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Melatonin Use In Sleep Disorders

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Summary

Melatonin is a widely publicized "magical drug". Claims of its use include regulation of sleep, circadian rhythm, mood, immune system and reproduction, anti-aging, protection against cancer, and treatment of AIDS. This article reviews the evidence for its use in sleep disorders. Its possible indications and adverse effects are discussed. (*HK Pract* 1997;19:669-672)

摘要

Melatonin在市場上被廣泛宣傳為"神奇藥物"，據稱具有多種功用，包括調節睡眠、生命週期、情緒、免疫系統和生殖系統，對抗老化、癌症，治療愛滋病等。本文探討其對睡眠疾病的作用，同時討論其適應證及副作用。

Introduction

Melatonin is secreted by the pineal gland in the brain. It is also present naturally in some foods. It has been widely publicized to have health benefits, including regulation of sleep, circadian rhythm, mood, reproduction, tumor growth, immune response, and even aging. Articles on melatonin appear in newspapers, books and magazines. A recent cover story in Newsweek boosted melatonin as a hot sleeping pill which is both natural and cheap[1]. In the US, sale of melatonin is estimated at 200 to 350 million dollars annually.[2] Melatonin can be bought without a prescription as a dietary supplement in Hong Kong. General practitioners may come across patients who seek their opinions on this widely publicized "magical drug". The author reviews here the recent scientific evidence on this topic and discusses the use of melatonin in sleep disorders.

Physiology, pharmacology and adverse effects

Melatonin secretion increases soon after the onset of darkness and its level is highest at 2-4 a.m. Its secretion is suppressed by a sufficient intensity of light (e.g. 2500 lux for 2 hours). However, light of domestic intensity e.g. 200-300 lux applied for 30 minutes could also partially suppress melatonin secretion.[3] Melatonin level is highest in childhood; and

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from puberty, there is a secular decline.[4] Physiological consequences of this decline in human remain unclear.

The nocturnal peak in melatonin secretion matches the trough of body temperature and the peak in sleep propensity in healthy individuals.[5] Nevertheless, suppression of melatonin secretion with adrenergic antagonists has not been shown to have major effects on sleep. In both nocturnal and diurnal animals, melatonin secretion occurs at night-time rather than at the time of sleep.[3] The evidence suggests that melatonin synchronizes sleep-wakefulness with the light-darkness cycle. It plays a role in the timing of sleep but does not directly induce sleep.

Exogenous melatonin has a very short half-life of half-an-hour. It is excreted within 2-4 hours after ingestion.[6] This is in contrast to the normal melatonin profile which lasts for 10-14 hours from early evening to the next morning. When exogenous melatonin is given to healthy adults, it produces a time-dependent hypnotic effect[7] (latency to maximum hypnotic effect varies from about 4 hours when melatonin is given at noon to 1 hour when melatonin is taken at 9 p.m.). The hypnotic effect can be produced by variable doses of melatonin (as low as 0.3 mg).[8] The bioavailability of orally administrated melatonin varies widely.[6] The usual oral dose (1 to 5 mg) that can be bought over the counter results in a 10 to 100 times higher serum melatonin concentration than that of the physiological night-time peak. The mechanism underlying its hypnotic effect is closely linked to melatonin's hypothermic property.[9]

Besides the hypnotic effect, melatonin also possesses a time-keeping property. When given in the early morning, melatonin can shift the body clock later and when melatonin is taken in the late afternoon or early evening, it can shift the body clock earlier.[3] This time-keeping property will be further elaborated under the section on its use in circadian rhythm sleep disorders.

When melatonin is used, subjects should pay attention to the preparation's purity and its adverse effects. A few recent editorials published in scientific journals have voiced concerns about melatonin's safety.[2,10,11] If the melatonin is derived from animal pineal glands, it can transmit viruses from the animal to human. Contaminants in melatonin during its manufacturing process may give rise to sensitivity reaction. Although studies on rodents have found low toxicity of melatonin on short term use,[12] no large scale and long term studies have been done in human. Arendt studied 386 subjects taking 5 mg of melatonin for 7 days to alleviate jet lag symptoms.[13] The side effects reported by the subjects were sleepiness (8.9%), headache (2.9%), giddiness (2%); and nausea (0.9%). In other studies, melatonin is reported to disturb sleep pattern,[14] worsen or precipitate depression, inhibit fertility, suppress sex drive, cause hypothermia and retinal damage.[2] Cerebral and coronary vasoconstriction induced by melatonin has also been reported in animal studies.[2] It is not yet clear how common the adverse effects are. Nevertheless, subjects on long term melatonin should receive regular monitoring.

Use of melatonin in sleep disorders

Insomnia

Insomnia is a very common complaint. Its prevalence in communities varies from 13.4-48%.[15] The primary diagnoses amongst 216 insomnic patients according to the International Classification of Sleep Disorders (ICSD)[16] are sleep disorder associated with mood disorder (32.3%), psychophysiological insomnia (12.5%), delayed sleep phase syndrome (7%), inadequate sleep hygiene (6.2%), and sleep disorder associated with anxiety disorder (5.4%).[17] Previous studies have reported that patients with primary insomnia (includes psychophysiological insomnia, sleep state misperception and idiopathic insomnia in the ICSD) have a lower peak melatonin concentration than age-matched controls.[18,19] Melatonin has also been used in patients with primary insomnia and the results are mixed. A few studies have found that melatonin can improve sleep initiation, maintenance and quality.[20,21] On the other hand, Ellis[22] and James[23] both reported that melatonin was not superior to placebo in improving sleep in patients with primary insomnia.

In view of the diagnostic heterogeneity in patients with insomnia, the tasks of the family physician are careful evaluation and accurate diagnosis of the complaint. At present, treatment of primary insomnia with melatonin should not be recommended until there is further evidence of its efficacy from clinical trials.

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Key messages

1. Melatonin is secreted by the pineal gland and its level peaks at 2-4 a.m.
2. Melatonin synchronizes sleep-wakefulness with the light-darkness cycle and possibly other circadian rhythms. It does not directly induce sleep.
3. Preliminary evidence supports the use of melatonin in the treatment of jet lag and sleep phase syndromes.
4. The efficacy of melatonin in primary insomnia patients and shift workers is not adequately documented by clinical trials. Its routine use is not recommended.
5. Use of low dose (1-5 mg) of melatonin is recommended. Beware of the preparation's purity and its adverse effects. Regular monitoring by a clinician is recommended.

Circadian rhythm sleep disorders

Jet lag

Jet lag is a common problem for air travelers after a flight through several time zones. Disturbed sleep, loss of mental efficiency, and tiredness during the day are commonly reported in the first few days after the air travel. The symptoms are considered to be due to desynchronisation of circadian rhythms, such as the sleep-wake cycle, with local time and due to lack of sleep. Melatonin has been used successfully to reduce the symptoms of jet jag in previous studies.[24,25] For westwards flight (e.g. Hong Kong to London), 5 mg of melatonin can be given postflight for 4 days at local bedtime. When traveling eastwards, the same dose of melatonin can be taken preflight for 3 days at the late afternoon and for 4 days postflight at local bedtime.

Sleep phase syndromes

In the ICSD, sleep phase syndromes consist of advanced sleep phase syndrome, delayed sleep phase syndrome, irregular sleep-wake pattern and non-24-hour sleep-wake disorder. They are disorders in which the sleep onset and wake times are respectively advanced (e.g. desired bedtime from 7 p.m. – 2 a.m.); delayed (e.g. desired bedtime from 4 a.m. – noon); disorganized; or chronically delayed for 1-2 hour daily, in relation to the conventional social sleep and wake times (e.g. midnight - 8 a.m.). Insomnia, difficulty in awakening spontaneously and excessive sleepiness are common complaints because of the mismatch between the desired and the conventional social sleep and wake times. Melatonin has been used successfully in delayed sleep phase syndrome[26] and in blind subjects[27] or brain damaged children[28] with irregular sleep-wake pattern or non-24-hour sleep wake disorder. Melatonin 5 mg can be given at the socially desirable bedtime (e.g. 10 p.m.) to stabilise the sleep onset time. Relapses have been reported when melatonin is stopped.

Shift work

There is very few published data on the use of melatonin in shift work. One preliminary report described shift workers taking melatonin at the desired bedtime (6 – 7 a.m.) during their 7 days of night shift.[29] The subjects reported that melatonin use could improve sleep and on-shift alertness. Nevertheless, there is a concern by some researchers that wrongly timed melatonin may induce sleepiness at work.

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Conclusion

Studies on the clinical use of melatonin are very limited. This can be explained by a lack of financial support from pharmaceutical companies. Melatonin is present naturally in foods and hence nobody can claim the product license. When compared to the revenue from melatonin sales, the resources used in melatonin research is meagre.

In conclusion, there is preliminary evidence to support using melatonin in the treatment of jet lag and circadian rhythm sleep disorders. In patients with primary insomnia and for shift workers, melatonin is not yet recommended for clinical use until its efficacy and safety issues are more clearly defined. ■

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