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Clinical Aspects of Melatonin Hormone

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ABSTRACT

Melatonin is a hormone secreted by the pineal gland in the brain. It helps regulate other hormones and maintains the body's circadian rhythm. In animals circulating levels of the hormone melatonin vary in a daily cycle, thereby allowing the entrainment of the circadian rhythm of several biological function. Chemically melatonin and its metabolites can function as endogenous free-radical scavengers and broad-spectrum antioxidants. Jet lag, shift work, and poor vision can disrupt melatonin cycles. Melatonin also helps control the timing and release of female reproductive hormones. It helps determine when a woman starts to menstruate the frequency and duration of menstrual cycles and when a woman stops menstruating (menopause). Some researchers also believe that melatonin levels may be related to aging for example, young children have the highest levels of night time melatonin. Researchers believe these levels drop as we age. Some people think lower levels of melatonin may explain why some older adults have sleep problems and tend to go to bed and wake up earlier than when they were younger. However, newer research calls this theory into question. Melatonin has strong antioxidant effects. The immunomodulatory properties of melatonin are well known and it acts on the immune system by regulating cytokine production of immunocompetent cells. Experimental and clinical data showing that melatonin reduces adhesion molecules and pro-inflammatory cytokines and modifies serum inflammatory parameters. As a consequence melatonin improves the clinical course of illnesses which have anti-inflammatory etiology.

KEY WORDS: circadian rhythm, antioxidants, free-radical, menstrual cycles, anti- inflammatory.

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1. INTRODUCTION

Melatonin is a natural hormone chemically known as N-acetyl-5-methoxytryptamine produced in the brain that has a critical role in the body's sleep cycle. It's sometimes called the "hormone of darkness" because its levels rise to their peak just before we habitually go to bed and drop within about an hour of when we usually wake up. The daily cycling of melatonin helps us to sleep through the night and stay awake during the day. The circadian rhythm is an internal 24-hour "clock" that plays a critical role in when we fall asleep and when we wake up. When it is dark your body produces more melatonin, when it is light the production of melatonin drops. Being exposed to bright lights in the evening or too little light during the day can disrupt the body's normal melatonin cycles[1,2]. Melatonin is ubiquitously distributed and because of its small size and amphiphilic nature, it is able to reach easily all cellular and sub cellular compartments.

Melatonin mostly found in microbes animals and plants. It may also be produced by a variety of peripheral cells such as bone marrow cell lymphocytes and epithelial cells. Usually, the melatonin concentration in these cells is much higher than that found in the blood but it does not seem to be regulated by the photoperiod. It is using in the treatment of Alzheimer's disease, insomnia and other sleeping disorders. Products containing melatonin have been available over-the-counter as a dietary supplement in the United States since before 1994. In many other countries, sale of the hormone remains illegal or requires a prescription[3,4].

2. HISTORY

Melatonin is related to the mechanism by which some amphibians and reptiles change the colour of their skin and indeed, it was in this connection the substance first was discovered As early as 1917, McCord and Allen discovered that extract of the pineal glands of cows lightened frog skin. Dermatology professor Aaron B.Lerner and colleagues at Yale University in the hope that a substance from the pineal might be useful in treating skin diseases isolated and named the hormone melatonin in 1958[5,6,7]. In the mid-70s Lynch *et al.* Demonstrated that the production of melatonin exhibits a circadian rhythm in human pineal glands. The discovery that melatonin is an antioxidant was made in 1993. Around the same time the hormone got a lot of press as a possible treatment for many illnesses. The New England Journal of Medicine editorialized in 2000: "The hype and the claims of the so-called miraculous powers of melatonin several years ago did a great disservice to a scientific field of real importance to human health. Our 24-hour society with its chaotic time cues and lack of natural light may yet reap substantial benefits."[8,9].

3. MELATONIN AND ITS RECEPTORS

Melatonin functions by acting through G-protein coupled membrane receptors MT1 and MT2 and through nuclear receptors RZR/ROR. Melatonin also stimulates a host of antioxidative enzymes including SOD, glutathione peroxidase (GPx) and glutathione reductase (GRd), these actions further reduce the oxidation state of cells Melatonin inhibits the activity of nitric oxide synthetase and dopamine release, potentiates the inhibitory effect of GABA in the central nervous system, modulates the serotonin receptors and potentiates the opioid analgesic[10,11,12]. Melatonin has several additional anti-inflammatory effects, which are probably related to a direct interaction with specific binding sites located in lymphocytes and macrophages[13,14]

4. ROLE OF MELATONIN

4.1 IN THE CIRCADIAN RHYTHM

The circadian rhythm is the body's natural pattern of physiological and behavioral processes that are timed to a near 24-hour period. These processes include things like the sleep-wake cycle as well as variations in body temperature, blood pressure, and the release of hormones. Melatonin levels increase after the onset of darkness and peak in the middle of the night between 11pm and 3am. Melatonin seems to promote sleep and can influence the timing of the sleep period[15,16,17].

4.2 MELATONIN IN INSOMNIA

Melatonin may be effective in treating circadian rhythm disorders in which the desire for sleep is disrupted in its timing, resulting in difficulty falling a sleep or inappropriate sleepiness. There are many common conditions that may be helped, such as[18,19]:

- Shift work sleep disorder
- Advanced sleep phase syndrome
- Delayed sleep phase
- Blindness, which blocks the perception of the natural light-dark cycle.

Studies suggest that melatonin supplements may help people with disrupted circadian rhythms (such as people with jet lag or those who work the night shift) and those with low melatonin levels (such as some seniors and people with schizophrenia) to sleep better. A review of clinical studies suggests that melatonin supplements may help prevent jet lag, particularly in people who cross five or more time zones. A few clinical studies suggest that when taken for short periods of time (days to weeks) melatonin is more effective than a placebo in reducing the time it takes to fall asleep, increasing the number of sleeping hours, and boosting daytime alertness. It' s not clear how well melatonin works, however – some studies suggest that it only reduces the amount of time to fall asleep by a few minutes. A number of human studies have measured the effects of melatonin supplements on sleep in healthy people. A wide range of doses has been used, often taken by mouth 30 - 60 minutes prior to sleep time. Results have been mixed. Some evidence suggests that melatonin may work best for people over 55 who have insomnia. One study of 334 people aged 55 and older found that sustained-release melatonin seemed to help people fall asleep faster, sleep better, be more alert in the morning, and improve quality of life in people with primary insomnia[20,21].

4.3 MELATONIN IN MENOPAUSE

Melatonin supplements may help with sleep problems associated with menopause. However, it does not appear to relieve other symptoms of menopause, such as hot flashes. Peri or postmenopausal women who use melatonin supplements should do so only for a short period of time since long term effects are not known[22,23].

4.4 MELATONIN IN BENZODIAZEPINE WITHDRAWAL

Some clinical research has found that melatonin may help elderly people with insomnia who are tapering off or stopping benzodiazepines such as diazepam (Valium), alprazolam (Xanax), or lorazepam (Ativan). Taking controlled-release melatonin improved sleep quality in those stopping benzodiazepine use. the More study is needed in this field.[24]

4.5 MELATONIN IN BREAST CANCER

Several studies suggest that melatonin levels may be associated with breast cancer risk. For example, women with breast cancer tend to have lower levels of melatonin than those without the disease. Laboratory experiments have found that low levels of melatonin stimulate the growth of certain types of breast cancer cells, while adding melatonin to these cells slows their growth. Preliminary evidence also suggests that melatonin may strengthen the effects of some chemotherapy drugs used to treat breast cancer. In a study that included a small number of women with breast cancer, melatonin (given 7 days before beginning chemotherapy) prevented the lowering of platelets in the blood. This is a common complication of chemotherapy that can lead to bleeding. In another small study of women who were taking tamoxifen for breast cancer but seeing no improvement, adding melatonin caused tumors to modestly shrink in more 28% of the women. Women with breast cancer should ask their doctors before taking melatonin[25,26].

4.6 MELATONIN IN PROSTATE CANCER

Studies show that people with prostate cancer have lower melatonin levels than men without the disease. In test tube studies, melatonin blocks the growth of prostate cancer cells. In one small-scale study, melatonin combined with conventional medical treatment- improved survival rates in 9 out of 14 men with metastatic prostate cancer. Interestingly, since meditation may cause melatonin levels to rise it appears to be a valuable addition to the treatment of prostate cancer. More research is needed before doctors can make recommendations in this area[27].

4.7 MELATONIN AS A THERAPEUTIC AGENT FOR ALZHEIMER'S DISEASE

Melatonin (3 mg p.o. for 21 days) as a sleep-promoting agent was first tried in a small non-homogenous group of elderly patients with primary insomnia associated with dementia. Seven out of 10 dementia patients having sleep disorders treated with melatonin (3 mg p.o. at bed time) showed a significant decrease in sundowning and reduced variability of sleep onset time. In another study, 14 AD patients who exhibited irregular sleep-wake cycles, treated with 6 mg for 4 weeks, showed a significantly reduced percentage of night time activity as compared to a placebo group

The efficacy of 3 mg melatonin/day at bedtime in improving the sleep and alleviating sundowning was shown in 11 elderly Alzheimer,s Disease patients .Table-1

4.8 EFFECT OF MELATONIN ON NEURODEGENERATIVE DISORDERS

The inherent biochemical and physiological characteristics of the brain, including high polyunsaturated fatty acids and energy requirements, make it particularly susceptible to free radicals mediated insult . Increasing evidence indicates that accumulation of aberrant or misfolded proteins, protofibril formation, ubiquitin proteasome system dysfunction, excitotoxic insult, oxidative and nitrosative stress, mitochondrial injury and failure of axonal and dendritic transport represent unifying events in many slowly progressive neurodegenerative disorders . Several effects of melatonin through its receptors may account for its ability to prevent oligodendroglial damage: free radical scavenger production by activated microglia , improvement of membrane fluidity and reduction of edema and polymorphonuclear cell infiltration into damaged tissue, prevention of translocation of the nuclear factor factor kappa-B (NF-B) to the nucleus and the subsequent reduction of pro-inflammatory cytokines expression, which play a relevant role in the inflammatory reaction . In addition, melatonin could modulate astrocyte reactivity or death through an up regulation of astrocytic anti-oxidative defenses.

4.9 EFFECT OF MELATONIN ON TRAUMATIC CNS INJURIES

Traumatic CNS injuries include traumatic brain injury (TBI) and SCI, depending on the anatomical region damaged. It is crucial to relate melatonin's efficacy to the aberrant Ca^{2+} homeostasis-driven signaling pathways as they form a common denominator to any traumatic CNS injury. Melatonin is highly effective in preventing molecular mutilation due to aberrant Ca^{2+} homeostasis. A recent

TABLE 1. CLINICAL STUDIES ON MELATONIN EFFICACY IN ALZHEIMER'S DISEASE

Design	Subjects (M, F)	Treatment	Study´s Duration	Measured	Results
Open-label Study	10 (6, 4) demented patients	3 mg melatonin p.o. daily at bed time	3 weeks	Daily logs of sleep and wake quality completed by caretakers	Seven out of ten dementia patients having sleep disorders treated with melatonin showed a significant decrease in sundowning and reduced variability of sleep onset time[28]
Open-label Study	22 (8, 14) AD patients	9 mg melatonin p.o. daily at bed time	22 to 35 Months	Daily logs of sleep and wake quality completed by caretakers. Neuropsychological assessment.	At the time of assessment, a significant improvement of sleep quality was found. Sundowning was not longer detectable in 12 patients and persisted, although attenuated in 2 patients. Clinically, the patients exhibited lack of progression of the cognitive and behavioral signs of the disease during the time they received melatonin.[29]
Case report	Monozygotic twins with AD of 8 years duration	Patients was treated with 9 mg p.o. daily bed time.	36 Months	Neuropsychological assessment. Neuroimaging.	Sleep and cognitive function severely impaired in the twin not receiving melatonin as compared to the melatonin treated twin.[30]
Open label, Placebo controlled Trial	14 AD Patients	6 mg melatonin p.o. daily at bed time or placebo	4 weeks	Daily logs of sleep and wake quality completed by care takers. Actigraphy	The 7 AD patients receiving melatonin showed a significantly reduced percentage of night time activity compared to a placebo group [31].
Open-label Study	11 (3, 8) AD patients	3 mg melatonin p.o. daily at bed Time	3 weeks	Daily logs of sleep and wake quality completed by the nurses.	Analysis revealed a significant decrease in agitated behaviors in all three shifts and a significant decrease in daytime sleepiness [32].
Open-label Study	45 (19, 26) AD patients	6–9 mg melatonin p.o. daily at bed time	4 months	Daily logs of sleep and wake quality completed. Neuro-psychological assessment.	Melatonin improved sleep and suppressed sundowning, an effect seen regardless of the concomitant medication employed totreat cognitive or behavioral signs of AD [33].

experimental study in aged mice found that oral administration of melatonin restored the metabolic function of cells with improvement in several aspects of Ca^{2+} signaling such as the amplitude and frequency, the size of intracellular Ca^{2+} pools, capacitative Ca^{2+} entry, and the mitochondrial potential. Such aberrant Ca^{2+} homeostasis during aging is undoubtedly a slow and gradual process that causes the accumulation of molecular debris over time. Some benefits of melatonin may also be expected when sudden neurotrauma disturbs tightly regulated Ca^{2+} signaling processes[34,35]. This evidence comes from the experimental studies where melatonin alleviated the impaired large conductance of Ca^{2+} activated K^{+} channel activity in hippocampal neurons, which were injured as a result of intermittent hypoxia or in ischemia-reperfusion injury in chronically hypoxic rats [36,37].

4.10 ANTIINFLAMMATORY ACTIONS OF MELATONIN

Antiinflammatory actions of melatonin depend on its inhibition of the expression of iNOS and, here, mitochondrial iNOS. It was recently reported that the brain melatonin metabolite N1-acetyl-5-methoxykynuramine (AMK) is a better antioxidant than its precursor AFMK and it is a highly efficient NO scavenger, which forms a stable product that does not easily re-donate NO . AMK was more potent than melatonin in inhibiting in vitro and in vivo striatal NOS activity , and both compounds, melatonin and AMK, easily cross the brain-blood barrier after their administration, reaching neuronal and glial cells . Moreover, several of the melatonin metabolites, in addition to AMK, and including 3-hydroxymelatonin and AFMK are likewise free radical scavengers . With regard to the anti-inflammatory effects of melatonin, the most important feature is its inhibition of iNOS expression. Antioxidant and anti-inflammatory properties of melatonin are relevant in mitochondrial physiology and they may play a neuroprotective role in PD. AMK is a potent inhibitor of mitochondrial iNOS activity and a more efficient NO scavenger than its precursor melatonin[38,39,40,41].

5. OTHER USES OF MELATONIN

- **SUNBURN:** A few small clinical studies suggest that gels, lotions, or ointments containing melatonin may protect against sunburn and other skin damage. Studies examined using melatonin alone or combined with topical vitamin E prior to UV light exposure from sun.
- **IRRITABLE BOWEL SYNDROME:** Some preliminary studies suggest that people with IBS who take melatonin reduce some symptoms of IBS, such as abdominal pain. But results are mixed as to whether melatonin may help improve other symptoms, such as bloating and frequency of bowel movements.

- **EPILEPSY:** Some studies suggest melatonin may reduce the frequency and duration of seizures in children with epilepsy. But other studies suggest melatonin may increase the frequency of seizures. Do not take melatonin for epilepsy or give it to a child without talking to your doctor first.
- **ATTENTION DEFICIT HYPERACTIVITY DISORDER (ADHD)--** Some evidence suggests that melatonin may help promote sleep in children in ADHD, although it does not seem to improve the behavioral symptoms of ADHD [42,43].

6. HOW TO TAKE MELATONIN

Melatonin is available as tablets, capsules, cream and lozenges that dissolve under the tongue. There is currently no recommended dose for melatonin supplements. Different people will have different responses to its effects. Lower doses appear to work better in people who are especially sensitive. Higher doses may cause anxiety and irritability.

The best approach for any condition is to begin with very low doses of melatonin. Keep the dose close to the amount that our bodies normally produce (< 0.3 mg per day). You should only use the lowest amount possible to achieve the desired effect. Your doctor can help you determine the most appropriate dose for your situation, including how to increase the amount, if needed [44,45].

PEDIATRIC:

- Always ask your doctor before giving melatonin to a child. Keep doses to less than 0.3 mg/day. There is not enough information to say that doses greater than 0.3 mg per day are safe in children under age 15. In fact, doses 1 - 5 mg may cause seizures in this age group.

ADULT:

- Insomnia: 1 to 3 mg 1 hour before bedtime is usually effective, although doses as low as 0.1 - 0.3 mg may improve sleep for some people. If 3 mg per night does not work after 3 days, try 5 - 6 mg 1 hour before bedtime. You should work with your doctor to find the safest and most effective dose for you. The right dose for you should produce restful sleep with no daytime irritability or fatigue.
- Jet lag: 0.5 - 5 mg of melatonin 1 hour prior to bedtime at final destination has been used in several studies. Another approach that has been used is 1 - 5 mg 1 hour before bedtime for 2 days prior to departure and for 2 - 3 days upon arrival at final destination [46].

PRECAUTIONS:

- Because of the potential for side effects and interactions with medications, people should take dietary supplements only under the supervision of a knowledgeable health care provider. Some people may have vivid dreams or nightmares when they take melatonin. Taking too much melatonin may disrupt circadian rhythms (your "body clock").
- Melatonin can cause drowsiness if taken during the day. If you are drowsy the morning after taking melatonin, try taking a lower dose. Additional side effects include stomach cramps, dizziness, headache, irritability, decreased libido, breast enlargement in men called (gynecomastia), and decreased sperm count. Pregnant or nursing women should not take melatonin because it could interfere with fertility [47].

ANTIDEPRESSANT MEDICATIONS: In an animal study, melatonin supplements reduced the antidepressant effects of desipramine and fluoxetine (Prozac). More research is needed to know if the same thing would happen in people. In addition, fluoxetine (a member of a class of drugs called selective serotonin reuptake inhibitors, or SSRIs) can cause low levels of melatonin in people.

ANTIPSYCHOTIC MEDICATIONS: A common side effect of antipsychotic medications used to treat schizophrenia is a condition called tardive dyskinesia, which causes involuntary movements. In a study of 22 people with schizophrenia and tardive dyskinesia caused by antipsychotic medications, those who took melatonin supplements had fewer symptoms compared to those who did not take the supplements.

BENZODIAZEPINES: The combination of melatonin and triazolam (Halcion) improved sleep quality in one study. In addition, a few reports have suggested that melatonin supplements may help people stop using long-term benzodiazepine therapy. (Benzodiazepines are habit-forming.)

BLOOD PRESSURE MEDICATIONS: Melatonin may make blood pressure medications like methoxamine (Vasoxyl) and clonidine (Catopres) less effective. In addition, medications in a class called calcium channel blockers may lower melatonin levels. Calcium channel blockers include:

- Nifedipine (Procardia), Amlodipine (Norvasc), Verapamil (Calan, Isoptin), Diltiazem (Cardizem), Felodipine (Plendil), Nisoldipine (Sular), Bepridil (Vascor).

BETA-BLOCKERS: Use of beta-blockers may lower melatonin levels in the body. Beta-blockers include:

- Acebutolol (Sectral), Atenolol (Tenormin), Bisoprolol (Zebeta), Carteolol (Cartrol)
- Metoprolol (Lopressor, Toprol XL), Nadolol (Corgard), Propranolol (Inderal).

BLOOD-THINNING MEDICATIONS (ANTICOAGULANTS): Melatonin may increase the risk of bleeding from anticoagulant medications such as warfarin (Coumadin).

INTERLEUKIN-2: In one study of 80 cancer patients, use of melatonin along with interleukin-2 led to more tumor regression and better survival rates than treatment with interleukin-2 alone.

NONSTEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS): NSAIDs such as ibuprofen (Advil, Motrin) may lower levels of melatonin in the blood.

STEROIDS AND IMMUNOSUPPRESSANT MEDICATIONS: Melatonin may cause these medication to lose their effectiveness. Do not take melatonin with corticosteroids or other medications used to suppress the immune system.

TAMOXIFEN: Preliminary research suggests that the combination of tamoxifen (a chemotherapy drug) and melatonin may benefit some people with breast and other cancers. More research is needed to confirm these results.

OTHER: Caffeine, tobacco and alcohol can all lower levels of melatonin in the body [48,49].

7. CONCLUSION

Melatonin has the potential and it has been justified in large number of disorders of different etiologies. However, unequivocal evidence of its efficacy has been established only for a few conditions like jet lag, depression, Prostate cancer, breast cancer, insomnia and in some other diseases. The oncostatic use of melatonin has become a part of an anticancer drug regimen. An anti- Alzheimer's and anti-inflammatory effect of melatonin has been consistently observed in animal models. Some evidences suggest that an antioxidant role of melatonin with the possibilities of beneficial effects in parkinsonism, cardiovascular, gastrointestinal problems. Larger studies of melatonin effects on postmenopausal

women with hot flashes are needed. After working with following article it has found that melatonin requires further extensive research and we cannot overlook this natural hormone.

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