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REVIEW ARTICLE

Melatonin and Regulation of Immune Function: Impact on Numerous Diseases

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Abstract: Melatonin is well known as a neuroendocrine hormone that promotes sleep. However, the many other attributes of melatonin are less apparent and not as widely appreciated. The purpose of this review is to summarize the qualities of melatonin relating to immune function. The relevance of melatonin in partially or wholly restoring optimal function, in a series of disorders related to immune dysfunction, is addressed in this report. This includes the potential relief of both autoimmune diseases and many other ailments involving abnormal immune responses, including the overall diminished effectiveness of body defenses occurring with aging. Disease states affecting a wide range of organ systems have been reported as benefitting from melatonin administration and are discussed here. A separate section addresses the potential role of melatonin in the mitigation of age-related neurological diseases, in view of the increasing importance of this area. The likely mechanistic basis of the properties by which melatonin may confer protection by its acting on immune function is also described.

Keywords: Melatonin, autoimmune disorders, inflammation, aging, neurodegeneration, immune regulation, clinical studies.

1. INTRODUCTION

Melatonin is a methoxyindole released by the pineal gland and best known for its effects on the circadian rhythm. Endogenous levels of melatonin decrease markedly with age [1]. Levels of night-time secretion of the neurohormone are progressively reduced throughout the lifespan [2]. This has led to the concept that many chronic, age-related diseases may be related, at least in part, to this decline in melatonin levels. These include heart disease [3], cancer [4], and neurodegenerative disorders, such as Alzheimer's disease [5]. Broad metabolic regulatory roles have been observed for melatonin and these may underlie its potential to restrain pathways linked to various disease states.[6] One property of melatonin is its capability to initiate anti-oxidant processes, which has been reviewed by several investigators [7,8] and a Special Issue of the International Journal of Molecular Sciences [9].

Another feature of melatonin which underlies many of its diverse effects is its ability to modulate immune function [10-13]. Melatonin is not a blunt anti-inflammatory agent but rather acts to modulate the immune system in a more complex manner. Thus, an effective immune defense is initially fostered by melatonin and this is followed by the prevention of chronic and harmful inflammatory events [14]. The maintenance of an effective immune system appears to be

promoted while the persistent and non-productive inflammatory events are restrained. Since many age-related deleterious changes found in a variety of organs are associated with prolonged and fruitless inflammation, the moderating influence of melatonin may account for its reported breadth of utility across many degenerative diseases.

The number of pathological conditions associated with deviant immune function is extensive. Some features of several common disorders involving immune dysfunction are briefly outlined. A prolonged immune attack either targeted upon specific tissues or more generally, characterizes these disorders. This brief description will illustrate the frequency with which the immune events may be harmful. Evidence for the possible utility of melatonin treatment for these is discussed.

In many aberrant immune states, the activity often leads to an inappropriate inflammatory response that, if harmfully extended, eventually causes tissue damage and organ failure [15]. One factor that may be responsible for such uncontrolled reactivity may be the inability of bone-derived macrophages to convert their polarity from the M1 inflammatory state to the M2 tissue reconstruction form, especially in the age [16]. The role of melatonin in macrophage biology and its impact on various disease states that have been associated with macrophage dysfunction has been recently reviewed [13]. Overall, excessive but ineffective immune reactions characterize the disease state more commonly than ineffectually attenuated responses.

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The intent of this review is to describe the potential utility of melatonin in the treatment of immune disorders distinguished by disproportionate and harmful inflammation. There is sufficient breadth of evidence to suggest that the therapeutic utility of melatonin has been underestimated.

2. ROLE OF MELATONIN IN CONDITIONS INVOLVING ABERRANT IMMUNE ACTIVITY

2.1. Multiple Sclerosis (MS)

Multiple Sclerosis (MS) is an autoimmune condition that has a complex etiology and pathophysiology. The immune attack in this disease is confined to the myelin of the central nervous system. This leads to cycles of demyelination followed by repeated attempts at remyelination. Consequently, the disease spectrum can have many different signs, such as vision loss, pain, fatigue, and impaired coordination. The disease is characterized by periodic waxing and waning of these symptoms.

While the etiology of MS is multifactorial, sleep disturbance due to shift work has been associated with an increased risk [17]. A role for abnormal production of melatonin from the pineal gland in the age of onset of symptoms and exacerbation of MS has been suggested [18]. Disruption of melatonin secretion in MS can lead to sleep disturbance and fatigue. Serum levels of melatonin were found to be significantly lower in relapsing-remitting multiple sclerosis patients (21.3 ± 17.6 pg/ml) compared to healthy controls (60.3 ± 51.4 pg/ml) and this was linked to an increase in the pro-inflammatory cytokine tumor necrosis factor alpha (TNF- α) levels (RRMS: 4.1 ± 2.2 pg/ml, Control: 1.9 ± 1.3 pg/ml) [19].

Although not dramatic, melatonin may improve some aspects of this disorder [20]. This has been attributed to the anti-oxidant properties of melatonin, but MS often involves relapsing-remitting cycles, and disruption of melatonin cycling is common [21]. Most of the studies that have evaluated the effect of melatonin supplementation in MS have focused on the effect of the neurohormone on indices of oxidative stress. In patients with SPMS ($n = 16$), supplementa-

tion with 10mg/day of melatonin for 30 days was shown to increase the activity of the anti-oxidants superoxide dismutase and glutathione peroxidase in red blood cells. This was correlated with a decrease in malondialdehyde, a marker of lipid peroxidation [22]. In a separate study, it was observed that melatonin supplementation (5mg/day for 90 days) was able to reduce the total oxidant status in the serum of MS patients who were also subjected to various other different disease-modifying treatments [20]. To what extent these results were correlated with the severity of the disease is unknown. Based on the search engine, clinicaltrials.gov, there have been six clinical studies on the role of melatonin in patients with MS. The sample size for all trials are rather small ($N = 25-50$ patients). None of the studies have posted results.

2.2. Rheumatoid Arthritis (RA)

Rheumatoid arthritis is a chronic inflammatory autoimmune disease associated with severe joint damage and disability. In this autoimmune condition, antibodies are formed that target self-proteins that have undergone post-translational modifications such as the conversion of arginine residues to citrulline. The formation of these autoantibodies form immune complexes that activate the complement cascade and enhance the inflammatory response [23]. RA has a complex pathophysiology influenced by both genetic and environmental factors. These include the HLA-DRB1 locus of the major histocompatibility complex class II gene, which seems to have a higher binding affinity to autoantigens, such as citrullinated proteins [24]. Some of the environmental factors connected to RA pathogenesis are the history of cigarette smoking, obesity, and diet [25].

The results of melatonin treatment for RA have been promising, neither in a human study [26] nor in animal models of rheumatoid arthritis [27, 28]. The conflicting evidence as to the effects of melatonin on this disease has been summarized [29]. One clinical study has been described (Table 1).

2.3. Inflammatory Bowel Disease (IBD)

IBD is an umbrella term that is used to describe conditions that affect the gastrointestinal tract. Crohn's disease

Table 1. Reported clinical trials on melatonin.

Organ System	Date Initiated	ClinicalTrials.gov. Bethesda (MD); National Library of Medicine (US). Website and Identifier number
Rheumatoid Arthritis	2/2006	https://clinicaltrials.gov/ct2/show/results/NCT00287794
Glucose tolerance	1/2007	https://clinicaltrials.gov/ct2/show/NCT01705639
Ulcerative Colitis	12/2009	https://clinicaltrials.gov/ct2/show/NCT00790478
Insomnia with Diabetes	5/2009	https://clinicaltrials.gov/ct2/show/NCT00869128
Hypertension	12/2015 2/2016	https://clinicaltrials.gov/ct2/show/record/NCT01114360 https://clinicaltrials.gov/ct2/show/record/NCT01114373
Burning Mouth Syndrome	10/2015	https://clinicaltrials.gov/ct2/show/record/NCT02580734
Sleep with Hypertension	11/2017	https://clinicaltrials.gov/ct2/show/record/NCT00238108
Cognition	10/2019	https://clinicaltrials.gov/ct2/show/record/NCT03954899

and ulcerative colitis both involve an autoimmune attack encompassing an inappropriate inflammatory response that may also be directed against the intestinal microbiota. While ulcerative colitis is confined to the rectum and may involve part or all of the colon, Crohn's disease can occur anywhere in the intestines. [30]. In IBD, monocyte-macrophage differentiation is altered in a manner that results in defective resolution of an inflammatory response, which, in turn, causes damage to the intestinal epithelium [31]. Fatigue is a symptom present in 80% of patients who are experiencing active disease and 50% of patients who are in clinical remission, and the cause has been attributed to nutritional deficiency as well as psychological factors linked to the gut-brain axis [32].

Melatonin therapy greatly prolonged the remission time of disease inactivity for patients with ulcerative colitis [33], perhaps by the restoration of a more normal circadian rhythm as well as immunomodulation of macrophages that allowed resolution of the inflammatory response and regaining of intestinal homeostatic state. Melatonin has favorable effects on ulcerative colitis in both clinical studies and animal models [34]. The significance of circadian events on colitis is illustrated in a mouse model of this disease where sleep deprivation exacerbated mortality and this was blocked by melatonin administration [35]. Only one study related to the use of melatonin in ulcerative colitis is found in the clinicaltrials.gov website (Table 1).

2.4. Systemic Lupus Erythematosus (SLE)

Similar to other autoimmune conditions described above, systemic lupus erythematosus is typified by a loss of self-tolerance, which leads to an inappropriate immune response. Both environmental and genetic factors play a role in the disease pathogenesis. What is unique regarding SLE is the formation of anti-nuclear antibodies, which are formed due to the faulty clearance of apoptotic debris and abnormalities in adaptive immune responses. The formation of autoantibodies leads to immune-complex formation and deposition, which further leads to a sustained inflammatory attack on multiple organs and systems [36]. This disease involves seasonal variation and can cause damage to the joints, skin, kidneys, blood, heart, and lungs [37-38].

The current treatment for SLE includes the use of immunosuppressive agents, such as glucocorticoids. Clinicians need to consider the balance between controlling the disease and the adverse effects of therapy [39]. Therefore, it would be worthwhile to assess the role of other potential immunomodulating, possibly disease-modifying agents with minimal adverse effects, such as melatonin, in SLE patients. There are limited data on the use of melatonin in ameliorating symptoms of systemic lupus erythematosus. Melatonin has a beneficial effect on pristane-induced lupus [40]. Victims of lupus are primarily women and several features of the disease appear to be sex-linked. In an animal model of this disease, melatonin improved the course of the disease in females while worsening it in males [41].

2.5. Aging

Aging is characterized by an ever-increasing inflammatory state combined with an ever-decreasing efficiency of

immune responses [42]. In consequence, this decline in immunocompetence is also associated with an elevated increase in the incidence of age-related diseases. This decreased competence also accounts for a rapidly rising incidence of cancer with age [43]. Effective immune surveillance can lead to the recognition and removal of senescent cells, which permits the regeneration of tissues containing them. With further aging, however, the efficiency of this process can decline, and senescent cells can then accumulate [44]. The presence of such cells attracts immune activity, which, if unsuccessful in clearing the abnormality, may lead to a state of chronic inflammation, ultimately leading to tissue fibrosis [45].

The gene expression profile of the brains of aged mice differs from that of more youthful mice, especially as the expression of inflammatory genes is increasingly elevated with age. This may reflect the cumulative effect of a succession of inflammatory events occurring throughout life as the brain appears to remember such events for an extended time [46]. Melatonin treatment of such aged mice has the capacity to restore the mRNA expression profile so as to cause it to more closely resemble that of younger animals [47]. This partial reversal of the genetic contour of aging is likely to retard the velocity of overall aging. This may account for the positive effects of melatonin on neurodegenerative disease and also on the incidence of cancer in aged mice. Many of the diseases described in other sections are predominantly found in the aged, and the effect of melatonin in increasing longevity is discussed in the section on cancer. Thus, several avenues of evidence ranging from the pattern mRNA expression to the lifespan of experimental animals imply that the aging process can be slowed by orally ingested melatonin.

2.6. Type II Diabetes Mellitus

Diabetes mellitus is a metabolic disorder characterized by defects in insulin production or action that leads to hyperglycemia. There are two types of diabetes. Type I (juvenile) diabetes can result from a focused autoimmune attack upon the insulin-producing beta cells within the pancreatic islets, which causes loss of insulin production. Type II (adult onset) diabetes is characterized by insulin resistance and is associated with obesity, hypertension, and systemic inflammation [48]. Immune reactive cells gradually inhibit the ability of the fat cells to respond to insulin [49]. Unlike type I diabetes, obesity-associated insulin resistance is reversible through weight loss from lifestyle changes [50]. Obesity itself can cause failure of the body's normal self-tolerance mechanisms [51]. The consequent generation of a chronic inflammatory environment, can lead to the promotion of autoimmune diseases. Melatonin administration can improve glycemic control in plasma of type 2 diabetes mellitus patients [52] and reduced melatonin levels, or mutations of melatonin receptors, which have been related to an increased risk of developing type 2 diabetes [53-54].

There are a number of clinical trials that have evaluated the benefits of melatonin use in patients with type II diabetes. In one of the completed studies, it was reported that prolonged release of melatonin formulation (2 mg per night for three weeks) helped mitigate insomnia in type II uncontrolled diabetic patients who tend to produce less of the neurohormone and have abnormal sleep patterns (Table 1). In

another completed interventional clinical trial, glucose tolerance was evaluated among individuals that had a variant of the melatonin receptor 1B (MTNR1B) gene linked to a greater risk of developing type II diabetes (Table 1). A decrease in insulin release and an increase in glucose concentrations were observed in all participants and this was most pronounced in the melatonin receptor risk variant [55]. The authors suggest that melatonin-induced reduction of insulin may be a physiologically protective effect to counter nocturnal hypoglycemia.

2.7. Chronic Pain

Melatonin has mild but persistent analgesic properties and can relieve several types of chronic pain, such as repeated headaches, back pain, endometriosis, and fibromyalgia, as well as pain associated with several disorders enumerated in this review [56-58]. There is only one clinical study that evaluated the role of melatonin treatment in burning mouth syndrome (BMS), which is an example of chronic neuropathic pain. A reduction in pain symptoms was reported following this treatment (Table 1).

2.8. Cardiovascular Disease and Atherosclerosis

The risk of cerebrovascular disease is elevated in those afflicted with autoimmune diseases, such as systemic lupus erythematosus and arthritis [59]. The atherosclerotic plaque contains several constituents of the intrinsic and adaptive immune systems [60]. The recruitment of immune cells to the arterial wall seems to characterize the pathological artery [61]. The putative antigens involved in atherosclerosis include oxidized low-density lipoprotein and apolipoprotein H [62]. Such infiltration of immune cells into the vascular wall is also found in hypertension. Macrophages can establish inflammatory responses even in the absence of an antigen and mice lacking these have an attenuated hypertensive response to provocative stimuli. [63].

Useful results have been obtained after the melatonin therapy of hypertensive patients [64-67]. However, the circadian aspects of any melatonin intervention need to be carefully considered, as patients with no depression of nocturnal blood pressure ("non-dippers") may not respond well to such treatment [68]. There are also several recent reports on improved disease status effected by melatonin in various atherosclerotic mouse models [69-71].

There are three completed clinical studies that have evaluated the efficacy of melatonin treatment in hypertension. In an interventional study of hypertensive patients on beta-blockers, the simultaneous use of 2.5 mg melatonin for 3-4 weeks was shown to increase the quality of sleep (Table 1). The other two studies evaluated the effect of either 8 mg (n=37) or 24 mg (n=40) of melatonin for four weeks. None of the primary outcomes, including night-time systolic or diastolic blood pressure, were significantly different between the melatonin or placebo group (Table 1).

2.9. Cancer

The relation between cancer and the immune system is very complex. An effective immune response can promote apoptosis in abnormal cells before their complete transfor-

mation [72]. This protective strategy probably occurs very frequently in normal individuals. On the other hand, a chronic unresolved inflammatory response characterizes both the pre-cancerous and cancer state [73]. Adding to this complexity is the intimate relation between inflammatory events and the occurrence of oxidative stress. It is uncertain which state is the primary initiator of the trajectory toward carcinogenesis, but both states acting together can actively create a milieu that facilitates initiation and promotion of carcinogenic events [73]. By this means, several cytokines, such as TNF- α , IL-6, TGF- β , and IL-10, take part in promoting the progression of cancer [74]. Inflammatory reactions can also result in antitumor activity. Macrophages can exist in either a pro-inflammatory M1, cancer-suppressing state, or in an immunosuppressive cancer-promoting M2 macrophage state [75]. The classical M2/M1 distinction is overly simplistic as M1 induced inflammation can also promote tumor metastasis [76] and M2 macrophages are also present in tumors [77]. Furthermore, despite the ability of melatonin to enhance the ratio of M2 to M1 macrophages and thereby reduce stress-induced inflammation after acute spinal cord injury, it has never been reported as carcinogenic [78-79].

Treatment of aged mice with 40 ppm dietary melatonin, for 3 months, results in a 60% reduction of incidence of visible tumors [80]. In addition, the size of tumors found in melatonin treated mice was significantly smaller compared to those apparent in control mice. The overall spontaneous death rate was reduced in mice receiving melatonin. This extension of longevity led to a 50% reduction of mortality in the mice during the entire course of the study (from 18% to 9%), when surviving mice were aged 26 months.

There are also reports of a reduced incidence of tumors and their slower progression in animals subjected to carcinogens or tumor cells when receiving melatonin [81-83]. These outcomes are likely to be germane to human populations, since age-related changes in expression of specific genes in mice have clear parallels in humans [84]. The addition of melatonin to clinical therapeutic protocols appears to enhance the effectiveness of chemotherapeutic agents and radiation procedures and diminishes the severity of undesirable side effects [27]. The cancer-retarding properties of melatonin have recently been summarized in a study [85]. Overall, melatonin usage in a clinical setting increases the likelihood of substantial reductions in cancer incidence at little cost and with minimal risk of adverse side effects.

2.10. Septicemia

Sepsis can result from ineffective immune function whereby the response to bacterial infection is massive but futile. The consequent uncontrolled systemic inflammation leads to the release of many inflammatory agents, including cytokines and extracellular vesicles containing pro-inflammatory miRNAs, into the general circulation [86]. This can lead to organ failure and, ultimately, a septic shock, which can have a mortality rate of over 50% [87].

There is considerable clinical and pre-clinical evidence for the utility of melatonin in the treatment of sepsis [88-90]. The effectiveness of such treatment may be critically dependent on the early administration of melatonin before symptoms of sepsis become severe [91]. A meta-analysis of

several independent studies on neonatal sepsis gives clinical support for this. It is noteworthy that intrinsic levels of circulating melatonin rise markedly with sepsis [92].

3. ROLE OF MELATONIN IN NEUROLOGICAL DISORDERS:

3.1. Alzheimer's Disease (AD)

There is evidence that Alzheimer's disease (AD) can involve immune activation, mediated by the aberrant processing of amyloid precursor protein. This leads to the formation of abnormal amyloid peptides, which tend to aggregate and form senile plaques, a characteristic feature of AD [93]. People who have systemic inflammation or autoimmune disorders are more likely to develop dementia [94, 95]. The brains of Alzheimer patients have excessive levels of inflammation, as judged by levels of a variety of markers [96]. This increase is superimposed upon the normal age-related intensification of basal immune activity within the brain. Age-related neuroinflammation is further exacerbated in AD both in humans and animal models [97, 98] and may reflect a deterioration of glial function. The ability of melatonin to regulate immune responses suggests that it may possess utility in the treatment of AD.

It has been suggested that even a non-specific ability of melatonin treatment to delay the onset of indices of neuro senescence, would automatically curb the incidence of AD [99]. A specific effect of melatonin on enhancing α -secretase production while inhibiting the transcription of β - and γ -secretases, has also been described [100]. α -secretase mediates the appropriate processing of amyloid precursor protein while β - and γ -secretases promote the formation of the pathogenic forms of amyloid beta proteins found in senile plaques. There are several conflicting reports concerning the use of melatonin or its analogs in the treatment of the frequently encountered sleep disturbances associated with AD. These range from no beneficial outcome [101] to producing clear improvement on delirium [102]. There is currently a clinical trial that is recruiting participants to determine how dietary supplements with 5mg of melatonin for nine months would improve biomarkers of AD, as well as cognitive function in individuals with or without mild cognitive impairment (Table 1).

3.2. Parkinson's Disease (PD)

Parkinsonism is typified by the progressive loss of dopaminergic neurons leading to tremor and immobility [103]. There are many possible causes of loss of dopamine producing cells, but the prime causal factors remain unclear. Progressive systemic inflammation can precede the development of Parkinson's disease [104]. PD often involves seasonal flareup and disruption of sleep patterns. The melatonin agonist ramelteon and melatonin itself can improve the sleep profile but motor dysfunction was not improved [105, 106]. Melatonin has been described as improving both behavioral and biochemical indices of Parkinsonism in a rotenone-induced rat model [107]. In contrast, in the same animal model, agomelatine, a synthetic analog of melatonin, exacerbated rotenone toxicity [108]. Another report describes the

severity of Parkinsonian symptoms in both patients and in a rat model, to be related to levels of circulating melatonin [109]. Overall, there is sufficient conflicting data in this area so as not to allow a clear conclusion.

3.3. Traumatic Brain Injury (TBI)

TBI can result in the release of brain proteins into general circulation, either intact or as proteolytic fragments. Such proteins are recognized by the immune system as antigens of exogenous origin, which could then provoke the systemic antibody production and an immune attack upon the brain. Transport of such fragments is likely to occur by way of cellular microparticles (MPs) generated by injured cells [110]. While the brain is initially the target of TBI, ensuing inflammatory events can also lead to adverse effects on systemic functioning [111]. Studies on the effects of melatonin on TBI are largely confined to experimental animals but are broadly positive [112, 113]. Melatonin receptor levels are decreased after such injury [114]. In human studies, it is noteworthy that in the most severe TBI, serum melatonin levels are elevated [115, 116]. This may represent a protective response to reduce further damage.

4. SPECIFIC MECHANISMS OF ACTION:

4.1. Impact on Circadian Rhythm

The relation of melatonin to the functioning of the sleep-wake cycle is a key feature in health promotion and has been somewhat overlooked. Melatonin plays a major role in the regulation of metabolic oscillations enabling harmonious linking of organismic functioning to the external environment [117]. Many disorders involve circadian disruption and this is especially true for autoimmune diseases [38]. Administration of exogenous melatonin may facilitate the restoration of normal homeostasis and attenuation of disease intensity. In the case of dementia, where sleep disturbances are prevalent, such an effect has often been described. However, chronodisruption is also found in several other common non-neurological abnormalities, such as diabetes where secretion of and sensitivity to insulin occurs in a circadian manner [53].

4.2. The centrality of Receptor Activation

Melatonin is not a blunt anti-oxidant or anti-inflammatory agent. Its actions are very much dependent on each cell type. For example, melatonin can act in a pro-oxidant manner in tumor cells, the opposite of its general protective effect in non-transformed cells [118, 119]. While melatonin is generally anti-apoptotic and stimulates neurogenesis [120] in tumor cells, it can downregulate Sirt1 and promotes pro-apoptotic events [121]. In the spleen, melatonin given during the day, enhances the inflammatory response to lipopolysaccharide while elevated nocturnal levels of melatonin attenuate the reaction to an inflammogen [122]. A recent review well describes this dichotomous behavior of melatonin in detail [123]. The multitude of effects of melatonin are complex and have been described as "incoherent". However, some general inferences concerning melatonin's mechanism of action can be obtained.

Fig. (1). Example of potential melatonin-initiated signal trajectory from cell surface receptors, leading to the modification of gene expression.

The concentration of melatonin is very low and it is, thus, unable to contribute directly as a significant anti-oxidant. Its potency derives from its ability to bind to specific receptor sites, many of which probably remain uncharacterized. Through activation of these specific sites, cascades of events can be initiated, leading to epigenetic changes. These include upregulation and activation of key transcription factors. Thus, activation of Sirt1 can lead to derepression of the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2), which can then lead to elevated expression of key anti-oxidant target genes [124]. Melatonin may promote such derepression [125].

The binding of melatonin to the G-protein coupled membrane-bound melatonin receptors MT1/MT2, can modulate the activity of several transcription factors, either by way of a GTPase pathway or by phospholipase C (Fig. 1) [126]. Melatonin is clearly involved with the signaling of the nuclear orphan receptor, ROR [119, 127]. The means by which this operates is unclear. ROR reduces NF-kB activity, thus lessening inflammation [128]. Many of melatonin's anti-inflammatory capacities are clearly mediated by sirtuin-1, as inhibition of SIRT1 blocks many of the effects of melatonin [123]. It has been suggested that epigenetic regulation of MT1/MT2 receptor expression can be a therapeutic direction for the improvement of age-related events and disorders, where these receptors may be reduced in number [129].

CONCLUDING COMMENTS

Effectively responding to xenobiotic antigens is the most important and beneficial function of the immune system. By this means, infections can be contained and damaged tissue repair. Sometimes a response to an exogenous immune stimulus can become diffuse or excessive and intrinsic tissues may become involved. An exaggerated reaction can lead to allergies and anaphylaxis, where harmful hypersensitivity takes place. The formation of haptens between a specific intrinsic protein and a small non-allergenic exogenous molecule can lead to immune responses, not only to the hapten but to the original unmodified protein as well. This abnormal reactivity can lead to autoimmune disease. The deterrence or improvement of several disorders by melatonin may be linked directly to its immune-modulating ability. Furthermore, melatonin can retard the advance of several indicators that are characteristic of the aging process [130]. An indirect consequence of such non-selective slowing of aging is that the incidence of many pathological states that are strongly linked to aging may also be reduced. For example, the rate of incidence of cancer is many times greater than in younger mice and this major increase can be greatly reduced by extended melatonin administration.

Regarding reported human studies in clinical trials.gov, some generalizations can be made. Firstly most of these involve sample sizes ranging between 12 and 160. Only three

reports involving over 200 subjects are available. Secondly, many outcomes reflect indices of quality of life, measures not readily quantitated. Finally, many of these small reports appear to have been inconclusive in that no clear outcome is presented. The results of most of these trials are not published in the open literature and, thus, not available for evaluation. Therefore, the volume of relevant studies in this area is lamentably small and often incomplete. This may be related to the lack of commercial development possible for an inexpensive and readily available material. However, this does not detract from the enormous potential utility of this agent, suggested by the wealth of findings from studies on animal and isolated systems.

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CONFLICT OF INTEREST

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