Melatonin in Disease and Health

Subjects: Respiratory System

Contributor: Adam Wichniak

Melatonin is a derivative of tryptophan, synthesized mainly in the pineal gland. Its synthesis is characterized by a regular circadian rhythm, with a peak concentration in plasma reached in the night hours. The intensity of melatonin production is related to exposure to light, with an increase of its synthesis in the dark part of the day.

COVID-19 melatonin physiological effects disease progression treatment

1. Introduction

The pandemic caused by the coronavirus disease 2019 (COVID-19) increased the awareness of several health-related factors that reduce the risk of infection and decrease the likelihood of a severe course of the disease. A good sleep quality is identified among those factors, as sleep plays numerous essential functions, promoting health, regenerative, and immunomodulatory processes. Thus, a poor sleep quality impairs the immune system and increases the organism's susceptibility to infection [1]. The empirical evidence shows a link between a short sleep duration (below 6 h) before viral exposure and increased (over four times) susceptibility to developing a common cold after the administration of nasal drops containing the rhinovirus [2]. A short sleep duration was demonstrated to negatively affect antibody responses to influenza and hepatitis B vaccinations [3][4]. Taking into account that a good sleep quality also plays a crucial role in the regulation of emotions [5], the clinical data strongly support the role of educational activities and interventions aimed at improving sleep quality as essential strategies to protect society against COVID-19 and help people to cope with the stress related to the COVID-19 pandemic.

Experts in cognitive-behavioral therapy proposed several operationalized behavioral interventions to counteract the deterioration of sleep quality related to the COVID-19 pandemic. Psychological treatment aims to help people cope with the stressors associated with the COVID-19 pandemic, promote sleep regulation, focusing on homeostatic sleep drive and circadian sleep rhythm, and change negative cognitions related to the bed and the bedroom from not sleeping into reformulated cognitions linked with good quality sleep. These interventions address, first of all, the negative sleep-related consequences of home confinement due to the COVID-19 pandemic, reducing physical activity and social interactions and disturbing sleep rhythm [6]. However, despite their efficacy and general recommendations that hypnotics should be avoided, because their effectiveness is questionable and can have some side effects if taken long-term [7][6], many patients still require pharmacological treatment. One of the drugs frequently used as an alternative to hypnotics to treat sleep disturbances is melatonin, which is widely available in many countries as an over-the-counter medicine.

The high safety of melatonin treatment, the essential role of social rhythm changes, negatively influencing circadian sleep rhythm and causing deterioration of sleep quality during COVID-19 confinement, the lack of dependence risk of melatonin treatment, and the fact that melatonin has no adverse effect on respiratory drive have caused researchers and clinicians to consider melatonin not only as a recommended treatment for sleep disturbances, but also as an adjuvant treatment for COVID-19.

2. COVID-19 and Potential Clinical Applications of Melatonin

COVID-19 is a disease resulting from an infection with the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). The most frequent symptoms include fever, fatigue, anosmia with ageusia, coughing, and dyspnea, which usually occur around 3–5 days from the initial infection [8]. The spectrum of the disease is broad, ranging from true asymptomatic or paucisymptomatic infection to fatal disease complications [9]. The disease affects not only the respiratory system, but also the nervous, digestive, and circulatory systems. It may also affect the kidneys, bone marrow, and other organs [10][11]. However, respiratory tract involvement is the most common cause of death among COVID-19 patients. The mechanism of death is almost always associated with acute respiratory failure and, finally, acute respiratory distress syndrome (ARDS) [12].

To date, no effective drug against SARS-CoV-2 has been approved for human use. However, evidence-based medicine permits us develop treatment guidelines [13]. The optimal strategies based on early recognition and intervention seem to be the best option [14].

The search for new drugs and the study of the properties of the already known molecules in the fight against the COVID-19 pandemic is the subject of intensive research. While no empirical data supported by clinical trial results are available on the usefulness of melatonin in the treatment of COVID-19, the general knowledge on melatonin pharmacodynamics may facilitate its hypothesized use in the treatment of COVID-19 and promote clinical research [15]. The effects of melatonin in COVID-19 may include both the preclinical period, the acute phase of the disease, acute phase complications, and late complications of COVID-19 [16][17].

Particular attention should be paid to the possibility of using melatonin in connection with vaccination [18]. The use of melatonin in the period before falling ill could also potentially reduce the severity of the disease and increase the percentage of people who are asymptomatic and suffer a mildly advanced disease. Furthermore, the effects of melatonin may be of particular importance in people with COVID-19 lung involvement. The protective effects of melatonin on lung injury have already been reviewed [19]. Notably, the concepts of melatonin's action are based not only on its sleep-regulating effect, but also on the described anti-inflammatory, antioxidant, and immunomodulatory properties (**Table 1**).

Table 1. Potential effects of melatonin on the course of COVID-19 (modified from: [17][19][20][21]).

COVID-19 Phase	Effect of Melatonin Treatment	Recommended Dose
Prophylaxis	Circadian sleep–wake rhythm disorder treatment	0.5–5 mg
	Insomnia treatment Adjuvant to anti-SARS-CoV-2 vaccines	2–5 mg [1] 0.5–2 mg [2]
Early infection phase/mild clinical symptoms	Improvement of sleep quality Inhibition of viral invasion Free oxygen species scavenging Cytokine suppression	2–12 mg [3]
Pulmonary phase/severe clinical symptoms	Improvement of sleep quality Anti-inflammatory effects Reduction of “cytokine-storm” Protection of lungs and tissues from oxidative injury Risk reduction of ventilator-induced lung injury	2–12 mg [3,4]
Post-infection period	Improvement of sleep quality Stabilization of the disrupted circadian sleep rhythm Antioxidant properties Reduction of post-covid pulmonary fibrosis	0.5–5 mg

[1] Preferred prolonged-release form [22]. [2] high doses should be avoided, as they may decrease the immune response [18]. [3] The optimal dose is unknown due to a lack of randomized clinical trials. [4] Doses as high as 400 mg per day have also been suggested [20].

3. Physiological Effects of Melatonin Inhibiting COVID-19 Progression

Apart from its crucial function in sustaining sleep–wake rhythm, melatonin is suggested to play a role in other physiological and pathological processes, although whether this is a direct effect of this neurohormone or indirect consequence of a melatonin-driven fluctuation in the diurnal activity of the organism is still debated. Nevertheless, a significant role of melatonin is postulated, for instance, in neurodegenerative processes [23], metabolism control [24], cardiovascular disorders [25], and (which has a special meaning in the context of this review) in inflammatory diseases [26]. The last connection is additionally underlined by the fact that melatonin is produced by cells of the immune system (mononuclear cells, lymphocytes, and macrophages), stimulated by bacterial antigens [27]. Therefore, it is widely postulated that melatonin possesses anti-inflammatory potential, which may be beneficial in bacterial or viral infections.

There is a line of evidence proving that melatonin may exert anti-inflammatory action, which could hypothetically be useful in the treatment of inflammation evoked by SARS-CoV-2 infection. In this context, the following features of melatonin have specific significance: interaction with the renin-angiotensin system, suppression of proinflammatory cytokines, and antioxidant properties.

The abovementioned finding leads to the hypothesis that reducing the RAS activity, with a lower expression of ACE2 on the cell's membrane, may lower the virus's potential to invade the cell. The antagonism between melatonin and RAS was described previously, and the available clinical observations allowed researchers to coin the term, "angiotensin–melatonin axis" [28]. On the sub-cellular level, it was discovered that the surface expression of ACE2 is regulated by calmodulin [29]. Melatonin can bind calmodulin and inhibit its action [30][31]. Therefore, it is plausible that melatonin, through the inhibition of calmodulin, may reduce the expression of ACE2 and limit viral invasion, although this was not proven clinically.

All the abovementioned anti-inflammatory features of melatonin made plausible the hypothesis that it has a therapeutic role in generalized inflammation and sepsis. Indeed, in a series of experiments performed on animal models of sepsis, melatonin was proven to reduce the inflammatory response and protect tissues from oxidative injury [32][33][34]. The literature review by Biancatelli et al. [35] concluded with the suggestion that melatonin can be used in patients with severe sepsis and septic shock, albeit while emphasizing the scarce clinical evidence. So far, it was proven in an ex vivo study of blood taken from human volunteers and treated with bacterial lipopolysaccharides that melatonin causes a reduction of oxidative stress and the proinflammatory activity of cytokines [36]. Certainly, these data are not sufficient to include melatonin in the antiseptic or anti-inflammatory armamentarium, though it opens a promising area of clinical studies (**Table 2**).

Table 2. Current data on the physiological effects of melatonin, which may be beneficial in bacterial or viral infections.

In Vitro Studies	Animal Models	Human Studies
Inhibition of calmodulin [30]	Regulation of anti/proinflammatory cytokines balance [32]	Inhibition of IL-6, IL-1, TNF-alpha [37]
Inhibition of metalloproteinases [38]	Restoration of ATP production [39]	Reduction of the concentration of IL-1 beta [40]
Reduction of the production of IL-8 [41]	Organ protection [34]	Reduction of lipid peroxidation [42]

4. Protective Role of Melatonin in Lung Diseases

The fatal consequence of SARS-CoV-2 infection is pneumonia, resulting in respiratory insufficiency, and probably the most prominent long-term effect of COVID-19 is disability resulting from an injury of the lungs. Therefore, it is

noteworthy that melatonin in animal models appears to be a therapeutic/protective agent in acute and chronic pulmonary diseases.

From a clinical point of view, the crucial area for melatonin use in the treatment of severe COVID-19 is related to its action in preventing diffuse alveolar damage (DAD). DAD is considered the histological hallmark for the acute phase of acute respiratory distress syndrome (ARDS) [43]. Numerous experimental studies in animal models have shown a beneficial effect of melatonin on lung tissue [19]. It was shown that melatonin improved the histopathology of pulmonary contusion and distant organs. Ozdinc et al. [44] found that in rats treated with melatonin, histopathological changes resulting from pulmonary contusion were less severe than in non-treated animals. The authors suggested that this is the effect of the antioxidant properties of the neurohormone [44]. Moreover, melatonin reduces leukocyte and macrophage infiltration, interstitial hemorrhages, epithelial desquamation in bronchioles and alveoli, and an intra alveolar edema [45].

The other aspect is the ability of melatonin to decrease lung ischemia/reperfusion injury (LIRI). Chiu et al. [46] revealed that melatonin significantly diminished pulmonary microvascular permeability and attenuated the lipid peroxidation in the lungs. In fish, melatonin significantly inhibited the NF-kB expression and downregulated the activity of nuclear factor-erythroid-2–related factor 2 synthesis in hepatic ischemia/ reperfusion-induced lung injury [47].

Moreover, melatonin was proven to be helpful in post-radiation lung fibrosis [48]. It was also shown to inhibit apoptosis and reduce inflammation in animal models of chronic obstructive pulmonary disease (COPD) [49][50]. Melatonin also attenuates fibrotic processes in COPD [51]. Hosseinzadeh recently published a review of the evidence for a possible protective role of melatonin in idiopathic pulmonary fibrosis [52]. It was also shown that melatonin exerts a beneficial effect in experimental models of asthma by remodeling airways [53] and suppressing inflammation [54]. All of the abovementioned discoveries were recently described in animal models. Therefore, they cannot be directly translated to human medicine. Nevertheless, they are sufficient to warrant the proposal of melatonin as a candidate “pneumo-protective” drug in viral infections.

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