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Impact of melatonin on immunity: a review

Review Article

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Abstract: Melatonin is a hormone produced by the pineal gland. In addition to its hormonal effect, it has strong antioxidant properties. Melatonin is probably best known for its ability to control circadian rhythm; it is sold in many countries as a supplement or drug for improving of sleep quality. However, melatonin's effect is not limited to control of circadian rhythm:. it is involved in other effects, including cell cycle control and regulation of several important enzymes, including inhibition of inducible nitric oxide synthase. Melatonin affects immunity as well. It can modulate the immune response on disparate levels with a significant effect on inflammation. The role of melatonin in body regulatory process is not well understood; only limited conclusions can be drawn from known data. The current review attempts to summarize both basic facts about melatonin's effects and propose research on the lesser known issues in the future.

Keywords: *Melatonin • Inflammation • Neuroinflammation • Antioxidant • Sleep • Lymphocyte • Macrophage • Autoimmunity*

Abbreviations

Bcl-XL	B-cell lymphoma-extra large
IL	interleukin
MT	melatonin receptor
NK	natural killer
NOS	nitric oxide synthase
NREM	non-rapid eye movement
RORA	retinoic acid receptor-related orphan receptor α
TC	cytotoxic T lymphocytes
T_h	T helper lymphocytes
TLR	Toll-like receptor
TNF	tumor necrosis factor
TRIF	TIR-domain-containing adapter-inducing enterferon-β
UV	ultra violet

1. Introduction

Melatonin is a hormone produced mainly in the pineal gland. However, minor regions of production can be found in other tissues, such as in the retina of some vertebrates [1,2]. A high content of melatonin is presented in gut as well [3]. In the body, melatonin is responsible for circadian biological rhythms, including physiological and mental activities [4,5]. Control of sleep regulation is probably the best known effect [6]. However, melatonin is responsible for seasonal body weight alteration, as well as evocation and depression of sexual activities in seasonally reproducing animals [7]. Even vocal signatures in birds can be also controlled by melatonin [8]. Melatonin receptors (MTs) are expressed in various tissues and organs: the brain, cardiovascular system, liver, intestine, kidney, and immune cells can receive signals from the pineal gland through melatonin [9].

Melatonin is an extensively researched compound as it has been found to be involved in some beneficial effects in the body when administered as a supplement or drug. Moreover, some pathological processes were found in persons with reduced melatonin production. For example, a protective effect of melatonin was shown in acute pancreatitis [10]; its ability to ameliorate neurodegenerative disorders has been discussed [11]; and it can regulate adipocytes, which may prevent obesity [12]. The opposite situation can appear when melatonin production is affected: night workers are thought to have reduced melatonin production [13]. In these workers, some detrimental adverse effects can occur. For example, increased incidence of cancer in the night workers is assumed to be caused by insufficient production of melatonin [14].

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Though much information about melatonin has been described in scientific reports, no simple conclusion can be provided. The present paper reviews the effect of melatonin on immune system. The facts are presented in the context of overall melatonin effects in the body. Moreover, regulation of immunity can also be a link between melatonin hormonal action and its effect as an antioxidant [15-17].

2. Melatonin interaction with receptor molecules

Four different MTs can be found in the body, enabling some other biomolecules to interact with melatonin; a summary of those biomolecules is depicted in Table 1. MT_1 and MT_2 are membrane, G protein coupled, receptors specific to melatonin, whereas MT_3 and retinoic acid receptor-related orphan receptor α (RORA) are cytosolic molecules with a wide specificity to agonists [18]. Initiation of MT_1 and MT_2 is necessary for sleep promotion; initiation of those receptors leads to inhibition of neuronal activity and phase shift circadian firing rhythms in the suprachiasmatic nucleus [19]. For that reason, selective agonists have been studied as potent drugs for sleep regulation [11,20]. Surprisingly, the receptors have unequal efficacy and their role in the body is not well understood. Recently, MT_2 selective agonist IIK7 was reported to decrease non-rapid eye movement (NREM) sleep onset latency; therefore, MT_2 is expected to be involved in this regulation [21].

MT_3 is identical with an enzyme quinone oxidoreductase 2 (E.C.1.10.99.2). The enzyme is involved in detoxification of quinones; it is speculated that it is responsible for the so-called French paradox as it can participate in the metabolism of quinone derivatives presented in red wine [22]. Initially, melatonin was hypothesized to be a co-substrate of MT_2 because the enzyme accepts flavin adenine dinucleotide, which is reportedly reduced by melatonin to the active hydrogenated form [23]. In later research, the hypothesis that melatonin is a co-substrate quinone oxidoreductase 2 was rejected and strong inhibition of the enzyme by melatonin was shown even by melatonin in pharmacological concentrations [24,25]. It should be emphasized that quinone reductase 2 has hydrogen peroxide as a side product [26]. As will be discussed later in this article, melatonin is a potent antioxidant and its antioxidant potency is above that of other indoles [15]. Prevention of hydrogen peroxide production by inhibition of quinone reductase 2 can be one reason why melatonin can be considered as a “super” antioxidant when compared with other endogenous antioxidants.

RORA also interacts with melatonin. This receptor is responsible for control of the cell cycle and regulation of apoptosis. Melatonin is an agonist of that receptor [11]. In this pathway, melatonin is involved in mediation of signals through RORA; the receptor can become expressed in course of melatonin as well [27]. RORA is not sensitive to all-trans retinoic acid as are other retinoic acid receptor-related orphan receptors [28]. The RORA receptor also participates in disparate regulations. Immunity, where it promotes generation of T_{h17} and regulatory T (T_{reg}) lymphocytes, is one of the major effects [29]. Other regulation of immunity by melatonin through RORA has also been discussed [30]. Melatonin can also impact also other retinoic acid receptor-related orphan receptors, for instance, mRNA for the β variant of the retinoic acid receptor-related orphan receptors had slowed degradation in presence of melatonin [31]. However, no conclusive data exists about the affinity of melatonin to retinoic acid receptor-related orphan receptors β and γ to show whether melatonin action can be mediated through the receptors. The effect can be assumed because the receptors are members of one superfamily, and thus affinity of melatonin for more members of the family might be assumed [32]. More work on the issue is expected in the future: response to the question about melatonin effect to the β and γ receptors will further understanding of melatonin’s role in disparate pathways, including some immune regulation processes.

The aforementioned structures are known receptors of melatonin. However, the effect of melatonin can be mediated through disparate targets in the body. Most of them are not well known, or it is not clear whether melatonin can act on them in vitro only when presented in high concentration or can regulate them in physiological concentrations. Nitric oxide synthase (NOS) and cyclooxygenase 2 are known as relevant targets of melatonin [11,33]. Melatonin acts as their inhibitor; its inhibitory effect can significantly contribute to a melatonin-linked anti-inflammatory mechanism. Owing to inflammation, inhibition of inducible NOS (iNOS) activation is an extensive effect observable for melatonin presented in nanomolar concentrations [34]. In another review paper, inhibition of iNOS was described: melatonin synthetic analogs were compared as candidates for novel drugs [35]. Reduced expression of iNOS can be expected after melatonin intake as well. The effect was proved using an ischemic brain model: the iNOS expression was extensively regulated in comparison with the endothelial and neuronal forms [36].

Table 1. Summarization of chosen targets for melatonin.

Biomolecule	Effect on the biomolecule	Effect of melatonin in the body	References
MT_1 and MT_2	Melatonin is an agonist	Sleep promotion and inhibition of neuronal activity; regulation of circadian rhythm	[12,23,24]
MT_3	Inhibition of enzyme activity	Unknown; reduction of hydrogen peroxide production and improving of oxidative homeostasis in thus way	[5,6,27]
RORA	Melatonin is an agonist, it can promote expression of the receptor as well	Unknown; regulation of immunity, promotion of T_{h17} and T_{reg} lymphocytes	[10,22,23,26,29]
iNOS	Inhibition and reduced expression	Anti-inflammatory effect	[7,20,25,30]

MT – melatonin receptor; iNOS – inducible nitric oxide synthase; RORA – retinoic acid receptor-related orphan receptor α

3. Antioxidant effect

Though sleep regulation by administration of melatonin was known in early 1960s [37], melatonin's antioxidant ability was not discovered until many decades later. The first experiments with plausible confirmation of melatonin´s antioxidant properties were described in the 1990s. Surprisingly, the studies showed the superiority of melatonin antioxidant capacity when compared with standard endogenous antioxidants present in the same molar concentration. Namely, melatonin was proved to be more potent than vitamin E, ascorbic acid, and glutathione [38,39]. Compared to standard hydrophilic antioxidants, melatonin can simply cross the blood brain barrier but remains partially soluble in water [40].

Melatonin acts as a terminal (or suicidal in some sources) antioxidant. It has quite high antioxidant potency when compared with the other indoles [15]. The designation terminal antioxidant for melatonin indicates that melatonin is oxidized into products such as 6-hydroxymelatonin, 3-hydroxymelatonin and N-acetyl-N-formyl-5-methoxykynurenamine [41]. The products of oxidation cannot simply be converted to melatonin by oxidation of a substrate. It is unlike the other endogenous antioxidants that can act as pro-oxidants once oxidized. Structures of melatonin and its oxidation products following oxidation are depicted in Figure 1.

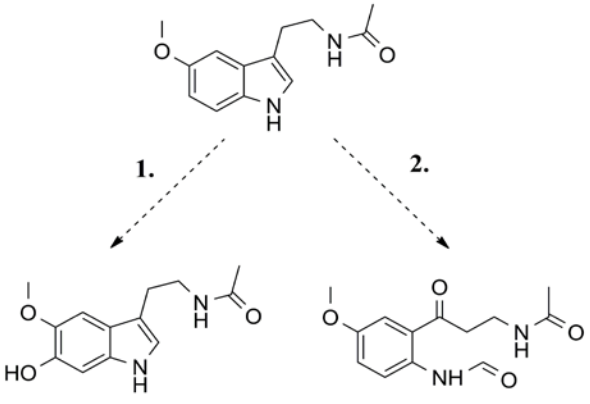

Figure 1. Heart rate (HR) and respiratory rate (RR) variations during drug administration. At time T_0 starting values of HR were similar in both.

The superiority of melatonin as an antioxidant when compared with the other low molecular weight antioxidants can likely be explained by two reasons. Firstly, melatonin can inhibit enzymes producing reactive oxygen (e.g. quinone oxidoreductase) and nitrogen species (e.g. NOS), as mentioned previously. Secondly, melatonin works through other stoichiometry than the other antioxidants. It is believed that one molecule of melatonin can scavenge at least 10 reactive oxygen or nitrogen species [42]. In addition to those effects, melatonin has been proposed to regulate enzymes that participate in fighting with oxidative stress, the so-called high molecular weight antioxidants [16,17]. In one experiment, UV radiation initiated depletion of the antioxidant enzymes catalase, glutathione peroxidase, and superoxide dismutase [43]. Melatonin was potent enough to ameliorate the effect and even protect from oxidization of DNA: 8-hydroxy-2´-deoxyguanosine was significantly reduced. Similar findings were shown in laboratory animals exposed to cadmium and treated with melatonin [44].

Several pathologies are tightly connected to oxidative stress or even caused by long-lasting oxidative insults. Melatonin would be a suitable tool for resolving of the results of oxidative insult. Some studies on that issue have been done: the beneficial effects include amelioration of hyperglycemia-induced liver injury [45], reduction of hypoxia induced pathologies [46] and reduction of poisoning with chlorpyrifos [47]. Despite the promising findings, there is a long path before melatonin can be reasonably used for treatment of the pathologies: there is no known molecular mechanism that describes both the pathology and the melatonin-based therapy. Bringing the therapeutic processes into use for humans will be a complicated process, and more experiments are needed to be done on the issue.

4. Regulation of immunity in the body

The fact that melatonin can modulate immunity was clearly recognized in small rodents with seasonal activ-

Table 2. Regulation of immunity by melatonin.

Effect on immune system	Stimulus	Organism	Reference
Reduction of T_C lymphocytes, promotion of NK	None	mouse	[44]
Up-regulation of T_{h1} lymphocytes, suppression of T_{h2} lymphocytes	Trypanosoma cruzi	rat	[46]
Suppression of macrophages, enhanced IL-10 and IL-2	Trypanosoma cruzi	rat	[47]
Attenuation of cyclooxygenase-2, iNOS, TNF-α, IL-1β and IL-6	lipopolysaccharide	murine macrophages	[48]
Anti-inflammatory effect via promotion Bcl-XL and procaspase-3	lipopolysacchardie	mouse	[49]

Abbreviations: Bcl-XL – B-cell lymphoma-extra large; iNOS – inducible nitric oxide synthase; IL – interleukin; NK – natural killer; T_C lymphocyte – cytotoxic T lymphocyte; T_h – T helper lymphocyte

ity. It showed that mice can promote or reduce individual types of lymphocytes as changes in day length. At night, reduction of cytotoxic T (T_C) lymphocytes, and promoted natural killer (NK) cells, activated both T and B lymphocytes were shown in C3H/HeN inbred mice [48]. It appears that melatonin plays a pivotal role in regulation of immunity in animal models; however, the findings remain inconclusive. Soon after discovering melatonin's regulatory effect, accelerated promotion of acquired immunity resulting in significantly promoted amelioration of some pathologies, including cancer, was posited [49].

The effect of melatonin on immunity has not satisfactorily been confirmed in all subsequent experiments. The study by Santello and coworkers [50] showed an alteration in T helper (T_h) lymphocytes. Whereas T_{h1} lymphocytes were up-regulated, the suppressive action of melatonin on T_{h2} lymphocytes in rats infected with *Trypanosoma cruzi* was shown. On the other hand, Brazao and coworkers demonstrated significant down-regulation of macrophages with melatonin treatment in *T. cruzi*-infected Wistar rats [51]. The authors also reported increased levels of IL-10 and IL-2. The effect of melatonin was significantly enhanced by zinc. The effect of both melatonin and zinc treatment was visible in the infected animals only. Non-infected animals had no alteration in the mentioned cytokines after melatonin treatment.

Though melatonin is able to interfere with some regulatory pathways in the immune system, more specific experiments are necessary to trace all molecular mechanisms of melatonin in the body. However, an anti-inflammatory effect of melatonin that seems to be more extensive than the other effects has been revealed in disparate experiments. Moreover, the anti-inflammatory effect is readily proven using cell lines. For example, melatonin attenuated up-regulation of cyclooxygenase-2, iNOS, TNF-α, IL-1β and IL-6 in lipopolysaccharide-stimulated murine RAW264.7 macrophages [52]. The authors concluded that melatonin modulates inflammation through TLR-4 inflammatory genes. In more detail, myeloid differentiation factor 88 and TRIF-dependent signaling pathways seem to be responsible for the effect. It is an interesting finding because melatonin involving in TLR activation can be suitable not only in inflammation regulation, but it would also be involved in regulating progression of infectious diseases. The aforementioned inhibition of iNOS can be cited as another target for the anti-inflammatory effect. Using ICR mice as a model, melatonin was found to be able to reduce inflammatory process in lungs treated with lipopolysaccharide [53]. The study concluded with the statement that melatonin can act as an anti-inflammatory drug by means of interfering lipopolysaccharide-initiated reduction of Bcl-XL and procaspase-3. The findings are in agreement with later experiments [54]. The pathway based on iNOS can thus act synergistically with the TLR pathway. The proven effects of melatonin in immunity are summarized in Table 2.

As discussed so far, melatonin has no unique pathway that produces immunity. Melatonin more likely meets disparate pathways in which both hormonal and antioxidant effects can occur. Interpretation of findings is somewhat complex, as reactive oxygen and nitrogen species are not only toxic compounds but also messengers. Namely, deubiquitinating enzymes [55], Ras/MEK pathway [56] and transforming growth factor-signaling pathways [57] are regulated by reactive species. Melatonin can scavenge those species, interfering with their pathways. It can be assumed that melatonin is involved in disparate pathways and its effect can be altered in course of conditions, melatonin dose and antigen stimulus. On the other hand, complex experiments on the issue should be done.

5. Disease alteration in course of melatonin effect on immunity

Melatonin was considered for use as a drug for ameliorating cancer [58], epilepsy [59] and neurodegenerative disorders [11], non-specific drug for treatment of viral infections [60] and others. Drugs containing a covalently bound melatonin moiety were also prepared in the past as a suitable preparation for Alzheimer dis-

ease therapy [61,62]. Melatonin is applied as a drug for sleep therapy; it is thought that immune regulation, including a shift in the T_{h1}/T_{h2} balance, is a side effect [63]. Melatonin's affect on immunity may lie in another regulation than those previously mentioned. The immune response to antigenic stimulation differs significantly during stages of life. Differing inflammatory reactions can be expected in young and adults, as depicted on a pig model [64]. In elderly people, impaired immunity functions can arise [65,66]. Some studies have shown that melatonin application can resolve dysfunctions of oxidative homeostasis in animal models [67] and prevent telomerase shortening [68]. For these reasons, melatonin has also been considered for use as a neurodegenerative disorder therapy [11]. According to that data, melatonin would be useful as a drug to ameliorate age-related immunity dysfunction. However, findings about melatonin's effect on age-related disorders, including immunity impairment, should be considered carefully. Most knowledge about melatonin's effect on the age related disorders comes from animal models and experiments on cell lines. Melatonin has been researched for quite a short time when considered life expectancy in developed countries. Moreover, knowledge drawn from human volunteers comes from clinical trials that last only for a few years. The potency of melatonin to solve the age-related pathologies cannot be discounted; however, some special studies on the issue are needed to resolve the many questions involved.

As previously mentioned, melatonin can be involved in regulation of inflammation. Moreover, it has minimal toxicity and it is not involved in any adverse affects. Evidence of melatonin's potency to ameliorate inflammatory bowel disease led to the conclusion that melatonin can perceptively improve the condition of patients [69]. Melatonin has sufficient potencyto regulate immunity via T_h lymphocytes 22 and IL-22 in rats with pancreatitis-associated lung injury [70]. The regulatory mechanism proposed by Huai and coworkers is quite interesting, as IL-22 is a cytokine that regulates innate and adaptive immune response. Melatonin can modulate the balance between the immunity responses and tissue healing. Spontaneous alteration in melatonin level is probably responsible for seasonally occurring diseases such as rheumatoid arthritis [71]. According to that evidence, application of melatonin would be suitable for relief from those diseases and can be designated as a drug for supportive care [72]. The supportive role of melatonin in burn therapy [73,74] and inflammatory bowel disease [75] are two examples.

6. Conclusions

Melatonin is a simple compound with great pharmacological potential. Regulation of immunity seems to be one of the major affects of melatonin; also, its potential to ameliorate pathologies linked to inflammation can be put forth. Unfortunately, there is limited knowledge about melatonin's effects in the body; more extensive research should be done in the future.

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