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Efficacy of Melatonin as a Sleep-Promoting Agent

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Abstract Numerous studies have demonstrated sleep-promoting effects of melatonin treatment in humans, as evidenced by subjects' self-reports, polysomnographic recordings, and continuous actigraphic registration of motor activity. The sleep-promoting effects of either physiological or pharmacological doses of melatonin typically are observed within 1 h following treatment regardless of the time of melatonin administration. This fact indicates the acute nature of this effect of melatonin on sleep, independent of any effect of the melatonin treatment on circadian organization. This article considers a dose dependency of melatonin effects on sleep, interindividual variability, and age-related differences in circulating melatonin levels produced in response to a given dose of the hormone. Possible side effects of melatonin treatment, and the use of an animal model to serve as a guide in the development of therapeutic applications, also are considered.

Key words melatonin, sleep, human, age, dose, primate

The initial report of a sedative effect of melatonin infusion in humans came from the laboratory of Aaron Lerner shortly after he had identified and named melatonin (Lerner and Case, 1960). Further interest in the possible effects of melatonin on human sleep stemmed not only from this initial report but also because of several indirect signs that link sleep and melatonin production. In laboratory animals, the activities of the pineal enzymes that synthesize melatonin were shown to be elevated at night (Wurtman et al., 1963). With the gradual development of the assay methods that allowed measurement of circulating melatonin concentrations as well as levels of its major metabolite, 6-sulfatoxymelatonin, in urine, it became possible to assess pineal function in man. These measurements showed that melatonin production in humans is concurrent with nocturnal sleep (Lynch et al., 1975) and that the increase in melatonin levels in the evening correlates with the onset of self-reported evening sleepiness (Åkerstedt et al., 1979; Zhdanova et al., 1996b) or with the increase in the evening sleep propensity (Tzischinsky et al., 1993). Observations in human babies revealed a correlation between the consolidation of nocturnal sleep and the normal onset of rhythmic melatonin secretion, both of which occur when infants are about 3 months old (Kennaway et al., 1992). The declines of both melatonin secretion and sleep efficiency with age were postulated to be related phenomena; for example, middle-aged and elderly insomniacs exhibit lower melatonin production than do good sleepers of the same age (Haimov et al., 1994; Hajak et al., 1995). Studies of circadian phase shifts in humans also showed that the shift in the onset of melatonin secretion correlates with the shift in sleepiness, a phenomenon widely observed in shift workers and in transmeridian jet travelers. Acute changes in melatonin levels due to the suppression of melatonin production by, for example, β-blockers, were reported to cause insomnia, whereas an increase in circulating melatonin via suppression of metabolizing enzymes

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Table 1. Acute effects of melatonin treatment on human sleepiness and sleep.

Author(s)	*Year*	*Dose(s)*	*Sleep*	*Test(s)*	*Results*
Lerner and Case	1960	200 mg (i.v.)	Normal	Subjective	↑S
Anton-Tay et al.	1971	100 mg (i.v.)	Normal	Subjective	↑S
Anton-Tay	1974	250 mg	Normal	PSG	↑Stage 2, ↓Stage 4, ↑REM
Cramer et al.	1974	50 mg (i.v.)	Normal	PSG	↓SL
Vollrath et al.	1981	1.7 mg (i.n.)	Normal	Subjective	↑sedation, ↑tiredness
Lieberman et al.	1984	240 mg	Normal	Subjective	↑S
Arendt et al.	1984	2 mg	Normal	Subjective	↑fatigue
James et al.	1987	1 mg, 5 mg	Normal	PSG	↑REM latency (5 mg)
Nickelsen et al.	1989	50 mg	Normal	Subjective	↑fatigue
James et al.	1990	1 mg, 5 mg	Insomnia	PSG	↑REM latency (1 mg)
Waldhauser et al.	1990	80 mg	Normal	PSG	↓SL, ↓AW, ↑SE, ↑Stage 2
Dahlitz et al.	1991	5 mg (4 weeks)	Insomnia	Subjective, PSG	←SO, ↓SL(2)
MacFarlane et al.	1991	75 mg	Insomnia	Subjective	↑TST
Dollins et al.	1994	0.1-10.0 mg	Normal	Subjective, behavioral	↓SL, ↑S
Tzischinsky and Lavie	1994	5 mg	Normal	PSG, MSLT	↑SP
Jan et al.	1994	2.5-10.0 mg	Insomnia	Parents' reports	↓SL, ↑SE
Zhdanova et al.	1995	0.3, 1.0 mg	Normal	PSG	↓SL, ↑SE, ↑S
Cajochen et al.	1995	5 mg	Normal	PSG	w:↑θ, s:↑REMs, ↑Stage 2
Nave et al.	1995	3 mg, 6 mg	Normal	PSG	↓SL, ↑TST
Garfinkel et al.	1995	2 mg	Insomnia	Actigraph	↑SE, ↓WASO
Wurtman and Zhdanova	1995	0.3 mg	Insomnia	Actigraph	↓SL, ↓M, ↓AW
Attenburrow et al.	1996	0.3, 1.0 mg	Normal	PSG	↓SL, ↓Stage 1, ↑SWS
Zhdanova et al.	1996b	0.3 mg, 1.0 mg	Normal	PSG	↓SL, ↑Stage 2
Hughes and Badia	1997	1-40 mg	Normal	PSG	↓SL, ↑SE, ↑Stage 2, ↓SWS

NOTE: Melatonin treatment was by oral administration unless indicated otherwise (i.v. = intravenous; i.n. = intranasal). AW = number of awakenings; SP = sleep propensity; M = number of movements per sleep period; REM = number of rapid eye movements in sleep; S = sleepiness; SL(2) = sleep latency (Stage 2); SL = sleep latency; SE = sleep efficiency; w: = while awake; SWS = slow-wave sleep duration; s: = while asleep; θ = theta frequency; WASO = time awake after sleep onset; ← SO = advanced sleep onset; TST = total sleep time; PSG = polysomnography; MSLT = multiple sleep latency test.

induces sleepiness. Although these correlational observations do not prove a causal relationship between melatonin secretion and sleep, they tend to substantiate direct experimental results.

Numerous studies during the past four decades, summarized in Table 1, have documented the effects of intravenous or oral administration of pharmacological doses of melatonin in humans using subjects' self-reports, polysomnographic overnight or nap recordings, continuous actigraphic recordings of motor activity, multiple sleep latency tests with the ultrashort paradigm, and psychological and performance testing. Except for a few negative or inconclusive results, the majority of these studies have shown that a substantial increase in circulating melatonin levels was associated with sedation, fatigue, decreased alertness, significantly increased reaction time, shortening of latency to sleep, increased sleep efficiency and total sleep time, or increased sleep propensity. Although these studies established a hypnotic effect of exogenous melatonin in humans, they did not answer the question of whether this effect represents or is related to a normal physiological function of the pineal hormone in humans. The skepticism about a physiological role for melatonin was based largely on the fact that only pharmacological doses had been tested and that, in those cases in which circulating levels of the hormone were measured, such treatment was shown to induce circulating melatonin concentrations ranging from several-fold to several thousand-fold over those that normally occur in humans. Thus, the sleep-promoting property of melatonin was commonly dismissed as a side effect of an overdose of the pineal hormone. This notion was supported by the lack of a clear dose dependency of the effect in those studies in which pharmacological doses of melatonin were used.

However, when melatonin doses under 1 mg were tested, the dose dependency of the sleep-promoting effect was revealed (Dollins et al., 1994). All the doses tested augmented subjective sleepiness or shortened latency to sleep onset; however, a dose of 0.1 mg was less potent than a dose of 0.3 mg or higher doses. The endogenous nocturnal circulating melatonin concentrations typically do not exceed 200 pg/ml in adults. Thus, these results demonstrated that the low melatonin doses (0.1 or 0.3 mg) used in this study promoted

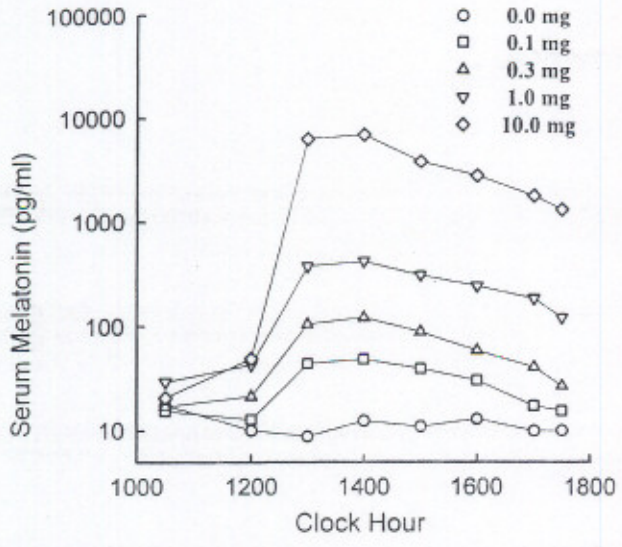

Figure 1. Mean serum melatonin profiles of 20 subjects sampled at intervals after ingesting 0.1, 0.3, 1.0, and 10.0 mg of melatonin or placebo at 1145 h.
SOURCE: Dollins et al. (1994). Reprinted with permission from National Academy of Sciences, U.S.A.

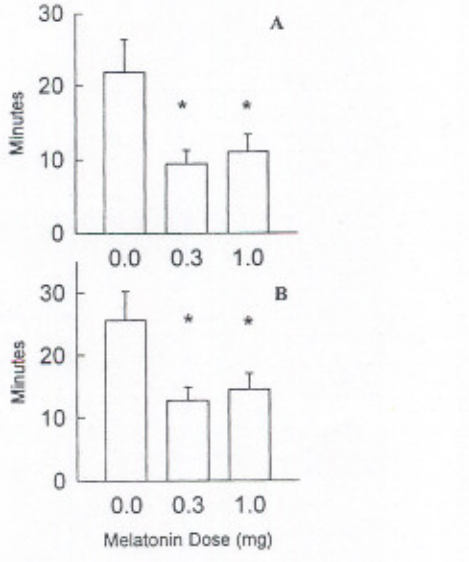

Figure 2. Effects of melatonin (0.3 or 1.0 mg) on average (±*SEM*) latency to (A) sleep onset and (B) Stage 2 sleep relative to placebo ($N = 11$). Asterisks indicate $p < .005$.
SOURCE: Zhdanova et al. (1996b). Reprinted with permission.

sleepiness and sleep while inducing serum melatonin levels comparable to those that normally occur nocturnally in humans (Fig. 1).

A further series of studies comparing the effects of a 0.3-mg dose to those of a 1-mg dose or to placebo confirmed that increasing circulating melatonin levels to within the physiological range promotes polysomnographically detected sleep onset of afternoon naps (Zhdanova et al., 1995) and of overnight sleep (Zhdanova et al., 1996b) in young healthy volunteers (Fig. 2). This effect was not accompanied by significant changes in sleep architecture, a common complication with many existing hypnotics. The tendencies we could observe in polysomnographic data included a decrease in the duration of Stage 4 and an increase in the duration of Stage 2 in some of our subjects. The lack of dramatic changes in the duration or relative amount of different sleep stages is likely to be a general feature of the sleep-promoting effect of melatonin, independent of the dose used in the short term, as similar results were reported after administration of high pharmacological doses of the hormone (Anton-Tay, 1974; Cramer et al., 1974; Waldhauser et al., 1990).

Latency to rapid eye movement (REM) sleep or REM sleep duration typically does not change after the administration of either physiological or pharmacological doses of melatonin. However, some reports have suggested that the quality of REM sleep might be different when circulating melatonin levels are increased. One of the first studies that explored melatonin effects on sleep documented an increase in the number of REMs during REM sleep and an increase in subjects' dream recall after they were treated with a high (250 mg) dose of melatonin (Anton-Tay, 1974). Some of our subjects, both young and old, described an increase in dreaming or the occurrence of more vivid dreams, even after ingesting a low (0.3 mg) dose of melatonin. This effect was especially striking among older people, many of whom reported that as they aged, they experienced fewer dreams that were remembered in the morning than they had experienced earlier in life. Whether these subjective reports reflect an increase in dreaming as a result of melatonin treatment or better recall of dreams is not clear. Neither the effects of melatonin on memory function nor the objective parameters of REM sleep under treatment conditions have been adequately studied.

A continuous actigraphic recording of motor activity for several days or weeks in different populations treated with a 0.3-mg dose of melatonin or placebo close to bedtime also showed the sleep-promoting effect of physiological doses and low pharmacological doses of melatonin. Similar to what was observed when elderly people received a 2-mg dose of a slow-release melatonin preparation (Garfinkel et al., 1995), administration of a 0.3-mg dose to people over 50

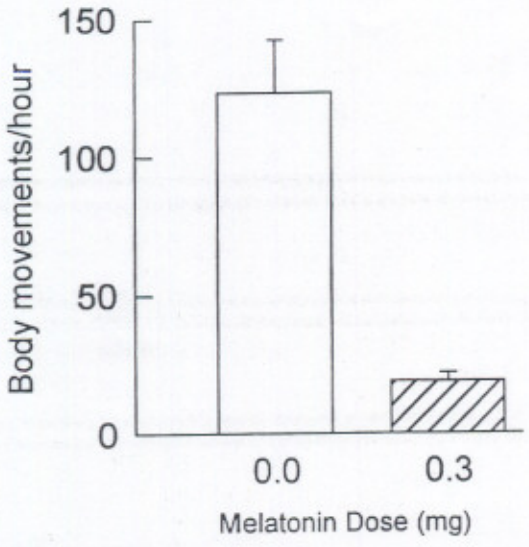

Figure 3. **Mean number of body movements per hour of the sleep period in Angelman syndrome children before and during melatonin treatment ($N = 13$).**
SOURCE: Zhdanova et al. (unpublished data).

years old a half hour prior to their habitual bedtimes caused a decrease in nocturnal motor activity and improved self-reported sleep quality (Wurtman and Zhdanova, 1995).

The same 0.3-mg dose of melatonin was shown to improve sleep significantly in a group of children who suffer from a rare genetic disorder, Angelman syndrome, a condition characterized by severe mental retardation, absent speech, seizures, ataxia, and disturbed sleep (Zhdanova et al., 1996a). Although endogenous melatonin levels in these children tend to be low, an increase in circulating levels of the hormone to within normal physiological range typical for this age group, or to low pharmacological levels, regularized their highly disturbed sleep, significantly increased their sleep time, and significantly decreased their motor activity during the sleep period (Fig. 3). These results are consistent with those reported after the administration of pharmacological oral doses of melatonin (2.5-5.0 mg) to multiple disabled children with severe sleep disorders who failed to respond to conventional management (Jan et al., 1994).

In summary, the human studies undertaken to explore the acute effects of melatonin on sleep generate a compelling picture of the phenomenon of sleep promotion by melatonin used in physiological or pharmacological doses. These observations suggest that melatonin, along with other endogenous or exogenous factors, normally participates in the regulation of sleep-wake behavior. They also imply that melatonin deficiency might be a significant factor in the origin or exacerbation of existing insomnias. The article by Lavie (1997) in this issue comments extensively on possible effects of melatonin treatment in the elderly, who typically have low melatonin production. Successful melatonin treatment of insomnia in children with neurological disorders, or in those who do not produce melatonin due to pineal tumors, presents additional examples of how melatonin replacement therapy might be effective in sleep disorders.

The effectiveness of any biologically active molecule, whether it is normally involved in physiological processes or exogenous in nature, will depend on a number of factors including the dose, the individual sensitivity of the organism, and, in some cases, the time of administration. The experimental evidence suggests that an acute sleep-promoting effect of melatonin, independent of the dose used, typically is manifested within 30 to 60 min after treatment (Zhdanova et al., 1995; Nave et al., 1995). The sleep process initiated under the influence of melatonin appears to have a shorter latency to sleep onset, less susceptibility to arousals, and a subjective perception of a deeper or more restful sleep. This effect of melatonin treatment occurs independent of the time of administration and is observed while either physiological or pharmacological melatonin doses have been administered at different times from 1200 to 2100 h (Tzischinsky and Lavie, 1994; Zhdanova et al., 1995). The latter observation adds another strong argument against interpreting the acute sleep-promoting effect of melatonin as a part of its phase-shifting activity. Melatonin-induced shifts in circadian rhythmicity are limited to 20 to 60 min per day after administration of a single dose of the hormone at a favorable time point (Lewy et al., 1992; Zaidan et al., 1994).

Interindividual differences in sensitivity to melatonin are reflected both in a different time interval necessary for the sleep-promoting effect to occur and in a different degree of effect, from a robust sleepiness in some individuals to a lack of any effect in others, independent of the dose used (Zhdanova et al., 1995). The cause of this interindividual sensitivity to melatonin is not clear. A wide range of doses, from those that induce physiological concentrations of the hormone to those that increase melatonin levels up to a thousand-fold over normally occurring melatonin levels in humans, are effective in acute sleep promotion;

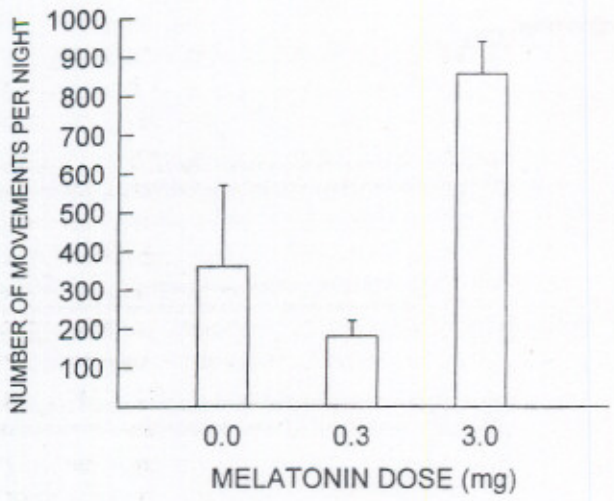

Figure 4. Total nocturnal motor activity in a 67-year-old man after the administration of 0.3-mg and 3.0-mg doses of melatonin or placebo.

however, some individuals might be more sensitive to particular effects of melatonin that may affect the quality of their sleep. Ingestion of a pharmacological dose of the hormone may disrupt the mechanism of the "biological clock" and, if repeated daily for a protracted period of time, may dissociate mutually dependent circadian body rhythms. Moreover, we find that the repeated administration of a pharmacological (3 mg) dose of melatonin may disrupt, rather than improve, sleep in some people. As Fig. 4 illustrates, for example, a decrease in motor activity was observed in a 67-year-old man after administration of a 0.3-mg dose of melatonin a half hour before his habitual bedtime; however, ingestion of a 3-mg dose of the hormone led to a substantial increase in his nocturnal motor activity. It is not clear in this case whether the increase in motor activity was related to the more intense dreaming after melatonin administration, as reported by the subject, or to some other reason(s). Interestingly, according to the self-reports of this subject on his sleep, during the week of a 3-mg melatonin treatment, sleep was perceived as "deeper" than usual, whereas daytime alertness was perceived as less than usual. In some of our subjects, repeated administration of pharmacological doses of melatonin (7 days) have been associated with reports of daytime fatigue, headache, and increased irritability, whereas no sleep complaints were present.

Individual variations in the response to melatonin also might be related to the variations in circulating levels of the hormone induced. Whereas in young people we found that a 0.3-mg dose of melatonin induces serum levels of the hormone ranging from 142 to 205 pg/ml, the range of interindividual variation was significantly higher in older subjects (76-423 pg/ml) treated with the same melatonin preparation. Thus, in some individuals, especially those over 50 years old, even a low melatonin dose may induce supraphysiological circulating levels of the hormone and cause untoward side effects. However, other people might not absorb enough melatonin or might metabolize it too quickly, and that also will jeopardize the efficacy of the treatment.

Although, in our opinion, enough data are available to support the conclusion that melatonin is a physiological component of the sleep process, it also is clear that our present knowledge of the effectiveness of the pineal hormone is not complete. More human studies, including those involving long-term melatonin administration, should be initiated with an emphasis on physiological mechanisms underlying its sleep-promoting function. To facilitate such experimental investigation, it may be useful to develop adequate animal models of sleep-related melatonin effects. Although there are extensive animal data regarding circadian effects of the pineal hormone, there are few animal studies of its acute effects that have led to contradictory conclusions.

Implantation of crystalline melatonin (15-30 μg) into cats' subcortical structures caused initiation of sleep soon thereafter, with an increase in the amplitude and a slowing of the electrical activity in the structures tested (Marczynski et al., 1964). Intraventricular injection of 1 to 100 ng melatonin (Goldstein and Pavel, 1981) induced slow-wave sleep in cats, a 3-h suppression of REM sleep, and a subsequent rebound of this sleep stage. A somnogenic or sleep-potentiating effect of intraperitoneal injection of melatonin (2.5-10.0 mg/kg) or its analogs (Sugden, 1995) has been described in rats; however, in other studies, similar or lower doses of the hormone were reported to be ineffective (Tobler et al., 1994) or even to cause a reduction in sleep in the same species (Mendelson et al., 1980). Such inconsistencies may be explained by the extremely high pharmacological concentrations of melatonin in blood, cerebrospinal fluid, and brain tissue that probably were produced by the doses used. Another major factor to be considered is differences in

the temporal relationships of the sleep-wake cycles and melatonin rhythms in the nocturnally active rats and crepuscular cats studied and those in diurnally active humans. In nocturnal species, melatonin rhythm is similar to that of humans in that melatonin levels are higher at night; however, diurnal animals normally sleep at this time, whereas nocturnal animals are at the peak of their alertness and activity at this time. Thus, melatonin may have a quite different biological meaning in nocturnal and diurnal species.

We conducted a pilot study in monkeys, *Macaca nemestrina* and *Macaca mulatta*, administering either a physiological (0.05 mg) or a low pharmacological (0.1 mg) oral dose of melatonin in the afternoon. Behavioral observations in 3 monkeys and a continuous actigraphic recording in 2 of them showed frequent yawning, an increase in "comforting" behavior (e.g., grooming), a decrease in spontaneous motor activity, and an earlier sleep onset according to a computerized analysis of their actigraphic records (Sleepwatch software program, Mini-Mitter, Sunriver, OR). In the study conducted in collaboration with P. H. Schiller, 1 of the monkeys was trained to participate in a "visual detection" experiment. This sophisticated methodological approach allowed the study of a motivated visual performance after a period of water deprivation. The animal was rewarded with juice after it performed a correct saccadic movement, monitored using the scleral search-coil technique, in response to a visual stimulus. Although spontaneous behavior after the administration of a 0.1-mg dose of melatonin at noon in this animal was similar to that described previously, melatonin treatment did not alter the monkey's performance in the visual test under a condition of high motivation. Our observations in human subjects led us to a similar conclusion. We suggested (Zhdanova et al., 1996b) that an increase in serum melatonin levels within the physiological range, occurring either during the daytime or late in the evening, is not an imperative signal for sleep but is rather a gentle promoter of general relaxation and sedation, elements of sleepiness that, in favorable conditions, might significantly facilitate sleep onset and that are typical for a period of what conventionally is called "quiet wakefulness." However, when a person is adequately motivated, he or she can overcome these "feelings" and be both alert and productive for some time.

The results that we have obtained in this preliminary work with monkeys suggest that nonhuman primates may serve as a useful model in which to study complex sleep-promoting and behavioral effects of different melatonin doses at various times of day. This also may help to explain variability among individuals in responses to the pineal hormone.

Inasmuch as melatonin, labeled "a dietary supplement," is readily available to the American public (albeit usually via preparations of unknown purity and inappropriate doses), it seems important that research be accelerated on the mechanism of melatonin's physiological effects on sleep and on other possible effects that might occur when it is present in circulation at physiological concentrations.

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