Review

NeuroImmunoModulation

Neuroimmunomodulation 2008;15:93–101
DOI: 10.1159/000148191

Received: February 1, 2008
Accepted: March 5, 2008
Published online: August 5, 2008

Immunomodulation by Melatonin: Its Significance for Seasonally Occurring Diseases

Venkataramanujam Srinivasan[a] D. Warren Spence[b] Ilya Trakht[c]
Seithikurippu R. Pandi-Perumal[d] Daniel P. Cardinali[e] Georges J. Maestroni[f]

[a]Department of Physiology, School of Medical Sciences, University Sains Malaysia, Kubang Kerian, Malaysia; [b]Center for Addiction and Mental Health, and [c]Sleep and Neuropsychiatry Institute, Toronto, Ont., Canada; [d]Division of Clinical Pharmacology and Experimental Therapeutics, Department of Medicine, College of Physicians and Surgeons of Columbia University, New York, N.Y., USA; [e]Departamento de Fisiología, Facultad de Medicina, Universidad de Buenos Aires, Buenos Aires, Argentina; [f]Center for Experimental Pathology, Cantonal Institute of Pathology, Locarno, Switzerland

Key Words
Immune mechanisms · Infectious diseases · Melatonin · Rheumatoid arthritis · Seasonal affective disorder · Seasonality

Abstract
Melatonin is not only synthesized by the pineal gland but also in many other organs and tissues of the body, particularly by lymphoid organs such as the bone marrow, thymus and lymphocytes. Melatonin participates in various functions of the body, among which its immunomodulatory role has assumed considerable significance in recent years. Melatonin has been shown to be involved in the regulation of both cellular and humoral immunity. Melatonin not only stimulates the production of natural killer cells, monocytes and leukocytes, but also alters the balance of T helper (Th)-1 and Th-2 cells mainly towards Th-1 responses and increases the production of relevant cytokines such as interleukin (IL)-2, IL-6, IL-12 and interferon-γ. The regulatory function of melatonin on immune mechanisms is seasonally dependent. This fact may in part account for the cyclic pattern of symptom expression shown by certain infectious diseases, which become more pronounced at particular times of the year. Moreover, melatonin-induced seasonal changes in immune function have also been implicated in the pathogenesis of seasonal affective disorder and rheumatoid arthritis. The clinical significance of the seasonally changing immunomodulatory role of melatonin is discussed in this review.

Introduction

Melatonin (N-acetyl-5-methoxytryptamine) is a methoxyindole secreted by the pineal gland of all mammals and primates including man [1, 2]. In humans, it is not only synthesized in the pineal gland but also in many other organs and tissues, including the eye [3], gastrointestinal tract [4, 5], skin [6], lymphocytes [7] and thymus [8]. The finding that melatonin is synthesized in lymphoid organs and, further, the fact that diurnal and seasonal changes in immune function can be correlated with melatonin synthesis and secretion [9] support the concept that melatonin is involved in the regulation of the human immune system [10]. The role of melatonin as the possible mediator of seasonal effects on immune func-

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

1021–7401/08/0152–0093$24.50/0

Accessible online at:
www.karger.com/nim

G.J. Maestroni
Cantonal Institute of Pathology
CH–6601 Locarno (Switzerland)
Tel. +41 91 816 0791, Fax +41 91 816 0799
E-Mail georges.maestroni@ti.ch

tion has been well recognized in animals [11–13]. In humans, the seasonal changes in melatonin secretion and neuroimmune function may be one of the major causes of seasonal affective disorder (SAD) [14]. The decline in immune function with aging and its correlation with the decline in hormone levels, especially melatonin, have been argued to be one of the major causes for the increased incidence of neoplastic and infectious diseases encountered in the elderly [15–17]. This review will discuss the effects of melatonin on various parameters of immune function, and how seasonal changes in melatonin levels could contribute to seasonally dependent disease states associated with an increased incidence of infectious and neoplastic diseases.

Melatonin Biosynthesis and Its Regulation

Melatonin is biosynthesized from tryptophan, which is taken up from the blood and converted via 5-hydroxytryptophan to serotonin [18]. Serotonin is then acetylated to form N-acetylserotonin by the enzyme arylalkylamine N-acetyltransferase, which is subsequently converted into melatonin by hydroxyindole-O-methyltransferase [18]. These key enzymes involved in melatonin biosynthesis have been identified in human lymphocytes [7] and in the human thymus [8].

In humans and in most mammals examined so far, pineal melatonin biosynthesis and secretion exhibit a circadian rhythm with low levels being produced during the daytime and high levels at night. This circadian rhythm of pineal melatonin production and secretion is regulated by a complex neural circuit beginning with fibers originating in the retina which project to the suprachiasmatic nucleus of the hypothalamus via the retinohypothalamic tract [19]. Special photoreceptor retinal ganglion cells containing the photopigment melanopsin are involved in transducing light information in this pathway [20, 21]. Projections from the suprachiasmatic nucleus pass through the paraventricular nucleus, medial forebrain bundle and reticular formation to the intermediolateral horn cells of the spinal cord, which are the preganglionic sympathetic neurons innervating the superior cervical ganglion [19]. Postganglionic sympathetic fibers from these ganglia terminate on the pinealocytes and regulate the synthesis and secretion of melatonin by releasing norepinephrine. Via its binding to β-adrenergic receptors in the pinealocytes, norepinephrine promotes cyclic AMP formation, which in turn stimulates melatonin synthesis [22].

Although melatonin is synthesized in a number of tissues, circulating melatonin is almost exclusively derived from the pineal gland. The half-life of melatonin ranges from 20 to 40 min [2]. With very high interindividual variability [23], the day-night differences in the melatonin rhythm are greatly decreased in elderly individuals [24].

Seasonal Variations in Melatonin Secretion

Based on convincing evidence obtained in animals, Wehr [25] suggested that a close association existed in humans between the duration of nocturnal melatonin secretion and the dark phase of the daily photoperiod, and that seasonal changes in the length of the scotophase were the trigger for parallel changes in melatonin secretion. Indeed, results in several mammalian species support this view. For example, seasonal variations in the amplitude of melatonin secretion in the Siberian [26] and European hamster [27] are noteworthy. In the European hamster, the nocturnal peak of pineal melatonin secretion during long naturally occurring photoperiods in summer is 5 times greater than daytime values with a duration of 4 h. By contrast, nocturnal melatonin secretion in naturally occurring short photoperiods in winter shows a 15-fold increase over the daytime value, with a duration of 9 h. This indicated that duration and magnitude of melatonin secretion are strongly correlated with the changing photoperiods of the season [28].

Seasonal changes in melatonin secretion are observed in humans, e.g. an earlier peak of melatonin secretion in summer as compared to winter [29]. In a study on young Japanese women exposed to naturally occurring light, Ueno-Towatari et al. [30] reported seasonal variations in melatonin levels. Peak levels and duration of nocturnal melatonin secretion throughout the year were as follows: winter, 15.80 ± 8.18 pg/ml plasma (4.05 h ± 81 min); spring, 15.22 ± 3.38 pg/ml plasma (3.25 h ± 118 min); summer, 21.46 ± 10.52 pg/ml plasma (3.37 h ± 85 min), and autumn, 97.60 ± 67.56 pg/ml plasma (5.31 h ± 75 min). A delay in the peak time of melatonin secretion was also found in the autumn season. The study of Ueno-Towatari et al. [30] clearly shows that the progressive shortening of the duration of daylight is associated with the increase in nocturnal melatonin secretion during autumn, supporting the suggestion that, in humans as well as in animals, a linkage exists between seasonal changes and melatonin output.

Immunomodulation by Melatonin

Melatonin receptors and signaling mechanisms are detectable in immunocytes [31]. Melatonin exerts most of its physiological actions by acting through membrane-bound MT_1 and MT_2 receptors [32]. These receptors belong to the superfamily of G-protein-coupled receptors containing the typical seven transmembrane domains and account for several immunological actions of melatonin. Melatonin has been shown to act specifically on MT_2 receptors expressed in immunocompetent cells and regulate both cellular and humoral responses [33]. A decrease in cyclic AMP concentration is the frequently observed effect seen after the action of melatonin on membrane-bound receptors [32]. In the cytoplasm, melatonin interacts with calmodulin [34] and other proteins, like tubulin [35]. Melatonin also interacts with nuclear binding receptors, e.g. ROR α1 and ROR α2, identified in human lymphocytes and monocytes [36]. These receptors appear to be involved in the immunomodulatory actions of melatonin.

Ever since it was demonstrated that inhibition of melatonin synthesis causes inhibition of cellular and humoral immune responses in mice [37], many studies in animals and humans have shown that melatonin affects both cellular and humoral arms of the immune response [10, 38, 39]. When administered to birds or mammals, including humans, melatonin has been shown to influence the immune system. Melatonin is of therapeutic value to enhance the immune response of aged individuals or patients with immunocompromised conditions [40, 41]. The enhancement of cytokine production, e.g. interleukin (IL)-2, IL-6 and interferon (IFN)-γ, by melatonin was demonstrated in cultured human mononuclear cells [42], a finding attributed to the upregulation of cytokine gene expression [43]. By increasing the production of cytokines such as IL-12, melatonin increases IFN-γ production by T helper (Th)-1 cells and enhances natural killer (NK) cell activity [41, 42, 44].

Melatonin and Thymus

The thymus is a primary lymphoid organ in which the T-cell repertoire and tolerance to self-antigens are established through positive and negative selection mechanisms driven by the affinity of the T-cell receptor binding to self-MHC molecules. The thymus is also frequently referred to as an 'organ of youth' in mammals, the process of thymic involution being considered one of the most remarkable physiological changes occurring with age [45, 46]. Many factors such as hormonal deficiencies, dietary impairment, exposure to stress or bacterial endotoxins have all been suggested as instrumental for increasing the physiological involution of the thymus which is seen at advanced age. The age-associated regression in size, weight and cellularity of the thymus as well as an increased apoptosis of the thymic cortex are considered to be the most important contributing factors to thymic cell death [47]. Regression of the thymus can be induced by pinealectomy [48] and, conversely, the process can be reversed by melatonin administration [49]. Similarly, the age-associated involution of the thymus can also be reversed by melatonin administration [50].

A number of mechanisms have been proposed to account for the action of melatonin in arresting thymic involution. Melatonin exerts anti-apoptotic effects on the thymus [51], probably by inhibiting glucocorticoid receptor nuclear translocation in thymocytes [52, 53], by modifying intra-thymic zinc levels [54] or through its antioxidative actions [50].

Melatonin partly exerts its influence on thymic function by acting through membrane-bound MT_1 and MT_2 receptors and through nuclear orphan receptors, such as the thymus-specific melatonin ROR γt receptor [31]. MT_1 and MT_2 receptors have been detected in thymic cells of different populations [33, 55, 56] and play an important role in influencing cytokine production, i.e. the nuclear receptor ROR γt has a specific role in different thymopoietic processes [31]. It has been suggested that melatonin modulates thymocyte maturation and converts the immature thymocytes into mature cells, protecting thymocytes from apoptosis for positive selection and maturation [8].

The presence of high levels of melatonin in cultured rat thymocytes and the expression of mRNAs encoding arylalkylamine N-acetyltransferase and hydroxyindole-O-methyltransferase within rat and human thymus cells have shown conclusively that melatonin is synthesized within thymocytes [8]. Thus, melatonin seems to exert intracrine, autocrine and paracrine functions within the thymus.

Melatonin-Opioid Interaction in Cellular and Humoral Responses

It is well established that melatonin positively correlates with both cell-mediated [57] and humoral immunity [58]. Pinealectomy has been shown to reduce both

cellular and humoral responses in birds, whereas melatonin replacement restored cellular and humoral immunity back to normal levels [59]. Melatonin has been found to be most active in counteracting immunodeficiencies secondary to acute stress or drug treatment. This effect of melatonin could be abolished in mice by administration of the opioid antagonist naltrexone [60], suggesting that the opioid peptides are potential mediators of the immunoenhancing effects of melatonin. This immunoenhancing action of melatonin has been further substantiated by experiments employing the co-administration of opioid peptides such as dynorphins 1–13 and β-endorphin [61]. It was then proposed that by binding with melatonin receptors present in the CD4+ Th cells melatonin induces the secretion of opioid peptides, and thus modulates immune function at both lymphocyte and thymus gland level [62]. Indeed, an increase in the number of CD4+ Th cells is seen after melatonin treatment of rats [63].

Melatonin-induced opioid involvement in the immunoenhancing effect has also been reported in birds. In Japanese quails, melatonin administration alone (50 μg/ml) for 3 weeks increased both cellular and humoral responses by 22 and 34%, respectively, an effect blocked by the concomitant administration of naltrexone [64].

The relative balance of Th-1 vs. Th-2 cytokine expression plays a crucial role in the regulation of cellular immune responses [65, 66]. These responses in turn play a critical role in determining the susceptibility to infectious diseases and progression of inflammatory disorders. In conditions of immunodeficiency, melatonin favors the Th-1 lymphocyte response [43]. During the normal progression of a human immunodeficiency virus (HIV-1) infection, an impairment in IL-12 production precedes a switch from Th-1 to Th-2 stage of immunity [43]. Decreased levels of serum melatonin and IL-12 in a cohort of 77 HIV-infected individuals have been found, pointing to the possibility that impairment in the Th-1 immune response may have been a causal factor in the decreased melatonin level [67]. It has been noted in turkeys that embryonic exposure to melatonin accelerated the development of both cellular and humoral immune responses and that the responses continued to increase above the typical immune response in adult turkeys [68]. These findings provide support for the hypothesis that embryonic immune alterations caused by melatonin exposure could afford the animal a healthy immune advantage in later life.

Melatonin in Innate Immunity

Macrophages and neutrophils are important components of the innate immune system. It has been demonstrated that melatonin has a stimulatory influence on the production of granulocytes and macrophages [69, 70]. Inasmuch as both of these cells are components of the nonspecific immune system, their increased production could effectively contribute to the arrest of neoplastic growth and to the destruction of virus-infected cells. Several possible mechanisms by which melatonin enhances the production of these cells have been suggested. Exogenous melatonin administration augments both NK cell and monocyte activity after a brief latency of 7–14 days [71]. The enhanced monocyte production induced by melatonin may be due either to its direct action on melatonin receptors or to the increased monocyte sensitivity to stimulants such as IL-3, IL-4, IL-6 or granulocyte-macrophage colony-stimulating factor [72, 73].

Melatonin not only increases the production of monocytes and macrophages but also influences their physiological actions. Upon activation by Toll-like receptor agonists and/or inflammatory cytokines, macrophages may produce large amounts of nitric oxide (NO). Excessive NO production can be harmful to the body, e.g. they can cause the development of degenerative diseases [74]. It has been found that melatonin decreases NO concentration in macrophages by suppressing the inducible NO synthase expression [75]. Since melatonin has chemotactic effects on human and rat leukocytes both in vitro and in vivo [76], this action can reflect the ability of endogenously produced melatonin to regulate leukocyte infiltration and function during the inflammatory response.

Season, Immune Function and the Role of Melatonin

Changing seasons exert fundamental effects on immune function and melatonin may play a crucial role in this aspect [11, 12, 77–81]. In mammals, the association between the duration of the environmental light period and the immune response has been reported inasmuch as short photoperiods (8 h of light, 16 h of dark) have a greater enhancement effect on humoral immunity than long photoperiods (16 h of light, 8 h of dark) [82]. It has been suggested that the augmentation of the immune response occurring in hamsters exposed to short days confers a survival advantage because it helps the animal to cope with seasonal stressors such as low temperature or reduced food availability that otherwise would increase its

susceptibility to infections [79]. Fishes also exhibit seasonal fluctuations in their susceptibility to different infectious diseases [83].

The photoperiodic timing of seasonal physiology in mammals depends on entrainment of the suprachiasmatic nucleus by the light-dark cycle, a process which is codified by changes in the synthesis of melatonin (the *'encryption'* of the photoperiodic time cycle [84]). This information is then decodified by the tissues that may sense the melatonin signal. In accordance with this view, seasonal changes in the duration of nocturnal melatonin secretion can encode seasonality for the immune function [13].

In humans, seasonal changes in immune function have also been described. Proinflammatory cytokines such as IFN-α and IFN-γ are increased during winter compared to the summer season [85]. Increases in IFN-γ and decreases in IL-10 were reported in a study undertaken in Antarctica during the winter season [86]. These seasonal variations in immune parameters may be well mediated through photoperiodic changes in the duration of melatonin secretion [13].

Infectious Diseases, Seasonality of the Immune Function and the Possible Role of Melatonin

Seasonal outbreaks of infectious diseases, with their predictable occurrence compressed into a few months of the year, have made their management an important public health issue [87]. The universal nature of the seasonal cycles of infectious diseases has been explained by many theories. For example, in the case of dengue infection, a mosquito-transmitted pathogen infects nearly 50 million people worldwide per year and may result in the development of fatal dengue hemorrhagic fever and dengue shock syndrome. Much of the recent debate has focused on the role of immune responses in dengue infection and dengue hemorrhagic fever [88]. In Thailand, it has been found that the epidemic pattern of dengue fever is the result of cross-protective immunity and is subject to alterations in changes in inter-serotype immune reaction [89]. Preexistence of dengue virus antibodies and a cascade of other immune responses initiated by memory T lymphocytes have been implicated in the immunopathogenesis of dengue virus infection [89]. Seasonal changes in poliomyelitis, measles and other seasonal infectious diseases are also attributed to changes in seasonally dependent immune functions [87]. These annual variations in the incidence of many infectious diseases, such as the seasonal physiologic cycles of many mammalian species, are linked to changes in the light-dark cycle, and could thus be linked to changes in the duration of melatonin.

Seasonally dependent immune phenomena were investigated in a double-blind, placebo-controlled trial conducted on human volunteers in the former Soviet Union [90]. In January, the intranasal administration of a live influenza virus vaccine to 360 volunteers in Leningrad resulted in febrile reactions in 6.7% whereas only 0.8% of 197 volunteers inoculated in June showed similar reactions ($p = 0.003$). These findings correlated with an increase in antibody titer in 31–40% in January as compared to 4.3–4.8% in May and October ($p < 0.001$) [90]. Given the increasing evidence that the seasonality in host susceptibility is linked to more fundamental changes in immune functions, melatonin could hold considerable potential as an adjunct therapeutic agent for the management of infectious illness and/or for vaccines.

Such a possibility has been the subject of several investigations. Injections of melatonin to Siberian hamsters 4 h before the onset of darkness (so as to lengthen the endogenous melatonin profile) mimicked the effects of short days on febrile response to a simulated infection, thus emphasizing the importance of the duration of melatonin secretion in controlling the host's response to infection [91]. In a recent study in Siberian hamsters, it was noted that exposure to short days increased the number of circulating leukocytes and several lymphocyte subtypes. The short-day exposure also attenuated both the magnitude and the duration of two major consequences of bacterial infection, namely anorexia and cachexia [92]. The investigators found that the effect of short photoperiods on circulating leukocyte counts was abolished by pinealectomy. Additionally, behavioral and somatic responses (sickness behavior) decreased [92]. The findings were interpreted to support the conclusion that melatonin affected the responses of the peripheral immune system to short photoperiods, and thus had a regulatory influence on the neural-immune responses characteristic of sickness behavior.

The link between melatonin and the immune system in patients affected with HIV-1 infection has been explored [67]. In a study of 77 HIV-1-infected individuals, serum melatonin and serum IL-12 measurements were obtained. The levels of serum melatonin were significantly lower in HIV-1-affected individuals than in healthy controls ($p < 0.001$). Although mean serum IL-12 levels in HIV-1-affected individuals did not significantly differ from healthy controls, the IL-12 levels of HIV-1 patients with advanced disease (CDC stage C) were significantly lower ($p < 0.01$) than those of patients in less advanced

CDC stages B and A. Serum IL-12 levels run parallel with serum melatonin levels as the disease advances [67]. These results are strongly suggestive of the relationship between immune function and melatonin: a reduction in serum melatonin could possibly affect IL-12 production thereby contributing to the progress of HIV-1 infection.

Immune Dysfunction, Winter Depression and the Role of Melatonin

Seasonal variations in immune function, manifested by changes in cytokine levels such as IL-6 and IFN-γ or by alterations in Th-1 and Th-2 responses, have been suggested as probable causes for changes in mood and behavior occurring in SAD [14]. SAD is more prevalent in northern latitudes, with long winter periods [93]. Melatonin has been implicated in the pathophysiology of depressive disorders [94] and recently the melatonin agonist agomelatine has emerged as an effective antidepressant for controlling major depressive disorder [95] as well as SAD [96].The question of whether the increased duration of melatonin secretion seen in winter could trigger the manifestation of symptoms of winter depression through alterations in cytokine levels has been a topic of debate in recent years [97]. Increased plasma levels of IL-6 have been documented in SAD patients [14].

A hypothesis linking photoperiod, melatonin secretion and immune function has been entertained as the probable trigger for the symptoms of SAD [14]. The decreasing photoperiod of winter, via stimulation of melatonin secretion, activates macrophages and T lymphocytes and can tilt the balance between Th-1 and Th-2 towards Th-1 responses with a consequent increase in the production of proinflammatory cytokines such as IL-1, IL-6 and IFN-γ. By altering the neurotransmitter levels in the brain (norepinephrine, serotonin and dopamine), these cytokines cause the characteristic symptoms of SAD [14]. Further studies are needed to assess the validity of this hypothesis.

Melatonin, Immune Function and Rheumatoid Arthritis

As reviewed above, there is considerable evidence that melatonin, an arm of the circadian clock, has an important regulatory role in the cyclical changes that are seen in immune system responses that occur throughout the year [98]. In addition, the seasonal effects on the production of proinflammatory cytokines in human monocytes and T cells may also act as a trigger for rheumatoid arthritis [99].

By acting on specific nuclear receptors present in monocytes and T cells, melatonin has been found to activate the production of proinflammatory cytokines [10]. Further, when compared to healthy controls, patients with rheumatoid arthritis show greater nocturnal concentrations of melatonin in serum and synovial fluid [100, 101]. This evidence has been interpreted to support the suggestion that melatonin has a disease-promoting role in rheumatoid arthritis [102]. In an extended study, serum melatonin concentration was higher in rheumatoid patients from a northern European country (Estonia) than matched patients from a southern European country (Italy) [103]. This could account for the higher prevalence and severity of rheumatoid arthritis in northern European countries.

Concluding Remarks and Perspectives

The role of melatonin in immunomodulation is now well established. It includes effects on cellular and humoral immune mechanisms as well as on innate immunity. Melatonin augments NK cell activity and increases the production of monocytes. By acting on the specific melatonin receptors on immunocompetent cells, melatonin increases the production of cytokines such as IL-2, IL-6, IL-12 and IFN-γ. Its immunoregulatory role has a cyclicity which shows both circadian and seasonally dependent characteristics. As the available evidence shows that only pineal melatonin is modulated by the photoperiod, this would suggest that only pineal-derived melatonin mediates seasonal immunomodulation. As reviewed herein, there is an association between the duration of melatonin secretion and the functioning of the immune system. The duration of this secretion in turn is affected by the length of the environmental photoperiod, thus implicating the involvement of melatonin in the seasonal changes seen in the outbreak of infectious diseases. However, as melatonin can be synthesized in lymphoid organs in large amount, we cannot exclude that other photoperiod-dependent signaling to peripheral lymphoid organs may alter the sensitivity to melatonin. Future studies should be aimed at investigating possible differences in the immunomodulatory role of pineal-derived melatonin from that of endogenous 'immune' melatonin. It has also been suggested that melatonin has a disease-promoting role in SAD and rheumatoid arthritis.

References

1 Cardinali DP, Pevet P: Basic aspects of melatonin action. Sleep Med Rev 1998;2:175–190.
2 Claustrat B, Brun J, Chazot G: The basic physiology and pathophysiology of melatonin. Sleep Med Rev 2005;9:11–24.
3 Lundmark PO, Pandi-Perumal SR, Srinivasan V, et al: Role of melatonin in the eye and ocular dysfunctions. Vis Neurosci 2006;23:853–862.
4 Bubenik GA: Gastrointestinal melatonin: localization, function, and clinical relevance. Dig Dis Sci 2002;47:2336–2348.
5 Konturek SJ, Konturek PC, Brzozowska I, et al: Localization and biological activities of melatonin in intact and diseased gastrointestinal tract (GIT). J Physiol Pharmacol 2007;58:381–405.
6 Slominski A, Fischer TW, Zmijewski MA, et al: On the role of melatonin in skin physiology and pathology. Endocrine 2005;27:137–148.
7 Carrillo-Vico A, Calvo JR, Abreu P, et al: Evidence of melatonin synthesis by human lymphocytes and its physiological significance: possible role as intracrine, autocrine, and/or paracrine substance. FASEB J 2004;18:537–539.
8 Naranjo MC, Guerrero JM, Rubio A, et al: Melatonin biosynthesis in the thymus of humans and rats. Cell Mol Life Sci 2007;64:781–790
9 Skwarlo-Sonta K: Melatonin in immunity: comparative aspects. Neuro Endocrinol Lett 2002;23(suppl 1):61–66.
10 Maestroni GJ: The immunotherapeutic potential of melatonin. Expert Opin Investig Drugs 2001;10:467–476.
11 Nelson RJ, Demas GE: Role of melatonin in mediating seasonal energetic and immunologic adaptations. Brain Res Bull 1997;44:423–430.
12 Nelson RJ, Demas GE: Seasonal changes in immune function. Q Rev Biol 1996;71:511–548.
13 Nelson RJ, Drazen DL: Melatonin mediates seasonal changes in immune function. Ann NY Acad Sci 2000;917:404–415.
14 Lam RW, Song C, Yatham LN: Does neuroimmune dysfunction mediate seasonal mood changes in winter depression? Med Hypotheses 2004;63:567–573.
15 Karasek M: Melatonin, human aging, and age-related diseases. Exp Gerontol 2004;39:1723–1729.
16 Arlt W, Hewison M: Hormones and immune function: implications of aging. Aging Cell 2004;3:209–216.
17 Srinivasan V, Maestroni GJM, Cardinali DP, et al: Melatonin, immune function and aging. Immun Ageing 2005;2:17.
18 Axelrod J: The pineal gland: a neurochemical transducer. Science 1974;184:1341–1348.
19 Moore RY: Neural control of the pineal gland. Behav Brain Res 1996;73:125–130.
20 Brainard GC, Hanifin JP, Rollag MD, et al: Human melatonin regulation is not mediated by the three cone photopic visual system. J Clin Endocrinol Metab 2001;86:433–436.
21 Berson DM: Phototransduction in ganglion-cell photoreceptors. Pflugers Arch 2007;454:849–855.
22 Maronde E, Stehle JH: The mammalian pineal gland: known facts, unknown facets. Trends Endocrinol Metab 2007;18:142–149.
23 Bergiannaki JD, Soldatos CR, Paparrigopoulos TJ, et al: Low and high melatonin excretors among healthy individuals. J Pineal Res 1995;18:159–164.
24 Leger D, Laudon M, Zisapel N: Nocturnal 6-sulfatoxymelatonin excretion in insomnia and its relation to the response to melatonin replacement therapy. Am J Med 2004;116:91–95.
25 Wehr TA: Effect of seasonal changes in daylength on human neuroendocrine function. Horm Res 1998;49:118–124.
26 Ribelayga C, Pevet P, Simonneaux V: HIOMT drives the photoperiodic changes in the amplitude of the melatonin peak of the Siberian hamster. Am J Physiol Regul Integr Comp Physiol 2000;278:R1339–R1345.
27 Garidou ML, Vivien-Roels B, Pevet P, et al: Mechanisms regulating the marked seasonal variation in melatonin synthesis in the European hamster pineal gland. Am J Physiol Regul Integr Comp Physiol 2003;284:R1043–R1052.
28 Garidou ML, Diaz E, Calgari C, et al: Transcription factors may frame Aa-nat gene expression and melatonin synthesis at night in the Syrian hamster pineal gland. Endocrinology 2003;144:2461–2472.
29 Honma K, Honma S, Kohsaka M, et al: Seasonal variation in the human circadian rhythm: dissociation between sleep and temperature rhythm. Am J Physiol 1992;262:R885–R891
30 Ueno-Towatari T, Norimatsu K, Blazejczyk K, et al: Seasonal variations of melatonin secretion in young females under natural and artificial light conditions in Fukuoka, Japan. J Physiol Anthropol 2007;26:209–215.
31 Carrillo-Vico A, Reiter RJ, Lardone PJ, et al: The modulatory role of melatonin on immune responsiveness. Curr Opin Investig Drugs 2006;7:423–431.
32 Dubocovich ML, Markowska M: Functional MT1 and MT2 melatonin receptors in mammals. Endocrine 2005;27:101–110.
33 Drazen DL, Nelson RJ: Melatonin receptor subtype MT2 (Mel 1b) and not mt1 (Mel 1a) is associated with melatonin-induced enhancement of cell-mediated and humoral immunity. Neuroendocrinology 2001;74:178–184.
34 Benitez-King G: Melatonin as a cytoskeletal modulator: implications for cell physiology and disease. J Pineal Res 2006;40:1–9.
35 Cardinali DP, Freire F: Melatonin effects on brain. Interaction with microtubule protein, inhibition of fast axoplasmic flow and induction of crystalloid and tubular formations in the hypothalamus. Mol Cell Endocrinol 1975;2:317–330.
36 Garcia-Maurino S, Pozo D, Calvo JR, et al: Correlation between nuclear melatonin receptor expression and enhanced cytokine production in human lymphocytic and monocytic cell lines. J Pineal Res 2000;29:129–137.
37 Maestroni GJ, Conti A, Pierpaoli W: Role of the pineal gland in immunity. Circadian synthesis and release of melatonin modulates the antibody response and antagonizes the immunosuppressive effect of corticosterone. J Neuroimmunol 1986;13:19–30.
38 Guerrero JM, Reiter RJ: Melatonin-immune system relationships. Curr Top Med Chem 2002;2:167–179.
39 Cardinali DP, Esquifino AI, Maestroni GJM, et al: Circadian organization of the immune response: lessons from the adjuvant arthritis model; in Pandi-Perumal SR, Cardinali DP, Chrousos G (eds): Neuroimmunology of Sleep. New York, Springer, 2007, pp 59–84.
40 Pandi-Perumal SR, Zisapel N, Srinivasan V, et al: Melatonin and sleep in aging population. Exp Gerontol 2005;40:911–925.
41 Miller SC, Pandi-Perumal SR, Esquifino AI, et al: The role of melatonin in immunoenhancement: potential application in cancer. Int J Exp Pathol 2006;87:81–87.
42 Garcia-Maurino S, Gonzalez-Haba MG, Calvo JR, et al: Melatonin enhances IL-2, IL-6, and IFN-gamma production by human circulating CD4+ cells: a possible nuclear receptor-mediated mechanism involving T helper type 1 lymphocytes and monocytes. J Immunol 1997;159:574–581.
43 Liu F, Ng TB, Fung MC: Pineal indoles stimulate the gene expression of immunomodulating cytokines. J Neural Transm 2001;108:397–405.
44 Lissoni P, Rovelli F, Brivio F, et al: Circadian secretions of IL-2, IL-12, IL-6 and IL-10 in relation to the light/dark rhythm of the pineal hormone melatonin in healthy humans. Nat Immun 1998;16:1–5.
45 Mitchell WA, Meng I, Nicholson SA, et al: Thymic output, ageing and zinc. Biogerontology 2006;7:461–470.
46 Gruver AL, Hudson LL, Sempowski GD: Immunosenescence of ageing. J Pathol 2007;211:144–156.
47 Quaglino D, Capri M, Bergamini G, et al: Age-dependent remodeling of rat thymus. Morphological and cytofluorimetric analysis from birth up to one year of age. Eur J Cell Biol 1998;76:156–166.

48 Csaba G, Barath P: Morphological changes of thymus and the thyroid gland after postnatal extirpation of pineal body. Endocrinol Exp 1975;9:59–67.
49 Oner H, Kus I, Oner J, et al: Possible effects of melatonin on thymus gland after pinealectomy in rats. Neuro Endocrinol Lett 2004;25:115–118.
50 Tian YM, Li PP, Jiang XF, et al: Rejuvenation of degenerative thymus by oral melatonin administration and the antagonistic action of melatonin against hydroxyl radical-induced apoptosis of cultured thymocytes in mice. J Pineal Res 2001;31:214–221.
51 Sainz RM, Mayo JC, Uria H, et al: The pineal neurohormone melatonin prevents in vivo and in vitro apoptosis in thymocytes. J Pineal Res 1995;19:178–188.
52 Sainz RM, Mayo JC, Reiter RJ, et al: Melatonin regulates glucocorticoid receptor: an answer to its antiapoptotic action in thymus. FASEB J 1999;13:1547–1556.
53 Presman DM, Hoijman E, Ceballos NR, et al: Melatonin inhibits glucocorticoid receptor nuclear translocation in mouse thymocytes. Endocrinology 2006;147:5452–5459.
54 Mocchegiani E, Bulian D, Santarelli L, et al: The immuno-reconstituting effect of melatonin or pineal grafting and its relation to zinc pool in aging mice. J Neuroimmunol 1994;53:189–201.
55 Pozo D, Delgado M, Fernandez-Santos JM, et al: Expression of the Mel1a-melatonin receptor mRNA in T and B subsets of lymphocytes from rat thymus and spleen. FASEB J 1997;11:466–473.
56 Carrillo-Vico A, Garcia-Perganeda A, Naji L, et al: Expression of membrane and nuclear melatonin receptor mRNA and protein in the mouse immune system. Cell Mol Life Sci 2003;60:2272–2278.
57 Champney TH, Prado J, Youngblood T, et al: Immune responsiveness of splenocytes after chronic daily melatonin administration in male Syrian hamsters. Immunol Lett 1997; 58:95–100.
58 Akbulut KG, Gonul B, Akbulut H: The effects of melatonin on humoral immune responses of young and aged rats. Immunol Invest 2001;30:17–20.
59 Moore CB, Siopes TD: Effect of melatonin supplementation on the ontogeny of immunity in the Large White turkey poult. Poult Sci 2002;81:1898–1903.
60 Maestroni GJ, Conti A, Pierpaoli W: The pineal gland and the circadian, opiatergic, immunoregulatory role of melatonin. Ann NY Acad Sci 1987;496:67–77.
61 Maestroni GJ, Conti A: Beta-endorphin and dynorphin mimic the circadian immunoenhancing and anti-stress effects of melatonin. Int J Immunopharmacol 1989;11:333–340.
62 Maestroni GJ, Conti A: The pineal neurohormone melatonin stimulates activated CD4+, Thy-1+ cells to release opioid agonist(s) with immunoenhancing and antistress properties. J Neuroimmunol 1990;28: 167–176.
63 Castrillon PO, Esquifino AI, Varas A, et al: Effect of melatonin treatment on 24-h variations in responses to mitogens and lymphocyte subset populations in rat submaxillary lymph nodes. J Neuroendocrinol 2000;12: 758–765.
64 Moore CB, Siopes TD: Melatonin enhances cellular and humoral immune responses in the Japanese quail *(Coturnix coturnix japonica)* via an opiatergic mechanism. Gen Comp Endocrinol 2003;131:258–263.
65 Calcagni E, Elenkov I: Stress system activity, innate and T helper cytokines, and susceptibility to immune-related diseases. Ann NY Acad Sci 2006;1069:62–76.
66 Chaouat G: The Th1/Th2 paradigm: still important in pregnancy? Semin Immunopathol 2007;29:95–113.
67 Nunnari G, Nigro L, Palermo F, et al: Reduction of serum melatonin levels in HIV-1-infected individuals' parallel disease progression: correlation with serum interleukin-12 levels. Infection 2003;31:379–382.
68 Moore CB, Siopes TD: Enhancement of cellular and humoral immunity following embryonic exposure to melatonin in turkeys *(Meleagris gallopavo)*. Gen Comp Endocrinol 2005;143:178–183.
69 Maestroni GJ, Conti A: Melatonin and the immune-hematopoietic system therapeutic and adverse pharmacological correlates. Neuroimmunomodulation 1996;3:325–332.
70 Maestroni GJ: Is hematopoiesis under the influence of neural and neuroendocrine mechanisms? Histol Histopathol 1998;13:271–274.
71 Currier NL, Sun LZ, Miller SC: Exogenous melatonin: quantitative enhancement in vivo of cells mediating non-specific immunity. J Neuroimmunol 2000;104:101–108.
72 Maestroni GJ, Conti A, Lissoni P: Colony-stimulating activity and hematopoietic rescue from cancer chemotherapy compounds are induced by melatonin via endogenous interleukin 4. Cancer Res 1994;54:4740–4743.
73 Maestroni GJ, Covacci V, Conti A: Hematopoietic rescue via T-cell-dependent, endogenous granulocyte-macrophage colony-stimulating factor induced by the pineal neurohormone melatonin in tumor-bearing mice. Cancer Res 1994;54:2429–2432.
74 Minagar A, Shapshak P, Fujimura R, et al: The role of macrophage/microglia and astrocytes in the pathogenesis of three neurologic disorders: HIV-associated dementia, Alzheimer disease, and multiple sclerosis. J Neurol Sci 2002;202:13–23.
75 Zhang S, Li W, Gao Q, et al: Effect of melatonin on the generation of nitric oxide in murine macrophages. Eur J Pharmacol 2004; 501:25–30.
76 Pena C, Rincon J, Pedreanez A, et al: Chemotactic effect of melatonin on leukocytes. J Pineal Res 2007;43:263–269.
77 Nelson RJ, Demas GE, Klein Sl, et al: The influence of season, photoperiod, and pineal melatonin on immune function. J Pineal Res 1995;19:149–165.
78 Bilbo SD, Nelson RJ: Photoperiod influences the effects of exercise and food restriction on an antigen-specific immune response in Siberian hamsters. Endocrinology 2004;145: 556–564.
79 Bilbo SD, Nelson RJ: Sex differences in photoperiodic and stress-induced enhancement of immune function in Siberian hamsters. Brain Behav Immun 2003;17:462–472.
80 Bilbo SD, Dhabhar FS, Viswanathan K, et al: Photoperiod affects the expression of sex and species differences in leukocyte number and leukocyte trafficking in congeneric hamsters. Psychoneuroendocrinology 2003;28: 1027–1043.
81 Prendergast BJ, Bilbo SD, Nelson RJ: Photoperiod controls the induction, retention, and retrieval of antigen-specific immunological memory. Am J Physiol Regul Integr Comp Physiol 2004;286:R54–R60.
82 Prendergast BJ, Hotchkiss AK, Nelson RJ: Photoperiodic regulation of circulating leukocytes in juvenile Siberian hamsters: mediation by melatonin and testosterone. J Biol Rhythms 2003;18:473–480.
83 Bowden TJ, Thompson KD, Morgan AL, et al: Seasonal variation and the immune response: a fish perspective. Fish Shellfish Immunol 2007;22:695–706.
84 Hazlerigg DG: What is the role of melatonin within the anterior pituitary? J Endocrinol 2001;170:493–501.
85 Katila H, Cantell K, Appelberg B, et al: Is there a seasonal variation in the interferon-producing capacity of healthy subjects? J Interferon Res 1993;13:233–234.
86 Shearer WT, Lee BN, Cron SG, et al: Suppression of human anti-inflammatory plasma cytokines IL-10 and IL-1RA with elevation of proinflammatory cytokine IFN-gamma during the isolation of the Antarctic winter. J Allergy Clin Immunol 2002;109:854–857.
87 Dowell SF: Seasonal variation in host susceptibility and cycles of certain infectious diseases. Emerg Infect Dis 2001;7:369–374.
88 Wearing HJ, Rohani P: Ecological and immunological determinants of dengue epidemics. Proc Natl Acad Sci USA 2006;103: 11802–11807.
89 Adams B, Holmes EC, Zhang C, et al: Cross-protective immunity can account for the alternating epidemic pattern of dengue virus serotypes circulating in Bangkok. Proc Natl Acad Sci USA 2006;103:14234–14239.
90 Shadrin AS, Marinich IG, Taros LY: Experimental and epidemiological estimation of seasonal and climato-geographical features of non-specific resistance of the organism to influenza. J Hyg Epidemiol Microbiol Immunol 1977;21:155–161.

91 Bilbo SD, Nelson RJ: Melatonin regulates energy balance and attenuates fever in Siberian hamsters. Endocrinology 2002;143:2527–2533.
92 Wen JC, Dhabhar FS, Prendergast BJ: Pineal-dependent and -independent effects of photoperiod on immune function in Siberian hamsters *(Phodopus sungorus)*. Horm Behav 2007;51:31–39.
93 Mersch PP, Middendorp HM, Bouhuys AL, et al: Seasonal affective disorder and latitude: a review of the literature. J Affect Disord 1999;53:35–48.
94 Srinivasan V, Smits M, Spence W, et al: Melatonin in mood disorders. World J Biol Psychiatry 2006;7:138–151.
95 Pandi-Perumal SR, Srinivasan V, Cardinali DP, et al: Could agomelatine be the ideal antidepressant? Expert Rev Neurother 2006;6:1595–1608.
96 Pjrek E, Winkler D, Konstantinidis A, et al: Agomelatine in the treatment of seasonal affective disorder. Psychopharmacology (Berl) 2007;190:575–579.
97 Leu SJ, Shiah IS, Yatham LN, et al: Immune-inflammatory markers in patients with seasonal affective disorder: effects of light therapy. J Affect Disord 2001;63:27–34.
98 Esquifino AI, Pandi-Perumal SR, Cardinali DP: Circadian organization of the immune response: a role for melatonin. Clin Appl Immunol Rev 2004;4:423–433.
99 Iikuni N, Nakajima A, Inoue E, et al: What's in season for rheumatoid arthritis patients? Seasonal fluctuations in disease activity. Rheumatology (Oxford) 2007;46:846–848.
100 Maestroni GJ, Sulli A, Pizzorni C, et al: Melatonin in rheumatoid arthritis: a disease-promoting and modulating hormone? Clin Exp Rheumatol 2002;20:872–873.
101 Sulli A, Maestroni GJ, Villaggio B, et al: Melatonin serum levels in rheumatoid arthritis. Ann NY Acad Sci 2002;966:276–283.
102 Maestroni GJ, Cardinali DP, Esquifino AI, et al: Does melatonin play a disease-promoting role in rheumatoid arthritis? J Neuroimmunol 2005;158:106–111.
103 Cutolo M, Maestroni GJ, Otsa K, et al: Circadian melatonin and cortisol levels in rheumatoid arthritis patients in winter time: a north and south Europe comparison. Ann Rheum Dis 2005;64:212–216.