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Melatonin as a Food Supplement for Sleep Disorders

Ioulia K. Tseti

Abstract

N-acetyl-5-methoxytryptamine commonly known as melatonin is a neurohormone produced in the pineal gland as a response to decrease in ambient light and regulates the sleep-wake cycle. Melatonin is a derivative of the amino acid tryptophan and is produced in humans and other mammals. Melatonin supplements are used to treat insomnia and sleep disorders and to adjust sleep schedules due to jet lag. Synthetic melatonin is available as a food supplement in various dosage forms such as pills, granules for oral solution, orodispersible granules, and syrups in order to address patients' needs. Melatonin is often combined with water-soluble vitamins such as B complex vitamins and minerals like zinc in order to be more effective.

Keywords: melatonin, food supplements, jet lag, sleeping disorder, dosage forms

1. Introduction

In 1960, the chemical structure of melatonin was defined [1] since significant attention was attracted towards its use a few years earlier when the dermatologist Dr. Lerner and his colleagues observed that melatonin could cause the lightening of frog skin [2]. Melatonin has been found to affect a wide range of physiological processes such as sleep-wake cycles [3], circadian rhythms [4], sexual maturation [5], and aging [6].

Since then, exogenous melatonin has demonstrated a series of clinical effects [7, 8], and numerous clinical studies have been conducted, where improved sleep quality was documented following exogenous melatonin administration [9]. Recent studies demonstrated analgesic [10], anxiolytic [11], anti-inflammatory, and anti-oxidative effects [12] following administration of melatonin.

2. Melatonin as a food supplement and its uses in modern life

Melatonin is synthesized from tryptophan via 5-hydroxytryptophan and 5-hydroxytryptamine (serotonin). This is followed by *N*-acetylation of serotonin by *N*-acetyltransferase (arylalkylamine *N*-acetyltransferase, AA-NAT) to *N*-acetylserotonin (NAT) and *O*-methylation by acetylserotonin *O*-methyltransferase (ASMT) [previously known as hydroxyindole-*O*-methyltransferase (HIOMT)] to melatonin (*N*-acetyl-5-methoxytryptamine). The rhythm of melatonin production is endogenous, being generated by clock genes in the suprachiasmatic nuclei (SCN), the major central rhythm-generating system or “clock” in mammals. The rhythm, as for

the circadian system in general, is synchronized to 24 h primarily by the light-dark cycle acting via the retina and the retinohypothalamic projection to the SCN [13].

In humans melatonin is metabolized, 70% to 6-sulphatoxy melatonin (aMT6s), primarily within the liver, by 6-hydroxylation, followed by sulfate conjugation; this mechanism varies through species. A number of minor metabolites are also formed, including the glucuronide conjugate. *N1*-acetyl-*N2*-formyl-5-methoxykynuramine and *N1*-acetyl-5-methoxykynuramine were initially reported as brain metabolites [14, 15], but were proved difficult to detect in plasma or urine except after administration of exogenous melatonin [16]. Exogenous oral fast release or intravenous melatonin has a short metabolic half-life, i.e., 20–60 min, depending on the species—with a large hepatic first-pass effect and a biphasic elimination pattern [17]. Slow release, prolonged release, and surge sustained preparations are designed to extend the time of high circulating melatonin [18]. Melatonin has low bioavailability, in general, although it has been found that transmucosal administration increases bioavailability [19]. A critical feature of exogenous melatonin with regard to its clinical uses is its very low toxicity and lack of addictive properties [20, 21].

A $T_{\max}$ of approximately 50 min has been reported following oral immediate-release formulation of melatonin. $T_{1/2}$ of both oral and intravenous melatonin was about 45 min [22]. Over 80% of melatonin dose is excreted exclusively in the urine, as 6-sulfatoxymelatonin (6-SMT) following first-pass hepatic metabolism [23, 24]. Melatonin is short-lived in humans with a half-life in plasma of only 40–50 min [23]. Following oral administration, it is rapidly absorbed with peak plasma levels occurring between 20 min and 2 h depending on dose [14].

Administration of melatonin 45 min before intended clinical effect may therefore be recommended. However, external factors, such as caffeine [25], smoking [26], and other medications [27, 28], which may potentially affect the pharmacokinetics of melatonin, should be considered prior to exogenous melatonin administration.

Long-term use of sedative-hypnotics for insomnia lacks evidence of treatment and has traditionally been discouraged for reasons that include concerns about potential adverse drug effects, such as cognitive impairment, daytime sedation, motor incoordination, and risk of motor vehicle accidents and slips and falls. In addition, the effectiveness and safety of long-term use of these agents remain to be determined [29]. Moreover, several studies have been conducted to assess the effects of sleep hygiene interventions and various non-pharmacological interventions, such as physical activity, bright light exposure, and noise abatement, but no definite effect on nighttime sleep has been reported [29]. Many people seek treatment for insomnia using alternative and complementary medicine [30]. Generally, the main goal of non-pharmacological remedies in the treatment of primary insomnia is to correct behavior patterns that are not conducive to a good quality sleep, and nutrients might play a significant role in this setting, but no evidence is available as to the preferred alternative treatment of insomnia.

In addition to melatonin, other micronutrients, such as zinc and magnesium, may play a role in facilitating sleep. Zinc exhibits an antidepressant-like activity, as observed in a preclinical model of depression [31–34]. Significant clinical correlates were shown [35] related to its action as an antagonist of the glutamate/*N*-methyl-*D*-aspartate receptor. Magnesium has beneficial effects on mood and is crucial, together with zinc, in the endogenous synthesis of melatonin [36]. Various food supplements contain combinations of melatonin with either magnesium or zinc.

Since melatonin production declines with age and is lower in middle-aged and elderly adults with insomnia than in good sleepers [37], supplementation with exogenous melatonin is very common. Exogenous melatonin can effectively treat

insomnia by mimicking the natural endogenous melatonin, binding to the same receptors, and activating the same downstream pathways. The effect of melatonin on sleep is believed to be a consequence of mechanisms that involve an increase in sleep propensity by enhancing the amplitude of circadian clock oscillations via melatonin type 1 (MT1) receptors and the synchronization of the circadian clock via melatonin type 2 (MT2) receptors [39]. By activating MT1 (melatonin type 1 receptor) and MT2 (melatonin type 2 receptor) receptors, melatonin and nonselective MT1/MT2 receptor agonists have shown to improve sleep quality, increase total sleep time, improve sleep efficiency, and decrease sleep onset latency in insomnia patients [38].

The mammalian circadian clock covers a wide range of physiological processes and plays a pivotal role in reproduction [40, 41]. It is currently accepted that dysregulation of the circadian rhythm caused by night shifts, jet lag, and sleep deprivation has a detrimental effect on the reproductive system [42, 43]. Melatonin is produced not only by the pineal gland but also in glial cells, meningeal cells, and in other peripheral tissues, and its cyclical pattern of secretion is responsive to zeitgebers [44]. Melatonin permeability into the central nervous system was described decades ago [45], and its efficient transport through the blood-brain barrier promotes accumulation in the brain at levels higher than the ones existing in the blood. Melatonin also possesses neuroprotective and antioxidant properties [42]. Modulation of redox signaling systems influences the reproductive system in both animals and humans [43, 46], and it is known that insufficient endogenous production of melatonin has been associated with disturbances in the reproductive system due to increased levels of reactive oxygen species (ROS), which are harmful to the male and female gametes [47]. Unhealthy lifestyles and psychosocial stress are aspects of modern life that have a negative impact on gynecological health and reproduction [48]. Epidemiological studies show that night shifts may negatively influence fetal development and may exacerbate gynecological and metabolic disorders, including endometriosis, diabetes, and obesity [49]. Consequently, melatonin supplementation has been considered as a therapeutic approach in gynecological practice owing to its antioxidant properties and its action as hormone modulator.

The neurohormone melatonin is not stored in the pineal gland, but rather is released into the bloodstream and can penetrate all body tissues [50]. It is important to note that “darkness” stimulates the pineal gland to secrete melatonin, whereas exposure to light inhibits this mechanism [51].

Regarding the actual administration of melatonin, it has been shown that the timing of melatonin administration is more crucial in producing the best results than the actual dose; this is secondary to the normal physiologic function of the circadian rhythm [51]. It has been reported that when melatonin was administered at bedtime as a “sleeping pill,” it was not effective unless high doses were used [52]; however, when small doses of melatonin were administered to patients about 2–4 h before bedtime, it was shown to be effective in decreasing sleep latency [53].

Garfinkel et al. [54] investigated 12 elderly subjects (mean age 76 ± 8 years) with chronic illness and insomnia in a crossover study using wrist actigraphy comparing administration of PR-melatonin for 3 weeks with placebo. PR-melatonin 2 mg produced a statistically significant improvement in sleep efficiency and wake time after sleep onset was shorter. Sleep latency decreased, but this was not statistically significant, while total sleep time was not affected.

The side effect profile of melatonin therapy is quite reassuring and is largely superior to other sleep-inducing agents. For example, melatonin therapy does not cause withdrawal or dependence symptoms, unlike benzodiazepines (BZDs) and z-drugs such as zolpidem [55].

Potential harmful effects of exogenous melatonin therapy might result in amenorrhea when used in large doses, which is likely due to suppression of gonadotropin-releasing hormone (GnRH) [56]. However, this effect is readily reversible with cessation of the medication.

Sleep disorders, regardless of the etiology, are frequently encountered by physicians and other health-care providers. According to data from the Centers for Disease Control and Prevention (CDC), up to about 70 million Americans suffer from chronic sleep problems [57], while according to the American Psychiatric Association (APA), approximately 30% of all adults suffer from sleep disorders [58]. Considering that, supplements containing melatonin are widely used. Over the counter (OTC) melatonin-containing supplements can be easily found either online or at pharmacy stores, with beneficial claims on jet lag [59], as well as occasional sleepiness, sleep problems caused by stress, overall mood, and overall health.

Melatonin is often combined with vitamins, such as B complex vitamins and micronutrients, i.e., zinc or magnesium. Clinical studies have been conducted demonstrating the synergistic effect of these combinations [60]. Magnesium supplementation improves sleep efficiency, sleep time and sleep onset latency, early morning awakening, and insomnia objective measures such as the concentration of serum renin, melatonin, and serum cortisol, in older adults [61]. Meanwhile, there is clear evidence on the antidepressant effect of vitamin B12 [62] and vitamin B6 for therapy of hormone-related depression in women [8].

OTC melatonin food supplements are supplied in various pharmaceutical dosage forms in order to accommodate all patients' needs. Usually these food supplements contain 1 mg of melatonin in order to be able to bear the EFSA claim of "Melatonin contributing to the reduction of time taken to fall asleep and to the alleviation of subjective feelings of jet lag" [34].

Pharmaceutical dosage forms of melatonin-containing supplements include tablets and granules either for direct administration or for oral solution preparations, while recently the push and drink form is becoming popular. In this dosage form, the solid mixture containing melatonin and other ingredients is airtightly separated from the solution used for dissolution of the solid. This is achieved by using a container based on a closing storage cap-vial system, in which the closing storage cap contains the solid composition, while the vial contains the solution composition. The nutritional supplement is prepared just prior to use by an immediate procedure, and it can be consumed directly from the vial.

3. Conclusions

Since melatonin has a very low side effect profile and limited evidence of habituation and tolerance, it is widely used among people that suffer from sleep disorders. Various clinical trials have been conducted proving the efficacy of melatonin in treating sleep disorders regardless of the etiology. A plethora of OTC melatonin-containing food supplements, displayed in various pharmaceutical dosage forms, is nowadays available covering the needs of the patients.

Conflict of interest

The authors declare no conflict of interest.

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