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REVIEW ARTICLE

# Melatonin: therapeutic and clinical utilization

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**SUMMARY**

Melatonin, acting through melatonin receptors, is involved in numerous physiological processes including circadian entrainment, blood pressure regulation, oncogenesis, retinal physiology, seasonal reproduction, ovarian physiology, immune function and most recently in inducing osteoblast differentiation. Moreover, melatonin was proved to be a potent-free radical scavenger and a broad-spectrum antioxidant. More research is required into the effects of therapeutically modulating the melatoninergic system on circadian haemodynamics and rhythm under varying physiopathological conditions and the possible impact on morbidity and mortality in humans.

**What's known?**

Melatonin secreted by the pineal gland is involved in the regulation of the circadian rhythm of several biological functions. Melatonin is involved in numerous physiological processes including circadian entrainment, blood pressure(BP) regulation, oncogenesis, retinal physiology, seasonal reproduction, ovarian physiology, immune function and osteoblast differentiation. Melatonin was also proved to be a potent-free radical scavenger and a broad-spectrum antioxidant.

**What does this review add?**

The use of melatonin as a drug has been explored and opens new opportunities for the management of several diseases from a circadian perspective.

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**Disclosures**

The authors state that they have no interests which might be perceived as posing a conflict or bias.

## Introduction

Melatonin secreted by the pineal gland in a suprachiasmatic nuclei (SCN)-driven circadian fashion is involved in the regulation of the circadian rhythm of several biological functions. The circadian rhythm of melatonin is also compromised with ageing and certain medical conditions, such as cardiovascular and neurodegenerative diseases. Melatonin, acting through melatonin receptors, is involved in numerous physiological processes including circadian entrainment, blood pressure (BP) regulation, oncogenesis, retinal physiology, seasonal reproduction, ovarian physiology, immune function and most recently in inducing osteoblast differentiation (Table 1; 1). Also, melatonin was proved to be a potent-free radical scavenger and a broad-spectrum antioxidant. The use of melatonin as a drug has been explored and opens new opportunities for the management of several diseases from a circadian perspective.

## Synthesis and secretion of melatonin

Melatonin, a derivative of an essential amino acid, was first isolated from the bovine pineal tissue and identified as *N*-acetyl-5-methoxy-tryptamine 50 years ago; this indole is now known to be the major secretory product of the pineal gland in all mammals, including humans. The major regulator of melatonin production is the prevailing light/dark environment. In this regard, the pineal gland is an end organ of the visual system not unlike the visual cortex. Only during darkness at night does the pineal gland produce melatonin in abundance. A neural message is transferred to the anterior hypothalamus via axons of retinal ganglion cells in the optic nerve; this is a part of the so-called retino-hypothalamic tract. In the hypothalamus, the axons from the retina terminate in the SCN, a type of nucleus whose neurons exhibit inherent circadian electrical rhythms. Between the SCN and the pineal gland, the neural pathways, at least centrally, are somewhat less defined but are believed to be as follows: SCN; paraventricular nuclei; preganglionic sympathetic neurons; superior cervical ganglia (postganglionic sympathetic neurons) and pineal gland. This circuitous pathway conveys information about the light/dark environment to the pineal gland and thereby determines the melatonin synthesis cycle.

Melatonin is synthesised from tryptophan in a four-step pathway (Figure 1). First, tryptophan is converted to 5-hydroxytryptophan by tryptophan 5-monooxygenase. Aromatic-l-amino acid decarboxylase then catalyses the conversion of 5-hydroxytryptophan to serotonin (5-hydroxytryptamine). Arylalkylamine-*N*-

**Table 1** Some beneficial effects of melatonin

| Effects of melatonin |
|---|
| Corrects distrupted circadian rhythms |
| Improves sleep disorders and jet lag |
| Regulates immunomodulatory cytokines |
| Is a potent inhibitor of apoptosis |
| Has oncostatic properties |
| Enhances efficacy of cancer chemotherapy and reduces its toxicity |
| Has a protective effect on atherosclerosis |
| Decreases blood pressure |
| Has anti-anginal and anti-ischaemic effects |
| Prevents I/R-induced cardiac infarct size |
| Has protective and preventive effects on contrast-induced nephropathy |
| Modulates neuronal activity |
| Has anticonvulsant activity |
| Improves migraine and cluster headache |

acetyltransferase (AANAT) acetylates serotonin to *N*-acetylserotonin, the immediate precursor of melatonin. This process takes place mainly in the pineal gland, where AANAT is expressed. The primary neurotransmitter released from the postganglionic sympathetic terminals that terminate in the pineal gland is norepinephrine (NE); during darkness at night, NE is discharged onto the pinealocytes, the endocrine cells of the gland, where it couples especially with beta1-adrenoceptors, and this process is further potentiated by stimulation of alpha1-adrenoceptors. This leads to a marked rise in intracellular cAMP levels, to *de novo* protein synthesis and eventually to the stimulation of the rate-limiting enzyme in melatonin production, AANAT. The last step in this biosynthetic pathway is catalysed by hydroxyindol-*O*-methyltransferase, which leads to the formation of melatonin. Melatonin is eliminated from the body by two concomitant processes. 1. The classical hydroxylation pathway. In this pathway, cytochrome P450 1A2 catalyses the formation of 6-hydroxymelatonin, which undergoes further conjugation with either sulphate, catalysed by sulphotransferase ST1A3, to form 6-sulphomelatonin, or glucuronic acid, catalysed by UDP-glucuronosyltransferase, to form 6-hydroxymelatonin glucuronide. 2. Alternatively, the indole core of melatonin is opened during oxidation catalysed by indoleamine-2,3-dioxygenase and/or myeloperoxidase. The compound formed during this process is the unstable intermediary compound *N*1-acetyl-*N*2-formyl-5-methoxy-kynurenine, which is de-formylated to the more stable *N*1-acetyl-5-methoxy-kynurenine. A proportion of melatonin is excreted unchanged.

Unlike other endocrine organs, the pineal does not store melatonin for later release after it is synthesised. Rather, melatonin quickly diffuses out of the pinealocytes into the rich capillary bed within the gland and possibly directly into the cerebrospinal fluid of the third ventricle. Melatonin displays high lipid and water solubility which facilitates passage

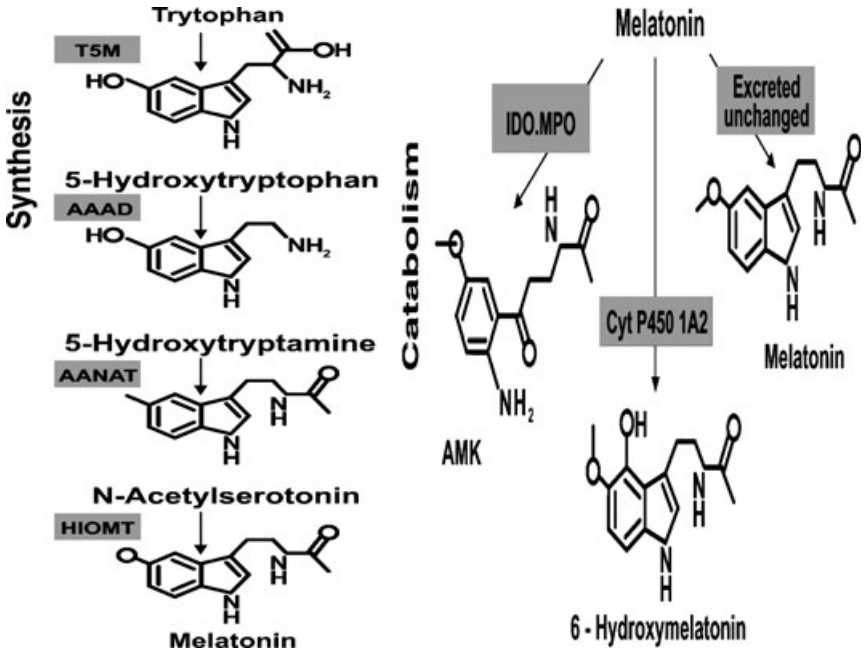


**Figure 1** The synthesis and catabolism of melatonin. T5M, tryptophan 5-monooxygenase; AAAD, aromatic-l-amino acid decarboxylase; AANAT, arylalkylamine-*N*-acetyltransferase; HIOMT, hydroxyindol-*O*-methyltransferase; IDO, indoleamine-2,3-dioxygenase; MPO, myeloperoxidase; AMK, *N*1-acetyl-5-methoxy-kynurenine; Cyt P450 1A2, cytochrome P450 1A2

 

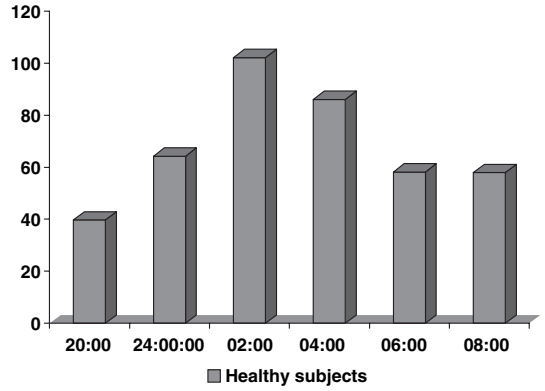


**Figure 2** The average melatonin profile shows an evening rise between 20:00 and 24:00 hours, reaches peak values between 02:00 and 04:00 hours, and then drops to low daytime levels (usually, 10 pg/ml) (from Ref. 64)

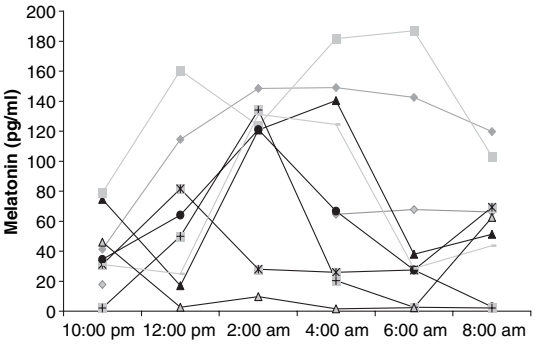


**Figure 3** Nocturnal secretion patterns of melatonin in healthy subjects (from Ref. 49)

across cell membranes. After release in the circulation, it gains access to various fluids, tissues and cellular compartments (saliva, urine, cerebrospinal fluid, preovulatory follicle, semen, amniotic fluid and milk). The plasma hormone profile faithfully reflects the pineal activity. The average melatonin profile in the temperature zone shows an evening rise between 20.00 and 24.00 hours, reaches peak values between 02.00 and 04.00 hours and then drops to low daytime levels (usually 10 pg/ml) (Figure 2). Circulating nocturnal levels of melatonin are commonly 10–20 times higher than concentrations measured during the day. Among individuals of the same age, the night-time rises in blood melatonin concentrations vary widely (Figure 3). In contrast to large between subject variability, individual melatonin profiles have a remarkably reproducible day-to-day pattern.

To date, three mammalian melatonin receptors have been described: MT1, MT2 and MT3. First two are G-protein-coupled receptors and their activations modulate a wide range of intracellular messengers, e.g. cAMP, cGMP or $[Ca^{2+}]_i$. The MT3-binding site has been identified as quinone reductase protein and its physiological significance remains to be clarified. In mammals, both MT1 and MT2 receptor subtypes are expressed in a wide variety of tissues including specific brain structures and peripheral organs.

## Insomnia and phase shift conditions: jet lag and shift work

Evidence from studies in both day-active animals and humans that the circadian pacemaker promotes wakefulness at certain times of day, together with evidence that neuronal firing of the mammalian SCN is inhibited by SCN Mel1a receptor-specific melatonin binding, has led to the hypothesis that melatonin may act to facilitate sleep by inhibiting the circadian drive for waking that emanates from the SCN (2). The direction in which melatonin phase shifts the circadian system depends on its time of administration. When given late in the subjective day (at dusk), melatonin phase advances the clock while its administration early in the subjective day (at dawn) phases delays circadian rhythms. Although results are still controversial, studies suggest that night-time melatonin administration help induce sleep in people with disrupted circadian rhythms (such as those suffering from chronic insomnia or jet lag or poor vision or those who work the night shift) and those with low melatonin levels (such as some elderly subjects) (3–11). When used to improve sleep, i.e. to decrease sleep latency and/or cause more prolonged sleep, it is taken roughly 30 min prior to bedtime. Melatonin has been successfully used with various degrees of effectiveness to enhance sleep processes in elderly individuals with insomnia and in individuals with restless leg syndrome, REM sleep disorder behaviour, delayed sleep phase syndrome, manic patients with insomnia and in patients with fibromyalgia. Recently, in a meta-analysis by Brezinski et al. (8), in which 17 studies were included to investigate the sleep-promoting potency of melatonin, it was found that melatonin has only a modest sleep-promoting effect, with an increase in sleep efficiency of 2–3%. Jet-lag is the result of long distance travel east/west crossing time zones at a rapid rate. Symptoms such as sleep disturbance, loss of appetite, reduced psychomotor efficiency and general malaise may occur. Circadian rhythms need about 1 day to adapt for each time zone crossed. In other words, 5-h time difference will require approximately 5 days of adaptation. In fact, a recent review of scientific studies found that melatonin supplements help prevent phase-shift conditions: shift work and jet lag, particularly in people who cross five or more time zones (11). Multi-centre clinical trials are needed to investigate whether chronic

melatonin administration may be beneficial for the treatment of phase-shift conditions and chronic insomnia. In addition to the potential beneficial influences on sleep, chronic night-time melatonin administration may also be of clinical relevance in the treatment of hypertensive patients with an impaired BP rhythmicity (12–14).

## Immunity

Circadian rhythmicity is revealed in circulating cells, lymphocyte metabolism and transformability, circulating hormones and other substances that may exert various actions on different targets of the immune system, cytokines, receptors, and adhesion molecules, cell cycle events in health and cancer, reactions to antigen challenge, and disease aetiology and symptoms (15). Interactions between melatonin and the immune system have been known for nearly three decades, and in virtually all cases, melatonin has been proven to have immunoenhancing effects. Currently, accumulated evidence shows that the pineal is able to play an important role in modulating the immune response (16–19). Melatonin can stimulate the immune response and correct immunodeficiencies secondary to acute stress, viral diseases or drug treatment. Binding of melatonin to its specific receptors resulted in an up-regulation of cytokine production and immune function. In humans, daily oral melatonin administration increases natural-killer cell activity (16,17). Additionally, melatonin reportedly regulates gene expression of several immunomodulatory cytokines including tumour necrosis factor-α, transforming growth factor-beta and stem cell factor by peritoneal macrophages as well as the levels of interleukin-1beta, interferon gamma, tumour necrosis factor-α and stem cell factor by splenocytes (18,19). The rise in blood melatonin levels in humans at night stimulates associated rise in the thymic production of peptides including thymosin 1a and thymulin (20). Finally, melatonin is a potent inhibitor of apoptosis in immune cells (21). In addition, interactions between the pineal gland and the immune system are bidirectional as interleukins and cytokines (interferon gamma) affect melatonin synthesis and release (22). Also, there has been described melatonin scavenging of nitric oxide or free radicals in lymphoid cells, which could explain the melatonin-modulated circadian variation in the experimental chronic inflammation.

This kind of approach raises new questions regarding the mechanism of chronic inflammation, in disorders such as rheumatoid arthritis and nocturnal asthma, diseases that present rhythmic symptoms during a 24 h period (23,24). It is clear that melatonin provides a functional link between the neuroendocrine and immune-haematopoietic systems. The pineal neurohormone melatonin has been widely shown to exert an immunostimulatory and anti-apoptotic role, mainly by acting on Th cells and on T- and B-cell precursors respectively. The increased prevalence of autoimmune diseases, such as rheumatoid arthritis, which is seen in northern Europe also may be related to the increased immunostimulatory effects that are exerted during the night by melatonin and to a reduced neuroendocrine modulation during the light phase of the photoperiod (cortisol) (25–27). Nocturnal asthma is associated with elevation and phase delay of peak serum melatonin levels (28). Elevated melatonin levels might contribute to the pathogenesis of nocturnal asthma. However, melatonin can improve sleep in patients with asthma (29). Further studies looking into long-term effects of melatonin on airway inflammation and bronchial hyper-responsiveness are needed before melatonin can be recommended in patients with asthma. However, for individuals with chronic sarcoidosis who do not respond to corticosteroids, melatonin may be an effective alternative therapy. In one study, individuals with sarcoidosis who did not respond to corticosteroid therapy experienced the following improvements after taking melatonin for 4–12 months: improved breathing; decreased lymph node swelling and normalisation of blood tests (30). Once the melatonin supplements were discontinued, however, these improvements disappeared. Given that melatonin is generally considered to be immunostimulatory, the question as to whether it should be taken by individuals with an autoimmune disease has been raised. To date, the information is meagre on this issue, although in one case of Crohn's disease, a condition of excessive immune reactivity of the gut wall was reported; melatonin did aggravate the condition (31). Whether this will be a general finding in autoimmune diseases, however, remains to be established.

## Cancer

For more than two decades, many investigators have been working on the hypothesis of the possible oncostatic role of melatonin on several kinds of tumours. A considerable amount of evidence has been amassed from studies on experimental animals (32,33) and trials in humans (34–36). As with the sleep-promoting function of melatonin, the concentrations of the indole that reduce cancer cell proliferation, tumour growth and the incidence of metastases vary from

physiological to pharmacological. There is also some evidence to indicate that the efficacy of melatonin in limiting tumour cell proliferation depends on the time of the day of its administration, with melatonin given late in the light phase being more effective (33).

The oncostatic properties of melatonin could be explained in variety of ways based on different known actions of the indoleamine. Thus, the antitumour actions of melatonin may be considered: (i) as indirect effects derived from its interaction with the neuroendocrine reproductive axis leading to a down-regulation of some of the hormones influencing tumour growth, especially gonadal oestrogens; (ii) as a consequence of its interaction with oestrogen receptors on the epithelial mammary cells in a similar way as classic anti-oestrogens act; (iii) dependent on its immuno-enhancing effects; (iv) as a consequence of its antioxidant properties or (v) derived from its inhibitory effects on telomerase activity in tumour cells (37–40). These properties, collectively, make melatonin an interesting anticancer drug in the prevention and treatment of tumours, as it has the advantage of acting at different levels of the hormone-signalling pathways. Melatonin as an inhibitor of hormone-dependent cancers in humans is worthy of test. A phase II study showed that a total pineal endocrine replacement therapy by an exogenous administration of the overall four pineal indoles (melatonin, 5-methoxytriptamine and 5-methoxytryptophol and 5-methoxy-indole acetic acid) may induce disease-control in about 60% of untreatable metastatic solid tumour patients. Then, these results would be clearly superior with respect to those described with melatonin alone, by confirming in humans that melatonin is not the only hormone responsible for the anticancer property of the pineal gland (35).

In addition to its potential direct antitumour activity, melatonin has proved to modulate the effects of cancer chemotherapy, by enhancing its therapeutic efficacy and reducing its toxicity. The increase in chemotherapeutic efficacy by melatonin may depend on two main mechanisms, namely prevention of chemotherapy-induced lymphocyte damage and its antioxidant effect, which has been proved to amplify cytotoxic actions of the chemotherapeutic agents against tumour cells. Recently, Lissoni et al. (36) performed a study to assess the 5-year survival results in metastatic non-small cell lung cancer patients obtained with a chemotherapeutic regimen with or without the concomitant night-time administration of melatonin. They found that both the overall tumour regression rate and the 5-year survival results were significantly higher in patients concomitantly treated with melatonin. In particular, no patient treated with chemotherapy alone was alive after 2 years, whereas a 5-year survival was achieved in three of 49 (6%) patients treated with chemotherapy and melatonin. Moreover, chemotherapy was better tolerated in patients treated with melatonin. This study confirmed, in a considerable number of patients and for a long follow-up period, the possibility to improve the efficacy of chemotherapy in terms of both survival and quality of life by a concomitant administration of melatonin (36). The implications of the accumulated observations suggest that it is time to consider clinical trials using melatonin for cancer inhibition either given as a single treatment or in conjunction with anticancer drugs (41).

Malnutrition from anorexia and reduced nutrient intake is common in patients with cancer. Abnormalities in gastrointestinal function caused by the tumour or treatment of the tumour may be direct causes for nutrition challenges. However, other patients may present with cancer cachexia, a wasting syndrome characterised by weight loss, anorexia, early satiety, progressive debilitation and malnutrition that results in a greater risk of organ dysfunction and death. Lissoni et al. (42) showed that melatonin administration for cancer cachexia indication decreased weight loss and tumour necrosis factor levels. In contrary, recently Persson et al. (43) reported that fish oil, melatonin or their combination did not induce major biochemical changes indicative of a strong anti-cachectic effect. However, the weight-stabilizing effect seemingly produced by melatonin and previous observations justify their inclusion in additional clinical trials.

## Cardiovascular diseases

Cardiovascular diseases (coronary heart disease, stroke, etc.) remain the major cause of death in most developed countries. The clinical importance of circadian biological rhythms has been strengthened by a number of studies showing a circadian distribution of cardiovascular events such as myocardial infarction, stroke, complex arrhythmia or sudden cardiac death. Incidence of cardiovascular events showed a maximum during the early morning hours after awakening from sleep. In addition, a number of pathophysiological mechanisms have been identified to coincide with this peak including BP and heart rate surges, decreased endothelial dilatory capacity of peripheral and coronary arteries, enhanced sympathetic activity, decreased cardiac electrical stability and increased platelet aggregation. This time window of high risk for the incidence of cardiovascular events

has been identified as a target for new treatment and prevention strategies including new release forms of antihypertensive and anti-ischaemic drugs. Decreased melatonin production was found in several cardiovascular diseases (44–64). The use of melatonin as an antihypertensive, antioxidant and anti-ischaemic drug has been explored and opens new opportunities for the management of cardiovascular dysfunction and disease from a circadian perspective (65).

A role of melatonin in the control of cardiovascular rhythmicity is supported by animal and human studies. Pinealectomy of laboratory rats results in hypertension while the hypertensive effect of pinealectomy was blocked by administration of exogenous melatonin (66,67). There is an inverted relationship between plasma melatonin concentrations and acrophase of the BP rhythm in man, as high melatonin level coincides with lower BP values. In humans, administration of exogenous melatonin decreases BP in normotensive patients (68,69), in patients with essential hypertension (48,70–73) and in patients with diabetes mellitus type 1 (57,58). Single exogenous melatonin intake can lower BP, but only when melatonin is taken during the daytime, when general SCN neuronal activity is high and endogenous melatonin levels are low. On the contrary, repeated nighttime melatonin intake supports the endogenous melatonin rhythm, improving circadian rhythmicity (74–76).

Synthesis and release of melatonin are stimulated by NE via beta1-adrenoceptors, and this process is further potentiated by stimulation of alpha1-adrenoceptors (77,78). Accordingly, beta-blockers have been shown to reduce the production of melatonin (79–83). Carvedilol is an effective adrenergic alpha1- and beta1-antagonist. However, Stoschitzky et al. (83) reported that carvedilol does not decrease nocturnal melatonin production. Verapamil does not alter melatonin release (83). Lacidipine treatment in hypertensive patients increases endogenous melatonin production (47). However Lusardi et al. (46) showed that the chronic evening ingestion of melatonin in hypertensive patients well-controlled by nifedipine GITS induces a BP increase and a heart-rate acceleration. Kinetic or pharmacodynamic interaction between melatonin and nifedipine, is able to impair the antihypertensive efficacy of the calcium-channel blocker. This suggests caution in uncontrolled use of melatonin in hypertensive patients. As the pineal hormone might interfere with calcium-channel blocker therapy, it cannot be considered simply a dietary supplement. Zaslavskaia et al. (84) showed that combination losartan and melatonin-reduced BP more noticeably than losartan alone. Recently, this group also showed that combination moxonidine and melatonin is more effective on haemodynamic parameters in patients with arterial hypertension than moxonidine alone (85). Melatonin (1–5 mg) has been widely used as a nutritional supplement in the United States for several years, without any serious adverse side effects being reported. Daytime exogenous melatonin intake may result in sleepiness and hypothermia during the day and should thus be avoided (86). Melatonin taken at night could thus be a gentle alternative or supplement to regular antihypertensive medication.

The increased formation of cardiac malondialdehyde and serum nitric oxide, and the decreased activity of cardiac antioxidant enzymes (i.e. superoxide dismutase, glutathione peroxidase and catalase) were found on chemotherapeutic drug-induced oxidative damage in the heart tissue (87–90). Paskaloglu et al. (91) showed that melatonin or insulin alone can provide limited protection against hyperglycaemia-induced oxidative damage in diabetes. Combined treatment with insulin and melatonin can suppress hyperglycaemia, prevent oxidative damage and can restore endothelial function completely, implying that treatment of diabetes mellitus with this combination would be beneficial. Zaslavskaya et al. (92) studied melatonin effects on contractile myocardial function; patients with postmyocardial infarction and heart failure, assessed as stage II-III by New York Heart Association (NYHA). They found melatonin associated anti-anginal and anti-ischaemic effects, indicating improvement of contractile function. The ejection fraction increased; the anti-anginal effect appeared by the fifth day of treatment. Thus O'Rouke (93) showed that additional anti-ischaemic effect of melatonin, acting via specific melatonin receptors, inhibits nitrate tolerance in coronary arteries and that this effect is dependent on the presence of vascular endothelium. Melatonin has been found to protect heart tissues against oxidative damage induced by other free radical-generating agents and processes.

Disturbances in renal haemodynamics and direct cytotoxicity have been identified as key factors in the pathogenesis of contrast induced nephropathy (CIN). Contrast agents markedly aggravate this physiological hypoxia of the outer medullary layer because they cause enhanced metabolic activity and oxygen consumption as a result of osmotic diuresis and increased salt delivery to the distal nephron. The result of the haemodynamic changes is hypoxia followed by oxidative stress and repair. Recently, we experimentally demonstrated for the first time that pre- and post-treatment with melatonin did prevent and protect renal function as measured by Fe-Na, serum Cr and Cr clearance in rats with CIN (94).

Melatonin protects renal function against the development of CIN and opens a new era in the management of CIN. This study revealed that only pretreatment with melatonin was not sufficient to prevent renal deterioration completely and improve renal function in CIN. However, rats pre- and post-treated with melatonin showed significant improvement in their renal function possibly related to ongoing continuous melatonin effect.

Several recent publications present evidence that melatonin has significant protective actions against the cardiac damage and altered physiology that occurs during ischemia/reperfusion (I/R) injury (95–100). Sahna et al. (97–99) showed that physiological concentrations of melatonin were important in preventing I/R-induced cardiac infarct size. The results showing increased I/R-induced cardiac injury after reduction in physiological levels of melatonin have implications for elderly people in as much as in old individuals endogenous levels of melatonin are significantly lower than in young individuals. Several studies have reported that humans with cardiovascular diseases have noticeably lower circulating melatonin levels than do age-matched subjects without significant cardiovascular deterioration (42–63). Similarly, patients suffering from cardiac syndrome X have an attenuated nocturnal peak in serum melatonin levels relative to those of age-matched individuals with no cardiac pathology (64). It remains unknown, however, whether the reduced endogenous melatonin levels in patients with cardiovascular disease is a cause, an effect or even related to the compromised cardiovascular function.

## Neurological disorders

A large number of individuals suffer from primary headache (migraine and cluster headache). Migraine and cluster headache can be viewed as transient disturbances of the body adaptive response to internal or external environmental changes. Among these factors, light is a major precipitating or aggravating factor of attacks (101,102). Abnormalities in the secretion of melatonin and cortisol in patients with migraine and cluster headache have been documented (103,104). Melatonin mechanisms are related to headache pathophysiology in many ways, including its anti-inflammatory effect, toxic free radical scavenging, reduction of proinflammatory cytokine upregulation, nitric oxide synthase activity and dopamine release inhibition, membrane stabilisation, gama-aminobutyric acid (GABA) and opioid analgesia potentiation, glutamate neurotoxicity protection, neurovascular regulation, serotonin modulation and the similarity of chemical structure to that of indomethacin. Treatment of headache disorders with melatonin is promising, particularly in cluster headaches, hypnic headaches, indomethacin-responsive headaches and migraine (101,103,104).

Recent studies showed disruption of nocturnal surge of melatonin in ischaemic stroke patients and patients with acute cerebral haemorrhage (105–107). Endogenously produced and exogenously administered melatonin may reduce the degree of tissue damage and limit the biobehavioural deficits associated with ischaemia/reperfusion injury in the brain (i.e. stroke). Melatonin's protective actions against ischaemia/reperfusion injury are believed to stem from its direct free radical scavenging and indirect antioxidant activities, possibly from its ability to limit free radical generation at the mitochondrial level (108). Recently, a meta-analysis demonstrated a marked efficacy of melatonin in animal models of focal cerebral ischaemia, identified priority areas for future animal research, and suggested melatonin as a candidate neuroprotective drug for human stroke (109).

The decline in melatonin production in aged individuals has been suggested as one of the primary contributing factors for the development of age-associated neurodegenerative diseases. Parkinsonism is the second most common neurodegenerative disorder after Alzheimer's disease. Melatonin not only plays an important role in the regulation of circadian rhythms, but also acts as an antioxidant and neuroprotector that may be of importance in ageing and neurodegenerative diseases. Melatonin has been shown to be effective in arresting neurodegenerative phenomena seen in both *in vivo* and *in vitro* studies of Alzheimer's disease and Parkinsonism (110–112).

Decreased melatonin levels have also been reported in patients with some forms of epilepsy. Some authors suggest a potential use of melatonin as an adjunct to anti-epileptic therapy because of its diverse spectrum of action as an antioxidant, neuroprotector and free radical scavenger, thus offering the advantage of reducing oxidant stress and subsequent damage. The beneficial effects of melatonin on sleep, its wide safety window and its ability to cross the blood–brain barrier have the potential to improve quality of life in paediatric epilepsy (113). Molina-Carballo et al. (114) showed that high doses of melatonin as adjunctive anti-epileptic therapy in a child with severe myoclonic epilepsy improved both the frequency of seizures and the EEG tracing. Melatonin could be beneficial in combination with other anti-epileptic medications (113–115). However, Sheldon (116) showed that pro-convulsant effects of melatonin in neurologically disabled children.

 

Although melatonin had a positive effect on sleep disorders, four of six children with severe neurological disabling conditions and seizures had increased seizure activity after melatonin treatment. Seizure frequency returned to baseline after melatonin was discontinued and re-challenge resulted in recurrence (116).

## Psychiatric diseases

In normal subjects, the secretion of melatonin, the pineal hormone that regulates the rhythm of many functions, exhibits a circadian pattern synchronised with the day–night cycle. An alteration of this secretory pattern has been found in various psychiatric disorders [seasonal affective disorder (SAD), bipolar disorder, unipolar depression, bulimia, anorexia, schizophrenia, panic disorder, obsessive compulsive disorder and delirium] (117). Numerous studies have reported low melatonin secretion in depression, but other studies have suggested no deficit or an increase (118–121). Recent studies evidence conflicting results (normal melatonin peak, normal or phase delay rather than phase advanced peak) which could be explained by methodological differences (size of samples, duration of drug wash-out, selection of patients and comparison of patients with not strictly matched controls) and seniority of the disease (119–121). Seasonal affective disorder is a condition of regularly occurring depressions in winter with a remission the following spring or summer. In addition to depressed mood, the patients tend to experience increased appetite and an increased duration of sleep during the winter. SAD is a relatively common condition, affecting 1–3% of adults in temperate climates, and it is more prevalent in women. SAD patients' circadian rhythms are delayed relative to the sleep/wake or rest/activity cycle (122). Melatonin levels in the SAD patients were found to be on average 2.4 times as high as in the controls (123). Heterogeneous results were also observed for melatonin profiles in schizophrenia and anorexia nervosa (124). Delirium is a common syndrome among hospitalised elderly patients. In humans, sleep and circadian rhythms are disturbed during delirium, and both are influenced by the hormone melatonin. Recently, a study showed that urinary melatonin metabolite during delirium was higher in hypoactive and lower in hyperactive patients (125). At present, it is not known if such alterations have an aetiological role or are secondary to the dysfunctions underlying various psychiatric disorders. An understanding of the role of the melatonin and of its alterations in psychiatric diseases could help to identify the biological mechanisms underlying such disorders.

## Current use of melatonin

The use of melatonin in cultural and traditional settings may differ from concepts accepted by current Western medicine. Melatonin is sold as a dietary supplement, not as a drug, often in health food and other grocery stores and some drug stores. Because it is not labelled as a drug, Food and Drug Administration (FDA) regulations that apply to medications sold in the United States do not apply to melatonin. The FDA does not require manufacturers of melatonin to demonstrate that their product is safe and effective nor to monitor its safety and efficacy, as is the case for drugs. All potential risks and/or advantages of melatonin may not be known. Additionally, there are no regulated manufacturing standards in place for these compounds. Because of concerns about transmission of viruses through animal products, melatonin derived from cow or sheep pineal glands should not be taken. Melatonin has been banned from over-the-counter sale in Great Britain, Canada and many European countries. Most melatonin sold in the United States is synthetic, although some health food store clerks may confuse customers by insisting the products are 'all natural'. Melatonin is available from numerous manufacturers generically: capsules – 1, 2.5, 3, 5 and 10 mg; liquid – 1 mg/ml and 1 mg/4 ml; lozenges – 0.5 and 3 mg; sublingual tablets – 1 and 2.5 mg; tablets – 0.2, 0.3, 0.5, 1, 3, 5 and 10 mg; tea; and timed release tablets – 1, 2 and 3 mg.

## Conclusion

There are more over 12,000 citations related to melatonin in PubMed, it is not possible to mention all the data which document the clinically relevant aspects of melatonin. Melatonin has been administered in both physiological and pharmacological amounts to humans and there is widespread agreement that it is a non-toxic molecule. In human volunteers, oral administration of melatonin in doses of 1–300 mg or 1 g of melatonin daily for 30 days resulted in no observable negative side effects (126). Sebra et al. (127) conducted a randomised double blind clinical trial in healthy adult male subjects by oral administration of melatonin (10 mg/day for 28 days or a placebo) and reported no evidence of toxicity. Thus, giving female rats 200 mg melatonin/kg body weight (the equivalent of an average-weight human consuming 14 g melatonin daily) throughout pregnancy caused no maternal and fetal toxicity (128). More research is required into the effects of therapeutically modulating the melatoninergic system on circadian haemo-

dynamics and rhythm under varying physiopathological conditions and the possible impact on morbidity and mortality in humans.

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