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Review

Immunoregulatory properties of melatonin in the humoral immune system: A narrative review

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ABSTRACT

Melatonin is the major product both synthesized and secreted by the pineal gland during the night period and it is the principal chronobiotic hormone that regulates the circadian rhythms and seasonal changes in vertebrate biology. Moreover, melatonin shows both a broad distribution along the phylogenetically distant organisms and a high functional versatility. At the present time, a significant amount of experimental evidence has been reported in scientific literature and has clearly shown a functional relationship between the endocrine, nervous, and immune systems. The biochemistry basis of the functional communication between these systems is the utilization of a common chemicals signals. In this framework, at present melatonin is considered to be a relevant member of the so-called neuro-endocrine-immunological network. Thus, both *in vivo* and *in vitro* investigations conducted in both experimental animals and humans, have clearly documented that melatonin has an important immunomodulatory role. However, most of the published results refer to information on T lymphocytes, i.e., cell-mediated immunity. On the contrary, fewer studies have been carried out on B lymphocytes, the cells responsible for the so-called humoral immunity. In this review, we have focused on the biological role of melatonin in the humoral immunity. More precisely, we report the actions of melatonin on B lymphocytes biology and on the production of different types of antibodies.

1. Introduction

Melatonin (N-acetyl-5-methoxytryptamine) was discovered and isolated from bovine pineal gland in 1958 by Lerner and co-workers [1]. Melatonin is the main product synthesized and secreted to blood circulation by the pineal gland during the nocturnal period and is the main chronobiotic hormone responsible for regulating circadian and seasonal rhythms in vertebrate biology [2,3]. Its biosynthesis is carried out starting from the essential amino acid tryptophan and involves four intracellular steps catalyzed by tryptophan hydroxylase (EC 1.14.16.4, TPH), aromatic amino acid decarboxylase (EC 4.1.1.28, AADC), arylalkylamine-N-acetyltransferase (EC 2.3.1.87, AA-NAT), and hydroxyndole-O-methyltransferase (EC 2.1.1.4, HIOMT) [4]. Although melatonin was originally discovered in the pineal gland, further research showed that this molecule appeared very early during evolution. Thus, melatonin has been found in bacteria, unicellular eukaryotes, invertebrate and vertebrates, algae, fungi and plants and even in various edibles, such as herbs, fruit, vegetable and seeds [5,6]. In mammals, it has been communicated that melatonin is synthesized in many organs and tissues, such as respiratory, gastrointestinal, genitourinary, immune systems, and skin [7–12]. Moreover, melatonin shows great functional versatility exhibiting antioxidant [13–16], oncostatic [17,18], antiaging [19,20], and immunomodulatory [10,11,21] effects. The biochemical mechanisms involved in all of these actions of melatonin involves both receptor-dependents [22,23] and receptor-independents mechanisms [24–26].

A broad body of evidence has shown a relationship between endocrine, nervous, and immune systems and, at the present time, it is very clear that these systems use a common biochemical language for intra- and inter-system communication [27]. In this context, pineal-synthesized melatonin is currently considered one of the components of the complex neuro-endocrine-immunological network and the existence of a bidirectional communication between the pineal gland and the immune system is now fully accepted [28,29]. In this context, many *in vivo* and *in vitro* investigations have clearly shown that melatonin has a fundamental role in the function of both innate and adaptative immune systems [10,11] and a clear correlation between melatonin production and the circadian and seasonal rhythms in the

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immune system has also been reported [21,30,31]. Conversely, immunological signals produced by the immune system cells are received by the pineal gland and provides a feedback regulation of pineal function [32,33].

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 immunocompetent cells [10,11,23,34]. These melatonin receptors are located in plasma membrane of the immune cells. Using the melatonin agonist 2-[^{125}I]-iodomelatonin, 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 [35–37], rodents [23,38–41], and human lymphocytes [23,42,43]. Moreover, both in rodents and human lymphocytes, functional studies have shown that several second messengers such as cyclic AMP (cAMP), cyclic GMP (cGMP), and diacylglycerol have been involved in the signaling of melatonin in these cells [39,40,42,43]. In this context, it is important to indicate that the classification and denomination of plasma membrane melatonin receptors have been realized by using the official nomenclature suggested by the IUPHAR committee [44]. Thus, the so-called Mel1a receptors were renamed mt1 and more recently MT1 and the Mel1b receptors were renamed mt2 and after MT2. The expression of both MT1 and MT2 plasma membrane melatonin receptors have been reported in both organs and immune cells of different species including human [45–48]. Moreover, the so-called Mel2 receptors were renamed MT3, and it is now known that this so-called receptor is currently considered the binding of melatonin to an enzymatic molecule, more specifically to quinone reductase 2 (QN2), and is often referred as cMT3/QN2 complex [49]. Finally, it should be noted that the so-called Mel1c receptor is expressed in non-mammalian organisms such as birds, fish and amphibians [50]

Inside the mechanism of action of melatonin, it is important to note the interaction between melatonin and nuclear receptors as the basis for the so-called melatonin nuclear receptors. These nuclear receptors belong to the RZR/RORα subfamily of nuclear receptors and includes three splicing variants of RORα (RORα1, RORα2 and RORα3) [51]. This possible nuclear receptor for melatonin is a controversial issue that is currently not fully clarified. Thus, recent both crystallography data and functional data show that RORα is a receptor for cholesterol, sterols and secosteroids [52–54]. However, other studies postulate that melatonin interacts with RORα and modulates its activity [55,56]. Therefore, the existence or not of a nuclear receptor for melatonin is a biological subject that needs to be fully clarified [57]. In this context and in relation to the cells of the immune system, it is important to indicate that the existence of RORα has been described in different cell lines and subpopulations of human lymphocytes [48,58–60] and in mouse thymus and spleen [46]. Moreover, a specific binding of melatonin to the nucleus of different immune cells has been reported in several species, including humans [41,61].

Most of the data published to date on the mechanism of action and biological effects of melatonin on lymphocytes have been mostly performed on T lymphocytes, which are responsible for the so-called cell-mediated immunity [45,48,60,62,63]. However, few studies have been conducted regarding the biological effects and biochemical mechanisms utilized by melatonin on B lymphocytes, which are responsible for humoral immunity. B lymphocytes, after antigen-specific recognition, they undergo differentiation into plasma cells which produce antibodies specific for the antigenic molecule that primarily activated the B lymphocyte [64,65]. Thus, humoral immunity is carried out by antibodies synthesized by plasma cells, and its physiologic function is defense against both extracellular microbes and microbial toxins [66,67]. The types of microorganisms that are combated by humoral immune system are extracellular bacteria, fungi, and even obligate intracellular microbes, such as viruses, which are targets of antibody molecules before they infect cells or when they are released from infected cells [68–70]. Humoral immunity is the form of adaptive immunity that can be transferred from immunized to naive individuals through serum that contains antibodies [71].

This review is focused on the role of melatonin on B Lymphocytes, the protagonist cells of humoral immunity.

2. Melatonin receptors and B lymphocytes

One of the first molecular requirements to be analyzed for a biological action of melatonin on B lymphocytes is whether these lymphocytes express specific membrane receptors for melatonin. In this context, in a pioneering research was reported the presence of high-affinity binding sites for melatonin in human circulating T lymphocytes, but not in B lymphocytes [62]. However, and in this same paper, the authors stated that a binding of melatonin by B lymphocytes cannot be discarded [62]. Later, the same research group showed by RT-PCR the presence of a subtype of melatonin membrane receptor (Mel1a) in different lymphocytes subpopulations from rat thymus (CD4 positive, CD8 positive, double positive, double negative, and B cells) and spleen [45] and also the genetic expression of the subtype of melatonin membrane receptor MT1 in human B lymphocytes (CD19^{+} cells) [48]. On the other hand, pharmacologic investigations in chickens have shown that melatonin mediates the cell division of B lymphocytes in response to green monochromatic light through the so-called membrane receptors of the type Mel1a and Mel1c [72,73]. In addition, it has been showed expression of both MT1 and MT2 receptors in B lymphocytes from murine spleen and this expression in influenced by circadian time and lighting conditions [74]. With respect to the so-called nuclear melatonin receptors (RZR/RORα), it has been reported the expression of the so-called melatonin nuclear receptor RZR/RORα in different subpopulations of human immune cells [48]. Thus, in this research the expression of RZRα and the three isoforms of the RORα (RORα1, RORα2 and RORα3) was studied in B lymphocytes (CD19^{+} cells), T helper lymphocytes (CD14^{-} CD14^{+} cells), cytotoxic T lymphocytes (CD56^{-} CD8^{+} cells), monocytes (CD14^{+} cells), and natural killer (NK) lymphocytes (CD56^{+} cells). As far as B lymphocytes are concerned, both RZRα and RORα2 expression was observed [48]. Besides, in the lymphoid organs (spleen and thymus) of the tropical squirrels *Funambulus pennati* the expression of RORα has also been described and it has been shown that this expression is regulated by photoperiod [75]. Finally, and through a pharmacological approach, has been reported the presence of RORα in chicken B lymphocytes [72]. Therefore, there are experimental data that support the existence of receptors for melatonin in B lymphocytes and this would be a biochemical basis for the action of melatonin in these lymphocytes.

3. Biological actions of melatonin on B lymphocytes

A first approach to study the actions of melatonin on humoral immune system is to study the effects of pinealectomy on the humoral immunity. Thus, it has been reported that the abolishment of the pineal function reduces both the humoral and cellular immune response in the rodents (Siberian hamster and *Funambulus pennanti*) [76,77] and in the birds (chicks and Japanese quail) [78,79].

Another approach in the study of the actions of melatonin on humoral immune system is to investigate the actions of melatonin administration in immunosuppressed animals by different mechanisms. Thus, although the administration of pineal gland extracts increased both the number of antibody-forming cells produced and the biological response against sheep red blood cells (SRBC) immunization in mice spleen [80,81], other researchers have found no effect of melatonin in mice [82] or Syrian hamsters [83]. However, Maestroni and co-workers have reported in immunosuppressed mice by propranolol or corticoids that melatonin counteracts the decrease on primary antibody response to SRBC and the reduction reactivity against antigens in spleen [84,85].

In addition to the aforementioned experimental approaches, other studies have described different biological actions of melatonin on B

lymphocytes. Thus, different in vivo studies in chickens have been demonstrated that exogen administration of melatonin is able to stimulate the proliferation of B lymphocytes [72,86]. Similar results in birds have been obtained in studios conducted in vitro [73,87]. In the case of mice, it has also been shown that melatonin is able to stimulate the proliferation of B lymphocytes [88]. In humans, it has been demonstrated in cultured tonsil lymphocytes from patients with recurrent acute tonsillitis and analysed by flow cytometry that the administration of melatonin increases the amount of B lymphocytes [89]. Furthermore, in human B lymphocytes it has been shown that melatonin, through the specific binding of the nuclear receptor RZR/RORα to the promoter of 5-lipoxygenase, inhibits the expression of the gene for this enzyme [90]. Since 5-lipoxygenase is a key enzyme in the biosynthesis of leukotrienes, which are involved in inflammatory and allergic processes, melatonin may be involved in these immunological reactions [90].

Another well-studied biological effect has been the role of melatonin in B-lymphocyte apoptosis. Thus, a study of mice given melatonin in their drinking water has shown that melatonin inhibited bone marrow B-cell apoptosis and this effect was limited mainly to the earliest stages of B-cell differentiation [91]. Similar results were shown by Lu et al., in mouse bone marrow B lymphocytes, where they observed that melatonin inhibited pre-B cell apoptosis probably through stimulation of stromal cells [92]. Therefore, melatonin can be a checkpoint regulator in early B-cell development and can also contribute to the diurnal rhythm in bone marrow B-lymphocyte production. Although this effect could be considered as a potentiation of humoral immunity, it should be taken into account that an increased production of B-lymphocytes could allow genetically aberrant B-lymphocytes to evade the normal deletion process, and this is a clear potential risk factor for the development of B-cell lymphoma. In this context, it is important to indicate that melatonin can inhibit apoptosis in the BL41 Burkitt lymphoma cell line [93]. However, despite all the above mentioned, the role of melatonin in B lymphocyte apoptosis is not fully clarified since it has been demonstrated that melatonin stimulates caspase activation and apoptosis in different human malignant B lymphocyte cell lines and that this effect is independent of both MT1 and MT2 receptors [94].

4. Melatonin and IgG

Several studies focusing exclusively on the immunomodulatory role of melatonin on IgG production has been published. Thus, in a preliminary study was reported that melatonin increased the production of IgG1 antibody and reduced IgG2a isotype in female BALB/c mice [95]. While another study showed that melatonin tended to decrease IgG plasma levels in mink [96]. Moreover, in male golden hamster it has been reported that photoperiod can modulate the plasma melatonin levels to improve several immune parameters including an increase in the IgG production [97]. in studies with another experimental approach, it has been well established the immunoenhancing properties of melatonin on the immunocompromised status induced by glucocorticoid. Thus, it has been showed that melatonin increases IgG production in dexamethasone-treated tropical rodent *Funambulus pennanti* [98] and in male golden hamster [99]. Moreover, melatonin inhibited the increase in IgG production produced by LPS-stimulated mouse mammary tissue in vitro [100]. On the other hand, it has been shown that melatonin improves the colostrum quality based on IgG concentration [101]. In addition, prenatal melatonin treatment of pregnant ewes has been reported to increase the plasma IgG levels of their infected offspring with *Eimeria* species [102]. Finally, it has been reported that melatonin treatment improves colonic homeostasis in ageing gerbils by reducing inflammation, regulating the intestinal microbiota and reducing serum IgG and TNFα levels [103].

On the signaling pathway used by melatonin to exert its effects on IgG production, it has been showed that melatonin receptor subtype MT2 but not MT1 receptor is involved in the melatonin-induced enhancement of both cell-mediated and humoral immunity [104].

5. Melatonin and IgM

Several studies have been shown an effect of melatonin on IgM production (and in some of them also on IgG). In a preliminary study was reported that melatonin administered in the evening enhances both IgG and IgM antibodies in vivo according to a dose-response manner and that the opioid receptors blocker naltrexone antagonizes this effect [105]. Subsequently, it has been investigated the effects of melatonin administration on humoral immune responses of young and aged rats. Thus, was communicated that melatonin increased the levels of IgG1 and IgM in aged rats. In the young rats, the IgG1 control group levels were significantly higher than that of the melatonin treated group, while IgM levels were not significantly different [106]. In another study has been reported that melatonin mediated photoperiod control of both endocrine adaptations and humoral immune response in male Siberian hamsters [107]. In an interesting research has been investigated the effect of suppressed melatonin synthesis on the production of different antibody in BALB/c mice immunized with both T-cell-independent (TD) and T-cell-dependent (TI) antigens and kept under normal lighting, constant exposure to light and exposed to constant light and treated daily with melatonin [108]. The results found showed melatonin modulated both TD and TI antibody production. Thus, abolished melatonin synthesis increased the production of IGM, IgG1, IgG2b and IgG3 after immunization with TI antigen. Moreover, the levels of TD antibodies IgM, IgG2a, IgG2b and IgG3 also increased, while the levels of IgG1 significantly decreased in mice exposed to light. The diary melatonin treatment returned the antibody level back to normal. Furthermore, the antibodies concentration in the blood of mice kept at normal lighting condition was significantly higher when the immunizations were performed in the evening. Finally, and also in this paper, it was shown both *in vitro* and *in vivo* an action of melatonin on B lymphocytes via MT2 receptor [108].

On the other hand, it has been shown that melatonin increases both the plasma IgM and IgG levels both in aging laying hens [109] and in goldfish *Carassius auratus* exposed to water at elevated temperature induced stress [110].

In addition to these physiological studies, also it has been studied the effect of melatonin on humoral immunity in experimental models of lupus. Thus, in MRL/Mpj-Fas(Ipr) mice, which develop spontaneously an autoimmune disease that has many features resembling human systemic lupus erythematosus, it has been reported that female mice treated with melatonin showed a diminution of titers of total serum IgG and IgM. However, in male mice treatment with melatonin exhibited the opposite effect. Similar effects were observed in cultured lymphocytes from lymph nodes and spleen [111]. The authors proposed that melatonin observed effects in MRL/Mpj-Fas(Ipr) mice are gender dependent, probably through modulation and inhibition of sex hormones [111]. This hypothesis was confirmed in a further study by the same group [112]. Similar effects of melatonin on IgM levels were observed in a pristane-induced lupus mice model [113].

6. Melatonin and IgA

Several studies have been conducted on the role of melatonin on IgA production. Thus, it has been shown in humans that melatonin is able to increase IgA levels in saliva [114]. In addition, it has been reported that the melatonin administration in humans 30 minutes before intense physical exercise increases serum IgA levels after exercise [115]. On the other hand, it has been reported that exposure to bright light during the daytime affects circadian rhythms of melatonin excretion in urine and salivary IgA levels. Thus, urinary melatonin excretion was significantly higher during the night-time after the bright light condition than during the dim light condition. Moreover, both the concentration and the quantity of salivary IgA tended to be higher in the condition of bright light that in the dim light condition [116]. In relation to the above described, also it has been shown a circadian and homeostatic

sleep-wake regulation of secretory IgA [117]. On the other hand, it has been reported that the decrease of IgA production in duodenum in a chicken model of intestinal inflammation produced by lipopolysaccharide was attenuated by melatonin [118]. It has been shown that melatonin is able to increase the plasma IgA levels in aging laying hens [109]. Finally, it has been described that prepartum supplementation with tryptophan in Holstein cows increases plasma melatonin levels and increases colostrum IgA levels [119].

7. Melatonin and IgE and IgD

To date, very few studies have been conducted about the effects of melatonin on the IgE production and most of the existing data derive from studies realized in experimental models of atopic dermatitis. Thus, different experimental data indicate that melatonin is able to inhibit the development of atopic eczema and reduces serum total IgE [21,120]. Moreover, in in a rat model of ovalbumin-induced allergic rhinitis, it has been demonstrated that melatonin reduced serum ovalbumin-specific IgE concentrations [121]. On the other hand, in studies conducted in LPS-treated RAW264.7-line cell, the administration of melatonin-loaded extracellular vesicle-mimetic nanovesicles effectively suppressed serum IgE levels [122]. Moreover, melatonin treatment restored 2,4-dinitrofluorobenzene (DNFB)-induced skin microbiota dysbiosis in a mouse model of atopic dermatitis. More specifically, melatonin improved lesion size, different inflammatory parameters (mast cells, IgE, IL-4 and IL-13) and skin microbiota imbalance [123].

The immunological role of IgE is closely related to the biology of mast cells. Mast cells are one of the main effector cells with a protective role against parasitic and bacterial infections [124]. It is interesting to note that mast cells activation and distribution are associated with the circadian clock, and it should not be forgotten that the main mediator involved in the circadian rhythm is melatonin [125]. In this context, it is important to indicate that it has been demonstrated the both synthesis and release of melatonin by mast cells (RBL-2H3 cells) and the existence of both MT1 and MT2 melatonin receptors in these cells [34], which provides a molecular basis for a possible regulatory effect of melatonin on inflammatory reactions mediated by these cells [34]. Thus, it has been shown that the anti-inflammatory actions of melatonin would be carried out through the NF-κB factor inhibition [126]. Finally, it is interesting to note that melatonin shows a protective role both concentration and time-dependent against mast cells cytotoxicity mediated by phorbo12-myristate 13-acetate plus calcium ionophore A23187 [26].

Regarding the effects of melatonin on the production of IgD, there is no experimental data to date.

8. Melatonin and vaccination: an emerging area

One of the fields in which melatonin has an interesting biomedical potential is the area of vaccines. Vaccines have been developed and used to generalize or enhance immunity against a given disease. The ability of a vaccine to promote immune protection is determined not only by the antigen used in the creation of the vaccine, but also by the adjuvant substances capable of promoting and generalizing an efficient immune response against the infectious agent of interest. Based on the immunoregulatory properties of melatonin, its use in vaccination processes has been investigated. Thus, it has been shown that melatonin increases the humoral responses in sheep vaccinated against the strains A1 and C of *Dichelobacter nodosus*, which is the bacteria that causes ovine footrot, which is the main cause of lameness in sheep [127]. In this study, the administration of subcutaneous slow-release melatonin implants increased antibody levels against the two serotypes of *Dichelobacter nodosus*. in synergy with aluminum hydroxide. More specifically, melatonin administration increased serum IgG levels and also increased the number of T lymphocytes $CD4^+$ and B lymphocytes IgG^+ in peripheral blood [128,129]. On the other hand, the beneficial of melatonin on the immune response to vaccination against *Clostridium perfringens type D* in sheep have also been described [130]. Interestingly in this study it was observed that the highest increases in melatonin-induced serum antibody levels were obtained when vaccination took place in the prepartum period, suggesting that the timing of immunization plays an important role in the effects of melatonin on the immune response. These beneficial effects of melatonin in vaccination could be explained by two mechanisms: melatonin could stimulate antibody production by increasing antigenic presentation or melatonin could increase the production of cytokines involved in stimulating the humoral immune response [11,12,131]. Another investigation has demonstrated the potentiating effect of melatonin on the efficacy of vaccination against *Schistosoma mansoni* antigens in hamsters [132]. Interestingly, in this study it was shown that the effect of melatonin was accompanied by significantly higher GSH concentrations. In this context, it is necessary to comment that, based on its antioxidant properties, melatonin protected against inflammation associated with Aβ vaccination via direct and indirect mechanisms [133], suggesting that melatonin could also be an effective molecule adjuvant in vaccines developed for immunotherapy of Alzheimer's disease. Thus, it is well known that the functions of the immune cells are strongly influenced by the oxidant/antioxidant balance and the antioxidant status play an important role in the physiology of these cells, protecting them of oxidative stress and preserving the cellular function. These antioxidant properties of melatonin were also observed in an open-field vaccination procedure in sheep against *Dichelobacter nodosus* [134] it being noted that the co-administration of melatonin with footrot vaccine neutralized the increase of serum nitric oxide (NO) found in vaccinated animals. This effect could be explained by the direct action of melatonin on NO or by the inhibition of iNOS activity [135]. Finally, it is important to indicate the interesting role of melatonin in the recent pandemic caused by the coronavirus disease virus 2019 (COVID-19). COVID-19 is a life-threatening infectious respiratory disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and it has caused morbidities and deaths worldwide. This pandemic revealed the urgent need to find pharmacological agents and/or vaccines. In this context, melatonin has been postulated as a possible and effective adjuvant therapeutic agent to be considered in the treatment of this disease [136–138].

9. Concluding remarks

A large amount of experimental evidence has been reported suggesting a direct link between the pineal gland/melatonin and the immune system; this evidence indicates a bidirectional communication where melatonin influences immune system while immune signals also affect pineal function. However, most of the published data refer to studies performed with lymphocytes, and more specifically, with T lymphocytes. Therefore, it is information on the immunomodulatory role of melatonin in cellular immunity [10,23,60,62,63]. However, there are few studies concerning the effects of melatonin on B lymphocytes, which are the cells responsible for the so-called humoral immunity. B lymphocytes, after activation by antigen-specific recognition, differentiate into plasma cells, which are responsible for the synthesis and secretion of antibodies [64,65]. Therefore, humoral immunity is mediated by antibodies secreted by plasma cells, and its physiologic function is defense mainly against extracellular microbes and microbial toxins [66,67]. In this review, we have focused on the role of melatonin on B Lymphocytes, the cells involved in humoral immunity (Fig. 1). The data collected in this review, together with all the existing information on the immunomodulatory effects of melatonin, reinforce the postulate of the important role of melatonin in both the physiology and pathophysiology of the immune system (Fig. 2).

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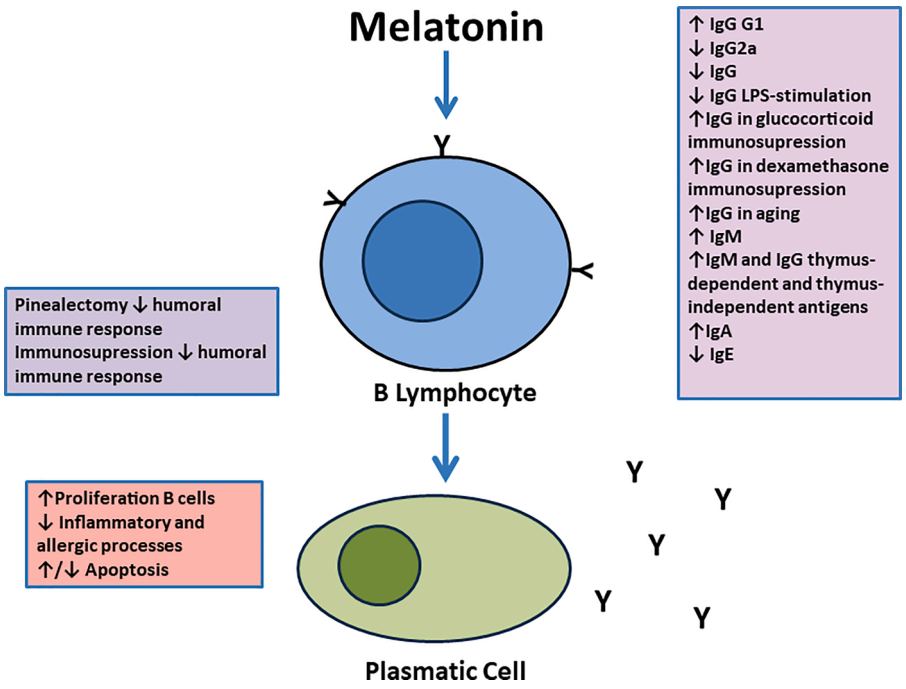

Fig. 1. Effects of melatonin in humoral immune system.

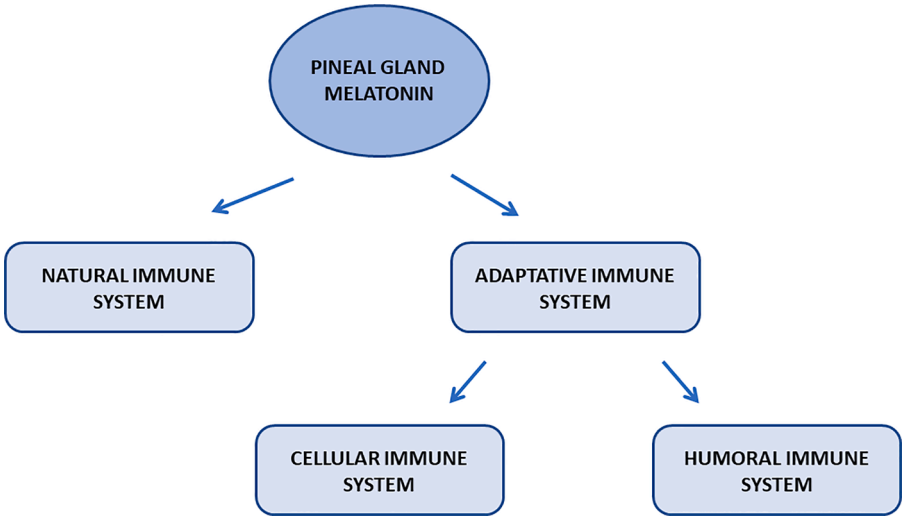

Fig. 2. Simplified scheme showing that melatonin has effects on the different compartments of the immune system.

CRediT authorship contribution statement

Juan R. Calvo: Writing – original draft, Visualization, Validation, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **María D. Maldonado:** Visualization, Validation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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