

Melatonin and its Agonists, Circadian Rhythms and Psychiatry

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Abstract

The pineal gland has long been implicated in psychiatric disorders, but only after the discovery of melatonin has the physiology behind these theories been better researched and understood, especially its role in chronobiology. The role of melatonin in sleep is well known and the interrelatedness with mood and other disorders is also receiving increasing attention. Circadian rhythm disorders are also common, and often cause psychiatric symptoms, resulting in impairment in daily functioning. Together with other factors, melatonin has an integral role in the pathogenesis and treatment of these conditions. The role of melatonin in various neurological disorders is also of interest and warrants further investigation. Changes in melatonin levels related to ageing have important clinical implications and should be considered in sleep and cognitive disorders in the aged.

Key words: Melatonin; Circadian Rhythm Disorders; Sleep Disorders; Psychopathology

Received: 13-05-2008

Accepted: 15-07-2008

Introduction

Melatonin is an indolamine hormone (N-acetyl-5-methoxytryptamine), synthesized from tryptophan in pinealocytes in a series of four enzymatic steps.^{1,2} It is widely distributed in nature, occurring in plants, fungi and animals, but was only identified in 1958.^{3,4} In humans, melatonin is exclusively involved in the signalling of "time of day" and "time of year" to all tissues in the body. It is primarily synthesized in the pineal gland, but synthesis also occurs in the retina, GIT, skin, bone marrow and lymphocytes, from where it may influence other physiological functions.³ In lower vertebrates, the pineal gland is photosensitive, and is the site of a self-sustaining circadian clock. In humans, the gland has lost direct photosensitivity, but responds to light via a multisynaptic pathway.^{1,5} In the retina, it acts as a paracrine signal, since it apparently does not enter the circulation from there.¹

Melatonin exerts chronobiological effects via membrane G-protein coupled receptors (MT₁ and MT₂) in the

suprachiasmatic nucleus (SCN). It acutely inhibits neuronal firing in the SCN via the MT₁ receptor, which is likely to be responsible for the regulation of sleep. The phase-shifting effects of melatonin are mediated via the MT₂ receptor.⁶

Melatonin has also been described as a "photoperiodic molecule" with important regulating effects in seasonal reproduction in photoperiodic species, such as hamsters and sheep. The importance of this in humans remains under investigation.^{3,4}

Contrary to what might be expected, melatonin is not required for sleep in humans. Patients who have undergone pinealectomies, have shown little disturbances in their sleep-wake cycles.⁴ Nevertheless, exogenous melatonin has beneficial effects on promotion of sleep. When administered at night (23h30), it has little sedative properties, but when administered earlier (18h00), it is comparable to temazepam.⁴

Melatonin is also involved in the modulation of the pituitary/adrenal axis. Pinealectomy leads to adrenal hypertrophy, which is reversed by administration of exogenous melatonin.² It is also an effective anti-oxidant with strong anti-apoptotic signalling function. It acts as a free radical scavenger and stimulates a number of antioxidative enzymes.¹ This might have practical implications in the treatment of neurodegenerative disorders.³ The administration of melatonin could have a role in the treatment of various eye disorders, such as age-related macular degeneration, glaucoma and myopia.¹

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Melatonin also has immune-enhancing and oncostatic properties. Red wine contains significant amounts of melatonin, and this might explain some of the beneficial health effects of moderate amounts of red wine.⁷

In pregnancy, a placental hormone seems to upregulate maternal melatonin production. It appears to be essential for successful pregnancies and deficits may be related to abortions, pre-eclampsia and neonatal neurological problems.⁸

Unfortunately the use of melatonin as an oral agent is limited by its short half-life and high first-pass metabolism.⁴

Circadian rhythms

Biological rhythmicity is fundamental to various physiological processes and these rhythms are described according to frequency, period length, amplitude and phase.⁹ Circadian frequency implies that one repetition occurs every 24 hours. In humans, the following physiological variables attain peak levels during sleep: TSH, prolactin, melatonin, ACTH, FSH, LH, cortisol, and lymphocyte and eosinophil counts. Catecholamine and blood pressure surges occur during the transition from sleep to wakefulness. Other variables, e.g. blood viscosity, platelet adhesiveness, erythrocyte count, FEV, body temperature, blood levels of insulin and cholesterol, attain peak activity during wakefulness while gastric acid secretion and white cell count peak during the transition from wakefulness to sleep.⁹

Circadian rhythms are generated by the SCN in the hypothalamus and are influenced by a variety of factors. These include sleep, cyclical hormone secretion and daily rhythms of core body temperature.^{10,11} Chronobiological disorders are the result of these rhythms failing to remain synchronized with environmental rhythms.

Interestingly, human circadian rhythms have a frequency of 23,8 to 27,1 hours and not 24 hours exactly.^{10,12} This discrepancy occurs when external time cues are removed, e.g. by putting a test subject in a room which is isolated from external input. Entrainment is thus needed to synchronize the intrinsic circadian cycle to 24 hours. The most important entrainment factor is environmental light. Others include food and meals, hormones (melatonin, thyroid and adrenal cortex hormones), social factors and physical activity, although these are not as potent as photic stimulation.^{9,11}

Circadian disorders

The most common circadian rhythm disorders are caused by jet lag and shift work, but also include delayed sleep phase syndrome (DSPS), advanced sleep phase syndrome (ASPS), irregular sleep-wake pattern (ISWP) and non-24-hour sleep-wake syndrome.^{4,6}

Although jet lag could be described as normal adaptation to forced changes in sleep rhythmicity, the resulting symptoms could impair function.¹³ Studies have also shown that jet lag exacerbates existing mood disorders. Symptoms of jet lag include reduced alertness, loss of appetite, depressed mood, poor psychomotor coordination and reduced cognitive skills. The severity of these symptoms is affected by the number of time zones travelled as well as the direction of travel. Eastward travel affects sleep latency while westward travel affects sleep maintenance. Delays in the light/dark cycle produce fewer symptoms and therefore westward flights tend to be less disruptive.^{6,14,15}

The use of melatonin in circadian rhythm disorders

The treatment of circadian rhythm disorders in special populations, such as pilots, has always been problematic, due to the side-effect profile of conventional hypnotics. In cases of "jet lag", melatonin should be taken only after arrival and effectiveness could be attenuated by the appropriate use of bright light. Numerous studies have documented the efficacy of melatonin in these subjects^{2,6,16}, but some contradicting studies have also been published.¹⁵ A wide dose range (0,5-5mg) has been studied, but 5mg seems to be the most effective dose and should be taken close to the target bedtime at the destination (22h00-24h00). Doses higher than 5mg appear to have no further benefits.^{6,14} Duration of treatment seems to be in the region of 5 days.⁶

Nevertheless, entrainment to a new circadian rhythm is not always advised, especially when the jet-lag sufferer is to return to the place of original departure within a few days.⁶

The Need for Sleep

Several epidemiological studies have confirmed the concept of the need for 7-8 hours of sleep per night, as this amount of sleep is associated with the lowest mortality and morbidity.¹⁷ Even a short period of sleep deprivation causes abnormal endocrine responses, leading to further complications if the insomnia is not resolved.¹¹ Short sleepers experience a number of physiological sequelae, including impaired glucose tolerance, increased blood pressure, sympathetic activation, reduced levels of leptin and increased inflammatory markers.¹⁷

Long sleep also seems to be associated with an increased risk in long-term health effects, but the pathology behind this needs to be evaluated further.¹⁷ The bottom line is that healthy sleep should not be considered a luxury, but instead a basic necessity for a healthy life. Nevertheless, the treatment of insomnia remains problematic, since the commonly used hypnotics are not without side effects leading to daytime impairment and abuse and dependence remains a potential problem.

Sleep and depression

For patients with depression, disrupted sleep is of major significance.^{18,19} Both the treatment and the response to treatment are influenced by the quality and duration of sleep. In practice, between 40% and 95% of subjects with depression have poor sleep quality.^{18,20,21} These findings have been corroborated by physiological criteria from polysomnographic studies - 40% to 60% of outpatients and 90% of inpatients with depression have polysomnographic abnormalities.²⁰ The following associations of the causal relationship between insomnia and depression have been reported¹⁸:

- Insomnia increases the risk of onset of depression. Persistent insomnia is associated with a 40-fold increase in risk of depression.
- Insomnia increases the risk of recurrence of depression.
- A stable sleep-wake rhythm and good sleep hygiene are essential in the prevention of further relapses in depressed patients.

Insomnia could also contribute to worsening of symptoms already caused by depression - e.g. irritability, decreased cognitive functioning, poor executive functioning.

Circadian rhythms and depression

Disturbances in circadian rhythms play a role in the pathogenesis of depression.^{20,21} Cortisol and temperature levels are increased and melatonin levels are decreased – mainly due to amplitude reduction. Some patients respond dramatically to treatment modalities that manipulate circadian rhythms. Circadian rhythms return to normal after recovery.²²

The use of melatonin in insomnia

The use of hypnotics in patients with insomnia is potentially associated with daytime sedation and other impairments, but the same could be said of the daytime complications of a disturbed sleeping pattern. In the treatment of this population, melatonin, 2mg at night, was found to be equal to zopiclone 5mg at night, regarding quality of sleep and inducing onset of sleep with negligible daytime consequences.³ Unfortunately, exogenous melatonin has a very short half-life, and is quickly cleared from the circulation. Prolonged release melatonin with a $t_{1/2}$ of 8-10 hours has been developed and mimics the physiological profile more closely. It has been studied in older patients (55-80 years) and meaningful improvements in sleep quality, daytime alertness, sleep onset latency and general quality of life was obtained.²³

Ramelteon is a selective melatonin receptor agonist at both MT₁ and MT₂ receptors and has a longer half-life than melatonin in humans. It reduces the evening circadian arousal signal and thus enhances the ability to fall asleep and stay asleep during the early part of the night.^{24,25} It is used at a dose of 8mg at night, and no evidence of abuse or dependence has been reported.⁶ It has also received FDA approval for long-term use in adults. Ramelteon has a benign side effect profile, but some hormonal changes have been reported (e.g. reduced testosterone).²⁵

Melatonin and psychiatric disorders

Mood disorders

Various authors have described the use of melatonin in the treatment of depression, often as self-medication and in undiagnosed cases.²⁶ Although there may be coincidental physiological logic behind this practice, it is of limited clinical benefit.

Whereas melatonin levels are decreased at night in patients with major depression and dysthymia, elevated levels have been observed in mania.^{2,27} In depression, there is also a phase advance of the blunted nocturnal peak. Some antidepressants increase melatonin synthesis in humans and conversely, serotonin levels in the brain rise after administration of melatonin.²⁷ Some patients experience Major Depressive Disorder with Seasonal Pattern (MDD-SP), which is characterized by depressive episodes which occur at the same time every year.^{27,28} The mood usually worsens as the duration of light hours is reduced in the winter. The circadian rhythms in these patients are usually in a phase-delay status. Melatonin does not seem to have a direct role in the causation of the disorder, but may be an important marker in the diagnosis.²⁷

Administration of melatonin by itself does not seem to have a direct beneficial effect on depression, except for the alleviation of insomnia, but in synergy with selective serotonin antagonism, there are definite benefits.^{21,29} Agomelatine is a novel antidepressant – acting as an agonist at MT₁ and MT₂

melatonin receptors, and an antagonist at 5-HT_{2c} receptors.^{4,32,21} Rapid onset of improved sleep quality without daytime sedation is achieved with oral administration together with effective antidepressant and anxiolytic activity. There also does not appear to be any significant discontinuation symptoms.²¹ Most antidepressants disturb sleep architecture, with resulting effects on sleep quality, initiation and maintenance, whereas agomelatine improves nocturnal sleep from initiation of treatment.⁶ Changes in sleep patterns occur early after administration, and precede improvement in mood. Agomelatine has proven antidepressant efficacy compared to several antidepressants, with rapid efficacy in improving subjective sleep.^{21,29} Chronic treatment with agomelatine leads to increased cell proliferation and neurogenesis in the ventral dentate gyrus in animals, suggesting that this might be at least partially responsible for its effect in humans.²¹ Because it acts on the main pathophysiological cause, agomelatine has also been found to be effective in restoring the disrupted circadian rhythms in seasonal affective disorder.⁶

Eating disorders

There is a seasonal pattern in bulimia which is more pronounced than in anorexia.^{27,30} Bulimic behaviour exhibits a peak in winter months, which is not related to seasonal mood changes in these patients. Daytime plasma levels of melatonin are increased in patients with bulimia, but this could be related to the increased synthesis of serotonin, secondary to the increased intake of carbohydrates.³¹ Melatonin concentrations are elevated both during the day and at night in patients with untreated anorexia. This might be explained by haemoconcentration or by hypothalamic hypogonadism.²⁷

Schizophrenia

Many 17th and 18th century physicians have associated the pineal gland with "madness", but the reason for this association is not clearly described.³³ Soon after its discovery, melatonin was hypothesised to be involved in the pathogenesis of schizophrenia. The reason being structural similarity with some hallucinogenic substances and the fact that intravenous administration of melatonin to schizophrenia patients in remission worsens psychotic symptoms.^{27,33}

Sleep abnormalities have been described in schizophrenia, but the results in studies have not been consistent.^{34,3} Blunting of the nocturnal peak of melatonin and phase advance in both treated and untreated patients have been indicated.²⁷ The pineal gland seems to be hyposecretory in schizophrenia patients and this does not improve after successful treatment of psychosis. Administration of melatonin does alleviate sleep problems in patients with schizophrenia.³⁶

The use of melatonin in other conditions

Melatonin stabilizes electrical activity in the brain and causes synchronization of EEG, whereas pinealectomy predisposes animals to seizures.³³ Melatonin levels have been shown to be reduced in patients with intractable epilepsy, and subsequent administration has led to clinical improvement in some patients. At this stage, melatonin cannot be recommended as an anti-epileptic drug, but may have a role as an adjuvant therapy.² Melatonin is an antioxidant and has been found to prevent cell death. This has obvious potential benefits for degenerative neurological conditions. In patients with

Alzheimer's disease, CSF melatonin levels have been found to be significantly reduced.²

Melatonin and ageing

Melatonin levels decline with age, and the nocturnal peak is almost lost which contributes to the homeostatic sleep drive decreasing with age.^{2,4,10,23,37}

The circadian clock advances or shifts earlier with ageing, and may play a role in sleep problems in the aged.^{10,38} The need for day-time naps is often related to poor night-time sleep, but may be related to the primarily disturbed circadian rhythms in the elderly. Because of relative safety and its role in the pathogenesis, melatonin should be a consideration when treating these patients.⁴⁰

Various age-related physiological changes may be modulated by the decrease in melatonin, and some authors have suggested supplemental melatonin to be beneficial in general age-related deterioration.³⁷ Degenerative conditions like Alzheimer's disease are associated with even more pronounced lowering of melatonin levels.⁴ This could explain the phenomenon of 'sundowning', where elderly patients develop ataxia, confusion and falling (usually at night or late afternoon), and several studies have shown beneficial effects of melatonin in these patients. Further deterioration of cognitive function and behaviour have also been prevented in some patients with Alzheimer's Dementia.^{41,42}

The Use of Melatonin in Children:

Melatonin is well tolerated in children and does appear to reduce the time to sleep onset as well as minimizing night time awakenings. It is effective in hyperactive and neurologically compromised children and developmental gains have been reported after treatment with melatonin. The dosing seems to be similar to that used in adults, 2,5-5mg administered in the evening, approximately 30-60 minutes before bedtime.⁴³

Side effects and toxicology of melatonin

Minor adverse effects like headache, insomnia, GIT effects and nightmares have been described, but toxicity seems to be of little concern. In animals, doses of 800mg/kg have not been lethal, but high doses could lead to reversible delay in puberty and hypogonadism.²

As mentioned before, poorly timed administration of melatonin may exacerbate various mood disorders and the importance of adhering to physiologically sound timing should be emphasized. High doses in healthy subjects also causes drowsiness, decreased attention and prolonged reaction time.²⁷

Conclusion

Although only discovered 50 years ago, melatonin is well established in the treatment of circadian rhythm disorders like jet lag. Nevertheless, it is probably still underutilized in medicine, especially in the treatment of insomnia where it is a safe and effective treatment option, even in prolonged use. Whilst not effective by itself in the treatment of depression, exciting developments have proven efficacy of melatonin receptor agonism in synergy with serotonin antagonism. Possible applications in the treatment of other neuropsychiatric conditions have been suggested, and further investigation could add to the importance of melatonin as a treatment option.

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