AUTHOR QUERY FORM

ELSEVIER	**Book: Gupta-1611234** **Chapter: CH036**	**Please e-mail your responses and any corrections to:** **E-mail: l.perez@elsevier.com**

Dear Author,

Any queries or remarks that have arisen during the processing of your manuscript are listed below and are highlighted by flags in the proof. (AU indicates author queries; ED indicates editor queries; and TS/TY indicates typesetter queries.) Please check your proof carefully and answer all AU queries. Mark all corrections and query answers at the appropriate place in the proof using on-screen annotation in the PDF file. For a written tutorial on how to annotate PDFs, click http://www.elsevier.com/__data/assets/pdf_file/0007/98953/Annotating-PDFs-Adobe-Reader-9-X-or-XI.pdf. A video tutorial is also available at http://www.screencast.com/t/9OIDFhihgE9a. Alternatively, you may compile them in a separate list and tick off below to indicate that you have answered the query.

Please return your input as instructed by the project manager.

Uncited references: References that occur in the reference list but are not cited in the text. Please position each reference in the text or delete it from the reference list.

Missing references: References listed below were noted in the text but are missing from the reference list. Please make the reference list complete or remove the references from the text.

Location in Chapter	**Query / remark**	
AU:1, page AK	As per style, reference citations are not allowed within the abstract. Chen et al. (2011) has been removed.	☐
AU:2, page 503	Please cite Figure 1 in text. Figure 1 pdf file accompanies this manuscript but there is no mention of it and no figure legend provided in the ms document.	☐
AU:3, page 509	Please provide the volume number and page range for references Ekeløf et al., 2014; Fallah et al., 2014; Shokrzadeh et al., 2014.	☐

c0036 CHAPTER

36

Melatonin: A Safe Nutraceutical and Clinical Agent

Edward H. Sharman and Stephen C. Bondy

s0010

INTRODUCTION

p0010 AU:2 Melatonin is an indoleamine with the chemical name *N*-acetyl-5-methoxytryptamine and is found in animals, plants, and bacteria. It has endocrine and antioxidant properties in both animals and plants. It is biosynthesized from the neurotransmitter serotonin, which in turn is made from the essential amino acid tryptophan. Because its normally charged amino group is acetylated and a methoxy rather than a hydroxyl group ~~and~~ is present in the 5 position, melatonin is a relatively nonpolar compound that readily crosses the blood–brain barrier and easily enters cells of all types. In mammals, melatonin has several roles; it is involved in circadian regulation and modulation of reproductive and immune responses, mood, and aging. It is produced by the pineal gland and several peripheral tissues, notably the gut (Chen et al., 2011). Because it is liberated into the bloodstream from the pineal and acts through receptors located in a wide variety of body tissues, it can be considered a systemic hormone.

p0015 ~~Levels of melatonin vary diurnally: they are highest during hours of darkness, seasonally in some mammals, and throughout the life cycle, and are lowest among the elderly.~~

p0020 This chapter focuses on two areas: (i) recent findings suggesting a variety of therapeutic applications—ranging from improvement of disturbed sleep patterns and mood disorders to adjuvant cancer treatment and surgery and fertility enhancement and (ii) support for the safety of exogenously supplied melatonin. The potential molecular mechanisms underlying these potentially clinically beneficial uses are also discussed.

s0015

RANGE OF CONDITIONS WHERE MELATONIN MAY HAVE CLINICAL UTILITY

p0025 The evidence for the beneficial properties of melatonin in the derangements described is often derived from studies on animal models of disease, but any relevant human findings are also added to each section.

s0020

Disturbances of Sleep Patterns

p0030 Melatonin is perhaps most well-known for its ability to induce sleep. Plasma levels are highest during hours of darkness and decline rapidly at the onset of light. Thus, melatonin is widely used to reset normal circadian sleep patterns after disruption by jet lag. Sleep quality can be defined by tiredness upon waking, feeling rested, and the number of awakenings experienced during the night. This can be partly correlated with objective polygraphic measures to determine the extent of fragmentation of sleep. Melatonin has been found to improve sleep quality in patients with a variety of diseases. A dosage of 3 mg/day taken at bedtime for 24 days in a group of 2,062 patients with chronic cerebral ischemia improved multiple types of subjective sleep characteristics (Poluéktov et al., 2012). An analysis was made combining results from four clinical trials studying the effects in 401 hypertensive patients aged 55 years or older. The analysis determined that 2 mg/day of prolonged-release melatonin taken 2 h before bedtime for 3 weeks improved quality of sleep and morning alertness (Lemoine et al., 2012). The improvements in sleep quality were maintained during a follow-up

Nutraceuticals.
DOI: http://dx.doi.org/10.1016/B978-0-12-802147-7.00036-X

period of 6 months; moreover, the rate of adverse events was lower in the patients using melatonin. Although melatonin had no significant effect on blood pressure in this study, a meta-analysis of seven other clinical trials demonstrated that 2–3 mg/day of controlled-release (but not fast-release) melatonin over periods of 28–90 days significantly reduced nocturnal blood pressure in a variety of subjects, including those with hypertension (Grossman et al., 2011). In a study of 36 type 2 diabetic individuals, a regimen of 2 mg/day of prolonged-release melatonin taken 2 h before bedtime for 3 weeks resulted in significant improvement in sleep efficiency, wake time after sleep onset, and reduced number of awakenings (Garfinkel et al., 2011).

p0035 The melatonin receptor agonist ramelteon has been used to treat chronic insomnia clinically with success (Liu and Wang, 2012). Some studies demonstrate that melatonin improves sleep quality more modestly. In a recent review of 35 randomized clinical trials, use of melatonin by healthy adults was found to show limited promise for preventing phase shifts from jet lag and for improving insomnia; both healthy adults and insomniacs benefited. However, available data could not confirm a positive benefit for either the initiation of sleep or sleep efficacy (Costello et al., 2014).

p0040 Aging is associated with an altered sleep profile; sleep time is shortened and sleep is more disrupted. Sleeplessness is often found with cardiovascular disease, obesity, type 2 diabetes, cancer, and a range of inflammatory disease states. There is evidence that melatonin can be of use in amelioration of the disrupted sleep associated with Alzheimer's disease (Cardinali et al., 2011), but this is disputed (McCleery et al., 2014). Melatonin has also found utility in hypertensive patients in the treatment of sleep disruption caused by depression of intrinsic melatonin production by beta-blockers (Scheer et al., 2012). Reports of the add-on utility of melatonin to the treatment of several disorders, including epilepsy (Goldberg-Stern et al., 2012), may primarily be attributable to the improved quality of the sleep–wake cycle (Gupta et al., 2004), but melatonin has also been shown to directly potentiate the anticonvulsant efficacy of phenobarbital (Forcelli et al., 2013).

p0045 Melatonin is effective as an adjuvant for improving cognitive function and sleep quality impaired by a number of disorders. A study group of 73 outpatients with mild to moderate Alzheimer's disease took 2 mg prolonged-release melatonin or placebo daily 1–2 h before bedtime for 24 weeks in combination with an acetylcholinesterase inhibitor (with or without memantine). Those using melatonin experienced a lower rate of cognitive decline and improved sleep quality. These benefits were more pronounced in a subpopulation with insomnia (Wade et al., 2014). Melatonin (5 mg/day orally at bedtime) improved sleep quality among clinical trial participants with myofascial temporomandibular disorder (TMD) and pain (Vidor et al., 2013).

MELATONIN AND MOOD DISORDERS

s0025

p0050 The clinical applicability of melatonin and pharmacological agents active at its receptors to depressive and anxiety mood disorders has been reported. The principal antidepressant drug used is agomelatine, which acts as a melatonin MT1 and MT2 receptor agonist. However, agomelatine also acts as a serotonergic 5-HT(2C) receptor antagonist, and this could also contribute its antidepressant activity (Fuchs et al., 2006). Ramelteon, another MT1/MT2 agonist, has no serotonergic antagonistic activity but retains antidepressant properties (Hardeland and Poeggeler, 2012). The mechanism of action may involve both restoration of a normal sleep cycle and the intrinsic anxiolytic and analgesic properties of melatonin, which has opioid activity (Srinivasan et al., 2010). Ramelteon has also been reported to protect against delirium (~~Tresguerres et al., 2012;~~ Hatta et al., 2014). The biochemical and behavioral deficits found in animal models of several neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease, and cerebral stroke, are mitigated by melatonin treatment (Patki and Lau, 2011; García-Mesa et al., 2012; Chern et al., 2012). However, reports involving melatonin intervention in these diseases in human trials are very limited. Restoration of deranged sleep patterns may account for the majority of benefits seen in clinical testing of melatonin (Rothman and Mattson, 2012).

p0055 Melatonin has shown promise for managing some troublesome side effects of drugs used to treat mood disorders. In a study of schizophrenic patients, treatment with 3 mg/day of melatonin for 8 weeks reduced the metabolic side effects of weight gain, abdominal obesity, and hypertriglyceridemia induced by olanzapine (Modabbernia et al., 2014). However, 20 mg/day of controlled-release melatonin for 1 month was no more effective than placebo for reducing dependence on benzodiazepines in a group of 92 elderly outpatients (Lähteenmäki et al., 2014).

SLOWING OF COMMON AGE-RELATED PROCESSES

s0030

p0060 Aging is associated with an increasingly elevated level of inflammatory events (Bondy and Sharman, 2010). Inappropriate and excessive immune responses characterize many diseases associated with aging, including a range of cardiovascular and neurodegenerative disorders. This heightened level of inflammation appears to be unprovoked by exogenous agents and may reflect the

inappropriate continuation of earlier and more relevant immune responses (Qin et al., 2007). In the nervous system, many of the genes whose expression is elevated with age relate to immune function, and melatonin treatment has been shown in aged experimental animals to reverse this trend and restore a more youthful pattern of mRNA production (Sharman et al., 2007). This is also reflected by reversal of age-associated morphological and biochemical changes in brain (Zhou et al., 2014). Another important feature of brain aging where melatonin may be of value concerns adult neurogenesis, which has significance that is increasingly being acknowledged. Diminished neurogenesis precedes old age (Leuner et al., 2007), and this decline can be delayed by supplementation with melatonin (Ramirez-Rodriguez et al., 2012). In addition, the maintenance of dendritic complexity is enhanced by melatonin (Ramirez-Rodriguez et al., 2011). Studies on melatonin in aging humans are relatively scarce, but several promising reports exist. Daily use of 3 mg melatonin protected the retina by delaying macular degeneration—a leading cause of severe visual loss in older people (Yi et al., 2005). Even low doses of melatonin used during the evening increased daytime activity of healthy elderly people (Valtonen et al., 2005).

s0035

MELATONIN AND INFLAMMATORY DISEASE

p0065 Chronic inflammation characterizes several common diseases. Many of the disorders for which melatonin therapy has been found to be of use involve inflammatory changes. Collating evidence from both animal models and the clinical situation, such diseases include hypertension (Hrenak et al., 2015), ocular inflammation (uveitis) (Sande et al., 2014), a human model of endotoxemia (Alamili et al., 2014), reflux esophagitis (Konturek et al., 2013), sepsis (Sharman and Bondy, 2014), pancreatitis (Jaworek et al., 2012), and cerebral edema (Rathnasamy et al., 2014).

p0070 A review of the effects of melatonin treatment for inflammatory bowel syndrome reveals that melatonin typically supplemented at 3 mg/day for periods varying from 2 weeks to 6 months is generally effective in reducing the abdominal pain associated with this disease (Siah et al., 2014). Other studies reviewed by Siah et al. (2014) reported an increase in pain threshold and improvements in bowel symptoms, visceral pain, abdominal bloating, overall IBS scores, and quality of life.

p0075 Symptoms of endometriosis—another disease with a large inflammatory component—were relieved in a clinical trial involving 40 affected women aged 18–45 years (Schwertner et al., 2013). After 8 weeks of using a regimen of 10 mg/day of oral melatonin taken at bedtime, daily pain scores were reduced by 40%, dysmenorrhea was reduced by 38%, and quality of sleep was improved. Interestingly, the women using melatonin also reported an 80% reduction in analgesic usage.

MELATONIN AND DISEASE RELATED TO IMMUNE FUNCTION

s0040

p0080 Melatonin has also been found to be of utility in the treatment of other diseases and adverse health states in which excess inflammation may not constitute a major element of pathogenesis but where immune function is likely a factor, including cancer (Cutando et al., 2012; Seely et al., 2012; Lissoni et al., 2012). Supplementation of the diet of aged mice with melatonin leads to a major reduction of tumor incidence (Sharman et al., 2011). Although melatonin is generally reported as supporting cell survival, it appears to promote apoptosis in malignant cells (Sánchez-Hidalgo et al., 2012). Several meta-analyses have shown that adjuvant treatment of cancer—particularly solid tumor cancers—with melatonin significantly improves outcomes (Cutando et al., 2012). Similarly, two recent case studies have reported encouraging results in patients with breast cancer (Di Bella et al., 2013) and hepatocellular carcinoma (Tomov et al., 2013). Encouraging but modest benefits were reported very recently in a clinical trial involving 151 advanced nonsmall cell lung cancer patients also receiving chemotherapy. In this study, 10 or 20 mg/day of melatonin taken at night for 6 months following initiation of chemotherapy decreased DNA damage and tended to improve quality of life; however, even though the longest-living survivors were among those patients receiving melatonin, supplementation did not lengthen survival time significantly overall (Sookprasert et al., 2014).

p0085 Melatonin therapy can also speed the rate of healing of diverse types of wound (Celinski et al., 2011; Drobnik et al., 2013). In an experimental model of multiple sclerosis—which certainly reflects inappropriate immune responses—melatonin was able to reverse demyelination (Kashani et al., 2014).

MELATONIN AND OXIDATIVE STRESS

s0045

p0090 There are several states that are predominantly characterized by excessive generation of reactive oxidant species. These include strenuous exercise and chronic pulmonary obstructive disease. Melatonin has been shown to be able to reduce indices of free radical damage in each of these in humans (Ochoa et al., 2011; de Matos Cavalcante et al., 2012). The relatively low tissue content of active unconjugated melatonin is approximately 1 pM (Lahiri et al., 2004), which makes a direct antioxidant effect unlikely because several other potent antioxidants such

as water-soluble glutathione and lipophilic α-tocopherol are present at much higher intracellular concentrations. Nonetheless, melatonin has been shown to reduce indices of oxidative stress in several clinical situations, including metabolic syndrome (Koziróg et al., 2011), Duchenne muscular dystrophy (Chahbouni et al., 2011), and in severely ill children (Marseglia et al., 2013).

MELATONIN AND NOCICEPTION

Melatonin may be effective for reducing chronic pain associated with some diseases. Being antinociceptive, it can act to support conventional anesthetics (Marseglia et al., 2015). In a randomized, placebo-controlled clinical trial involving 32 patients with myofascial TMD pain, pain levels evaluated by two different measurements were reduced in those using 5 mg/day at bedtime over a course of 4 weeks; moreover, these patients also reported requiring smaller and smaller amounts of other analgesics to cope with their pain as the trial progressed (Vidor et al., 2013).

REDUCED TOXICITY OF VENOMS AND PHARMACOLOGICAL AGENTS AFTER MELATONIN ADMINISTRATION

Melatonin has been found to ameliorate the venom-induced hemorrhage and myonecrosis incurred after a snake bite (Katkar et al., 2014). It is also protective against the nephrotoxicity of tenofovir, a reverse-transcriptase inhibitor used in the treatment of HIV infection (Ramamoorthy et al., 2014). The toxicity of several antineoplastics, such as neocarbazine and cyclophosphamide, is reduced in the presence of melatonin (Alp et al., 2014; Shokrzadeh et al., 2014).

BENEFICIAL EFFECTS OF MELATONIN USE DURING SURGICAL PROCEDURES

Melatonin improves survival of animals after heart transplantation both in the presence and absence of cyclosporine (Liu et al., 2014). Prior administration of melatonin also improved survival rates after kidney transplantation (Li et al., 2009). The persistence of ovaries following transplantation was also increased (Hemadi et al., 2012). Clinical studies in these areas are very limited, but melatonin had only marginally beneficial effects in major liver resection surgery (Nickkholgh et al., 2011). However, it has been shown to be nearly as effective as clonidine as an agent for sleep induction preceding surgical anesthesia in children aged 1–5 years (Almenrader et al., 2013). Moreover, melatonin administration has been reported to lead to improved outcome following organ transplant procedures (Liu et al., 2014) and neonatal surgery (Gitto et al., 2004). The more successful reports used much higher doses of melatonin.

Melatonin appears to have clinical utility in reducing the damage incurred by ischemia-reperfusion injury in the liver, which is very susceptible to such fluxes in vascular supply (Li et al., 2014). However, several trials on the potential of melatonin to mitigate the effects of reperfusion injury on the heart have not been proven to be successful (Kücükakin et al., 2010; Ekeløf et al., 2014).

MIGRAINE AMELIORATION BY MELATONIN

Melatonin shows promise for reducing severity of migraine headaches in adults and children. In a recent study of 60 children (mean age, 10.3 years), monthly frequency of migraines was reduced by 55%, duration was reduced by 51%, and severity was reduced by 43%; the most frequent side effect was daytime sleepiness that occurred in seven subjects (Fallah et al., 2014).

MELATONIN SUPPLEMENTATION AND FERTILITY

The quality of oocytes used for *in vitro* fertilization has been reported to be improved by treatment of the donors with melatonin (Rizzo et al., 2010; Batıoğlu et al., 2012). The efficacy of oral melatonin supplementation on oocyte and embryo quality in patients in an assisted reproductive technologies program has been studied (Nishihara et al., 2014). Patients were treated with 3 mg/day melatonin for at least 2 weeks. To evaluate the cumulative effect of melatonin supplementation, cycle outcomes between the first (no supplementation) and second cycles (melatonin supplementation) of patients who completed two treatment cycles were compared. There were no significant differences in maturation rates, blastocyst rates, and the rate of good-quality blastocysts between the first and second cycles. However, melatonin increased the fertilization rate from 35.1% to 68.2% and the proportion of good-quality embryos from 48.0% to 65.6%; these effects were ascribed to a reduction in oxidative damage.

SAFETY OF MELATONIN

The term nutraceutical implies that a substance has little or no toxicity even when consumed for long periods of time. Although melatonin is considered to have little toxicity, much of the evidence for this comes from

short-term studies (Bruni et al., 2015; Fallah et al., 2014). In attempting to assess its safety as a nutraceutical, in addition to considering short-term toxicity data, a careful evaluation of any information pertaining to melatonin's long-term consumption should be performed. The only adverse report of potential harmfulness of melatonin is a report indicating that, in an isolated system, its metabolite 6-hydroxymelatonin promoted metal-ion–induced lesions to guanine and thymidine residues in DNA (Sakano et al., 2004). Most redox-capable antioxidants such as ascorbic acid and lipoic acid can also facilitate this cycling. Neither short-term treatment nor extended treatment of humans with melatonin has led to symptoms of dependence, tolerance, rebound insomnia, or withdrawal (Lyseng-Williamson, 2012).

p0130 With respect to evaluating the safety of melatonin, it is important to distinguish two possible applications: its low-dose nutraceutical consumption by relatively healthy individuals and the acute administration of high dosages to patients with serious medical conditions. The former involves the oral, possibly chronic, intake of relatively low dosages (0.3–10 mg/day), anticipated to be taken at bedtime or when the induction of nocturnal physiological conditions is desired. Frequently, the goal is the restoration or modulation of normal homeostatic function to compensate for age-related changes or circadian cycle disruption, rather than as treatment of serious disease. Here, safety considerations need to focus on the presence or lack of association of low-dose, possibly chronic, consumption of melatonin with increased incidence of disease or pathology in humans. Although high-quality, long-term clinical studies would provide the best evidence for or against such an association, the lack of such studies means that one has to rely on shorter-term, less powerful ones. Nevertheless, the safety and toxicity of melatonin have been the focus of a number of studies, and this hormone is frequently characterized as being both safe and nontoxic (Garfinkel et al., 2011; Reiter and Korkmaz, 2008; Seabra et al., 2000).

p0135 The safety of melatonin used as a nutraceutical ingredient in food has been challenged on at least one occasion in a Food and Drug Administration (FDA) warning letter (U.S. Food and Drug Administration, 2011). Rather than restate evidence for melatonin's safety, insight from a different perspective may be gained by scrutinizing—at least as an illustrative case—the opposing evidence provided in this document in which it may be presumed that the strongest available references would be selected for characterizing melatonin as being toxic and/or unsafe. The warning letter cited 23 reports that "have raised safety concerns" about melatonin. Of these, the entire text of 21 could be accessed. Surprisingly, terms such as "safe," "safety," "toxic," "toxicity," or "adverse" did not occur at all in these 21 or they occurred in statements actually supporting the safety and/or nontoxicity of melatonin.

p0140 Most of these references provide poor or no support for safety concerns either in humans or in the experimental models studied in rodents or *in vitro*. Among the references cited as raising concerns over melatonin's effects on blood glucose homeostasis, two of the studies (Puchalski et al., 2003; Rasmussen et al., 1999) performed no glucose measurements and mentioned no concerns; a third study in rats (Peschke et al., 2010) found that melatonin induced no change in blood glucose. A fourth study (Cagnacci et al., 2001) reported decreased glucose tolerance and insulin sensitivity in older women treated with 1 mg of melatonin *in the morning*. Typically, long-term supplementation of melatonin is recommended to be used only at bedtime, and not in the morning. As noted by the study's authors, the effects measured may merely represent the induction during the daytime of the reduced nocturnal glucose sensitivity observed in normal, healthy humans. In contrast to the results of this study, beneficial improvements in HbA1c and no such possibly deleterious effects on glucose metabolism were found in a more recent study of diabetic patients (Garfinkel et al., 2011).

p0145 There were two adverse reports among studies cited to support reproductive concerns. Singh et al. (2011) observed *strain-specific* mortality in rat pups when dams received a 250-times higher dose (on a weight basis, for a 75-kg human) than the 3 mg/day frequently recommended for humans. The strain-specificity and high dosage suggest these results may not be relevant to typical human nutraceutical usage. A second study reporting reduced semen quality in men receiving 3 mg/day of melatonin for 3 months (Luboshitzky et al., 2002) is of more concern. However, this reduction occurred in only two of eight subjects, suggesting that only a minority of males may be affected; in any case, a much larger study is required for confirmation. With regard to females, an *in vitro* study merely exposed cultured human granulosa cells to melatonin without expressing any safety implications (Woo et al., 2001). Additional human studies in which no safety concerns were mentioned included those of Okatani et al. (1998) and Cagnacci et al. (1995a,b), but only the abstracts could be checked.

p0150 Rodents were used in seven of the reports cited in the FDA warning letter. In rodents, adverse effects were observed only at melatonin concentrations much higher than the 0.5–10 mg typically suggested for long-term nutraceutical consumption in humans. Moreover, all but one of the rodent experiments were performed on animals that modeled human disease, and thus they may have questionable applicability to healthy humans. For example, Puchalski et al. (2003) studied castrated rats without adverse effects, whereas Wiechmann et al. (2007) reported that under normal conditions, increased retinal cell death and thinned outer nuclear layer in retinas of *non-pigmented* rats were associated with administration of 100-times the melatonin dosage typical of human intake.

p0155 Because melatonin may have greatly different effects in humans compared to rodents in certain circumstances (Peschke et al., 2010), caution needs to be used in applying the results of animal studies when evaluating the safety of melatonin consumption by humans. Tailleux et al. (2002) showed that large amounts of melatonin fed to mice in an atherogenic diet exacerbate plaque formation, but they state that "melatonin had no toxicity on animal health even at this high dose" and express caution by noting that one cannot infer "that high melatonin doses (in mice) would have any deleterious effect on atherosclerosis development in humans." In humans, other vascular studies—those of Cook et al. (2011), Kitajima et al. (2001), Arangino et al. (1999), Cagnacci et al. (1998), and Nishiyama et al. (2001)—expressed no safety concerns. Similarly, authors of a vision-related study in humans (Rufiange et al., 2002) expressed no concerns about melatonin's safety.

p0160 Safety concerns of melatonin may apply when treating patients with specific medical conditions, but not in healthy humans using melatonin at bedtime. Gagné et al. (2009) reported that a single 15 mg dose of melatonin administered during the daytime lowered input to subjects' retinal cones; no safety concerns were raised other than cautioning that melatonin should not be taken during the daytime, and the authors concluded that this effect "may serve to promote (normal) night vision."

p0165 Further suggesting that undesirable effects may not be a concern in healthy individuals, serious adverse events were reported only in studies of small numbers of human subjects with medical conditions. In this regard, Whittom et al. (2010) reported that exogenous melatonin, in conjunction with late-night bright light, exacerbated symptoms in eight patients with restless legs syndrome, and Sheldon (1998) observed an increased incidence of seizures among six children with neurological disabilities who had undergone multiple medical procedures.

p0170 In summary, this examination of references supporting the "safety concerns" raised against melatonin supports the notion that there is little evidence engendering significant generalized concerns about melatonin's safety, particularly with regard to typically recommended dosages of melatonin consumption in healthy humans. There is no doubt that the toxicity of melatonin is extremely low. Thus, even 800 mg/kg body weight has not been proven lethal in experimental animals (Barchas et al., 1967). Few nutraceutical vitamins or cofactors have such a large margin of safety.

s0080

CONCLUDING REMARKS AND FUTURE DIRECTIONS

p0175 The processes underlying the properties of melatonin have not been fully defined. The pleiotropic and interconnected nature of the many effects of melatonin makes the delineation of a smaller number of initiating events difficult. The existence of several specific melatonin receptor types (Singh and Jadhav, 2014) suggests that melatonin primarily has a signaling role that ultimately impacts gene expression. The emergence of an antioxidant and immunomodulatory role resulting from altered gene output could account for many of the reported properties of melatonin. The primary mechanisms of melatonin action involve alteration of gene expression, suggesting very low concentrations of melatonin in the cytosol. Melatonin is an immunomodulator; although it can suppress inflammation, it can also be supportive of immune function. This is in contrast to many anti-inflammatory drugs, which generally act in a nonspecific manner and can also suppress desirable immune responses. In the context of supporting immune function, melatonin appears to have utility as a vaccination adjuvant (Regodón et al., 2009).

p0180 The potential benefits of melatonin are often only partially understood and not wholly delineated. However, the high degree of safety and nontoxic nature of this agent allow it to be safely used in situations in which its utility is probable but not certain. Melatonin is inexpensive and readily available, and this may have limited its commercial testing for health benefits and consequent promotion. There is a large body of evidence suggesting its applicability in a broad range of clinical situations. The very breadth of its apparent beneficial qualities gives a panacea-like impression, and this also may have limited the recognition of its value in the treatment of specific disorders. There is no doubt that the gradually expanding number of positive reports of the use of melatonin in medicine will ultimately lead to greater acknowledgment of the value of this agent in the support of human health.

References

Alamili, M., Bendtzen, K., Lykkesfeldt, J., et al., 2014. Melatonin suppresses markers of inflammation and oxidative damage in a human daytime endotoxemia model. J. Crit. Care 29, 184.e9–184.e13.

Almenrader, N., Haiberger, R., Passariello, M., 2013. Steal induction in preschool children: is melatonin as good as clonidine? A prospective, randomized study. Paediatr. Anaesth. 23, 328–333.

Alp, B.F., Kesik, V., Malkoç, E., et al., 2014. The effect of melatonin on procarbazine induced testicular toxicity on rats. Syst. Biol. Reprod. Med. 20, 1–6.

Arangino, S., Cagnacci, A., Angiolucci, M., et al., 1999. Effects of melatonin on vascular reactivity, catecholamine levels, and blood pressure in healthy men. Am. J. Cardiol. 83, 1417–1419.

Barchas, J., DaCosta, F., Spector, S., 1967. Acute pharmacology of melatonin. Nature 214, 919–920.

Batıoğlu, A.S., Sahin, U., Gürlek, B., et al., 2012. The efficacy of melatonin administration on oocyte quality. Gynecol. Endocrinol. 28, 91–93.

Bondy, S.C., Sharman, E.H., 2010. Melatonin, oxidative stress and the aging brain. In: Bondy, S.C., Maiese, K. (Eds.), Oxidative Stress

in Basic Research and Clinical Practice: Aging and Age-Related Disorders Humana Press, Totowa, NJ, pp. 339–357.

Bruni, O., Alonso-Alconada, D., Besag, F., et al., 2015. Current role of melatonin in pediatric neurology: clinical recommendations. Eur. J. Paediatr. Neurol. 19, 122–133.

Cagnacci, A., Paoletti, A.M., Soldani, R., et al., 1995a. Melatonin enhances the luteinizing hormone and follicle-stimulating hormone responses to gonadotropin-releasing hormone in the follicular, but not in the luteal, menstrual phase. J. Clin. Endocrinol. Metab. 80, 1095–1099.

Cagnacci, A., Soldani, R., Yen, S.S., 1995b. Exogenous melatonin enhances luteinizing hormone levels of women in the follicular but not in the luteal menstrual phase. Fertil. Steril. 63, 996–999.

Cagnacci, A., Arangino, S., Angiolucci, M., et al., 1998. Influences of melatonin administration on the circulation of women. Am. J. Physiol. 274, R335–R338.

Cagnacci, A., Arangino, S., Renzi, A., et al., 2001. Influence of melatonin administration on glucose tolerance and insulin sensitivity of postmenopausal women. Clin. Endocrinol. 54, 339–346.

Cardinali, D.P., Furio, A.M., Brusco, L., 2011. The use of chronobiotics in the resynchronization of the sleep/wake cycle. Therapeutical application in the early phases of Alzheimer's disease. Recent Pat. Endocr. Metab. Immune Drug Discov. 5, 80–90.

Celinski, K., Konturek, P.C., Konturek, S.J., et al., 2011. Effects of melatonin and tryptophan on healing of gastric and duodenal ulcers with *Helicobacter pylori* infection in humans. J. Physiol. Pharmacol. 62, 521–526.

Chahbouni, M., Escames, G., López, L.C., et al., 2011. Melatonin treatment counteracts the hyperoxidative status in erythrocytes of patients suffering from Duchenne muscular dystrophy. Clin. Biochem. 44, 853–858.

Chen, C.Q., Fichna, J., Bashashati, M., et al., 2011. Distribution, function and physiological role of melatonin in the lower gut. World J. Gastroenterol. 17, 3888–3898.

Chern, C.M., Liao, J.F., Wang, Y.H., et al., 2012. Melatonin ameliorates neural function by promoting endogenous neurogenesis through the MT2 melatonin receptor in ischemic-stroke mice. Free Radic. Biol. Med. 52, 1634–1647.

Cook, J.S., Sauder, C.L., Ray, C.A., 2011. Melatonin differentially affects vascular blood flow in humans. Am. J. Physiol. Heart Circ. Physiol. 300, H670–H674.

Costello, R.B., Lentino, C.V., Boyd, C.C., et al., 2014. The effectiveness of melatonin for promoting healthy sleep: a rapid evidence assessment of the literature. Nutr. J. 13, 106.

Cutando, A., López-Valverde, A., Arias-Santiago, S., et al., 2012. Role of melatonin in cancer treatment. Anticancer Res. 32, 2747–2753.

de Matos Cavalcante, A.G., de Bruin, P.F., de Bruin, V.M., et al., 2012. Melatonin reduces lung oxidative stress in patients with chronic obstructive pulmonary disease: a randomized, double-blind, placebo-controlled study. J. Pineal Res. 53, 238–244.

Di Bella, G., Mascia, F., Ricchi, A., et al., 2013. Evaluation of the safety and efficacy of the first-line treatment with somatostatin combined with melatonin, retinoids, vitamin D3, and low doses of cyclophosphamide in 20 cases of breast cancer: a preliminary report. Neuro Endocrinol. Lett. 34, 660–668.

Drobnik, J., Owczarek, K., Piera, L., et al., 2013. Melatonin-induced augmentation of collagen deposition in cultures of fibroblasts and myofibroblasts is blocked by luzindole—a melatonin membrane receptors inhibitor. Pharmacol. Rep. 65, 642–649.

Ekeløf, S.V., Halladin, N.L., Jensen, S.E., et al., 2014. Effects of intracoronary melatonin on ischemia-reperfusion injury in ST-elevation myocardial infarction. Heart Vessels [Epub ahead of print] PMID: 25319673.

AU:3

Fallah, R., Shoroki, F., Ferdosian, F., 2014. Safety and efficacy of melatonin in pediatric migraine prophylaxis. Curr. Drug Saf. [Epub ahead of print] PMID: 24909684.

Forcelli, P.A., Soper, C., Duckles, A., et al., 2013. Melatonin potentiates the anticonvulsant action of phenobarbital in neonatal rats. Epilepsy Res. 107, 217–223.

Fuchs, E., Simon, M., Schmelting, B., 2006. Pharmacology of a new antidepressant: benefit of the implication of the melatonergic system. Int. Clin. Psychopharmacol. 21 (Suppl. 1), S17–S20.

Gagné, A.M., Danilenko, K.V., Rosolen, S.G., et al., 2009. Impact of oral melatonin on the electroretinogram cone response. J. Circadian Rhythms 7, 14.

García-Mesa, Y., Giménez-Llort, L., López, L.C., et al., 2012. Melatonin plus physical exercise are highly neuroprotective in the 3xTg-AD mouse. Neurobiol. Aging 33 (1124), e13–e29.

Garfinkel, D., Zorin, M., Wainstein, J., et al., 2011. Efficacy and safety of prolonged-release melatonin in insomnia patients with diabetes: a randomized, double-blind, crossover study. Diabetes Metab. Syndr. Obes. 4, 307–313.

Gitto, E., Romeo, C., Reiter, R.J., et al., 2004. Melatonin reduces oxidative stress in surgical neonates. J. Pediatr. Surg. 39, 184–189.

Goldberg-Stern, H., Oren, H., Peled, N., et al., 2012. Effect of melatonin on seizure frequency in intractable epilepsy: a pilot study. J. Child Neurol. 27, 1524–1528.

Grossman, E., Laudon, M., Zisapel, N., 2011. Effect of melatonin on nocturnal blood pressure: meta-analysis of randomized controlled trials. Vasc. Health Risk Manag. 7, 577–584.

Gupta, M., Aneja, S., Kohli, K., 2004. Add-on melatonin improves quality of life in epileptic children on valproate monotherapy: a randomized, double-blind, placebo-controlled trial. Epilepsy Behav. 5, 316–321.

Hardeland, R., 2013. Melatonin and the theories of aging: a critical appraisal of melatonin's role in antiaging mechanisms. J. Pineal Res. 55, 325–356.

Hardeland, R., Poeggeler, B., 2012. Melatonin and synthetic melatonergic agonists: actions and metabolism in the central nervous system. Cent. Nerv. Syst. Agents Med. Chem. 12, 189–216.

Hatta, K., Kishi, Y., Wada, K., et al., 2014. Preventive effects of ramelteon on delirium: a randomized placebo-controlled trial. JAMA Psychiatry 71, 397–403.

Hemadi, M., Shokri, S., Pourmatroud, E., et al., 2012. Follicular dynamic and immunoreactions of the vitrified ovarian graft after host treatment with variable regimens of melatonin. Am. J. Reprod. Immunol. 67, 401–412.

Hrenak, J., Paulis, L., Repova, K., et al., 2015. Melatonin and renal protection: novel perspectives from animal experiments and human studies. Curr. Pharm. Des. 21, 936–949.

Jaworek, J., Szklarczyk, J., Jaworek, A.K., et al., 2012. Protective effect of melatonin on acute pancreatitis. Int. J. Inflam. 2012, 173675.

Kashani, I.R., Rajabi, Z., Akbari, M., et al., 2014. Protective effects of melatonin against mitochondrial injury in a mouse model of multiple sclerosis. Exp. Brain Res. 232, 2835–2846.

Katkar, G.D., Sundaram, M.S., Hemshekhar, M., et al., 2014. Melatonin alleviates *Echis carinatus* venom-induced toxicities by modulating inflammatory mediators and oxidative stress. J. Pineal Res. 56, 295–312.

Kitajima, T., Kanbayashi, T., Saitoh, Y., et al., 2001. The effects of oral melatonin on the autonomic function in healthy subjects. Psychiatry Clin. Neurosci. 55, 299–300.

Konturek, P.C., Brzozowska, I., Targosz, A., et al., 2013. Esophagoprotection mediated by exogenous and endogenous melatonin in an experimental model of reflux esophagitis. J. Pineal Res. 55, 46–57.

Kozirόg, M., Poliwczak, A.R., Duchnowicz, P., et al., 2011. Melatonin treatment improves blood pressure, lipid profile, and parameters of oxidative stress in patients with metabolic syndrome. J. Pineal Res. 50, 261–266.

Kücükakin, B., Wilhelmsen, M., Lykkesfeldt, J., et al., 2010. No effect of melatonin to modify surgical-stress response after major

vascular surgery: a randomised placebo-controlled trial. Eur. J. Vasc. Endovasc. Surg. 40, 461–467.

Lahiri, D.K., Ge, Y.-W., Sharman, E.H., et al., 2004. Age-related changes in serum melatonin in mice, higher levels of combined melatonin and melatonin sulfate in the brain cortex than serum, heart, liver and kidney tissues. J. Pineal Res. 36, 217–223.

Lähteenmäki, R., Puustinen, J., Vahlberg, T., et al., 2014. Melatonin for sedative withdrawal in older patients with primary insomnia: a randomized double-blind placebo-controlled trial. Br. J. Clin. Pharmacol. 77, 975–985.

Lemoine, P., Wade, A., Katz, A., et al., 2012. Efficacy and safety of prolonged-release melatonin for insomnia in middle-aged and elderly patients with hypertension: a combined analysis of controlled clinical trials. Integr. Blood Press Control. 5, 9–17.

Leuner, B., Kozorovitskiy, Y., Gross, C.G., et al., 2007. Diminished adult neurogenesis in the marmoset brain precedes old age. Proc. Natl. Acad. Sci. U.S.A. 104, 17169–17173.

Li, Y., Yang, Y., Feng, Y., et al., 2014. A review of melatonin in hepatic ischemia/reperfusion injury and clinical liver disease. Ann. Med. 46, 503–511.

Li, Z., Nickkholgh, A., Yi, X., et al., 2009. Melatonin protects kidney grafts from ischemia/reperfusion injury through inhibition of NF-kB and apoptosis after experimental kidney transplantation. J. Pineal Res. 46, 365–372.

Lissoni, P., Messina, G., Rovelli, F., 2012. Cancer as the main aging factor for humans: the fundamental role of 5-methoxy-tryptamine in reversal of cancer-induced aging processes in metabolic and immune reactions by non-melatonin pineal hormones. Curr. Aging Sci. 5, 231–235.

Liu, C., Hong, T., Shao, M., et al., 2014. Melatonin synergized with cyclosporine A improves cardiac allograft survival by suppressing inflammation and apoptosis. Mol. Med. Rep. 10, 1323–1328.

Liu, J., Wang, L.N., 2012. Ramelteon in the treatment of chronic insomnia: systematic review and meta-analysis. Int. J. Clin. Pract. 66, 867–873.

Luboshitzky, R., Shen-Orr, Z., Nave, R., et al., 2002. Melatonin administration alters semen quality in healthy men. J. Androl. 23, 572–578.

Lyseng-Williamson, K.A., 2012. Melatonin prolonged release: in the treatment of insomnia in patients aged ≥55 years. Drugs Aging 29, 911–923.

Marseglia, L., Aversa, S., Barberi, I., et al., 2013. High endogenous melatonin levels in critically ill children: a pilot study. J. Pediatr. 162, 357–360.

Marseglia, L., D'Angelo, G., Manti, S., et al., 2015. Analgesic, anxiolytic and anaesthetic effects of melatonin: new potential uses in pediatrics. Int. J. Mol. Sci. 16, 1209–1220.

McCleery, J., Cohen, D.A., Sharpley, A.L., 2014. Pharmacotherapies for sleep disturbances in Alzheimer's disease. Cochrane Database Syst. Rev. 3, CD009178.

Modabbernia, A., Heidari, P., Soleimani, R., et al., 2014. Melatonin for prevention of metabolic side-effects of olanzapine in patients with first-episode schizophrenia: randomized double-blind placebo-controlled study. J. Psychiatr. Res. 53, 133–140.

Nickkholgh, A., Schneider, H., Sobirey, M., et al., 2011. The use of high-dose melatonin in liver resection is safe: first clinical experience. J. Pineal Res. 50, 381–388.

Nishihara, T., Hashimoto, S., Ito, K., et al., 2014. Oral melatonin supplementation improves oocyte and embryo quality in women undergoing *in vitro* fertilization-embryo transfer. Gynecol. Endocrinol. 30, 359–362.

Nishiyama, K., Yasue, H., Moriyama, Y., et al., 2001. Acute effects of melatonin administration on cardiovascular autonomic regulation in healthy men. Am. Heart J. 141, 13A–17A.

Ochoa, J.J., Díaz-Castro, J., Kajarabille, N., et al., 2011. Melatonin supplementation ameliorates oxidative stress and inflammatory signaling induced by strenuous exercise in adult human males. J. Pineal Res. 51, 373–380.

Okatani, Y., Okamoto, K., Hayashi, K., et al., 1998. Maternal-fetal transfer of melatonin in pregnant women near term. J. Pineal Res. 25, 129–134.

Patki, G., Lau, Y.S., 2011. Melatonin protects against neurobehavioral and mitochondrial deficits in a chronic mouse model of Parkinson's disease. Pharmacol. Biochem. Behav. 99, 704–711.

Peschke, E., Schucht, H., Mühlbauer, E., 2010. Long-term enteral administration of melatonin reduces plasma insulin and increases expression of pineal insulin receptors in both Wistar and type 2-diabetic Goto-Kakizaki rats. J. Pineal Res. 49, 373–381.

Poluéktov, M.G., Levin, I.I., Boĭko, A.N., et al., 2012. The results of Russian multicenter open-label observational study of the efficacy and safety of мelaxen (melatonin) for the treatment of disordered sleep in patients with chronic cerebral ischemia. Zh. Nevrol. Psikhiatr. Im. S S Korsakova 112, 26–31.

Puchalski, S.S., Green, J.N., Rasmussen, D.D., 2003. Melatonin effect on rat body weight regulation in response to high-fat diet at middle age. Endocrine 21, 163–167.

Qin, L., Wu, X., Block, M.L., et al., 2007. Systemic LPS causes chronic neuroinflammation and progressive neurodegeneration. Glia 55, 453–462.

Ramamoorthy, H., Abraham, P., Isaac, B., 2014. Preclinical efficacy of melatonin in the amelioration of tenofovir nephrotoxicity by the attenuation of oxidative stress, nitrosative stress, and inflammation in rats. J. Basic Clin. Physiol. Pharmacol. 27, 1–13.

Ramirez-Rodriguez, G., Ortiz-Lopez, L., Dominguez-Alonso, A., et al., 2011. Chronic treatment with melatonin stimulates dendrite maturation and complexity in adult hippocampal neurogenesis of mice. J. Pineal Res. 50, 29–37.

Ramirez-Rodriguez, G., Vega-Rivera, N.M., Benitez-King, G., et al., 2012. Melatonin supplementation delays the decline of adult hippocampal neurogenesis during normal aging of mice. Neurosci. Lett. 530, 53–58.

Rasmussen, D.D., Boldt, B.M., Wilkinson, C.W., et al., 1999. Daily melatonin administration at middle age suppresses male rat visceral fat, plasma leptin, and plasma insulin to youthful levels. Endocrinology 140, 1009–1012.

Rathnasamy, G., Ling, E.A., Kaur, C., 2014. Therapeutic implications of melatonin in cerebral edema. Histol. Histopathol. 29, 1525–1538.

Regodón, S., Ramos, A., Morgado, S., et al., 2009. Melatonin enhances the immune response to vaccination against A1 and C strains of *Dichelobacter nodosus*. Vaccine 27, 1566–1570.

Reiter, R., Korkmaz, A., 2008. Clinical aspects of melatonin. Saudi Med. J. 29, 1537–1547.

Rizzo, P., Raffone, E., Benedetto, V., 2010. Effect of the treatment with myo-inositol plus folic acid plus melatonin in comparison with a treatment with myo-inositol plus folic acid on oocyte quality and pregnancy outcome in IVF cycles. A prospective, clinical trial. Eur. Rev. Med. Pharmacol. Sci. 14, 555–561.

Rothman, S.M., Mattson, M.P., 2012. Sleep disturbances in Alzheimer's and Parkinson's diseases. Neuromolecular Med. 14, 194–204.

Rufiange, M., Dumont, M., Lachapelle, P., 2002. Correlating retinal function with melatonin secretion in subjects with an early or late circadian phase. Invest. Ophthalmol. Vis. Sci. 43, 2491–2499.

Sakano, K., Oikawa, S., Hiraku, Y., et al., 2004. Oxidative DNA damage induced by a melatonin metabolite, 6-hydroxymelatonin, via a unique non-o-quinone type of redox cycle. Biochem. Pharmacol. 68, 1869–1878.

Sánchez-Hidalgo, M., Guerrero, J.M., Villegas, I., et al., 2012. Melatonin, a natural programmed cell death inducer in cancer. Curr. Med. Chem. 19, 3805–3821.

Sande, P.H., Dorfman, D., Fernandez, D.C., et al., 2014. The post-treatment with melatonin attenuates experimental ocular inflammation. Br. J. Pharmacol. 171, 5696–5707.

Scheer, F.A., Morris, C.J., Garcia, J.I., et al., 2012. Repeated melatonin supplementation improves sleep in hypertensive patients treated with beta-blockers: a randomized controlled trial. Sleep 35, 1395–1402.

Schwertner, A., Conceição Dos Santos, C., Costa, G., et al., 2013. Efficacy of melatonin in the treatment of endometriosis: a phase II, randomized, double-blind, placebo-controlled trial. Pain 154, 874–881.

Seabra, M.L., Bignotto, M., Pinto Jr., L.R., et al., 2000. Randomized, double-blind clinical trial, controlled with placebo, of the toxicology of chronic melatonin treatment. J. Pineal Res. 29, 193–200.

Seely, D., Wu, P., Fritz, H., et al., 2012. Melatonin as adjuvant cancer care with and without chemotherapy: a systematic review and meta-analysis of randomized trials. Integr. Cancer Ther. 11, 293–303.

Sharman, E.H., Bondy, S.C., 2014. Melatonin as a therapeutic agent for sepsis. In: Srinivasan, V., Gobbi, G.V., Shillcutt, S.D. (Eds.), Melatonin, Therapeutic Agents and their Value CRC Press, Boca Raton, FL, pp. 71–88.

Sharman, E.H., Bondy, S.C., Sharman, K.Z., et al., 2007. Effects of melatonin and age on gene expression in mouse CNS using microarray analysis. Neurochem. Int. 50, 336–344.

Sharman, E.H., Sharman, K.Z., Bondy, S.C., 2011. Extended exposure to dietary melatonin reduces tumor number and size in aged mice. Exp. Gerontol. 46, 18–22.

Sheldon, S.H., 1998. Pro-convulsant effects of oral melatonin in neurologically disabled children. Lancet 351, 1254.

Shokrzadeh, M., Chabra, A., Naghshvar, F., et al., 2014. Protective effects of melatonin against cyclophosphamide-induced oxidative lung toxicity in mice. Drug Res. [Epub ahead of print]. PMID: 24668577.

Siah, K., Wong, R., Ho, K., 2014. Melatonin for the treatment of irritable bowel syndrome. World J. Gastroenterol. 20, 2492–2498.

Singh, H.J., Keah, L.S., Kumar, A., et al., 2011. Adverse effects of melatonin on rat pups of Wistar-Kyoto dams receiving melatonin supplementation during pregnancy. Exp. Toxicol. Pathol. 64, 751–752.

Singh, M., Jadhav, H.R., 2014. Melatonin: functions and ligands. Drug Discov. Today 19 (9), 1410–1418.

Sookprasert, A., Johns, N., Phunmanee, A., et al., 2014. Melatonin in patients with cancer receiving chemotherapy: a randomized, double-blind, placebo-controlled trial. Anticancer Res. 34, 7327–7337.

Srinivasan, V., Pandi-Perumal, S.R., Spence, D.W., et al., 2010. Potential use of melatonergic drugs in analgesia: mechanisms of action. Brain Res. Bull. 81, 362–371.

Tailleux, A., Torpier, G., Bonnefont-Rousselot, D., et al., 2002. Daily melatonin supplementation in mice increases atherosclerosis in proximal aorta. Biochem. Biophys. Res. Commun. 293, 1114–1123.

Tomov, B., Popov, D., Tomova, R., et al., 2013. Therapeutic response of untreatable hepatocellular carcinoma after application of the immune modulators IL-2, BCG and melatonin. Anticancer Res. 33, 4531–4535.

Tresguerres, J.A., Kireev, R., Forman, K., et al., 2012. Effect of chronic melatonin administration on several physiological parameters from old Wistar rats and SAMP8 mice. Curr. Aging Sci. 5, 242–253.

U.S. Food and Drug Administration, 2011. Warning Letters> HBB, LLC dba Baked World 7/28/11. Available from: <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm266129.htm> (February 17, 2015.).

Valtonen, M., Niskanen, L., Kangas, A.P., et al., 2005. Effect of melatonin-rich night-time milk on sleep and activity in elderly institutionalized subjects. Nord. J. Psychiatry 59, 217–221.

Vidor, L., Torres, I., Custódio de Souza, I., et al., 2013. Analgesic and sedative effects of melatonin in temporomandibular disorders: a double-blind, randomized, parallel-group, placebo-controlled study. J. Pain Symptom Manage. 46, 422–432.

Wade, A.G., Farmer, M., Harari, G., et al., 2014. Add-on prolonged-release melatonin for cognitive function and sleep in mild to moderate Alzheimer's disease: a 6-month, randomized, placebo-controlled, multicenter trial. Clin. Interv. Aging 9, 947–961.

Whittom, S., Dumont, M., Petit, D., et al., 2010. Effects of melatonin and bright light administration on motor and sensory symptoms of RLS. Sleep Med. 11, 351–355.

Wiechmann, A.F., Chignell, C.F., Roberts, J.E., 2007. Influence of dietary melatonin on photoreceptor survival in the rat retina: an ocular toxicity study. Exp. Eye Res. 86, 241–250.

Woo, M.M., Tai, C.J., Kang, S.K., et al., 2001. Direct action of melatonin in human granulosa-luteal cells. J. Clin. Endocrinol. Metab. 86, 4789–4797.

Yi, C., Pan, X., Yan, H., et al., 2005. Effects of melatonin in age-related macular degeneration. Ann. N.Y. Acad. Sci. 1057, 384–392.

Zhou, J., Yang, F., Zhou, L., et al., 2014. Dietary melatonin attenuates age-related changes in morphology and in levels of key proteins in globus pallidus of mouse brain. Curr. Aging Sci. 5, 242–253.

NON-PRINT ITEM

Abstract

Melatonin is an indoleamine with the chemical name *N*-acetyl-5-methoxytryptamine and is found in animals, plants, and bacteria. It has endocrine properties in both animals and plants. It is biosynthesized from the neurotransmitter, serotonin, which in turn is made from the essential amino acid, tryptophan. Because its 5-hydroxy and charged amino groups are both acetylated, it is a relatively nonpolar compound. In mammals, melatonin has several roles; it is involved in circadian regulation and modulation of reproductive and immune responses, mood, and aging. It is produced by the pineal gland and several peripheral tissues, notably the gut. Because it is liberated into the bloodstream from the pineal, it can be considered a systemic hormone. Levels of melatonin vary diurnally, being highest during hours of darkness, and also vary throughout the life cycle, being lowest among the elderly. This chapter focuses on recent findings suggesting a variety of therapeutic applications and supporting the safety of exogenously supplied melatonin. The potential molecular mechanisms underlying these potentially clinically beneficial uses are also discussed.

AU:1

Keywords

Melatonin; nutraceutical