Review

Protection by melatonin in respiratory diseases: valuable information for the treatment of COVID-19

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ABSTRACT

High mortality rates in severe progression of COVID-19 are predominantly caused by pulmonary failure due to high-grade airway inflammation. As investigations on the efficacy of melatonin in this disease are still in their beginning, it may be worth-while to recall the body of evidence on protective effects in other respiratory dysfunctions, which have been studied pre-clinically and clinically. In various diseases and corresponding animal models, melatonin has been shown to be protective, mainly because of its anti-inflammatory and antioxidant properties. This was documented in pathologies as different as allergic airway inflammation, toxicologically or radiation-induced acute lung injury, respiratory disorders such as COPD, obstructive sleep apnea, neonatal respiratory distress syndrome, bronchopulmonary dysplasia and asphyxia, impaired respiration in sepsis, idiopathic pulmonary fibrosis, and pulmonary hypertension. The prevailing outcome has been protection or amelioration by melatonin, in conjunction with reduced expression and release of proinflammatory cytokines, such as IL-1β, IL-2, IL-6, IL-8, and TNFα, which was often explained by interference with toll-like receptors, inhibition of NLRP3 inflammasome activation and suppression of NF-κB signaling. In several studies, these beneficial effects were partially related to the upregulation of sirtuin-1 (SIRT1) by melatonin. The body of knowledge on melatonin's efficacy in respiratory diseases is encouraging for the use of this powerful agent in COVID-19.

Key words: airway inflammation, COPD, COVID-19, cytokines, fibrosis, lung injury, melatonin, pulmonary hypertension, sirtuin-1.

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1. INTRODUCTION

The actual, sometimes desperate combat against COVID-19 requires effective strategies for bridging the time until the availability of an effective and well-tolerated vaccine. Several anti-viral drugs are meanwhile under investigation, but it will also take considerable time to test their suitability and tolerability at required doses. A presumably recommendable agent could be melatonin, which has been shown to be effective in suppressing overshooting inflammation under many conditions, including viral and bacterial infections (1, 2). As the severe forms of disease progression in COVID-19 are associated with high-grade airway inflammation leading

to pulmonary failure and a frequently fatal outcome, the available information on melatonin's action in respiratory diseases should be of particular value for assessing the presumed suitability of this agent in the treatment of this worrying condition. This review summarizes the most relevant details of melatonin's efficacy in pulmonary diseases and dysfunction, with focus on the mechanistic basis.

2. PRE-CLINICAL FINDINGS IN AIRWAY INFLAMMATION

Because of the meanwhile established relationship between melatonin and suppression of overshooting inflammation (1-4), the first look has to concern effects of melatonin treatment in experimental airway inflammation (Table 1). This contains also several findings on lung injury that likely comprise an inflammatory aspect. Most remarkably, melatonin proved to be protective under numerous conditions, by challenges as different as allergens, toxins, a mechanically acting irritant, the potent inducer of inflammation LPS, ionizing radiation, different methods of hypoxia, but also acute respiratory distress syndrome induced by100% oxygen, and finally, infection of cultured macrophages with the respiratory syncytial virus. Regardless of the differences in species, challenges and methods, the outcome has typically been rather similar. It often consisted in suppression of toll-like receptor (TLR) signaling, prevention of NLRP3 inflammasome activation and downstream actions of NF-κB. As a consequence, expression and/or release of proinflammatory cytokines, especially TNFα, IL-1β, IL-6, and iNOS expression were reduced. In addition, antioxidative protection by melatonin and tissue preservation were repeatedly observed in these studies. Another remarkable fact has also become evident in some more recent investigations, namely, the involvement of SIRT1 in several of melatonin's actions. Increasing evidence indicates that several of melatonin's effects are mediated by sirtuins, most often demonstrated for SIRT1, in cases in which changes induced by melatonin were blocked by sirtuin inhibitors such as EX527 or sirtinol (3, 4, 27-30). These observations have given rise to the conclusion that melatonin signaling is not restricted to its proximate effects transmitted by MT_1/MT_2-coupling G proteins, but comprises actions of sirtuins in terms of an extended or secondary signaling (29, 30). Notably, SIRT1 displays several antioxidant and anti-inflammatory properties that are reminiscent of melatonin's actions and seem to complement them. The SIRT1 connection has been also observed in a rat COPD model, in which melatonin attenuated ER stress and reduced apoptosis (31). Corresponding results were obtained in a study in human bronchial epithelial cells exposed to a cigarette smoke extract (32). The anti-inflammatory actions of melatonin have been confirmed in a COPD model using acrolein exposure of human pulmonary fibroblasts, in which iNOS, IL-1β, and IL-6, Il-8 were downregulated, whereas antioxidant factors such as GSH and SOD were upregulated (33). More details have been summarized elsewhere (34). Another specific, but, in practical terms, important aspect of COPD and other respiratory disorders concerns the overproduction of mucus. In both human mucoepidermoid carcinoma cells and in a murine model of allergic asthma using ovalbumin as allergen, melatonin reduced the production of a major mucin constituent, MUC5AC (35).

Other aspects of respiratory disorders that are associated with oxidative stress and shown to be mitigated by melatonin concern lung fibrosis, vasodilation and microvascular pathologies. These were studied in models of obstructive sleep apnea by applying intermittent hypoxia to mice (36) and Syrian hamsters (37). In a rat model of hepatopulmonary syndrome induced by biliary duct ligature, melatonin did not only attenuate the aforementioned symptoms, but also

improved the gas exchange (38). Beneficial effects of melatonin were also observed in a murine model of idiopathic pulmonary fibrosis using bleomycin as a fibrotic inducer (39). Further details have been reviewed elsewhere (40).

Table 1. Protective actions of melatonin in experimental airway inflammation.

Organism/cells	Damage	Main effects of melatonin	Refs.
Mouse	Allergic airway inflammation by ovalbumin (OVA)	Reduced expression of TLR2 and NLRP3, reduced proinflammatory cytokines and inflammation	(5, 6)
Rat	Lung inflammation by aerosolized pancreatic fluid	Reduction of iNOS, nitrotyrosine, MPO, TNFα, neutrophil counts, airway obstruction and hyperreactivity	(7)
Mouse	Formaldehyde and diisononyl phthalate (murine asthma model); sensitization by OVA	Inhibition of asthmatic symptoms; reduced neuroinflammation; inhibition of NF-κB signaling and decreased IL-1β and IL-17 levels	(8, 9)
Rat	Airway inflammation by cigarette smoke, LPS (COPD model)	Upregulation of SIRT1; reduced NLRP3 activation and IL-1β (inhibited by EX527)	(10)
Mouse	Lung inflammation by LPS + sleep deprivation	Reduced alveolar damage, apoptosis and MDA	(11)
Guinea pig	Particulate matter 2.5	Reduced lung inflammation and cough	(12)
Rat	CCl_4	Reduced inflammation, macrophage infiltration, NO, oxidative damage; enhanced GSH and catalase	(13, 14)
Mouse	$K_2Cr_2O_7$	Upregulation of SIRT1 causing Nrf2 signaling, expression of antioxidant enzymes and reduced inflammation	(15)
Rodents	Sulfur mustard	Protection of lung tissue	(16)
Rat	Nitrogen mustard (mechlorethamine)	Reduction of IL-1β	(17)
Rat	Phosgene	Reduced MDA, iNOS, NO, MPO and p-p38 positive infiltrating inflammatory cells	(18)
Rodents	Ionizing radiation	Reduced inflammation and infiltration of inflammatory cells	(19, 20)
Rat	Acute respiratory distress syndrome by100% oxygen	Reduced expression of NF-κB, TNFα, and attenuated oxidative stress, mitochondrial damage and apoptosis	(21)
Rat	Chronic hypoxia	Reduction of TNF-α, IL-6, CRP and pulmonary hypertension	(22, 23)
Mouse	Lung ischemia-reperfusion injury	Reduced NF-κB, TNFα, IL-1β, and apoptosis; improved tissue preservation	(24)
RAW264.7 macrophages	Infection with RSV (respiratory syncytial virus)	Reduction of TLR3-mediated NF-κB signaling, decreased TNFα and iNOS	(25)
HEp-2 cells	*Chlamydophila pneu-moniae* or *C. felis* infections	Limited infection	(26)

Two recent pre-clinical studies concern protection by melatonin in the perinatal phase of lambs (41, 42) and are of particular interest to corresponding investigations in humans (cf. subsequent section). Melatonin was administered to lambs born at an altitude of 3,600 meters, i.e., under hypobaric conditions, between 4 and 21 postnatal days (41). In these animals, melatonin enhanced the expression of prostacyclin synthase mRNA and prostacyclin receptor at protein level, components of a vasodilator pathway, whereas vasoconstriction via the thromboxane pathway was not affected. Moreover, COX-2 expression was decreased, which may indicate reduced pulmonary inflammation. Pregnant ewes kept at 3,600 meters altitude were treated during days 100-150 (last third of gestation) with melatonin (42). The newborn lambs exhibited higher antioxidant capacity in the blood plasma, but not in lung, in which they showed lower levels of 4-hydroxynonenal and nitrotyrosine, indicating lower oxidative and nitrosative stress (42).

3. CLINICAL EVIDENCE

The quantitatively most comprehensive studies in humans concern the protective effects of melatonin in newborns and preterm infants, which have already been multiply reviewed (43-51). Therefore, these results will not be discussed in every detail, but only emphasis will be put on findings related to melatonin's anti-inflammatory and antioxidant actions. In asphyxiated newborns, melatonin reduced blood MDA levels and the NO metabolites nitrite/nitrate (44, 47, 52). In surgical neonates, who needed correction of malformations and exhibited, in a number of cases, respiratory distress, melatonin reduced NOx, IL-6, IL-8 and TNFα (53). Similar results were obtained in preterm infants with respiratory stress syndrome (54, 55), in the latter study based on cohorts of 120 children (60 melatonin, 60 placebo). These findings are reminiscent of other studies on melatonin in neonatal pathologies (46), especially sepsis (50, 56, 57). The efficacy and tolerability of melatonin in neonates is under two aspects particularly remarkable. First, it should be noted that the secretion of melatonin is negligibly low in the first days after birth (58). Second, it is far from being self-evident that melatonin is free of adverse effects in this especially vulnerable phase of human life, even in the preterm infants.

The body of evidence for beneficial actions of melatonin in adults with respiratory problems is even smaller. Although COPD is nowadays a frequent pathology, clinical data on the use of melatonin are rare. In a randomized, double-blind, placebo-controlled study (59), melatonin was shown to reduce the levels of 8-isoprostane as a marker of oxidative stress and IL-8. Moreover, improvements of dyspnea were reported. Other melatonin-related clinical studies on COPD did not focus on aspects of major relevance to respiratory problems, but rather concerned sleep disturbance and circadian issues. The same can be stated for another frequent breathing disorder, obstructive sleep apnea (OSA), which was, however, found to be associated with dysphased circadian melatonin rhythms (60), perhaps a hint for melatonin dysfunction. Although the melatonin effects on sleep are presumably not central to severe inflammatory pathologies of the respiratory tract, a respective study on melatonin in COPD had, in fact, been conducted in intensive care patients, though with the aim of resynchronizing the circadian system (61). Authors indicated an improved sleep that may have supported processes of healing. As various respiratory disorders are associated with lung fibrosis, effects of melatonin would also be of interest. Although oxidative and nitrosative stress as well as inflammation are involved in its pathogenesis, the assumed utility of melatonin (62, 63) has not yet reached the required clinical level. Another disease that affects the lung, but also other organs, and causes

respiratory problems, sarcoidosis, has been successfully treated with melatonin (64, 65), although a broader basis would be desirable.

Although these findings do not provide direct information on SARS-CoV-2, they can be regarded collectively as a sufficiently broad basis that justifies the use of high-dose melatonin for the treatment of other diseases, especially in cases in which no approved pathogen-eliminating or entrance-inhibiting drug is available and in which a serious disease progression is possible or even developing in a patient. This is the actual situation with COVID-19. In addition to the more numerous pre-clinical data, the clinical findings clearly demonstrate that melatonin is extremely well-tolerated at high doses far beyond those approved for other treatments such as sleep initiation, sleep quality, and circadian readjustments. The concerns that had limited the approved doses for such purposes and the admitted age of treatment were mainly caused by overcautious fears related to reproduction physiology, development and assumed problems in age-related malfunction of organs as well as reduced melatonin catabolism by drugs interfering with cytochrome P_{450} (CYP) enzymes (66). However, all these concerns are without validity in cases of life threatening diseases: [1] Contrary to the above-mentioned applications, treatment duration will not exceed a few weeks in diseases like COVID-19. [2] High doses of melatonin have been shown to be well-tolerated in clinical settings. In seriously diseased patients with ALS, 300 mg daily were given as suppositories for up to two years, without substantial adverse effects (67). [3] The concern related to increased melatonin levels in connection with CYP inhibiting drugs may have been relevant to all-day functioning of individuals in normal life, but not in heavily diseased patients, perhaps treated in an intensive care unit. [4] In these patients, reproduction biology is not of importance relative to the aim of rescuing them. Even if they are middle-aged or younger, they will recover from the few weeks under melatonin medication. [5] The experience in neonatology clearly shows that a temporally limited treatment with melatonin is not harmful in developmental terms.

Most importantly, the clinical data show that melatonin can be successfully used in various respiratory diseases of different etiology. With regard to the particular respiratory problems in the serious forms of disease progression in COVID-19, the findings summarized in this section are encouraging for the use of melatonin in the combat against SARS-CoV-2.

4. THE RELEVANCE OF ANTI-INFLAMMATORY AND ANTIOXIDANT TREATMENT OF RESPIRATORY DISEASES AND THE RELATIONSHIP TO COVID-19

The suitability of melatonin in treating respiratory diseases and disorders, as summarized in this article, has a profound basis on two properties of this agent, its anti-inflammatory and antioxidant actions. Some of these properties are certainly mediated by melatonin receptors such as MT_1 and MT_2. This would only require low concentrations of melatonin, according to the receptor affinities in the range of circulating melatonin concentrations. This may be also the case in the indirect antioxidant actions of melatonin via upregulation of antioxidant enzymes. Elevated doses as required for successful treatment of respiratory diseases and, as far as can be actually judged, in COVID-19, would make melatonin available for extended periods to overcome the short half-life on melatonin in the circulation. If this were the only reason, it would not be that much convincing. However, at strongly elevated doses of several hundred milligram per day, melatonin's direct antioxidant activities, which are of minor importance at nanomolar concentrations, gain higher relevance. This concerns particularly the scavenging of

reactive oxygen and nitrogen species (ROS, RNS) (68-71). In the first line, this will presumably concern the hydroxyl radical (68-70). However, another radical that is frequently overlooked, may be of specific relevance under conditions of impaired respiration, the carbonate radical, which is also oxidizing and likewise scavenged by melatonin (72, 73). Among several possibilities of formation, its mitochondrial generation may be the most important one. Under conditions of reduced gas exchange, the organism tries to enhance the arterial blood supply by producing the relaxant NO at higher rates. At the same time, the hypoxic condition can impair the mitochondrial electron flux and cause electron dissipation, which results in superoxide formation. In the presence of high NO concentrations, superoxide combines with NO to peroxynitrite ($OONO^-$), which forms in the presence of high CO_2, due to mitochondrial formation and also to hypercapnia, an adduct ($OONOCO_2^-$) (73). This decomposes readily into NO_2 and the carbonate radical, $CO_3^{\bullet-}$. Many oxidative reactions have been shown to be strongly enhanced by the presence of CO_2/HCO_3^-, via the formation of carbonate radicals. Interestingly, melatonin does not only scavenge this oxidant, but also reduces its formation, by improving the mitochondrial electron flux and, thereby, decreasing superoxide generation. If additional sources of NO are operating, such as iNOS under inflammatory conditions, the downregulation of iNOS (74-76) by melatonin is another mechanism that reduces the formation of carbonate radicals (73). Generally, the protection of mitochondria by melatonin, from the prevention of bottlenecks in the electron transport chain that cause enhanced free radical formation, control over duration of permeability transition pore opening, maintenance of intramitochondrial redox balance to the support of mitochondrial integrity, represents a field of premier relevance to the return to a healthy state (77-85), in particular, with regard to respiratory diseases including the severe forms of COVID-19.

The anti-inflammatory and antioxidant properties of melatonin are also of substantial interest to pulmonary functioning under intensive care conditions. Artificial ventilation of patients bears the problem of causing undue mechanical stress to the lungs. Ventilator-induced lung injury has been shown to initiate oxidative stress and inflammation. In a murine model, melatonin increased the level of the anti-inflammatory IL-10, along with improved oxygenation and reduced histological damage to the lungs (86). A recent study on ventilator-induced lung injury in rats using the melatonergic agonist ramelteon showed strong reductions in the oxidative markers MDA and protein carbonyl, reduced edema, neutrophil infiltration and apoptosis, decreased NF-κB activation and iNOS expression, lower levels of TNFα, IL-1β, IL-6, and the chemokine CXCL-1 but increased IL-10 levels in the broncheoalveolar lavage fluid (87). Another practical problem in patients with severe COVID-19 concerns reductions of pulmonary gas exchange due to surfactant impairments by lipid peroxidation, as caused by infiltrating neutrophils. In vitro experiments have shown that melatonin can associate with surfactant lipids (88) and also reduces their peroxidation (89).

The anti-inflammatory actions of melatonin are also, in part, associated with mitochondrial functions, as recently outlined in the context of COVID-19 (1). The protective mechanisms by which melatonin acts, especially under conditions of high-grade inflammation and in aging, have been repeatedly reviewed (3, 4, 90). A particular aspect that has emerged during the last years concerns the involvement SIRT1 in melatonin's anti-inflammatory actions (3, 4, 27-30). An overview over the most important anti-inflammatory mechanisms of melatonin is provided in Fig. 1.

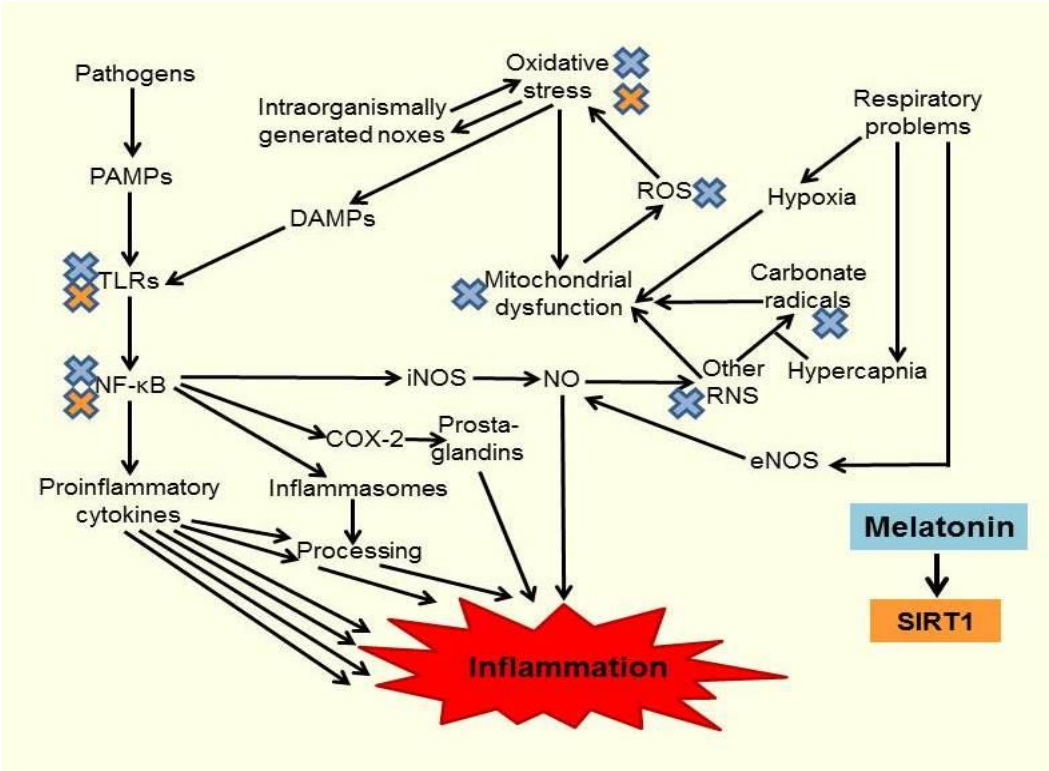

Fig.1. The vicious network of inflammation, contribution of respiratory malfunction, and the multiple ways of interruption by melatonin.

For reasons of reducing complexity, a simplified scheme is presented. Other details, especially on signaling routes and factors involved can be found elsewhere (3, 4). *Additionally, melatonin's actions of changing macrophage polarity from the proinflammatory type M1 to the anti-inflammatory type M2 should be noticed* (91). *Abbreviations: COX-2, cyclooxygenase-2; DAMPs, damage-associated molecular patterns; TLRs, toll-lile receptors; for other abbreviations see current text. Blue crosses indicate inhibition or elimination by melatonin, orange-colored crosses inhibition by SIRT1.*

5. CONCLUSION

Melatonin has been shown to be highly effective in treating respiratory diseases, in both animal models and in clinical settings. The information concerning humans is relatively broad in neonates, but would require extended studies in adults. However, the collective body of evidence should be seen as being strongly encouraging for translating these findings to other diseases that cause high-grade inflammation and pulmonary symptoms, in particular, to COVID-19, in which rapid success in efficient therapies is urgently needed with regard to the dramatically increasing numbers of lethal outcomes. Other reasons supporting this conclusion concern melatonin's efficacy in protecting against various viral diseases, including several by (+)ssRNA viruses, a category to which coronaviruses belong (1, 2). The relationship between viral and non-viral respiratory diseases has to be seen in their inflammatory aspect. The multitude of different pathologies that are treatable by melatonin indicates that its main effects are not due to specificity against certain pathogens, but rather to the common potential of suppressing high-grade inflammation. This does not exclude that melatonin could have some additional virus-directed properties, which are under investigation by other researchers, but this

would require convincing evidence that cannot be expected in the actual state. The exceptional tolerability of melatonin allows treatments with high doses and preliminary evidence on successful treatments of COVID-19 patients with respiratory problems may indicate this can be a preferable way of proceeding as long as no vaccine or approved anti-viral drug is available (92). As soon as such a drug will be in use, melatonin may also be a valuable medicament for an adjunct therapy.

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AUTHORSHIP

RH and DXT both wrote and edited this article.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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