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Review Article

Current Position and Future Perspectives of Melatonin and Its Supplements in Pulmonary Hypertension

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Abstract

Melatonin, which is secreted principally by the pineal gland at night, affects several cardiovascular conditions including arterial hemodynamics, right ventricle functions, and pulmonary artery functions. Pulmonary hypertension is a hemodynamic and pathophysiological condition defined as an increase of average pulmonary artery pressure exceeding 20 mmHg at rest. In the light of the literature data, as discussed in this study, melatonin and its supplements may play a role in the pathogenesis and treatment of pulmonary hypertension.

Keywords: Inflammation; melatonin; pulmonary hypertension; supplement.

Pulmoner Hipertansiyonda Melatonin ve Takviyelerinin Mevcut Konumu ve Geleceğe Yönelik Perspektifleri

Özet

Esas olarak geceleri epifiz bezinden salgılanan melatonin, arteriyel hemodinami, sağ ventrikül fonksiyonları ve pulmoner arter fonksiyonları dahil olmak üzere birçok kardiyovasküler durumu etkiler. Pulmoner hipertansiyon, istirahatte ortalama pulmoner arter basıncının 20 mmHg'yi aşması olarak tanımlanan hemodinamik ve patofizyolojik bir durumdur. Literatür verileri ışığında, bu çalışmada da tartışıldığı gibi, melatonin ve desteklerinin pulmoner hipertansiyon patogenez ve tedavisinde rol oynayabileceği düşünülmektedir.

Anahtar sözcükler: Inflamasyon; melatonin; pulmoner hipertansiyon; takviye.

Introduction

Pulmonary hypertension is characterized by an average pulmonary artery pressure exceeding 20 mmHg at rest.[1] Multiple molecular pathways, vasoconstriction, endothelial and smooth muscle proliferation and dysfunction, inflammation, and thrombosis collectively contribute to increased pulmonary vascular resistance and subsequent elevation of pulmonary arterial pressure.[2,3]

Melatonin is a hormone produced by the pineal gland, chemically known as N-acetyl-5-methoxytryptamine. It physiologically exhibits varying concentrations in serum and possesses anti-apoptotic, anti-oxidant, anti-inflammatory, and vasodilator effects. The anti-inflammatory effects of melatonin arise from the inhibition of cytokine release (including tumor necrosis factor-α, interleukin-1β, and interleukin 6) and aggregation of inflammatory cells.[4] These effects of melatonin may inhibit pulmonary hypertension progression and ameliorate right ventricular dysfunction.

In a prospective cohort study, it has been demonstrated that lower plasma melatonin levels at the time of diagnosis predict worse long-term survival in pulmonary arterial hypertension (PAH) patients.[5] Thus, the study suggests that melatonin may play a role in the prognosis of PAH patients.

Maarman et al.[6] demonstrated in a pre-clinical study that chronic melatonin therapy (75 ng/L or 6 mg/kg) reduced right ventricular hypertrophy, improved right ventricular function, decreased

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plasma oxidative stress parameters, and reduced cardiac interstitial fibrosis. Similar results have been observed in two different pre-clinical studies, indicating that melatonin slows the progression of PAH and improves right ventricular function. These studies have shown that melatonin's properties in reducing oxidative stress, pulmonary edema, vascular remodeling, vasoconstriction, and inflammation have an impact on PAH.[7,8] Hung et al.[7] confirmed the presence of melatonergic receptors in the pulmonary trunk of rats and suggested that the vasoreactive effect of melatonin is not mediated through the nitric oxide pathway. The findings from this study indicate that the loss of vasorelaxant effect of melatonin may be influential in the development of pulmonary hypertension.[9] In a previous study, it has been demonstrated that melatonin plays a role in gene regulation through the MT-1 receptor, whereas the MT-2 receptor is implicated in vasodilation.[10] In a study conducted with rats having hypoxia-induced pulmonary hypertension, it has been demonstrated that melatonin reduces hypoxia-induced inflammation and pulmonary arterial smooth muscle proliferation, and it is acknowledged as a potential preventive agent against hypoxic pulmonary hypertension.[11] In a study conducted in 2015 with newborn sheep with pulmonary hypertension, it was found that daily melatonin administration (1 mg/kg/day) for 8 days reduced pulmonary oxidative stress markers and increased anti-oxidant capacity in the group receiving melatonin. In addition, it was observed that these effects were associated with an increase in pulmonary artery lumen diameter and a mild decrease in pulmonary artery wall thickness.[12]

The doses of melatonin given in pre-clinical studies, typically ranging around 10 mg of melatonin administered orally or intravenously, lead to blood melatonin levels up to 5,000 times higher than physiological concentrations. As a result, it is uncertain whether these levels exceeding physiological concentrations will demonstrate the normal physiological effects of melatonin.[13]

Wang et al.[14] demonstrated that melatonin treatment in rat models of PAH induced by monocrotaline, is a pyrrolizidine alkaloid and is used to create an experimental model of pulmonary hypertension, was associated with a decrease in systolic pulmonary arterial pressure and right ventricular mass compared to the untreated PAH group. The study showed that melatonin increased the expression of H19 and miR-675-3p whereas decreasing the expression of miR-200a, thereby mitigating vascular remodeling by suppressing the proliferation of pulmonary arterial smooth muscle cells through these pathways.[14] In another study conducted on rats with cardiomyocyte hypertrophy induced by arginine vasopressin administration and PAH induced by monocrotaline, melatonin was observed to reduce cardiomyocyte hypertrophy and fibrosis by reactivating the Mst1-Nrf2 signaling pathway.[15] These two studies have led to the emergence of potential therapeutic targets.

In a study, melatonin likely contributes to reducing pulmonary arterial smooth muscle cell proliferation by decreasing hypoxia-inducible factor-1-α protein stability and to endothelial cell preservation by reducing oxidative stress and apoptosis in hypoxic PH induced by dasatinib in rats.[16]

A study conducted on newborn lambs with PAH of newborns evaluated the effects of melatonin administered orally at midnight for 21 days. It has been demonstrated that melatonin reduces cellular pro-oxidant reactive oxygen species and plays an anti-oxidant role in the right ventricle.[17] Another study conducted with newborn lambs revealed that post-natal melatonin heightened the activity and expression of vasodilatory prostanoids in small pulmonary arteries in PAH of newborns.[18] Another study conducted on lambs with PAH of newborns has shown that melatonin treatment had no effect on the passive mechanical behavior of the aorta and main pulmonary artery, while providing an anti-proliferative effect at the microstructural level.[19]

Jacobs et al.[20] in a review of literature based on the role of melatonin as a crosstalk agent between the gut and lungs stated that studies could investigate whether the microbiota and melatonin genes play a role in the epigenetic aspects of PAH. This is because dysbiosis can decrease melatonin levels and signaling or reduce cellular concentrations of melatonin in the gut.

Dietary modification is an important step in cardiovascular disease treatment. For example, while the treatment of arterial hypertension involves dietary modifications including the consumption of vegetables, fresh fruits, and fish, it has not been specific recommendations for nutrient supplementation for PAH.[21] Nonetheless, the relationships between nutrients such as fish oil, protein, leucine, and PAH have been reported.[22] Although there is no experimental or clinical evidence, some dietary factors including melatonin, coenzyme Q10, n-3 polyunsaturated fatty acids, and vitamin E may theoretically effect in patients with PAH.[21] In their research, An et al.[23] identified a total of 884 randomized controlled intervention studies evaluating 27 micronutrient types among 883,627 participants (4,895,544 person-years). They showed that supplementation with Vitamin D, magnesium, n-3 fatty acid, n-6 fatty acid, L-arginine, L-citrulline, folic acid, zinc, α-lipoic acid, coenzyme Q10, melatonin, catechin, curcumin, flavanol, genistein, and quercetin showed moderate-to-high-quality evidence for reducing cardiovascular disease risk factors.

Conclusion

Even if some pre-clinical studies provide supporting evidence of the effect of melatonin on PAH patients, further experimental and clinical studies are needed to elucidate the fundamental relationship between PAH and melatonin and its supplements. These studies should specifically address various aspects such as the timing and route of melatonin administration, as well as dosage adjustments based on gender and age. Additional research is required to fully understand the potential benefits and optimal use of melatonin in the treatment of PAH.

Disclosures

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