Melatonin: A Primer

By Patricia Keller

Melatonin, known scientifically as the indoleamine N-acetyl-5-methoxytryptamine, is a hormone with neurotransmitter modulatory activity, and it can be found in most living things from some of the simplest plants to humans. It is produced in minute quantities by the pineal gland when the eyes detect decreasing light, total darkness, or during sleep. Melatonin is also produced by the retina and, in vastly greater amounts, by the gastrointestinal system.[1] In fact, 400 times more melatonin can be found in the gastrointestinal system than in the pineal gland or bloodstream, where levels typically range from 0.1 to 10 nmol/L.[2] Melatonin receptors are present in central nervous system tissues, peripheral tissues, and steroidogenic tissues, including myometrial tissues of both pregnant and non-pregnant women. It is naturally synthesized in humans from the amino acid tryptophan (via synthesis of serotonin) by the enzyme 5-hydroxyindole-O-methyltransferase. Production of melatonin by the pineal gland is under the influence of the suprachiasmatic nucleus of the hypothalamus (SCN) which receives information from the retina about the daily pattern of light and darkness. Melatonin is also synthesized in various plants, such as onions, bananas, corn and cherries, and ingested melatonin has been shown to be capable of reaching and binding to melatonin binding sites in the brains of mammals.

Melatonin is a substance that an increasing number of people are taking without being knowledgeable about its variety of possible benefits, side effects and dosages. Many companies currently manufacture melatonin as a supplement. There are two kinds of non-prescription melatonin available--synthetic or natural (animal derived). If you are not going to be taking a prescription grade formula, it is often recommended to take a synthetic version of the supplement which is close to the molecular make-up of our own naturally produced melatonin. The "natural" melatonin supplements may contain animal parts through which viruses and diseases can be carried, or proteins that could cause an antibody response.

A little historical perspective: one theory examines the common evolutionary origin of cells in the pineal gland and retina. David Klein, Ph.D. has theorized that in the ancestor of today's higher animals, the conversion of serotonin to melatonin increased at night as a way to make vision more sensitive to low light conditions. The conversion kept serotonin from combining with retinaldehyde (a form of vitamin A) at night, when it was needed to detect low levels of light, so that these ancestral animals could function well under dim light. Since this required a steady supply of serotonin as a precursor, which in turn depleted retinaldehyde (needed for low light vision), a second photoreceptor cell evolved which functioned to produce its own melatonin. Eventually these melatonin-making cells evolved into what is now the pineal gland. Dr. Klein points out that the photoreceptor cells of the retina strongly resemble the cells of the pineal gland and that the pineal cells of sub-mammals (such as fish, frogs and birds) detect light. In addition, melatonin's origin in the ancestral photoreceptor cell is indicated by the capacity of the retinas of mice, fish, frogs, and birds to make small amounts of melatonin. [3]

Melatonin is being studied for its possible benefits regarding a host of medical issues including cluster headache. A frequently cited Italian study looking into the circadian secretion of melatonin, demonstrated that episodic cluster headache patients were shown to have low blood plasma melatonin levels during cluster periods. [4] The following year some of the same researchers followed up with a study of both episodic and chronic patients in a double-blind placebo-controlled study of 10 mg. oral melatonin doses, showing some positive results for the episodic group. [5] While the effectiveness of melatonin for cluster

headache remains unclear because of conflicting studies, its role, if any, may be in the initial prevention of attacks, theoretically by resetting the circadian rhythm.

Melatonin has become a frequent target of scientific and commercial interest in recent years. Besides melatonin's benefit for some cluster headache sufferers, it has been studied for a wide variety of other medical issues. Smaller studies of melatonin have been done for conditions from sleep issues such as jet lag and insomnia to its possible effect on Alzheimer's disease, cancer treatment, psychological disorders, HIV, and many others. A study published in November of 2006 looked at the use of melatonin for ALS patients. It suggested that high-dose melatonin is suitable for clinical trials aimed at neuroprotection through antioxidation in ALS. [6] A promising study for gastro esophageal reflux disease was performed because melatonin has known inhibitory activities on gastric acid secretion and nitric oxide biosynthesis. When melatonin was combined with a group of other supplements and compared with omeprazole, there was a significant positive result with the melatonin with no significant side effects. [7]
Because of its antioxidant properties, melatonin is getting some attention for possible use in strengthening the immune system. Melatonin's immunoenhancing properties was discussed and confirmed in a study which strongly suggested our immune systems also have melatonin receptors, but there hasn't been enough work done in this area to show the mechanism of this function. [8] Melatonin in combination with cancer treatments is showing some promising results. A number of studies showed that patients who used melatonin supplements had consistently better chemotherapeutic responses, significantly fewer side effects, and significantly higher survival rates overall compared to patients who did not use melatonin. Some of the cancers included in these data include lung, colorectal, and breast. A notable study was performed to assess the 5-year survival results in metastatic non-small cell lung cancer patients who combined melatonin with their chemotherapy regimen. The study suggested the possibility to improve the efficacy of chemotherapy in terms of both survival and quality of life by a concomitant administration of melatonin. [9] It should be noted that in many of the studies mentioned here, the melatonin administered to the subjects was of a pure pharmaceutical grade and in therapeutic level doses.

Along with the increased attention by medical research, commercial interests have begun to show interest in melatonin. Two pharmaceutical companies have recently brought melatonin related products to market for sleep issues. In the EU, Neurim Pharmaceuticals Ltd has received approval for their product Circadin 2 mg (prolonged-release melatonin) as monotherapy for the short-term treatment of primary insomnia. In the United States and elsewhere, Takeda Pharmaceuticals North America is aggressively marketing Rozerem (ramelteon) for insomnia, particularly for delayed sleep onset. Ramelteon is a melatonin receptor agonist, and it is thought to promote more normal sleep patterns by restoring maintenance of the circadian rhythm. It is the first in a new class of sleep agents that selectively binds to the melatonin receptors in the suprachiasmatic nucleus (SCN), versus binding to GABA-A receptors, such as with drugs like zolpidem, eszopiclone, and zaleplon. Unlike earlier classes of sleep agents, ramelteon has not been shown to produce dependence and so far has demonstrated no potential for abuse. No published studies have indicated whether ramelteon is more or less safe or effective than melatonin supplements which are widely available in the U.S. in a less expensive non-prescription form. Commercial interest in melatonin has also spread to the "natural" supplement and cosmetic industries. It is not unusual to find melatonin included in the ingredient lists of numerous products from "miraculous" anti-ageing pills to wrinkle creams.

There are reported risks involved in the use of melatonin. Based on available studies and clinical use, melatonin is generally regarded as safe in recommended doses for short-term use. Available trials report that overall adverse effects are not significantly more common

with melatonin than placebo. However, case reports raise concerns about risks of blood clotting abnormalities (particularly in patients taking warfarin), increased risk of seizure, and disorientation with overdose, including increased risk of seizure in children with severe neurological disorders. Melatonin supplementation should be avoided in women who are pregnant or attempting to become pregnant, based on possible hormonal effects. Commonly reported adverse effects include fatigue, dizziness, headache, irritability, and sleepiness, although these effects may occur due to jet-lag and not to melatonin itself. Fatigue may particularly occur with morning use or high doses, and irregular sleep-wake cycles may occur. Disorientation, confusion, sleepwalking, vivid dreams and nightmares have also been noted, with effects often resolving after cessation of melatonin. Due to risk of daytime sleepiness, those driving or operating heavy machinery should take caution. [10]

In conclusion, melatonin has been used successfully to help alleviate circadian rhythm imbalances, including imbalances in some cluster headache sufferers. While its use for these issues is becoming more widely accepted, research has a long way to go before its benefits can be applied to all the areas of health care that are trying to lay claim to melatonin's possible uses. Most clinical research has used pharmaceutical grade melatonin in higher doses than can be obtained in over the counter supplements. As with any new supplement or prescription regimen, always consult your healthcare provider first to make certain that you will not be incurring adverse interactions with other drugs you may be taking.

References

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