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REVIEW ARTICLE

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Prognostic Value of Melatonin in Patients with Chronic Obstructive Pulmonary Disease

Andrey V. Budnevsky[1], Sergey N. Avdeev[2], Evgeniy S. Ovsyannikov[1], Karina V. Vostrikova[1], Sofiya A. Budnevskaya[1], Avag G. Kitoyan[1]

[1]*Voronezh State Medical University named after N.N. Burdenko, Voronezh, Russia*
[2]*I. M. Sechenov First Moscow State Medical University (Sechenov University), Moscow, Russia*

Abstract

The article outlines a detailed examination of multiple scientific studies investigating how melatonin affects COPD's advancement and growth. The severity of oxidative stress in COPD, a complex disease with multiple factors, is significantly reduced by melatonin by activating intracellular antioxidants, as suggested by the data acquired. Considering the available data, we can conclude that melatonin has a protective role against oxidative stress in COPD patients in addition to regulating the circadian rhythm.**(International Journal of Biomedicine. 2024;14(2):227-230.)**

Keywords: COPD • oxidative stress • reactive oxygen species • melatonin

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Abbreviations

COPD, chronic obstructive pulmonary disease; **CAT,** catalase; **GLT**, glutathione; **MDA**, malondialdehyde; **ROS**, reactive oxygen species; **SOD**, superoxide dismutase.

Introduction

Chronic obstructive pulmonary disease (COPD) is recognized by the WHO as a leading cause of death worldwide, with an estimated 3 million people falling victim to it annually. According to Rosstat, COPD accounts for 14.1% of the morbidity structure and 26% of the mortality structure. [1-4] By the year 2060, it is projected that there will be a staggering 5.4 million deaths annually from COPD and related illnesses due to the rise in smoking rates in low- and middle-income countries and to the growing number of elderly patients in high-income nations.

In the pathogenesis of COPD, oxidative stress plays a crucial role as it disrupts the delicate equilibrium between antioxidants and oxidants. Reactive oxygen species (ROS) are generated by electron leakage from the electron transport chain within mitochondria, which is a natural occurrence. However, a myriad internal and external factors intensify this phenomenon.[5]

Mitochondria are key regulators of metabolism, redox homeostasis, and cell proliferation. An imbalance in COPD has been determined at the level of various tissues: alveolar cells, epithelial cells of lung tissue, smooth myocytes of the respiratory tract, alveolar macrophages, striated muscles, mesenchymal stromal cells, and progenitor cells.[6]

External factors such as smoking and air pollution, and internal factors (ROS released by inflammatory cells, especially neutrophils and macrophages), can lead to oxidative stress in the lung tissues.[7] Oxidative stress damages all structural components of the lungs and leads to irreversible changes in the pulmonary parenchyma, respiratory tract, and pulmonary vessels.[8]

***Corresponding author**: Karina V. Vostrikova. Department of Faculty Therapy of the Voronezh State Medical University named after N.N. Burdenko. Voronezh, Russia. E-mail: prudnikova.2012@inbox.ru*

The most studied mechanisms of oxidative stress's influence on the body of patients with COPD are excessive formation of ROS and reactive nitrogen species and a decrease in the activity of enzymes in the antioxidant system. Oxidative stress in COPD is one of the factors that support chronic inflammation and cellular aging and disrupt autophagy by ROS, which leads to decreased DNA repair, increased autoimmune reactions, increased mucus production, and a weakened anti-inflammatory response.[9]

Patients with COPD showed a significant rise in oxidative stress markers, with a notable increase in MAD, a decrease in SOD, and a substantial elevation in ROS content. This contrasted sharply with the control group, indicating a clear imbalance in the antioxidant defense system of individuals with this respiratory condition.[10] The development of endothelial dysfunction and thromboembolic complications is directly linked to the level of fibrinogen in the blood, as has been illustrated by the correlation of ROS values.

Activation of autophagy by ROS promotes cell adaptation, reducing the circulation of damaged macromolecules and dysfunctional cellular organelles. Oxidative stress causes changes in signaling pathways, which ultimately regulate autophagy. The important role of autophagy in the pathogenesis of COPD as a response to oxidative stress has been highlighted. Exploring the mechanisms of oxidative stress and autophagy in COPD is crucial to pave the way for innovative treatment options tailored to combat this illness. The focus should be on uncovering novel insights that can guide future research in this field.[11]

Autophagy is an important process in which cells break down parts of themselves inside. This process supports cell survival and homeostasis by removing molecules, mainly proteins, damaged organelles, and cytoplasmic macromolecules, as well as processing product decay. One of the special forms of autophagy is the selective removal or degradation of mitochondria. Various forms of cellular stress, such as oxidative stress, hypoxia, and pathogenic infections, can affect autophagy, causing the formation of free radicals and reactive oxygen species, which, in turn, stimulate the antioxidant response.[12]

Mast cells are known to play a crucial role in shaping the microenvironment of tissues, impacting diverse physiological and pathological functions within the organism. By releasing tryptase and/or chymase, mast cells actively modulate inflammatory processes, promote the formation of new blood vessels, cause allergic reactions, and influence cancer-related activities. Research using laboratory cell cultures and living organisms has highlighted the vital role of reactive oxygen intermediates in controlling the release of mast cell granules.[13]

It was found that hospitalized patients with COPD showed increased levels of MDA, protein products of increased oxidation, and total oxidative status. At the same time, SOD activity was significantly lower both during hospitalization and at discharge.[14]

As the condition of patients suffering from COPD worsened, a decrease in the level of catalase (CAT) and glutathione (GLT) activity and an increase in the level of MDA was noted.[15] The Tiffeneau index (FEV1/FVC) in patients is positively correlated with the activity of CAT and SOD and negatively with the level of MAD, which confirms the presence of an oxidant-antioxidant imbalance in COPD patients and emphasizes the importance of glutathione peroxidase in maintaining lung function.

During the various stages of COPD progression, a notable variance in the indicators of oxidative stress has been was observed. In patients with mild to moderate COPD, the levels of CAT, SOD, and glutathione peroxidase were found to be significantly decreased, compared to those with the most severe form of the disease. The study's findings suggest a correlation between the extent of oxidative stress and COPD severity.[16]

Sotgia et al.[17] assessed the blood concentration of the total and reduced forms of the low-molecular-weight thiol antioxidant glutathione in COPD patients, compared with healthy people. The control group showed a markedly higher level of glutathione thiol, compared to the patients, as indicated by recent findings.

Initially, the release of ROS from mitochondria triggers a stress response in the respiratory tract's epithelial cells, causing oxidative damage to membranes and organelles. Furthermore, damage occurs to DNA and proteases. Mitochondrial antioxidants and DNA are involved in activating the NLRP3 inflammasome, along with the DNA sensors cyclic GMP-AMP synthase and a stimulator of interferon genes (STING). These activations accelerate cell death pathways, including caspase activation, leading to inflammation and increased alveolar septa destruction, remodeling, and fibrosis.[18]

Systemic inflammation, which develops during long-term COPD, is also a pathogenetic mechanism for the development of coronary artery disease. A high concentration of systemic inflammation markers is associated with worsening atherosclerosis, the development of its complications, and the progression of coronary artery disease.[19]

Over the past 15 years, attention has been focused on the intimate link between COPD and cardiovascular disease as a key component of the broad range of effects COPD has on the body. The enduring presence of a mild, chronic inflammatory response throughout the body in COPD patients is the primary factor behind the elevated occurrence of cardiovascular disease in this group.[20]

Chronic heart failure (CHF) and COPD are characterized by widespread prevalence and high mortality, especially when combined. Diagnosing comorbidity of CHF and COPD can pose challenges due to the overlap in risk factors, shared disease pathways, and similar symptomatology. Nevertheless, enhancing diagnostic accuracy and optimizing outcomes for these individuals is achievable.[21]

It is known that melatonin can restore the structural and functional organization of damaged lung tissue through several mechanisms, including the regulation of signaling molecules, oxidative status, lipid homeostasis, and support of optimal mitochondrial membrane potential. The role of melatonin in various lung diseases is believed to be linked to its interaction with the alpha-7 nicotinic receptor and the aryl hydrocarbon receptor, which together regulate mitochondrial function and integrate the effects of this hormone.[22] The mechanism of the

antioxidant action of this hormone is its ability to bind free radicals and exogenous carcinogens.[23] At the same time, by activating several enzymes, melatonin is able to enhance the formation of glutathione as well as increase the activity of SOD and CAT. Due to this, the balance between antioxidant and prooxidant enzymes ultimately shifts towards antioxidants.[22]

A study by Morvaridzadeh et al.[24] confirmed the relationship between melatonin consumption and a significant increase in the body's total antioxidant capacity. COPD patients experienced a notable rise in the levels of glutathione, SOD, glutathione peroxidase, and glutathione reductase, alongside a reduction in MDA. In addition to the fact that exogenous melatonin helps reduce the intensity of oxidative stress and the severity of shortness of breath in COPD, it also inhibits phosphorylation of ERK kinase and Sp1 expression and reduces the level of 8-isoprostane by 1.6 times.[25]

In vivo and in vitro, the observed protective effect of melatonin on damaged lung tissue is clearly evident.[26] The melatonin effect is to weaken the inflammatory process in the lungs. It activates intracellular Trx1, inhibits TXNIP/NLRP1, and inhibits impaired mitophagy mediated by inflammasome activation. PINK-1, a protein that regulates autophagy and is linked to microtubules (LC3B-II), demonstrates a rising expression level. Melatonin also improves the overall antioxidant status of the lungs in COPD by restoring the transcription factor NRF-2-HO-1.

A new target of melatonin is the NLRP3 inflammasome, which promotes increased IL-1β levels, activation of caspase-1, and stimulation of pyroptosis. By inhibiting NLRP3, melatonin reduces inflammation and affects various molecular pathways, such as SIRT1, microRNA, long non-coding RNA, and Wnt/β-catenin.[27]

In a study conducted on rats,[28] the influence of melatonin on the progression of COPD was confirmed, showing its ability to reduce the functioning of the NLRP3 and IL-1β inflammasomes. Additionally, an increase in SIRT1 levels was noticed in the lung tissues of rats with COPD, indicating a decrease in the protective effects of melatonin against COPD when SIRT1 activity was suppressed.

In addition to the antioxidant effects of melatonin, there is evidence of the potential benefit of melatonin in reducing the severity of COPD symptoms by improving sleep quality. Melatonin significantly improved Pittsburgh Quality of Life Index (PSQI) scores, especially sleep quality, duration, and efficiency. During the daytime, there was no observable discrepancy in levels of drowsiness, lung capacity, or oxygen saturation.[29]

Correction of sleep disturbances with the use of melatonin in elderly patients with COPD increased the effectiveness of its treatment and reduced the frequency and duration of exacerbations, as well as the number of outpatient visits and hospitalizations.[30] In addition, several studies have assessed the effectiveness of integrating patient education, smoking cessation, exercise training, and nutritional interventions into standard COPD therapy. Results showed significant reductions in COPD exacerbations, hospitalizations, and symptom severity, as well as improvements in quality of life and exercise capacity.[31]

Considering the available data, we can conclude that melatonin has a protective role against oxidative stress in COPD patients in addition to regulating the circadian rhythm.

Competing Interests

The authors declare that they have no competing interests.

Disclaimer

We state that the views expressed in the submitted article are ours and not an official position of the institution or funder.

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