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Sleep-Promoting Effects of Melatonin: At What Dose, in Whom, Under What Conditions, and by What Mechanisms?

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Summary: Differing conclusions regarding the sleep-promoting effects of melatonin may be the result of the broad range of doses employed (0.1–2000 mg), the differing categories of subjects tested (normal subjects, insomniac patients, elderly, etc.), and the varying times of administration (for daytime vs. nighttime sleep). We conclude that melatonin may benefit sleep by correcting circadian phase abnormalities and/or by a modest direct soporific effect that is most evident following daytime administration to younger subjects. We speculate that these effects are mediated by interactions with specific receptors concentrated in the suprachiasmatic nucleus (SCN) that result in resetting of the circadian pacemaker and/or attenuation of an SCN-dependent circadian alerting process. **Key Words:** Melatonin—Circadian rhythms—Suprachiasmatic nucleus—Insomnia—Sleep disorders.

Aaron Lerner, who discovered melatonin, described "mild sedation" following intravenous administration of 100 and 200 mg to patient volunteers (1). These and other early observations of melatonin-induced sleepiness (2–4), coupled with the finding that melatonin is produced only at night, aroused speculation that melatonin might be a "sleep hormone"; that is, an endogenous hypnogogue.

From the start, the stage was set for controversy. Early investigators had no way of knowing that the doses of melatonin they administered resulted in blood levels that were many thousands of times greater than endogenous levels and were therefore of questionable relevance for making inferences regarding the physiological role of melatonin. Furthermore, the concept of melatonin as a sleep hormone ignored its association with wake and activity in nocturnal species. Hence, from a broader biological perspective, melatonin is correctly considered a "darkness hormone" but not necessarily a sleep hormone, although it is possible that it has been recruited for this role in diurnal mammals.

The idea that melatonin might promote sleep in humans stimulated clinical trials as early as 1971 (5). Although many early studies lacked the methodological rigor considered necessary by current standards, some were quite sophisticated; for example, the experiments of Cramer and colleagues (2), published in 1972, employed polysomnographic (PSG) outcome measures in a placebo-controlled design. By contrast, many recent studies have employed wrist actigraphic estimates of sleep (not polysomnography) and may therefore lack the sensitivity and specificity of some of the earlier work, not to mention a lack of data regarding sleep stages. In any case, after 26 years of investigation, the purported sleep-promoting effects of melatonin remain controversial. Melatonin appears to have some soporific activity in humans, but at what dose? in whom? of what magnitude? under what conditions? and by what mechanisms? These issues remain controversial.

While these questions were still under investigation, a melatonin craze swept the U.S. Given its widespread current use, investigators need to carefully define any benefit that melatonin might have for sleep, as well as any risks that might be involved with long-term treatment.

As with any evolving field of research, the literature concerning the sleep-promoting effects of melatonin in humans consists of a rather confusing panoply of studies, employing widely varying doses and varying durations of treatment, in diverse populations with small-sized samples, employing a variety of outcome measures, and leading to varying conclusions. In this pa-

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per, we highlight several of the important controversies in the field and try to give some direction for future research.

We also propose a model that may explain the sleep-promoting effects of melatonin in humans by its interactions with known receptor sites in the suprachiasmatic nucleus (SCN), the site of the circadian pacemaker. Specifically, we postulate that melatonin improves sleep by 1) producing corrective circadian phase shifts and thereby improving the alignment of the endogenous sleep-propensity rhythm with the desired sleep schedule, and/or 2) attenuating the daytime alerting signal generated by the SCN. Because these effects are thought to be related to the physiological role of melatonin, they are predicted to occur at both physiological and pharmacological doses. Sleep-promoting effects that are seen only with pharmacological doses are presumed to require additional mechanisms.

WHAT IS THE EFFECTIVE DOSE?

Melatonin administration studies to date have employed a huge range of doses—from 0.1 mg to several grams. It is important to note that oral doses up to about 0.5 mg produce plasma levels that are roughly in the range of endogenous melatonin, although much depends on a formulation's rate of release. Gelatin capsules using cornstarch or lactose as a filler have an immediate release and produce a "spike" in blood levels followed by a rapid wash-out (half-life of about 45 minutes) (6). A capsule formulated with psyllium as a filler can apparently slow the process of absorption and prolong blood levels (7). Specific slow-release formulations have been devised that come even closer to mimicking the endogenous profile (8). At the high end of the dosage range, blood levels can be thousands of times larger than normal. Given these considerations, 0.5 mg is generally understood to mark the cutoff between "high physiological" and "low pharmacological" doses, although in many subjects, even a 0.5-mg dose can transiently elevate melatonin blood levels into the pharmacological range. (Note: the dose of melatonin sold as dietary supplements is typically 3 mg and produces peak levels that are at least 10 times physiologic concentrations.)

There have been just a few studies of the sleep-promoting effects of melatonin using physiological doses. In general, these have shown that sleep latency is reduced when physiological doses of melatonin are administered during the day (9) or in the evening at bedtime (6,10–12); but overnight total sleep time was not increased, nor was sleep consolidation improved. Although effects on sleep appear to be modest, physiological doses clearly induce circadian phase shifting (13–15) and produce hypothermic effects (16).

Recently, Attenburrow and colleagues (17) reported that 1.0 mg of melatonin, but not 0.3 mg, given 2 hours prior to bedtime to healthy, middle-aged subjects, significantly increased total sleep time and sleep efficiency. This study suggests a supraphysiological threshold for sleep-promoting effects.

Using doses in the pharmacological range, some studies have suggested a dose-response effect on sleep (18) as well as hypothermic response (19). If there is a dose-response relationship for sleep-promoting actions of melatonin, the curve is quite flat; that is, very large increases in dose produce only modest increases in response. For example, in comparing two of our studies of melatonin and sleep in the elderly, the increase in sleep efficiency produced by a 100-fold increase in dose [i.e. 0.5 mg dose (6) compared to a 50 mg dose (Singer, in preparation)] was very small. High doses extend the duration of elevated blood levels, which may account for the prolonged duration of sleep found in some studies (18); such an effect might also be accomplished by a lower dose using a slow-release formulation.

The dose-response curve for melatonin's effect on sleep is clearly different from those of currently recognized hypnotic agents. As the dose of a benzodiazepine or barbiturate is increased, increasing degrees of sleepiness and eventually coma result. In contrast, melatonin doses of several grams, given to humans, can raise blood levels to concentrations that are over 1000 times physiological levels (20) but never produce involuntary loss of consciousness; indeed, some people may not even become overtly sleepy. More direct comparisons of melatonin with standard sedative-hypnotic drugs are needed to place the magnitude of soporific actions of melatonin in perspective (21).

Wurtman and Zhdanova (10) argued that physiological doses are a priori safer, but to date, no serious detrimental effects have been reported with either low or high doses of melatonin, when used for short periods of time. No systematic long-term trials have been performed.

In summary, more studies need to be conducted with doses and formulations that mimic endogenous melatonin secretion so that valid inferences about its physiological role in sleep can be made. In addition, more data on dose-response relationships within subjects are needed to further define the threshold for sleep-promoting effects.

WHO WILL RESPOND?

Melatonin for sleep has been tested in normal subjects across the age spectrum and in patients with specific sleep disorders, especially circadian rhythm sleep disturbances and elderly insomniacs. Because melato-

nin does not appear to benefit everyone, there has been a search for a subgroup of responders who fit a particular treatment rationale or clinical profile; for example, low melatonin producers, elderly, insomniacs, and circadian rhythm disorders.

James and colleagues (22) tested melatonin (1 and 5 mg) in normal young subjects, and were unable to show an effect on any PSG variable, with the exception of a shortening of rapid eye movement latency (5-mg dose only). However, their study could have missed a soporific action because of a "sleep ceiling effect" problem. In their subject population, sleep efficiency for an 8-hour sleep opportunity in the placebo condition was 91%. It is difficult to improve on sleep that is this good. Another example of a possible ceiling effect is provided by Dijk et al. (23), in which young, partially sleep-deprived subjects with high sleep efficiencies in the placebo condition showed no change in any sleep parameters after melatonin administration preceding an afternoon nap (although there was an overall reduction in electroencephalogram power in the lower frequencies).

Therefore, a first approximation for defining a melatonin-responsive subgroup should involve subjects with sufficiently disrupted sleep to demonstrate a treatment effect. The problems of a ceiling effect might be overcome by either intentionally disrupting sleep (artificial insomnia) or testing melatonin in patients with clinical insomnia. Disrupted sleep induced by artificial traffic noise was improved by high-dose melatonin (80 mg) in the Waldhauser et al. study (20). In our 50-mg treatment trial, we found a greater likelihood of response in patients with low baseline sleep efficiency (Singer et al., in preparation). Daytime studies of melatonin administration might also be considered to involve disrupted sleep because the sleep opportunity is at the wrong circadian phase (when sleep propensity is low) (18).

It is well documented that as people grow older, there is a decline, on average, in melatonin concentrations (24,25), and consequently it has been suggested that the elderly might benefit from a melatonin replacement strategy. Haimov et al. (26) found that elderly insomniacs produced less melatonin than normal age-matched good sleepers, and that melatonin treatment (2 mg at h.s. in a group of patients with low melatonin production) significantly decreased wrist activity in the first 6 hours of the night (data for the full night were not reported) (27). Similar results were reported by Garfinkle et al. (28). Both studies used wrist actigraphy (rather than PSG) as the major outcome measure, leaving more room for error in determining sleep; furthermore, the elderly subjects in the Garfinkle et al. study were taking a variety of other medications besides melatonin. Wurtman and Zhdanova (10) found a shortened sleep latency following a physiological dose (0.3 mg) given at bedtime to elderly insomniacs, but only a preliminary report has been provided.

Our recent melatonin trial (0.5 mg) in a highly refined population of healthy, medication-free, elderly insomniacs, utilizing PSG outcome measures, confirmed that a physiological dose of melatonin shortened sleep latency (6). But in contrast to previous reports, we found no relationship between endogenous melatonin production and any sleep parameter in the baseline or placebo condition.

In regard to nonelderly insomniacs, only one study has reported positive results (29); the results of two others were negative (30,31). MacFarlane found an increase in subjective total sleep time and next-day alertness following a large pharmacological dose (75 mg) (29). The James et al. study (30) focused on subjects with sleep misperception whose placebo-condition sleep efficiency was quite high; thus, response to treatment could have been limited by a ceiling effect, as discussed above. Melatonin does not have anxiolytic or amnestic properties that may limit its usefulness in psychophysiological or sleep misperception insomnia.

In summary, the characteristics of patients who may differentially respond to melatonin remain to be identified. An attractive hypothesis suggests that melatonin may specifically benefit people with low endogenous levels, such as the elderly, but the data are mixed. Ironically, it may be the young who are more sensitive to melatonin's soporific effects.

HOW MUCH EFFECT ON SLEEP?

Most studies to date find modest benefits (if any) from melatonin treatment. For example, in the Haimov et al. study (26), the effects of melatonin treatment on sleep efficiency were highly significant statistically ($p = 0.0008$), but the magnitude was not large. Sleep efficiency in the placebo condition was 77.4% and increased to 78.8% with an immediate-release 1-mg formulation and to 80.4% with a slow-release 1-mg formulation. Treated patients did not achieve the levels of sleep efficiency (88.2%) seen in a comparison group of normal sleepers. Attenburrow et al. (17) reported a somewhat more robust response. Sleep efficiency increased from 86.3% in the placebo condition to 91.5% with the 1.0-mg dose. Likewise, total sleep time increased from 397.9 to 419.5 minutes. The data were generated from 12 subjects who had one PSG per condition, so more data are needed to obtain confidence regarding the magnitude of effect. At best, the direct soporific effects of melatonin on nighttime sleep must be described as modest.

TIME OF ADMINISTRATION?

Some of the most robustly positive studies demonstrating a soporific action of melatonin have involved daytime administration (9,18,32,33). A time-of-day effect was reported by Tzischinsky and Lavie (34), who tested melatonin administration (5 mg) at 1200, 1700, 1900, 2100 hours using their ultrashort ("7/13") sleep schedule paradigm. There was a progressive decrease in the latency between time of administration and peak effect through the day. Melatonin caused a disappearance of the forbidden zone for sleep in the late afternoon. In a follow-up study focusing on this time frame, Nave et al. (35) administered melatonin (3 and 6 mg) at 1800 or 2000 hours to healthy young subjects in a balanced design. All four treatment conditions shortened sleep latency in a 2-hour nap opportunity, and there was no statistical difference between the treatments.

It is interesting that all four of these daytime studies tested young subjects whose average age was about 27 years old. Many were presumably students and, if typical, were probably somewhat sleep deprived. This raises the question of whether daytime effects would be as robust in older subjects, and whether a buildup in underlying homeostatic sleep drive ("sleep debt") is necessary for melatonin to produce manifest sleepiness.

It is striking that only one melatonin treatment study to date (17) has shown a statistically significant increase in overnight total sleep time; furthermore, reports of subjective improvement in overnight sleep compared with placebo are rare (29). Also, there has been no reported evidence that nighttime melatonin increases subsequent daytime alertness, which is a major goal of therapy. In general, benefits to nighttime sleep have been limited to a shortening of sleep latency when melatonin was administered in the day or evening and sometimes to an improvement in sleep consolidation indicators (3,10,11,20,26,27,36–38).

POSTULATED MECHANISMS UNDERLYING THE SLEEP-PROMOTING EFFECTS OF MELATONIN

Thermoregulatory hypothesis

Some investigators have suggested that melatonin-induced hypothermia may underlie a sleep-promoting action. This concept is supported by several studies that have shown that daytime administration of melatonin reduces core body temperature in an apparent dose-dependent manner (19,39,40), which seems to be correlated with its sleep-promoting actions. On the other hand, our recent study (6) showed that while melatonin administration consistently lowered body temperature at night, hypothermia was not necessarily correlated with increased sleep propensity. Because pharmacological alteration of body temperature can be achieved by central drug effects on the thermoregulatory set point, changes in peripheral vasomotor tone (affecting heat loss), ambient thermal perception, and many other behavioral and endocrinological factors, specifically linking melatonin's soporific effects to altered thermoregulation is somewhat premature. Further studies are needed to establish causal links between melatonin-induced hypothermia and sleep propensity.

GABAergic hypothesis

Another interesting notion is that melatonin promotes sleep by acting on the GABA chloride channel complex (41). In this hypothesis, the sleep-promoting actions of melatonin are analogous to those of benzodiazepines. Very high doses of melatonin have been required in animal studies to show an effect on the GABA system; thus, this mechanism may be relevant only to the very high dose clinical studies in humans (20,42). Furthermore, evidence to the contrary was reported by Nave et al. (43), who showed that flumazenil, a benzodiazepine receptor antagonist, failed to block either the hypnotic or hypothermic effects of melatonin. This study indicates that melatonin is not binding to BZ-1 receptors; it leaves open the possibility that melatonin could influence flux at the GABA-dependent chloride channel by some other mechanism.

Melatonin and circadian timing system

Currently there is no compelling neurobiological mechanism that explains the soporific effects of melatonin in humans. Futhermore, melatonin is not soporific in most laboratory rodents, hindering basic research efforts. Thus, there is a need to establish new and testable hypotheses for plausible soporific mechanisms in humans. With this goal in mind, we propose that the observed sleep-promoting effects of melatonin can be parsimoniously explained by its actions on the SCN, namely 1) phase shifting of the circadian pacemaker, located in the SCN, and/or 2) attenuation/antagonism of the SCN-dependent mechanism that promotes and maintains cortical and behavioral activation at particular times of day (Fig. 1). For the purposes of this exercise, both effects are presumed to be related to the normal physiological role for melatonin, and therefore the model applies only to physiological doses of melatonin. If pharmacological doses of melatonin are necessary to promote sleep, it is doubtful that the effect is confined to the normal role of endogenous melatonin.

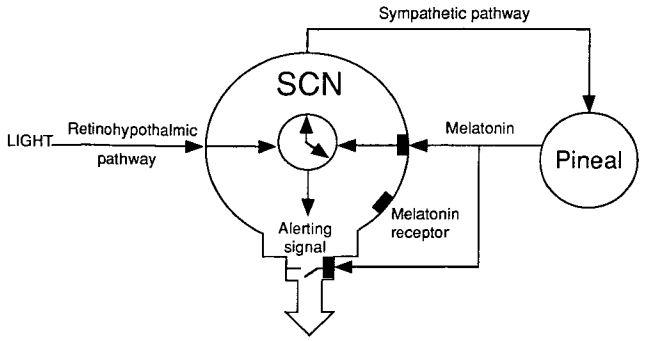

FIG. 1. The interactions between the suprachiasmatic nucleus (SCN) and the pineal gland are shown in a schematic diagram. The timing of melatonin production by the pineal is controlled by the circadian pacemaker (shown as a clock). The phase of the pacemaker is set primarily by the phase-shifting actions of light; light early in the day advances the rhythm, whereas light late in the day delays it. The phase-shifting actions of melatonin are opposite to light; that is, melatonin early in the day delays the rhythm, whereas melatonin late in the day advances it. According to our hypothetical model (see text), melatonin also antagonizes an SCN alerting signal that functions to maintain daytime wakefulness. Thus, melatonin can influence sleep by adjusting the phase (timing) of daytime alertness (by way of its phase-shifting actions) and by antagonizing the intensity of the SCN alerting signal. Both actions are presumably mediated by specific melatonin receptors (portrayed as dark rectangles).

Melatonin and the SCN

Melatonin is produced by the pineal gland at night. The timing of its production is controlled by the circadian pacemaker in the SCN, which is entrained to the solar light–dark cycle via the retinohypothalamic tract (Fig. 1) but is also strongly inhibited by light (in both diurnal and nocturnal species). In all mammals, high-affinity binding sites, as well as specific melatonin receptors, are concentrated in only a few areas of the hypothalamus; especially, the SCN and the *pars tuberalis,* a group of cells in the stalk of the pituitary that mediate the neuroendocrine effects of melatonin in seasonally breeding species (44). In humans, melatonin receptors are abundant in the SCN (45) but are not detected in the *pars* (even in young women of reproductive age). This feature of human neuroanatomy may explain the lack of seasonal reproductive cycles in humans.

Melatonin receptors in the SCN provide the link for an SCN-pineal feedback circuit (Fig 1). This loop does not appear to involve conventional negative feedback inhibition (analogous to glucocorticoid regulation) (46), so it presumably modulates some other aspect of SCN function. We hypothesize that this feedback loop mediates circadian phase shifting and perhaps attenuates the SCN-dependent alerting mechanism in humans as well. There are melatonin binding sites in many other areas, including the vascular tree (47), but it remains unproved whether these are functional receptors. Although it is possible that other subtypes of melatonin receptors will be discovered, the known neuroendocrine and circadian functions of melatonin in animals have been satisfactorily correlated with the specific well-characterized receptor sites in the SCN and *pars tuberalis.*

Melatonin-induced phase shifting

The circadian phase-shifting actions of melatonin are clearly mediated by the SCN and have been documented from the cellular to the behavioral level. Phase resetting was first demonstrated behaviorally in mammals by Redman et al. (48). They showed that daily injections of melatonin could produce phase advances sufficient to entrain rats to a 24-hour cycle who were previously free running, with a circadian period greater than 24 hours, in constant dim-light conditions. Sack et al. (13,49) reported phase shifting in blind people with free-running rhythms, employing a protocol based on the Redman et al. experiment. Lewy et al. (14) subsequently published a complete phase response curve for physiological melatonin administration (0.5 mg) in sighted people in which melatonin caused advances when given in the late subjective day and delays in the late subjective night. A few years later, Zaidan et al. (15) reported similar phase shifts immediately following intravenous administration of melatonin. Gillette and McArthur (50) documented phase advances of the SCN action potential firing rhythm *in vitro,* which corresponded precisely with the behavioral effects reported by Redman et al. (48). The circadian phase-shifting properties of melatonin have been applied to several clinical disorders (see below), and melatonin is now considered prototypical for a category of drugs termed "chronobiotics". [For further reviews, see Dawson and Armstrong (51) and Sack et al. (52).]

The benefit of melatonin-induced phase shifting is based on the principle that sleep quality and quantity are maximal if sleep occurs at the optimal circadian phase. When sleep and other body rhythms are desynchronized in temporal isolation experiments, alerting is consistently associated with the increase in body temperature following the temperature nadir (53–55) [this is also the time that pineal melatonin production ceases (56)]. It has been suggested that even a small degree of desynchrony might result in initial insomnia symptoms (57) because the timing of maximal alertness in the evening (the "sleep forbidden zone") (58) is so close to the opening of the "sleep gate" (59).

From the available clinical literature, there is substantial evidence that melatonin treatment can phase-shift circadian rhythms [for reviews, see Dawson and Armstrong (51) and Sack et al. (52)], and that correction of an abnormal phase relationship between the sleep propensity rhythm and sleep schedule can im-

prove sleep. For example, Sack et al. (13,49) found that melatonin could phase-shift the free-running rhythms of totally blind people and thereby improve sleep. McArthur et al. (60) recently reported the entrainment of a sighted individual with a non-24-hour sleep–wake syndrome, using a physiological dose of melatonin (0.5 mg at the same time each day). Several groups have reported benefits to patients with delayed sleep-phase syndrome, on the basis of a presumed phase-shifting action of melatonin (32,61–63); however, phase measurements were not made in these patients, so a direct soporific effect cannot be ruled out. Sack et al. (64) have also shown benefits to the sleep of night-shift workers who phase-shift in response to melatonin treatment. Because melatonin can cause advances or delays, depending on the timing of administration, treatment may potentially worsen sleep if it is given at the wrong circadian time and results in a more unfavorable phase relationship.

In summary, there is strong evidence that melatonin can phase-shift circadian rhythms, and optimal alignment of the circadian phase with desired sleep time is a critical ingredient of good sleep. Phase shifting can occur with near-physiological doses and is presumably mediated by melatonin receptors in the SCN.

Does melatonin antagonize an SCN-dependent alerting signal?

An alternate explanation for the subtle soporific effects of melatonin (that remains to be specifically tested) suggests that melatonin somehow attenuates the SCN-dependent mechanism responsible for promoting and maintaining cortical and behavioral arousal at particular times in the circadian cycle. Edgar and colleagues (65) demonstrated the existence of an SCN-dependent alerting mechanism by evaluating the effects of SCN lesions on sleep–wakefulness in squirrel monkeys and proposed that the sleep–wake cycle results from the opponent interaction of SCN-dependent alerting and homeostatic sleep drive—a concept derived from the widely supported belief that two processes govern the mammalian sleep–wake cycle (40). As SCN-dependent alerting increases to high levels late in the day, a sleep "forbidden zone" or "wake maintenance zone" occurs (59,66). Despite prior sleep loss, sleep tendency is always lowest during the hours preceding habitual bedtime (55,58,67). At night, when the SCN-dependent alerting signal decreases, accumulated sleep drive is no longer opposed and is dissipated through the sleeping process.

If melatonin antagonizes an SCN-dependent alerting signal, it follows that its direct sleep-promoting properties would be proportional to 1) the amount of underlying homeostatic sleep drive (which, in turn, depends on the duration of prior wakefulness) and 2) the strength of the SCN alerting signal, which is greatest late in the day. Accordingly, exogenous melatonin would be predicted to have its greatest effect on sleep when administered during the day, especially during the evening hours, when both the homeostatic sleep drive is greatest and the hypothesized opponent alerting signal from the SCN is the strongest (55). In contrast, the sleep-promoting effects of melatonin are predicted to be minimal at times when the SCN alerting signal is quiescent and/or sleep drive has been discharged; for example, the latter part of the night and the early morning. In other words, according to this working model, melatonin cannot generate sleep propensity; it can only release or unmask it.

This working model might explain the relatively flat melatonin dose-response curve for soporific effects by invoking a saturation of the relatively small number of melatonin receptors in the SCN (compared with the relatively large number and broad distribution of GABA receptors that mediate the effects of benzodiazepines). The model might also explain the very modest response observed in our recent study of elderly subjects (6). If the elderly have attenuated homeostatic sleep drive (68), then melatonin would be predicted to have less impact on sleep–wake regulation. With these considerations in mind, one might also predict that young people would be more responsive to melatonin than the elderly. Indeed, some of the most robust effects of melatonin on sleep have involved melatonin administration during the day to young (possibly sleep-deprived) subjects (9,18).

As mentioned above, several investigators have argued that the sleep-promoting effects of melatonin may be mediated by its hypothermic actions (69). It is plausible that hypothermia and sleepiness are both caused by a decrease in the alerting signal from the SCN. A major efferent pathway passes from the SCN to the preoptic area of the hypothalamus (70), an important center for thermoregulation. Alternatively, melatonin-induced hypothermia might be mediated by a direct action on receptors in blood vessels.

Our concept that melatonin may attenuate a circadian alerting signal is similar to "disconnecting the clock", proposed by Dawson and Armstrong (51), who suggested that melatonin administration allows people to be more "phase tolerant"; that is, to sleep during the wrong circadian phase.

CONCLUSIONS

Current evidence suggests that melatonin can benefit sleep by correcting circadian phase abnormalities, and that it has modest direct sleep-promoting effects that are most evident following daytime administration to

younger subjects. These responses may be related to the normal physiology of endogenous melatonin, mediated by specific receptors in the SCN. Soporific actions at very high doses may involve other pharmacological (nonphysiological) mechanisms and sites of action.

The clinical role for melatonin or melatonin analogs remains to be defined. If ultimately deemed safe and effective, melatonin compounds could be useful in patients with insomnia caused by some form of circadian phase disturbance; in these patients, synergism between clock resetting and a direct sleep-promoting effect could often be advantageous. Melatonin seems unlikely to replace currently available sedative drugs for psychophysiological insomnia, which depend on anti-anxiety and amnestic properties for much of their therapeutic activity.

Although widespread use of melatonin has not produced any disastrous consequences to date, no systematic surveillance is currently being applied. What appears to be a relatively benign safety record should not detract from vigorous efforts to define scientifically the efficacy and long-term safety of melatonin in sleep disorders medicine.

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Note added in proof: After acceptance of our manuscript, we learned that Lavie and colleagues also proposed that melatonin could hypothetically interact with SCN-dependent arousal mechanisms.

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