A REVIEW ON MELATONIN – A MIRACULOUS DRUG AND ITS APPLICATIONS

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ABSTRACT
Melatonin is the primary neurohormone produced the pineal gland, was isolated in 1958 from bovine epiphysis by Lerner. The secretion follows circadian pattern with high levels during the dark cycle. In addition to the pineal gland, melatonin is synthesized in several other structures - enterochromaffin cells, eye retina, peripheral teleneurons and the gastrointestinal tract. Melatonin is very popular as a sleep remedy and a natural treatment for insomnia. Studies show that it can be used as an antioxidant, cancer protective agent, skin protective agent, contraceptive and as a treatment for seasonal affective depression. There are other uses of melatonin, which are still being studied today.

KEY WORDS: Broad activity, melatonin, night hormone, pineal gland, tryptophan.

1. INTRODUCTION
Melatonin is a slightly off-white, crystalline powder, which is soluble in tetrahydrofuran and methanol, slightly soluble in ethyl acetate and insoluble in water. Melatonin is an indole amide neurohormone primarily secreted by pineal gland, located behind the third ventricle in the brain,¹ this bioactive substance also has extra pineal sites of synthesis²⁻⁹. Melatonin has been tried in number of disorders.¹⁰ Although melatonin is very popular as a sleep remedy and as a natural treatment for insomnia. Melatonin has other uses aside from improving sleep. Studies show that it can be used as an antioxidant, cancer protective agent, skin protective agent, contraceptive and as a treatment for seasonal affective depression. Melatonin is thus a multi-functional hormone that is produced naturally by the human body.
1.1. CHEMISTRY
Chemically, melatonin is defined as N-acetyl-5-methoxytryptamine. It can be isolated from the pineal glands of beef cattle or synthesized from 5-methoxyindole as a starting material via 2 different routes. It is a relatively low molecular weight hormone (M.W. 232.27) and is a pale yellow crystalline material.\textsuperscript{11} In the synthesis of melatonin, tryptophan is hydroxylated to 5-hydroxytryptophan, which in turn is decarboxylated to 5-hydroxytryptamine (serotonin). Serotonin is converted to the melatonin precursor and metabolite N-acetylserotonin by the enzyme N-acetyl transferase.\textsuperscript{12-14} N-acetylserotonin is methylated via the enzyme hydroxyindole-o-methyltransferase to produce melatonin.\textsuperscript{15}

Biosynthesis of Melatonin

![Diagram of melatonin biosynthesis]

Approximately 90 percent of melatonin is cleared in a single passage through the liver. A small proportion of unmetabolized melatonin is also excreted in the urine.\textsuperscript{15} Commercially available melatonin may be isolated from the pineal glands of beef cattle\textsuperscript{16} or chemically synthesized.

![Chemical structure of melatonin]

**Figure I: Chemical structure of Melatonin**

Melatonin has a chemical formula of $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_2$
1.2. PHARMACOLOGY
Pharmacological disruption of melatonin production can occur via beta-1 and alpha-1 receptors because of sympathetic innervation in the pineal gland. Tryptophan is converted to serotonin, the immediate precursor of melatonin.\textsuperscript{17-19} Its synthesis is inhibited by light and stimulated by periods of darkness independent of sleep. To date, three G-protein-coupled melatonin receptors have been cloned as well as one nuclear receptor (figure II).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{melatonin_receptors.png}
\caption{G-protein-coupled melatonin receptors}
\end{figure}

They are present in the periphery and CNS.\textsuperscript{20} Once in circulation; melatonin is metabolized in the liver with more than 85\% excreted as 6-sulphatoxyMEL, a reliable marker for melatonin production. Plasma half-life is short, 20 to 50 minutes,\textsuperscript{17,18,21} and plasma levels return to baseline within 24 hours after discontinuation of chronic dosing (less than 10 mg/day).\textsuperscript{18,22} Melatonin doses of 5 mg produce estimated peak blood levels 25 times above physiological levels but do not alter endogenous melatonin production.\textsuperscript{18,22}

1.3. TOXICOLOGY
There is little or no evidence of any major toxicities with melatonin, even at high doses. There are very few short-term and no long-term safety data. Toxicological studies have shown that an LD\textsubscript{50} could not be obtained even at extremely high doses. Researchers gave human volunteers 6 g of melatonin each night for 1 month and found no major problems, except for stomach discomfort or residual sleepiness.\textsuperscript{23}
2. MELATONIN SECRETION IN BRAIN
Melatonin is one of the many natural hormones. The pineal gland situated within the brain (figure.III) of a human body secretes this hormone. Size of the pineal gland is almost equal to a pea. It is more precisely located just above the middle of the brain. The pineal gland acts like the internal clock of the human body specifically the brains. This internal clock is responsible to commands the brain that it is time to go to bed or when to sleep. Release of melatonin in human body is inhibited by the presence of bright light. Because of this characteristic of the melatonin hormone is often termed as the “Dracula of hormones” that only surfaces in nights.  

Figure.III: A detailed diagram showing the structure of Brain

Melatonin secretion is inhibited by environmental light and stimulated by darkness, with secretion starting at 9p.m. and peaking between 2 and 4 a.m. for this reason, melatonin is sometimes known as “night hormone.” Nocturnal secretion of melatonin is highest in children and decreases with age.  

3. APPLICATIONS OF MELATONIN
In the 1990s, dozens of articles appeared in the medical literature on the various purported activities of melatonin. A selected overview of studies includes those regarding melatonin's role as an antioxidant and free radical scavenger, use in general health and disease, use in general health and disease, control of seasonality and winter depression oncostatic actions on estrogen-responsive MCF-7 human breast cancer cells, treatment of neoplastic cachexia effect on primary headaches and prophylaxis of cluster headache
direct effect on the immune system\textsuperscript{35,36} including activation of human monocytes\textsuperscript{37} role in GI physiology, \textsuperscript{38} function in thermoregulatory processes, \textsuperscript{39} involvement in the cardiopulmonary system, \textsuperscript{40} potentially beneficial cardiovascular effects \textsuperscript{41,42} including reduction in hypercholesterolemia, \textsuperscript{43} use in treatment of myoclonus in children, \textsuperscript{44} effects on puberty, \textsuperscript{45} improvement in tinnitus, \textsuperscript{46} its place in human and animal reproduction, \textsuperscript{47} studies on human sleep, \textsuperscript{48} use as a premedication for gynecological procedures, \textsuperscript{49} modulation of sympathetic neurotransmission,\textsuperscript{50} possible role in infant colic, \textsuperscript{51} as a proconvulsive hormone,\textsuperscript{52} and purported chronobiotic and anti-aging properties.\textsuperscript{53,54}

The broad activity spectrum of melatonin has attracted the attention of clinicians and encouraged attempts at using this compound in various fields of medicine.

\textbf{Jet lag.} Melatonin has been found to help alleviate the symptoms of jet lag in passengers traveling across several time zones. Melatonin's ability to modulate circadian rhythms has prompted several studies investigating the use of this agent in the prevention of jet lag.\textsuperscript{18,55,56,57} Although the effects have been variable, most patients have reported general improvement in daytime fatigue, disturbed sleep cycles, mood, and recovery times. These studies are limited by the small number of participants and a focus on subjective ratings of effects with little or no evidence of actual changes in circadian shift (ie, changes in oral temperature or cortisol levels). The most appropriate timing for melatonin administration appears to be preflight early evening treatment followed by treatment at bedtime for 4 days after arrival when traveling eastbound, whereas on a westbound flight it is better to take melatonin for 4 days at bedtime when in the new time zone.\textsuperscript{58}

\textbf{Insomnia.} Decreased circulating melatonin serum levels have been demonstrated in people of all ages with insomnia and in the healthy elderly.\textsuperscript{17,18} In patients with difficulty falling asleep, low doses of melatonin should be sufficient in promoting sleep onset. Administration of 5 mg of melatonin 3 to 4 hours before an imposed sleep period over a 4-week period decreased the time to sleep onset without affecting other sleep parameters, such as total duration or sleep architecture.\textsuperscript{59} However, in patients with difficulty maintaining sleep, low doses of melatonin may not produce sufficient blood concentrations to maintain slumber. A 2 mg oral melatonin dose produced peak levels \(\approx 10\) times higher than physiological levels, but it remained elevated for only 3 to 4 hours.\textsuperscript{18,21} To maintain effective serum concentrations of melatonin throughout the night, a high dose, repeated low doses, or a controlled-release formulation may be needed. When compared with placebo in a trial of 12 elderly people with
chronic insomnia, melatonin increased sleep efficiency (75% vs 83%) and decreased wake time after sleep onset (73 vs 49 minutes)\textsuperscript{18,60} Low doses (0.3 or 1 mg) administered to healthy volunteers at 6 p.m., 8 p.m., or 9 p.m. decreased onset latency and latency to stage 2 sleep, but did not suppress REM sleep nor induce hangover effects.

**Immunotherapeutic potential.** Activation of melatonin receptors has been shown to enhance the release of a number of cytokines, including gamma-interferon, IL-1, IL-2, IL-6, and IL-12 in human monocytes. It has been suggested that melatonin may be used to stimulate the immune system during viral and bacterial infections. A potential role has been postulated in the treatment of viral encephalitis, septic shock, and secondary immunodeficiencies (eg, acute stress). However, through this proinflammatory action, melatonin may play an adverse role in autoimmune diseases\textsuperscript{36}

**Oral contraceptive.** Because melatonin plays a role in the endocrine-reproductive system and reduces circulating LH, the use of melatonin as a contraceptive agent has been studied.\textsuperscript{18,61} Melatonin administered in various dosage combinations with a synthetic progestin in 32 women for 4 months produced anovulatory effects. The induction of sleepiness alone could make it a very effective contraceptive.\textsuperscript{62}

**Protection of skin from UV light.** Topical melatonin was tested in combination with vitamins C and E in a randomized, double-blind study. The agents were applied topically either alone or in combination 30 minutes before ultraviolet irradiation of the skin. The best protection was obtained using all 3 agents in combination. The role of reactive oxygen species and oxygen-derived free radicals, as well as potential sunscreening properties, may explain the photoprotective effect.\textsuperscript{63}

**Cancer.** Several studies suggest that partial responses and stabilization of disease occur, to varying degrees, with the use of melatonin as adjunctive therapy in patients with malignant solid tumors. However, the majority of these studies are open-labeled trials in patients in poor clinical condition with advanced disease who had not responded to conventional therapy. Melatonin has demonstrated some inhibitory effects on tumor growth in animal models\textsuperscript{64} and in vitro cancerous breast cell lines. European studies on B-Oval (containing melatonin) appear to show that it can slow the growth rate of human tumor cells. A nightly supplement (10 mg of melatonin) has been shown to improve 1-year survival rates in patients with
metastatic lung cancer. More trials are needed before the role of melatonin as an oncostatic agent can be confirmed.

Cluster headaches. A reduction in nocturnal plasma melatonin levels occurs in some patients with cluster headaches, suggesting that melatonin may play a role in the attacks.

Miscellaneous. There were attempts to use melatonin as a tocolytic agent for preventing premature delivery. A new direction in gastroenterology is related to the use of melatonin for the therapy of digestive organs, in particular, for the treatment of gastric and deodenal ulcers. Melatonin has ability to normalize the blood cholesterol level, decreases the content of corticosteroids, regulate the hormone secretion of thyroid gland and control growth hormone production serves as a base for attempts at using melatonin for treatment of cardiovascular pathology and diabetes. Some researchers believe that melatonin participates in regulation of the brain blood circulation and the brain fluid balance. There are data on the anxiolytic and antistressor activity of melatonin. One of special interest is the favorable action of melatonin upon some forms of depression, and the possibility of using this substance for the treatment of Alzheimer’s disease. It is theorized that the decrease in plasma melatonin during early menopause may contribute to the development of postmenopausal osteoporosis.

4. DOSAGE AND SAFETY

Melatonin is available in both immediate- and sustained-release formulations. In most studies, doses ranged from 0.3-5 mg 30-60 minutes before bedtime. When taken for jet lag, dose of 5-8 mg/day often used. Blind peoples and paediatric patients with neurologic disorders have been successfully treated with 0.3-10 mg given before bed time. Commercially available dosage forms contain synthetic melatonin. Daytime drowsiness, headache, dizziness, and mild hypothermia (0.5-1.5) are most common side effects of melatonin in therapeutic dosage.

REFERENCES


23. Melatonin:The Hormone Makes You Sleep;General Information,Sleep.sleep apnea,2009;Jan;17.
29. Partonen T. Involvement of melatonin and serotonin in winter depression. Med Hypotheses. 1994;43:165-166


62. Dreher F, Gabard B, Schwindt DA, Maibach H. Topical melatonin in combination with


