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Effects of Melatonin on the Immune System

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ABSTRACT

Melatonin is a hormone that is produced in the pineal gland, a small gland in the brain, and helps regulate the sleep-wake cycle in the body. Melatonin is a natural hormone that is secreted through the body. This hormone has several tasks and is actually a natural antidote. There are very small amounts of melatonin in foods such as meats, legumes, fruits and vegetables. Melatonin controls and regulates the body's biological rhythms and participates in most neurophysiological processes and helps to strengthen the immune system. This hormone is secreted from the pineal gland and puts you to a comfortable sleep. The production of this hormone is influenced by various factors such as age, light, environmental and physiological factors. Melatonin has a stimulating effect on the immune system and increases its function. Melatonin properties help us to be more resistant to stress conditions and deal with viral diseases easily. These strong molecules make the body safer against time and less aging and its complications. When our immune system is stronger, we deal well with diseases, and fortunately melatonin handles the immune system well. In this study, we investigated the effects of melatonin on the immune system.

KEYWORDS: Melatonin, Immunity, Human

INTRODUCTION

Melatonin N-acetyl-5-methoxy tryptamine It is one of the natural hormones in the body that is secreted from the pineal gland. In recent years, this hormone has been widely used. Melatonin easily crosses the blood-brain barrier and has few side effects (Ren et al., 2017). Melatonin or - N Steel methoxy triptaminin, first identified in the early e-tyle cow (Liu et al., 2011). In all animals including humans, melatonin is produced during the night by pinal, retina, gastrointestinal tract and several other organs. As can be seen in Figure 1, after tryptophan enters actively into the pinipal cells, it is converted into serotonin in two stages. Serotonin is produced during the day and decreases after the onset of darkness due to release from the piniple cells It decreases (Maestroni, 1993). During the next two stages, serotonin is converted to melatonin. The concentration of melatonin in humans in the first stage of darkness is related to the level of melatonin per day. In the dark-light cycle, 14 hours of light and 10 hours of darkness, the increase in melatonin overnight is delayed for several hours, but the daily melatonin concentration remains constant. , Decreases before the start to return to the daily value (Zhao et al., 2019)

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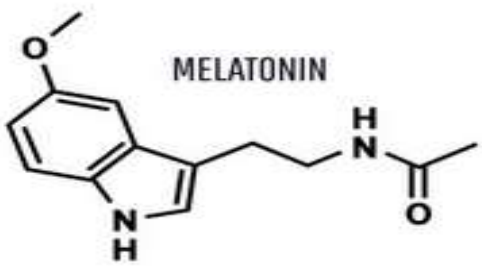

Figure 1. The chemical structure of melatonin.

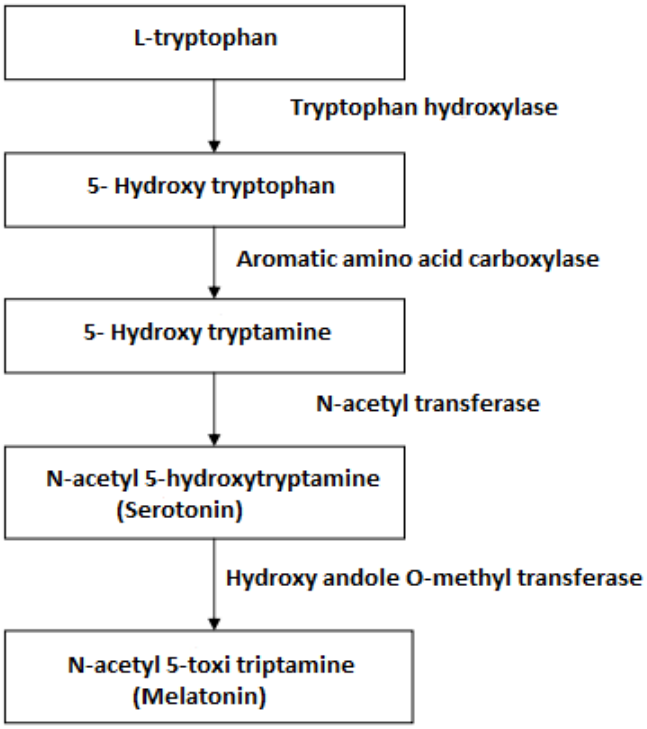

Figure 2. Stages of melatonin production (Kuklina, Glebezdina, & Nekrasova, 2016)

During the day, serum melatonin is low (about 10 to 20 pictograms per milliliter), which rises at night to about 80 pictograms per milliliter, reaching a peak between 12 noon and 3 am. Melatonin secretion usually begins at 9 to 10 pm and ends around 7 to 9 am. The rate of melatonin formation is controlled by two enzymes (Najafi et al., 2017).

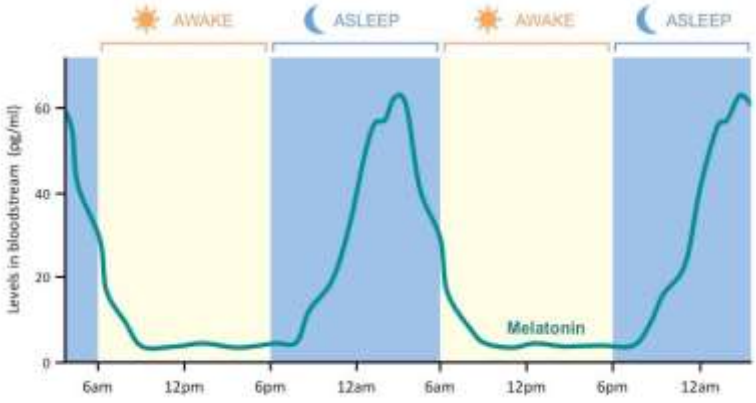

Figure 3. Melatonin levels during the day and night (Sutherland, Martin, Ellison, & Kraft, 2002)

Activation of melatonin receptors, by increasing the release of some cytokines that inhibit the immune system due to stress, can prevent deadly diseases in the human body. In addition, melatonin increases the mRNA of the enzymes Mn-SOD, ZN-SOD CU - and increases the expression of necrotic tumor. The thymus is one of the target tissues of melatonin, and the loss and depletion of its cells with age is one of the reasons for the reduced ability of the immune system in old age. (Venkataramanujam Srinivasan et al., 2008) .Many recent studies have shown that the change of seasons affects the function of the immune system, in which melatonin plays an important role. (Cardinali, Esquifino, Srinivasan, & Pandi-Perumal, 2008) .

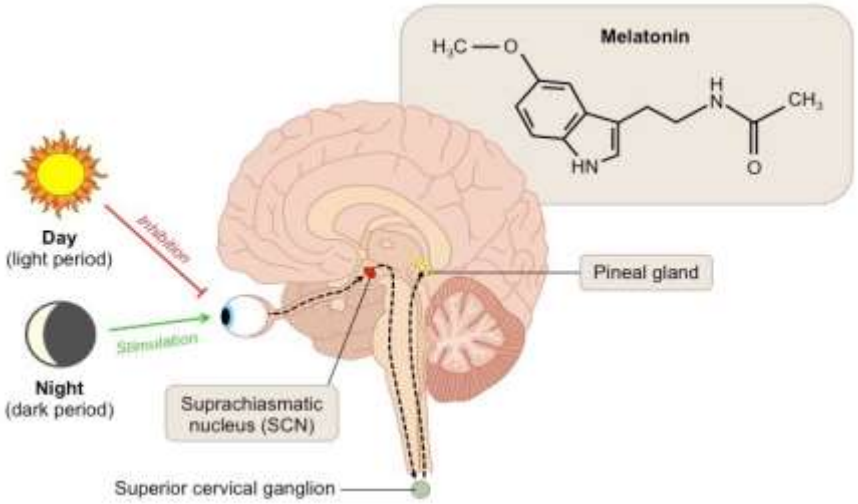

Figure 4. Mechanism of pineal gland activation.

Melatonin and Cellular Receptors

There are four receptors for melatonin in the body that enable it to interact with body parts. MT1 and MT2 are membrane receptors and are associated with G protein. Stimulation of these two receptors by melatonin will lead to sleep. The hypnotic effects of melatonin are linked to the activation of the MT1 receptor in the supra schematic nucleus (SCN), which has an inhibitory effect on brain activity. The MT1 melatonin receptor is located on the cell membrane. In humans, it is made up of 351 amino acids encoded on chromosome 4 (Giannoulia-Karantana, Vlachou, Polychronopoulou, Papassotiriou, & Chrousos, 2006) .Its main function here is as an adenylate cyclase inhibitor, which acts when MT1 binds to other G proteins. (Carrillo-Vico, Guerrero, Lardone, & Reiter, 2005) .

In humans, the MT1 subtype is expressed in the pars tuberculosis of the pituitary gland, retina, and supra sychomatic nuclei of the hypothalamus and is most likely found in human skin. With age, the expression of MT1 and SCN decreases because the reaction rate of MT1 decreases and the secretion of prolactin decreases (V Srinivasan et al., 2005) .The MT2 receiver has been shown to perform several functions in the body. In humans, expression of the MT2 subtype in the retina indicates the effect of melatonin on the mammalian retina that occurs through this receptor. Research shows that melatonin works to prevent the release of Ca2 + -dependent dopamine. The most important function that the MT2 receiver mainly mediates is the change of the internal circadian clock phase to absorb into the natural cycle of darkness and the darkness of the earth. As mentioned above, the MT1 receptor has been shown to play a role in phase change but this is secondary to the MT2 receptor (Gupta & Haldar, 2013) .Recently, the scientist is studying the relationship between the MT2 receptor and sleep disorders, anxiety, depression and pain. Because MT2 receptors have been found to help regulate sleep through NREMS and have anxiety-reducing effects, scientists have begun to consider MT2 as a therapeutic target for these disorders (Calvo, Rafii-El-ldrissi, Pozo, & Guerrero, 1995) .The MT3 receptor is the second most important melatonin receptor. With the effect of melatonin on this receptor, quinone enzyme oxidase reductase will be inhibited and will have an antioxidant role. MT3 also has a detoxifying role in the liver, heart, intestines, kidneys, muscles and fat (Wu et al., 2012) .ROR α receptor activity also interferes with melatonin. This receptor is responsible for controlling the cell cycle and regulating apoptosis. Melatonin is the agonist of this receptor. MT3, on the other hand, briefly describes its potential role in regulating fluid pressure inside the eye. Melatonin receptor ROR α has an antagonistic effect. The effect of melatonin on this ROR α receptor causes B and T lymphocytes to mature (Szczepanik, 2007) .Nitric oxide synthase (NOS) and cyclooxygenase 2 are known to be melatonin-related targets. Melatonin acts as their inhibitor. Its inhibitory effect can significantly contribute to a melatonin-related anti-inflammatory mechanism. It will reduce inflammation and increase the function of the immune system in general. After melatonin intake, iNOS receptor expression can be expected to decrease (Cutando, Gómez-Moreno, Arana, Acuña-Castroviejo, & Reiter, 2007) .Therefore, it can be proven that melatonin has an immune-boosting effect in many animal species as well as in humans (Luo et al., 2020) .

Melatonin and immune function

In recent years, much attention has been paid to the possible interaction of melatonin and the immune system. In 1986, Maestroni et al. First demonstrated that inhibition of melatonin synthesis inhibited cell and humoral responses in mice. Mice that were kept in constant light, or used beta-adrenergic blockers (propranolol) to inhibit melatonin synthesis, developed antibody inhibition, cell and spleen cell depletion, and were reversed by melatonin administration in the late afternoon (Sehirli, Sayiner, & Serakinci, 2020). Late-

afternoon melatonin injection enhances both primary and secondary antibody responses to SRBC. In adults and young humans due to the interaction of melatonin and the immune system, it was observed that nocturnal increase in blood melatonin in humans is associated with increased production of thymus peptides such as thymosin-1 alpha and thymolin (Cutolo, Seriolo, Craviotto, Pizzorni, & Sulli, 2003) .The stimulant effect of melatonin on the immune system has been proven. Melatonin consumption stimulates the immune system and increases life expectancy. Under the influence of melatonin, TH-2 lymphocytes can produce more interleukin-3, boost the production of EFN gamma, and thus regulate the immune function of the human body. Melatonin increases the cytotoxic effect of natural killer cells (NK-cells) (Claustrat & Leston, 2015) .Melatonin is able to counteract the effects of the hormone "cortisol", which reduces immunity. Melatonin has an anti-cancer effect by protecting cells against radicals. Melatonin also has an immune-stimulating effect (Pandi-Perumal et al., 2006) .The effect of melatonin in cancer prevention is due to the effect of this hormone in protecting cells against radicals, the effect of melatonin in stimulating the immune system, the anti pro liferative effect and the anti mitotic effect (property of preventing cell division) which is an inhibitor. Melatonin also has a positive effect on overcoming stress. Relationship between epiphysis and thymus may explain decreased immune function of aging function leading to malignant tumors, aging and death (Maldonado et al., 2010) . Prostaglandin fatty acid compounds appear in areas where the body needs to defend itself against injury. Melatonin appears to play a modifying role in prostaglandin synthesis and limits its production if complete synthesis of this fatty acid is not necessary due to the condition of injury and low wound risk (Hardeland, 2009).

Melatonin and innate immunity in the immune system

Melatonin stimulates the production of progenitor cells for granulocytes and macrophages (GM-CFU) and has a general stimulatory effect on hematopoiesis. Melatonin receptors are detectable in terms of monocyte and macrophage race, and binding of melatonin to these receptors stimulates the production of GMCFU cells (Guan & Malkani, 2019 .The effect of melatonin on monocyte production may be due in part to its direct effect on melatonin receptors or may be due to increased monocyte sensitivity to stimuli such as IL-3, IL-4, IL-6, or the external colony stimulating factor (GM-CSF) Be. In addition to monocytes, bone marrow progenitor cells increase after increased melatonin synthesis. NK cells play an important role in cellular immunity against virus-infected cells (Ramos et al., 2018) .IL-2, IL-6, IL-12, and IFN-gamma have all been suggested as possible cytokines that increase the number of melatonin-induced NK cells. Auxiliary T cells contain melatonin receptors that may mediate melatonin action in the secretion of cytokines (Jahanban-Esfahlan et al., 2018).

Production of melatonin and cytokines

Melatonin has been suggested to regulate the immune system by acting on cytokines. Melatonin increases the production of IL2, IFN-gamma and IL-6 by human mononuclear cells. Melatonin increases the production of IL-1, IL-6, TNF-alpha and ROS by activating monocytes. Melatonin also increases the production of IL-12 by monocytes (Dragojevic Dikic et al., 2015) .

Repeated stimulation of Th helper cells (Th) in the presence of IL-12 differentiates Th cells from Th1 cells, which eventually produce IL-2 and IFN-gamma cells. Melatonin increases IFN-gamma production by Th1 cells. Severe loss of thymocytes with age is the main cause of structural thymic atrophy and weight loss of the thymus. Melatonin administration increased the total number of thymocytes in older mice (Brzezinski, 1997; Carlomagno, Minini, Tilotta, & Unfer, 2018) .

Function of melatonin on T lymphocytes

Melatonin enhances cellular and humoral immunity. Melatonin administration to normal or immunocompromised mice was increased in vitro and in vivo antibody responses. The role of melatonin immune stimulation is mainly applied to Th cells and T lymphocyte precursors (Dil, Doustimotlagh, Javadian, Asfaram, & Ghaedi, 2021) .The presence of specific melatonin binding sites in lymphoid cells provides evidence of the direct effect of melatonin on the regulation of the immune system. Melatonin also neutralizes the inhibitory effect of prostaglandin E2 on IL-2 production in human lymphocytes via the MT1 membrane receptor (Cardinali, Brown, & Pandi-Perumal).

Melatonin increases CD4 + lymphocytes and decreases CD8 + lymphocytes in the submaxillary lymph nodes of mice. Taken together, these studies suggest that melatonin has important immune-boosting properties and suggest that melatonin may lead to a Th-1 response (Ivankiv & Oleshchuk, 2020).

It has been observed that melatonin in people with AIDS is reduced and this effect has led to a decrease in the level of immunity of these people, which can be concluded that the defect in Th-1 in these patients has caused this (Luo et al., 2020).

In addition to secreting Th-1 proinflammatory cytokines, such as IFN-gamma, and administering melatonin IL2 to antigen-containing mice, it increases IL10 production, suggesting that melatonin may also stimulate Th-2-like anti-inflammatory immune responses. Activate in special circumstances. Therefore, it is not yet clear whether melatonin acts only on Th-1 cells or on Th-2 cells as well (Kong et al., 2020).

Mechanism of action of melatonin in immune responses

It has been suggested that Th-1 responses are easily overcome by Th-2 by reducing intracellular GSH. Therefore, depending on the relative antioxidant status of the cells, the body's immune activity may have Th-1 or Th-2 properties. Because

melatonin stimulates glutathione production, it may play a role in boosting the immune system, in part because of its effect on maintaining intracellular glutathione levels (Cardinali, Brown, Reiter, & Pandi-Perumal, 2020) .In fact, melatonin acts as a hypnotic. Finding melatonin is important to prevent the secretion of IL-8 and TNF-alpha because it may help reduce acute and chronic inflammation. Neutrophils respond to AFMK relative to monocytes, indicating that biosynthesis and melatonin metabolism are involved in the chemical association of leukocytes (Sieck, 2020) .

Melatonin and season-dependent immune function

A number of recent studies have shown that seasonal changes affect immune function, and melatonin may play an important role in this regard. Such seasonal changes in immune function have also been observed in humans. Increased production of proinflammatory cytokines IFN-gamma and alpha occurred in winter. The highest IL-6 production was reported in healthy volunteers in autumn / winter (Pool, Rickard, Pini, & de Graaf, 2020).

In humans, seasonal changes in immune function can be caused by changes in melatonin secretion time. Seasonal changes in cytokines such as IL-6, IFN-alpha, IFN, or balance in response to Th-1 and Th-2 can account for seasonal changes in mood, such as seasonal affective disorder (Hussein, Mokhtar, & Hassan, 2020).

Melatonin and the role of cancer suppression

Activation of tumor suppressor genes such as P53, oncostatic activity, modulation of estrogen and androgen, modulation of the immune system, increase in cytokine production are all effects of melatonin on cancer suppression (Samanta, 2020).

Melatonin and autoimmune diseases

Patients with autoimmune diseases such as rheumatoid arthritis or organ transplants are advised to be careful when taking melatonin supplements. Melatonin stimulates immune function by producing interleukins IL-1, IL-2, IL-6, IL-12 and interferon-gamma, T helper, cytotoxic T cells, the primary form of B cells and the primary form of T cells. The clinical significance of this effect has not yet been determined (Peschechera & Veronesi, 2020; Skarlis & Anagnostouli, 2020).

CONCLUSION

Melatonin is a simple compound with medicinal properties. Immune system regulation seems to be one of the most important positive effects of melatonin on the immune and anti-inflammatory systems that can be studied in immunological studies. But in the end it seems that in autoimmune diseases this substance must be controlled to control the immune responses. So far, limited human studies have been conducted in this field and the need for these studies is felt.

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