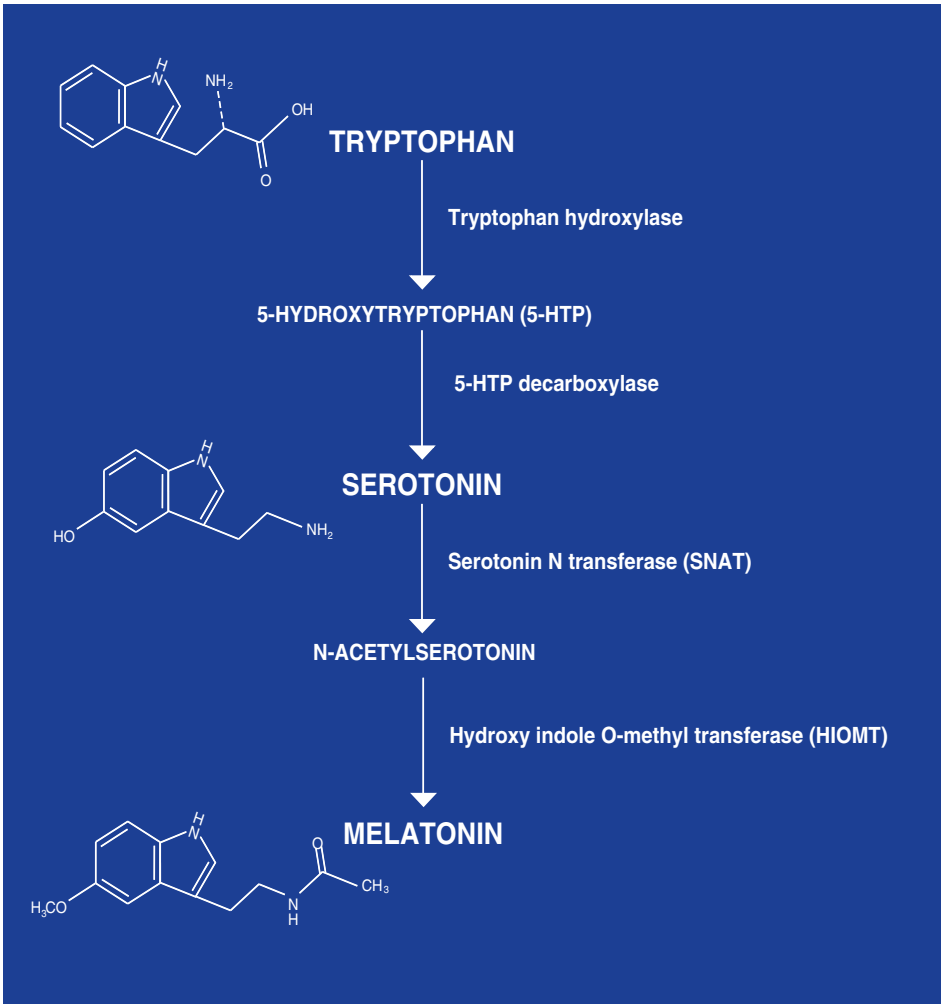

Melatonin

Introduction

Melatonin, the primary hormone of the pineal gland, acts as a powerful "chronobiotic," maintaining normal circadian rhythms. In patients with sleep disorders and altered circadian rhythms, such as occur in jet lag, night shift work, and various neuropsychiatric disorders, oral administration of melatonin can provide the necessary resynchronization of those cycles, at dosages ranging from 0.3 to 8 mg. Synthesis of melatonin from the amino acid tryptophan is decreased by exposure to magnetic fields and by the aging process. Melatonin is a potent scavenger of free radicals and exerts direct inhibition of cancer growth. Various cancer types have been shown to be responsive to oral melatonin (10-50 mg daily), including breast cancer, non-small-cell lung cancer, metastatic renal cell carcinoma, hepatocellular carcinoma, and brain metastases from solid tumors. Melatonin has also been reported to lower LDL- and total cholesterol levels. Abnormally low melatonin levels have been theorized to be a factor in multiple sclerosis, coronary heart disease, epilepsy, and postmenopausal osteoporosis. These reports, while preliminary, serve to further illustrate the wide range of potential effects exerted by melatonin.

Biochemistry

Endogenous synthesis of melatonin displays a pronounced circadian rhythm. The production of melatonin (N-acetyl-5-methoxytryptamine) from the amino acid tryptophan is primarily nocturnal and is controlled by exposure to cycles of light and dark, independent of sleep. Melatonin synthesis is inhibited by exposure to light; production is stimulated during periods of darkness by way of a multi-synaptic neural pathway connecting the pineal gland to the external environment via the retina.[1] Serum melatonin levels are highest prior to bedtime. In addition to the pineal gland, some melatonin is synthesized in the retina,[2] bone marrow,[3] gastrointestinal tract, and bile.[4] The gut appears to produce proportionally more melatonin than the pineal gland.[5]

Melatonin secretion varies from individual to individual. In patients considered to be "high secretors," peak nighttime melatonin levels can range from 54-75 pg/mL; "low secretors" typically have peak nighttime levels in the range of 18-40 pg/mL.[6] Numerous publications claim endogenous melatonin secretion decreases with age.[7,8] However, other research indicates this may not be true in most elderly adults. Zeitzer et al found no significant difference in plasma melatonin concentrations between a group of 34 healthy elderly subjects (ages 65-81 years,) and 98 healthy drug-free young men (ages 18-30 years). The difference between the results of this study and others previously published might be due to the extensive medical screening of patients. Subjects on melatonin-suppressing medications commonly used by the elderly (NSAIDS, beta-blockers, aspirin, etc.), subjects consuming alcohol, caffeine, and nicotine, and those with other medical conditions were excluded from the Zeitzer study.[9]

Pharmacokinetics

Endogenous Melatonin

Endogenous melatonin synthesized by the pineal gland is released quickly into the bloodstream and then into other bodily fluids, including cerebral spinal fluid (CSF),[10] saliva,[11] and bile.[12] Melatonin levels in bile and CSF are several times higher than levels seen in serum.[10,12] Of the melatonin found in the bloodstream, 50-75 percent is bound reversibly to albumin and alpha$_1$-acid glycoprotein, proteins found in the plasma.[13,14] Serum melatonin half-life is estimated to be 30-60 minutes, and first-pass metabolism in the liver results in a clearance rate of 90 percent.[14,15] Hepatic enzymes convert melatonin to 6-hydroxymelatonin. Seventy percent of 6-hydroxymelatonin is subsequently bound to sulfate (6-sulfatoxymelatonin) with six percent bound to glucuronide and excreted in the urine.[15]

Exogenous Melatonin

Orally administered melatonin is rapidly absorbed and peak serum levels are observed at 60-150 minutes. Peak concentrations after oral dosing are significantly higher (350-10,000 times) than those seen with endogenous melatonin secretion.[16,17] Melatonin bioavailability from an oral dose ranges from 10-56 percent.[18] Exogenous melatonin is metabolized and excreted via the same pathways as endogenous melatonin. The half-life of exogenous melatonin is 12-48 minutes.[16,19]

Mechanisms of Action

Hypnotic/Sedative

Melatonin administration, regardless of dosage time, exerts a hypnotic and sedative effect when given in doses of 0.3-5.0 mg (close to the physiologic range of endogenous melatonin). If taken before onset of endogenous melatonin secretion, even low doses can induce sleep.[20] Melatonin is thought to potentiate the affects of gamma-aminobutyric acid (GABA) via direct interaction with GABA receptors.[21,22] Research indicates melatonin exerts a sleep-promoting action by accelerating sleep initiation, improving sleep maintenance, and marginally altering sleep architecture.

Phase-shifting

Both endogenous and exogenous melatonin can shift circadian rhythms if given at the appropriate time of day. Retinal light exposure appears to regulate the circadian rhythm of melatonin secretion. When trying to advance the sleep phase, melatonin should be given 1-2 hours before 9 pm and when trying to delay the sleep phase, melatonin should be given in the early morning.[23] Melatonin administration also results in a slight decrease in core body temperature, a factor contributing to sleep.[24] The mechanism behind this effect is not known, but may be attributed to melatonin's effect on the hypothalamus and its thermoregulatory centers.[25]

Immunomodulation

Melatonin appears to have several immunomodulating effects. Via melatonin receptors, it is capable of stimulating cytokine production by T-helper 1 lymphocytes, including interleukin-2 (IL-2) and gamma-interferon.[26] Melatonin may also potentiate the immunostimulatory properties of IL-2 (as evidenced in cancer patients) by increasing T lymphocytes, natural killer cells, and eosinophils.[27,28] Depressed circadian biosynthesis of melatonin has also been linked to reversible immunosuppression.[29]

Antiproliferative

Melatonin has shown direct inhibition of cancer growth *in vitro* in the human breast cancer cell line MCF-7[30] and in animal models.[31] Melatonin has been shown to inhibit mitotic cell division during metaphase,[32] aid in cancer cell differentiation, and decrease metastatic activity of certain cancer cell types via changes in cell surface adhesion molecules and intercellular communication. Melatonin also directly induces apoptosis in some cancer cells.[33]

Antioxidant

Melatonin is a powerful scavenger of reactive oxygen species (ROS), including the hydroxyl[34,35] and peroxyl radicals,[36] as well as singlet oxygen,[37] and nitric oxide.[38] In addition to scavenging ROS, melatonin stimulates the antioxidant enzymes superoxide dismutase, glutathione peroxidase, and catalase.[39-41] Melatonin reduces lipid peroxidation *in vivo* more efficiently than either vitamins C or E.[42,43]

Hormonal Effects

Exogenous melatonin has an affect on numerous hormones. It has been shown to enhance luteinizing hormone levels in women during the follicular phase of the menstrual cycle,[44] and cortisol levels in older (but not younger) women.[45] Both endogenous and exogenous melatonin enhance prolactin secretion without affecting its circadian rhythm,[46] and exogenous melatonin decreases plasma progesterone and estradiol levels in healthy women.[47] Glucose tolerance and insulin sensitivity are reduced by melatonin. Melatonin may increase insulin levels via a direct effect on the pancreas.[48,49]

Other Mechanisms

Research has also demonstrated melatonin's anti-inflammatory properties via down-regulation of proinflammatory cytokines[50] and inhibition of nitric oxide and methylenedioxyamphetamine (MDA) production.[51] In addition, melatonin may protect the gastric mucosa against ulceration and ethanol insult via its effects on prostaglandins;[52] possess anticonvulsant properties via altered GABA neurotransmission;[53] and act as a hypotensive agent by relaxing smooth muscle in the aortic wall, by direct effect on the hypothalamus, or because of its antioxidant properties.[54]

Clinical Indications

Sleep Disturbances

The primary physiological role identified for melatonin is its ability to influence circadian rhythms. When administered in pharmacological doses, melatonin acts as a powerful "chronobiotic," maintaining synchronicity.[55] Because the hours of highest melatonin secretion correlate to normal hours of sleep, the hormone has been investigated for use in sleep disorders. Attenburrow et al demonstrated that patients with insomnia have decreased nocturnal melatonin secretion.[56]

Research has investigated the use of both high[57] (75 mg at 10 pm) and low[58-60] (0.1-2.0 mg nightly) doses of melatonin in the treatment of insomnia. Subjects receiving melatonin (regardless of dose) had significant increases in total sleep time as well as improved daytime alertness and decreases in time needed to fall asleep, compared to placebo.

The aforementioned research is confirmed by more recent studies. Rajaratnam et al demonstrated low doses of melatonin (1.5 mg daily for eight days at 4 pm) to eight healthy men without sleep complaints resulted in a significant increase in percentage of stage 2 EEG sleep, as well as an advance in the timing of sleep.[61] Another study using higher doses of melatonin (10 mg one hour prior to bedtime for 28 days) demonstrated a significant reduction in sleep latency in the melatonin group (n=30) compared to the placebo group (n=10).[62]

In a placebo-controlled trial of eight subjects with delayed sleep-phase insomnia, Dahlitz et al found melatonin acted as a "phase-setter" for sleep-wake cycles. Subjects were given placebo or melatonin (5 mg nightly at 10 pm) for four weeks with a one-week washout period before crossing over to the other treatment, and were allowed to awaken naturally. In all subjects, the onset of sleep occurred earlier during melatonin treatment (mean change = 82 minutes; $p<0.01$); there was also a slight decrease in the total amount of time asleep.[63] Similar results were obtained by another group of researchers who administered 5 mg melatonin nightly to six subjects with delayed sleep-phase insomnia. The onset of sleep was an average of 115 minutes earlier when the subjects were taking melatonin, compared to pre-melatonin findings.[64] In the past 10 years, numerous other

randomized, controlled trials support melatonin's effectiveness for improving various aspects of normal sleep.

The time-dependent nature of melatonin's effectiveness has also been demonstrated. Tischinsky and Lavie administered either 5 mg melatonin or placebo to 18 subjects following an overnight sleep deprivation, varying the time of administration from noon to 9 pm. Melatonin was effective at increasing both the subjective and objective sleepiness of the subjects at all times of administration; however, the time delay between administration and maximal effect varied linearly from 3 hours 40 minutes at noon to one hour at 9 pm.[65]

Two studies by Paul et al compared melatonin to sleep-inducing pharmaceuticals for their ability to induce sleep and the effect on psychomotor performance. In a double-blind, placebo-controlled trial, melatonin (6 mg single dose) was compared to a single dose of zaleplon (Starnoc®), zopiclone (Imovane®), or temazepam (Restoril®). The sleep-inducing potential of test medications (in decreasing order of effect) was: zopiclone>zaleplon>melatonin >temazepam.[66] The researchers (using the same patient group and melatonin dosage) also demonstrated that, despite a surprisingly prolonged period of perceived sleepiness (up to 4.75 hours), melatonin was superior to the other medications in lack of impact on performance of four separate tasks: serial reaction time, logical reasoning, serial subtraction task, and a multi-task test battery.[67]

Jet Lag

Melatonin is effective for minimizing the effects of jet lag in travelers crossing multiple time zones. In a study of intercontinental jet lag, 37 subjects flying overnight from North America to France who had previously experienced jet lag on eastward intercontinental flights were given 8 mg melatonin at 10 pm France time on the day of departure and 8 mg at bedtime for the next three days. A follow-up questionnaire revealed significant differences between melatonin and placebo in overall effectiveness, with less morning and evening sleepiness.[68]

A 2002 meta-analysis of eight studies confirms melatonin's effectiveness in preventing or reducing jet lag, especially when traveling east across two or more time zones, at doses 0.5-5.0 mg, with the higher doses being more effective. Benefit was also greater the more time zones travelers crossed. Timing of melatonin administration is important; if given too early in the day, melatonin results in daytime sleepiness and delayed adaptation to local time.[69] In patients with altered circadian rhythms, such as occurs in jet lag, administration of melatonin can provide the necessary resynchronization of those cycles.

Shift Work

In sleep disorders associated with night-shift work, two small, randomized, controlled trials (n=17; n=21) using 5 mg and 1.5 mg melatonin, respectively, demonstrated a small-to-moderate benefit in improving quality and length of daytime sleep.[70,71]

Neuropsychiatric Conditions and Sleep Disorders

Numerous neuropsychiatric and neurodevelopmental conditions, including mental retardation,[72] epilepsy,[53] autism,[73] attention deficit hyperactivity disorder,[74] depression,[75] blindness,[76] Alzheimer's disease,[77] schizophrenia,[78] and seasonal affective disorder,[79] are characterized by sleep problems. Studies conducted on patients with these conditions show melatonin administration (dosages of 2-6 mg) can be of significant benefit in promoting normal sleep patterns. A recent meta-analysis of three studies (n=35) in children with various neurodevelopmental disabilities demonstrated melatonin, at doses of 0.5-7.5 mg in the evening, significantly decreased time-to-sleep onset compared to placebo.[80]

Cancer

Various cancer types have shown to be responsive to melatonin, including breast cancer,[30,81] non-small-cell lung cancer,[82] metastatic renal cell carcinoma,[83] hepatocellular carcinoma,[84] and brain metastases from solid tumors,[85] at dosages of 10-50 mg daily. Timing of the melatonin dosage appears to be important, with the most effective protocol being a diurnal cycle similar to the physiological rhythm of melatonin secretion.[30] In a study of 14 metastatic breast cancer patients who had not responded to initial therapy with tamoxifen, 20 mg of melatonin

was administered daily in the evening along with tamoxifen. A partial response was seen in 28 percent of patients whose disease would have otherwise been expected to progress rapidly. In those who responded clinically, significant declines were also found in serum levels of the tumor growth factor IGF-1 ($p<0.001$). This response was irrespective of estrogen-receptor status.[81]

Non-small-cell lung cancer (NSC) is one of the cancers least responsive to conventional therapy. In a randomized study, 63 consecutive NSC patients, with metastatic disease that did not respond to initial therapy with cisplatin, were placed on either melatonin (10 mg daily at 7 pm) or supportive care alone. Mean survival time was significantly higher for those in the melatonin group than for those receiving supportive care alone (7.9 ± 1 versus 4.1 ± 0.5 months; $p<0.05$).[82]

In patients with advanced solid tumors, one of the most clinically unfavorable events is the development of brain metastases. In these patients, few treatment options are available, and survival time is often less than six months. Fifty cancer patients with brain metastases, whose disease had progressed under initial therapy, were randomized to receive either supportive care alone or supportive care plus melatonin (20 mg daily at 8 pm). The number of subjects surviving one year (9/24 versus 3/26; $p<0.05$), mean survival time (9.2 ± 0.9 versus 5.5 ± 0.7 months; $p<0.05$), and time free from brain progression (5.9 ± 0.8 versus 2.7 ± 0.6 months; $p<0.05$) were all significantly higher in the group receiving melatonin.[85]

In a study of 30 patients with untreatable metastatic solid tumors, 20 mg oral melatonin daily in conjunction with low doses of the anti-tumor cytokines, IL-2 and interleukin-12 (IL-12), significantly increased lymphocyte proliferation and the anticancer immunity of these cytokines.[86]

Research conducted by Lissoni et al using melatonin alone or in conjunction with chemotherapy found melatonin may be a beneficial therapeutic tool for patients with colorectal cancer,[87,88] soft tissue sarcoma,[89] or metastatic hepatocellular carcinoma.[84] A meta-analysis of 10 randomized, controlled trials demonstrated melatonin therapy for various cancers reduced the relative risk of death at one year by an average of 34 percent. These results were independent of cancer type and melatonin dosage, which ranged from 10-40 mg daily; no adverse events were reported.[90]

Chemotherapy Side Effects

Several clinical trials by Lissoni et al demonstrated the beneficial effects of melatonin on chemotherapy-induced thrombocytopenia.[91-93] Most studies used either intravenous or subcutaneous melatonin, which resulted in a stimulation of thrombosis. Other studies indicate melatonin may be of benefit in reducing or preventing chemotherapy-associated cachexia, stomatitis, and neuropathy.[94,95]

Cardiovascular Health

In at least three separate clinical trials of both young and postmenopausal women on hormone replacement therapy, Cagnacci et al demonstrated melatonin at a dose of 1 mg daily exerted a beneficial effect on blood pressure and internal carotid pulsatility index (PI).[96-98] Significant decreases (4-10 mm Hg) in blood pressure and PI were observed in all studies. In contrast to other studies of melatonin and inflammation, increased nitric oxide levels were observed in women on hormone replacement therapy, possibly indicating an increase in vascular reactivity and improved endothelial function.[98] Other research has confirmed the beneficial effects on the cardiovascular system using higher melatonin doses in both healthy men (2 mg daily; n=26) and type 1 diabetic teenagers (5 mg daily; n=11).[99,100]

Melatonin administration at 6 mg daily may exert a favorable affect on lipoprotein metabolism, resulting in lower total cholesterol and more favorable lipid profiles.[101] In patients with multiple sclerosis, decreased nocturnal plasma melatonin levels were associated with significantly higher serum cholesterol levels, indicating melatonin administration may help normalize lipid profiles in these patients.[102]

Epilepsy

Melatonin use in patients with epilepsy is controversial. Numerous case reports indicate nighttime melatonin administration may improve seizure activity in children.[103-105] On the other hand, melatonin has also been reported to lower seizure threshold, resulting in an increase in seizure activity.[106] Gupta et al demonstrated melatonin dosages of 3-9 mg daily

have a beneficial effect on both antioxidant enzyme levels and quality of life in children with seizure disorders. Melatonin's ability to cross the blood-brain barrier, coupled with its antioxidant and neuroprotective properties, suggest it may be of benefit in improving quality of life in this population.[107,108]

Migraines

Several studies have examined endogenous melatonin secretion and its circadian rhythm in migraine patients, as well as the effect of melatonin administration on migraine sufferers. Studies on endogenous melatonin secretion demonstrate decreased nocturnal melatonin secretion[109-111] and lower melatonin levels during a migraine.[111] Studies utilizing a low dose of 20 μg melatonin infused IV over four hours prior to bedtime for three nights,[112] or 3-5 mg oral melatonin for up to one month,[113,114] reported decreases in headache frequency,[113,114] intensity,[112,114] and duration.[113,114]

Preoperative Sedation

Clinical trials comparing melatonin to placebo or standard sedative and anxiolytic drugs have shown promising results. Melatonin has been shown to be equally effective as midazolam (Versed®) and superior to placebo as a preoperative sedative/anxiolytic.[115,116]

Other Clinical Indications

Other conditions for which melatonin may provide significant benefit include skin protection from UV light damage,[117,118] glaucoma,[119] and benzodiazepine tapering.[120,121]

Melatonin-Drug Interactions

Hepatic metabolism of melatonin is primarily via the cytochrome p450 enzyme CYP1A2.[122,123] Therefore, drugs that alter CYP1A2 enzyme activity may have an effect on melatonin metabolism. Drugs that inhibit CYP1A2 and can increase serum melatonin include fluvoxamine, cimetidine, ciprofloxacin, erythromycin, and tricyclic antidepressants.[124]

Endogenous melatonin levels are increased by caffeine consumption. Therefore, melatonin supplementation may have an additive effect, necessitating a decrease in dosage in persons consuming significant amounts of caffeine.[125,126] Conversely, NSAIDs, such as ibuprofen and naproxen, can suppress endogenous melatonin production, necessitating supplemental melatonin.[127] Preliminary evidence indicates melatonin use in conjunction with blood-thinning agents, such as coumadin (warfarin), may increase the risk of bleeding.[128]

Melatonin administration has been shown to lower blood pressure 4-10 mm Hg, even at 1-mg dosages; therefore, using melatonin in conjunction with beta-blockers[129] and other anti-hypertensives[96,97] may result in a potentiation of hypotensive action. Similarly, melatonin's sedative properties may potentiate the effect of sedative medications.[58]

Melatonin's hormonal effects may impact blood glucose and insulin levels; therefore, caution should be used when prescribing melatonin in conjunction with glucose-lowering medications.[48,49]

Melatonin-Botanical Interactions

Botanicals with sedative, hypoglycemic, and anticoagulant activity may potentiate the effects of exogenous melatonin.[128,130] *Vitex agnus-castus* (Chasteberry) increases endogenous melatonin secretion and may increase the effect of melatonin supplementation.[131]

Melatonin and Magnetic Fields

There is some evidence that circadian rhythms in humans may be disrupted by exposure to electromagnetic fields from power lines, appliances, and cellular phones.[132,133] Altered neural function from exposure to extremely low frequency fields (found near high-voltage power lines) and suppressed melatonin levels have been reported.[134]

Side Effects and Toxicity

Adverse effects of melatonin are few and it is generally regarded as safe in recommended dosages. There are isolated case reports of psychomotor disturbances (disorientation, fatigue, headache, dizziness, etc.), increased seizure risk, and blood clotting abnormalities associated with melatonin alone or in combination with other medications.[128]

Warnings and Contraindications

Based on its hormonal effects, women who are pregnant should consult a health care practitioner prior to supplementing with melatonin.

Dosage

Evening oral doses of melatonin as low as 0.3 mg have been shown to be adequate in improving sleep quality, although doses as high as 5-10 mg have been used successfully as well. For most non-sleep related disorders, including cancer, doses from 10-50 mg daily have been used safely and effectively.

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