

MELATONIN AND ALLERGY

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Symptoms of allergic diseases (e.g., wheezing in asthma or itching in allergic dermatitis) can disrupt sleep. However, these symptoms may not be the only reason for sleep disruption: some research indicates that the impaired production (or utilization) of melatonin may be a factor in allergy. For example, a Chinese study¹ found that children with allergic dermatitis had lower-than-normal nocturnal melatonin secretion, and other research² has demonstrated that administering melatonin to people with asthma is helpful in reducing asthma symptoms. Such findings could someday lead to the use of melatonin to improve sleep and symptoms in people with allergic diseases.

An allergy is a hyperimmune response that occurs after an exposure to a substance (i.e., allergen) that the body recognizes as foreign. After the exposure, a series of actions occur such as the release of inflammatory substances (e.g., histamine) that result in symptoms such as runny nose, airway constriction, and, at worst, anaphylactic shock (i.e., a potentially fatal allergic reaction characterized by a sudden drop in blood pressure, dilated blood vessels, swelling, hives, and breathing difficulties, rapid pulse, and loss of consciousness). Some common allergens are pollen, bee venom, viruses, bacteria, and pet dander.

An immune response can be antibody-mediated in which a protein, called an antibody, binds with and neutralizes the effects of an allergy-inducing substance (i.e., antigen), or an immune response can be cell-mediated in which immune cells such as T-lymphocytes interact with an antigen (e.g., bacteria, virus) to neutralize its harmful effects. An antibody-mediated immune response manifests immediately because antibodies travel through the blood and can quickly reach the site of an antigen. A cell-mediated response manifests some time after the exposure to an antigen because immune cells require time to reproduce and travel to the site of the antigen.

Some research suggests that the sleep-promoting hormone melatonin modulates antibody-mediated and cell-mediated immune responses.³⁻⁷ Melatonin is produced by the pineal gland, which has connections to the suprachiasmatic nucleus, a

group of specialized cells that control the circadian rhythmicity of many processes such as sleep and wake cycles. The optic nerves relay information about the level of external light to the suprachiasmatic nucleus. This photic information is then relayed to the pineal gland. In response, the pineal gland produces melatonin when the external light level is low and reduces melatonin production when the external light level is high. As a result, the melatonin level is highest during the night and lowest during the day.

Melatonin interacts with the immune system in a variety of ways. For example, melatonin receptors on the outer membrane and nuclear membrane of T-helper 1 and T-helper 2 cells allow melatonin to induce lymphocytes, monocytes, and other immune cells to synthesize immunomodulating proteins (i.e., cytokines, which mediate immune responses such as cell migration, cytotoxic activity, and inflammation).^{1,7,8} Examples of cytokines are interferon-gamma, interleukin (IL)-2, IL-6, and IL-12. Melatonin neutralizes free radicals (i.e., a highly reactive molecule, atom, or ion such as the hydroxyl ion [OH⁻] that are involved in oxidative reactions) and upregulates the activity of antioxidant enzymes (i.e., glutathione peroxidase, catalase, and superoxide dismutase) on cellular membranes.⁸ In this way, melatonin exerts antioxidant and cytoprotective effects.^{4,9-11} Melatonin has been detected in skin cells, lymphocytes, mast cells, airway epithelial cells, brain, retina, and other cells in the body.⁸ This factor may allow melatonin to modulate symptoms such as runny nose or itching in allergic diseases.

Whether improper amounts or improper utilization of melatonin—rather than allergic symptoms—contributes to disrupted sleep in people with allergic diseases has been investigated in some studies. To this end, Yung-Sen Chang and colleagues¹ explored sleep disturbances in children with allergic dermatitis and possible contributing factors. They measured the nocturnal activity level (using actigraphy) and urinary melatonin levels of children with allergic dermatitis and children without allergic dermatitis (i.e., controls). They found that children with allergic dermatitis had a greater number of movements during sleep, greater sleep disruption (as reflected by reduced sleep efficiency, longer sleep onset latency, more sleep fragmentation, and less nonrapid eye movement sleep), and some children had a higher-than-normal secretion of nocturnal melatonin, compared to the controls. Chang was surprised at the latter finding since some investigators have found lower levels of melatonin in individuals with allergic dermatitis.^{12,13} Chang conjectures that the increased melatonin production in their study may reflect the



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body's attempt to modulate the sleep disturbance. In support of this, they noted that the children with allergic dermatitis who had a higher nocturnal melatonin level had better sleep efficiency, longer total sleep time, and less sleep fragmentation, compared to children without allergic dermatitis.

Researchers who have found decreased levels of melatonin in people with allergic diseases speculate that impaired melatonin production may have a role in the disease. For example, Schwarz and colleagues¹³ found that, among 18 patients with severe eczema, six patients had a low serum melatonin level and lacked the normal circadian rhythmic change in melatonin secretion, eight patients had a lower-than-normal increase in the nocturnal melatonin level, and four patients had a normal secretion pattern of melatonin. Schwarz suggests that these findings indicate a dysfunction of the pineal gland. Munoz-Hoyos and colleagues¹² found that circadian differences in melatonin production between symptomatic and asymptomatic people with dermatitis was significant only for the daytime levels. From this finding, Munoz-Hoyos hypothesized that the nocturnal peak of melatonin produced by the pineal gland in a person with allergic dermatitis may mask that the person has a lower-than-normal daytime production of melatonin from extrapineal sources. (Melatonin-synthesizing enzymes have been identified in many tissues such as the brain, airway epithelium, skin, immune system cells, and endothelial cells; these tissues may provide melatonin during the day when the pineal gland decreases its production.)

The use of melatonin on a continual basis to improve sleep while treating allergic diseases is problematic. Despite the encouraging results of melatonin in reducing allergic symptoms, melatonin may need to be used with caution when treating certain allergic diseases. For example, some investigators have found that melatonin improves asthma symptoms by reducing airway inflammation,² whereas other investigators have found that melatonin increases airway inflammation,¹⁴ possibly by stimulating the migration of inflammatory cells to the airway. If melatonin were to be used as a treatment to improve sleep in people with allergic diseases, another factor that may be important is the time of its administration. Maestroni and colleagues⁴ demonstrated that the immunostimulatory effect of melatonin was enhanced only when mice in which an allergic reaction had been induced were treated with melatonin before evening. Future studies that address these and other problematic factors may soon make it possible to strategically use melatonin to improve sleep, as well as symptoms, in people with allergic diseases.

REFERENCES

1. Chang YS, Chou YT, Lee JH, et al. Atopic dermatitis, melatonin, and sleep disturbance. *Pediatrics*. 2014;134:e397-405.
2. Shin IS, Park JW, Shin NR, et al. Melatonin reduces airway inflammation in ovalbumin-induced asthma. *Immunobiology*. 2014;219:901-908.
3. Lin GJ, Huang SH, Chen SJ, et al. Modulation by melatonin of the pathogenesis of inflammatory autoimmune diseases. *International Journal of Molecular Sciences*. 2013;14:11742-11766.
4. Maestroni GJ, Conti A, Pierpaoli W. Role of the pineal gland in immunity: II. Melatonin enhances the antibody response via an opiate mechanism. *Clinical Experimental Immunology*. 1987;68:384-391.
5. Marseglia L, D'Angelo G, Manti S, et al. Melatonin and atopy: Role in atopic dermatitis and asthma. *International Journal of Molecular Sciences*. 2014;15:13482-13493.
6. Miller SC, Pandi-Perumal SR, Esquifino AI, et al. The role of melatonin in immuno-enhancement: Potential application in cancer. *International Journal of Experimental Pathology*. 2006;87:81-87.
7. Srinivasan V, Maestroni, GJ, Cardinali DP, et al. Melatonin, immune function and aging. *Immunity and Ageing*. 2005;2:17.
8. Chang YS, Chiang BL. Mechanism of sleep disturbance in children with atopic dermatitis and the role of the circadian rhythm and melatonin. *International Journal of Molecular Sciences*. 2016;17:462.
9. Caffarelli C, Santamaria F, Vottero A, et al. Progress in pediatrics in 2013: Choices in allergology, endocrinology, gastroenterology, hypertension, infectious diseases, neonatology, neurology, nutrition and respiratory tract illnesses. *Italian Journal of Pediatrics*. 2014;40:62.
10. Silvestri M, Rossi GA. Melatonin: Its possible role in the management of viral infections—a brief review. *Italian Journal of Pediatrics*. 2013;39:61.
11. Princ F, Maxit AG, Cardalda C, et al. In vivo protection by melatonin against delta-aminolevulinic acid-induced oxidative damage and its antioxidant effect on the activity of haem enzymes. *Journal of Pineal Research*. 1998;24:1-8.
12. Munoz-Hoyos A, Espin-Quirantes C, Molina-Carballo A, et al. Neuroendocrine and circadian aspects (melatonin and beta-endorphin) of atopic dermatitis in the child. *Pediatric Allergy and Immunology*. 2007;18:679-686.
13. Schwarz W, Birau N, Hornstein OP, et al. Alterations of melatonin secretion in atopic eczema. *Acta Dermmato-Venerologica*. 1988;68:224-229.
14. Sutherland ER, Ellison MC, Kraft M, et al. Elevated serum melatonin is associated with the nocturnal worsening of asthma. *Journal of Allergy and Clinical Immunology*. 2003;112:513-517. ❖