepsis and mortality rate in adult patients with severe coronavirus infection (COVID-19) included 82 patients, while the control group consisted of 76 patients. In comparison to the control group, thrombosis and sepsis developed significantly less frequently ($p<0.05$) in the melatonin group during the second week of infection, while mortality was significantly higher in the control group ($p< 0.05$). Their conclusions were that adjuvant use of melatonin may help to reduce thrombosis, sepsis, and mortality in COVID-19 patients (22).

Other clinical trial study showed that the combination of oral melatonin tablets and standard treatment could substantially improve sleep quality and blood oxygen saturation in hospitalized COVID-19 patients (23). Farnoosh et al. (24) evaluated the clinical efficacy of adjuvant, use of melatonin in patients with COVID-19, and their conclusions were that the adjuvant use of melatonin has a potential to improve clinical symptoms of COVID-19 patients and contribute to a faster return of patients to baseline health. With respect the current evidence surrounding nutritional/nutraceutical approaches for the therapy in patients with COVID-19, Borges et al. (25) founded only three concluded studies that assessed zinc supplementation and melatonin therapy in patients with COVID-19, but with inconclusive data, relatively small sample size, and early termination of the trial. On the other hand, vitamin C therapy appears to reduce hyperinflammation and improve the oxygen support status of patients with COVID-19. However, a large part of this research involves pilot trials, and there are still conflicting data regarding mortality rate, mechanical ventilation, and duration of symptoms of patients with COVID-19. Melatonin, zinc, and vitamin C supplementation should be investigated further on the nutritional status-immune response, and data from ongoing trials are needed to understand these molecules as a therapy strategy in patients COVID-19.

In conclusion, again, the protective effect of MLT warrants further investigation of the possibility of using this hormone for the treatment of humans infected with different viruses, and the COVID-19, constitutes a health threat that needs to be managed.

Bibliografía

1. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. Lancet Infect Dis [Internet]. 2020 [Publication in advance]. Disponible en: https://www.thelancet.com/journals/laninf/article/PIIS1473-3099(20)30120-1/fulltext. DOI: 10.1016/S14733099(20)30120-1

2. Valero-Cedeño NJ, Mina-Ortiz JB, Veliz-Castro TI, Merchán Villafuerte KM, Perozo-Mena AJ. COVID-19: La nueva pandemia con muchas lecciones y nuevos retos. Kasmera. 2020; 48(1): e48102042020. doi:10.5281/zenodo.3745322

3. Li YC, Bai WZ, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. J Med Virol. 2020. doi: 10.1002/jmv.25728.

4. Yang N, Shen HM. Targeting the endocytic pathway and autophagy process as a novel therapeutic strategy in COVID-19. Int J Biol Sci. 2020;16(10):1724-1731. doi: 10.7150/ijbs.45498. eCollection 2020.

5. Ben-Nathan D, Maestroni GJ, Lustig S, Conti A. Protective effects of melatonin in mice infected with encephalitis viruses. Arch Virol. 1995; 140(2):223-30.

6. Bonilla E, Valero N, Pons H, Chacín-Bonilla L. Melatonin protects mice infected with Venezuelan equine encephalomyelitis virus. Cell Mol Life Sci. 1997; 53(5):430-4.

7. Montiel M, Bonilla E, Valero N, Mosquera J, Espina LM, Quiroz Y, Álvarez-Mon M. Melatonin decreases brain apoptosis, oxidative stress, and CD200 expression and increased survival rate in mice infected by Venezuelan equine encephalitis virus. Antivir Chem Chemother. 2015; 24(3-4):99-108.

8. Valero N, Mosquera J, Alcocer S, Bonilla E, Salazar J, Álvarez-Mon M. Melatonin, minocycline and ascorbic acid reduce oxidative stress and viral titers and increase survival rate in experimental Venezuelan equine encephalitis. Brain Res. 2015; 1622:368-76. doi: 10.1016/j.brainres.2015.06.034.

9. Bonilla E, Valero N, Chacín- Bonilla L, Medina-Leendertz S. Melatonin and viral infections. J Pineal Res. 2004 Mar;36(2):73-79.

10. Huang SH, Cao XJ, Liu W, Shi XY, Wei W. Inhibitory effect of melatonin on lung oxidative stress induced by respiratory syncytial virus infection in mice. J Pineal Res. 2010; 48:109–116. doi: 10.1111/j.1600-079X.2009.00733.x.

11. Tan DX, Korkmaz A, Reiter RJ, Manchester LC. Ebola virus disease: potential use of melatonin as a treatment. J Pineal Res. 2014; 57:381–384. doi: 10.1111/jpi.12186.

12. Paemanee A, Hitakarun A, Roytrakul S, Smith D. Screening of melatonin, - -tocopherol, folic acid, acetyl-l-carnitine and resveratrol for anti-dengue 2 virus activity. BMC Res Notes. 2018; 11: 307. doi: 10.1186/s13104-018-3417-3

13. Dashti-Khavidaki S, Khalili H. Considerations for statin therapy in patients with COVID-19. Pharmacotherapy. 2020. doi: 10.1002/phar.2397.

14. Favero G, Franceschetti L, Bonomini F, Fabrizio Rodella L, Rezzani R. Melatonin as an Anti-Inflammatory Agent Modulating Inflammasome Activation. Int J Endocrinol. 2017. https://doi.org/10.1155/2017/1835195

15. Zhang R, Wang X, Ni L, Di X, Ma B, Niu S, Liu C, Reiter RJ. COVID-19: Melatonin as a potential adjuvant treatment. Life Sci. 2020 Mar 23; 250:117583. doi: 10.1016/j.lfs.2020.117583.

16. Reiter RJ. The melatonin rhythm: both a clock and a calendar. Experientia. 1993; 49: 654–664. https://doi.org/10.1007/BF01923947

17. Scholtens R, van Munster B, van Kempen M, de Rooij S. Physiological melatonin levels in healthy older people: a systematic review. J Psychosom Res. 2016; 86:20-27. doi: 10.1016/j.jpsychores.2016.05.005

18. Karasek M, Reiter RJ. Melatonin and aging. Neuro Endocrinol Lett. 2002;23 Suppl 1:14-6. PMID: 12019345.

19. Hardeland R. Melatonin and the theories of aging: a critical appraisal of melatonin's role in antiaging mechanisms. J Pineal Res. 2013; 55(4):325-56. doi: 10.1111/jpi.12090.

20. Feng Y, Ling Y, Bai T, Xie Y, Huang J, Li J, Xiong W, Yang D, Chen R, Lu F, Lu Y, Liu X, Chen Y, Li X, Li Y, Summah HD, Lin H, Yan J, Zhou M, Lu H, Qu J. COVID-19 with Different Severity: A Multi-center Study of Clinical Features. Am J Respir Crit Care Med. 2020 Apr 10. doi: 10.1164/rccm.202002-0445OC.

21. Lippi G, Mattiuzzi C, Sanchis-Gomar F, Henry BM. Clinical and demographic characteristics of patients dying from COVID-19 in Italy versus China.J Med Virol. 2020. doi: 10.1002/jmv.25860.

22. Hasan ZT, Atrakji DMQYMAA, Mehuaiden DAK. The Effect of Melatonin on Thrombosis, Sepsis and Mortality Rate in COVID-19 Patients. Int J Infect Dis. 2022; 114:79-84. doi: 10.1016/j.

ijid.2021.10.012. PMID: 34653660; PMCID: PMC8506572.

23. Mousavi SA, Heydari K, Mehravaran H, Saeedi M, Alizadeh-Navaei R, Hedayatizadeh-Omran A, Shamshirian A. Melatonin effects on sleep quality and outcomes of COVID-19 patients: An open-label, randomized, controlled trial. J Med Virol. 2022; 94(1):263-271. doi: 10.1002/jmv.27312. PMID: 34460132; PMCID: PMC8662261.

24. Farnoosh G, Akbariqomi M, Badri T, Bagheri M, Izadi M, Saeedi-Boroujeni A, Rezaie E, Ghaleh HEG, Aghamollaei H, Fasihi-Ramandi M, Hassanpour K, Alishiri G. Efficacy of a Low Dose of Melatonin as an Adjunctive Therapy in Hospitalized Patients with COVID-19: A Randomized, Double-blind Clinical Trial. Arch Med Res. 2022; 53(1):79-85. doi: 10.1016/j.arcmed.2021.06.006. PMID: 34229896; PMCID: PMC8220995.

25. Borges L, Gennari-Felipe M, Dias BB, Hatanaka E. Melatonin, Zinc, and Vitamin C: Potential Adjuvant Treatment for COVID-19 Patients. Front Nutr. 2022; 8:821824. doi: 10.3389/fnut.2021.821824. PMID: 35155533; PMCID: PMC8826215.

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