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A Review on Melatonin – A New Drug Therapy for Sleep

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INTRODUCTION

THEORY:

MELATONIN is a hormone secreted by the pineal gland which inhibits melanin formation and is thought to be concerned with regulating the reproductive cycle.

Melatonin is a hormone made by the pineal gland , a small gland in the brain. Melatonin helps control your sleep and wake cycles. Very small amounts of it are found in foods such as meats, grains, fruits, and vegetables. You can also buy it as a supplement. Our body has its own internal clock that controls your natural cycle of sleeping and waking hours. In part, your body clock controls how much melatonin your body makes. Normally, melatonin levels begin to rise in the mid- to late evening, remain high for most of the night, and then drop in the early morning hours. Light affects how much melatonin your body produces. During the shorter days of the winter months, your body may produce melatonin either earlier or later in the day than usual. This change can lead to symptoms of seasonal affective disorder (SAD), or winter depression. Natural melatonin levels slowly drop with age. Some older adults make very small amounts of it or none at all.

Chemically N-acetyl-5-methoxy tryptamine, is a substance found in animals, plants, fungi and bacteria. In animals, it is a hormone that anticipates the daily onset of darkness; however in other organisms, it may have different functions. Likewise, the synthesis of melatonin in animals differs from that in other organisms. In animals, melatonin is involved in the entrainment (synchronization) of the circadian rhythms of physiological functions including sleep timing, blood pressure regulation, seasonal reproduction and many others. Many of melatonin's biological effects in animals are produced through activation of melatonin receptors ,while others are due to its role as a pervasive and powerful antioxidant, with a particular role in the protection of nuclear and mitochondrial DNA. The hormone can be used as a sleep aid and in the treatment of some sleep disorders. It can be taken orally in liquid form as well as capsules or tablets in immediate- or prolonged-release form. It is also available in a form to be used sublingually, and as transdermal patches. Melatonin is sold over-the-counter in the U.S. and Canada. In other countries it may require a prescription or it may be unavailable. [1]

DISCOVERY OF MELATONIN IN PLANTS:

The presence of melatonin was described for the first time in the bovine pineal gland by Lerner and coworkers. The isolated substance was able to stimulate melanin aggregation, lightening the skin of frogs and other amphibians but not of mammals. In 1959, melatonin was identified as Nacetyl- 5-methoxytryptamine and, soon after, its biosynthetic pathway from tryptophan, with serotonin as intermediary, was discovered. In 1959, melatonin was detected in humans and in the 1960s and 70s, its presence was described in many mammals and vertebrates such as birds, amphibians, and fish. In the 1980s, melatonin was discovered in invertebrates such as planarians, annelids, molluscs, insects, and crustaceans, among others. [2]

In higher plants, the first identification of endogenous melatonin was described in 1993 by van Tassel and O'Neill in a congress communication. The authors had detected melatonin by radioimmunoassay (RIA) and gas chromatography with mass spectrometry (GC-MS) in the Convolvulaceae ivy morning glory (Pharbitis nil L., syn. Ipomoea nil L.) and in tomato fruits (Solanum lycopersicum L.), although the results were not published extensively until 1995. Also in 1995, two papers published simultaneously demonstrated the presence of melatonin in higher plants. Dubbels and coworkers used RIA and HPLC-MS to measure the melatonin levels in extracts of Nicotiana tabacum L. and in five edible plants. Two months later another publication appeared, in which the presence of melatonin in extracts of a large number of edible plants was quantified by RIA and liquid chromatography (HPLC) with fluorescence detection. Another communication appeared in the same year, in which a Czech research group identified the presence of melatonin in Chenopodium rubrum L. using liquid chromatography with mass identification (LC-MS/MS). Successive studies have quantified the presence of melatonin in many plants and it is now accepted that melatonin is present in animals, plants, and in all the other kingdoms. [3][4]

PRODUCTION AND FUNCTION:

Melanin is a pigment that is produced by cells known as melanocytes in the skin of most animals, including humans. This pigment comes in different shades, depending on the genetic makeup of the individual. Melanin comes in two basic forms and can range from yellowish-red to dark brown. Eumelanin is the most common form of melanin and is brownish in colour. The other basic form is called pheomelanin, which produces reddish-brown colour that is often associated with freckles and red hair. The production of melanin in the individual is determined by several factors. [5] Genetically speaking, every individual on earth has approximately the same number of melanocytes. The difference, then, in the production of melanin is affected by:

- Exposure to UV radiation: Melanin is produced as a response to UV radiation in order to prevent damage to the DNA in the integument. Individuals, who are exposed to UV light, such as the sun, will produce more melanin for protection.
- Genetic makeup: Different ethnicities and cultures are genetically pre-disposed to producing particular shades and amounts of melanin due to inheritance. This is, essentially, one of the primary indicators used in determining race in the human population. It is important to note that this is, and has historically been, a controversial form of human identification.
- Size of melanocytes: Melanocyte size varies in different individuals and may lead to a difference in the amount of melanin produced per cell.
- Disease conditions: Several diseases may affect melanin production, including albinism, a genetic inability to produce melanin, and vitiligo, a progressive loss of melanocytes. [6]

FOOD PRODUCTS:

Melatonin has been reported in foods including cherries to about 0.17–13.46 ng/g, bananas and grapes, rice and cereals, herbs, olive oil, *wine* and beer. When birds ingest melatonin-rich plant feed, such as rice, the melatonin binds to melatonin receptors in their brains. When humans consume foods rich in melatonin such as banana, pineapple and orange, the blood levels of melatonin increase significantly.

As reported in the New York Times in May 2011, beverages and snacks containing melatonin are sold in grocery stores, convenience stores, and clubs. The FDA is considering whether these food products can continue to be sold with the label "dietary supplements". On 13 January 2010, it issued a warning letter to Innovative Beverage, creators of several beverages marketed as drinks, stating that melatonin is not approved as a *food additive* because it is not *generally recognized as safe.* [7]

BIOSYNTHESIS AND PHARMACOLOGY:

Melatonin biosynthesis in humans and some other organisms involves four enzymatic steps from the essential dietary amino acid tryptophan, which follows a serotonin pathway; in other organisms, through the shikimic acid pathway.[8]

In the first two steps, L-tryptophan is first converted to 5-hydroxy-L-tryptophan (5-HTP) by an enzyme, tryptophan 5-hydroxylase. 5-HTP is then decarboxylated (CO2 removal) by 5hydroxytryptophan decarboxylase to produce serotonin. This point is the rate limiting stage such that further reaction is determined by light-dark conditions. [9]

Only in darkness, the key enzyme, aralkylamine N- acetyltransferase (AANAT) is activated and converts serotonin to N-acetyl serotonin, which is ultimately converted to melatonin by the final enzyme, acetylserotonin O-methyltransferase.It is the key regulator of melatonin synthesis from tryptophan, as its gene AANAT is directly influenced by photoperiod.

In bacteria, protists, fungi, and plants, melatonin is synthesized indirectly with tryptophan as an intermediate product of the shikimic acid pathway. In these cells, synthesis starts with derythrose- 4-phosphate and phosphoenolpyruvate, and in photosynthetic cells with carbon dioxide. The rest of the reactions are similar, but with slight variations in the last two enzymes. [10]

TOXICOLOGY:

The knowledge of the fundamental mechanism of action of melatonin, including molecular biology, also needs to be taken into account for evaluation of possible side effects. Two types of melatonin receptors have been cloned (related to cyclic AMP), and the possibility of intracellular action of melatonin cannot be excluded. Melatonin receptors are present in the periphery and also at the level of the central nervous system, particularly on the supra-chiasmatic nucleus that "drives" a circadian rhythm to many other areas on which it projects. Among those, the hypothalamus (which has melatonin receptors) plays a fundamental role in the hormonal homeostasis and modulation control of the organism. Special preclinical and pharmacological studies that take into account all these parameters need to be designed for safety evaluation and risk assessment of this specific neurohormone. [11]

PREVENTING ISCHEMIC DAMAGE:

Melatonin has been shown to reduce tissue damage in rats due to ischemia in both the brain and the heart; however, this has not been tested in humans.

Sleep aid

Melatonin may be used as an adjunct to sleep in children, for certain diagnostic tests.

Headaches

Several clinical studies indicate that supplementation with melatonin is an effective preventative treatment for migraines and cluster headaches.

Depression

Melatonin has been shown to be effective in treating one form of depression, seasonal affective disorder.

Other

Some studies have shown that melatonin has potential for use in the treatment of various forms of cancer, HIV, and other viral diseases; however, further testing is necessary to confirm this. Histologically speaking, it is also believed that melatonin has some effects for sexual growth in higher organisms. [12]

USE AS MEDICAL SUPPLIMENT:

Exogenous melatonin, usually taken orally, is, together with light therapy, the standard treatment for delayed sleep phase syndrome. It appears to have some use against other circadian rhythm sleep disorders, such as jet lag. It has been studied for the treatment of cancer, immune disorders, cardiovascular diseases, depression, seasonal affective disorder (SAD), and sexual dysfunction. A study by Alfred J. Lewy and other researchers at Oregon Health & Science University found that it may ameliorate SAD and circadian misalignment, but as of 2006 it is known to affect the timing of endogenous melatonin production during long-term melatonin treatment in rats, raising the risk that it can exacerbate both clinical depression and SAD. Basic research indicates that melatonin may play a significant role in modulating the effects of drugs of abuse such as cocaine.

SAFTY FOR SUPPLIMENTATION:

Melatonin derived from animal sources may be contaminated with viral material, so synthetic melatonin is generally used to avoid this risk. Melatonin is practically nontoxic and exhibits almost no short-term side effects. No studies have as yet been conducted to determine whether there are any long-term side effects. There are, however, case reports about patients who have taken the supplement for years.

Ingesting melatonin supplements may cause some unwanted side effects, especially at high doses (~more than 3 mg/day): hormone fluctuations, irritability, reduced blood flow, and increased sleep disturbances, including vivid nightmares.

Melatonin taken in combination with monoamine oxidase inhibitors (MAOIs) can lead to overdose because MAOIs inhibit the breakdown of melatonin by the body. [13]

CONCLUSION

Melatonin has been seen to be involved in several physiological aspects in plants, where it acts as a circadian regulator, cytoprotector and growth promotor. It also acts in rhizogenesis, cellular expansion and stress-protection. In this respect, several reviews with summarized data can be consulted. Currently, two aspects of phytomelatonin arouse the most interest:

1. Its application as biostimulator in agriculture and
2. Its use as human natural nutraceutical.

As regards the first aspect, trials with melatonin have shown that the application of exogenous melatonin to plants produces an improvement in important aspects of their development, including better adaptation to stress situations such as drought, salinity, pollutants, cold, heat, and radiation, among others. Melatonin also enhances the rate of germination and growth and plant productivity. It acts as a retardant in stress-induced leaf senescence. All this leads us to the idea that exogenous melatonin-treatment of cultivated plants or obtaining melatoninoverproducing plants might help crops resist more easily many adverse environmental conditions from which they normally suffer throughout their development. Another proposal concerns the use of plants rich in melatonin as a tool in phytoremediation techniques for the recovery of contaminated soils such as mining operations, industrial waste, or soils containing high levels of phytochemicals due to agricultural use.

The second of the above-mentioned aspects refers to the possibility of introducing melatonin-rich plants foods into our diet. Contrary to what frequently occurs with dietary supplements, increasing blood melatonin levels through eating natural foods such as plants could be considered a healthy habit. An oral dose of melatonin of up to 1 gram per day produces no adverse effects in humans. In addition, melatonin is easily absorbed via the gastrointestinal tract. So, its use as a nutraceutical product through the intake of melatonin-rich plants seems to have a promising future as a healthy phytochemical. It would, therefore, seem a worthwhile task to search for plants with high levels of endogenous melatonin that could be used as a natural source of nutraceuticals.

Very little attention has been paid to the possible side effects of melatonin. Nightmares, hypotension, sleep disorders, abdominal pain, etcetera, have been reported. In fact, analysis of the known pharmacological profile of melatonin and/or of its metabolites, based on scientific preclinical studies, constitutes a basis for prediction of adverse drug reactions or side effects.

These includes :-

1. The central nervous system,
2. The cardiovascular system and platelet aggregation,
3. Glucose metabolism,
4. Immunology, and
5. Cancer.