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Review

Melatonin and Allergic Rhinitis

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ABSTRACT

Atopy is a tendency to produce Ig-E antibodies in response to allergens and to develop allergic clinical symptoms such as allergic rhinitis, allergic bronchial asthma, and atopic dermatitis. Among them, allergic rhinitis (AR) is a chronic inflammatory disease of the intranasal mucosa, characterized by nasal symptoms reducing the quality of life. Management of AR maintains entirely symptomatic and is intended only to relieve the undesirable effects of mediators resulting from the allergic inflammatory reaction. The only disease-modifying treatment is immunotherapy, which can eliminate the pathophysiology of the disease. However, it is a long-lasting modality with several limitations and contraindications. In recent years, melatonin has been evaluated in various allergic inflammatory disorders due to its anti-inflammatory and antioxidant properties and has been suggested as a promising therapeutic. The role of melatonin has not been investigated in the treatment of AR, even though AR has a similar pathogenesis to those of atopic dermatitis and allergic bronchial asthma. This review is aimed to examine the pathophysiological mechanism of AR and illuminate the common pathways with atopic dermatitis and allergic bronchial asthma to discuss the potential hypothetical therapeutic role of the melatonin in AR, similar to the other two atopic diseases.

Keyword: melatonin, allergic rhinitis, atopy, asthma, atopic dermatitis, interleukin

Allergic rhinitis (AR) is a chronic disease of the upper airways, characterized by IgE-mediated inflammation of the nasal mucous membranes in the nose. Atopy and environmental factors play a role in the etiology of AR. The symptoms of AR are a runny nose, nasal congestion, sneezing, and nasal itching (1, 2). When exposed to the allergen, the dendritic cells (Langerhans cells), the antigen-presenting cells in the nasal mucosa, receive the allergen by endocytosis. Then the Langerhans cell proteolyzes the allergen into peptide sequences and expresses the antigen of the allergen in its surface MHC-Class II antigen recognition site. The allergen is then transported to the regional lymph node to be introduced to naive CD4 + T lymphocytes (1). In response, Th0 cells differentiate into Th2 lymphocytes through various cytokines and transcription factors one of which is interleukin (IL)-4 released from Type 2 innate lymphoid cells. Cytokines such as IL-3, IL-4, IL-5, and granulocyte macrophage - stimulating factor (GM-CSF) are secreted from T2 lymphocytes to induce the maturation, activation, and chemotaxis of eosinophils (through IL-5); and IgE expression from B lymphocytes (through IL-4 and IL-13). Specific IgE antibodies bind to the membrane receptors of mast cells in tissues and circulating basophils. When exposed to the allergen, the allergen binds to the mast cell with its specific

IgE receptors, resulting in degranulation (1-3). Various mediators such as histamines, proteases, proteoglycans, and TNF-α (tumor necrosis factor-alpha) are immediately released by mast cell degranulation. The platelet-activating factor (PAF), leukotrienes (LCT4, LTD4, LTE4) and prostaglandins (PGD2) are synthesized *de nova* and released in minutes (4).

This process is called early phase and manifests itself in increased vascular permeability through substance P, neurokinin-A, vasointestinal peptide (VIP), and calcitonin gene-associated peptide (CGRP); exudation; increased nasal secretions from the submucosal glands; congestion; sneezing; and nasal itching (1, 3). The amount of histamine may not always correlate with findings other than sneezing, and even high levels of histamine may be present in nasal secretions of non-AR individuals. However, the number of leukotrienes and prostaglandins are often correlated with symptoms that occur in the early phase (1).

The late phase of AR usually begins within 4-6 hours after the allergen exposure, peaks after 6-12 hours and mainly characterized by the prolongation of early phase symptoms, particularly nasal congestion (1). Interleukins synthesized from mast cells (IL-4, IL-5,

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IL-6, IL-1b, and IL-13), cytokines, and chemokines such as GM-CSF and TNF-α are involved in this phase. These mediators contribute to eosinophilic, basophilic, and T lymphocytic infiltration of the nasal mucosa by increasing the expression of vascular adhesion molecules in endothelial cells (3).

Within four to eight hours, these inflammatory cells in the tissue begin to activate and release their inflammatory mediators. Activated epithelial cells release the thymic stromal lymphopoietin (TLSP), IL-25 and IL-33, contributing to the Th2 response, some leading to apoptosis (2). This remodeling process, which is characterized by tissue damage, inflammatory (especially eosinophilic through IL-5) cell infiltration, epithelial atrophy, goblet cell hyperplasia, and extracellular matrix thickening, is the result of the late phase of AR (3).

Regulatory T lymphocytes (Treg) also play a role in the exacerbation of Th2 lymphocyte response, particularly through IL-10 (2). A decrease in Treg cell number and function has been demonstrated in patients with AR (5). Th17 plays a role in atopy related autoimmunity and allergic disorders, as well. A balance between Th17 and Treg cells is crucial such that excess in Th17 function and a defect in Treg function may trigger the development and progression of allergic asthma and rhinitis (6).

Melatonin as a promising treatment modality

Synthesis and release of melatonin
Melatonin (5-methoxy N-acetyl tryptamine), released from the suprachiasmatic nucleus in the pineal gland, is a neurohormone that has been under consideration for its known effects on the circadian rhythm as well as its impact on the immune system in recent years (7). In addition to the pineal gland, many tissues are known to synthesize melatonin, such as ovarian, lens and bone marrow cells in mammals, and spleen, thymus, platelets and other immune cells in rats (8).

The precursor of melatonin is tryptophan. Tryptophan is converted to N-acetyl serotonin by the enzyme N-acetyltransferase and then to melatonin by the hydroxy indole-O-methyltransferase enzyme. The activity of N-acetyltransferase is regulated periodically in a photosensitive manner. In the presence of light, the suprachiasmatic nucleus and other hypothalamic structures are stimulated, while in the dark serotonin and N-acetyltransferase are released from the stores via noradrenaline. Between 20.00 and 23.00, the melatonin level gradually increases and peaks around 01.00-05.00. Normally, serum melatonin levels are around 0-20 picograms (pg) / milliliters (ml) in daytime and 20-200 pg / ml (average 60-70 pg / ml) at night.

Pharmacokinetics of melatonin
The hormone is highly lipophilic and partially hydrophilic. It can be administered orally by dissolving in gelatin capsules or intravenously in ethanol, and intraperitoneally. When administered intravenously, melatonin is eliminated in minutes because of its short half-time (0.5 to 5.6 minutes) however after oral administration it takes approximately 60 minutes to reach a peak. After oral administration, plasma distribution follows a biphasic pattern with a half-life of respectively 2 and 20 minutes and serum peak concentration is reached approximately in 60 minutes (8). The bioavailability of melatonin ranges between 10 and 56% (mean 33%). Melatonin is metabolized rapidly and mostly in the liver and to a lesser extent in the kidney. When administered in the oral route, a ratio of 95% is exposed to a hepatic first-pass in which cytochrome P450 enzyme CYP1A2 takes a role and leads the production of a principal urinary extraction metabolite called the "6-sulfatoxymelatonin (6-SM)" (8).

Melatonin, of which synthesis is diminished by light activation, has been described in photo-immunomodulation for seasonal and intraday circadian effects on the immune system. According to data from studies on many vertebrates and humans, it is known that, as the duration of exposure to light decreases, especially during sleep and in winter, the level of melatonin increases to strengthen the immune system (7).

Mechanisms of action of melatonin
The melatonin effects in humans and other mammals by G-protein coupled membrane receptors, nuclear receptors, calmodulin and antioxidant properties (9). Melatonin G-protein coupled membrane receptors are present in the peripheral organs (spleen, thymus and all lymphocyte types, caudal artery, etc.) as well as cerebrum (cortex and suprachiasmatic nucleus) in humans (8, 10, 11). These are the high-affinity Mel1a (ML1, ML1a, MT1, MTNR1A) mainly located in the suprachiasmatic core of the hypothalamus and low-affinity affinity Mel1b (MT2, ML1b, MTNR1B) receptors. Although post-receptor signaling mechanisms are usually carried out via the inhibition of adenylate cyclase and reduction of cAMP, Mel1b receptors also inhibit guanylate cyclase and reduce cGMP, and are known to act through different signaling mechanisms in non-human species, too (8, 10, 11). Mel1a is mainly located in various sites of brain such as the pituitary gland, hypothalamus (suprachiasmatic nucleus), thalamus, cortex, basal ganglia, nucleus accumbens, amygdala, hippocampus, cerebellum, skin, and retina whereas Mel1b is basically seen in retina and cornea, and less frequently in cortex, hippocampus, paraventricular nucleus, and cerebellum (8, 11). MT3 (ML2, Quinone reductase enzyme-2 (NQO2), QR2) receptors are detoxification enzymes and located in liver, kidney, heart, lung, intestine, muscle, and brown fat tissue (11).

Melatonin might function through two types of nuclear receptors; the orphan receptor retinoid Z receptor (RZR)- β and the retinoic acid - related orphan receptor (ROR) - α, β, and γ (8, 12). The nuclear receptors of melatonin are crucial for the mast cells to achieve inflammation, immune response, cell proliferation, and apoptosis mechanisms and are thought to be coupled with the transcription of NF-KB as the post-receptor signaling pathway, similar to corticosteroids (13). The transcription factor NF-kB, which is typically combined with an inhibitory molecule (I-kB) in the mast cell cytoplasm; is activated by phosphorylation and degradation of the I-kB when the mast cells are stimulated. During inflammation, NF-kB induces endogenous melatonin

(MEL-n) synthesis from inflammatory cells to reguylate mast cells, by stimulating the arylalaminamine-acetyltransferase enzyme, possibly due to the presence of NF elements in the promoter and intron regions of the gene encoding this enzyme, encoding this enzyme (14). Exogenously administered melatonin does not affect the endogenous melatonin level in the presence of unstimulated mast cells. But, in the presence of stimulated mast cells, it inhibits NF-KB and reduces the endogenous melatonin level in a dose-dependent manner. This effect is assumed to suppress the exaggerated inflammatory response (13).

Mechanisms of non-receptor mediated effects of melatonin

1. Antiapoptotic effect
Calmodulin-mediated processing, is often associated with breast cancer. It is suggested that melatonin facilitates dephosphorylation and nuclear import of histone deacetylase 4, leading to inactivation of calmodulin-dependent protein kinase II alpha and apoptosis which may slow down the cell cycle and stop breast cancer growth. Melatonin has antiapoptotic effects in healthy cells (15).

2. Antioxidant and cytoprotective effects
Melatonin can easily pass through the cell membrane and reach the nucleus through its hydrophilic and lipophilic properties where it will show antioxidant and cytoprotective effects. Melatonin is a free radical scavenger and an antioxidant. It stimulates superoxide dismutase, glutathione peroxidase, and glutathione reductase enzymes. In addition to antioxidant enzyme stimulation, it also neutralizes molecules such as hydrogen peroxide, oxygen radicals, peroxynitrite anion, nitric oxide and hypochloride acid (16). Melatonin, which does not have pro-oxidative activity, is more capable than glutathione and vitanim E to neutralize free hydroxyl (OH) radicals. Furthermore, unlike antioxidative substances such as vitamin E, vitamin C and beta carotene, the intermediates produced during the antioxidant reactions of melatonin are also antioxidant (17). Thus, the cell membrane, nucleus, and DNA are protected from lipid peroxidation and neutralizing toxic radicals (8, 16). A recent experimental study demonstrated decreased apoptosis in the nasal mucosa of rhinosinusitis induced rats when treated with the melatonin (18).

3. Immunomodulatory effects
Melatonin receptors are also present in human lymphocytes, and human lymphocytes are shown to synthesize, secrete, and respond to melatonin (8, 12). Furthermore, melatonin plays a role in T cell differentiation and activation somehow (12). It promotes the production of interferon (IFN) - γ and IL-2 by both the membrane and nuclear receptors, suggesting that it may activate human Th1 lymphocytes (9). To the best of our knowledge, melatonin is an immunomodulatory hormone and influences Th1, Th2, Th17, and Treg responses, but in a varying manner. In the case of immunosuppression, melatonin inhibits the Th1, Th17, and Treg responses, while in the case of immune-exacerbation it stimulates the Treg pathways (12). Its immunomodulatory mechanism allows

the production of various cytokines such as interleukin-1 (IL-1), IL-2, IL-6, IL-10; increases T lymphocyte activity and regulates lymphocyte proliferation; thus indirectly increases antibody production. Increased IFN-γ and IL-2 positively feedback the synthesis of melatonin and IL-12. In addition, increased IL-2 levels lead increased Natural Killer (NK) activity (9).

Typically, CD4 + T lymphocytes are transformed into Th1 lymphocytes producing IFN-γ and IL-2 and Th2 lymphocytes producing IL-4, IL-9, IL-10 and IL-13, which enable the maturation and activation of eosinophils. In AR, this pathway shifts to Th2 increase, Th1 decrease and IFN-γ level decrease (19-21). As known, IFN-γ is released mainly from Th1, cytotoxic T, naïve CD4 + T, and NK cells, and secondarily from dendritic cells, macrophages, and even B lymphocytes. The promoter region of the IFN-γ gene has a binding site of various transcription factors such as NF-KB. IFN-γ regulates approximately five hundred genes. These include increased transcription of antigen-presenting cells genes, differentiation of naïve CD 4+ T lymphocytes towards Th 1 cell direction, increased apoptosis and B lymphocyte response, increased immunoglobulin heavy chain production (increased IgG and decreased IgE), and regulation of various inflammatory cells cytokines and adhesion molecules (21).

The role of melatonin in the pathogenesis of atopic diseases (Table 1)

Atopic eczama and melatonin

Atopic eczema (AE) is dominated by aggravated Th2 response in the acute phase, which is particularly mediated by IL-4, IL-5, and IL-13, and manifests itself with a relatively decreased Th1 response and IFN-γ levels. As the IFN-γ increases, melatonin synthesis and serum IFN-γ levels decrease in AE patients, and the reduced serum melatonin concentration may lead sleep disorders and stress, which results in an over-decrease in melatonin (22). The nocturnal melatonin increase was diminished in patients with atopic dermatitis compared to the control group (23), and the serum melatonin levels were significantly lower in the patients with atopic dermatitis (24). Furthermore, sleep disorders were common in patients with atopic dermatitis and found to be associated with the severity of atopic dermatitis (25). As known, the nocturnal increase of melatonin during sleep is usually associated with increased Th1 response and high serum IFN-γ level (26). Since reactive oxygen species and free radicals contribute to the skin damage in AE (27), melatonin may be a promising therapeutic by its antioxidative and free radical scavenger effects. The IFN-γ to IL-4 ratio was significantly lower in the subgroup of atopic dermatitis patients with poor sleep efficiency which exhibited lower nocturnal serum melatonin levels (28).

Furthermore, atopic dermatitis-like lesions were supressed by melatonin treatment in a murine model (29). Thus, these two studies have also suggested melatonin as a treatment alternative in atopic dermatitis(28, 29). Another entity is called "indole-aminic theory" which has been speculated to underly the pathogenesis

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Table 1. The studies which have revealed the potential effects of melatonin in bronchial asthma, atopic dermatitis, and allergic rhinitis in historical order.

Animal Studies

Martins et al., 2001 (32)	Airway inflammation was healed by administring exogenous melatonin in pinealectomized rats through restoring the ability of cells to migrate from the bone marrow to the bronchoalveolar fluid.
Kim et al., 2009 (29)	Atopic dermatitis-like dermatitis was supressed by melatonin in a murine model by reducing total IgE in serum, and IL-4 and IFN-γ production by activated CD4+ T cells.
Shin et al., 2014 (36)	Melatonin-treated mice exhibited a significant reduction in MUC5AC (a major component of the airway mucin) expression in an experimental asthma model.
Shin et al., 2014 (38)	Melatonin inhibited specific matrix metalloproteinases (MMP 9) induced by the production of Th 2 cells, contributing to the anti-inflammatory effect in a murine model of allergic asthma.
Wu et al., 2016 (37)	The expression of TLR9 (Toll like receptor 9) increased in a murine model of asthma and it corralated with the airway inflammation, and decreased serum and bronchoalveolar levels of melatonin, whereas TLR9 deficiency reversed the outcome by restoring melatonin biosynthesis.

Clinical Trials

Schwarz et al., 1988 (23)	Nocturnal melatonin increase was diminished in patients with atopic dermatitis compared to the control group.
Sutherland et al., 2002 (35)	Melatonin has been shown to improve symptoms in allergic asthma by modulating the release of various inflammatory cytokines and the behavior of inflammatory cells.
Sutherland et al., 2003 (41)	In patients with nocturnal asthma, serum peak melatonin levels were significantly higher than those of the controls.
Fei et al., 2004 (33)	In the exacerbation periods of allergic asthma, both the basal and peak melatonin levels were significantly reduced compared to the healthy control group, and the severity of symptoms was correlated with the decrease in melatonin levels.
Dimitro et al., 2004 (26)	Nocturnal increase of melatonin during sleep was associated with increased Th 1 response and high serum IFN-γ level.
Chamlin et al., 2005 (25)	Sleep disorders were common in patients with atopic dermatitis and found to be associated with the severity of atopic dermatitis.
Muñoz-Hoyos et al., 2007 (24)	The serum melatonin levels were significantly lower in the patients with atopic dermatitis.
Kimata H., 2007 (22)	As the IFN-γ increases, melatonin synthesis and serum IFN-γ levels decrease in AE patients, and the reduced serum melatonin concentration may lead sleep disorders and stress, which results in an over-decrease in melatonin.
Gumral et al.,, 2009 (34)	Serum melatonin levels and various antioxidant enzymes such as glutathione peroxidase and glutathione reductase decreased in the exacerbation period of asthma.
Karasu-Minareci et al., 2012 (47)	Melatonin strengthened contraction responses, but did not affect relaxation responses in rat tracheal smooth muscle preparations which can be considered to play a role in the pathogenesis of nocturnal asthma.
Fidan et al.,2013 (44)	The basal and peak salivary melatonin levels of patients with allergic rhinitis were significantly lower than controls.
Shin et al., 2014 (38)	Melatonin inhibited specific matrix metalloproteinases (MMP 9) induced by the production of Th 2 cells, contributing to the anti-inflammatory effect in a murine model of allergic asthma
Chang et al., 2014 (28)	The nocturnal melatonin level was found to be significantly associated with sleep disturbance in the patients with atopic dermatitis. The IFN-γ to IL-4 ratio was significantly lower in the subgroup of patients with atopic dermaittis with poor sleep efficiency which exhibited lower nocturnal serum melatonin levels.
Wu et al., 2016 (37)	The expression of TLR9 (Toll like receptor 9) increased in a murine model of asthma and it corralated with the airway inflammation, and decreased serum and bronchoalveolar levels of melatonin, whereas TLR9 deficiency reversed the outcome by restoring melatonin biosynthesis.
Sarnowski et al., 2016 (39)	A genetic receptor variant of melatonin (MTNR1A) was found to be associated with the paternally transmitted hereditary AR and asthma comorbidity.
Kleiner et al., 2016 (46)	Basophil deposition with increased melanocortin receptor MC1R (receptor to which melatonin-stimulating hormone binds) was observed in the nasal mucosa of both patients with allergic rhinitis and allergic rhinitis induced mice. α− melanocyte-stimulating hormone (α−MSH) was shown to inhibit allergic airway inflammation.
Chang et al., 2016 (31)	In children with atopic dermatitis and sleep disorder, 3 mg / g oral melatonin for four weeks has been reported to significantly reduce the severity of atopic dermatitis compared to placebo.
Bayrak-Degirmenci et al., 2018 (6)	Lower serum IFN-γ levels were documented in AR patients compared to controls.

of AE, as well. Accordingly, as the serum levels of melatonin decrease somehow, various immunological defects become more prominent, and finally the organism becomes more sensitive to the environmental triggers (30). In children with atopic dermatitis and sleep disorder, 3 mg/g oral melatonin for four weeks has been reported to significantly reduce the severity of atopic dermatitis compared to placebo (31).

Bronchial asthma and melatonin

Experimental studies confirmed healing in airway inflammation by administring exogenous melatonin in pinealectomized rats (32). In the exacerbation periods of allergic asthma, both the basal and peak melatonin levels were significantly reduced compared to the healthy control group, and the severity of symptoms was correlated with the decrease in melatonin levels (33). Besides, serum melatonin levels and various antioxidant enzymes such as glutathione peroxidase and glutathione reductase reduce in the exacerbation period of asthma (34). Melatonin has been shown to improve symptoms in allergic asthma by modulating the release of various inflammatory cytokines and the behavior of inflammatory cells (35). Antiinflammatory and antioxidant effects, as well as their effects on transcription and inhibition of mucus secretion, are among the therapeutic mechanisms of action

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found in experimental models of allergic asthma (36). Another potential therapeutic target may be the TLR9, a receptor among the toll-like receptors (TLRs) family, which is shown to have a role in the pathogenesis of bronchial asthma. Experimental studies documented that the expression of TLR9 increases in asthma and it corralated with the airway inflammation, decreased serum and bronchoalveolar levels of melatonin. On the other hand, TLR9 deficiency reversed the outcome by restoring melatonin biosynthesis (37). It is also known that melatonin inhibits specific matrix metalloproteinases (MMP 9) induced by the production of Th 2 cells, contributing to the anti-inflammatory effect in allergic asthma (38). Moreover, it has been described that genetic melatonin receptor variants can cause hereditary AR and asthma overlap (39). On the other hand, the use of melatonin is generally avoided in the patients with severe nocturnal asthma, whose serum melatonin levels are higher than the non-nocturnal matches because the nocturnal exacerbation has been speculated to depend on high melatonin levels which physiologically increases the contractility of airway smooth muscle and thus may result in bronchospasm (40, 41).

Allergic rhinitis and melatonin

IFN-γ deficiency provides the basis for allergic diseases and aggravates symptoms. Similarly, the decline of Th2 cytokines to normalize IFN-γ level is compatible with the improvement of allergies (21). IFN-γ suppresses Th2 response while increasing Th1 response (21), reduces eotaxin receptor expression, inhibits eosinophil differentiation and regulates eosinophilic response (42). IFN-γ also increases NO synthesis by inducing the induced nitric oxide (NO) synthase enzyme, thereby preventing Ig-E mediated degranulation of mast cells (43). Lower serum IFN-γ levels were documented in AR patients compared to controls (6). In a study comparing salivary melatonin levels of AR patients with healthy volunteers, it was observed that both baseline and peak levels of AR were significantly lower than those of control

subjects and the circadian rhythm pattern was impaired (44). Low melatonin levels reduce IFN-γ synthesis, which reduces melatonin synthesis (9, 28, 29). On the other hand, IFN-γ stimulation is known to increase melatonin synthesis (45). Basophil deposition with increased melanocortin receptor (receptor to which melatonin-stimulating hormone binds) was observed in the nasal mucosa of patients with AR and mice (46).

In conclusion, atopic dermatitis and allergic asthma share a common pathophysiological process similar to AR; and that's why the melatonin, which plays an essential role in both atopic dermatitis and allergic asthma may also have a potential task in AR. To our knowledge, the only treatment modality that can modify the underlying pathogenesis of AR is subcutaneous or sublingual immunotherapy that converts the Th1 response to Th2 response (48). However, immunotherapy has several contraindications or limitations to use (49, 50). Nevertheless, various cytokines, receptors, and interleukins that play a role in the pathogenesis of AR have been investigated recently for potential disease-modifying effects but have not been approved yet (50). On the other hand, the evidence-based data suggests melatonin as a very promising therapeutic agent in atopic dermatitis and allergic asthma. However, there is also insufficient data on how melatonin can be effective in AR and whether can be used for the treatment of AR. Therefore, this hypothesis should be studied either in experimental studies or in clinical trials, in all aspects.

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