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Review

The role of melatonin in autoimmune and atopic diseases

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Abstract: Melatonin is the main secretory product synthesized and secreted by the pineal gland during the night. Melatonin is a pleitropic molecule with a wide distribution within phylogenetically distant organisms and has a great functional versatility, including the regulation of circadian and seasonal rhythms and antioxidant and anti-inflammatory properties. It also possesses the capacity to modulate immune responses by regulation of the T_H1/T_H2 balance and cytokine production. Immune system eradicates infecting organisms without serious injury to host tissues, but sometimes these responses are inadequately controlled, giving rise to called hypersensitivity diseases, or inappropriately targeted to host tissues, causing the autoimmune diseases. In clinical medicine, the hypersensitivity diseases include the allergic or atopic diseases and the hallmarks of these diseases are the activation of T_H2 cells and the production of IgE antibody. Regarding autoimmunity, at the present time we know that the key events in the development of autoimmunity are a failure or breakdown of the mechanisms normally responsible for maintaining self-tolerance in B lymphocytes, T lymphocytes, or both, the recognition of self-antigens by autoreactive lymphocytes, the activation of these cells to proliferate and differentiate into effector cells, and the tissue injury caused by the effector cells and their products. Melatonin treatment has been investigated in atopic diseases, in several animal models of autoimmune diseases, and has been also evaluated in clinical autoimmune diseases. This review summarizes the role of melatonin in atopic diseases (atopic dermatitis and asthma) and in several autoimmune diseases, such as arthritis rheumatoid, multiple sclerosis, systemic lupus erythematosus, type 1 diabetes mellitus, and inflammatory bowel diseases.

Keywords: melatonin; autoimmunity; atopic diseases

1. Introduction

Melatonin (N-acetyl-5-methoxytryptamine) was discovered in 1958 in the bovine pineal gland by Lerner and co-workers [1]. Melatonin is the major secretory product synthesized by this the pineal gland during the night and it is the main chronobiotic hormone that regulates the circadian rhythms and seasonal changes in vertebrate physiology via its daily nocturnal increase in the blood [2,3]. Melatonin is converted in two steps from the amino acid tryptophan into serotonin and is then acetylated by arylalkylamine N-acetyltransferase (EC 2.3.1.87, AANAT), after which it is converted into melatonin by hydroxyndole-O-methyltransferase (EC 2.1.1.4, HIOMT) [4]. Although melatonin was originally recognized as a pineal hormone, subsequent studies showed that this indoleamine appeared very early during evolution. Thus, melatonin is present in bacteria, unicellular eukaryotic organisms, invertebrates and vertebrates, algae, plants and fungi, and is also found in various edibles, such as vegetables, fruit, herbs, and seeds [5,6]. In mammals, melatonin is synthesized in many tissues and organs, such as gastrointestinal, respiratory, genitourinary, immune systems, and skin [7–13]. Additionally, melatonin shows a remarkable functional versatility exhibiting antioxidant [14–18], oncostatic [19,20], antiaging [21,22], and immunomodulatory [11,12,23] effects. The molecular mechanisms responsible for the pleiotropic effects of melatonin involve mechanisms of action receptor-dependents [24,25] as well as receptor-independents [25–28].

A large body of evidence has shown a relationships between nervous, endocrine and immune systems and now it is very clear that these systems use a common chemical language for intra- and inter-system communication [29]. In this framework, currently pineal-synthesized melatonin is considered one of members of the complex neuro-endocrine-immunological network and the existence of a bidirectional communication between the pineal gland and the immune system is completely accepted [30,31]. Thus, a number of *in vivo* and *in vitro* studies have clearly documented that melatonin plays a fundamental role in the function of both innate and immune systems [11,12] and a direct correlation between melatonin production and the circadian and seasonal variations in the immune system has also been documented [32,33]. Reciprocally, immunological signals produced by the immunocompetent cells are perceived by the pineal gland and provides a feedback for the regulation of pineal function [34–36].

On the other hand, it is important to note that currently the skin is considered a very important organ within of the neuro-endocrine-immune network [37,38]. The skin is strategically located at the interface between the external and internal environment where detects, integrates, and responds to diverse stressors and stimuli through regulated production of different chemical messengers [38]. Thus, all of the elements controlling the hypothalamus-pituitary-adrenal axis, such as corticotropin releasing hormone (CRH), urocortin, and proopiomelanocortin (POMC)-derived neuropeptides, are expressed in the skin [39]. Moreover, the skin produces many other products biologically active, including a serotoninergic/melatoninergic system [40]. In fact, melatonin is synthesized from serotonin and the enzymatic machinery necessary for the biosynthesis of melatonin is expressed in the skin [40,41]. Moreover, both specific receptors for serotonin and melatonin are expressed in keratinocytes, melanocytes, and fibroblasts [42]. In these cells, melatonin has effects on cellular proliferation and apoptosis [43]. Moreover, melatonin exerts receptor-independent effects, such as oxidative stress protection and cellular metabolism modifications [42,44]. Finally, it is important to note that melatonin is metabolized in the skin through kynuric and indolic pathways and the metabolites produced are 6-hydroxymelatonin, N(1)-acetyl-N(2)-formyl-5-methoxykynuramine and 5-methoxytryptamine [41,45–48]. In this context, it

has been shown that melatonin and its metabolites have antiproliferative effects on human primary epidermal keratinocytes and stimulate differentiation in human epidermis, indicating to have an important function in maintaining the skin barrier [46–49].

The molecular basis for the neuroimmunomodulatory effect of melatonin on the immune system is supported by the existence of specific melatonin receptors in immune organs as well as in immunocompetent cells [11,12,50–52]. Thus, these melatonin receptors are located in plasma membrane of the immunocompetent cells. Using radioligands, specific binding sites for melatonin have been located and characterized in plasma membranes of the several types of immunocompetent cells of different species including birds [53–55], rodents [50,56,57], and human lymphocytes [50,58,59]. Moreover and in human lymphocytes, several second messengers such as cyclic AMP, cyclic GMP, and diacylglicerol, have been involved in the mechanism of action of melatonin in these cells [60,61]. Finally, it is important to note that the classification and denomination of plasma membrane melatonin receptors have been realized by using the official nomenclature suggested by the IUPHAR committee [62]. Thus, the expression of two types of plasma membranes melatonin receptors (called MT1 and MT2 receptors) have been reported in both organs and immune cells of different species including human [63–67].

In the context of mechanism of action of melatonin, it is important to note that in the past the nuclear transcription factor retinoic acid-related orphan receptor α (RORα), a member of the orphan nuclear receptor family, was proposed as the putative nuclear receptor for melatonin, but recent both crystallography data and functional data clearly show that RORα is a receptor for cholesterol, sterols and secosteroids [68–70]. Therefore, a putative nuclear melatonin receptor remains to be identified [52].

The immune system is functionally organized in innate immunity and adaptive immunity. Both immune responses types serve the important function of host defense against microbial infections. Normally, the immune response eradicates infecting organisms without serious injury to host tissues. However, sometimes these responses are inadequately controlled, giving rise to the called hypersensitivity diseases, or inappropriately targeted to host tissues, causing the autoimmune diseases [71]. The hypersensitivity diseases involve a particular subtype of T lymphocyte called T_H2 cells, immunoglobulin E (IgE), mast cells, eosinophils, and a variety of biochemical mediators. These mediators collectively cause increased vascular permeability, vasodilation, and bronchial and visceral smooth muscle contraction. This reaction is called immediate hypersensitivity because it begins rapidly, within minutes of antigen challenge, and has major pathologic consequences. Following the immediate response, there is a more slowly developing inflammatory component called the late-phase reaction characterized by the accumulation of neutrophils, eosinophils, macrophages, and $CD4^+$ T_H2 cells. This later reaction is triggered by cytokines produced by the T_H2 cells and by mast cells, as well as by lipid mediators secreted by mast cells and the term immediate hypersensitivity is commonly used to describe the combined immediate and late-phase reactions. In clinical medicine, these reactions are called allergy or atopy, and the associated diseases are called allergic, atopic, or immediate hypersensitivity diseases [72,73].

The hallmarks of allergic or atopic diseases are the activation of T_H2 cells and the production of IgE antibody. Repeated bouts of these reactions can lead to chronic allergic diseases, with tissue damage and remodeling. Allergic diseases are the most common disorder of immunity, affecting 20% of all individuals in the United States. The clinical and pathologic manifestations of immediate hypersensitivity consist of the vascular and smooth muscle reaction that develops rapidly after repeated exposure to the allergen and a delayed inflammatory reaction. All these reactions may be triggered by IgE-mediated mast cell activation, but different mediators are responsible for different components of

the immediate and late-phase reactions. Immediate hypersensitivity reactions are manifested in different ways, depending on the tissues affected, including rashes, sinus congestion, bronchial constriction, abdominal pain, diarrhea, and systemic shock [74–77]. In this review, we will summarize the role of melatonin in several hypersensitivity diseases, such as atopic dermatitis and asthma.

Regarding autoimmunity, we now know that the key events in the development of autoimmunity are a failure or breakdown of the mechanisms normally responsible for maintaining self-tolerance in B lymphocytes, T lymphocytes, or both, the recognition of self-antigens by autoreactive lymphocytes, the activation of these cells to proliferate and differentiate into effector cells, and the tissue injury caused by the effector cells and their products [78,79]. Autoimmunity is an important cause of disease in humans and is estimated to affect 2–5% of the U.S.A. population. Our understanding of autoimmunity has improved greatly during the past two decades, mainly because of the development of a variety of animal models of these diseases and the identification of genes that may predispose to autoimmunity [80,81]. Nevertheless, the etiology of most human autoimmune diseases remains obscure. However, at the present we know that the major factors that contribute to the development of autoimmunity are genetic susceptibility and environmental triggers, such as infections. Autoimmune diseases may be either systemic or organ specific and various effector mechanisms are responsible for tissue injury in different autoimmune diseases [78,82]. This review will summarize the role of melatonin in several autoimmune diseases, such as arthritis rheumatoid, multiple sclerosis, systemic lupus erythematosus, type 1 diabetes mellitus, and inflammatory bowel diseases.

2. Melatonin and atopic diseases

2.1. Atopic dermatitis

Atopic dermatitis, also called in Clinical Medicine atopic eczema, is an increasing common childhood multifactorial and chronic inflammatory skin disease that also affects adults [83]. The immunopathological basis of atopic dermatitis is complex, but at the present time we know that it is mediated by a T_H1/T_H2 biphasic inflammatory response that involves several cytokines, such as IL-4, IL-5, IL-13 and IFN-γ [84–86]. Regarding to melatonin and atopic dermatitis, a first report shown evidences of a dysfunction of the melatonin secretion in patients with atopic eczema, possibly due to a partially reduced activity of the sympathetic nervous system, which is involved in the control of melatonin secretion [87]. Later, it was shown an elevation of salivary melatonin in patients with atopic eczema [88]. By contrary, in the phases of disease outbreaks it has been documented a reduction in the serum levels of both melatonin and β-endorphin. In the case of melatonin, the difference is statistically significant only during the day, although nocturnal levels are greater for both hormones [89]. On the other hand, it has been reported that melatonin suppresses the development of atopic dermatitis-like skin lesions in 2,4-dinitrofluorobenzene-treated NC/Nga mice by reducing total IgE in serum and IL-4 and IFN-γ production by activated $CD4^+$ T cells [90]. Moreover, it has been shown that melatonin inhibited the inflammatory response associated with contact hypersensitivity [91] and that melatonin treatment attenuated the delayed-type hypersensitivity (DTH) caused by sub-chronic treatment of propoxur in rats [92]. Finally, it has been recently reported that the combined use of deltaran and melatonin are available to correct the alteration in both humoral and cellular immunity observed in an experimental rat contact dermatitis [93].

The potential use of melatonin in the treatment of atopic dermatitis has been postulated. In fact,

melatonin might protect skin integrity thorough both antioxidant and antiapoptotic effects [94–96]. Moreover, melatonin might be involved in the pathogenesis of atopic dermatitis through is regulatory effects on the production of several cytokines, such as IFN-γ and IL-4. Thus, a relationship between IFN-γ, melatonin and atopic dermatitis has been suggested [88,97,98] and it has been also postulated that melatonin might reduce IgE and IL-4 production thereby preventing the development of atopic dermatitis [90]. On the other hand, it is known that sleep disturbance is very frequent in patients with atopic dermatitis and it has been reported that melatonin supplementation is both safe and effective to improve the sleep-onset latency [99]. Despite all above mentioned, no clinical trial has investigated the administration of melatonin in human atopic dermatitis patients.

2.2. Asthma

Asthma is a clinical syndrome characterized by chronic airway inflammation, airway responsiveness, and expiratory airflow limitation. Moreover, patients with asthma have circadian variations in the airway inflammation and lung function [100]. Both nocturnal symptoms and overnight decreases in lung function are a common part of the asthma clinical syndrome and also appear to be associated with asthma-related mortality [101,102]. At the present time, it is considered that this disease is developed through complex interactions between genetic and environmental factors and an imbalance between oxidative stress and antioxidant defenses may play a critical role in both the development and progression of disease [103,104]. Current treatments reduce asthma related mortality, but do not modifies the natural history of the disease [105].

An accumulating body of evidence suggests that melatonin could be involved in the pathogenesis of asthma. Thus, in bronchial asthma patients has been found alterations in circadian rhythms of melatonin and cortisol [106,107], disorders in circadian rhythm of urine 6-sulphatoxymelatonin (a melatonin metabolite) excretion [108], and asthmatic postmenopausal women treated with glucocorticosteroids showed lowered circadian secretion of melatonin [109]. Moreover, in an asthma clinical phenotype called aspirin-sensitive asthma (ASA), it has been shown a lower level of 6-sulphatoxymelatonin excretion than in aspirin-tolerant asthma (ATA) patients [108].

At the present time, it is known that platelets are involved in the pathogenesis of bronchial asthma. Preincubation of platelet-rich plasma with melatonin resulted in an increase in both the intensity and the rate of the first platelet aggregation phase in the ASA patients compared with the ATA patients and control subjects [110]. In addition, in ASA patients has been shown a reduced melatonin synthesis in platelets [111] and a melatonin expression in nasal polyps [112]. Available clinical data on ASA indicate that ASA patients have certain disturbances in the nervous, endocrine, immune, and other body systems. Thus, it has been found that such patients have a lower melatonin production in daytime, a pathology of the platelet membrane-receptor complex, and a pathological response to exogenic melatonin and acetylsalicylic acid [113].

Another clinical classification of asthma is nocturnal asthma and non-nocturnal asthma and patients with nocturnal asthma demonstrate circadian variations in airway inflammation [114]. In this context, it has been reported that melatonin showed differential immunomodulatory effects based on asthma clinical phenotype (nocturnal and non-nocturnal asthma) [114]. Moreover, it has been shown that elevated serum melatonin is associated with the nocturnal worsening of asthma [115]. These results suggest that melatonin might play a role in the pathogenesis of nocturnal asthma and also may indicate an adverse effect of exogenous melatonin in asthma [114]. Therefore, clinicians should be very aware of the

importance of melatonin to nocturnal exacerbation of asthma symptoms and alert asthmatic patients that use exogenous melatonin supplementation could have potential negative effects [102].

On the other hand, it is interesting to note that it has been found an increased oxidative stress in the exacerbation period of patients with bronchial asthma and chronic obstructive pulmonary disease, whereas the antioxidant enzymes and melatonin were reduced [116,117]. Moreover, disturbed sleep is common in asthma and it has been reported that melatonin can improve sleep in these patients [118].

Asthma is an inflammatory lung disease characterized by cell migration, bronchoconstriction and hyperresponsiveness, and can be induced in experimental animals by ovalbumin (OVA) sensitization followed by a challenge. In this experimental model, pinealectomy reduced the total cell number present in the lung and bone marrow cell proliferation, without changing the number cells in the bone marrow or in the peripheral blood [119]. This fact suggests that melatonin is important in the control of cell recruitment from the bone marrow and the migration to those cells to the lung. Thus, melatonin administration to pinealectomized rats seem to restore the ability of cells to migrate from the bone marrow to the bronchoalveolar fluid [119]. Moreover, pinealectomy reduced the total inflammatory cell number in the asthmatic rat lung [120]. As consequence, it has been hypothesized that melatonin may modulate the circadian inflammatory variations in asthma by stimulating the expression of chemotactic agents in the lung epithelial cells. In fact, studies with culture lung epithelial cells suggest that melatonin might synergize with pro-inflammatory cytokines to modulate the asthma airway inflammation through promoting the expression of chemotaxins [120].

Nuclear factor-kappa B (NF-κB) is a critical transcription factor governing the expression of many cytokines that are involved in the pathogenesis of inflammatory diseases, such as asthma. In Sprague-Dawley rats sensitized with OVA, melatonin inhibited the expression of NF-κB, down-regulated the activity of inducible nitric oxide synthase (iNOS) in lung tissue and decreased the production of nitric oxide (NO) in bronchoalveolar lavage fluid (BALF). These data suggest that the inhibitory effect of melatonin probably play a role in decreasing airway hyperresponsiveness and airway inflammation of asthmatic rats models [121]. In addition, in a murine model of chronic asthma it has been described that melatonin inhibited airway collagen accumulation, probably by the inhibition of metalloproteinase-9 [122]. Finally, it is interesting to note that another mechanism which melatonin may be beneficial in asthma is by regulating the mucus production. Thus, recently it has been shown that melatonin inhibited mucus production in an asthma murine model [123].

In summary and at to the current date, the role of melatonin in asthma is controversial and it is not clear. Thus, the beneficial effects of melatonin would a consequence of its antioxidants properties, while the negative effects would a consequence of its pro-inflammatory activity [96]. Thus, further studies are required to investigate the long-term effects of melatonin on airway inflammation and bronchial hyperresponsiveness in humans and so to have a clear criterion to recommend or not the use of melatonin in these patients.

3. Melatonin and autoimmunity

The effects of melatonin on the immune response may not always be beneficial. Thus, the effects of melatonin in different autoimmune diseases are not clear, even some studies have implicated melatonin in the development of different autoimmune diseases. Autoimmune diseases affect approximately 5% of the population in Western countries. These diseases can be systemic, such as lupus erythematosus (SLE), or organ-specific, such as type 1 diabetes mellitus (T1D) [78]. Our

understanding of autoimmunity has improved greatly during the past two decades, mainly because of the development of a variety of animal models of these diseases and the identification of genes that may predispose to autoimmunity [81,124]. Nevertheless, the etiology of most human autoimmune diseases remains obscure. We now know that the autoimmunity results from a failure or breakdown of the mechanisms normally responsible for maintaining self-tolerance in B cells, T cells, or both and, consequently, the recognition of self-antigens by autoreactive lymphocytes, the activation of these cells to proliferate and differentiate into effector cells, and the tissue injury caused by the effector cells and their products [78,79,82].

In this review we will focus the effects of melatonin in several autoimmune diseases, such as rheumatoid arthritis (RA), multiple sclerosis (MS), systemic lupus erythematosus (SLE), type 1 diabetes (T1D), and inflammatory bowel disease (IBD).

3.1. Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammation of the joints characterized by progressive erosion of both cartilage and bone that is associated with the formation of proliferated pannus. The pathogenesis of RA is associated with hyperplasia, increased vascularity, and infiltration of inflammatory immune cells to the synovial membrane of the joints. Activated $CD4^+$ T cells stimulate monocytes, macrophages, and synovial fibroblasts to produce different inflammatory cytokines, such as IL-1β, IL-6, and TNF-α. $CD4^+$ T lymphocytes also stimulate B lymphocytes to produce immunoglobulins [125,126]. The role of melatonin on RA, a common autoimmune disease suffered by approximately 1% of the world's population [127], is not clear [128,129].

Different studies using experimental animal models of arthritis have suggested deleterious actions for both endogenous and exogenous melatonin. Thus, an earlier study reported that constant darkness increases the development of collagen-induced arthritis and exhibit higher titers of serum anti-collagen antibodies than those kept under constant light or a normal photoperiod [130]. The effects of constant darkness were not observed in pinealectomized animals [131]. Furthermore, administration of melatonin to DBA/1 mice immunized with rat collagen II injected subcutaneously and kept under constant light, showed increased development of collagen-induced arthritis (CIA), via enhancement of T lymphocytes priming, when it was injected at the beginning of the immunization, whereas melatonin injection at the onset of the disease (day 30–39), did not affect the clinical signs of the disease [132,133]. Another study showed that melatonin increased serum anti-collagen antibody titer and IL-1β and IL-6 levels both in the serum and joints of arthritic rats, while it decreased oxidative markers in serum but not in joints. Once more, pinealectomy reduced antibodies, cytokine levels and oxidative stress in joints, but also elevated oxidative markers in serum [134]. Moreover, it has been documented increased nocturnal pineal production of melatonin induced by Freund's adjuvant in an experimental model of arthritis [135] and a recent study found that melatonin increased the severity of CIA, probably via attenuation of the expression of *cryptochrome 1* [136]. Thus, factors that enhance endogenous melatonin production might play a role in the etiology of RA. However and conversely, in an adjuvant-induced arthritis in rats, prophylactic and/or therapeutic treatment with melatonin reduced hind paw swelling similar to indomethacin [137]. These contradictory observations may result from the different dosages utilized or different experimental models used in these studies. It is interesting to note that androgens have been found to exert a protective effect against the development of RA [138]. Thus, it has been shown that rat Leydig cells express melatonin receptors and the secretion of testosterone in these cells was

reduced in the presence of melatonin [139]. This effect has been suggested to be the cause of the lower incidence of RA in men.

It has been shown that the geographical distribution of RA shows a north-south gradient, with higher latitudes being associated with an increased incidence and severity of RA, suggesting that augmented melatonin production during long winter nights could be related to RA [140]. Moreover, the risk of arthritis is inversely associated with UVB exposition [141], which is radiation known to reduce pineal synthesis of melatonin [142]. In this context, it is important to note that and additional explanation for incidence of autoimmune diseases in the North is lower production of vitamin D due to shortage of UVB [143]. However, there are UVB immunosuppressive effects independent on the vitamin D production [144,145]. On the other hand, it has been reported that the clinical symptoms of RA show a circadian variation with joint stiffness and pain being more prominent in the early morning [146,147], coinciding with high levels of pro-inflammatory cytokines (especially IL-6 and TNF-α) and low serum concentrations of cortisol [147–149]. Interestingly, some authors have reported a rise in blood melatonin levels during the early morning in RA patients compared with healthy controls, a positive correlation between melatonin levels and disease activity scores, and an advance in the nocturnal melatonin peak compared to control subjects [140,147,150]. However, a recent study denoted that, although morning melatonin serum levels were higher in RA patients than in healthy volunteers, melatonin and RA disease activity do not correlate [151]. In this context it is possible to speculate that the higher levels of melatonin in RA patients might not be the cause of the symptoms but as a consequence of the disease, because the RA is a stressor and the stress would stimulate the synthesis of melatonin to protect the further injury [128,129]. On the other hand, other authors have reported significantly lower levels of morning serum melatonin [152] and even other authors have been observed in RA patients that serum melatonin levels exhibit a wider plateau than in healthy people [153]. It is very interesting to note that a clinical trial of melatonin treatment in RA patients has been conducted. In this study, patients received 10 mg melatonin at night over six months. There was an increase in inflammatory indicators, such as neopterin and erythrocyte sedimentation rates, and low antioxidant profiles. However, there were not significant effects on clinical symptoms or on the levels of TNF-α, IL-1β and IL-6 [154].

Regarding *in vitro* studies, it is interesting to indicate that macrophages infiltrating the synovial fluid of RA show specific melatonin receptors [155] and produce high levels of IL-12 and NO after melatonin administration [156]. In addition, it has been shown that synovial fluid from RA patients has relatively high levels of melatonin [155] and that melatonin inhibits the excessive proliferation of RA fibroblast-like synoviocytes through activation of the cyclin-dependent kinase inhibitors P21 (CIP1) and P27 (KIP1) mediated by ERK [157]. On the other hand, synovial fibroblasts from RA patients show impaired circadian expression of timekeeping genes and pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6 [158]. More recently, in a study with human mesenchymal stem cells, it has been shown that melatonin significantly reduced reactive oxygen species (ROS) and increased superoxide dismutase (SOD) expression, restored the expression of cartilage matrix and chondrogenic genes, and prevented the cartilage degradation by downregulating matrix metalloproteinases (MMPs) [159].

In summary, the immunoregulatory and antioxidant properties of melatonin have led scientist to address its involvement in RA. Nevertheless, preliminary data suggests that the utility of melatonin in the treatment of this disease is ambiguous or negative [129,160]. However, it is interesting to note that a recent paper has shown in an experimental rat model of rheumatoid arthritis that the effect of melatonin on several hematologic indices of inflammation and immunologic reactivity was more potent than that of diclofenac [161].

3.2. Multiple sclerosis

Another serious autoimmune disease that might be related to melatonin is multiple sclerosis (MS). MS is the most common inflammatory demyelinating disease of the central nervous system (CNS) in young adults [162], with a worldwide prevalence of 1.1–2.5 million cases [163]. This disease results from the loss of the neuronal myelin sheath because of attack by autoantigen-specific immune cells. Both adaptive and innate immune cells, as well as proinflammatory cytokines, are associated with the pathogenesis of MS [164,165]. These cytokines also lead to the generation of ROS in the affected sites and markers of oxidative stress have been reported in the sera of MS patients [166,167] and in the CNS of experimental animals [168].

An association between melatonin and MS has been suggested by several observations. Thus, although the etiology of MS is not currently fully understood, one environmental factor that appears to be implicated is latitude, so that shorter winter days could be involved in its etiology [169–173]. In addition, the prevalence of the disease increases in northern countries [174] and a diminished prevalence has been described in mountainous areas with respect to neighboring lower areas [175]. Furthermore, a recent study investigated the relationship between melatonin pathway and MS in a high-risk Finnish population by studying the single nucleotide polymorphisms in the genes coding for enzymes and receptors involved in the melatonin pathway. The results of this investigation showed the association of polymorphisms in the tryptophan hydroxylases 2 and melatonin receptor 1B genes with the progressive subtypes of MS and disability and suggest a dysregulation in melatonin pathway [176]. Finally and in relation to the role of melatonin in the pathogenesis of MS, epidemiological studies have hypothesized a role of the changes in pineal melatonin secretion during puberty in the onset of MS [177].

It has been suggested a relationship between an altered melatonin circadian rhythm and MS. Thus, shiftwork at a young age has been associated with increased incidence of MS, with a positive correlation between the risk of MS and the duration of shift work [178]. Moreover, it is interesting to note that sleep disruption is a frequent complaint in MS patients [179,180]. On the other hand, MS patients exhibit impaired circadian rhythms for both melatonin and its catabolic product, the 6-sulfatoxymelatonin. Furthermore, a high percentage of patients with exacerbated MS were shown to display an inverted melatonin circadian rhythm [181] and a lower total urine excretion of 6-sulfatoxymelatonin than healthy controls [182]. Additionally, patients exhibited significantly reduced night-time excretion of 6-sulfatoxymelatonin when compared with controls, which was normalized by IFN-β treatment [183]. These observations may suggest that a dysregulation of physiological level of melatonin may be involved in both the pathogenesis and severity of MS [160,184,185].

In addition to studies of melatonin action over the course of the MS, endogenous melatonin has been related to the clinical complications of disease. Thus, serum melatonin levels inversely correlate with depression in MS patients [186]. Additionally, diurnal vision impairment related to MS was shown to be linked to the melatonin circadian rhythm and, more importantly, it was improved by oral treatment with melatonin [187]. On the other hand, it has been suggested a relationship between melatonin and the prevalence of seizures associated with MS [188]. Despite everything mentioned above suggest a detrimental effect for melatonin in MS, other authors have found that neither winter-type short days nor melatonin supplementation influence the development or severity of the disease [189]. Moreover, other recent research suggests a beneficial role of melatonin in multiple sclerosis. Thus, melatonin supplementation in MS patients was a positive effect on serum antioxidant capacities and improved the quality of life of the patients [190]. More recently, it has been reported a possible role of

melatonin in reducing oxidative stress in MS through its effect on sirtuin 1 (SIRT1) an antioxidant enzymes manganese superoxide dismutase (mnSOD) and catalase in peripheral blood mononuclear cells (PBMCs) from MS patients [191]. Moreover, a recent report has shown that melatonin administration improves primary progressive MS [192]. Finally, it is very important to note that a recent publication shows that natalizumab, the most currently successful treatment for MS, causes significant increase in serum melatonin levels and also reduces several oxidative stress biomarkers [193].

The role of melatonin in the pathogenesis of MS it has also been studied using experimental models. Experimental autoimmune encephalomyelitis (EAE), the most frequently used animal model of MS, has also reported contradictory results. Thus, one study showed that exogenous melatonin reduced both the severity and the duration of EAE-induced paralysis in Lewis rats. Moreover, melatonin administration also diminished macrophage and $CD4^+$ and $CD8^+$ T cell infiltration in the spinal cord and ICAM-1 expression in the blood vessels close to EAE lesions [194] and a recent report has shown that melatonin had a protective effect on mitochondrial injury in a murine model of MS [195]. Recently, it has been reported that melatonin protected against EAE by controlling peripheral and central T effector/regulatory balance [196]. Moreover, it has been recently shown that melatonin exhibited a therapeutic role by ameliorating the clinical severity and restricting the infiltration of inflammatory Th17 cells into the central nervous system of mice with myelin oligodendrocyte glycoprotein (MOG)-induced EAE [197]. In this same experimental model, melatonin also enhanced IL-10 expression in regulatory T cells [197]. In this context, it is important to indicate that these cellular and molecular effects of melatonin have been also demonstrated by other authors [198,199]. However, another study demonstrated that a melatonin receptor antagonist, luzindole, suppresses EAE [200]. Luzindole acts as a selective melatonin receptor antagonist, with a higher affinity for the MT2 receptor than for the MT1 receptor [201] and both receptors are expressed in lymphocytes, so that this antagonist may trigger a complex effect in lymphocytes that could explain these contradictory results. Finally, it has been reported that when new-born rats were pinealectomyzed, they suffered extensive pathological damage and severe neurological deficits after EAE induction, but adult pinealectomized rats were protected against the development of EAE [202].

3.3. Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a multifactorial autoimmune disease resulting from damage to tissues by immune cells. This disease may manifest at any age and in either sex, but women are more frequently affected than men. SLE has a yearly incidence of 1 to 10 and an estimated prevalence of approximately 20–150 cases per 100,000 people [203]. A hallmark of SLE is the formation of immune complexes in blood and tissues that cause extensive tissular damage [204]. More specifically, the pathogenesis of SLE involves activation of autoreactive T lymphocytes that subsequently initiate the hyperactivity of B lymphocytes. B cells activated leads to polyclonal hypergammaglobulinemia and immune complex deposition [204]. Either T_H1 or T_H2 immune responses can be involved in this disease. The levels of T_H1 cytokines, such as IL-2 and IFN-γ, and of T_H2 cytokines, mainly IL-4, are elevated in SLE patients [205]. However, SLE is still considered a T_H1-dominat disease [206]. In addition, TNF-α and IL-6 also are involved in the disease and the importance of the IL-23-T_H17 axis has also been documented [207]. In summary, the sustained immune response causes SLE patients to develop localized inflammatory episodes that give rise to a vicious circle in which the autoimmune response leads to a number of immunological abnormalities and tissue destruction [208,209].

The role of melatonin in SLE is unclear [160]. The first published paper reported a significantly enhancement in the survival of female NZB/W lupus mice when melatonin were given in the morning versus afternoon [183,210]. On the other hand, an uncoupled melatonin circadian rhythm has been described in MRL-*Fas*^{lpr} mice, a mouse model of SLE [211]. In MRL-*Fas*^{lpr} animals, IL-10 deficiency exacerbates the development of disease, including a reduction in the survival rate, increased tissues lesions, enhanced production of autoantibodies, and increased number of IFN-γ-producing T cells, suggesting that IL-10 has a protective role in SLE [212]. In this context, one study found that melatonin administration reduced serum levels of autoantibodies, decreased the production of inflammatory cytokines, and increased the production of IL-10 in female MRL-*Fas*^{lpr} mice [213]. By contrast, in male mice, melatonin treatment shifted the T_H2 response to a T_H1 profile that displayed higher levels of both inflammatory cytokines and autoantibodies [213]. Their data show a gender-dependent effect of melatonin. In fact, a later study shown that this gender-dependent effect of melatonin is through modulation of sex hormones [214]. On the other hand, another study in mice with pristine-induced lupus shown that melatonin treatment had a beneficial effect, reducing the serum titers of both anti-single-stranded DNA and anti-histone antibodies and the production of IL-6 by splenic lymphocytes [215]. Moreover, it has been shown that melatonin treatment ameliorates murine membranous nephritis through its antioxidant, antiapoptotic, and immunomodulatory effects [216].

Regarding the role of melatonin in SLE patients, very few reports have been published. Thus, a study shown no association of melatonin levels and seasonal light variations with disease activity in SLE patients from a subarctic region [217]. Moreover and recently, it has been reported a decreased daily serum melatonin levels in women with SLE and this parameter was inversely correlated with the activity of the disease [218]. In summary and based on all the above mentioned studies, it has been suggested that melatonin treatment could be beneficial for therapy in SLE.

3.4. Type 1 diabetes

The insulin-dependent diabetes mellitus (IDDM), also known as type 1 diabetes (T1D), is a T cell-mediated autoimmune disease in which the immune response against pancreatic β-cells causes an insulin deficit [219]. Although T1D only accounts for 5–10% of all cases of diabetes, its incidence is rising worldwide [220]. As for most autoimmune pathologies, a latitudinal gradient of T1D incidence has been demonstrated, with cases increasing with latitude. It has been proposed that this relationship is associated with UV exposure and vitamin D levels [221], although melatonin involvement cannot be ruled out.

The animal model more used to study the T1D is the newborn non-obese diabetic (NOD) mice. The NOD mouse strain spontaneously develops T cell-dependent β cell destruction resembling human T1D [222]. This mouse strain exhibits a sexual dimorphism in the development of the diabetes. Thus, 80–90% of female mice develop diabetes, while only 40–50% of male mice develop the disease [223]. It has been well documented that an imbalance between T_H1 and T_H2 responses predisposes NOD mice to developing the diabetes [224,225]. Thus, it has been shown in NOD mice that the $CD4^+$ T cells show a T_H1-dominant phenotype, which manifests as increased IFN-γ and decreased IL-4 production by activated $CD4^+$ T cells [226].

Regarding melatonin and T1D, it has been shown that pinealectomy of newborn NOD mice significantly diminished survival and induced glycosuria, whereas chronic administration of melatonin increased survival and delayed the onset of the disease, facilitating the maintenance of glucose

homeostasis [227]. Moreover, melatonin reduced the proliferation of splenocytes and T_H1 cells, prolonging the survival of pancreatic islet grafts in NOD mice [160,228]. On the other hand and interestingly, in streptozotocin (STZ)-treated rats and in LEW.1AR1-iddm (insulin-dependent diabetes mellitus) rats, two animal models of T1D, it has been shown that low levels of insulin correlated with increased production of melatonin [229,230]. Moreover, in one of these experimental models the insulin administration normalized the pineal changes [230]. To explain the above mentioned antagonism between melatonin and insulin production, it has been suggested a new hypothesis that involves catecholamines. Thus, catecholamines may control insulin-melatonin interactions by decreasing insulin levels and stimulating melatonin synthesis [231]. In support of this hypothesis, in the T1D rat models, the increased catecholamine and melatonin levels appear together with decreased insulin levels [231]. This result agrees with the suggestion that T1D is associated with stress and enhanced melatonin secretion. Furthermore, an explanation of the increased melatonin levels could be that the melatonin protects the organism by attenuating oxidative stress-induced β-cell damage [231]. Final and recently, it has been reported a significant association between melatonin and children and adolescents T1D patients [232].

In summary, melatonin is not only useful for preventing the development of T1D, but also shows protective effects against diabetes-associated cardiovascular disturbances by improving vascular contractile performance in diabetic rats [233] and reducing blood pressure in T1D teenagers [234]. Finally, the immunosuppressive actions of melatonin have also been revealed as a useful tool for avoiding allorejection in islet transplantation, a potential therapy for T1D [160,228].

3.5. Inflammatory bowel disease

Inflammatory bowel disease (IBD) encompasses a group of intestinal inflammatory diseases that includes ulcerative colitis and Crohn's disease. For these two diseases, both the innate and adaptive immune responses appear to be implicated and they are characterized by idiopathic, chronic and relapsing inflammation in the small and large intestine [235,236]. Accumulation of immune cells in the intestine tissues is one characteristic of IBD. The cells infiltrating the lamina propia include neutrophils, macrophages, dendritic cells, and B and T lymphocytes. Activation of these immune cells in the intestinal mucosa induces inflammatory response and increases the local levels of several cytokines, such as TNF-α, IL-1β, IFN-γ, and IL-6 [237]. Furthermore, both T_H1 and T_H2 lymphocytes are involved in the pathogenesis of Crohn's disease and ulcerative colitis, respectively [238]. Thus, T cells isolated from the lamina propia of Crohn's disease produce increased amounts of IFN-γ, indicating a T_H1 phenotype. By contrast, T cells from ulcerative colitis produce increased amounts of IL-5, suggesting a T_H2 response [239]. In addition, recent genetic studies have demonstrated that the IL-23-T_H17 pathway also are involved in the pathogenesis of IBD [240–243].

An impairment of circadian rhythmicity has been shown to be related to the course of IBD in experimental models. Thus, mice subjected to continuous changes of the light/dark cycle or to sleep deprivation have been shown to exhibit more severe colitis with increased weight loss and mortality compared to control animals [244,245]. Furthermore, in experimental models of colitis in rodents, melatonin reduced visceral hyperalgia [246] and diminished disease severity [158,247–250] by antioxidant mechanisms, reducing lipid peroxidation, nitrosative stress [248,251], and protecting endogenous antioxidants from depletion [252]. In addition, melatonin was shown to modulate the immune attack on the colonic mucosa by regulating the activities of macrophages [253] and matrix

metalloproteinases (MMP) 2 and 9 [249,254], and by suppressing iNOS and cyclooxigenase-2 (COX-2) activities [249,251], pro-inflammatory cytokine levels [249,250,252,255], and adhesion molecules [256]. Moreover, melatonin has been shown to modulate apoptosis in colitis models [255] and intracellular actions, such as NF-κB inhibition and c-Jun activation, have also been associated with the effects of melatonin on colitis [255,256]. On the other hand, it has been shown that the combination of erythropoietin and melatonin may exert more beneficial effects than either agent used alone [257].

In summary, although available data regarding melatonin treatment in experimental models of colitis suggest positive effects via its antioxidant, anti-apoptotic, and anti-inflammatory properties, to date, no clinical trials have been conducted to investigate the effects of melatonin on IBD and very few reports have been published, each with different results. Thus, a patient suffering ulcerative colitis observed that melatonin caused the disappearance of clinical symptoms and that these symptoms reappeared when melatonin consumption stopped [258]. By contrary, in other two cases, one an ulcerative colitis patient and the other a patient with Crohn's disease, experienced an exacerbation of their respective diseases, which remitted after melatonin intake ceased [259,260]. On the other hand, it has been reported that the use of melatonin in combined therapy for IBD (both ulcerative colitis and Crohn's disease) considerably improves the results of treatment and promotes a more complete ultrastructural recovery of the colonic mucosa [261]. Moreover, a study reviewed and analyzed three clinical trials and fifteen non-clinical studies [262]. The results of this investigation show that in the majority of these studies melatonin has a positive effect on IBD with no or negligible side effects. Such results have been mostly explained through free radical scavenging and diminishing inflammation [262,263]. However, another extensive review about the clinical uses of melatonin indicates that the preliminary data regarding the utility of melatonin in the treatment of ulcerative colitis and Crohn's disease are either ambiguous or negative [129]. On the other hand, a recent study has evaluated adjuvant treatment with melatonin in ulcerative colitis patients. This strategy kept the treated patients in remission for the 12 months of their study period and suggests that adjuvant melatonin therapy should be helpful in ulcerative colitis patients [264].

It is interesting to note that there is a considerable bulk of information supporting the connection between autophagy and human diseases, including IBD. Autophagy represents a homeostatic cellular mechanism for the turnover of organelles and proteins, through a lysosome-dependent degradation pathway. Also during starvation, autophagy facilitates cell survival through the recycling of metabolic precursors. Additionally, autophagy can modulate other vital processes, such as programmed cell death (e.g., apoptosis), inflammation, and adaptive immune mechanisms and thereby influence disease pathogenesis [265–267]. In this context, some of the opposite effects than have been reported for melatonin in IBD could be related to the duality of its effects on autophagy, which itself can be beneficial or detrimental [268]. Finally, several recent studies have demonstrated a relationship between altered sleep circadian rhythm and the pathogenesis of IBD [269–271].

4. Conclusions

A growing body of evidence has been accumulated suggesting a direct link between the pineal gland/melatonin and the immune system and, at the present time, is very clear the existence of a bidirectional interaction where melatonin influences immune system while immune signals also affect pineal function [30]. The immune system is functionally organized in innate immunity and adaptive immunity. Both immune responses types serve the important function of host defense against microbial infections. Normally, the immune response eradicates infecting organisms without serious injury to host

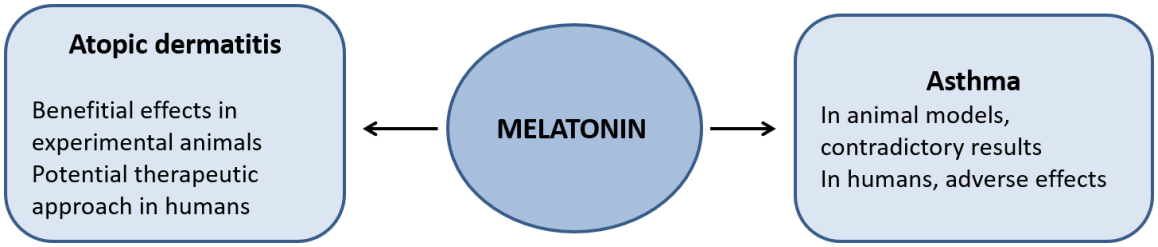

Figure 1. Effects of melatonin in atopic diseases.

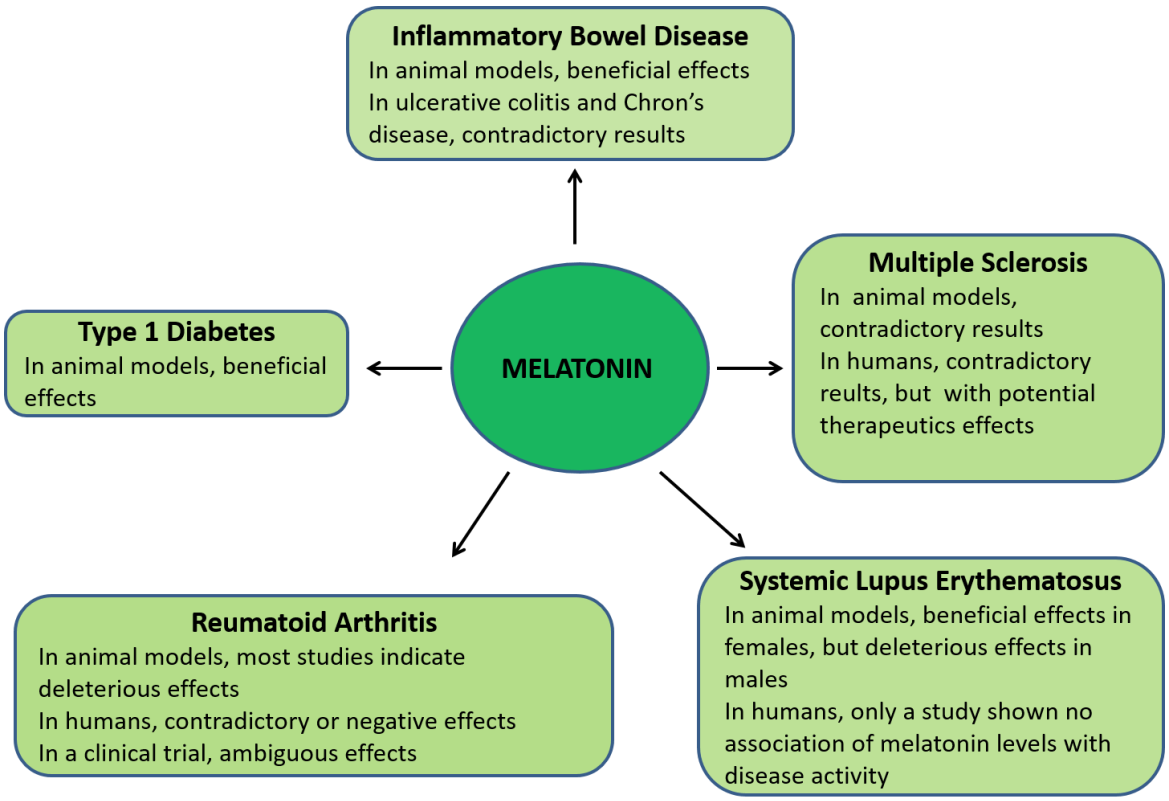

Figure 2. Effects of melatonin in several autoimmune diseases.

tissues. However, sometimes these responses are inadequately controlled, giving rise to the called hypersensitivity diseases, or inappropriately targeted to host tissues, causing the autoimmune diseases [71]. In this review, we have focused the role of melatonin in both atopic diseases (atopic dermatitis and asthma) and in several autoimmune diseases (arthritis rheumatoid, multiple sclerosis, systemic lupus erythematosus, type 1 diabetes mellitus, and inflammatory bowel disease). Regarding the effects of melatonin in atopic diseases, the results summarized in this review are not clear and conclusive and melatonin shows both beneficial and adverse effects depending on the animal model and clinical disease studied (Figure 1). Regarding melatonin and autoimmune diseases, the effects of melatonin have been investigated in several animal models and evaluated in patients with clinical autoimmune disease. For most of the autoimmune diseases discussed in this review, melatonin effects are not clear and conclusive and depending on both the specie studied and the experimental condition utilized (Figure 2) [129,154,160,272,273]. Moreover, these effects are a consequence of antioxidant, anti-inflammatory, and immunomodulatory properties of melatonin [274,275]. However, it has been

suggested that melatonin treatment could be beneficial in inflammatory bowel disease, systemic lupus erythematosus, type 1 diabetes, and multiple sclerosis [129,160,192,264]. The data analyzed in this review suggest an important role of melatonin in the pathogenesis of autoimmune diseases and a potential clinical application of melatonin in the treatment of some autoimmune diseases.

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Conflict of interest

The authors do not have a financial relationship with any commercial entity that has an interest in the subject of this manuscript. Moreover, all authors declare no conflicts of interest in this paper.

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