Sleep, 20(10):899–907
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Melatonin: A Sleep-Promoting Hormone

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Summary: This review discusses the issue of a dual effect of melatonin on sleep: acute sleep promotion that typically occurs within one hour of administration, and the ability to alter the phase of an underlying circadian pacemaker after a repeated melatonin treatment. The authors suggest that both mechanisms are at work, that they are complementary, and that they may manifest jointly or separately. The review provides some basic information on melatonin, an overview of the literature, and the authors' experience in studying the acute effects of melatonin treatment in humans of different age groups. This review also illustrates the authors' cautious attitude toward melatonin treatment that induces supraphysiologic circulating levels of the hormone. **Key Words:** Melatonin—Sleep—Human—Circadian.

The unbridled exuberance that has greeted the abundantly publicized claims about melatonin's positive effects has overshadowed the acquisition of knowledge about what the pineal hormone really does. Many questions remain about melatonin's effects in humans. This paper assembles some basic information about the pineal hormone's role in humans. It specifically reviews the available data on melatonin's acute hypnotic effect and considers the relation between this effect and melatonin's ability to alter the phase of an underlying circadian pacemaker. Our view is that melatonin directly affects rest–activity mechanisms, promoting the rest phase in humans, and that its ability to suppress the activity of the circadian pacemaker, thus shifting its phase, is part of its net effect.

The identification of melatonin as a pineal hormone was a twentieth century event. It began with studies performed by McCord and Allen (1) in 1915, who showed that mammalian pineal tissue contains a substance that causes the skin of tadpoles to blanch. In 1958, Lerner et al. (2) isolated and identified the pineal principal responsible for the blanching effect as melatonin (N-acetyl-5-methoxytriptamine).

In 1961, Axelrod and Weissbach (3) demonstrated that pineal tissue contains all the enzymes needed to synthesize melatonin from its circulating amino acid precursor, tryptophan. Their discoveries established that the pineal gland converts tryptophan to serotonin (5HT), and that pineal 5HT becomes melatonin through a two-step process that involves serotonin's N-acetylation, catalyzed by N-acetyltransferease (NAT), and then its methylation, catalyzed by hydroxyindole-O-methyltransferase (HIOMT). Soon thereafter, Wurtman et al. (4) showed that melatonin does function in mammals as a hormone. Initially, the only way one could estimate the rate of melatonin production in a pineal gland was to infer this rate from the enzyme activity measured *in vitro* (5). In the 1960s, using this approach, it was shown that in rats the rate of melatonin synthesis is low when animals are exposed to light, and high in darkness (6), and that information about ambient lighting conditions reaches the pineal via a pathway involving the eyes, central neural tracts, and the pineal's sympathetic innervation (7). Subsequent development of melatonin assay methods has made it possible to confirm these basic tenets of pineal physiology and further to establish that melatonin, a lipid soluble hormone, is released directly into the blood stream and the cerebrospinal fluid as it is synthesized. Inactivation of melatonin occurs in the liver, where it is converted to 6-hydroxymelatonin by the P-450-dependent microsomal mixed-function oxidase enzyme system. Most of this 6-hydroxymelatonin is excreted in the urine and feces as a sulfate conjugate (6-sulfatoxymelatonin) (8).

The advent of melatonin assay methods allowed pineal function to be studied in humans for the first time. Lynch et al. (9) demonstrated in 1975 that in humans, as in rats, melatonin is secreted at night but not to a great extent in daytime, so that nocturnal circulating melatonin levels in young adults are 10–40 times higher than those found at midday. This rhyth-

Accepted for publication July 1997.

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mic pattern of melatonin secretion persists in people maintained in constant darkness (10); however, the abrupt imposition of bright light can suppress it (11). The human fetus and newborn infant do not produce melatonin but rely on hormone supplied by the placental blood and, postnatally, by the mother's milk. After infants are 9–12 weeks old, rhythmic melatonin production increases rapidly (12), with highest nocturnal melatonin levels attained in children under five years of age. Thereafter, melatonin levels decrease with physiologic aging (13). Marked interindividual variations in nocturnal melatonin levels are observed in all age groups; however, the circulating melatonin pattern for a given individual tends to remain surprisingly constant from day to day.

MELATONIN AND SLEEP

Numerous indirect and direct observations link melatonin secretion and sleep. The earliest observations on melatonin secretion in humans documented the concurrence of melatonin release from the pineal gland and the habitual hours of sleep (9). Reports from various laboratories confirmed this temporal relationship and correlated the daily onset of melatonin secretion with the onset of nocturnal sleepiness (14,15) or the opening of the so-called "sleep gate" (16). A relevant observation in human babies is that consolidation of nocturnal sleep and stabilization of the sleep–wake cycle occur when the infant is about 3 months old, an age coincident with the normal onset of rhythmic melatonin secretion (12). Both melatonin secretion and sleep efficiency tend to decline with age. These phenomena may be related (17,18). Though such correlations do not prove a causal relationship between melatonin secretion and sleep, they are consistent with and tend to substantiate direct experimental results.

The very earliest report of a soporific effect of melatonin treatment appeared in the pioneering work of Lerner and Case (19). Initial studies specifically addressing melatonin's effects on sleep were conducted at a time when sensitive methods for measuring circulating melatonin levels were not available. In the absence of knowledge of normal melatonin levels, initial studies employed enormous doses of the hormone. Intravenous administration of 50 or 100 mg of melatonin reportedly induced sleepiness and significantly reduced latency to sleep onset, without altering normal sleep architecture (20,21). The daily oral administration of 1 g of melatonin for 6 days to healthy subjects increased the duration of their stage 2 sleep, decreased the duration of stage 4 sleep, and increased the number of rapid eye movements (REMs) during REM sleep (22). Oral administration of a divided 240-mg dose of melatonin to healthy volunteers induced fatigue, significantly increased reaction time, and diminished subjects' alertness (23). An oral 50-mg melatonin dose was reported to increase self-rated fatigue during a 3-hour period following its ingestion if given at 9:00 a.m. but not if given at 7:00 p.m.; latency to sleep onset tended to decrease after both morning and evening treatment; however the magnitude of this effect, compared with that produced by placebo, did not achieve statistical significance in the volunteers studied (24). A group of investigators, led by Vollrath (25), reported that morning intranasal administration of a 1.7-mg melatonin dose promoted sleep onset in 7 of 10 subjects, whereas only one of the subjects on placebo fell asleep. A well-documented effect of melatonin on polysomnographically recorded overnight sleep was obtained by using an 80-mg oral dose of melatonin in situational insomnia induced by exposing subjects to recorded traffic noise (26). In that study, treatment of 20 healthy subjects with melatonin at 9:00 p.m. significantly reduced sleep latency, the number of nocturnal awakenings, the duration of stage 1 sleep, and the mean REM interval. Melatonin treatment also increased sleep efficiency and the duration of stage 2 sleep. Other sleep parameters were not altered.

The effects of lower but still pharmacologic doses of melatonin (1–6 mg) were examined next in different laboratories, and most of the studies also found the treatment to induce fatigue, sleepiness, or increases in sleep propensity. A 1-mg or higher dose administered at 10:00 a.m. significantly reduced latency to sleep onset, increased sleep efficiency, increased the relative duration of stage 2 sleep, and decreased that of slow-wave sleep (27). Similarly, a 5-mg oral dose of melatonin given at 6:00 p.m. increased subjectively assessed fatigue within 90 minutes, as well as the theta band of subjects' electroencephalogram spectrum while they were awake (28,29). An extensive study conducted in Israel assessed polysomnographically recorded sleep propensity after a 5-mg dose of melatonin was administered to young adults at noon, 5:00, 7:00, or 9:00 p.m. (30). The hormone significantly increased sleep propensity at all the time points studied and increased the duration of stage 2 sleep. In the discussion of this study, the authors suggested that melatonin exerts a delayed effect on sleep, the development of which requires 1–2 hours. However, a further examination of this phenomenon in the same laboratory led by Lavie (31) showed that the administration of the hormone 30 or 120 minutes prior to a nap significantly reduced sleep latency and increased total sleep time independent of the dose or time of its administration.

Though most of the studies that employed pharmacological doses of melatonin described changes in subjective and/or objective sleep parameters, there were also studies with negative or indeterminate find-

ings (32–34). Two complementary studies tested the effects of 1- and 5-mg oral doses of melatonin on sleep in normal volunteers (32) and in patients with insomnia (33). Normal volunteers displayed no consistent changes; however, for insomniacs, the authors reported that "although a trend in the induction of sleep with increasing dosages of melatonin was observed, no statistically significant difference was found in this parameter or in sleep duration, sleep efficiency, slow-wave sleep, or percent of movement time". The patients did not report any change in daytime sleepiness; however, "surprisingly, although they reported less sleep than usual when taking melatonin, subjects felt that the quality of the sleep had improved ($p = 0.03$)". The only remarkable effect of melatonin treatment described in both of these studies was an increase in latency to REM sleep among normal subjects receiving the 5-mg dose and among insomniacs receiving the 1-mg but not the 5-mg dose. Such an effect on REM sleep has not been described by other researchers. The negative results in these two studies regarding sleep onset latency may relate, in part, to the experimental design used by the Mendelson group (32,33), i.e. only a short 15-minute interval was allowed to elapse between administration of the hormone and experimental bedtime. The sleep promoting effects of melatonin have typically been observed when the hormone was administered at least 30 minutes prior to bedtime, an interval we find necessary to achieve a substantial increase in circulating melatonin levels after its oral administration. Because circulating melatonin levels induced by the particular melatonin preparation used in these studies were not measured, it is not clear when and to what extent serum levels increased.

The availability of new, sensitive assay methods that allow accurate measurement of circulating melatonin concentrations in the picogram-per-milliliter range has allowed the demonstration that melatonin doses in excess of 1 mg, which had been shown to induce soporific effects in humans, elevate circulating melatonin levels to very high, supraphysiologic levels. Thus, it was unclear whether or not the observed effects on sleep represented side effects of such pharmacologic doses of the hormone.

A program of studies to explore the dose dependency of melatonin's sleep-promoting effect was initiated in our laboratory in the early 1990s. In the first study, one of four melatonin doses (10, 20, 40, or 80 mg) was administered at noon to young healthy volunteers. Each treatment significantly decreased the number of correct responses in computerized performance tests and increased reaction time, self-reported fatigue, confusion, and sleepiness. However, in this dose range, no dose-response relationships were discernible (35). We next tested a still lower range of doses, now administering 0.1, 0.3, 1, or 10 mg of melatonin at noon to 20 young healthy volunteers. Measurements included serum melatonin levels, subjectively assessed sleepiness and mood, and performance using computerized visual and auditory tests, prior to and for 6 hours after the treatment (36). Sleep onset and duration were also studied, beginning 1.75 hours after the administration of melatonin or placebo, using a test involving involuntary muscle relaxation. Serum melatonin concentrations were found to be roughly proportional to the dose of melatonin ingested; peak amplitudes observed after the 0.1- and 0.3-mg doses yielded mean serum melatonin levels of 48 and 121 pg/ml, respectively, values within the physiological nocturnal range of human serum melatonin levels. Sleep onset latencies after ingestion of any of the doses tested were significantly shorter than those following ingestion of placebo. However, the magnitude of the effect induced by the 0.1-mg dose was discernibly smaller than that after any of the higher doses, suggesting dose dependency. Similar tendencies were detected using a profile of mood states test (POMS) and the Stanford sleepiness test. On the basis of these two dose-dependency studies, we concluded that treatments that result in pharmacological levels of circulating melatonin (i.e. serum levels over 200 pg/ml) induce sleepiness and promote sleep onset without clear dose dependency; however, treatments that result in *physiological* concentrations within the normal nocturnal range (i.e. 50–200 pg/ml) do demonstrate dose dependency of the soporific effect. Thus, we hereafter refer to doses of melatonin that produce serum levels of the hormone within the normal nocturnal range as *physiologic doses.*

These findings formed the basis for a new line of research into the physiologic role of melatonin in sleep. A series of experiments was initiated that involved polysomnographic recording of subjects' sleep, as well as mood and performance testing, after ingestion of physiologic doses of melatonin. One study determined that acute administration of a physiologic (0.3-mg) or a low pharmacologic (1.0-mg) dose of melatonin in the evening produced sedativelike effects, compared with placebo, similar to those we had observed when such doses were administered at noontime. Another question that we addressed was whether the effects of such doses varied depending on how many hours prior to habitual bedtime they were administered. Recognizing that individual variations exist in sensitivity to melatonin, we tested the same group of six subjects repeatedly, each subject receiving the hormone or placebo at 6:00, 8:00, and 9:00 p.m., with at least 5 days elapsing between treatments. The sleep-promoting effects of melatonin were tested before, during, and after a 2-hour experimental nap that

began 2 hours after the hormone was administered at 6:00 p.m. or 8:00 p.m., or 1 hour after it was administered at 9:00 p.m. (37). Either dose, given at any of the time points, decreased the mean duration of group latencies to sleep onset and to stage 2 sleep, in comparison with responses to placebo. The effects of the physiologic (0.3-mg) or the low pharmacologic (1.0-mg) dose of melatonin did not differ significantly with respect to any of the parameters measured; i.e. the higher dose did not enhance melatonin's hypnotic effect. The ability of melatonin to decrease a given subject's latency to sleep onset varied in proportion to that subject's sleep latency after placebo administration and to the subject's self-reported sleep onset latency at usual bedtime. Those subjects who normally required more than 20 minutes to fall asleep exhibited more robust responses to the exogenous hormone. None of the volunteers mistook the placebo for melatonin in their self-reports. At 8:00 p.m., four of the subjects receiving the 0.3-mg dose and five receiving the 1.0-mg dose recognized that they had been treated with a "hypnotic"; most perceived the hypnotic effect within 30–60 minutes of melatonin ingestion. One of our six subjects failed to respond to either melatonin dose at either time point.

In the next set of experiments we administered the same doses of melatonin (0.3 or 1.0 mg) or placebo at 9:00 p.m., 1 hour before experimental bedtime, to 12 young healthy volunteers (15). The subjects' overnight sleep was recorded polysomnographically, and their mood and performance were measured repeatedly at intervals on the morning following treatment. Sleep onset latency and latency to stage 2 sleep were significantly decreased following melatonin treatment. Neither dose of melatonin significantly altered the group sleep architecture; however, some subjects did exhibit decreases in latency to REM sleep, the duration of stage 4 sleep, or time awake during the night; and some showed increases in the duration of stage 2 sleep. Administration of the lower melatonin dose (0.3 mg) at 9:00 p.m. elevated serum melatonin to levels falling within the hormone's normal nocturnal range (113 ± 13.5 pg/ml) at the time the "sleep test" was initiated. Analysis of data on subjective sleepiness and of reaction times to visual or auditory stimuli on the morning following treatment (at 7:30 and 9:30 a.m.) revealed no "hangover" effects following melatonin treatment. These findings suggested that the administration of a single dose of melatonin, which is capable of generating normal nocturnal serum melatonin levels, may be sufficient to promote and maintain sleep. These data support the idea that a critical *endogenous* serum melatonin level may be important in the induction and maintenance of normal nocturnal sleep in humans.

Interestingly, analysis of the relationship between a subject's pattern of melatonin production and that subject's habitual sleep behavior revealed a clear correlation between the time of onset of the nocturnal melatonin increase and the time of onset of habitual evening sleepiness ($r = 0.81$) (15). Habitual bedtime did not significantly correlate with the onset of melatonin secretion among this group of healthy students, who are typically engaged in study or social activity late in the evening. These findings are consistent with our behavioral observation that physiological or low pharmacological levels of circulating melatonin do not represent an imperative signal for sleep induction. In most of our subjects, a moderate increase in serum melatonin, achieved using doses of 1 mg or less, promoted general relaxation and a diminished response to routine environmental stimuli, leading to quiet wakefulness and an easier transition to sleep, rather than an unbearable tiredness and an irresistible sleep drive. In the event a person is motivated to perform what that person regards as an important behavior, such increases in circulating melatonin levels do not seem to impair successful performance. This property of physiological melatonin concentrations provides for a seamless transition from wakefulness to sleep not associated with pressing feelings of extreme sleepiness and tiredness, as is seen when subjects take some synthetic hypnotics. This may explain the variability in insomniacs' self-reports on the effects of melatonin ingestion, especially among patients who formerly were treated with benzodiazepines and who expect similar experiences with melatonin (34). The subjective consequences of benzodiazepine and melatonin treatment seem to differ distinctly.

EFFECTS OF MELATONIN TREATMENT ON SLEEP IN CHILDREN

As mentioned earlier, young children normally exhibit the highest circulating melatonin levels, and these gradually decline with age. This may or may not be a significant factor in the lower incidence of insomnia in the young population; however, it raises an interesting question as to whether children with chronic sleep disturbances may have abnormalities in their melatonin pattern. A Canadian clinical study showed that the administration of pharmacological oral doses of melatonin (2.5–5 mg) to multiply disabled children with severe sleep disorders caused substantial improvements in their sleep patterns and increased sleep duration, as described in the reports of their caregivers (38). We recently studied 13 children with Angelman syndrome (AS), a rare genetic disorder characterized by severe mental retardation, absent speech, seizures, ataxia, and disturbed sleep (39). In our study, we ob-

tained continuous actigraphic recordings of the patients' activities during several consecutive days prior to treatment and also during the period in which each child received a daily 0.3-mg dose of melatonin 0.5 hour prior to bedtime. The children's endogenous serum melatonin levels were measured, as well as the levels induced by the hormone treatment. We found that AS children's peak melatonin levels tended to be lower than those reported for normal children of a similar age range, and 4 of our 13 subjects exhibited a phase delay in nocturnal melatonin secretion. Analysis of group data revealed a significant decrease ($p < 0.001$) in motor activity during the total sleep period following melatonin treatment. No significant difference in total sleep time and no significant day-of-treatment effect were observed. After 1–2 days of treatment with a daily low dose of melatonin, the children's nighttime sleep was regularized and significantly less interrupted. Their daytime behavior was not significantly affected by the melatonin treatment; however, in some patients, a decrease in hyperactivity was noticed by parents and school teachers, and this correlated with an increase in their attention.

EFFECTS OF MELATONIN TREATMENT IN OLDER POPULATIONS

Although only a few categories of children suffer from insomnia, many people over 50 years old complain of an age-related decline in sleep quantity and quality. There are certainly many factors that may contribute to this phenomenon of sleep deterioration; however, one of the factors may be melatonin deficiency. A recent study in our laboratory confirmed reports by others (17) of a significant decline in circulating melatonin levels with advancing age. Comparing 24-hour endogenous melatonin profiles in two groups of subjects of different ages (mean ages 29 ± 6 versus 60 ± 8 years), we found significantly lower peak serum melatonin levels in the older group (34 ± 15.4 versus 100 ± 48.5 pg/ml; $n = 18$ for each age group) (40). Both groups displayed high interindividual variability in this parameter.

Actigraphic records indicate that sleep patterns in elderly insomniacs have been improved by melatonin treatment using a pharmacologic 2-mg dose (41) or a physiologic 0.3-mg dose of the hormone (42). Recent preliminary findings in our laboratory among a group of subjects over 50 years old showed positive effects of late evening melatonin treatment (0.3 mg) on sleep parameters, as assessed polysomnographically, especially in those subjects with nocturnal melatonin deficiency. However, we found a substantially higher variability in the sleep-promoting effect of melatonin among the older population than among young healthy adults. This phenomenon might be related to the differences in the mean serum melatonin levels that we observed following administration of the same dose of the hormone, 0.3 mg, which tended to be higher among the older group of volunteers (254 ± 35.2 versus 170 ± 6.6 pg/ml in the younger group) (40). The range of interindividual variation was also significantly higher among the older subjects (76–423 pg/ml versus 142–205 pg/ml in the younger group; $p < 0.0001$). Thus, in some individuals over 50 years old, even a low, 0.3-mg, melatonin dose may induce supraphysiologic circulating levels of the hormone. This finding bears on the important issue of whether, for therapeutic purposes, melatonin doses should be individualized, as discussed below.

Another intriguing aspect of the melatonin-sleep relationship is the effect of the pineal hormone on dream quality and content. Though Anton-Tay (22) reported in 1974 that oral administration of 250 mg of melatonin facilitated subjects' dreaming and increased the number of rapid eye movements during REM sleep, this phenomenon has received little further attention. Some of our subjects, both young and old, described increases in dreaming or the occurrence of more vivid dreams after ingesting even a low, 0.3-mg, dose of melatonin. This effect was especially striking among older people, some of whom report that as they aged, they had experienced fewer dreams that were remembered in the morning than they had earlier in life. Whether these subjective reports reflect an increase in dreaming per se 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. What is repeatedly confirmed, however, is that, unlike some popular hypnotics, melatonin does not inhibit REM sleep (15,21,26).

SYNERGISM IN THE ACUTE SLEEP-PROMOTING AND PHASE-SHIFTING EFFECTS OF MELATONIN

As indicated above, studies conducted in many different laboratories have shown that melatonin administration results in hypnotic effects (Table 1). Are these effects due to an acute modulation of sleep-promoting processes by the pineal hormone or to melatonin's ability to alter the phase of an underlying circadian pacemaker? We suggest that both mechanisms are at work, that they are complementary, and that they may manifest jointly or separately.

Along with environmental stimuli (e.g. ambient light) or chemical agents (e.g. glutamate, neuropeptide Y, serotonin, substance P) (43–45), melatonin has been

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

Authors	Year	Dose	Sleep	Tests	Results
Lerner and Case (19)	1960	200 mg, IV	normal	subjective	↑S
Anton-Tay et al. (20)	1971	100 mg, IV	normal	subjective	↑S
Anton-Tay (22)	1974	250 mg	normal	PSG	↑stage 2; ↓stage 4; ↑REMs
Cramer et al. (21)	1974	50 mg, IV	normal	PSG	↓SL
Vollrath et al. (25)	1981	1.7 mg, IN	normal	subjective	↑sedation; ↑tiredness
Lieberman et al. (23)	1984	240 mg	normal	subjective	↑S
Arendt et al. (66)	1984	2 mg	normal	subjective	↑fatigue
James et al. (32)	1987	1 mg, 5 mg	normal	PSG	↑REM latency (5 mg)
Nickelsen et al. (24)	1989	50 mg	normal	subjective	↑fatigue
James et al. (33)	1990	1 mg, 5 mg	insomnia	PSG	↑REM latency (1 mg)
Waldhauser et al. (26)	1990	80 mg	normal	PSG	↓SL; ↓AW; ↑SE; ↑stage 2
MacFarlane et al. (67)	1991	75 mg	insomnia	subjective	↑TST
Dahlitz et al. (68)	1991	5 mg, 4 weeks	insomnia	subjective, PSG	←SO; ↓SL(2)
Dollins et al. (36)	1994	0.1–10 mg	normal	subjective, behavioral	↓SL; ↑S
Tzischinski and Lavie (30)	1994	5 mg	normal	PSG/MSLT	↑SP
Hughes et al. (27)	1994	1–40 mg	normal	PSG	↓SL; ↑SE; ↑stage 2; ↓SWS
Jan et al. (38)	1994	2.5–10 mg	insomnia	parents' reports	↓SL; ↑SE
Zhdanova et al. (37)	1995	0.3, 1 mg	normal	PSG	↓SL; ↑SE; ↑S
Cajochen et al. (28)	1995	5 mg	normal	PSG	w: ↑θ; s: ↑REMs; ↑stage 2
Nave et al. (31)	1995	3, 6 mg	normal	PSG	↓SL; ↑TST
Attenburrow et al. (69)	1995	0.3, 1 mg	normal	PSG	↓SL; ↓stage 1; ↑SWS
Garfinkel et al. (41)	1995	2 mg	insomnia	actigraph	↑SE; ↓WASO
Zhdanova et al. (39)	1996	0.3 mg	insomnia	actigraph	↓SL; ↓M; ↓WASO
Wurtman and Zhdanova (42)	1995	0.3 mg	insomnia	actigraph	↓SL; ↓M; ↓AW
Zhdanova et al. (15)	1996	0.3, 1 mg	normal	PSG	↓SL; ↑stage 2

AW, number of awakenings; IN, intranasal; IV, intravenous; M, number of movements per sleep period; MSLT, multiple sleep latency test; PSG, polysomnography; REMs, number of rapid eye movements per sleep period; s:, while asleep; S, sleepiness; SE, sleep efficiency; SL, sleep latency; SL2, sleep latency (stage 2 sleep); ←SO, advanced sleep onset; SP, sleep propensity; stage 1 (2, 3, or 4), duration of corresponding sleep stage; SWS, slow-wave sleep duration; TST, total sleep time; θ, theta frequency; w:, while awake; WASO, time awake after sleep onset.

Doses administered orally unless otherwise noted.

shown to acutely alter the activity of the suprachiasmatic nuclei (SCN) of the hypothalamus, the site of a major circadian oscillator in vertebrate animals. Stimulation or inhibition of SCN activity typically results in shifting the phase of its timing mechanism (46) and thereby modifies the temporal pattern of subsidiary physiological and behavioral rhythms, including the sleep–wake cycle. The magnitude and direction of such phase shifts depend on the quality of the alteration (stimulation or inhibition of SCN activity) and on the circadian time at which the agent was administered. Application of melatonin can acutely suppress the metabolic activity and the firing rate of SCN neurons (47–50). Possibly as a result, melatonin administration in the morning induces a delay in the circadian phase in humans, whereas its administration in the afternoon causes a phase advance (51). The maximum magnitude of these phase shifts in humans is reported to be 30–60 minutes per day of treatment (52,53). Thus, melatonin treatment, for example at 5:00 p.m., may shift the onset of evening sleepiness from 11:00 to 10:30 p.m. or, perhaps, even to 10:00 p.m. Such an effect of melatonin may be desirable if one wishes gradually to readjust the rhythms to a new circadian schedule, e.g. after a transmeridian flight, or in adapting to a shift in work schedule. However, the sleep-promoting effects of melatonin, observed in the studies described above, typically occur within 30–120 minutes following administration of the hormone, regardless of time of day. To explain such an acute onset of sleepiness following morning or noontime treatment (27,30,36) in terms of a phase shift of the circadian pacemaker, we would have to assume that a single dose of melatonin could induce a phase shift of 9–12 hours, an assumption contrary to all available experimental data (52,53). We rather suggest that melatonin has a dual role in sleep regulation: both an acute effect and a phase-shifting effect.

This dual role of melatonin in sleep is apparent in many of those studies that specifically addressed the phase-shifting property of the hormone. One of the first and most compelling descriptions of this phenomenon was that of the Australian group (54), which first described melatonin's ability to shift circadian phase in animals (55). In testing the possible use of melatonin to treat jet lag, they reported that their subject, who flew eastward from Australia to the U.S.A., was instructed to ingest a 5-mg dose of melatonin daily at the prevailing, U.S.A., bedtime and to take another capsule if he awoke during the night. "Contrary to previous trips no subjective feelings of jet-lag were experienced [after this trip] and the body temperature rhythm appear[ed] to have re-entrained by the fifth night when no melatonin was taken." The authors also

noticed that if melatonin's sleep-promoting effect deteriorated after several hours, presumably due to metabolism of the hormone, its supplementation with an additional dose provided a new wave of sleepiness the same night, a phenomenon that cannot be explained by a circadian phase shift. On his return trip, this world traveler flew to Germany and England, still taking melatonin at the local bedtimes, as instructed. In Europe, his "body temperature rhythm is flattened, the waveform irregular and hard to interpret. Nevertheless no subjective feelings of jet-lag were experienced and good sleep was reported." Finally, the volunteer returned home. "No melatonin was ingested, after returning to Melbourne, Australia, and nocturnal elevations in body temperature occurred during sleep for the first four to five days after arrival. . . . Although the subject slept well at night, during the day the subject reported feeling very tired and jet-lagged on these three days." The authors' conclusion of this case study was "that, for this subject, melatonin eliminated subjective feelings of jet-lag and allowed a good night's sleep. The duration of the sleep span was generally three to five hours and ingesting a second capsule induced a second sleep. It cannot be definitively stated that melatonin accelerated re-entrainment of the body temperature rhythm but the data are encouraging." This is a good illustration of how melatonin can help to initiate and maintain normal sleep at unusual circadian times. This acute effect does not exclude, rather it complements, the circadian component of melatonin action.

The mechanisms underlying melatonin's hypnotic effect are not clear. According to a recent study by Sugden (56), the sleep-promoting effects of melatonin and its analogs are not mediated by interactions with benzodiazepine or cannabinoid receptors. Because melatonin is a lipid soluble hormone, it is available to all cells of the body and could act at both the membrane-receptor level and intracellularly. This is reflected in its ability to affect such diverse tissues and cells as the SCN, pituitary gland (57), gonads (58), and blood cells (59). Thus, melatonin might acutely modulate the activity of many structures that are directly involved in sleep initiation and maintenance. An acute suppression of SCN activity by melatonin might also contribute to the sleep-promoting effect of the pineal hormone, relieving the mechanisms controlling sleep and wakefulness from the activating pressure of the circadian pacemaker during the day. Further studies are needed to elucidate the mechanisms of the acute sleep-promoting effect of melatonin, though they may remain obscure until the global mechanisms of sleep and wakefulness are clarified.

SHOULD MELATONIN BE USED THERAPEUTICALLY?

Available data on the sleep-promoting effects of modest increases in serum melatonin concentrations suggest that the hormone may have a normal physiological role in sleep initiation and maintenance. They further imply that a melatonin deficiency may impair the integrity, quantity, and quality of nocturnal sleep, and that melatonin replacement therapy might offer an effective and innocuous way of treating this insomnia, without disturbing normal sleep architecture. Such therapy, perhaps, would also support other physiological functions involving melatonin, including the entrainment of various biological rhythms. However, the optimal use of melatonin in hormone replacement therapy requires that the patient receive the correct dose at the proper time.

The current flurry of publicity surrounding the pineal hormone, peculiarly labeled a "dietary supplement", has probably encouraged millions of people to consume melatonin on a daily basis, in quantities that elevate their circulating hormone levels many-fold over those that occur normally. The notion that such pharmacologic doses are utterly safe rests on little research and on the common public experience of a lack of short-term toxic effects of the pineal hormone. However, the biological and medical sciences teach us that subtle but important toxicities can take years to develop, and that it is very unusual for an extreme excess or an extreme deficit of any hormone (or vitamin, amino acid, mineral, etc.) not to result in an imbalance in the vital functions of an organism. A lack of documented negative side effects does not mean an absence of such effects. Long-term clinical and experimental studies are needed to address this important question. Because there is no apparent physiologic benefit to pharmacologic melatonin doses, and because, as discussed below, such doses may induce undesirable side effects, why take them?

Even our present, limited knowledge of melatonin's effects raises concerns about its excessive use. Certain reproductive disorders in humans are reportedly associated with an increase in melatonin production: some cases of male primary hypogonadism and female amenorrhea are reportedly associated with elevated serum melatonin levels (60,61). Some patients with pineal tumors that increase melatonin secretion display delayed puberty; whereas nonparenchymal tumors, which may destroy pinealocytes and thus diminish melatonin production, are sometimes associated with precocious puberty, as first described by Heubner (62) in 1898. The administration of pharmacological doses of the pineal hormone increases nocturnal serum prolactin levels (63). Thus, an uncontrolled use of high mel-

atonin doses could conceivably provoke unwanted modifications in human reproductive function.

High, pharmacologic doses of melatonin significantly lower body temperature (64), reflecting acute changes in either energy metabolism or temperature regulation. Both of these fundamental functions are critical for adaptation and survival, and their disruption could be especially damaging in children and the elderly.

Abnormally high melatonin levels at night and in the day following consumption of a pharmacological dose of the hormone may disrupt the delicate mechanism of the "biological clock" and dissociate mutually dependent circadian body rhythms, as described in a recent study conducted in Arendt's laboratory [Middleton et al. (65)]. Moreover, we find that the administration of a pharmacological (3-mg) dose of melatonin may disrupt, rather than improve, sleep in some people (unpublished data). Like many other natural substances, melatonin may have bimodal dose-dependent effects. Repeated treatments using pharmacological doses of melatonin have also induced daytime fatigue, headache, dizziness, and increased irritability in some of our subjects.

Does all of this mean that melatonin should not be used to treat humans? This conclusion is also unwarranted. The last several decades of research has clearly established when our bodies normally produce melatonin and characterized the normal range of blood melatonin concentrations. Sensitive methods are now available for measuring melatonin levels in blood, saliva, and urine, thus making it possible to detect melatonin deficiencies and to evaluate the effects a particular dose produces in a particular individual. It is possible to adjust the therapeutic dose of melatonin so as to compensate for a deficiency while not raising circulating melatonin levels beyond the normal range. Thus, if we identify those symptoms that may result from melatonin deficiency (insomnia, for example), we have a way to prevent or treat them that is highly unlikely to cause harm. The sleep-promoting effects of melatonin may be of value to insomniacs but only if the hormone is used discretely and within normal physiological parameters.

In summary, we would emphasize that melatonin is a hormone and seems to have significant functions in humans, particularly related to sleep and circadian rhythms. The current public demand for the product and simply the logic of scientific progress demand further intensive investigation of melatonin's physiologic functions and mechanism(s) of action, and a thorough evaluation of possible side effects that might result from melatonin deficiency, excess, or untimely administration.

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