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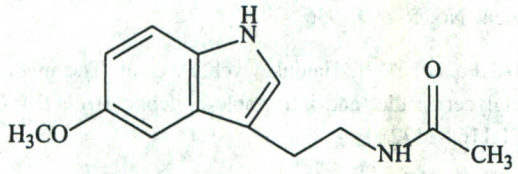
Melatonin

DESCRIPTION

Melatonin is the principal hormone of the vertebrate pineal gland, and it is also produced by extra-pineal tissues in amphibians. It is found in plants as well, but at much lower concentrations than in animals. This hormone is involved in setting the timing (entrainment) of mammalian circadian rhythms, as well as regulating seasonal responses to changes in day length in seasonally breeding mammals—so called photoperiodic responses. Photoperiodic responses include changes in reproductive status, behavior and body weight. Seasonal effects on reproduction in humans are subtle, and the role of melatonin here, if any, is unclear. Recently, melatonin supplementation has become popular as a possible aid for sleep disorders among other things.

Melatonin is synthesized endogenously by the pinealocytes of the pineal gland. The essential amino acid L-tryptophan is a precursor in the synthesis of melatonin. In this synthesis, L-tryptophan first gets metabolized to 5-hydroxytryptophan from which 5-hydroxytryptamine, also known as serotonin, is made. 5-hydroxytryptamine is converted to melatonin in a two-step process, occurring mainly in the pineal gland.

Melatonin is also known as N-acetyl-5-methoxytryptamine and N-[2-(5-Methoxy-1H-indol-3-yl) ethyl] acetamide. The structural formula is:



Melatonin

Melatonin is a solid, lipophilic, hydrophobic substance, which is available as a supplement in synthetic form. Melatonin derived from the pineal glands of beef cattle is also marketed.

ACTIONS AND PHARMACOLOGY

ACTIONS

Supplemental melatonin may have a hypnotic action. It may also have antioxidant and anti-apoptotic activity.

MECHANISM OF ACTION

Melatonin is derived in pinealocytes from L-tryptophan. 5-hydroxytryptamine or serotonin is an intermediate in the biosynthetic process. The rate limiting step in the synthesis of melatonin is the n-acetylation of the 5-hydroxytryptamine by the enzyme arylalkylamine N-acetyltransferase (AA-NAT). Melatonin synthesis displays a circadian rhythm that is reflected in serum melatonin levels. The rhythm is generated by a circadian clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus. The SCN clock is set to the 24 hour day by the natural light-dark cycle. Light signals through a direct retinal pathway to the SCN. The SCN clock sends circadian signals over a neural pathway to the pineal gland. This drives rhythmic melatonin synthesis. The neural input to the gland is norepinephrine, and the output is melatonin. Specifically, the rhythm of the enzyme AA-NAT is under SCN control, with the resulting melatonin rhythm characterized by high levels at night. Thus, the synthesis and release of melatonin are stimulated by darkness and inhibited by light.

The effects of hormones are typically mediated through receptors. Two forms of high-affinity melatonin receptors and one form of a low-affinity receptor have been identified. The high-affinity ML1 receptors are designated Mel1a and Mel1b. The low-affinity receptor is designated ML2.

The Mel1a receptor is expressed in the SCN and in the hypophyseal pars tuberalis. The SCN is the putative site of circadian action of melatonin, and the hypophyseal pars tuberalis is the putative site of its reproductive effects. The Mel1b receptor is expressed mainly in the retina. The ML1 melatonin receptors belong to the family of guanadine triphosphate-binding proteins or G protein-coupled receptors. Activation of the ML1 receptors results in inhibition of adenylate cyclase activity in target cells.

The distribution of the ML2 receptors has not yet been determined. These receptors are coupled to the stimulation of phosphoinositide hydrolysis.

In summary, melatonin is a hormone that has biological effects and that signals through a family of G protein-coupled receptors.

Melatonin has antioxidant activity. However, this activity is found only with very high pharmaceutical doses of this substance. The most significant antioxidant activity of melatonin appears to be its ability to inhibit metal ion-catalyzed oxidation processes, specifically the Fenton reaction.

Melatonin has been found to have anti-apoptotic activity in the thymus. Melatonin inhibits apoptosis in the thymus as well as in cultured dexamethasone-treated thymocytes (a standard model for the study of apoptosis). It is thought to do so by down-regulating the glucocorticoid receptor.

The mechanism of action of supplemental melatonin is speculative. The putative effect of melatonin as a hypnotic may be accounted for by receptor-mediated action on the limbic system. Pharmacologic doses of melatonin may produce a hypothermic effect, which may also play a role in its hypnotic effect.

PHARMACOKINETICS

The absorption and bioavailability of melatonin varies widely. Melatonin is absorbed from the small intestine and is transported by the portal circulation to the liver. Variable amounts of ingested melatonin are metabolized in the liver to 6-hydroxymelatonin. After conjugation with sulfuric or glucuronic acid, it is excreted by the kidneys. Nonmetabolized melatonin is transported via the systemic circulation to various tissues in the body. Serum half-life of ingested melatonin is approximately 35 to 50 minutes.

If melatonin causes drowsiness, this effect occurs about 30 minutes after ingestion and lasts for at least an hour. Melatonin given in the early evening appears to advance the nighttime peak of melatonin secretion by about three hours. Ingested melatonin that did not undergo first-pass metabolism in the liver is eventually metabolized, mainly in the liver, by hydroxylation to 6-hydroxymelatonin. After conjugation with sulfuric or glucuronic acid, it is excreted by the kidneys. A single nighttime dose is cleared by the following morning. With chronic dosing, however, some lipid storage occurs.

INDICATIONS AND USAGE

Melatonin may be indicated for some forms of insomnia and other sleep disturbances. Research results are mixed with respect to claims that melatonin can abolish some of the symptoms of jet lag. Use of the supplement in cancer and

immune disorders is unsupported by current research; there are some promising findings, but they are very preliminary. There is no evidence to substantiate claims that melatonin can delay aging, be useful in cardiovascular disease, depression, seasonal affective disorder or sexual dysfunction.

RESEARCH SUMMARY

Numerous studies, many of them well-designed, suggest that supplemental melatonin can be effective in some sleep disorders, principally insomnia. These studies show that, in doses that raise serum melatonin levels to those that approximate normal nocturnal levels, sleep can be induced and sustained in some. Through its effects on circadian rhythms and possibly through an induced hypothermic effect, melatonin, in doses administered at carefully timed intervals, may be able to normalize various sleep disorders, such as those sometimes experienced by shift workers, and thus diminish fatigue.

The complexity of appropriate timing and dosage, however, has prompted some researchers to caution against melatonin use for sleep disturbance outside of laboratory settings or without medical supervision—at least until more research sheds further light on these issues. Even marginal drowsiness or lack of mental alertness could prove hazardous for some shift workers, for example.

In addition, a cautionary note has recently been issued with respect to the use of melatonin to treat sleep disturbances in children with neurologic disorders. Six such children, aged nine months to 18 years, were given 5 milligrams of melatonin at bedtime in as effort to treat their sleep disorder. Quality and quantity of sleep quickly increased in five of the six children. But in four of the subjects, all of whom had a prior history of seizures, incidence of seizures increased while taking melatonin. Discontinuance of the supplements led to seizure-incidence returning to pre-supplementation levels. But resumption of melatonin supplementation, this time at a reduced level of 1 milligram doses, again caused an increase in seizures, and the study was halted.

Some criticized these researchers for using inappropriately high doses, but the typical dose range in studies of melatonin's effects on sleep disturbance has been 0.3 milligrams to 5 milligrams, with 2 to 3 milligrams commonly being used. Clearly, more research is needed before melatonin can safely be recommended for use in individuals, whether children or adults, with seizure history. In addition, safety data, in general, is lacking for use of this supplement, particularly for long-term use. Certainly, if more research better defines the proper use of melatonin in sleep disturbances, the supplement might make a significant contribution considering that many sleep-deprived individuals become dependent upon benzodiazepine and other sedating drugs with potentially serious adverse effects in search of insomnia relief.

This point was made in a recent well-designed study that tested the effects of melatonin (2 milligrams daily) in a controlled release formula against placebo. During the course of the study, 34 long-term users of benzodiazepine were encouraged to reduce their benzodiazepine dosage incrementally. The goal was complete discontinuance during weeks five and six. The study proceeded double-blind through the six weeks of period one and then single-blind through the six weeks of period two, during which all subjects received melatonin and efforts to discontinue benzodiazepine resumed.

At the end of the study, 14 of 18 subjects who received melatonin in period one had completely discontinued benzodiazepine use; only four of 16 in the placebo group achieved this goal. An additional six subjects in the placebo group achieved complete discontinuance of benzodiazepine in period two. Sleep quality scores were significantly higher for the melatonin group than for the placebo group. A six-month post-study followup showed that 19 of the 24 subjects who discontinued benzodiazepine therapy continued to maintain good sleep quality. These subjects continued to use melatonin after the study ended and they did not resume use of benzodiazepine.

The use of melatonin to help alleviate some of the symptoms of jet lag has produced mixed results in trials to date. Often some benefit has been noted, but many studies have been criticized for being small and poorly designed. In the largest controlled trial to date, researchers recently reported that melatonin exerts no beneficial physiological effect on jet lag. Melatonin was tested against placebo in two doses and with different administration times. No melatonin regimen was superior to placebo.

Claims that melatonin can be used to prevent or treat cancer or immune dysfunction are unsupported by current research. There is some very preliminary data suggesting some beneficial effects in animal models and in *in vitro* studies. A small amount of clinical work has been done, and more seems warranted.

Claims that melatonin can favorably influence lipids, lower blood pressure and help prevent heart attacks are entirely baseless, as are claims that it can correct sexual dysfunction or otherwise enhance sexual performance. It has demonstrated no effect in seasonal affective disorder and, rather than help dispel depression it has been reported to cause or worsen it in some cases.

The sensational claim that melatonin dramatically delays aging is similarly without foundation. The claim was based,

generally, on the long-held belief that endogenous melatonin secretion diminishes with age and, specifically, upon a single mouse study that has been criticized as seriously flawed by several researchers.

The idea that levels of serotonin fall with age was refuted in a recent study of 34 healthy subjects aged 65 to 81 in whom plasma melatonin concentrations were compared with those of a younger subject group (98 healthy individuals aged 18 to 30). No significant difference was noted between the two groups. The researchers have cautioned against the use of melatonin by the elderly, particularly since many of them may be using a variety of prescription drugs for which interactions with melatonin are unknown and could be potentially hazardous.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Known hypersensitivity to a melatonin-containing product.

PRECAUTIONS

Use of melatonin in children, pregnant women and nursing mothers is not advised.

Adverse reactions of supplemental melatonin include depression. Those who suffer from depression are advised against taking melatonin.

Because melatonin may cause both nighttime and daytime drowsiness, those who operate hazardous machinery are advised against taking melatonin.

Large doses of melatonin (not recommended) have been shown to inhibit ovulation. Women who are trying to conceive should avoid melatonin.

Melatonin use in some children with seizure disorders leads to increased seizure activity. Those with seizure disorders, both children and adults, should avoid melatonin supplements.

Those over 65 years old who take any sedating medications or herbs, or who use alcohol, should exercise caution in the use of melatonin.

ADVERSE REACTIONS

Adverse reactions associated with melatonin include stomach discomfort, morning grogginess, daytime "hangover," feeling of a "heavy head," depression, psychotic episodes (in combination with fluoxetine), headache, lethargy, fragmented disorientation, amnesia, inhibition of fertility, increased seizure activity, suppression of male sexual drive, hypothermia, retinal damage, gynecomastia and low sperm count. Typically, these reports are related to high doses. However, adverse effects have been reported and can occur with low doses as well.

INTERACTIONS

DRUGS

Aspirin and other NSAIDs: Concomitant use may lead to decreased melatonin levels.

Benzodiazepines, sedating antihistamines, sedating antidepressants and other sedating drugs: Concomitant use may cause additive sedation and increase incidence of adverse effects.

Beta blockers: Concomitant use may lead to decreased melatonin levels.

Corticosteroids: Concomitant use may interfere with the efficacy of the corticosteroids.

Fluoxetine: A psychotic episode associated with the use of melatonin in a subject taking the antidepressant fluoxetine has been reported.

Fluvoxamine: The bioavailability of oral melatonin is increased by coadministration of fluvoxamine. This is believed due to inhibition of the elimination of melatonin.

Interleukin-2: There is a report of melatonin augmenting the antitumor effect of this drug.

Isoniazid: There is a report of melatonin enhancing the activity of this antitubercular drug.

Progestin combinations: Melatonin can be additive in inhibiting ovarian function in women.

HERBS

Valerian or kava kava: Concomitant use may lead to additive sedation.

NUTRITIONAL SUPPLEMENTS

5-hydroxytryptophan: Concomitant use may lead to additive sedation.

ALCOHOL

Use of melatonin with alcohol may lead to additive sedation.

FOOD

No interactions are known.

OVERDOSAGE

None known. No apparent serious consequences have been reported in those taking up to 24 grams daily of melatonin for one month, though such doses are not recommended.

DOSAGE AND ADMINISTRATION

Those who use melatonin supplements for sleep disturbance or jet lag usually take no more than 0.3 milligrams to 3 milligrams at bedtime for short periods of time (no longer than two weeks). Higher doses and dosing for longer periods of time requires medical supervision. As with all nutritional supplements, the physician must know if his or her patient is

taking melatonin. Melatonin supplements derived from animals should be avoided.

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Methylsulfonylmethane (MSM)

DESCRIPTION

Methylsulfonylmethane, abbreviated MSM, is an organic sulfur-containing compound that occurs naturally in a variety of fruits, vegetables, grains and in animals, including humans in at least trace amounts. MSM has also been found in such plants as *Equisetem arvense,* also known as horsetail. The biological role of MSM, if any, is not known. MSM is a metabolite of dimethyl sulfoxide or DMSO (see Dimethyl Sulfoxide). It is believed that some of the possible effects of DMSO could be attributed to MSM.

MSM is a water-soluble, solid compound. It is also known as dimethyl sulfone, DMSO2, sulfonylbismethane and methyl sulfone.

ACTIONS AND PHARMACOLOGY

ACTIONS

Known hypersensitivity to an MSM-containing product.

PHARMACOKINETICS

Little is known about the pharmacokinetics of MSM in humans. Sulfur from MSM was found to be incorporated into protein methionine and cysteine when fed to guinea pigs. MSM was also detected in the brain of a normal 62-year old male, following its ingestion, using *in vivo* proton magnetic resonance spectroscopy. Thus, it appears that MSM gets absorbed and can cross the blood-brain barrier.

INDICATIONS AND USAGE

Claims for MSM include pain relief, particularly in arthritis, immune modulation in autoimmune disorders, muscle repair, sleep aid and diabetes therapy. There is no credible evidence to support any of these claims. There is very preliminary research suggesting some possible MSM anti-cancer effects.

RESEARCH SUMMARY

Two animal studies showed that MSM and other bipolar solvents can prolong latency period to time of tumor appearance in chemically induced animal model cancers. In one of these studies, there was no effect on tumor incidence; in the other, MSM seemed to reduce the incidence of poorly differentiated tumors. More research is indicated.

There is no research to support other claims made for MSM.

CONTRAINDICATIONS, PRECAUTIONS, ADVERSE REACTIONS

CONTRAINDICATIONS

Known hypersensivity to an MSM-containing product.

PRECAUTIONS

MSM should be avoided by pregnant women and nursing mothers.