Melatonin: The Immunology Perspective

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SUMMARY: Available literature suggests that melatonin has many important physiological functions in human body, but this review will focus on its role in immune system functioning. Existence of a relationship between melatonin and the immune system has been observed in a great number of studies in various species, including humans. The role of melatonin in circadian rhythm regulation, sleep-promotion and its ability to buffer immune system makes it interesting and unique from immunology perspective. It has been shown that melatonin acts as an immunostimulant under basal or immunosuppressive conditions, but as an anti-inflammatory compound in the presence of exacerbated immune responses. This characteristic function, as well as its antioxidant, antiviral, antibiotic, anti-parasitic and other properties make it also attractive as pharmacological target.

KEYWORDS: melatonin, immune system, immunostimulation, sleep, leukocytes, circadian rhythm, therapeutic applications of melatonin

Melatonin is N-acetyl-5-methoxytryptamine, a simple mehoxylated and N-acetylated product of serotonin produced by the pineal gland, as well as by retina, gut and immunocompetent cells including both bone marrow cells and lymphocytes. In vertebrates, it is primarily produced at nighttime by the pineal gland and it is known that it has vast physiological functions in bacteria, eukaryotes, plants and all phyla of multicellular animals. It is because of its ancient origin that this highly conserved indoleamine derived from tryptophan possesses numerous functions acquired throughout evolution. Many important biological effects of melatonin are produced through activation of melatonin receptors, but its powerful antioxidant properties and potential role in the protection of nuclear and mitochondrial DNA should not be forgotten. Melatonin was first isolated and named in 1958 by dermathology professor Aaron B. Lerner. His research was driven by a discovery from 1917 made by Carey Pratt McCord and Floyd P. Allen who found that feeding pineal gland extracts to tadpoles lightened their skin by contracting their dark epidermal melanophores. In 1993 antioxidant properties of melatonin were discovered. Afterwards melatonin became a popular topic of research and it was soon patented as a sleep aid. A lot of studies followed showing its potential beneficial effect in many diseases and its important physiological role. Melatonin synthesis in humans follows a serotonin pathway. It involves four enzymatic steps starting with hydroxylation of indole ring of dietary amino acid L-tryptophan resulting in formation of 5-hydroxy-L-tryptophan (5-HTP) by an enzyme tryptophan 5-hydroxylase. 5-hydroxy-L-tryptophan is decarboxylated by 5-hydroxytryptophan decarboxylase to produce serotonin. The key enzyme for production of melatonin is aralkylamine N-acetyltransferase (AANAT) which is activated to convert serotonin to N-acetyl serotonin, main substrate for melatonin production. The final step is methylation by the enzyme acetylserotonin O-methyltransferase. It is important to point out that aralkylamine N-acetyltransferase (AANAT), the key regulator of melatonin synthesis from tryptophan, is directly influenced by photoperiod [1]. It is believed that melatonin production is controlled by the light signal that reaches the suprachiasmatic nuclei (SCN) from retinal photosensitive ganglion cells of the eyes. Although available literature suggests that melatonin has many important physiological functions in human body, this review will focus on its role in immune system functioning.

Melatonin, the circadian rhythm regulator

Melatonin is well-established as a chronomodulator of biological systems. Circulating melatonin, which is derived exclusively from the pineal gland, follows a circadian rhythm, being at maximal levels during the dark period of the 24-h cycle, regardless of whether the species is diurnally or nocturnally active. The nocturnal synthesis and release of melatonin by the pineal gland are tightly controlled by the suprachiasmatic nuclei and inhibited by light exposure. It is proposed that the light signal first activates photoreceptive retinal ganglion cells (ipRGCs) and controls SCN via the glutamatergic retinohypothalamic tract (RHT) projection.[3]. Even though light signal greatly changes SCN activity its role is just modulation of cell-autonomous oscillatory function seen in these neurons.[4] We can therefore conclude that the essential role of retinohypothalamic tract (RHT) projection is, in fact, regulatory in nature and phase-adjusting function that synchronizes the clock oscillation with environmental cycling conditions such as light/dark cycle is the way organism can adapt to its environment. After its secretion melatonin distributes to the multitude of tissue targets expressing melatonin receptors. It is important to notice that due to expression of melatonin receptors on SCN ,endogenous melatonin is also able to feedback onto the master clock, although its physiological significance needs further characterization.[5] Expression of melatonin receptors on suprachiasmatic nuclei is pharmacologically interesting because of potential for re-

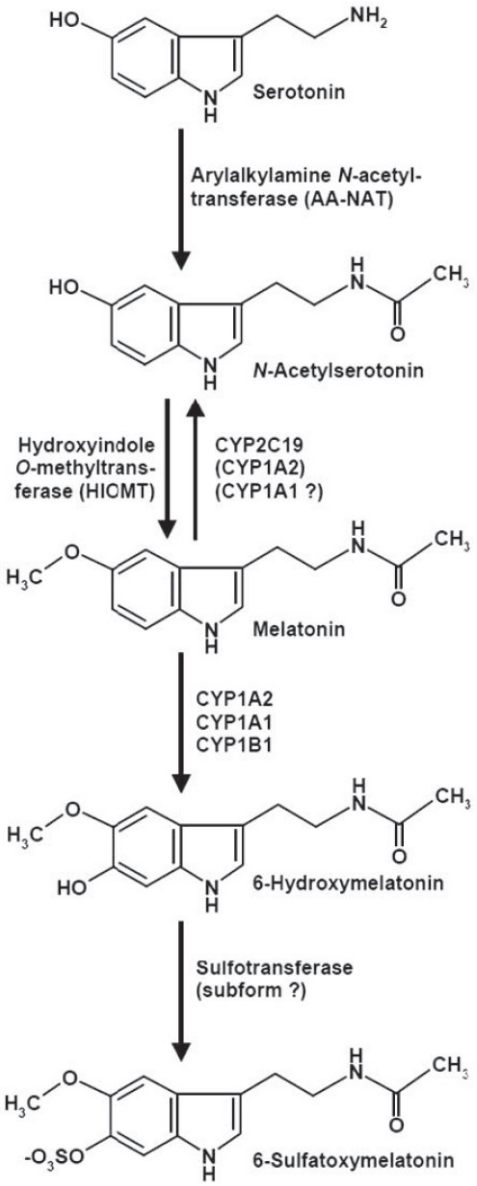

Fig 1. Synthesis and CYP metabolism of melatonin in the CNS [2]

synchronization of SCN clock after treatment with exogenous melatonin which has been reported in several studies.[6,7]. After its distribution to vast number of tissue targets melatonin activates or synchronizes tissue oscillatory activity. The way melatonin regulates tissue oscillator activity is through regulation of core clock components which are defined as genes whose protein products are necessary for the generation and regulation of circadian rhythms within individual cells throughout the organism.[8] At the molecular level the clock mechanism consists of a network of transcriptional–translational feedback loops that drive rhythmic expression patterns of genes[9]. Its role in synchronization is particularly interesting in pregnant women. Opposed to maternal circadian rhythm where SCN is the master clock, the fetus has no master clock of its own. The available data points to the fact that the fetal SCN and fetal tissues may be following orders from maternal circadian signals[10] . Furthermore, emerging evidence shows that maternal rhythm of melatonin plays a role in adjustment of fetal and neonatal circadian rhythms needed for life in future environment after birth. Some researchers also point out that maternal melatonin has an effect on fetal adrenal glands activity and fetal development overall[11]. N.Mendez et al. showed that maternal melatonin supression in rats resulted in fetal growth retardation, changes in mRNA of Per2, Bmal1, StAR, Mt1 and Egr1 and corticosterone content in adrenals. Another important finding is that exogenous melatonin successfully reversed the changes in intrauterine growth in light exposed rats[12].

Role of circadian rhythm in immunity

Circadian rhythm and the immune system are highly intertwined. It is hypothesized that changes in cortisol levels, sympathetic nervous system activity, growth hormone, prolactin, melatonin and other hormones that show systematic fluctuations during 24-hour period play an important role in regulation of both the number and the activity of leukocytes, lymphocyte proliferation, humoral immune response and cytokine levels[13,14]. The most important changes that originate from a combined influence of circadian system and sleep on number of serum lymphocytes that were reported during daytime are: quantitative increase in granulocytes, macrophages, natural killer (NK) cells, extrathymic T cells, γδ T cells, and CD8+ subset. The most important changes in number of leukocytes during nighttime was: increase in number of T cells, B cells, αβ T cells, and CD4+ subset[15]. Sympathetic and parasympathetic nervous system probably play an important role in observed difference in leukocyte count since humans are active and show sympathetic nerve dominance in the daytime and granulocytes and lymphocyte subsets with the daytime rhythm were found to carry a high density of adrenergic receptors. On the other hand, lymphocyte subtypes with the nighttime rhythm carry a high proportion of cholinergic receptors[15]. Cytokines also show circadian pattern. The available evidence seems to suggest that proinflammatory cytokines like interleukin 12 (IL-12) peak during nighttime, whereas anti-inflammatory cytokines such as interleukin 10 (IL-10) peak during daytime[13]. M.R.I.Young and colleagues described that serum levels of cytokines like tumor necrosis factor alpha (TNF-α), granulocyte-macrophage colony-stimulating factor (GM-CSF) and interleukin 10 (IL-10) follow biphasic temporal pattern. Serum peak of TNF-α was at 7:30AM and at 1:30 AM. IL-10 levels also exhibited a biphasic pattern, with one peak at 07:30AM and the second at 7:30AM. GM-CSF were last to rise with first peak at 1:30AM and the second at 7:30AM. IL-2 had a single peak at approximately noon 16. On top of that, several studies report autonomous fully functional circadian clockworks within immunological compartments like the spleen or lymph nodes. There are also results that provide confirmatory evidence that local, immune cell intrinsic clocks exist. Keller M. and colleagues demonstrated that, on the molecular level, >8% of the macrophage transcriptome oscillates

in a circadian fashion, including many important regulators for pathogen recognition and cytokine secretion[14].

Melatonin and sleep

The endogenous circadian rhythm of melatonin, driven by the suprachiasmatic nucleus, exhibits a close association with the endogenous circadian component of the sleep propensity rhythm and the endogenous circadian component of the variation in electroencephalogram (EEG) oscillations such as sleep spindles and slow waves. A closer look at the available data indicates that melatonin might have important role in regulating latency to sleep onset and sleep consolidation hence some researchers define it as circadian regulator of sleep. Moreover, administration of high doses of melatonin (5mg or more) before nocturnal sleep results in an increase in rapid eye movement (REM) sleep [17]. It is interesting that only high doses were able to achieve nighttime increase in sleepiness. By contrast, it seems that daytime administrations of melatonin induce increased sleepiness, even at doses that do not increase plasma levels of melatonin beyond its physiological levels[18]. Since melatonin receptors are found in vast number of tissues and because melatonin is a liposoluble molecule it is hard to determine specific mechanism by which melatonin exerts its sleep promoting effect, but some scientists suggest that the sleep-promoting and sleep/wake rhythm regulating effects of melatonin are attributed to its action on G-protein coupled MT1 and MT2 melatonin receptors, especially receptors present in the suprachiasmatic nucleus (SCN) of the hypothalamus[19].

It is also suggested that melatonin exerts its hypnotic effects through thermoregulatory mechanisms. Lowering of body core temperature reduces arousal and increases sleepiness. Hypothermia associated with sleep induction can also be seen in treatment with benzodiazepines although it should be stated that increase in sleepiness is linked to peripheral skin vasodilatation rather than the decline in core body temperature per se. Also, core body temperature decline is a consequence of heat loss and not a primary cause of sleepiness induction[20].

Finally, melatonin might modify brain levels of monoamine neurotransmitters, thereby initiating a cascade of events culminating in the activation of sleep mechanisms[21]. Regardless of the mechanism of action, melatonin promotes and sustains sleep in humans.

Sleep and immune function

Sleep and the circadian system exert a strong regulatory influence on immune functions. It is difficult to dissect the influence of sleep on immune function from that of the circadian rhythm or behevioral changes that follow similar circadian pattern but studies such as ones that compare effects of nocturnal sleep with 24-hour wakefulness help us understand effect of sleep on immune parameters. For most of the lymphocyte subsets, sleep, in contrast to wakefulness, was shown to reduce cell counts in blood during the night, whereas this decrease is compensated by increased cell numbers during subsequent daytime. This was shown for: Th cells, cytotoxic T lymphocytes CTL, activated T cells as well as NK cells. On the other hand B cell numbers did not show a compensating enhancement during the following day. Monocyte counts were also lower during sleep compared with nocturnal wakefulness. However, some newer studies highlight the importance of immune cell subtypes affected by sleep. In this regard, Dimitrov and colleagues showed that sleep reduced CD14dimCD16+ monocytes capable of noninflammed tissue invasion, while CD14+ CD16− monocyte counts remained unchanged during wakefulness. Similarly, cytotoxic NK cells were suppressed during sleep, while the immuno-regulatory CD16− CD56bright NK cells with low cytotoxicity remained constant [22]. Similar to circadian rythm, sleep selectively modulates some leukoyte subsets, while others remain unaffected. It is important to highlight that the reductions in leukocyte numbers observed during regular sleep should not be mistaken for general immunosuppression. Researchers suggest that this reduction s most likely represent a redistribution of the cells to different extravascular compartments or an enhanced margination to the endothelium of postcapillary venules[23].

Several studies also show that sleep has effect on cytokine production. There is consistent evidence that sleep favours the production of proinflammatory and Th1 cytokines. Sleep strongly induced the production of IL-12 which is a key cytokine for Th1 type adaptive immune response and suppressed production of anti-inflammatory IL-10 by monocytes. Interestingly, the difference between early and late sleep was observed. During early sleep there is a dominant Th1 cytokine production and during late sleep the production is shifted towards Th2 cytokine production. It should be stated that sleep does not non-specifically support production of proinflammatory cytokines in all cells. Sleep has a reducing effect on interferon γ (IFN-γ) as well as tumor necrosis factor α (TNF-α) production by cytotoxic T lymphocytes (CTL). However, some scientists suggest that this reduction could reflect the fact that due to a sleep-associated drop in epinephrine levels, cytokine producing effector leukocytes marginate to the vessel walls and are no more available for blood sampling and flow cytometric cytokine assessment. Another exception to the rule that sleep promotes proinflammatory cytokine production is

serum level of IL-6. Moreover, another studies did not show any effect of sleep on herpes simplex virus 1-stimulated production of IFN-α. Other proof of selective effects of sleep on immune function is enhanced production of proinflammatory IL-7, which supprots T cell growth and the differentiation of memory T cells. On the other hand, membrane bound IL-15 sharing some of the functions of IL-7 remains uninfluenced. Amongst the studies regarding effects of sleep on cytokine activity, there are some discrepant findings mostly attributed to differences in the assessment of cytokine activity. Nevertheless, despite the variety in the procedures used for assessing cytokine activity, the overall picture arising from these studies shows that sleep enhances proinflammatory cytokine production specifically by immune cells contributing to the development of adaptive immune responses[23]. Previous studies indicate that sleep can also modulate immune function through cytokine receptors. Dimitrov and colleagues have proposed that sleep strongly enhances concentrations of the soluble IL-6 receptor, while membrane-bound type of IL-6 receptors remained unchanged. They concluded that sleep serves to enhance trans-IL-6 signalling in cells that can receive IL-6 signals but don't carry membrane receptors[24]. It is interesting that, in this way, IL-6 can through its soluble receptor also influence other cells and systems including the brain. This possibility represents a potential feedback loop and, according to some authors, the way by which cytokines promote slow-wave sleep[23]. Sleep can also affect immune function during ongoing immune response. For several years great effort has been devoted to the study of effects of sleep on the response to vaccinations. A lot of studies have demonstrated that sleep promotes the adaptive immune response against the invading antigen. Lange and her team reported that sleep after vaccination doubled the frequency of Ag-specific Th cells and increased the fraction of Th1 cytokine-producing cells in this population. Sleep also increased Ag-specific IgG1. They emphasise the importance of slow-wave sleep and accompanying levels of immunoregulatory hormones (increased growth hormone and prolactin, decreased cortisol release). The most important finding regarding enhancement of adaptive immune response after vaccination is that these immuno-enhancing effects of sleep were still present at a 1-year follow up indicating that sleep affects not only initial formation of an adaptive immune response, but also maintenance of the antigenic memory[25].

Melatonin and the immune system

The idea that melatonin is involved in regulation of the immune system is not new. Bergman and co-workers gave the pineal gland extract to cats as far back as 1926, showing that it can enhance immune function.

The first study that suggested that melatonin is involved in regulation of immune system was performed by Csaba and Barath in 1975. They demonstrated that pinealectomy causes a depression in the immune system and that thymic cells stop proliferating after surgical removal of the pineal gland[26]. Other scientists successfully demonstrated that thymus gland shrink after pinealectomy in mice. Correlation between depression of the immune system and pinealectomy was confirmed by Beskonakli and co-workers after they proved that the removal of pineal gland results in a reduction in the number of lymphocytes, erythrocytes and leukocytes [27]. Many other experiments show that any procedure that inhibits melatonin synthesis and secretion, such as exposure to constant illumination, pineal denervation or ablation, depresses both, cellular and humoral activity. There are also numerous studies that demonstrate that such depressive immunological state can be partly counteracted by exogenous melatonin[28]. Available research indicates that melatonin exerts its immunomodulatory function through several mechanisms such as: action on T-helper lymphocytes (Th), action on T-lymphocyte precursors, modulation of both natural killer (NK) cell and monocyte function, regulatory role in endocrine system and others.

Melatonin receptors in the immune system

Two membrane bound melatonin receptors are identified and characterized, MT1 and MT2. Both of them belong to the family of G protein-coupled, seven transmembrane receptors. Some authors also reported potential MT3 receptor but this biological target of melatonin was found to actually be the cytosolic enzyme, quinone reductase 2. The MT1 receptor is 350 amino acids in length and coupled to Gi, specifically Giα2, Giα3, and Gq/11. Current literature indicates that MT1 receptors are expressed in the brain (predominantly in the hypothalamus, cerebellum, hippocampus, substantia nigra and ventral tegmental area), cardiovascular system (including peripheral blood vessels, aorta and heart), immune system, testes, ovary, skin, liver, kidney, adrenal cortex, placenta, breast, retina, pancreas and spleen 29. MT2 receptor is 60% homologous to the MT1 receptor and consists of 363 amino acids. The MT2 receptor is also a G-protein related and couples to the activation of Gi. MT2 has been found in the immune system, brain (hypothalamus, SCN), retina, pituitary, blood vessels, testes, kidney, gastrointestinal tract, mammary glands, adipose tissue, and the skin[29]. Although MT3 receptor (quinone reductase 2) has not yet been found in humans, it is expressed in the hamster's liver, kidneys,

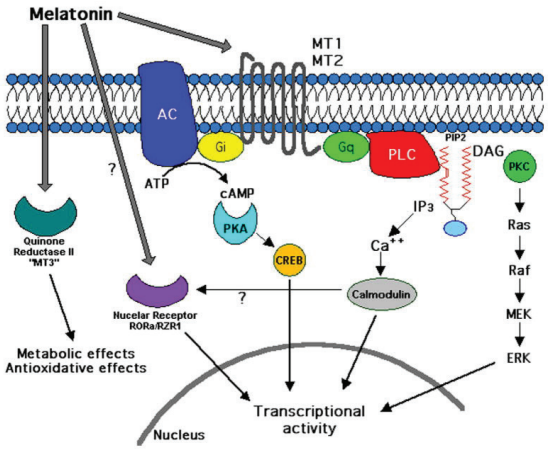

Fig 2. Melatonin signaling through MT1, MT2 and nuclear receptors.[1]

heart, adipose tissue and the brain and in retina of the rabbit. Melatonin may also exert its effects through retinoid orphan receptors/retinoid Z receptors (ROR/RZR) nuclear receptors.

Melatonin And Lymphocytes

Melatonin was shown to stimulate T-lymphocyte proliferation 30, enhance antigen presentation by macrophages to T cells by increasing the expression of major histocompatibility complex class-II molecules, activate splenic, lymph node and bone marrow cells, stimulate antibody-dependent cellular cytotoxicity and augment both innate and adaptive immunity[28].

Correlation between melatonin in several diseased states has been established. In ischaemic stroke patients, an impaired nocturnal urinary melatonin excretion was found to be associated with a decreased cell-mediated immunity, a prevalence of anergic status and changes in lymphocyte subsets, with an overall decrease in the number of circulating CD3+ lymphocytes. In HIV-1 infected patients reduction of melatonin secretion is in correlation with disease progression and scientists suggest it may be related to the impairment of Th1 mediated immunoresponses [31]. Literature also suggests the possible connection between IL-2 and melatonin in human lymphocytes. Lymphocytes produce IL-2 and IL-2 receptor (IL-2R) after melatonin administration. Moreover, inhibition of melatonin synthesis in leukocytes results in decrease of both IL-2 production and IL-2R expression[28].

Potentially important alternative effect on lymphocytes is also engaged in its immunomodulatory actions.

Melatonin also prevents apoptosis of T-cell precursors in the thymus. It appears to act on T-lineage cells throughout all their developmental stages.

Melatonin action on macrophages and monocytes

As previously stated, melatonin can enhance antigen presentation by macrophages to T cells. The main mechanism by which melatonin does this is increasing the expression of major histocompatibility complex class-II molecules. The ability of melatonin to enhance inflammatory cytokine production (including IL-12) from human monocytes and macrophages is in coincidence with previously interpreted data and points to the fact that the most relevant role of melatonin in the enhancement of T-cell immunity is in the control of the Th1 response[28]. Other authors demonstrated that melatonin is capable of reducing the generation of nitric oxide in stimulated murine macrophages which is important in context of excessive NO production, possible pathophysiological mechanism underlying development of degenerative diseases[19]. Another important mechanism by which melatonin increases monocyte activity is its ability to increase monocyte sensitivity to stimulants like IL-3, IL-4, IL-6 or GM-CSF[19].

Melatonin and NK cells

Because NK cells are well-established killers of virus-infected cells and a wide variety of tumour cells, possible stimulatory activity of melatonin on NK cells is of particular interest. Melatonin is known to stimulate NK cells lytic function in vivo, but it remains unclear whether this is the result of direct stimulation through NK cell-surface receptors, or indirect stimulation through increased IL-2 production[28]. There is evidence that suggests melatonin ingestion quantitatively augments cells involved in tumour immunosurveillance (NK cells and monocytes)[32]. Anti-tumour potential of melatonin due to activation of NK cells should be observed in context of tumor etiology. Two interesting studies demonstrate this. First one was done by Currier and Miller who intravenously injected tumour cells to mice to induce erythroleukemia. They started administrating melatonin to mice at the time of leukemia onset. Melatonin administration resulted in 2.5-fold increase in NK cell number at 9 days. By the 27th day all mice in the control group (untreated) were dead. On contrary one-third of melatonin-consuming mice remained alive at and beyond 3 months after tumour initiation, indicating long-term survival[33]. Other study reported a negative influence of melatonin on the development of a tumor of hemopoietic origin (a T-cell lymphoma) which is understandable since melatonin is a strong T-lymphocyte stimulus[34].

Melatonin and B lymphocytes

The role of melatonin in modifying humoral immunity, or cells of the B-lymphocyte lineage that are responsible for mediating humoral immunity still remains controversial. High turnover rate is specific for B lymphocytes and some studies investigated role of melatonin in B- leukocyte production and apoptosis in mice. The results indicate that melatonin could inhibit B-cell apoptosis in the earliest stages of B-cell differentiation[35]. While it appears that melatonin treatment would result in a greater quantity of B lymphocytes produced, such excessive production could permit genetically aberrant B cells to evade the normal deletion process with defective B cells entering the circulation as preneoplastic cells potentially leading, thus, to frank B-cell

lymphoma[28].

Melatonin in disease and potential therapeutical application

Some scientists consider melatonin to be the immune system buffer because it acts as an immunostimulant under basal or immunosuppressive conditions, but as an anti-inflammatory compound in the presence of exacerbated immune responses, such as acute inflammation. This immunomodulatory function as well as its antioxidant properties make it potentially interesting therapeutic agent.

1) Potential role in tumor therapy

Because serum levels of melatonin become lower with advancing age the potential clinical use of exogenous melatonin could be of benefit for maintaining, prophylactically, youthful levels both of melatonin and of cells mediating tumor immunosurveillance but potential encouraging effect of melatonin on B-cell lymphomas could also be taken into account.

Because IL-2 has been used clinically to enhance T-cell immunity in patients with AIDS or cancer, melatonin was also used in an attempt to see whether it would enhance T-cell immunity in cancer patients. Literature suggests melatonin synergizes with IL-2 anticancer action[36]. Moreover, importance of melatonin in inhibition of early tumour growth was proved when it was discovered that melatonin shows oncostatic effect on some human tumors in vitro even in physiological concentrations[37]. Correspondingly, decreased nocturnal plasma melatonin levels was reported in patients with some tumors (such as breast cancer[38]).

2) Antiviral properties

In recent decades, melatonin has been reported to possess important functions as an antiviral, antibiotic and anti-parasitic molecule[39].

Several studies reported that melatonin can reduce viral levels after administrated to immunocompetent but not to immunocompromised animals. It is believed that melatonin exerts its antiviral activity through increasing serum levels of TNF-α, IFN-γ and especially IL-1β because IL-1β antibodies completely neutralized the protective role of melatonin[40]. Administration of melatonin also showed antiviral effect in several other studies against different viruses including: HIV-1, encephalomyocarditis virus (EMCV), parvovirus, Semliki Forest virus (SFV), West Nile virus (WN-25). Several publications have appeared in recent times documenting potential melatonin use in Ebola treatment. Since NK cells play important role in surviving Ebola virus infection some scientists suggest melatonin is a readily available treatment option. Moreover, under conditions of challenge, melatonin increases heme oxygenase-1 (HO-1), which inhibits Ebola virus replication. Melatonin has also protective effects in cases of septic shock, which, although bacterial, has similar end-point presentations involving blood vessel leakage [41,42].

3) Antibiotic properties

Melatonin in combination with isoniazid resulted in a marked reduction in bacterial loading in cultured strain of Mycobacterium tuberculosis while administration of either isoniazid or melatonin alone did not have any effect on macrophage mortality or viability[39]. Studies have also shown that peaks in M. tuberculosis infection coincide with both the end of winter and the beginning of the summer season suggesting that seasonal changes in the immune system caused by annual fluctuations in melatonin levels could be involved. Some literature also suggests that plasma melatonin levels are lower in people with infection. Melatonin is also reported to inhibit chlamydial infection and proposed mechanism is synthesis of IFN-γ.

In vitro, melatonin exerts anti-microbial activity against various bacteria: Chlamydia trachomatis, Chlamydophila pneumoniae and Chlamydophila felis (50% reduction), multidrug-resistant Gram-positive and Gram-negative bacteria, methicillin-resistant Staphylococcus aureus, carbapenem-resistant Pseudomonas aeruginosa and Acinetobacter baumannii[39] . This field of research could be of additional interest since melatonin seems to have anti-microbial activity against some of the common nosocomial pathogens. In recent years research on potential benefit of exogenous melatonin in treatment of sepsis has become very popular. The mechanisms of melatonin action in sepsis reflect the pleiotropic capacity of the molecule. Melatonin blocks the overproduction of pro-inflammatory cytokines, especially TNF-α, increases IL-10, increases the weight of the spleen and counteract sepsis-induced apoptosis in the spleen, neutralises inflammatory infiltration in different tissues of septic animals, increases antioxidant capacity, decreases reactive oxygen species (ROS) and reactive nitrogen species (RNS) important in pathophysiology of sepsis and protects against sepsis-induced mitochondrial damage. Interestingly, septic patients hospitalized in intensive care units were found to have altered circadian rhythms. Nocturnal plasmatic melatonin levels were found to inversely correlate with illness severity and exogenous melatonin has also been shown to improve clinical outcome for septic newborns by reducing lipid peroxidation, white cell counts, neutrophil counts and C-reactive protein levels[43].

4) Anti-parasitic action

TNF-α, IFN-γ and IL-12 are important for an efficient adaptive host response in parasite infections. Therefore, several studies have examined the effects of melatonin combined with other drugs in the control of parasite infections. In experimental models of T.cruzi infections the combined treatment with melatonin and meloxicam significantly enhanced the release of IL-2 and INF- γ. Furthermore, the blockade of PGE(2) synthesis and the increased release of NO by macrophage cells in infected animals contributed to regulate the production of Th1 subset cytokines significantly reducing the parasitemia[44]. Other studies reported that melatonin and dehydroepiandrosterone (DHEA) reduced parasite load in blood and tissue and that melatonin in combination with zinc could induce thymocyte proliferation in rats inoculated with T. cruzi. The focus of some recent research has been on melatonin modulation the P. falciparum cell cycle[45].

5) Melatonin in other diseases

Due to its pleiotropic capacity, melatonin could be of benefit for various diseased states. Moreover, it is hypothesised that dysfunction of melatonin in the body can lead to various health problems. Some studies indicate that melatonin could play a role in some autoimmune diseases, although evidence is often contradictive. Carrillo-Vico and colleagues described potential role of melatonin in rheumatoid arthritis (RA), multiple sclerosis (MS), systemic lupus erythematosus (SLE), type 1 diabetes (T1D) and inflammatory bowel disease (IBD), psoriasis, autoimmune hearing loss and autoimmune glomerulonephritis. Melatonin has also been proposed to increase the humoral responses to vaccination. This powerful immune response originating after the administration of melatonin might be explained through two primary mechanisms: melatonin could effectively augment the antibody response by enhancing antigen presentation to immunocompetent cells[46], or melatonin could modulate cytokine production at the beginning of the immune response and could therefore control important cellular responses. It has even been suggested as an adjuvant in vaccines against prostate cancer[39]. Melatonin has also been observed in the context of organ transplantation. Melatonin could prolong graft survival, inhibit the immune response, reduce apoptosis and necrosis in graft, inhibit cellular damage caused by surgical stress and ischemia-reperfusion injury, increase GSH and decrease oxidative stress[39]. Potential usefulness of melatonin is definitely present in many diseases, but regardless of immense number of studies on melatonin, further research is needed to fully understand its actions in human body. The role of melatonin reduction in ageing on many age-related pathophysiological conditions, such as increased susceptibility to infectious diseases, neoplasia, metabolic diseases, osteoporosis and autoimmune diseases that are directly associated with immunosenescence is an exciting field of research that could give us answers about both melatonin function and ageing.

CONCLUSION

Currently, the available data shows that melatonin immunomodulatory role is undeniable. Melatonin is an important part of the complex immune system network and its deficiency can result in a failure of immune system functioning and might lead to various pathophysiological conditions. Having this in mind, further research on melatonin and its role in immune system could lead us to exciting new physiological insights and pharmacological options.

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Melatonin: imunološki aspekt

SAŽETAK: Dostupna istraživanja pokazuju da melatonin ima mnogo važnih uloga u ljudskom tijelu, ali ovaj članak bit će usmjeren na ulogu melatonina u imunosnom sustavu. Mnoga istraživanja upućuju na to da postoji veza između melatonina i imunosnog sustava u mnogo životinjskih vrsta, uključujući i čovjeka. Uloga melatonina u regulaciji cirkadijanog ritma, poticanju spavanja i sposobnost da puferira imunosni sustav čini ga zanimljivim i jedinstvenim iz imunološke perspektive. Melatonin pokazuje imunostimulacijska svojstva pri bazalnim ili imunonedostatnim uvjetima, a protuupalna svojstva u prisutnosti pretjerano aktivne imunosne reakcije. Ova karakteristika, kao i antioksidacijska, antivirusna, antibakterijska, antiparazitna i druga svojstva čine melatonin atraktivnom farmakološkom metom.

KLJUČNE RIJEČI: Melatonin, Imunosni sustav, Imunostimulacija, Leukociti, Cirkardijalni ritam, Terapeutska primjena melatonina