REVIEW ARTICLE

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Melatonin and Effects on The Immune System

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Abstract

N-acetyl-5-methoxytryptamine (melatonin) which is a hormone synthesized primarily by the pineal gland and other tissues, affects a variety of biologic processes in organism with receptor dependent pathways and independent pathways. Both *in vivo* and and *in vitro* experiments show that the melatonin via its receptors, stimulates differentiation of immune cells and immune cell–target cell interactions. The influences of melatonin on immune system are generally associated with production of cytokines. In addition melatonin has powerful antioxidant and anti-apoptotic properties. The findings about the effects of melatonin on immune system are promising for therapy of immune system diseases. The present review attempts to summarize melatonin's effects on immune system.

Keywords: melatonin, immune regulation, pineal gland.

INTRODUCTION

Epiphyseal gland (epiphysis cerebri) is a neuroendocrine organ that responsible for a lot of periodic vital activity (Turgut et al. 2003). It is small, cone shaped, gray - reddish coloured organ and as its appearance resembles to miniature pine cone it is known as pineal gland (Reiter, 1981). Epiphyseal gland firstly determined by Herophilus in 300 BC (Erlich and Apuzzo, 1985). But the most important development was getting pineal hormone, which caused blenching of skin colour when it was given to amphibia, from pineal gland by Lerner and friends. This pineal hormone was melatonin (Lerner, 1961). That development became the pioneer of pineal gland searches and ten years later, it was reported that there was the effect of light on pineal gland functions (Palaoğlu and Beşkonaklı, 1998).

Pineal gland parenchyma consists of pinealocytes, which has photoreceptor role in lower class vertebrate and has neuroendocrine feature in mammalian, and less amount of astroglial cells (Paker, 1993). N- acetyl 5 methoxy tryptamine, which is known as melatonin, is secreted by pinealocytes under photoperiodic environmental control especially on the night (Atasoy and Erbaş, 2017). Although there is releasing of many hormone that in protein structure from pineal gland, the main released hormone is melatonin (Çetin, 2005).

Structure and Synthesis of Melatonin

N-acetyl 5- methoxytryptamine (Melatonin) is a natural neurotransmitter which has 232g/mol molecular weight and, carrying an indole group (Salt et al. 2017).

Melatonin is not synthesized only in epiphyseal gland, but also synthesized in retina.. But in there, synthesized melatonin less passes to circulation and it is mostly locally effective (Özçelik et al. 2013). Light is sensed by light-sensitive retinal photoreceptors and signals are transmitted to suprachiasmatic nucleus which is main regulator of circadian rhythm (Akıncı and Orhan, 2016). Then, the impulses respectively transmitted to the paraventricular and intramediolateral nuclei, reach the pineal gland via the superior cervical ganglionic neurons (Reiter, 1991). During darkness norepinephrine that released from sympathetic fibers is sensed by β-adrenergic receptors on pinealocyte membrane and stimulates melatonin synthesis and release under the control of circadian rhythm. Tryptophan is an essential aminoacid which is used in first step of melatonin synthesis and it is converted to N-acetyl seratonin by N- acetyl transferase in pinealocytes. The N-acetyl serotonin is converted to N-acetyl 5-methoxytryptamine by hydroxyindole-o-methyltransferase (HIOMT) enzyme. (Şener, 2010).

Melatonin release which rate is 29 mg per day, especially starts on between 09.00 pm and 10.00 pm. On between 02.00 am and 04.00 am, blood melatonin level reaches to peak and by 07.00 am it starts to decrease. Melatonin concentration during night can rise to 10 times compared to the daytime. When we look to change of melatonin by the age, significantly difference is observed. Levels of nocturnal melatonin can reach to 1400 pmol/l in between 1 and 5 years old, but in adults its level is 40-260 pmol/l (Ölmez et al. 2000).

Receptors of Melatonin

Melatonin accompanied by many biological processes by receptor dependent and independent pathways. By the developing technology and studies, presence of melatonin related receptors and enzymes nearly in all tissue and cells is revealed (Ma et al. 2019).

The most common melatonin receptors are MT1, MT2 and MT3 membrane receptors which are member of G protein-coupled receptor family (Csaba, 2013). MT1 receptor is generally related with reproduction, metabolic functions and vasoconstriction. In contrast, MT2 receptor is related with circadian rhythm in retina, dopamine release control related functions and vasodilatation. MT3 receptor is determined as quinone reductase-2 and related

with xenobiotic metabolism of cells (Ma et al. 2019). Melatonin, in addition to membrane receptors, can act by binding to members of the retinoic acid receptors-related orphan receptors/retinoid Z receptor orphan nuclear receptor subfamily (ROR/RZR) (Sun et al. 2020).

As for melatonin effect on reactive oxygen species and reactive nitrogen species, it occurs by receptor independent pathways. In this process, melatonin supplies protect against to ionizing radiation, ischemia/reperfusion, heavy metal, alcohol and drug toxicity (Ma et al. 2019).

Epiphysis and Thymus Relationship

Immune system and pineal gland relationship which was asserted approximately one hundred years ago, was proved on 1943 by revealing of long time application of epiphyseal gland extract which leads to increase in thymus weight in the studies of Milcu and Pitis (Milcu and Pitis,1943). All the end of a series of experiment, pinealectomy application during adulthood found to cause change in immune response and this finding was reported (Csaba et al. 1966). Following this, in another study atrophic timus and enlarged medulla in contrast to cortex was reported in neonatal pinealectomy applicated chickens. Thirty five percent of neonatal pinealectomised animals died in first 6 months with tetanic convulsions and 10 percent of animals that continue to live produced tetany (Csaba et al. 1973). Csaba and Barath (1975) reported that, neonatal pinealectomy as resemble to neonatal thymectomy stimulates a wasting disease that whole immune system gets harm.

Maestroni and Pierpaoli who was reached to first findings of melatonin effect on immune system, aimed decreasement of melatonin effect to least by keeping rat groups under the light during 3-4 generations. At the end of this study, non-normal growth of 3rd and 4th generation rats, impaired T cell dependent antibody response against to antigens, cellular decrease in thymus cortex and atrophy of white pulp in spleen were reported (Maestroni and Pierpaoli, 1981). Vermeulen et al. have stated that exogenous melatonin causes an increase of antibody-dependent cellular cytotoxicity which decreases by pinealectomy applicated in the first week of life (Vermeulen et al. 1993). In another study, searcher found rats' thymus cell membrane binds high amount of melatonin (Martin-Cacao et al. 1993). In the study that committed in 2006, partial or complete protection of cells by melatonin from transient involution that occurs in thymus during acute stress was revealed (Pertsov, 2006). Naranjo et al. reported that human and rats' thymus had a biosynthetic system for melatonin synthesis and cultured rats' thymus were containing high amount of melatonin (Naranjo et al. 2007).

Melatonin-Immune System Cells Relationship

Melatonin represents stimulatory effect on both humoral and cellular immunity by using specific binding regions of mammalian and birds' immune cells (Fraschini et al. 1998). But when needed for homeostasis of organism, it can represent depressory effect on immune functions (Radogna et al. 2010).

Melatonin and T cells

T cells, in addition to have membrane and nuclear melatonin receptors, also have 4 enzymes that needed for melatonin synthesis (aromatic L-amino acid decarboxylase, arylalkylamine N-acetyltransferase, N-acetylserotonin methyltransferase, tryptophan hydroxylase) and they can synthesize high amount of melatonin. In committed studies were reported that findings related to melatonin signalisation in the course of T cells development, activation, differentiation and memory (Ren et al. 2017). Findings show that melatonin's immune cells stimulation for leaving from G_0/G_1 phase and proliferation were documented (Yoo et al. 2016). Melatonin stimulates naive T cells differentiation to CD4(+) Th cells (Kaplan et al. 2015). It was also decreases interferon-gamma (IFN- γ) and interleukin-2 (IL-2) production. In contrast to increase IL-4 and IL-10 production. This situation shows that melatonin takes role in immune regulation by suppressing Th1 activity and increasing Th2 cell performance (Raghavendra et al. 2001). It was showed that melatonin can be an immune system improving pharmacological agent in older people that has weak immune system by especially increasing CD4(+) T cells function (Yoo et al. 2016). Studies represented that melatonin increases Treg count without changing amount of them in normal physiologic circumstances in rats which have experimental autoimmune encephalitis. However, as in inflammation, instead of immunosuppression melatonin can decrease Treg amount (Ma et al. 2019). Melatonin also effects Ki-67 and Bcl-2 genes amplitude, which is antigen specific T cells differentiation marker protein and which is important for long time protection of Tm cells, respectively (Ma et al. 2019).

Melatonin and B cells

It has been reported that melatonin application increases antigen presentation by spleen macrophages and antibody response of B cells against to antigens (Raghavendra et al. 2001). Melatonin increases IL-4 release from Th2 cells, in contrast, it inhibits IL-2 and IFN- γ release from Th1 cells. Melatonin is increased IL-4 release stimulated by leads to improvement of transmitted signals to B cells and by this way it leads to increased IgG1 production (Shaji et al. 1998). Also there are studies report that melatonin prevention from apoptosis during B lymphocytes formation in rat bone marrow (Yu et al. 2000).

Melatonin and NK (Natural killer) Cells

Melatonin is generally a strong immune regulator that increases NK cells cytotoxicity. In a part of melatonin effectivity against to cancer, mediation of increased NK cell cytotoxicity is thought (Anderson et al. 2015). Possible reason for increased NK cells lytic effect is amplified IL-2 production by Th cells (Miller et al. 2006).

Melatonin and Mast Cells

During inflammatory process, NF-κB (nuclear factor kappa B) pathway that activated by mast cells stimulates melatonin synthesis by arylalkylamine N-acetyltransferase (AA-NAT) enzyme. Mast cells that carry MT1 and MT2 receptors (Maldonado et al. 2010), structurally can synthesize endogen melatonin (Ma et al. 2019). Melatonin binding to MT1 and MT2 receptors and it leads to inhibition of NF-κB activation and by decreasing IL-6, IL-13 and tumor necrosis factor-alpha (TNF-α) cytokines level it negatively regulates mast cell activation, proliferation and differentiation (Pham et al. 2020). In a study was committed in 2019 it was observed that melatonin treatment in animals which are under the effect of influenza A virus, increased survival rate by significantly decrease in TNF-α, Il-6 and IFN-γ expression (Huang et al. 2019). Melatonin supports cellular oxidant-

antioxidant homeostasis protection, also it reveises the cells to their physiologic state by regulating pro-inflammatory and anti-inflammatory events (Maldonado et al. 2010).

Melatonin and Macrophages

There are many studies about melatonin signalization suppresses natural immunity via effecting inflammatory mediators on macrophages (Shatskikh and Luzikova, 2012; Shi et al. 2012). MT1 and MT2 melatonin membrane receptors expression by macrophages and they are known that upregulation of mRNA expression in macrophages by melatonin application (Xu et al. 2018). Melatonin inhibits M1 macrophage polarization by signal transducers and activators of transcription (STAT-1), NF-κB and NOD-like receptor family, pyrin domain containing 3 (NLRP3) pathways. In contrast, it supports M2 macrophage polarization by STAT-6 activation and phosphatidylinositol-3′-kinase - mammalian target of rapamycin (Pi3K-mTOR) pathways weakening (Xia et al. 2019). Also it is stated that melatonin is a negative regulator of toll-like receptor-9 (TLR9) mediated natural immunity in macrophages (Xu et al. 2018).

CONCLUSION

Melatonin takes major role in maintaing of circadian rhythm and also has a strong antioxidant role. It has a strong immune-modulatory function on immune system by directly different receptors mediated mechanisms or it created by indirect effects. As result of having beneficial effects on T lymphocytes, B lymphocytes, NK cells and macrophages' , melatonin is necessary for physiological functions' stabilisation especially in immune system. The proven evidence that melatonin reduces acute and chronic inflammation is promising for the treatment of this type of disease. Also exogen melatonin treatment is under investigation in the treatment of some disease and the obtained positive results are promoting the new and more comprehensive studies.

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Conflict of Interest

The authors declare that there is no conflict of interest in the content of the article

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