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The Therapeutic Potential of Melatonin: A Review of the Science

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Summary

Melatonin is a ubiquitous natural neurotransmitter-like compound produced primarily by the pineal gland. This agent is involved in numerous aspects of the biological and physiologic regulation of body functions. The role of endogenous melatonin in circadian rhythm disturbances and sleep disorders is well established. Some studies have shown that melatonin may also be effective in breast cancer, fibrocystic breast diseases, and colon cancer. Melatonin has been shown to modify immunity, the stress response, and certain aspects of the aging process; some studies have demonstrated improvements in sleep disturbances and "sundowning" in patients with Alzheimer's disease. The antioxidant role of melatonin may be of potential use for conditions in which oxidative stress is involved in the pathophysiologic processes. The multiplicity of actions and variety of biological effects of melatonin suggest the potential for a range of clinical and wellness-enhancing uses. This review summarizes the physiology of melatonin and discusses the potential therapeutic uses of melatonin.

Melatonin is a widely occurring neurotransmitter-like compound derived primarily from the pineal gland. It is also produced in a number of other areas, for example the gastrointestinal tract.[1–3] Once labeled as a master hormone, it has been found to be involved in numerous aspects of biological and physiologic regulation.

Synthesis and Physiologic Role in Humans

Melatonin is an indole hormone, widely distributed in both plant and animal sources, such as human milk,[4] bananas, beets, cucumbers, and tomatoes.[5] Chemically, melatonin is N-acetyl-5-methoxytryptamine, a derivative of serotonin, which in turn is derived from tryptophan. Serotonin is first acetylated by N-acetyltransferase (probably the rate-limiting step) and then methylated by hydroxyindole orthomethyltransferase to form melatonin.[6] Melatonin synthesis depends on intact beta-adrenergic receptor function.[7] Norepinephrine activates the N-acetyltransferase and beta-receptor blockers depress melatonin secretion.[8]

The enzymes of melatonin synthesis are activated and depressed, respectively, by darkness and light. Release of melatonin follows a circadian (*circa*: about; *dias*: a day) rhythm generated by the suprachiasmatic nuclei in response to daylight alterations.

Through melatonin release, the pineal gland maintains the internal clock governing the natural rhythms of body function. This apparent clock-setting property of melatonin has led to the suggestion that it is a "chronobiotic" substance that alters and potentially normalizes biological rhythms and adjusts the timing of other critical processes and biomolecules (hormones, neurotransmitters, etc) that, in turn, exert numerous peripheral actions.[9]

Sleep Disturbances

Studies[10–13] have suggested that a relationship exists among sleep, pineal function, and melatonin levels. Nocturnal melatonin levels and the quality of sleep both decline at puberty.[10] in elderly populations, periods of sleep tend to become shorter and the quality of sleep poorer. Controlled clinical trials have shown that melatonin is effective as a chronobiotic in a number of circadian rhythm sleep disorders.

Jet Lag

When melatonin is taken at the destination, between 10 pm and midnight, it can correct the sleep disturbances, mental inefficiency, and daytime fatigue (cumulatively known as "jet lag") that occur after flights across several time zones.[11–13] The biological rhythm disorganization caused by the rapid change of environment (and associated light/dark cues) apparently can be corrected by melatonin. The benefit is likely to be greater as more time zones are crossed and less for westward flights.[12] However, melatonin taken before travel can actually worsen symptoms as opposed to the benefit of melatonin initiated immediately upon arrival.[13] Parry[14] has reviewed the use and effectiveness of melatonin as a 'dark pulse' at night, with appropriately timed bright light to reduce symptoms of jet lag.

Insomnia

Nocturnal melatonin levels are reduced in primary insomnia.[15] Supplemental melatonin has been used successfully as a hypnotic for delayed sleep-phase syndrome, a type of insomnia characterized by wakefulness and the inability to fall asleep before 2:00 to 3:00 am. In several small studies, 5-mg doses of melatonin given at 10 pm resulted in an advance of the sleep phase (shortening of time to sleep) by about 1.5 hours[16,17] and reduced sleep duration by about 30 minutes,[16] suggesting a lowered sleep requirement as a consequence of improved sleep quality.[18]

Narcolepsy

Melatonin has also been used to alter sleep architecture in narcolepsy, a disorder of disturbed circadian sleep/wake rhythm and rapid-eye-movement (REM) sleep deficit. Changes in REM sleep patterns similar to those of narcolepsy also occur in animals and humans after removal of the pineal gland.[19] Pharmacologic doses of melatonin (50 mg) dramatically increased REM sleep time in both narcoleptics and normals and greatly intensified subjective dream phenomena.[19]

Several studies using varying doses of melatonin (2–20 mg/daily) have reported improved sleep quality, accelerated sleep initiation, and improved sleep maintenance without significantly altering memory, in contrast to benzodiazepines.[20,21]

Sleep Disorders in Children

Melatonin has also been used successfully to treat serious sleep disorders in hyperactive and neurologically compromised children, such as those with attention-deficit/hyperactivity disorder. In 1 study, doses of 2.5–5 mg nightly provided prompt sedation and improved sleep quality, noted in almost all the 15 subjects, with no side effects.[22] Irritability has been reduced, children have tended to become more alert and sociable, and developmental gains have been reported in children treated with melatonin.[22]

Endocrine Function and Immunity

A close, reciprocal relationship exists between the pineal and the pituitary/adrenal axis. Melatonin modulates the activity of this axis and the peripheral actions of corticoids. One study found that melatonin releases vasotocin, which lowers corticoid levels;[13] however, this work has never been confirmed, and recently, another study found that melatonin reduces the basal release of vasotocin.[23] In this latter study, substance P-induced secretion of vasotocin was also found to be inhibited.

The different responses observed in these studies may have been the result of the different doses used. Forsling and Williams[24] elegantly demonstrated that the increase in vasotocin secretion during hypertonic saline infusion and exercise was attenuated by high doses (5 mg) but augmented by low doses (0.5 mg) of melatonin. Pinealectomy causes adrenal hypertrophy, which is reversed by melatonin administration.[25] Some have proposed that melatonin acts as a corticotropin-releasing factor inhibitor, and that disinhibition of the pituitary/adrenal axis in major depression, in which melatonin levels are low,[26] results from a lack of this modulating influence by the pineal gland.[22] Melatonin levels are low in patients with Cushing's disease,[26] a pathologic variety of hyperadrenocorticism.

Melatonin antagonizes several effects of exogenous corticoids: immune depression[28] and hypercatabolism, thymic involution, and adrenal suppression.[29] These findings have led to the suggestion that melatonin might work as an antiadrenocortical or antistress factor.[29] The melatonin/corticoid relationship is significant because chronic hypercortisolemia has been linked to several aspects of aging and age-associated phenomena, including glucose intolerance, atherogenesis, impaired immune function, and cancer.[30]

In addition to high absolute levels of corticoids, disorganization of the normal rhythm of corticoid release is also pathogenic. Corticoids are normally high in the early morning and daytime, and low at night. Properly timed exogenous melatonin may entrain or reorganize, this critical endocrine rhythm, resulting in long-term systemic benefit. Indeed, the immune-enhancing and anticorticoid effects of melatonin, or putative mediators of melatonin action, appear to depend on nocturnal administration.[28,31] This may represent an integral immune-recovery mechanism by which melatonin acts as a kind of buffer against the harmful effects of stress on immune homeostasis.[28]

Beta-adrenoceptor blockers, which depress melatonin secretion, exert immunosuppressive effects, but only when given in the evening.[32,33] This is when blood melatonin (and the immunoenhancing effect of melatonin) is highest. Exogenous melatonin reverses beta-blocker-induced immunosuppression and enhances immune parameters in animals. A preliminary report of patients with AIDS who took melatonin 20 mg daily in the evening revealed uneven but generally beneficial effects on immune parameters.[34] It has been recommended that the dose be timed not only periodically within each day (at night only) but also periodically within the month, with treatment periods of 3–4 weeks, followed by a week-long "washout" period.[33]

Immunomodulatory effects of melatonin were also observed recently in healthy subjects and patients with bronchial asthma.[35] Melatonin increased production of interleukin (IL)-1, IL-6, and tumor necrosis factor-alpha, indicating the possibility of an adverse effect of exogenous melatonin in patients with asthma. On the other hand, in a model of adjuvant-induced arthritis, both prophylactic and therapeutic melatonin administrations inhibited the inflammatory response.[36] This inhibition was accompanied by enhanced thymocyte proliferation and IL-2 production by melatonin. In another animal study, melatonin was shown to possess both cellular and humoral immunoenhancing effects, and immune responses were augmented even in the absence of previous immunosuppression.[37] Melatonin-receptor immunoreactivity has also been detected in the human eye,[38] the physiologic function of which remains unclear.

Predictably, melatonin-induced corticoid antagonism and immune enhancement may not always be desirable. Melatonin should be used cautiously, if at all, in patients with autoimmune conditions and in those with known or suspected adrenocortical insufficiency. The effects of melatonin on the immune system are complex, occasionally contradictory, and depend on several factors, including the dose of melatonin, the immune status of the animal (as well as its age, sex, and species), the season during which the immune system is studied, circadian rhythm of immunity, pineal gland status, and presence of a stressful condition.[39]

Cancer

It has been suggested that the steady rise in the incidence of cancer in developed countries during the last 100 years is caused by the routine, artificial extension of the photoperiod by electric lights, or "light pollution."[40] A long photoperiod results in depressed melatonin secretion during the night. In animals, melatonin inhibits the incidence of chemically induced tumors, which is increased by pineal suppression (long light phase) or pinealectomy.[41] Pinealectomy stimulates and/or melatonin inhibits the growth and sometimes the metastasis of experimental cancers of the lung, liver, ovary, pituitary, and prostate as well as melanoma and leukemia.[42]

Breast cancer

Clinical evidence suggests a role for melatonin in the prevention and even the treatment of breast cancer.[43] For example, the circadian amplitude of melatonin was reduced by more than 50% in patients with breast cancer vs those with nonmalignant breast disease,[44] and high melatonin levels have been found in morning urine samples of breast cancer patients,[45] suggesting circadian disorganization. Melatonin downregulates estrogen receptors; inhibits estrogen-stimulated, breast cancer growth; and complements the oncostatic action of antiestrogen drugs (tamoxifen), leading to the suggestion that melatonin is a 'natural antiestrogen.'[46] Moreover, a synergy has been demonstrated between melatonin and all-*trans*-retinoic acid (ATRA), allowing the use of lower doses of ATRA and thus avoiding its adverse effects.[47]

The molecular mechanisms of melatonin have also begun to be better understood. Melatonin has been shown to shift forskolin- and estrogen-induced elevation of cyclic adenosine monophosphate (cAMP) levels by 57% and 45%, respectively,[48] thereby affecting signal-transduction mechanisms in human breast cancer cells.

Anisimov and coworkers[49] have found that constant treatment with melatonin reduced the incidence and size of breast carcinomas as well as lowered the incidence of lung metastasis, but interrupted treatment-promoted, mammary carcinogenesis in transgenic mice. They further observed that the life span of the group receiving interrupted treatment was shorter; however, this outcome could be attributed to the transgenic nature of mice used, but this needs further evaluation.

Prostate and Colorectal Cancers

Melatonin may also play a special role in prostate and colorectal cancers. Circadian amplitude of melatonin is reduced by two thirds in patients with prostate cancer as compared with those who have benign prostate disease,[44] and similar phenomena have been observed in patients with colorectal cancer.[50] In prostatic carcinoma, melatonin exerts complex interactions with androgen receptors and affects intracellular trafficking; melatonin does not affect cell growth in the absence of dihydrotestosterone.[51] In 1 study, 54 patients with metastatic solid tumors, primarily lung and colorectal, received intramuscular melatonin, 20 mg daily at 3 pm for 2 months and then 10 mg daily. This regimen resulted in stabilization of the disease and improved quality of life for about 40% of the recipients.[52] The antiproliferative and proapoptotic actions of melatonin on experimental colon carcinoma are probably mediated by melatonin MT(1) and MT(2) receptors.[53]

In another study, melatonin 10–50 mg daily at 8 pm potentiated IL-2 immunotherapy of pulmonary metastases.[33] As with melatonin therapy in patients with AIDS, the study encouraged treatment periods of 3–4 weeks with a 1-week washout.

Melatonin injections have been found to stimulate tumor growth if given in the morning, have no effect when given in midafternoon, and have a retarding effect in the evening.[45,46]

Some have suggested that melatonin be administered to patients at earlier stages of cancer, in parallel with standard oncologic treatment regimens.[54] However, some questions remain concerning the anticancer effects of melatonin,[55] and data from stringent, large, randomized clinical trials are required before melatonin can be universally accepted as an anticancer drug.

Brain Function, Neuropsychiatry, and Behavior

Seizures

The pineal, acting primarily but not exclusively through melatonin, is proposed to be a "tranquilizing organ" that promotes homeostatic equilibrium.[7] Melatonin stabilizes the electrical activity of the central nervous system and causes rapid synchronization of the electroencephalogram.[9] By contrast, pinealectomy predisposes animals to seizures.[9] Recent evidence from experimental work suggests that melatonin provides anticonvulsant activity in various models of epilepsy. In mice, intracerebroventricular administration of melatonin protected against seizures induced by kainate, glutamate, and N-methyl-D-aspartate;[56] however, it was ineffective against pentylenetetrazol-induced seizures, thereby suggesting a potential role in grand mal epilepsy. Similarly, melatonin antagonized the seizure-producing effects of cyanide[57] and ferric chloride.[58] The anticonvulsant effect of melatonin has also been demonstrated in amygdala-kindled rats.[59]

Some of these experimental data have been corroborated by clinical studies in patients with epilepsy. Bazil and colleagues[60] found melatonin levels to be reduced in patients with intractable epilepsy. In a study of 6 children with intractable seizures, administration of 3 mg of oral melatonin 30 minutes before bedtime in addition to the antiepileptic regimen led to clinical improvement in seizure activity in 5 of the children, by parent report.[61] However, because of the paucity of well-controlled studies, melatonin cannot, as yet, be recommended in any form of epilepsy, although it may have some role as an adjuvant therapy for children with intractable seizures.

Depression

Nocturnal melatonin levels are low in subjects with major depressive disorder and panic disorder.[62,63] This is particularly marked in subjects with abnormal pituitary-adrenal responses to exogenous corticoids (abnormal dexamethasone suppression)[27] who also have disturbed corticoid-secretion patterns. Healthy individuals with a dysthymic disposition (mild or episodic depression) also had lower-than-normal nocturnal melatonin levels[27] as did subjects with melancholic depression.[64] By contrast, higher-than-normal melatonin levels have been observed in manic subjects during the manic phase.[64] More significant than changes in the absolute melatonin level at any given time is the amplitude of the circadian melatonin rhythm, which is blunted in patients with depression and becomes normal on recovery.[65]

The link among melatonin levels, pineal function, and mood disorders is strengthened by epidemiologic and chronobiological evidence. Both seasonal affective disorder (SAD) and classic "nonseasonal" depressions demonstrate a marked seasonal incidence with peaks in the fall and spring, respectively.[66,67] This coincides with the troughs of the circannual melatonin rhythm.[68]

The requirement of intact beta-receptor function for melatonin synthesis and the stimulatory effect of norepinephrine on melatonin synthesis and release[7] point toward a theoretic relation of melatonin to depression. Several of the tricyclic antidepressants dramatically increase melatonin synthesis in humans.[69,70] In one study, 8 weeks of clomipramine treatment resulted in a lowering of melatonin levels at 12 am, 2 am and 4 am as well as an elevation of melatonin levels at 8 am, 2 pm, and 8 pm.[70] Thus, it is possible that the relation of norepinephrine action to affective disorders is mediated in part by effects on melatonin synthesis. Tricyclics often exert sedative effects and for this reason are often administered at night — an appropriate time to enhance melatonin rhythm amplitude. Furthermore, beta-receptor blockers depress melatonin secretion[8] and can cause neuropsychiatric problems, such as nightmares, insomnia, lassitude, dizziness, and depression.[71]

Brain serotonin levels rise after melatonin administration,[72] which may be significant because serotonin has been linked with an array of neuropsychiatric phenomena.[73–77] Diminished central serotonin, as indicated by low levels of the serotonin marker 5-hydroxy indole acetic acid (5-HIAA) in cerebrospinal fluid, is associated with impulsiveness, aggression and autoaggression,[72–75] alcoholism,[76] compulsive gambling, overeating, and other obsessive-compulsive behaviors.[22] Support of the serotonin system with serotonergic nutrients or drugs can elevate mood, reduce aggression, increase the pain threshold, reduce anxiety, relieve insomnia, improve impulse control, and ameliorate obsessive-compulsive syndromes.[77–79]

Endogenous Depression

Classic endogenous or "nonseasonal" depression is characterized by insomnia (especially early-morning awakening), appetite suppression and weight loss, and advanced onset of nocturnal melatonin release; these individuals are probably phase-advanced ("morning people"), although not very effectively.[80] Classic depression typically begins in the spring and persists through the summer,[67] the period of light-phase lengthening. This group may benefit from an induced phase delay (and light-phase shortening) effected by bright light exposure in the evening,[81] later rising with avoidance of bright light in the morning and melatonin administration (especially delayed-release melatonin) in the late evening or immediately before bed. Melatonin administration that prolongs the nocturnal melatonin rise may exacerbate SAD[82] and bipolar and classic depression.[83] In this latter study,[83] large quantities (> 1 g/day) of melatonin were taken in divided doses throughout the day, thus abolishing the normal, daily melatonin rhythm.

The use of large doses of melatonin in the morning and early afternoon represents exceedingly poor design for a study examining the hormone's effects on depression (or any other condition), especially when one considers the clear evidence that blunted amplitude and disturbed melatonin rhythm play a role in depression, rather than low absolute levels at any given time.[65,84] Thus, melatonin should be used only with caution in patients with depression and should always be appropriately timed and in conjunction with light therapy and sleep-phase change. Disruption of normal circadian rhythm by poorly timed melatonin administration can logically worsen depression.

In a recent study of postmenopausal women, melatonin administration led to a significant mitigation of depression.[85] In a large-dose-range trial, agomelatine, a melatoninergic agonist, was found to alleviate depression as well as anxiety.[86] However, another study found that the addition of melatonin to ongoing fluoxetine treatment had no beneficial effect on the 3-month outcome, postelectroconvulsive therapy.[87]

Seasonal Affective Disorder

SAD is characterized by late sleep, morning hypersomnia, increased appetite, and retarded onset of nocturnal melatonin release. SAD subjects are probably phase-delayed ("night people").[74,75] SAD typically begins in the fall and persists through the winter,[67] during the period of light-phase shortening. SAD sufferers may benefit from induced-phase advance (and light-phase lengthening), effected by bright light exposure in the morning (especially predawn), early rising (to the point of partial morning sleep deprivation, eg, rising at 3–4 am), and melatonin administration before bed, which should be early in the evening.[88]

The relationship between depression and light deprivation has been reviewed.[89,90] Phototherapy as an adjuvant in depression may accelerate responses to antidepressants among patients with depression.[91] Moreover, melatonin secretion has been shown to be wavelength-dependent as exposure to monochromatic light at 460 nm produced a 2-fold greater circadian phase delay.[92]

Antioxidant Uses

The antioxidant effects of melatonin have been well described[93–95] and include both direct as well as indirect effects. The mechanism of antioxidant effects has also been evaluated. Melatonin administration leads to increased expression of the antioxidant enzymes superoxide dismutase and glutathione peroxidase[96]

Central Nervous System

Melatonin has been found to prevent cell death and methylphenyltetrahydropyridine- (MPTP) induced damage to the substantia nigra in experimental parkinsonism, and thus prevented disease progression in these animals.[97] Melatonin pretreatment reduced cerebral infarct size and edema after middle cerebral artery occlusion and ischemia-reperfusion injury in rats.[98] Melatonin has been suggested as a candidate neuroprotective compound for patients with amyotrophic lateral sclerosis.[99] Furthermore, a study examining the neuroprotective effects of melatonin in various regions of the central nervous system demonstrated an antioxidant effect of melatonin in the total spinal cord, optic nerve, brain, and spinal cord white matter, with the most potent effects seen in the spinal cord white matter.[100]

In a rodent model of Alzheimer's disease, melatonin reduced plasma homocysteine and lipid levels,[101] and the investigators suggested that the antioxidant effect of melatonin may have been responsible for these results. In patients with Alzheimer's disease, cerebrospinal fluid melatonin levels have been found to be significantly reduced.[102] In a study of 14 patients at various stages of Alzheimer's disease,[103] melatonin supplementation for 22–35 months improved sleep and significantly reduced the incidence of "sundowning." Furthermore, patients experienced no cognitive or behavioral deterioration during the study period. The neuroprotective effects of melatonin are not mediated by membrane melatonin receptors and, thus, they may result from the antioxidant and antiamyloidogenic property of melatonin.[104]

Cardiovascular System

Cardioprotective activity,[105–109] mediated by antioxidant effects of melatonin,[109] has been observed in experimental models of myocardial ischemia-reperfusion[105,107] and myocardial infarction.[105,106] Melatonin reduced infarct size, suppressed the frequency as well as duration of ventricular tachycardia and fibrillation, and improved survival in these models.

One review noted that melatonin has cut cholesterol levels by 38% in human subjects and has reduced blood pressure and catecholamine levels, perhaps via relaxation of smooth muscles in aortic walls.[108] Melatonin also inhibits copper-induced oxidation of low-density lipoprotein (LDL),[109] thereby potentially contributing to an antiatherosclerotic effect. A study of 5 patients with cardiac syndrome X found that nocturnal melatonin levels were markedly reduced.[110]

Gastrointestinal System

Gastroprotective effects of melatonin have been observed in various models of gastric ulcers at several laboratories, including ours.[111–113] These effects may also be related to the antioxidant effects of melatonin. In experimental models of acute pancreatitis, melatonin has shown beneficial effects.[114,115] Other diseases for which melatonin may be added to existing therapies include irritable bowel syndrome, ulcerative colitis, and diarrhea.[3]

Renal Diseases

Melatonin has been found to be protective against glycerol-induced renal failure because of its antioxidant effect.[116] Melatonin also reduced interstitial renal inflammation and improved hypertension in spontaneously hypertensive rats.[117] More evidence from well-conducted clinical trials is required before a final recommendation can be made.

Miscellaneous Conditions

An animal study found melatonin and vitamins C and E to be protective against lung injury.[118] A series of 3 cases reported that melatonin improved platelet counts in patients with idiopathic thrombocytopenic purpura.[119] Melatonin was also found to be useful in cisplatin-[120] and cyclosporine-[121] induced acute renal injury, doxorubicin-induced cardiotoxicity[122] and a number of other drug-induced diseases. The beneficial effects of melatonin in this field have been reviewed.[123]

Comparison of Melatonin With Vitamins C and E in Animal Models

A few studies have compared the antioxidant effects of melatonin with other antioxidants.[124–126] Melatonin has been found to be more efficient than vitamin C in reducing the extent of oxidative stress in an experimental model of Alzheimer's disease.[124] In another animal model, melatonin was found to be at least as effective as a combination of vitamins C and E in reducing the oxidative stress induced by chlorpyrifos-ethyl in rats.[125] Melatonin was also found to reduce markers of oxidative stress more significantly than vitamin E or N-acetylcysteine against acetaminophen toxicity in mice.[126]

The antioxidant benefit of pharmacologic melatonin therapy has been questioned, however.[127] Moreover, in a 2003 study,[128] in iron-free medium, melatonin did not scavenge hydrogen peroxide and was found to be devoid of direct antioxidant effects. Only placebo-controlled, randomized clinical trials with hardcore clinical end points will provide a definite answer.

Antiaging Hormone

Studies linking melatonin loss to age-related phenomena and the case for melatonin as an antiaging substance have been highlighted in review articles.[9,129] One proponent of this hypothesis suggests that "the Melatonin Deficiency Syndrome is perhaps the basic mechanism through which aging changes can be explained."[129] Indeed, some believe that the data thus far support the possibility that supplemental melatonin may be beneficial.[130]

An experimental study found significant declines in plasma melatonin levels in aged ring doves.[131] In addition, the capacity of the animals for ingestion and destruction of *Candida albicans* and phagocytosis was reduced by aging and restored by exogenous administration of melatonin.

Melatonin levels decline with age in humans,[132] and the nocturnal melatonin peak is almost completely lost.[133] Because of the close reciprocal relation of melatonin and corticoids, this loss of melatonin rhythmicity may be responsible for the pituitary/adrenal axis disinhibition that has been described as a characteristic of aging. The adrenals of elderly humans are apparently hypersensitive to adrenocorticotropic hormone, and midnight corticoid levels (low in youth) are markedly elevated in old age.[134] The effects of melatonin on both the release of corticoids and their peripheral effects, the pathogenic conditioning influence of corticoid excess, and the phasic inhibitory influence of melatonin on the pituitary/adrenal axis have been discussed. Modification of corticoid-related phenomena could explain much of melatonin's apparent antiaging and other beneficial actions.

Despite the evidence linking lowered levels of melatonin with aging, the decline may not be so dramatic in reality. That is why melatonin cannot be unequivocally recognized as a substance that delays aging, although some of its actions may be beneficial to the process of aging.[135]

Blindness (which increases melatonin levels by virtue of effective constant darkness) and melatonin administration both increase the life span of rats.[130,136] However, in many cases melatonin levels are free-running, and in one study, low doses (0.5 mg) of melatonin entrained a blind person with free-running melatonin rhythms.[137]

Toxicology and Potential for Harm

The acute toxicity of melatonin as seen in both animal and human studies is extremely low. Melatonin may cause minor adverse effects, such as headache, insomnia, rash, upset stomach, and nightmares. In animals, an LD50 (lethal dose for 50% of the subjects) could not be established. Even 800 mg/kg bodyweight (high dose) was not lethal.[138] Studies of human subjects given varying doses of melatonin (1–6.6 g/day) for 30–45 days, and followed with an elaborate battery of biochemical tests to detect potential toxicity, have concluded that, aside from drowsiness, all findings were normal at the end of the test period.[139,140]

Animal studies suggest that melatonin can downregulate the pituitary/gonadal axis resulting in hypogonadism and/or delayed puberty. However chronic administration of low-dose melatonin in men did not alter blood levels of testosterone or luteinizing hormone.[141] One case of extremely high melatonin levels associated with delayed puberty and hypogonadism has been reported.[142] Pubertal development and resolution of the hypogonadism occurred spontaneously as melatonin levels declined over several years. Recent experimental evidence demonstrates that melatonin reduces sperm motility[143] and that long-term administration inhibits testicular aromatase levels.[144]

Melatonin has also been suggested for use as a contraceptive for women,[145] which might raise the question of whether melatonin damages the female reproductive system. Notably, no side effects were reported in a report of a phase 2 clinical trial in which 1400 women were treated with 75 mg of melatonin nightly for 4 years.[145]

Preliminary animal studies suggest that melatonin may accelerate the development of autoimmune conditions.[146] Melatonin transiently exacerbated neurologic symptoms in 1 patient with multiple sclerosis.[147]

Although melatonin is a potential adjunctive agent in the treatment of cancer and immune deficiency, poorly timed administration can produce opposite effects. Melatonin injections given in the morning stimulate tumor growth,[46,148] whereas the same doses in midafternoon have no effect but in the evening have a retarding effect. And although some people with depression may suffer from a "low melatonin syndrome,"[22] melatonin administration that unduly prolongs the nocturnal melatonin rise, or that is given throughout the day, may exacerbate SAD[82] and bipolar and classic depression.[83] Finally, animal studies have shown that moderately large doses of melatonin (equivalent in one study to about 30 mg in adult humans) increased light-induced damage to retinal photoreceptors.[149]

There is also some concern regarding increased atherosclerosis in the aorta in hypercholesterolemic rats caused by melatonin.[150] Moreover, in these animals LDLs were less well recognized by LDL-receptor metabolic pathways when melatonin was administered.

Melatonin is widely available as an over-the-counter supplement marketed by different companies. These supplements may not be similar in dosage and/or composition, and some of them may contain additional vitamins. Moreover, melatonin may interact with other over-the-counter drugs, although such interactions have not been systematically evaluated and, therefore, remain unreported.

Clinical Evaluation of the Patient

No definitive guidelines have been formulated for clinical evaluation of patients with low melatonin levels, in large part because a "melatonin deficiency syndrome" has not yet been defined as an independent entity. The secretion of melatonin is usually detected by analyzing the serum or salivary levels.[151] The salivary levels are considered equivalent to serum levels except in the elderly or in patients with dry mouth.[152] In the first situation, the validity, and in the second situation, the feasibility of salivary melatonin levels are compromised. If the treating physician suspects that melatonin deficiency may be responsible for a patient's symptoms, it is tempting to consider the possibility of exogenous administration of melatonin. However, we must await more substantive clinical evidence before any precise recommendations can be made.

Conclusion

Melatonin has the potential to be of use in a large number of disorders of different etiologies. However, unequivocal evidence of its efficacy has been established only for a few conditions — jet lag, depression, and insomnia. It has not yet been possible to effectively determine the immunomodulatory effects of melatonin because both immunosuppression and immunoenhancement have been observed in different settings. The oncostatic use of melatonin may become a part of an anticancer drug regimen. An anticonvulsant effect of melatonin has been consistently observed in animal models, but proof from well-controlled clinical trials is still lacking.

Some evidence suggests an antioxidant role of melatonin with the possibilities of beneficial effects in Alzheimer's disease; parkinsonism; and cardiovascular, gastrointestinal, and renal disorders. Definite evidence for the role of melatonin as an antiaging compound has not yet been obtained.

Melatonin can cause adverse effects, and long-term safety data are lacking. Furthermore, no information is available concerning the possibility of interactions with either prescription or nonprescription medications. Available in many countries as a nutritional adjunct, melatonin has managed to evade the drug-regulatory authorities. This has led to unregulated and uncontrolled use of melatonin, which must be prevented unless and until clear benefits are demonstrated.

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