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REVIEW ARTICLE

Role of Melatonin in the Inflammatory Process and its Therapeutic Potential

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Abstract: Melatonin is an indolamine synthesized and secreted by the pineal gland along with other extrapineal sources including immune system cells, the brain, skin and the gastrointestinal tract. Growing interest in this compound as a potential therapeutic agent in several diseases stems from its pleiotropic effects. Thus, melatonin plays a key role in various physiological activities that include regulation of circadian rhythms, immune responses, the oxidative process, apoptosis or mitochondrial homeostasis. Most of these processes are altered during inflammatory pathologies, among which neurodegenerative and bowel diseases stand out. Therapeutic assays with melatonin indicate that it has a beneficial therapeutic value in the treatment of several inflammatory diseases, such as Alzheimer, Amiotrophic Lateral, Multiple Sclerosis and Huntigton´s disease as well as ulcerative colitis. However, contradictory effects have been demonstrated in Parkinson´s and Chron´s diseases, which, in some cases, the reported effects were beneficial while in others the pathology was exacerbated. These various results may be related to several factors. In the first place, it should be taken into account that at the beginning of the inflammation phase there is a production of reactive oxygen species (ROS) that should not be blocked by exclusively antioxidant molecules, since, on the one hand, it would be interfering with the action of neutrophils and macrophages and, on the other, with the apoptotic signals activated by ROS. It is also important to keep in mind that the end result of an anti-inflammatory molecule will depend on the degree of inflammation or whether or not it has been resolved and has therefore become chronic. In this review we present the use of melatonin in the control of inflammation underlying the above mentioned diseases. These actions are mediated through their receptors but also with their direct antioxidant action and melatonin's ability to break the vicious cycle of ROS-inflammation. This review is aimed at evaluating the effect of melatonin on activity of the inflammatory process and at its immunomodulator effects.

Keywords: Melatonin, inflammation, immunomodulation, oxidative stress, neurodegenerative diseases, bowel diseases.

1. INTRODUCTION

In 1958, melatonin was isolated for the first time from the bovine pineal gland and was considered to be a new neurohormone exclusive of the vertebrate [1]. Principally melatonin is a hormone synthesized and secreted by the pineal gland that follows a circadian pattern, synchronized to a light/dark cycle secretion being suppressed during day light and enhanced during the night [2]. Melatonin is not only secreted into the circulatory system from the pineal gland, but also in a paracrine manner through the pineal recess to the third ventricle in the Central Nervous System (CNS) [3].

Synthesis of melatonin in the pineal gland is indirectly regulated by a neural stimulus from the suprachiasmatic nucleus through polysynaptic activation of beta-adrenergic receptors [4]. The synthesis of melatonin occurs in two steps from its precursor the tryptophan. First, this essential amino acid is hydroxylated by tryptophan-5-hydroxylase (TPH) resulting in 5-hydroxytryptophan, which is decarboxylated to 5-hydroxytryptamine (serotonin) by the action of L-aromatic amino acid decarboxylase. Then, serotonin is transformed into melatonin during the next two reactions: serotonin by arylalkylamine N-acetyltransferase is N- acetylated to form N-acetylserotonin, which is converted by N- acetylserotonin- O-methyltransferase to N- acetyl- 5- methoxytryptamine (melatonin). The synthesis of melatonin is limited by the latter reaction (Fig. **1**) [5].

There are other sources of melatonin in addition to the pineal gland that have been identified in several organs and tissues. These sources include: melatonin produced by retina, the Harderian gland, immune system cells, plus the brain, cerebellum, liver, airway epithelium, kidney, bone marrow, adrenals, gut, oral cavity, thymus, ovary, testes, thyroid, placenta, skin, pancreas, carotid body, endometrium, and endothelial, cells, *etc*., the gastrointestinal tract being an important source of melatonin [6], indicating the diversity of functions that melatonin has in different organs.

The function of melatonin was originally identified as a molecule that regulates sleep, circadian rhythms and energy metabolism [7]. In addition to its chronobiotic functions it is also reported to act in other biological process, such as the regulation of temperature, intestinal motility, or as an immunomodulatory, antioxidant, antigenotoxic and oncostatic agent regulating oxidative stress, apoptosis and mitochondrial homeostasis [8-10]. Also, it applies other actions in the central nervous system such as an antiexcitatory agent, regulator of intracerebral blood flow and of hormone secretion [11]. Melatonin as a multifaceted molecule has several beneficial effects such as improved sleep, prevention of free radical damage, modulating the immune system and possibly influencing longevity [8, 12, 13]. These pleiotropic effects are possible thanks to their molecular mechanisms of action, which can be classified into two main effects (Fig. **1**): receptor-mediated and receptor-independent. The effects of melatonin-bound receptors include actions of both high-affinity G-coupled membrane receptors, MT1 and MT2, and the nuclear receptor, Retinoid-related Orphan nuclear receptor (ROR / RZR). These receptors regulate the expression of various genes that control the production of a number of proteins. Among them are the main endogenous antioxidant enzymes, such as glutathione reductase (GR), catalase (CAT), glutathione peroxidase (GPx) and superoxide dismutase (SOD) [14]. Similarly, the expression of pro-oxidant, such as inducible nitric oxide synthase

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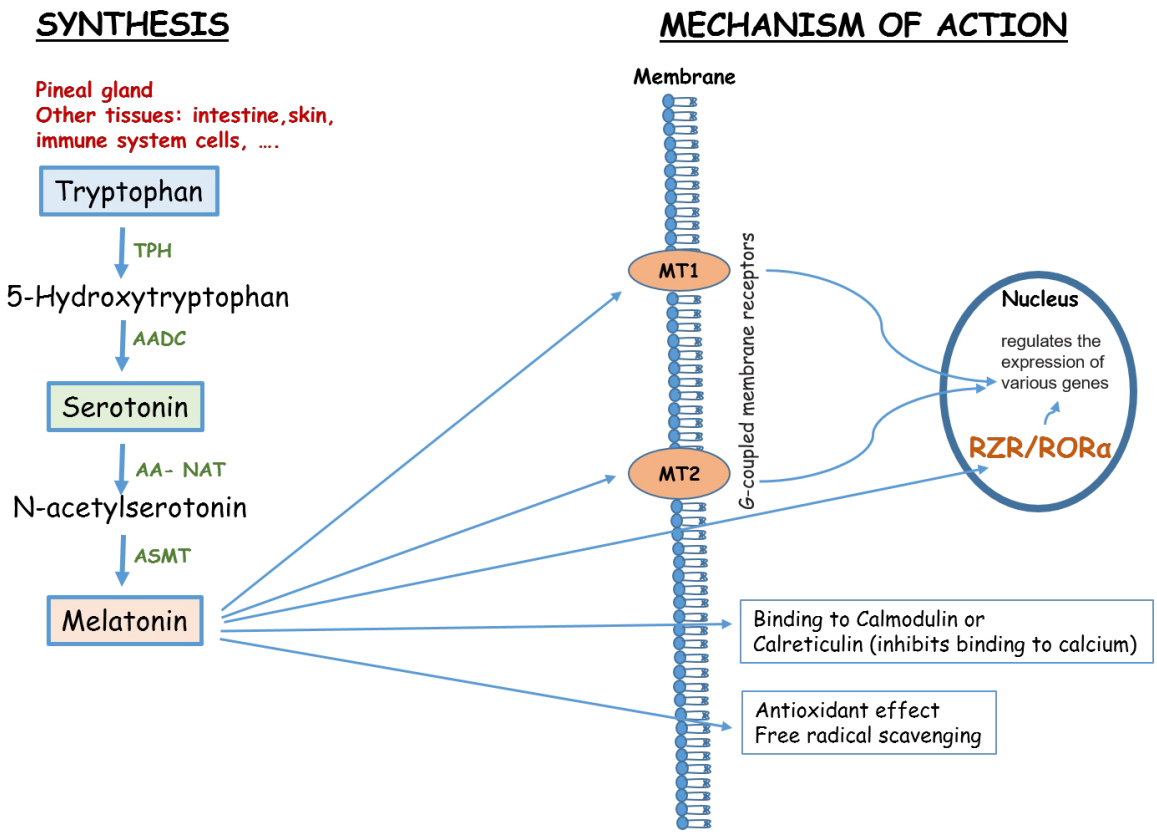

Fig. (1). Biosynthesis of melatonin from tryptophan and its molecular functions. Enzymes that intervene in the synthesis of melatonin: Tryptophan-5-hydroxylase (TPH), L-aromatic amino acid decarboxylase (AADC), N- acetylated by arylalkylamine N- acetyltransferase (AA- NAT), N- acetylserotonin- O-methyltransferase (ASMT). MT1 y MT2, melatonin membrane receptor. RZR/ROR, Retinoid-related Orphan nuclear receptor.

(iNOS), and pro-inflammatory enzymes, such as cyclooxygenase-2 (COX-2), are under genomic regulation of melatonin. There seems to be a collaboration between the two types of receptors, nuclear and membrane, in the regulation of these enzyme systems [15]. Those melatonin receptors in the body are located in many tissues such as: aorta, brain, brown and white adipocytes, the cardiac ventricular wall, the cardiovascular system, cecum and appendix vermiformis, cells of the immune system, colon, coronary and cerebral arteries, duodenal enterocytes, epithelial cells of prostate and breast, exocrine pancreas, kidney, liver, gallbladder, myometrium, ovary/granulosa cells, parotid gland, placenta and fetal kidney, platelets, retina, skin and in the gastrointestinal system especially in the jejunal and colonic mucosa [16, 17].

With respect to receptor-independent effects, melatonin, due to its lipophilic nature, can enter every cell compartment. It can interact with different targets inside the cell, mostly through its binding to mitochondrial and cell cytosol proteins, such as calmodulin and calreticulin, and then it can modulate signal transduction pathways. Both are calcium binding proteins that melatonin inhibits. While its interaction with calmodulin is of interest as a mechanism for regulating the cytoskeleton, framework that keeps the cell alive, binding to calreticulin has been associated with regulation of the action of different hormones in the cell nucleus [17, 18]. Other receptor-independent effects are a direct modulation of the redox process or the scavenging of free radicals [16]. In humans, supposedly at high pharmacological doses, these actions do not require receptors and signaling mechanisms, while the anti-inflammatory, circadian or anti-excitatory effects are mediated by receptor and also contribute to antioxidant protection by promoting the expression of antioxidant enzymes and reducing the formation of free radicals [19].

Inflammation is a normal complex and is an essential protective response in cells and connective tissues to exogenous and endogenous stimuli, such as pathogens or irritants, or damaged cells. The ultimate goal of this protective response is to get rid of both the initial cause of cell damage and the consequences of such injury, and to finally repair the tissue. A critical component of inflammation is the infiltration of inflammatory cells, like neutrophils, monocytes, and lymphocytes, at the site of stimulus. These activated inflammatory cells release many enzymes, reactive oxygen species (ROS) and chemical mediators [20, 21]. There are two types of inflammation, chronic and acute. Acute inflammatory response is essential for eliminating infections and during wound healing after a trauma. This inflammation lasts for a short period of time and has a beneficial effect. Normally, it is very well regulated, but in certain occasions it can lose control and prolong the inflammatory response, this exaggerated and uncontrolled situation can produce tissue damage and if this response continues it can progress to chronic inflammation. Chronic inflammation is the basis of several chronic human diseases [22] and is involved in the physiopathology and development of numerous diseases such as: Alzheimer's, Parkinson's, psychiatric disorders, traumatic brain injury, chronic kidney disease, cancer, diabetes mellitus II, atherosclerosis, periodontal disease, gastrointestinal (GI) inflammatory diseases (Ulcerative colitis and Crohn), multiple sclerosis, rheumatoid arthritis, hepatic diseases, along with others such as fibromyalgia [23], microbial and viral infections. Mechanisms underlying the chronic inflammatory responses are not clear; however, ROS are thought to be involved because an excessive production of ROS may cause tissue injury that could lead to an exacerbated and persistent inflammatory process [22].

Since pathological inflammation is the basis of different diseases and current anti-inflammatory drugs have important side effects (nausea, heartburn, indigestion, stomach bleeding or kidney problems), new approaches are needed to treat chronic inflammation. In this sense melatonin, a molecule that has several targets in the pathophysiology of several autoimmune and inflammatory diseases, demonstrates with these targets the basis for its use in the treatment of certain diseases [24].

The objective of this review is to evaluate the effect of melatonin on the activity of the inflammatory process and its immunomodulator effects. The mechanism of melatonin action and its influence on cells involved in the inflammatory process will be addressed as well as its possible therapeutic effect on inflammation and related disorders, with special emphasis on its role in inflammatory neurodegenerative and bowel diseases. The incidence of neurodegenerative disease due to the increasing life expectancy has also increased over the years. Consequently, these diseases have become important problems from medical and social points of view. Not only do the neurodegenerative diseases have the greatest impact on family, social and professional levels, they often lead to complete disability of the inflicted patients [25]. Therefore, it is essential to find and to develop treatments that will prevent and/or improve their quality of life. Additionally, recent evidence shows a possible relationship between neurodegenerative and bowel diseases, which we consider an interesting study area within the effects of melatonin in these pathologies.

2. PHARMACOLOGY OF MELATONIN

There are numerous *in vitro* studies that report higher doses of melatonin are needed as opposed to nocturnal plasma levels, in order to exert clear effects, thus generating interest in its potential therapeutic use. Melatonin is usually administrated orally, but other alternative forms are used, such as intravenous, intranasal, transbucal or transdermal. Only the intranasal administration presents a higher peak of plasma concentration and a longer time to reach maximal concentration with respect to the oral administration [26].

2.1. Melatonin Absorption and Bioavailability

Due to its liposolubility melatonin is easily absorbed when administered by any route, easily crossing the blood-brain barrier or even placenta. However, the absorption of melatonin presents individual variations as well as its distribution, metabolism and elimination [27]. The pharmacokinetics of oral melatonin formulations showed Tmax values of approximately 50 min. A T1 / 2 of approximately 45 minutes has also been reported in both oral and intravenous administrations. The first stage of melatonin metabolism makes its half-life extremely short in circulation, around 20 - 30 min, this low bioavailability is a major impediment to the use of melatonin as an effective drug [28]. In addition it is also eliminated quickly, which produces physiological levels for only 2-4 h.

In contrast, there are studies with slow-release oral formulations, such as Circadin®, in which the Tmax and T1 / 2 reached up to 167 and 91 minutes, respectively. There are also synthetic drugs such as Ramelteon® that is absorbed by the gastrointestinal tract much more easily and has a longer half-life, aprox 1-2 h, Ramelteon® being the only one among the melatonergic agonists with higher affinities to melatonin receptors. Undoubtedly, the natural hormone is metabolized and tolerated much better. With these synthetics the independent-receptor effects do not occur. However, further studies are needed to clarify the relevance of these actions [29].

2.2. Melatonin Metabolism and Excretion

Melatonin is metabolized mainly in the liver and less in the kidney. But when administered intravenously, its biodegradation is slower due to the absence of passage through the liver. The liver enzymes involved in metabolization of melatonin are the hepatic monooxygenases, CYP1A2, CYP1A2 and CYP1B which hydroxylate melatonin, allowing it to be conjugated with sulfuric acid (90%) or glucuronic acid (10%) giving rise to an inactive metabolite that is easily eliminated in urine, the 6-sulfatoxymelatonin (6-SM). The levels of this metabolite in urine correlate directly with plasma levels of melatonin. Also, plasma levels of melatonin can be assessed through salivary measurements [29, 30].

2.3. Limitations and Risk of Use of Melatonin

Safety of melatonin in humans has recently been reviewed [31]. From these recent studies, administered melatonin was observed to have minimal adverse effects, such as nightmares, insomnia, headaches, rash and upset stomachs and without danger to life even at doses of up to 1 g/day or 50 mg/kg [32, 33]. In studies on the effects on sleep disturbance the doses used were between 0.3-5 mg / day, whereas for other disorders such as Alzheimer´s (AD) and Parkinson's disease (PD), or inflammatory bowel diseases, doses used were between 0.1 mg to 200 mg / day [6].

In experimental animal models, melatonin can inhibit the reproductive system, leading to a delay of puberty or even hypogonadism. However, it has been reported that testosterone and luteinizing hormone levels are maintained in men when administered at low doses [34]. It has also been reported that melatonin reduces sperm motility [35] and inhibits testicular aromatase levels if it is administered long-term [36]. Melatonin has even been suggested for use as a contraceptive for women [37]. Circadin® (prolonged-release melatonin), approved in 2007 by the European Medicines Agency (EMA) is widely used in >40 countries. EMA's approval is routinely monitored showing a good ratio between risks, benefits and a safe profile [38, 39]. Most of these studies emphasize that melatonin is safe for short-term use, even when given in extreme doses. However, some groups are of the opinion that long-term safety of melatonin requires further studies. Therefore, it has been suggested that pregnant and breastfeeding women should not take exogenous melatonin [31].

In terms of inflammation, it is important to consider that treatments with NSAIDs and corticosteroids are exceptionally administered for a long time. Consequently, during a standard treatment of these drugs, supposedly taken in combination with melatonin, the benefits of the hormone would be much greater than its risks. Nevertheless, it is necessary to be cautious with the natural hormone melatonin and all melatonergic agonists in autoimmune diseases, because of melatonin's immune modulatory role. In addition to its anti-inflammatory effect, its immune-stimulant effect is an undesired situation, so that melatonin or melatonergic drugs may be contraindicated in such patients [18]. Although in a few cases melatonin seems to aggravate some inflammatory conditions [40], a large amount of studies in animal and human report that the toxicity of melatonin is extremely low, with a wide margin of safety with minor adverse effects, most of them related to sleepiness and fatigue [6, 23, 41].

In general, animal and human clinical studies, both in short- and long-term administration, show that melatonin treatments are safe even at high doses (1g / day) [31], although it would be necessary to do more research about dosage and possible serious adverse effects.

3. IMMUNOMODULATORY EFFECT OF MELATONIN

A large body of evidence has shown a communication in two directions in which the immune system acts on the neuroendocrine system and *vice versa*. Melatonin is considered a member of this network since it is a molecule with diverse effects on the immune system, the pineal gland being an immune target. Moreover, there is even evidence that the immune system also produces extrapineal melatonin [42]. In fact, the presence and distribution of membrane and nuclear melatonin receptors in organs and immune cells of several species of mammals and birds is well known [43, 44]. Thus,

MT1 and MT2 receptors seem to play different roles, with MT1 receptors as the main target in acquired immune response and MT2 receptors as the target for innate immune responses [14]. Despite numerous experiments, the influence of the hormone on the immune system is still controversial. Melatonin has been reported as affecting the immune response, acting as both an inhibitor and an activator of the inflammatory process. It seems that this hormone acts as an "immunological buffer". On the one hand, it has been reported exerting positive effects activating the impaired immunity in situations of immunosuppression, chronic stress or old age. On the other hand, it can suppress overreaction of the immune system in situations with exacerbated immune response [43].

As early as the 1980s it was observed that peak nocturnal melatonin secretion coincided with peak proliferation of granulocyte-macrophage grafts [45]. Also, melatonin levels are lowest during spring, a finding that correlates with the highest exacerbation rates of many autoimmune diseases. It is believed that seasonal and daily variation changes in melatonin concentration may be responsible for the development and/or severity of the seasonal occurrence of certain infectious diseases and autoimmune diseases such as rheumatoid arthritis or multiple sclerosis [46].

Melatonin can modulate the immune system through endogenous opioids, cytokines, influencing control of the hypothalamic-pituitary-adrenal axis and the hypothalamic-pituitary-gonadal axis, whose hormones modulate the function of the immune system [47, 48]. In its role as an immune modulator, it is produced by different types of leukocytes and in turn acts on them [43, 44, 49]. The leukocytes possess the necessary enzymes to synthesize melatonin and, in the communication of leukocytes, they can act in an autocrine or paracrine manner independent of the pineal gland. It has been reported that melatonin reaches micromolar concentrations in tissues such as bone marrow, this concentration is much higher than those circulating in the blood, which supports this idea of the paracrine / autocrine function of melatonin as a regulator of the immune system [50].

Several studies describe the different effects of melatonin on the mediators of inflammation (Table **1**). Nitric oxide (NO) is a molecule that participates in the inflammatory process and is produced by endothelial cells, macrophages and brain neurons by nitric oxide synthase (NOS). In various inflammatory processes melatonin has been observed able to reduce iNOS levels, exerting a protective effect in situations such as brain ischemia [51], or inflammatory neurological [52] bowel diseases [53, 54]. Other mediators of inflammation are produced from arachidonic acid by phospholipase A2 (PLA2). These are prostaglandins (PG) and thromboxan A2 that are produced by cyclooxygenases (COX) and leukotrienes that are generated by lipooxygenases (LOX). There is evidence, both *in vivo* and *in vitro*, that melatonin reduces the inflammation derived from the activation of PLA2 [55], LOX [56] and COX. It seems that the mechanisms involved in these effects are mediated by the MT1 / MT2 or ROR / RZR receptors [57]. In contrast, other studies have shown that melatonin activates, transiently is extinguished in two hours, PLA2 and LOX as a result of its binding to calmodulin [58]. So, on one hand melatonin could stimulate the production of pro-inflammatory mediators in early phases of inflammation by activating 5-LOX and PLA2 (through the binding of indolamine to calmodulin) and, on the other hand, could induce a subsequent inhibition of these same enzymes (through RZR or MT1 / MT2), which limits the inflammatory response [9, 50].

With respect to the release of cytokines, melatonin may be able to also exert pro- and anti-inflammatory effects [43, 44]. Nevertheless, these effects appear to depend on cells and especially on conditions of the inflammation grade. Different inflammatory diseases are associated with cytokines and his balance between those that are pro-inflammatory (*i.e.*, Interleukine (IL)-1b, IL-6, IL-2, IL-8, and Tumoral Necrosis Factor-α (TNF-α) and anti-inflammatory [*i.e.*, tumor growth factor (TGF-β) and IL-10]. In different pathophysiological situations melatonin seems to modulate both pro- and anti-inflammatory cytokines [9]. Carrillo-Vico *et al*. [43] describe some experimental situations (high doses of melatonin (500 mg/kg) or immunosuppressed animals) in which melatonin produces increased levels of pro-inflammatory cytokines such as IL-6, IL-1β, IL-12 or TNFα [59,60]. Conversely, in situations with exacerbated immune response melatonin has the opposite effect, neutralizing the exacerbated production of pro-inflammatory mediators, mainly cytokines such as TNF-α, IL-1β, IL-6, and IL-8 or increasing the production of anti-inflammatory IL-10 or IL-4 [61-68]. On the other hand, it seems that the anti-inflammatory effect of melatonin depends not only on the inhibition of pro-inflammatory cytokines, but also on various adhesion molecules such as vascular cell adhesion molecules (VCAM-1), intercellular adhesion molecules (ICAM-1) and endothelial cell selectin (E-selectin) [69].

Controversial effects have also been reported about the melatonin effect on leukocytes, especially concerning the changes in leukocyte expansion, activity or abundance in the different immune tissues including spleen, lymph nodes, gut and thymus [43, 44, 70]. Several studies have shown that in the innate immune response melatonin stimulated activity and cellularity of macrophages, neutrophils, monocytes and NK cells. Other studies showed a decrease in migration, infiltration and phagocytosis of neutrophils and macrophages- /- monocytes [71]. With regard to specific immunity, melatonin wields positive effects on the cellular and humoral responses under basal or immunosuppressed conditions, increasing levels of IgG1 or IgGM for example and, conversely, reducing the CD+19 B-cell population or IgE in some chronic diseases [43].

It has also been shown that melatonin has an antiapoptotic effect on different leukocytes. Studies in peripheral blood have suggested that this effect of inhibition of apoptotic processes is due to the antioxidant properties of melatonin. In other studies with U937 monocytes, it has been proposed that melatonin reduces apoptosis through interaction with MT1 / MT2 plasma membrane receptors by triggering signaling pathways acting on proapoptotic Bax and anti-apoptotic Bcl-2 proteins. The balance between Bax and Bcl-2 determines the response of the cells to an insult to respond either with apoptosis or with survival. Melatonin can promote cell protection and therefore maintain the viability of cells favoring inflammation [72].

The opposite results of the actions of melatonin seem to indicate that the pro-inflammatory effects are observed in basic conditions, while the anti-inflammatory effects are characteristic of high-grade inflammation. These observations confirm the idea that melatonin is a buffer of the immune system allowing immune stimulation in response to, for example, infectious challenges, but relieving high-grade inflammation [43]. Other authors consider that melatonin can only stimulate initial phases of inflammation and in more advanced states it slows down and prevents its chronification [50]. However, in situations such as aging it seems that the effect of melatonin is preferably anti-inflammatory. In old female rats, melatonin decreased the pro-inflammatory cytokines TNFα, IL- 1b and IL-6, whereas it strongly increased the anti-inflammatory IL-10 in the liver [11]. It is worth mentioning that in sepsis processes beneficial results of treatment with melatonin have been reported [73]. But it seems that in sepsis, melatonin would be effective in the initial inflammatory phase so it could be used as adjuvant therapy but not as a treatment for severe sepsis once systemic inflammation has begun [74].

Effects of melatonin on the immune system are mediated by different signal transduction pathways. The protective effects of melatonin appear to be related to its ability to reduce the activation of nuclear factor-kB (NF-kB). Several studies have shown that during inflammation melatonin can modulate the signaling pathway of NF-kB which, during the early stage by regulating the levels of oxidant and activating IκB kinase (IKK) and in the late stage by binding of NF-kB to DNA, modifies the expression of genes in-

volved in the inflammatory process, including iNOS, COX-2 and pro-inflammatory cytokines. [75]. This reduction of NF- kB suppress iNOS expression. This effect was observed in macrophages, in various organs and cells and notably also in microglia and astrocytes [52]. Equivalent changes in NF-kB activation and downregulation of COX expression were also reported following melatonin use in different macrophages [76]. It has also been reported that melatonin blocks the production of pro-inflammatory cytokines in rats by reducing the translocation of NF-kB in the nucleus [9].

Other critical factors may take part in the mechanism of melatonin´s anti-inflammatory effects. These include the inhibition of some factors such as Vascular Endothelial Cell Growth Factor (VEGF), the Hypoxia Inducible Factor (HIF), which controls the oxygen-dependent stimulation of erythropoietin and glycolytic enzymes. It has also been shown that melatonin suppresses the transcriptional activity of HIF-1a, which leads to the reduction of different angiogenic processes. [77]. Another transcription factor involved in the fight against inflammation and oxidative stress is Nrf2, a leucine zipper transcription factor, which regulates the expression of a number of antioxidant and detoxifying genes and modulates some inflammatory processes. It has been demonstrated that there is an increase in the expression and signaling of Nrf2 with the administration of melatonin, which decreases the activation of NF-kB and leads to the inhibition of the expression of pro-inflammatory cytokines and iNOS [9].

Melatonin can inhibit protein kinases involved in signal transduction from cell surface to the nucleus, such as mitogen-activated protein kinase (MAPK), by modulating the DNA binding capacity of transcription factors such as NF-kB or activator protein-1 (AP-1) [9]. It has been described that this inhibition of the MAPKs has a

Table 1. Summary of the effects of Melatonin on pro and anti-inflammatory modulators in different inflammatory experimental models.

Pro and Anti-inflammatory Modulators	Effect	Experimental Model	References
iNOS	↓	Brain ischemia in rats	[51]
	↓	Rat models of colitis	[52]
	↓	Neuronal MPTP-induced damage mice	[55]
	↓	(LPS)-induced macrophages	[53]
	↓	IBD	[56]
COX2	↓	(LPS)-induced macrophages	[53]
	↓	IBD	[56]
PLA2	↓	Rat pineal glands	[57]
	↑	Monocytes and lymphocytes culture	[58]
LOX	↓	Human B lymphocytes	[59]
	↑	Monocytes and lymphocytes culture	[58]
IL-1b	↓	(LPS)-induced macrophages	[60]
	↓	Acetic acid-induced colitis	[61]
	↓	Neuroinflammation by LPS	[62]
	↑	Phytohemaglutinin spleen cells treated	[63]
	↑	Trauma-hemorrhage inmunosuppresed mice	[64]
IL-6	↓	Acetic acid-induced colitis	[61]
	↓	Neuroinflammation by LPS	[62]
	↑	Trauma-hemorrhage inmunosuppresed mice	[64]
TNF-α	↓	Experimental colitis	[65]
	↓	Acetic acid-induced colitis	[61]
	↓	Neuroinflammation by LPS	[62]
IL-10	↑	Antigen primed mice	[66]
	↑	Mouse septic mouse	[67]
	↑	Acute pancreatitis	[68]
IL-4	↑	Bone marrow lymphocytes	[69]

beneficial effect on different experimental models of pathologies such as cancer, stroke, neurodegenerative diseases, bipolar disorders, diabetes type II, chronic inflammatory disease and sepsis [78].

On the other hand, it has been demonstrated that melatonin could modulate neonatal brain inflammation through miR-34a/SIRT1 pathway [79]. Also in AD it has been described that certain miRNAs, such as miRNA 16, miRNA 101, miRNA 200b, miRNA 186 and 290, are involved in its pathogenesis since they alter the rate of production or elimination of APP. Also, several miRNA participate in multiple pathways, such miRNA 125 in synaptic plasticity and apoptosis or miRNA 98, miRNA 219-5p, among others, in hyperphosphorylation of tau which affect different mechanisms in neuroinflammation [80]. So, at least in part, melatonin could exert its beneficial effects modulating miRNA expression.

4. FREE RADICALS, OXIDATIVE STRESS AND INFLAMMATION: A VICIOUS CYCLE

ROS mainly generated in detoxification reactions mediated by the microsomal cytochrome P-450 [81-83] and in the mitochondrial electron transport chain [82]. Other sources are the reactions catalyzed by NADPH oxidases, xanthine oxidases, cyclooxygenases and lipoxygenases, nitric oxide synthases, and ethanol metabolism [84-86] and autooxidation of several compounds, such as catecholamines and hydroquinone [87]. Also, free radicals can be induced exogenously by different exogenous stimuli such as ionizing radiation, UV light, tobacco smoke, environmental pollutants, exposure to herbicide/insecticides, food additives, drugs, etc. The extent of damage is termed oxidative stress [88]. Among the reactive species, the free radical superoxide anion (O_2^-) is the main specie produced in the cells [89]. Other reactive species of physiological significance are H_2O_2, hydroxyl radical (OH·), and ONOO−.

The hydroxyl radical (OH) is the most reactive species of activated oxygen. It causes oxidative damage to cells because they nonspecifically attack biomolecules [90] located less than a few nanometers from their site of generation. OH· is formed by Fenton reaction, where free iron (Fe^{2+}) reacts with hydrogen peroxide (H_2O_2) and the Haber-Weiss reaction that result in the production of Fe^{2+} when a superoxide reacts with ferric iron (Fe^{3+}). In addition to the iron redox cycling described above, a number of other transition-metals including Cu, Ni, Co, and V can also be responsible for OH· formation in living cells.

Oxidative stress has a direct toxic effect on cells. In the case of either acute uncontrolled overproduction of ROS or their production over a long period, significant damage may occur to cell structure and functions. High levels of reactive oxygen species ROS can directly affect important biomolecules, disrupt signal transduction, cause mutation and cell death, and lead to many diseases [91]. However, reactive oxygen species ROS are not always harmful. At low/ moderate concentrations ROS generation could play functional roles as they are involved in a variety of different cellular processes in some cell types [85]. For instance, ROS are important to pathogen defense during the respiratory burst. When certain leukocytes come into contact with bacteria or fungi NADPH oxidase, an enzyme on their outer membrane is activated to rapidly produce large amounts of superoxide which effectively kills the pathogen. ROS can also induce cellular senescence and apoptosis and can therefore function as anti-tumorigenic species.

4.1. Oxidative Stress and Inflammation: A Vicious Cycle

Thus, numerous studies support that oxidative stress and chronic inflammation are closely linked and potentiate each other [92]. The inflammatory cytokine IL-6 has been found to produce ROS through increased expression of NADPH oxidase 4 (NOX4) in non-small cell lung cancer [93]. As mentioned above, during the inflammatory process the activated neutrophils and macrophages produce ROS.

Inflammatory response generates reactive species that can diffuse out of the phagocytic cells, thus inducing localized oxidative stress and tissue damage [94]. Then, ROS can trigger an immune response *via* two main mechanisms: 1.- by oxidizing biomolecules, which immune cells do not recognize and 2.- by activating redox-sensitive protein inside the cell, which transcribes and increases the expression of many pro-inflammatory genes [95]. For instance, the ROS-induced DNA base modification induces a signaling cascade that ends in the activation of NF- κB pathway resulting in pro-inflammatory gene expression and inflammatory cell accumulation. The 8-isoprostane, a marker of lipid oxidative stress has been found to increase the expression of inflammatory chemokine IL-8 in human macrophages through activation of mitogen-activated protein kinases (MAP kinases) [96]. Furthermore, the oxidative stress induced oxidation of the extracellular redox potential of plasma cysteine (Cys) and its disulfide cystine (CySS) has been shown to trigger monocyte adhesion to vascular endothelial cells, activate NF-κB, and increase the expression of proinflammatory cytokine IL-1β [97]. Also, protein oxidation has been recognized as an inflammatory signal.

Many transcription factors are activated by oxidative stress [98] that can lead to the expression of over 500 different genes, including those for growth factors, inflammatory cytokines, chemokines, and cell cycle regulatory molecules [99]. As can be seen, oxidative stress seems to be an important mechanism underlying the progress of inflammation and a vicious circle creates a link between these two conditions. If oxidative stress appears as the primary abnormality in an organ, inflammation will develop and will further accentuate oxidative stress. Conversely, if inflammation is the primary event, oxidative stress will develop as a consequence that will further exaggerate inflammation so that basal levels of ROS and inflammation will steadily remain increased over the basal levels. Clearly, both processes are tightly linked and are interdependent. In fact, oxidative stress and inflammation are a common finding in many inflammatory diseases [100].

4.2. Using Antioxidants to Break the Vicious ROS-inflammation Cycle

Based on the interdependence of oxidative stress and inflammation discussed and because inflammation and oxidative stress are the major causes of many serious pathological conditions, several groups have investigated the use of antioxidants to reduce ROS-induced inflammation. The challenge is to investigate pharmacological approaches that allow the reduction of pathologic chronic inflammation without interfering with the physiological inflammatory response.

Results of the trials of this research show little benefit from antioxidant therapy and in some cases treatment was even found to produce harmful effects [101]. So, great care should be taken in the selection of an antioxidant agent and its dosage. Failure of antioxidant trials can be due to many reasons. In general, antioxidants may be good or bad for health depending on situations. For example, in a premalignant stage antioxidants are good since they can inhibit ROS induced DNA damage and malignant transformation of cells exposed to ROS carcinogens. However, in cancer cells, antioxidants can be harmful because they can decrease ROS and thereby can inhibit ROS-induced apoptosis of genetically damaged cells leading to increased cell survival, proliferation, and carcinogenesis [102]. Thus, the antioxidants may exert either beneficial or harmful effects depending on the cellular requirement for ROS in a particular situation. Also, it is important to note, that ROS produce beneficial health effects at least in some situations, for instance, wound healing [103]. Wound healing, is a highly coordinated process involving several biochemical events such as cell arrival at the injured site, cell proliferation, cell differentiation, biomolecules synthesis, cell death, and increased metabolic activity. The phases in wound healing are hemostasis, inflammation, proliferation (growth of new

tissue) and maturation (remodeling of the tissue) [104]. Each step starts as soon as the previous one has ended. This coordination is mediated by several molecules, including free radicals. In the inflammation step, polymorphonuclear neutrophils arrive within 1 h after the stimuli and they are the predominant cells in the wound for 1-2 days. They phagocyte debris and kill bacteria by releasing free radicals. After 2 days, they die by apoptosis. Then, macrophages arrive and phagocyte causes the death of neutrophils and starts secreting growth factors, permitting cytokines to enter the next phase. On day 4-5, the inflammatory phase declines. Angiogenesis and an increase in the number of fibroblasts are characteristic of the proliferation phase and on day 7-10 collagen synthesis peaks. By looking at these orchestrated steps, it is possible to understand that, in order to support the coordination of these processes, it is important to ensure that cells and tissues have everything they need (molecules, micronutrients, cofactors, etc) and in a hypothetical case of pharmacological intervention, this intervention does not interfere with these processes. Because oxidative stress plays a crucial role in signaling and management of the initial phase of inflammation, giving an antioxidant at a wrong time would produce an undesirable effect and a worse situation by blocking the apoptosis signal triggered by ROS [105] and by blocking the action of neutrophils and macrophages. Under these circumstances, down regulation of inflammation using antioxidants therapy could not be as straightforward as once thought and the right antioxidant administered at the right moment is crucial to get a positive effect.

4.3. The Use of Melatonin in Breaking the Vicious ROS-inflammation Cycle

As mentioned above, inflammation and oxidative stress are closely related. One of them may appear before or after the other. Treating only the primary abnormality may not always be successful, because once the process has already been started, both inflammation and oxidative stress act in concert to accentuate each other and to induce progressive damage.

An efficient anti-inflammatory approach requires antioxidants to brake this vicious cycle and to reduce the levels of inflammatory mediators. We will see that melatonin affect both inflammation and oxidative stress. This dual effect makes melatonin the ideal compound for treating diseases related to the vicious ROS-inflammation cycle (Fig. **2**). The advantage of using melatonin to break this vicious cycle is that melatonin may act as a modulator of the immune function and has a strong antioxidant potential able to reduce the oxidative environment of chronic inflammation [106], thus terminating the chain reaction before cell viability is seriously affected. Melatonin regulates many physiological processes and also is an active antioxidant [107-110]. In fact, several of its suggested uses are based on this antioxidant activity [111-114]. The antioxidant ability of melatonin and its metabolites have been reported by many authors [106, 108, 115-118]. It can increase either mRNA levels or the activities of several antioxidant enzymes [119, 120]. In addition, melatonin stimulates glutathione synthesis [121]. Melatonin also prevents the production of HNE and MDA adducts with proteins [12]. These antioxidant functions of melatonin are independent of its receptors as it can reach all subcellular compartments [122, 123].

Melatonin protects cell membranes when they are exposed to ROS [114, 124, 125]. Whereas some authors have shown that melatonin´s ability as a lipoperoxyl radical scavenger is weak [126], others report that melatonin is even more effective than vitamin E against the propagation of lipid peroxidation [127]. Previous work from our lab has shown that melatonin is involved in the molecular changes of protein synthesis caused by oxidative stress induced by exposure to oxidants in the hypothalamus, hypophysis, liver and pineal gland [12, 128]. The effect of melatonin may not only be the consequences of its antioxidant effects but also due to its anti-inflammatory properties [9]. The protective effect of melatonin has been described in many tissues, possibly as a consequence of its quick entrance into the cells with insignificant differences between organs [118, 129, 130].

In a previous report, we have shown that oxidative stress increased throughout the day [131], when circulating melatonin levels are at their lowest [132, 133]. It is tempting to suggest that the production of melatonin by the pineal gland during darkness may be a relevant step in determining this oxidative stress cycle.

As mentioned above, melatonin has endocrine, paracrine and autocrine effects on leukocytes. Due to its endocrine and paracrine effects, melatonin differentially controls production of inflammatory mediators such as cytokines and leukotrienes. As can be seen, the dual effect of melatonin makes this molecule a good candidate to break the vicious ROS-inflammation cycle since it may act as a regulator of the inflammatory process with a potent antioxidant capacity to reduce the oxidative environment of chronic inflammation. At a physiological dose, melatonin might promote early phases of inflammation and at supra-physiological amounts this hormone would contribute to its attenuation and complications of chronic inflammation (Fig. **2**)

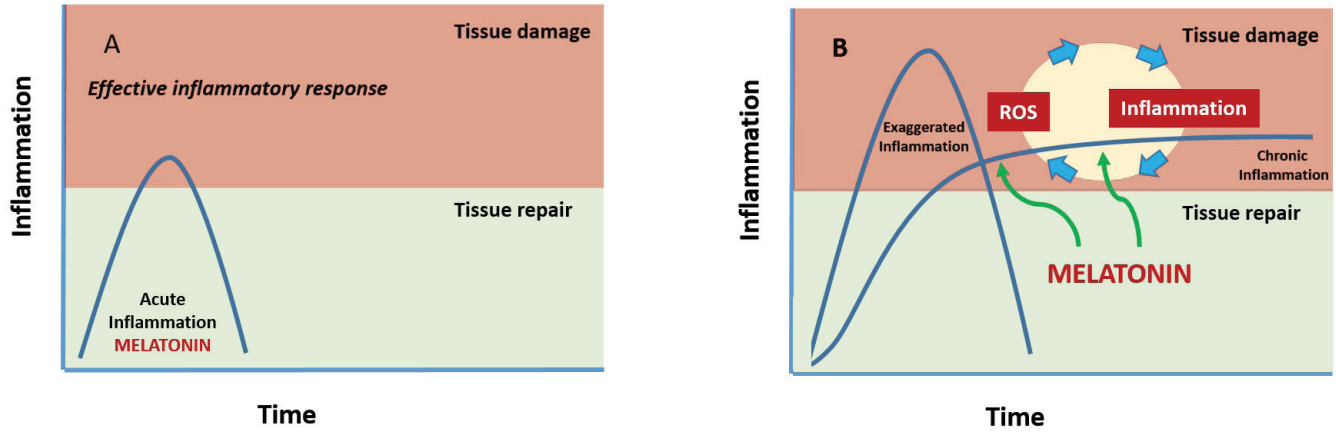

Fig. (2). Possible participation of melatonin in the resolution of inflammation. (A) An effective response requires ROS production by neutrophils and macrophages. In this situation, antioxidant administration can be harmful. But melatonin, at a physiological dose, would participate as modulator of this response. **(B)** In the case of exaggerated response or in the case that inflammation turns chronic, supraphysiological administration of melatonin would help in restoring tissue homeostasis.

5. NOTION OF BRAIN INFLAMMATION

Progression of neurodegenerative diseases shares different mechanisms, including inflammation, oxidative stress, mitochondrial dysfunction, excitotoxicity, genetically mediated factors, protein aggregation, etc. The degree of contribution of these mechanisms in each neurodegenerative disorder is still unclear. However, it is quite evident that a progressive and sustained inflammation, which at first is low-grade, is found repeatedly in neurodegenerative disorders [134, 135]. Neuroinflammation has been reported in amyotrophic lateral sclerosis (ALS) [136], frontotemporal lobar degeneration [137], multiple sclerosis [138], Huntington's disease [139], and PD [140]. In the CNS of patients with Alzheimer's Disease (AD) high levels of pro-inflammatory factors have also been found, among which are cytokines, peroxidants and pathogenic peptides [141]. The immune system protects the host, preserving the integrity of the organism. Immune responses elicited by microglia and macrophages act in a coordinated manner to elicit the first line of defense to destroy and remove the toxic agents, from both external and internal sources, and from injured tissues. The purpose of this process is to allow tissue repair [142]. When this beneficial response is uncontrolled under pathological conditions, inflammatory pathways initiates a chronic inflammation that results in undue cell damage and eventually cause the destruction of healthy tissue [143]. While inflammation is basically understood as a normal process, it is accelerated and aggravated in the brain under neuropathological conditions [11]. The term neuroinflammation refers to the set of processes that take place in the nervous system and that characterize inflammation, both acute and chronic [144]. It must be taken into account that CNS is no longer considered an immune privileged tissue. Inflammatory processes in CNS occur through direct infiltration of peripheral immune cells into brain parenchyma [145] due to blood-brain barrier integrity loss, but also by the expression of specific pattern recognition receptors in different brain cell types. Pathogen-associated molecules, misfolded proteins, aggregated peptides, and miss-localized nucleic acids originated from damaged cells are sensed by these receptors that can trigger inflammatory signaling pathways. In addition, neurons, microglia, astrocytes and endothelial cells can also express receptors for cytokines and inflammatory receptors that trigger inflammation. Different types of cells may participate in the inflammatory process, such as microglia, macrophages, neutrophils, lymphocytes and plasma cells, modulating inflammatory responses in the brain and spinal cord through innate immune receptors or interacting with neurons [146]. In fact, environment surrounding neuronal cells is strictly controlled by astrocytes, oligodendrocytes, and microglia to avoid possible neuronal damage. The reason must be sought in the high sensitivity of neurons to inflammatory stimuli, and hence any inflammatory reaction in the nervous tissue must be highly regulated [147]. Pro-inflammatory factors induce in the CNS the expression of various inflammatory mediators in glial cells that, in turn, cause neuroinflammation in the form of activation of microglia and astrocytes. Many studies suggest that inflammation is involved in a wide variety of brain pathologies characterized by activation of microglia and astrocytes, loss of the regulation of inflammatory response, and neuronal death *via* glia [148, 149]. High levels of proinflammatory factors expressed in glial cells have been found in PD patients, which would support the idea that glial dysregulation would be involved in PD neuroinflammation [150]. Furthermore, the infiltration of T lymphocytes and activated microglia in post-mortem PD brains [151] and the increased level of pro-inflammatory cytokines, such as TNF-α, interferon γ (IFN-γ), interleukin-1 beta (IL-1β) and interleukin-6 (IL-6) in the cerebrospinal fluid of PD patients [152] would show close relationship between neuroinflammation as a source for the pathogenesis of PD.

6. PHYSIOLOGICAL AND PATHOLOGICAL ROLES OF NEUROGLIAL CELLS IN CNS

In the CNS glial cells are identified as astrocytes, microglia and oligodendrocytes, each one playing a different role inside the nervous system. Among other items, they provide nutrients, neural factors, immune protection, and they optimize the transmission of nerve impulses [153].

Microglia cells are derived from myeloid precursors. These cells are derived from myeloid precursors that also give rise to monocytes and macrophages. Therefore, microglia cells can be considered as the resident macrophages of the innate immune system located within the CNS, which can be activated during the pathological process and transformed into immunocompetent antigen presenting cells [154]. In particular, microglia represents the major cellular component of the innate immune system of the brain. These cells act as the major pro-inflammatory cell type in the brain mediating the immune responses in the CNS responsible for its protection against several threatening, dangerous, or pathogenic factors [155]. Progenitors of the microglial cells invade the neural tissue during development acquiring a branched form, known as resting microglia, [153] and presenting, unlike macrophages, proliferation and longevity characteristics [156]. However, resting microglia is not characterized as a population of inactive cells. Branched microglia cells are active cells capable of safeguarding the central nervous microenvironment sensing the microenvironmental changes. Microglial migration is essential in achieving this purpose [157]. Under normal conditions, the resting microglial cells are constantly moving, interacting with neighboring neurons, astrocytes and blood vessels to allow the maintenance of brain tissue and neural plasticity [158] and to detect pathological disturbances [159]. Some signals are sensed by microglia when a nervous system is injured by chemical or physical events or invaded by pathogens, including molecules such as antigens, and endogenous brain molecules whose tissue levels are increased, diminished, or absent (*i.e.*, neurotransmitters, ATP, cytokines, growth factors). They sense changes in intracellular ion influx/efflux balance, and structural arrangement or ion redistribution of potassium, chloride, sodium and water [159]. Furthermore, microglia responds to injuries and pathogens by becoming activated. In a process known as microglial activation, microglia cells change their ramified morphology to an amoeboid shape rapidly, in less than 24 hours of exposure to the stimulus, by increasing the diameter of the cell bodies at the same time their projections are retracted [160, 161]. Activated microglia cells are consistently found during chronic inflammation in AD and PD [149, 162]. The activation and rapid transformation of microglia implies the presence of IL-1β, TNF-α, and other molecules such as superoxide (O_2^-) or NO [163, 164]. IL-1β and TNF-α are inflammatory cytokines that play a central role in the initiation and regulation of inflammatory responses [165], both significantly elevated in the cerebrospinal fluid of AD patients, the traumatic neuronal injury, and acute ischemia [166, 167]. When microglia cells are activated, they proliferate and migrate by amoeboid movements across the nervous system to lesioned tissues where they remove damaged cells and phagocytize and destroy pathogens. Moreover, cannabinoids, chemokines, and bradykinin have been proposed as chemotactic triggers for the microglial movements [168-171]. Depending on the received stimuli, the activation of microglia can give rise to neurodegenerative and phagocytic cells as well as others that are mainly neuroprotective or growth promoters [157]. Damaged tissues release dangerous signals that are named as Damage-associated Molecular Patterns (DAMPs). In addition, pathogenic viruses, bacteria and protozoa, possess several structural patterns (*i.e.*, carbohydrate residues, nucleic acid, lipid and protein) known as Pathogen-associated Molecular Patterns (PAMPs). Both

DAMPs and PAMPs are recognized by a Toll-like receptor (TLR) and NOD-like receptor family receptors that are expressed in microglia. DAMPs, PAMPs or cytokines (*i.e*. interferon- γ), produce an activation of microglia that plays a role in homeostasis, removal of dead cells by phagocytosis and release of trophic factors such as Glia-derived Neurotrophic Factor (GDNF) and brain-derived neurotrophic factor (BDNF) to enhance axonal sprouting [172, 173]. These activated microglia cells also start secreting inflammatory mediators including prostaglandins, TNF-α, IL-1β, and IL-6, that in turn, activate a larger number of microglia cells. Activation of iNOS to produce NO from arginine is also induced in these cells, thus increasing the production of ROS, as well as neurotoxic substances [174]. Although this response allows an efficient control of invasive pathogens, through its molecules it can lead to tissue damage and neuronal death. Along with this, an alternative activation of the microglia cells is produced by cytokines such as IL-4 or IL-13. This activated microglia secretes, by contrast, neurotrophic factors, anti-inflammatory cytokines such as IL-10 or tumor growth factor beta (TGF-β). In these cells the expression of the arginine hydrolytic enzyme arginase 1 is also induced through the TLR pathway to avoid biosynthesis of NO. These cells carry out a transition to protective adaptive responses, brain tissue repair, remodeling processes and neuroprotective functions [175]. Therefore, microglial cells may display quite heterogeneous properties in different areas of the CNS and neurodegenerative diseases.

Participation of astrocytes and oligodendrocytes in neuroinflammation is also worth mention. Both are highly specialized glial cells that arise from a common lineage of neural progenitor cells within the neuroectoderm [156]. In the human brain astrocytes represent about 40% of the total CNS cell population, and due to its anatomical disposition astrocytes are in close contact with meninges, vasculature, and neurons. Astrocyte cells exercise a wide range of functions under physiological conditions, that include water/extracellular ions and pH homeostasis, maintenance of the homeostasis in general, and the homeostatic redox state in particular, production of energy metabolites for neurons, clearance and extracellular modulation of neurotransmitters (*i.e.* glutamate), and they act during brain development as a guide for the migration of neurons. Astrocytes also produce growth factors and participate in injury-repair responses of damaged brain tissue. Besides, astrocytes are also responsible for the maintenance of the quiescent state of the microglia [176-178]. Accordingly, astrocytes sense and react, in a response that is known as reactive gliosis, to either cellular or molecular insults ranging from mechanical damage, chemicals, traumatic injury, ischemia, infection, and inflammatory stimuli [179, 180]. Reactive astrogliosis is a state characterized by functional and anatomic changes such as astrocytic proliferation and extensive cell body hypertrophy, when astrocytes are stimulated with IL-1β, TNF-α, or lipopolysaccharide [181, 182]. Abundant evidence has shown that astrocytes cells would also be involved in neurodegenerative diseases, among which is dementia [149, 183]. A positive interaction between astrocytes and the resident microglia result in tissue reconstitution after injury, maintenance of the blood-brain barrier to avoid the invasion of cells through the barrier, and the clearance of pro-inflammatory cytokines [159]. Astrocytes express a variety of cell surface receptors to cytokines such as IL-1β, IL-6, IL-13, TGF-β, TNF-α, IFN- γ, and components of the complement system (*i.e*. protein CD40L, CD154), to respond to inflammatory stimuli [184]. Astrocytes also display a set of receptors involved in innate immunity, including TLRs, to trigger the inflammatory response to DAMPS and PAMPS molecules [183, 185].

7. IMMUNE ACTIVATION, OXIDATIVE STRESS, AND NEURODEGENERATIVE DISORDERS

As previously discussed, brain inflammation is mediated by the infiltration of peripheral macrophages into brain parenchyma and glial activation, which generates ROS [145]. The production of ROS by activated microglia in CNS works as an immunological response against pathogens and provides the first line of defense against pathogens. Evidence suggests that increased ROS production in the brain causes an inflammation-derived oxidative stress that leads to the pathogenesis of human neurodegenerative diseases, namely as *substantia nigra* degeneration and accelerated progression in PD [186, 187]. The cell membrane of neurons is highly vulnerable to oxidative stress in which ROS alter ion transporters [188], and ionic voltage-gated channels [189, 190] either through alterations of cell membrane proteins or the intracellular signaling pathways [191] or through direct oxidation of lipids. Experimental studies have also shown that the effects of ROS on neuronal excitability include modifications in ionic gradients, values of the resting potential, characteristics of the action potential and spontaneous activity [192, 193].

Lipid peroxidation caused by oxidative stress is a process under which oxidants, such as free radicals, affect lipids containing carbon-carbon double bonds. Lipid peroxidation modifies membrane barrier properties increasing the permeability for water and ions, and to a lesser extent, high molecular weight compounds [194, 195]. Oxidant agents causing lipid damage penetrates the lipid bilayer membrane and alters aminoacids, and proteins [196, 197]. In works from our laboratory using *in vitro* prepared brain slices, we have demonstrated in motor cortex that lipid peroxidation, induced by an organic oxidant cumene hydroperoxide (CH), evokes dose and time dependent changes in the functional properties of pyramidal neurons compromising the generation of action potentials and then, the neuronal excitability [197, 198]. In these experiments, dramatic changes were observed in the capacity of repetitive discharge of action potentials. This effect was not a consequence of the early cell death of the cells studied, but rather of the modifications in the values of the resting potential and the voltage depolarization, and in parallel, alterations in the rheobase and the input resistance of the membrane, which led to a reduction in excitability. Specifically, resting membrane potential of neurons under CH exposure become progressively depolarized with no changes in voltage threshold. In addition, the resistance of the membrane exhibited changes in its value characterized by two stages, a transient increase at the beginning of the application of the oxidant and then a gradual decrease over time after longer periods of exposure. The changes observed in the resistance of the membrane produced, at the same time, compensatory variations in the rheobase current that led to a transient increase in excitability. In some neurons prolonged exposure to the drug caused the loss of its ability to produce repetitive firings of action potentials, however most of the neurons studied maintained their repetitive discharge, although they displayed values of decreased maximum frequency and gain [197, 198]. In the cells that maintained the capacity to produce action potentials, the cancellation of the repetitive discharge took place at intensities that were lower as a higher concentration of the oxidant and / or a greater exposure to CH was used. As a consequence, these cells displayed a narrower working interval. Our experimental data also suggested that the neurons studied had a greater sensitivity to the oxidant depending on their size, with large neurons presenting the most sensitivity. These observed changes were thought to be mainly caused by changes in the intrinsic membrane properties of the pyramidal cells [197,198]. However, in hypoglossal motoneurons, Nani *et al*. have shown that oxidative stress also affects synaptic transmission that is characterized by a decrease in the frequency of spontaneous postsynaptic currents due to alterations in the release of several neurotransmitters [192]. Hydrogen peroxide application in cortical neurons also decreased synaptic inhibition [199]. Therefore, we proposed that some of the reported changes in rheobase and membrane resistance in pyramidal neurons were the result of modifications in the release of neurotransmitters on these cells [200]. In fact, lipid peroxidation induced by CH produced significant alterations of synaptic inputs to layer V motor cortex pyramidal neurons. Thus, CH induced a time-dependent synaptic depression on pyramidal neurons, GABAergic transmission being the first

input affected [200]. The latter finding triggered a transient pyramidal hyperexcitability characterized by a decrease in the value of the rheobase that could be due to the blocking of a tonic inhibitory current. In parallel, CH evoked a depolarizing inward current [200]. These effects depended on time and dose. Reversibility in the changes observed occurred in the membrane properties by action of the oxidant being inversely proportional to the time of exposure, *i.e.*, the lower the exposure to the oxidant, the higher the reversibility. In the set of functional properties of the neuronal membrane that were analyzed, we found that the capacity of repetitive discharge of the action potentials was the intrinsic membrane property most affected by the oxidant and the one that presented less reversibility.

An interesting piece of evidence linking oxidative stress and neuronal damage comes from our report where we demonstrated that pretreatment of the brain slices with the antioxidant molecule melatonin prevented the observed effects on membrane properties under condition of oxidative stress [198]. Accumulation of lipid peroxidation products is reduced and protein synthesis is preserved when membranes are exposed to radical-generating agents, in both *in vivo* and *in vitro* studies [12, 120], by the action of melatonin. We could not rule out, therefore, that in our *in vitro* studies of preparations of brain slices other mechanisms, in addition to lipid peroxidation (such as protein oxidation), may be the cause of changes in membrane properties induced by the oxidant, which would also be avoided with melatonin administration. All these data provided evidence that oxidative stress (lipid peroxidation) alters physiological properties of neurons, which may be prevented by pretreatment of the tissue with the antioxidant agent, melatonin [197].

There is increasing evidence that oxidative stress is responsible for the onset of CNS inflammation that characterizes neurodegenerative disorders, since AD and PD are associated with overproduction of ROS under conditions of oxidative stress [201]. Furthermore, cooperative and synergic pathways support the concept that inflammation and oxidative damage converge to stimulate neurodegenerative processes [148, 202]. Therefore, neuroinflammation and oxidative stress are closely linked since neurodegenerative diseases present both the neuroinflammatory process and oxidative stress. In brief, excessive ROS levels produced by mitochondria and NADPH oxidase regulate the induction of the redox-sensitive transcription factors, and the expression and release of diverse pro-inflammatory factors that trigger inflammatory responses in CNS [144, 149, 183]. ROS act through upregulation of diverse inflammatory genes, including matrix metalloproteinases, iNOS, and adhesion molecules [203, 204]. It has been reported that IL-1β activates microglia and induces neurotoxicity through the release of free radicals [205]. In addition, TNF-α are also produced by microglia in response to oxidative stress, its overproduction being linked to neuronal cell death [206]. Therefore, these studies indicate that these cytokines contribute to the CNS inflammation and neurodegenerative diseases through redox signaling. Microglia cells detect the increased presence of ROS, and consequently, activate themselves and produce more reactive species, thus favoring both an inflammatory and oxidative environment. This sequence of events would generate a constitutive and chronic pro-inflammatory and pro-oxidant environment present in neurodegenerative diseases in which microglia initiates its phagocytic activity, the most important signal involved in neuroinflammation and oxidative stress that leads to neurodegeneration [207]. Described cooperative pathways between inflammation and oxidative damage, validate the concept that the design on therapeutic strategies against these major two components of brain damage (inflammation and oxidative stress) should consider the validation and use of agents equally combative [202]. Therefore, antioxidants such as melatonin could have not only had an anti-oxidative role but also an anti-inflammatory role in neurodegenerative diseases, a possibility that should be explored for therapeutic purposes (Fig. **3**).

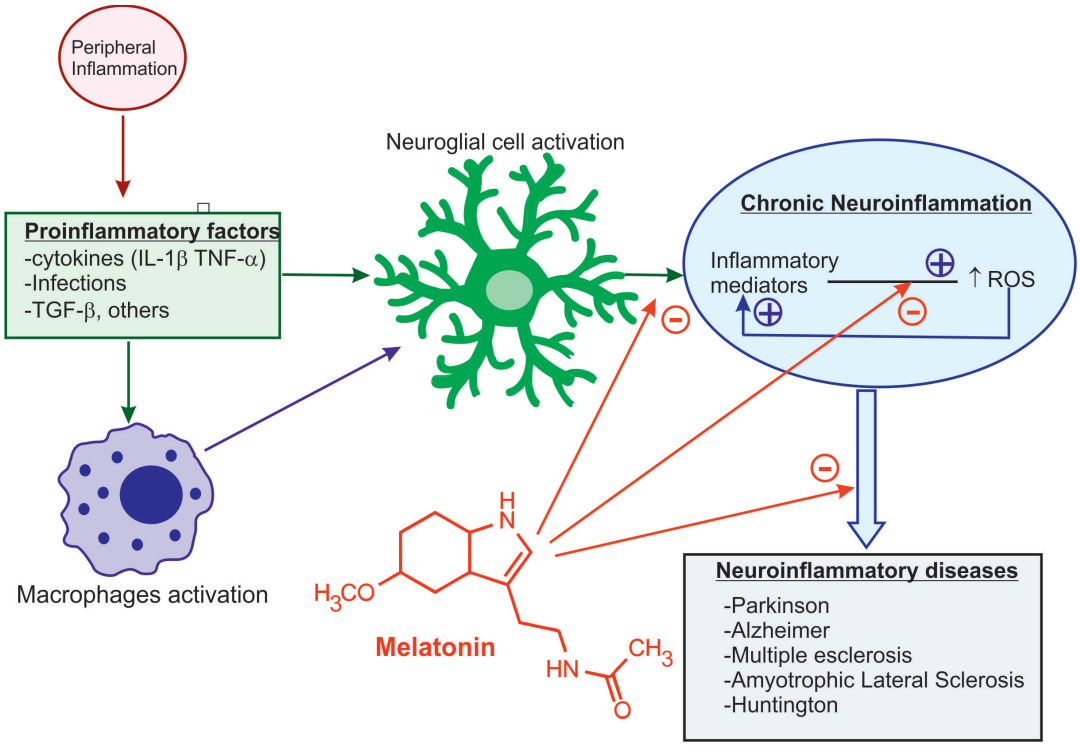

Fig. (3). Schematic representation of the anti-inflammatory and anti-oxidative role of melatonin. Chronic brain inflammation is mediated by the infiltration of peripheral macrophages and glial cells activation, which generates ROS. Melatonin can prevent chronic neuroinflammation and, then, neuroinflammatory diseases such as Parkinson's, Alzheimer's, Multiple Sclerosis, Huntington's or Lateral amyotrophic sclerosis, combatting both components of brain damage (inflammation and oxidative stress).

8. NEURODEGENERATIVE DISEASES AND MELATONIN

8.1. Multiple Sclerosis, Neuroinflammation and Melatonin

Multiple sclerosis is a chronic neuroinflammatory, neurodegenerative and immune-mediated pathology limited to the CNS affecting young adults with a prevalence of 5-200 cases per 100,000 persons [208]. Multiple sclerosis is likewise the main reason of non-traumatic incapacity in adolescents. Disorder is characterized by demyelination, extensive immune infiltration, microvascular changes, axonal damage and neuronal loss [209]. Glial cell death, specially oligodendrocytes, has a critical role in this pathology [210] The clinical manifestation of multiple sclerosis can be variable and can include visual and sensory alterations, motor and coordination impairments, as well as spasticity, pain, fatigue, and cognitive malfunctions [211]. Clinical signs and symptoms are related to the areas of the brain, optic nerve, and spinal cord affected by the infiltration of immune cells [212]. The disease subtype most common is the relapsing-remitting multiple sclerosis. This subtype of sclerosis is distinguished by acute outbreaks produced by inflammatory demyelination of focal zones by a partial or a complete reestablishment of the neurological impairment. A minor group of patients experience a steady and continuous deterioration of their symptoms from disease onset (primary progressive) or after several years of relapsing remitting disease (secondary progressive disease) [213].

CD4þ TH1 cells and TH17 cells are considered important participants to multiple sclerosis pathogenesis because they appear early during the formation of CNS lesions [214, 215]. Other subsets like Th9 and Th22 are also potentially pathogenic. Cytokines derived from these cells drive the inflammatory process in multiple sclerosis. Thus, the Th1 cytokines, IFN-γ and TNF-α, and the Th17 cytokines IL-17 and IL-22 have been identified in multiple sclerosis lesions [215,216] and are thought to be implicated in the pathology progression. TNF-α is produced by innate cells and lymphocytes and exerts pleiotropic effects that drive the inflammatory cytokine cascade. This is due to its pathogenic functions including induction of inflammatory mediators, recruitment of chemokine and adhesion molecules, endothelial cell activation, inhibition of T regulatory cells, and hypernociception [217]. Likewise, IFN- γ is a pathogenic mediator with pleiotropic functions and is pivotal in upregulating antigen-presenting and co-stimulatory molecules to bridge innate and adaptive immunity [218]. All this process is amplified by CNS microglia targeting myelin protein. CD8þ T cells are also present, sometimes at a higher frequency than CD4þ T cells. Their numbers are correlated with the amount of axonal damage [219]. In addition, clonally expanded B cells can be found in the cerebrospinal fluid of patients. Indeed, a widely recognized biomarker in multiple sclerosis is the appearance of immunoglobulins secreted by clonally expanded B cells, known as oligoclonal bands [220]. Opposing the pro-inflammatory actions of Th1 and Th17 lymphocytes, FoxP3þ regulatory T cells (Tregs) and IL-10 secreting type 1 regulatory T cells (Tr1 cells) are key regulators of effector T cells. Indeed, deficiency in Tregs and Tr1 cells have been demonstrated in multiple sclerosis, along with the suggestion that they have an main inhibitory role especially in the later phases of the disease [221]. CD8þ T cells and B cells can also display regulatory activity and have been linked to positive responses to immunotherapy in multiple sclerosis [212]. As can be seen, an accurate equilibrium between effector and regulatory T cells govern multiple sclerosis disease activity [214, 215].

There are other mechanisms that could underlay multiple sclerosis pathogenesis including oxidative stress, damage secondary to mitochondrial dysfunction, or to energy imbalances [222]. Reactive oxygen and nitrogen species play an important role in tissue impairment in multiple sclerosis *via* a number of pathways including damage to lipids, proteins, carbohydrates, and DNA, directly from inflammatory products [223], or non-inflammatory damage resembling that seen in classical neurodegenerative diseases [224]. In multiple sclerosis greater biomarkers of oxidative damage are present and a lower antioxidant status [225]. Multiple sclerosis injuries have bigger levels of DNA and lipid oxidation [226], and the expression of iNOS in macrophages and microglia at the end of active lesions are elevated [227]. The involvement of oxidative damage in early multiple sclerosis pathology has in addition been confirmed by raised levels of lipid peroxidation indicators in the cerebrospinal fluid of multiple sclerosis subjects [228] and by the presence of an upregulated level of myeloperoxidase, marker for oxidative stress produced by macrophages, in demyelinating white matter and cortical injuries [229].

Several studies have demonstrated that both, serum melatonin levels [230] and the levels of its main metabolite in urine, 6- sulphatoxymelatonin [231] have a nocturnal decrease in subjects with multiple sclerosis. Besides, those alterations are correlated with not only severity of the disease [232] but also with symptoms such as fatigue, insomnia, and depression [233]. Furthermore, serum levels of melatonin have been shown to correlate positively with IL- 10 expression and negatively with IL- 17 expression in peripheral CD4+ T cells from patients with multiple sclerosis [234]. It has also been shown that single nucleotide polymorphisms in the genes encoding tryptophan hydroxylase 2, the enzyme that catalyzes the first step of melatonin biosynthesis, and MT2, are associated with an increased risk of progressive multiple sclerosis [235]. So, taken together, the collected evidence and due to the potent immunomodulatory [43] and antioxidant actions [116, 236] of melatonin, the therapeutic use of melatonin on multiple sclerosis has been extensively studied. These studies have been performed on humans but mostly on murine models of EAE, on cuprizone mouse models of demyelization and other models that are commonly used as animal models for multiple sclerosis.

In several animal models of multiple sclerosis, it has been reported that exogenous melatonin ameliorates the inflammatory process by decreasing immune infiltration in the CNS. Chen *et al*. found, in a rat model of EAE, that melatonin administration at a dose of 200 mg/kg attenuates the inflammatory process by diminishing the chemokines, such as IL-17 and INF [237] involved in immune cell recruitment to the CNS. Besides, Kang *et al*., demonstrated that after melatonin treatment the expression of adhesion molecules, involved in the pro-inflammatory process, diminished [238]. In the same model, several studies showed that melatonin decrease the Th1 and Th17 effector responses, especially on memory T cells, while enhancing the Treg response and improving clinical scores [234, 237, 239]. Wen *et al*. demonstrated that the treatment with N-acetilserotonin, a precursor of melatonin, and melatonin 20mg/kg improves clinical progression [240]. They reported significant reduced iNOS and p67phox immunoreactivity in the spinal cord white matter suggesting a minor inflammatory reaction, as well as less reactive nitrogen species formation, and decreased oligodendrocyte and axonal loss. In the cuprizone model of multiple sclerosis, melatonin application (5mg/Kg) was effective in reducing the demyelization process [241]

With regards to human patients, it has recently been demonstrate, in a case report, that oral consumption of melatonin (300 mg/day) in a patient diagnosed with primary progressive multiple sclerosis exhibited long-lasting improvement [242]. In other studies, melatonin administration has also been shown to ameliorate sleep and quality of life in multiple sclerosis subjects, in addition to reducing oxidative stress in the peripheral blood [243, 244]. Along with this, recent reports have stated that *in vitro* administration of melatonin reduced Th1 and Th2 pathogenic responses and increased the anti- inflammatory/pro- inflammatory ratio in peripheral cells of patients with multiple sclerosis and that peripheral blood mononuclear cells from subjects suffering multiple sclerosis show augmented expression of the melatonin effector/receptor system [245].

All the doses reported here go beyond the physiological concentrations of melatonin measured in the control groups and in multiple sclerosis patients [246]. Nevertheless, and taking into account the safety profile of this indolamine, higher doses may be necessary to ensure the full range of antioxidant and anti-inflammatory effects. The collective results demonstrate that melatonin shows beneficial immunomodulatory and antioxidant effects on multiple sclerosis and may support clinical trials with melatonin in patients with multiple sclerosis.

8.2. Lateral Amyotrophic Sclerosis, Neuroinflammation and Melatonin

ALS is a lethal neurological disease that results from degeneration of both the lower and upper motor neurons [247]. Upper motor neuron degeneration causes spasticity, hyperreflexia and compromises motor control, while degeneration of lower motoneurons is characterized by muscular weakness and cell death [248]. In a small percentage of cases, ALS has a genetic component, but 90% of the cases are sporadic with initial causes still unknown. Many preclinical investigations and clinical trials have been performed to examine the cause that underlies motor neuron degeneration in sporadic ALS; nevertheless, the precise mechanism remains unknown. It has been proposed, that this degeneration may be the consequence of a combination of mechanisms, including genetic predispositions, excitotoxicity, mitochondrial dysfunction, protein aggregation, oxidative stress and neuroinflammation [249].

In ALS pathology, the neuroinflammatory process has been shown together, with motor neuronal loss, even in the absence of clinical symptoms. An abundance of evidence from preclinical studies has considered cells from immunity system as either exerting negative or beneficial effects on motor neuron survival depending on the point of ALS moment [250, 251]. Increased levels of microglial activation and lymphocyte permeation has been demonstrated from cerebrospinal fluid and postmortem spinal cord samples of ALS patients [252], indicating that neuroinflammation must play a role in motor neuron degeneration. In fact, further research revealed that microglia, activated in the early stages of ALS, was able to play either a deleterious or a protective role [253]. Additionally, astrocytes became toxic and contributed to motor neuron death [254], while T lymphocytes controlled microglial response enhancing their neuroprotective action [255].

At this moment, there is no known effective therapy for ALS patients. The only drug approved by Food and Drug Administration (FDA) used in clinics for the treatment of ALS is riluzole [256]. This compound has an antiglutamatergic action that could prolong the survival of ALS subjects almost 3 months [257]. For this reason, it is necessary to find more acute treatments for ALS patients. In the last few years, many studies have focused on finding an effective treatment against the neuroinflammation produced in this disease. In fact, it has been demonstrated that many compounds with anti-inflammatory action enhance motor neuron survival in the SOD1 murine models of ALS, an animal that expresses mutant human SOD1 genes. This murine model is characterized by an age-depending neuronal loss with worsening motor strength, symptoms that look like those presenting in ALS patients. These treatments include celecoxib, erythropoietin, glatiramer acetate, minocycline, pioglitazone, and valproic acid none of which has been demonstrated to be efficient for ALS patients [258].

Therefore, due to the inefficacy of this drug for ALS treatment, other compounds like melatonin, which have not only anti-inflammatory properties but also antioxidant and antiapoptotic properties have been studied. Nevertheless, not many studies that use melatonin are available. One of the most relevant studies was carried out by Weishaupt *et al*., as much for the SOD1 mouse model as for ALS patients [259]. In the SOD1 murine model of ALS, oral administration of 57–88 mg/kg/day of melatonin delayed disease onset, prolonged disease progression and extended survival. However, the protective effects of melatonin disappeared at lower doses (9 mg/kg/day) and when the treatment was applied once the symptoms were clinically obvious [259]. In the ALS subjects, 5 mg/kg of melatonin was administered as a suppository, the duration of treatment was for 2 and 24 months. In general, melatonin was well tolerated and some of the ALS patients experienced greater sleep quality. Stress biomarkers levels, like protein carbonyl, decreased in the blood after more than 4 months of treatment related to initial levels [259]. On the contrary, Dardiotis *et al*. reported that intraperitoneal melatonin at doses of 0.5, 2.5 and 50 mg/kg did not seems to improve disease phenotype in the SOD1 murine model of ALS [260]. This difference could be due to the differences in the experimental design. Probably melatonin administered orally could be an advantage. Besides, Daridiotis *et al*. started the administration of melatonin on the 40th postnatal day, while in the Weishaupt *et al*. study melatonin was added to drinking water on the 28th postnatal day [259, 260].

Recently, melatonin has been described as an effective antioapoptotic agent at inhibiting cytochrome c release and preventing neuronal death [261]. Zhang *et al*. have demonstrated that melatonin could apply its neuroprotection in the SOD1 murine model of ALS, inhibiting the caspase-1/cytochrome c/caspase-3 pathways [262]. In this model, decreased levels of melatonin and a down-regulation of MT1 receptors have been found in the spinal cord. These alterations were attenuated by exogenous melatonin supplementation [262]. Therefore, although there are some controversial studies that did not support the beneficial effects of melatonin in ALS treatment, they primarily show neuroprotective actions and, for instance, we suggest that melatonin, together with the conventional drugs used for ALS therapy, must improve the results for ALS patients. New assays with melatonin, alone or combined with other medicines, are necessary to clarify the potential benefit of melatonin in ALS patients.

8.3. Alzheimer´s Disease, Neuroinflammation and Melatonin

AD is a progressive neurodegenerative disorder and the most usual kind of dementia in aged people. The clinical characteristics of AD are the gradual loss of memory and cognitive tasks, often accompanied by neuropsychiatric symptoms like depression or anxiety [263]. The pathological sign of AD is the aggregation of extracellular deposits of β-amyloid (Aβ) peptide in the brain, mainly in areas that are relevant for memory and cognition function [264]. Aβ aggregates are ensued by i) the development of intracellular neurofibrillary tangles primarily consisting of hyperphosphorylated forms of the tau protein ii) local inflammatory pathways activation, iii) and oxidative damage. Even though the etiology of AD remains obscure it has been proposed that Aβ aggregates, soluble Aβ oligomers, oxidative stress, dyshomeostasis of biometals, levels of acetylcholine, and neuroinflammation, are plausible mechanisms involved in the pathogenesis of AD [265].

The existence of neuroinflammation in AD is a reality and is well documented. The AD inflammatory process is different to those presenting autoimmune diseases of the CNS, such as multiple sclerosis, which occurs when T cells with specificity for CNS antigens infiltrate the brain and spinal cord. Nevertheless, as explained by the amyloid cascade hypothesis, inflammatory reaction in AD is brain associated and involves activation of microglia close to the Aβ plaques [266]. Postmortem immunohistochemically examinations of brain slices have revealed the presence of activated microglia surrounding Aβ plaques in AD [267]. Microglia have been reported to be distributed in graded concentrations in relation to their distance from Aβ deposits in transgenic mouse models of AD [268]. Moreover, the density of activated microglia correlates with the severity of the inflammatory response. It has been proposed that microglia attempt to clear the brain of amyloid through the phagocytosis of Aβ and secretion of proteolytic enzymes that degrade Aβ [269]. Furthermore, activated microglia begin to produce pro-

inflammatory cytokines, chemokines, complement proteins, and upon strong activation may release toxic free radicals [270]. In *in vitro* studies, Aβ peptides have been demonstrated to stimulate microglia and the production of NO [271]. When microglia co-cultured with hippocampal brain slices were treated with aggregated Aβ, there was an upregulation of various pro-inflammatory molecules and neuronal death [272].

The advance of therapeutic strategies for this neurodegenerative disease represents an important challenge to scientists. Currently, the sole approved treatments by FDA, includes five drugs that are used to treat the cognitive manifestations of AD, galantamine, rivastigmine, donezepil and tacrine, along with an NMDA receptor antagonist–memantine that targets symptoms optimally [273,274]. These compounds delay the breakdown of Ach, an important neurotransmitter with altered levels in this pathology. It has been shown that these drugs lightly slow the progression of cognitive manifestations and reduce altered behaviors in some patients in half of the treated AD patients, donepezil being the most effective. Besides, it is effective in reversing the symptoms for only a short period of time [265] and therefore other pharmaceutical approaches have to be tested.

In the last few years, several studies have been checking melatonin as a possible treatment for AD pathology. Rats have been shown to have experimentally decreased serum levels of melatonin, showing a phenotype AD-like with spatial memory deficits, tau hyperphosphorylation [275] and a prominent oxidative damage characterized by raised expression of endoplasmic reticulum stress-associated proteins [276]. Therefore, melatonin deficit can contribute to the pathology development, and healthful actions of this neurohormone could be possible in AD. Indeed, several experiments in mouse models of AD have been performed to test the potential therapeutical benefit of melatonin. In the APP transgenic mouse, an animal model of AD that overexpressed mutant familial AD Amyloid Precursor Protein (APP) genes, the administration of melatonin decreased nitration of proteins due to oxidative damage, and increased survival [277]. Melatonin was demonstrate to be efficient in hindering Aβ plaque formation in APP 695 transgenic mouse in which these aggregates arise in cortical areas at 8 postnatal months [278]. In this animal model, that had behavioral impairments and memory deficits, the administration of melatonin, 10 mg/kg/day, improved the clinical symptoms and decreased apoptotic neurons [278]. In other murine models of AD (APP/PS1), oral administration of melatonin in drinking water (100 mg/L; 0,5mg/day) from 2 months of age to their killing, 5 months later, attenuated cognitive deficiency. In this study, they found decreased levels of Aβ aggregates and inflammatory cytokines in the hippocampus and entorhinal cortex. Furthermore, reduced mRNA expression of SOD-1, GPx, and catalase antioxidant enzymes were found [279]. In another study with the same animal model of AD, melatonin treatment for 1 month diminished mitochondrial Aβ levels up to four times in separate brain areas [280]. An almost return of mitochondrial respiratory ratio, membrane potential, and ATP concentration in isolated mitochondria followed this change [280]. Melatonin was also efficient against the immunosenescence and cognitive deficit shown in the tripe transgenic mouse model of AD [281] as well as ameliorating anxiety and associated depression-like behavior [263]. This animal model is the only one that exhibits both Aβ and tau pathology [282]. In other studies performed on neuroblastoma cells, melatonin decreased tau hyperphosphorylation induced by wortmannin, calyculin A and okadaic acid [283-285] through modifications of the activities of protein kinases and phosphatases. Additionally, Hoppe *et al*. studied, in organotypic hippocampal slice cultures, the toxicity of Aβ agregation and the potential beneficial actions of melatonin. They proposed that melatonin exerts neuroprotection against Aβ-induced toxicity by decreasing the hyperphosphorylation of tau protein, maybe by blocking GSK-3b activation and glial activation, decreasing TNF-α and IL-6 concentrations and hence neuroinflammation [286]. From these neuroinflammation [286]. From these experiments, it is manifest that melatonin has neuroprotective effects against oxidative stress, tau phosphorylation and Aβ aggregation, improving the survival of nervous system cells and ameliorating AD-like symptoms in experimental models of AD.

The employ of melatonin in AD patients treatment seems to be convenient for at least 3 reason: i) the remarkable neuroprotective effects demonstrated in experimental studies. ii) melatonin levels being diminished in CSF and serum of AD patients. This decrease become more relevant with the progression of AD neuropathology and is even present when the patients have no cognitive deficits [287]. iii) the great sleep/wake disturbances present in AD patients [288]. Therefore, several studies have investigated the therapeutic use of melatonin in AD patients. Brusco *et al*. [289] examined the effect of melatonin (6-9 mg/day) on 14 AD patients with sleep disturbances and sundowning agitation for longer periods of time (2–3 years). Afterwards, all subjects improved in sleep quality and sundowning was no longer detectable in most of them (12/14). In addition, cognitive and amnesic decline seems to be arrested in comparison with a population of patients not receiving melatonin [289]. In another study, the administration of melatonin (6 mg/day) for 4 to 7 weeks in patients with AD with a variable sleep-waking period decreased the percentage of night activity related to control [290]. Cohen-Mansfield *et al*. described the effectiveness of this indolamine (3 mg/day) for ameliorating sleep and bettering sundowning in 11 aged AD patients [291]. Important reduction in agitated behavior and daytime sleepiness was found. The effects of melatonin improving sleep disturbance, ameliorating sundowning and cognition have been demonstrated in other groups of AD subjects [292-294]. In conclusion, melatonin seems to be a perfect candidate to design therapeutical strategies in AD treatment because it has been demonstrated to be suitable for symptomatic treatment, improving sleep quality, ameliorating sundowning, etc., including in a progressed phase [295, 296].

8.4. Parkinson´s Disease, Neuroinflammation and Melatonin

PD is a progressive neurological disorder characterized by the loss of dopaminergic neurons of *sustantia nigra pars compacta* and, for instance, by the decrease of dopamine levels in the striatum nucleus. Clinically it is characterized by motor symptoms like bradykinesia, muscular rigidity, static tremor, postural disturbance and non-motor symptoms that include neuropsychiatric, autonomic, gastrointestinal and sensory symptoms, plus sleep disorders [297]. The majority of cases (90-95 %) are idiopathic, affecting 5 % of the population over 85 years old. However, in 5–10 %, PD can have a genetic component showing recessive and/or dominant modes of inheritance. Several gene mutations have been identified that resulted in PD. Early onset PD or familial PD (occurring in people under 50 years of age) is less common, and recent data has identified some nuclear genes associated with familial PD, like LRRK2, PARK2, SNCA, PARK7, and PINK1 [298] Despite the knowledge derived from genetic research in PD, the accurate mechanism underlying the dopaminergic loss in PD is poorly understood. However, mitochondrial dysfunction and oxidative stress in which there is an increase of ROS production, abnormal protein handling, neuroinflammation, excitotoxicity, and apoptotic processes have a central role in PD pathogenesis.

The neuron's environment is a main contributor to neurodegeneration. A lot of evidence suggests that neurodegeneration can occur because of a cascade of events that affects the neuron's environment, called neuroinflammation. Inflammatory components of PD involve alteration of inflammatory pathways, probably because of genetic predispositions together with immune changes related to aging and the activation of glia due to neuronal injury. Various researchers have associated aging with chronic mild inflammation in the *substantia nigra pars compacta*, which makes dopaminergic neurons vulnerable to degeneration [299]. Active peripheral in-

flammation in PD contributes to the beginning and/or development of the pathology by aggravating the central inflammatory response promoting dopaminergic neuronal death. Activation of microglia *via* lipopolysaccharide in the proximity of dopaminergic neurons in SN causes its degeneration, whereas γ-aminobutyric-acid-ergic (GABAergic) and serotonergic neurons are spared, which suggests a selective vulnerability of dopaminergic neurons to inflammation [300].

Several studies have shown inflammation and immune responses to be the determinant factor in disease progression and responsible for pathogenic mechanisms in disease onset of both familial and sporadic PD [152]. A recent study reported the presence of activated microglia in the SN and putamen of patients with a PD diagnosis [301]. In a 2005 study, Ouchi *et al*. suggested involvement of a microglial-mediated inflammatory mechanism in an early step of parkinsonism [302]. In another study, Gillardon *et al*, Moehle *et al*, and Harms *et al* suggested that different genetic mutations in genes, such as α-synuclein (α-syn) or *LRRK2*, participate directly in the progression of chronic PD by stimulating inflammatory responses *via* microglia and astrocyte activation [303]. Both central and peripheral inflammation are responsible for sustained progression of PD. Degeneration of dopaminergic neurons occurs with infiltration of T-cells and activation of microglia, along with a raised generation of inflammatory cytokines and chemokines due to a pathological accumulation of α-syn.

Oxidative stress also plays a pivotal role in dopaminergic neurodegeneration in PD. The dopaminergic neurons themselves seem to contribute to ROS production through dopamine metabolism, which produces superoxide anion, hydroxyl radical, and hydrogen peroxide. Furthermore, the autoxidation of dopamine produces dopamine-quinone, a molecule that can damage protein structure [304]. Reactive species are involved in the protein aggregation. In PD, the presence of *α*-syn and ubiquitin aggregates in neurons in processes of degeneration is observed, especially in the dopaminergic neurons from *sustantia nigra pars compacta*. These aggregates accumulate in the soma and throughout axons. In PD, the axonal accumulation of α-syn into amyloid fibrils of distinct morphology, called Lewy neurites, is particularly abundant relative to Lewy bodies, accumulated in the soma. In brain areas such as the amygdala and striatum, these axonal Lewy neurites predominate over Lewy Bodies and appear early in the disease process [305].In general, these aggregates, are pathological markers for PD, being found in 85% of PD patient autopsies [306]. *α*-syn plays an important role in synapse and support of neurons and its expression is regulated during development, moving from the neuronal bodies to synaptic terminals during neuronal differentiation. Also, this protein is upregulated during periods of synaptic plasticity [306]. Studies suggest that the *α*-syn control the amount of dopamine inside nerve terminals by regulating the uptake of extracellular dopamine by the dopamine transporter and by packaging of cytosolic DA by the vesicular monoamine transporter 2. Thus, the aggregation of *α*-syn triggers cellular mechanisms that lead to progressive death of dopaminergic neurons.

The most effective treatment for PD involves dopamine replacement therapy, made by the administration of its precursor 3,4-dihydroxy-L-phenylalanine (L-DOPA) associated with dopadecarboxylase inhibitors (benserazide or carbidopa). Although such treatment improves motor symptoms of PD, the long-term treatment with L-DOPA is inefficient and causes numerous complications [307]. Aside from the treatment with L-DOPA, there are new treatment strategies focusing on the constant stimulation of the dopaminergic system, for example, the use of drugs with longer half-lives such as the dopamine receptor agonists ropinirole and pramipexole that allows the later use of L-DOPA or other drugs with a short half-life [308]. Despite all these options for PD treatment, none of these drugs prevents progression of the disease. Therefore, there is a need to develop drugs or interventions that prevent or slow the progression of the degeneration of dopaminergic and non-dopaminergic neurons in PD.

Some studies have demonstrated that PD patients show reduced levels of melatonin production and in the expression of melatoninergic receptors MT1 and MT2 in the *sustantia nigra pars compacta* [309]. As we have reported for other pathologyies of the nervous system, these characteristics, along with the antioxidant and anti-inflammatory action of melatonin have forced the study of its effect on PD animal models and patients. Diverse neurotoxins have been used to mimic behavioral and neurochemical characteristics of PD in laboratory animals, thereby improving understanding of the pathogenesis and molecular mechanisms of the disease that are useful for screening of potential new treatments. In this context, exogenous melatonin administration has demonstrated an excellent neuroprotective action in murine models of PD induced by different toxins such as 6- hydroxydopamine (6-OHDA), 1-methyl-4-phenyl,1-1,2,3,6-tetrahydropyridine (MPTP), rotenone, paraquat, and maneb [310-313]. In the animal model of MPTP, melatonin acted as a powerful hydroxyl radical scavenger in the mouse striatum and also in raising SOD activity [314]. Melatonin also prevents nigral dopaminergic cell death at the same time as ameliorated motor deficits are induced by chronic treatment with MPTP [315]. Furthermore, melatonin, when coadministered with L-DOPA, was able to improve the motor benefits induced by L-DOPA [313]. These benefits of melatonin are thought to be due, at least in part, to the increase in Complex I and IV activities of the mitochondrial electron transport chain [316]. In the 6-OHDA model of PD, the first animal model used to study PD [317], melatonin was shown to confer dopaminergic neuroprotection because of normalization of oxidative unbalance generated by 6-OHDA administration [318]. These effects are due to the ability of melatonin to neutralize reactive species or to the melatonin-induced increased activity and expression of antioxidant enzymes. On the other hand melatonin is able to protect the 6-OHDA-induced inhibition of complex I activity of the mitochondrial electron transport chain in mice [319]. It also led to c-Jun phosphorylation inhibition, increased Bcl-2 levels, and decreased caspase-3 activity, blocking the apoptosis induced by 6-OHDA [320]. The anti-inflammatory action of melatonin was also demonstrated in this mouse model of PD. Melatonin inhibited COX enzyme activity and reduced the prostaglandin E2 levels (PGE2) [321]. Finally, melatonin protected against the 6-OHDA-induced loss of tyrosine hydroxylase positive neurons in the *sustantia nigra* and striatal projections were accompanied by significant improvement of motor impairments in rodents [319].

As we reported previously, Lewy bodies, which are considered a hallmark of PD, comprise altered aggregation of tubulin, ubiquitin, microtubule associated protein (MAP) 1 and MAP 2 [322]. An *in vivo* study revealed that subcutaneous injections of amphetamine in rats significantly increased *α*-syn levels in the *sustantia nigra pars compacta*, nucleus accumbens, striatum, and prefrontal cortex. However, the concomitant administration of amphetamine and melatonin drastically reduced *α*-syn accumulation [323]. In a model of kainic acid-induced neurotoxicity in C57BL/6 mice, the hippocampal *α*-syn aggregation was reduced by oral administration of melatonin 1 h prior to kainic acid injection [143]. Taken together, these results demonstrate the potential of melatonin to modulate *α*-syn expression and protect dopaminergic cells against their undesirable toxic alterations.

In summary, melatonin demonstrated neuroprotective effects in different experimental models of PD. However, the models currently used to mimic the PD have limitations and do not accurately correspond to the disease in humans. In addition, some controversial studies reported adverse effects, demonstrating that melatonin exacerbates motor deficits. Tapias *et al*. in 2010 found in the rotenone model of PD in rats that melatonin treatment decreased striatal catecholamine levels, produced terminal loss in striatum, and nigral dopamine cell death, thus exacerbating the pathology [324]. Other

studies in rat experimental models of PD, have found that reducing melatonin levels by pinealectomy, or by rat exposure to bright light, improve PD like-symptoms while the administration of melatonin exacerbated motor impairments [325]. Thus, further studies using genetic models of PD instead of toxic models are necessary to confirm the neuroprotective potential of melatonin in this pathology.

With regards to the effect of melatonin treatments in human patients of PD, Medeiros *et al*. showed that melatonin administration (3 mg, 1 h before bedtime) for 4 weeks in PD patients was able to improve the quality of sleep but did not affect motor symptoms in these patients [326]. In a study performed in 40 PD patients where melatonin was administered in doses up to 50 mg/day, when 50 mg were used a significant increase in night time sleep and an improvement of sleep quality was demonstrate [327]. However not all the clinical studies demonstrated a beneficial role of melatonin in PD. Therefore, Willis and Turned have proposed that bright light has a beneficial role in treating the PD symptoms because it decreases melatonin levels and consequently activates the circadian system. These authors came to this conclusion when they exposed PD patients for 2-5 weeks to light for 1–1.5 h (1 h before bedtime) and detected improvement in bradykinesia, rigidity, agitation and psychiatric symptoms [328]. However, it has been shown that even though bright light exposition during the evening suppresses transiently melatonin secretion, late in the night causes a reflect rise in melatonin secretion [329]. Consequently, the light exposition may finally promote melatonin secretion instead of abolish it. Therefore, one must be cautious in evaluating the results concerning the effect of melatonin on Parkinsonism. Further studies are needed to demonstrate the ability of melatonin in Parkinson's patients.

8.5. Huntington's Disease, Neuroinflammation and Melatonin

Huntington's Disease (HD) is an autosomal dominant neurodegenerative motor neuronal disease that affects initially striatal and then cortical neurons. This pathology is caused by an expanded cytosine-adenine-guanine (CAG) repeat sequence in exon 1 of the Huntingtin gene (Htt). HD is characterized by movement disorder (progressive chorea), cognitive impairment, and psychiatric disturbance [330, 331]. Evidence of sleep disturbances [332-336], autonomic alterations [337] and metabolic irregularities [338, 339], are also reported even before the onset of motor signs [340, 341].

The pathological mechanism underlying the development and progression of this neurodegenerative disease is still inconclusive. It has been postulated that dopamine excitotoxicity could be underlying neuronal degeneration based on the fact that striatum contains high levels of its oxidized and hydroxylated metabolites that inhibit mitochondrial respiratory chain culminating in oxidative injury to the neurons [342-346]. Postmortem studies in HD patients demonstrated that complexes I–III and complex-II of the mitochondrial electron transport chain complexes are affected in HD [338, 347]. Direct association of the anomalous Htt aggregates with mitochondria was demonstrated earlier, which may lead to membrane depolarization, affecting the overall functioning of this organelle [348]. In fact, mitochondrial complex II inhibitor 3-nitropropionic acid replicate most of the features of HD and hence is used in an experimental model of HD [349-351].

On the other hand, a significant reduction in plasma melatonin concentrations has been reported in Huntington's disease patients, suggesting that melatonin secretion is disrupted [352]. Considering that oxidative stress exerts an important role in neuronal damage and degeneration in HD and melatonin levels are reduced in this pathology, therapeutic strategies against this neurodegenerative disease focus on melatonin use. Thus, in a 3-nitropropionic acid-induced rat animal model of HD, it is has been demonstrated that a previous administration of melatonin (1 mg/kg/day) prevented the changes induced by this toxicity such as the increment in lipid peroxidation and protein carbonyls content and the diminution in the activity of succinate dehydrogenase and the improvement in SOD activity [353]. Besides, melatonin attenuated 3-NP-induced increases in striatal glutamate levels, corrected dendritic spine damage in the striatum and the cortex, and restored dendritic arborization in cerebellar granule cells [354]. Additionally, in this animal model, the use of agomelatine, a selective melatonergic MT1/MT2 dual agonist, reduced the weight loss and locomotion, improved motor coordination, learning and memory and reduced brain striatum oxidation, increased activity of AChE and impaired mitochondrial enzyme complexes [355]. In the same way, previous administration of melatonin (5 or 20 mg/kg/day) reduced lipid peroxidation induced by quinolinic acid, a causative agent in HD [356] and decreased reactive species and protein carbonyl levels [357]. Beneficial effects of melatonin have also been demonstrated in a cellular model of HD (ST14A). Melatonin blocked mitochondrial cell death pathways by inhibiting Smac release and the activation of caspase-9 in apoptotic mutant-htt ST14A striatal cells [358]. Evidence supports the beneficial effects of melatonine/agomelatine in animal mouse models and in the cellular model of HD, but further human trials on the effect of melatonin on HD are required.

Although further clinical trials are necessary to asses if the use of melatonin is a successful treatment or not for neurological diseases, preliminary evidence suggest that, at least in MS and AD, melatonin is important in limiting the initiation and progression of the diseases (Table **2**). Thus, melatonin not only improves sleep disturbances associated to these pathologies but it also suppresses sundowning and ameliorates cognitive and motor impairment. However, while this is true, the cognitive and motor improvement seems to be limited. Therefore, future study with melatonin alone (modifying doses) and in combination with other pharmacological and non-pharmacological neuroprotective therapies are required. In this context, García-Mesa *et al*., has demonstrated, in a murine model of AD, that melatonin treatment plus exercise exerts complementary, additive or even synergistic effects against a range of disturbances present in AD. Thus, both treatments, separately, reduced soluble amyloid β oligomers, preserved against cognitive decay and brain oxidative damage whereas only melatonin reduced hyperphosphorylated tau and immunosenescence. On the other hand, physical exercise preserved against behavioral and psychological symptoms of dementia and only the combined treatment of physical exercise plus melatonin was efficient enough to counter the decrease of mitochondrial complexes [281]. In other studies, Know *et al*. proposed that melatonin and resveratrol in combination could be an efficient way to regulate oxidative damage and neuroinflammatory mechanism in the brain, together being more neuroprotective than either one alone [359, 360]. Additionally, intermittent fasting and caloric restriction was demonstrated to improve behavioral deficits that were dependent on aging in the triple-transgenic mouse model of AD [361]. A combination treatment of melatonin with caloric restriction could be potentially promising.

9. SOURCES OF NEUROINFLAMMATION: EVIDENCE THAT GASTROINTESTINAL INFLAMMATION OCCURS EARLIER IN NEUROLOGICAL DISEASES

As has been said, brain injury has its origin in the production of inflammatory cytokines by brain cells that would activate the microglial cells or in extrinsic processes that would attract the macrophages and other leukocytes. Although the specific mechanisms by which signals from outside the CNS are involved in the activation of microglia are not known, there is evidence to suggest that peripheral inflammatory signals reach the brain [362]. Therefore, inflammation in the CNS may be linked to systemic or peripheral inflammation occurring elsewhere in the body. Clinical studies have shown that in patients with peripheral inflammation (regardless of whether the cause is due to an infection or other causes, such as atherosclerosis, rheumatoid arthritis or diabetes) may have alterations in cognitive functions [363]. Also, neurological diseases may be associated with gut inflammation [364]. There is evidence that in

Table 2. Summary of the clinical trials of melatonin on inflammatory related pathologies.

Pathology	Subjects	Treatment	Study Duration	Results	References
ms (case report)	1 primary progressive multiple sclerosis patient	Oral administration of melatonin (50-300 mg/day) at bed time.	4 years	Before starting the treatment, the patient could hardly sleep due to muscles spasms but after melatonin treatment, she began her sleep improved. Clinically, she was unable to walk and was restricted to a wheelchair or bed with an EDSS score of 8.0. At the moment, she is able to go up and down stairs with help and walk alone with a cane about 100 m: her EDSS score is 6.0 as assigned by a neurologist.	[242]
ms (case control prospective study)	102 MS patients and 20 controls	Oral administration of melatonin (9 mg/day) at bed time.	90 days	Marked decrease in serum total oxidant status level and significant sleep improvement after melatonin treatment.	[222]
ALS (Open-label study)	31 Sporadic ALS patients	Chronic high-dose (300 mg/day) rectal melatonin administration at bed time.	2-24 months	Melatonin led to the normalization of serum protein carbonyls, markers for oxidative stress, which were significantly elevated prior to treatment in ALS patients. Besides, improve sleep disorders.	[259]
AD (Open-label study)	14 patients	Oral administration of melatonin (9 mg/day) at bed time.	22-35 months	Significant improvement of sleep quality was found in all subjects. Clinically, the patients exhibited lack of progression of the cognitive and behavioral signs of the disease during the time they received melatonin. Sundowning was no longer detectable in 12 patients and persisted, although attenuated, in 2 patients.	[289]
AD (Open-label study)	11 patients	Oral administration of melatonin (3 mg/day) at bed time.	3 weeks	Significant decrease on sundowning and in daytime sleepiness.	[291]
AD (Open-label study)	45 patients	Oral administration of melatonin (6-9 mg/day) at bed time.	4 months	Melatonin improved sleep and suppressed sundowning.	[292]
AD (Open-label study)	7 patients	Oral administration of melatonin (3 mg/day) at bed time.	3 weeks	Total or partial remission of sleep disturbances.	[293]
AD (double-blind, placebo-controlled study)	20 patients	Oral administration of placebo or 3 mg melatonin /day at bed time.	4 weeks	Melatonin significantly prolonged the sleep time and decreased activity in the night. Cognitive function was improved by melatonin.	[294]
PD (double-blind, placebo-controlled study)	18 patients	Oral administration of placebo or 3 mg melatonin /day at bed time.	4 weeks	Melatonin significantly improved subjective quality of sleep but motor dysfunction was not improve.	[326]
PD (double-blind, placebo-controlled study)	40 patients	Oral administration of placebo or 5 mg melatonin /day at bed time.		There was significant improvement in subjective sleep disturbance, sleep quantity, and daytime sleepiness during melatonin treatment.	[327]

(Table 2) Contd....

Pathology	Subjects	Treatment	Study Duration	Results	References
IBD (double-blind placebo-controlled study)	35 patients	Oral administration of placebo or 3 mg melatonin /day at bed time.	8 weeks	Melatonin significantly improved symptoms such as abdominal pain, abdominal distension, and abnormal sensation of defecation. The changes in sleep, anxiety, and depression scores were similar with either melatonin or placebo treatment.	[380]
IBD (double-blind placebo-controlled study)	40 patients	Oral administration of placebo or 3 mg melatonin /day at bed time.	2 weeks	Melatonin significantly decreased the abdominal pain score and increased rectal pain threshold. Bloating, stool type, and stool frequency were not different between the two groups and subjective sleep quality was not influenced by the treatment.	[383]
IBD (double-blind placebo-controlled study)	18 patients	Oral administration of placebo or 3 mg melatonin /day at bed time.	8 weeks	Melatonin improved all IBD symptoms as well as the quality of life of the patients.	[384]
UC (case report)	1 patient	self-administering of melatonin.	----------	Colitis symptoms were virtually absent while taking this indoleamine.	[385]
UC (double-blind placebo-controlled study)	64 patients	Oral administration of placebo or 5 mg melatonin /day at bed time.	12 months	Melatonin improved bowel symptoms in, but the mean sleep, anxiety and depression scores were similar after melatonin and placebo administration.	[382]

Abreviatures. ALS, Lateral Amyotrophic Sclerosis; AD, Alzheimer´s disease; IBD, irritable bowel syndrome; MS, multiple sclerosis; PD, Parkinson ´s disease; UC, ulcerative colitis.

patients with PD, gastrointestinal inflammation is closely related to glial dysregulation. Colonic biopsies of these patients showed elevated levels of glial markers that correlate with the levels of cytokine expression [364]. In fact, the increased expression of the pro-inflammatory factors IL-1β, IL-6, IFN- γ, and TNF-α observed in PD patients was similar to that found in diseases with functional abnormalities of the enteric nervous system [365]. Given that enteric neurons are in contact with the environment, it could be proposed that environmental factors contribute to diseases of the gastrointestinal tract that lead to neuronal degeneration and / or progression of neurodegenerative diseases [366, 367]. Experiments carried out in our laboratory would support this hypothesis, since the induction of ulcerative colitis in rats by ingesting sodium dextran sulfate results in an increase in the levels of inflammatory markers, and at the same time, in the *substantia nigra* a decrease in the number of dopaminergic neurons was found [368]. The induction of ulcerative colitis also enhanced the inflammatory and neurotoxic effects of the lipopolysaccharide injection in the *substantia nigra*, results suggesting that there is a link between intestinal inflammation and PD [368]. Overall, these results suggest a role for peripheral inflammation, especially gastrointestinal inflammation, in the pathophysiology of neurological diseases.

9.1. Melatonin´s Role in Bowel Diseases

Gastrointestinal melatonin is produced by enterochromaffin cells of the digestive mucosa where its concentrations may exceed that in the blood. The amount of gastrointestinal melatonin is estimated to be at least 400 times greater than in the pineal gland [369] and its levels in the gastrointestinal are 10–100 times higher than in serum [370], suggesting that melatonin may play an important role in the digestive system. Melatonin amounts in the digestive tract generally do not show daily fluctuations. Therefore, the photoperiod seems to have little regulatory effect on gastrointestinal melatonin content [6].

Due to the high lipophilicity of melatonin it is found in deeper layers through the mucosa and submucosa, acting on the muscularis mucosae or the myenteric plexus. In this sense, the functions and mechanisms of action of melatonin in the gastrointestinal are mediated by membrane receptors including (MT2) and serotonin (5-HT), along with its capacity to activate sympathetic neurons through the brain-gut connection system and antioxidant actions [371]. Melatonin seems to play a role in several gastrointestinal functions such as: a) regulation of gastrointestinal motility, exercising both excitatory and inhibitory effects on the gut smooth muscle. Low doses of melatonin accelerated intestinal transit while high doses may reverse this effect [372, 373]. In response to neuronal stimuli, duodenum discharge, melatonin stimulating bicarbonate ion secretion contributes to the maintenance of the intestinal mucosa barrier [370]; b) relieve visceral sensation, improving pain and distension. It is presumably due to the antinociceptor effect that has also been described for melatonin [374, 375]. However, the mechanism of melatonin as antinociceptive is not well defined and still needs to be further investigated [376]; c) modulation of the immune response in the gut by different mechanisms including inhibition of Nfkb and ON production, regulation of the activities of macrophages, reduction of metalloproteinase activity, COX-2 expression or TNF-α levels and modulation of apoptosis [370, 377].

Chronic inflammation of the intestinal tract leads to two major inflammatory bowel diseases: Crohn's disease and ulcerative colitis. They have different clinical symptoms and different histopathological characteristics but they have a relapsing immune activation in common which leads to an uncontrolled inflammation of the intestinal mucosa. Crohn's disease can affect any part of the digestive tract from the mouth to the anus while the ulcerative colitis is located at the colon of the large intestine. Moreover, each presents a different way of activating the immune response, an excessive TH2 and TH17 phenotype is linked to the development of ulcerative colitis while an excessive TH1 and TH17 response is associated with Crohn's disease [69, 371]. On the other hand, irritable bowel syndrome is a functional gastrointestinal disorder associated with visceral hypersensitivity and abnormal gastrointestinal motor function.

It appears that altered melatonin levels are important for the development of these diseases. It has been described that patients with abdominal pain and sleep disturbances or irritable bowel syndrome present lower urinary excretion of 6-sulphatoxy melatonin than healthy subjects [378]. Also, impairment of the circadian rhythm has been shown to be related to the course of inflammatory bowel diseases in experimental models [379]. Moreover, it has been shown that baseline saliva melatonin levels were lower in irritable bowel syndrome compare to normal control. Oral melatonin supplement was able to increase the level of melatonin in the saliva [380].

There are data regarding melatonin treatment in experimental models of colitis suggesting positive effects but little data on non-clinical and clinical studies on the efficacy of melatonin in the other inflammatory bowel diseases. The studies with animal models of ulcerative colitis show that melatonin plays an important role improving the disease through multiple mechanisms of action, based on recognized antioxidant and anti-inflammatory capacities [381]. It appears that patients with ulcerative colitis treated with melatonin reversed the clinical symptoms, which appeared when they stopped taking melatonin [380, 382-385]. It is interesting to note that recent studies also suggest that melatonin may be effective in preventing the progression of colitis-associated colon carcinogenesis due to its capacity to attenuate the induction of autophagy [386]. It is not the same with Crohn's disease since there are not many studies in patients with this pathology. In fact, only one has been reported, in which case the administration of 3 mg/kg melatonin aggravated the symptoms [40]. In Table **2** the few clinical human studies in which melatonin has a beneficial effect in inflammatory bowel diseases are summarized.

CONCLUSION

Anti-inflammatory medications include non-steroidal anti-inflammatory drugs, which target COX-2 and hence the synthesis of prostaglandins, particularly PGE-2. Synthetic forms of natural cortisol are also widely used to treat many inflammatory diseases. Both groups of drugs have important side effects when taken in high doses and for a long time. The challenge of the pharmaceutical industry is to develop more effective and less toxic drugs to treat acute as well as chronic inflammation. In this sense, melatonin represent a good complement to these treatments not only because of its plural mechanism of actions but also because of its extremely low toxicity. Melatonin is a molecule that has the capacity to interact with multiple targets in the immune system and even more to the point it has the capacity to modulate their functions. Thus offering a great field in which to explore new strategies in the treatment of inflammation.

In this review, we have highlighted the fact that melatonin involves not only modulation of the immune system but also oxidative stress production. This dual effect of melatonin on inflammation and oxidative stress is what gives it a greater therapeutic potential over a typical antioxidant. In addition, melatonin exerts an activating and inhibitory action on inflammation, according to the degree of inflammation and according to the dose (physiological or pharmacological). In the case of acute inflammation, the physiological doses would play an important role and therefore it is necessary to correct the melatonin deficits that can occur, for example, with age. But in the case of exacerbated and chronic inflammatory process supraphysiological doses of melatonin should be administered, bearing in mind that the final effect will depend on whether the chronicity is recent or not. Obviously, the anti-inflammatory effect of melatonin will be greater the sooner the inflammatory process is treated, for which a measurement of markers of inflammation and melatonin levels would be advisable.

Regarding neurodegenerative diseases, the protective effect of melatonin has been tested in numerous experimental systems in which oxidative stress and the inflammatory process are generated directly or indirectly. Prevention of cell death can be attributed to the antioxidant capacity of melatonin, but additional mitochondrial effects can be decisive. However, it should not be overlooked that experimental models represent artificial situations, which can only partially reproduce the illness of a patient. Although most of the results are promising so far, it should not be forgotten that in none of the experiments did melatonin prove to be a curative treatment in patients with degenerative diseases. Therefore, new experiments in setting new doses or new ways of applying melatonin either alone or in combination with other drugs will be necessary.

Nevertheless, that inflammatory bowel diseases can be a possible source of inflammation in neurodegenerative diseases must be taken into account, but to date there are few controlled clinical trials that have studied the efficacy of melatonin in their control; consequently, more studies are needed to help explore the therapeutic potential of melatonin in this field.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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