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CIRCADIAN PHASE SLEEP AND MOOD DISORDERS

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CIRCADIAN ANATOMY AND PHYSIOLOGY

Anatomy

The Suprachiasmatic Nucleus: Locus of the Biological Clock

Much is known about the neuroanatomic connections of the circadian system. In vertebrates, the locus of the biological clock (the endogenous circadian pacemaker, or ECP) that drives all circadian rhythms is in the hypothalamus, specifically, the suprachiasmatic nucleus (SCN) (1,2). This paired structure derives its name because it lies just above the optic chiasm. It contains about 10,000 neurons. The molecular mechanisms of the SCN are an active area of research. There is also a great deal of interest in clock genes and clock components of cells in general, not just in the SCN. The journal *Science* designated clock genes as the second most important breakthrough for the recent year; the year before it was also on the runner-up list. Although clock genes may endow most, if not all, cells with the capacity for circadian time keeping, only the SCN is an endogenous pacemaker. That is, only the SCN receives environmental time cues. In turn, the SCN passes on temporal information to the cells of the rest of the organism.

The Retinohypothalamic Tract: Pathway for Photic Effects

The SCN is sensitive to environmental time cues in the form of photic impulses that are conveyed from the retina via a specific neural pathway, the retinohypothalamic tract (RHT). The RHT is a separate pathway from that which mediates vision (3); however, bilateral enucleation causes circadian blindness, just as it causes visual blindness.

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SCN Efferent Pathways

Not much is known about how the SCN entrains overt circadian rhythms. We know that the SCN is the master pacemaker, but regarding its regulation of the rest/activity cycle, core body temperature rhythm and cortisol rhythm, among others, it is not clear if there is a humoral factor or neural connection that transmits the SCN's efferent signal; however, a great deal is known about the efferent neural pathway between the SCN and pineal gland.

The Pineal Gland

In mammals, the pineal gland is located in the center of the brain; however, it lies outside the blood–brain barrier. Postganglionic sympathetic nerves (called the nervi conarii) from the superior cervical ganglion innervate the pineal (4). The preganglionic neurons originate in the spinal cord, specifically in the thoracic intermediolateral column. The pathway between the SCN and the spinal cord synapses in the paraventricular nucleus (PVN) and traverses through the medial forebrain bundle.

Light has two effects on melatonin production. In common with all other circadian rhythms controlled by the SCN, the 24-hour cycle of ambient light and darkness synchronizes (entrains) the melatonin rhythm to a period of precisely 24 hours. The circadian rhythm of melatonin production is the only one in which basal levels are confined to the day alternating with increased levels at night; that is, melatonin production occurs within the margins of the scotoperiod (dark period).

Melatonin is unique in another way: Light acutely stops melatonin production (5). This effect can occur only between dusk and dawn, because melatonin levels remain low during the day given that the SCN turns off melatonin production for about 12 hours each day. That is, darkness during the day cannot increase melatonin production. These two effects of light combine to restrict the duration of melatonin production to about 12 hours or less during the night. In many animals, the changing duration of the scotoperiod across the year results in a corresponding change

in the duration of melatonin production, which is used as a seasonal time cue for regulating hibernation, migration, and estrous (6).

Sympathetic stimulation of the pineal results in the synthesis and secretion of melatonin into the venous circulation, as well as into the cerebrospinal fluid. A major target of melatonin is the SCN. Melatonin is synthesized from serotonin in two steps, one of which (*N*-acetylation) is rate-limiting (7). After conversion of serotonin to *N*-acetylserotonin, hydroxyindole-O-methyltransferase synthesizes melatonin (8). Although this enzyme is not rate-limiting, it may ultimately control the maximum amount of melatonin that can be produced each night.

Pharmacology and Physiology

Pineal Adrenergic Receptors

Norepinephrine (NE) is the neurotransmitter released by postganglionic sympathetic neurons. NE stimulates β-1-adrenergic receptors on the pinealocytes, resulting in activation of *N*-acetyltransferase (NAT) (9). NAT activation is potentiated by stimulation of α1-adrenergic stimulation of the pinealocytes (10). There are also α2-adrenergic autoreceptors on the postganglionic sympathetic neurons, which decrease melatonin production when stimulated by NE (11). Perhaps unique in the autonomic nervous system, there is no dual parasympathetic innervation opposing sympathetic control of pineal melatonin production; however, melatonin levels do not increase with general "fight or flight" sympathetic stimulation. Regulation of melatonin is tightly controlled by the SCN, which appears to be active during the day (12), thereby exerting inhibition of an otherwise always "on" signal in the PVN for increasing melatonin production (13). Nevertheless, melatonin production is a reliable measure of sympathetic and noradrenergic activity in the pineal gland. Consistent with the catecholamine hypothesis of affective disorders, melatonin production is greater in manic than in depressive states in bipolar patients (14,15), although the jury is out as to whether or not melatonin production is decreased in unipolar depression (16).

Pineal Pharmacology

Drugs that affect NE and its receptors can change melatonin levels. β-Blockers reduce melatonin production (17). In humans, changes in circulating levels in NE must be extreme if melatonin levels are to be increased, such as resulting from high-altitude marathon races; however, tricyclic antidepressants reliably increase melatonin production. Drugs that stimulate and block α2-adrenergic receptors also have the predictable effects on melatonin production. For example, clonidine decreases melatonin production in humans (11), whereas yohimbine increases it (18). Benzodiazepines are also reported to decrease melatonin production. Changes in melatonin duration probably are not as important in humans, who lack seasonal rhythms. Drugs that affect melatonin production generally lower or raise the entire nighttime profile symmetrically; therefore, a circadian phase shift is less likely to result. This concept is best understood after reviewing how melatonin feeds back onto the SCN in order to shift circadian phase (see the following).

SHIFTING CIRCADIAN PHASE USING BRIGHT LIGHT

Intensity of Light

Acute Suppression of Nighttime Melatonin Production

One of the most remarkable effects of light is suppression of nighttime melatonin production (19). However, scientists in the late 1970s had concluded that humans lacked this and other chronobiologic responses to light. This erroneous thinking was based on temporal isolation studies that showed that social cues were more effective than light in entraining human circadian rhythms (20) and on studies in which light failed to suppress melatonin production in humans (17,21,22). In both types of cases, ordinary-intensity room light was used. These negative findings caused some scientists to speculate that humans lacked the neural pathways for mediating chronobiologic effects of light.

However, in 1980 we reported that bright light could suppress melatonin production in humans (the brighter the light, the greater the effect) (23) (Fig. 129.1). One implication of this finding was that humans might have biological rhythms that were cued to sunlight and were relatively unperturbed by ordinary-intensity indoor light. A second implication was that bright artificial light might be substituted for sunlight, in order to experimentally, and perhaps therapeutically manipulate biological rhythms in humans.

Winter Depression

Following our discovery of bright light suppression of melatonin production in humans (23), researchers began to treat depressed patients with bright light (24). We have been concentrating on treating winter depression, or seasonal affective disorder (SAD). We were unaware of the existence of SAD until Herb Kern contacted us, because of a history of an annual rhythm in mood changes: During the winter he became depressed, which he was able to document using a diary he had kept over for over 13 years (25). Since 2,000-light was effective in suppressing melatonin production, we assumed that this intensity would have other chronobiologic effects as well. Mr. Kern responded to a regimen of 2,000-lux light given between 6 and 9 AM and 4 and 7 PM (26).

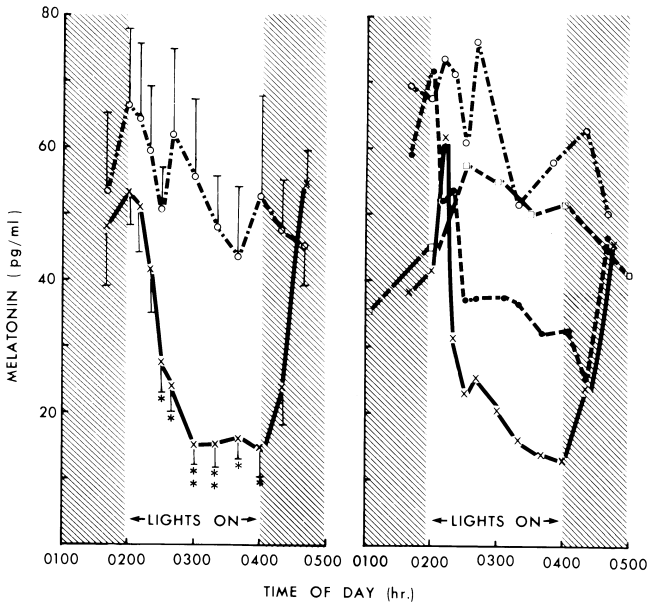

FIGURE 129.1. Left: Effect of light on melatonin secretion. Each point represents the mean concentration of melatonin (±standard error) for six subjects. A paired *t*-test, comparing exposure to 500 lux with exposure to 2,500 lux, was performed for each data point. A two-way analysis of variance with repeated measures and the Newman-Keuls statistic for the comparison of means showed significant differences between 0230 and 0400 (*, $P < .05$; **, $P < .01$). **Right:** Effect of different light intensities on melatonin secretion. The averaged values for two subjects are shown. Symbols: (o) 500 lux; (**x**) 2,500 lux; (●) 1,500 lux; and (□) asleep in the dark. From Lewy AJ, Wehr TA, Goodwin FK, et al. Light suppresses melatonin secretion in humans. *Science* 1980; 210:1267–1269, with permission.

We exposed him to bright light at these times, because animals tell time of year by the interval between the twilight transitions (6): Our thinking was that we could increase the length of his biological day by scheduling bright light as soon as he awakened, followed by another exposure ending 13 hours later. (Mr. Kern's depression would usually spontaneously remit in the spring.) These two studies (23,26) were critical in starting the field of bright light treatment, not only for SAD but for using bright light in other chronobiologic disorders as well (discussed in the following).

Wavelength of Light

With George Brainard (27), we have shown that the peak wavelength for suppressing melatonin production is 509 nm (blue-green light). Most white light sources have this wavelength, which is in the middle of the scotopic spectral distribution. Generally, we prefer to use regular fluorescent light. Rods, not cones, are most sensitive at this wavelength; however, the precise retinal photoreceptors that mediate chronobiologic effects of light have not yet been identified.

Timing of Light

The Light Phase Response Curve

The next step in the course of our work was to address the circadian phase-shifting effects of light. As mentioned in the preceding, Mr. Kern (and most of the other early SAD patients) was treated with bright light based on the idea of lengthening their winter photoperiod to one more typical of spring, the time of year when they spontaneously remitted (26,28). It occurred to us that we should have the same phase response curve (PRC) to light commonly found in other animals, except that humans would need bright light to most reliably demonstrate these effects (29). Hence, we postulated the human light PRC, which can be described as follows. A phase advance (shift to an earlier time) results from light exposure between the middle of the night and morning. A phase delay (shift to a later time) results from light exposure between the evening and middle of the night. These phase shifts are greatest in the middle of the night. During the day there are decreased responses to light. Rutger Wever, who previously was the driving force behind the importance of social cues, published a study in 1983, demonstrating that continuous bright light during the day had a more potent effect on the human circadian system than did ordinary-intensity light (30).

Phase-Typing Circadian Rhythm Disorders

Our much less elegant anecdotal report the same year indicated that bright light could be used to treat circadian phase disorders in humans (29); however, we specified that bright light should be confined either to the morning or evening. We proposed that there were two types of circadian disorders, the phase-delayed and phase-advanced types (Table 129.1). We also showed how bright light scheduled in the morning could be used to treat delayed sleep phase syndrome (DSPS) in order to provide a corrective phase advance and that evening bright light could be used to treat at least the early morning awakening of nonseasonal depressives in order to provide a corrective phase delay. However, the first person to treat this latter group of patients was Dan Kripke (24), who used a different approach, giving them bright light in the morning, not to cause a phase shift but

TABLE 129.1. PHASE TYPING SLEEP AND MOOD DISORDERS

Phase-Advanced Type	Phase-Delayed Type
ASPS	DSPS
East to west jet lag	West to east jet lag
Adjusting to night work	Readjusting to off-work
	Winter depression

rather to illuminate a "critical interval." Suffice it to say that no one in those early days, except Wever and our group, was thinking about the circadian phase-shifting effects of light. The following year we showed that—holding the sleep/wake cycle constant—we could shift the melatonin rhythm (a biological marker that we had proposed would be ideal for assessing circadian phase position in humans) by shifting the light/dark cycle (31,32).

The Phase Shift Hypothesis for Winter Depression

When we proposed "phase typing" circadian disorders (29), we hypothesized that most people with SAD were of the phase-delayed type (33). It was our thinking that circadian rhythms drift later with the later dawn of winter and that this is the cue for some people to get depressed at this time of year. Accordingly, we hypothesized that the optimum time for bright light exposure was in the morning, which would provide a corrective phase advance. We further hypothesized that morning light would advance the circadian rhythms that were tightly coupled to the ECP, such as the melatonin rhythm, with respect to the sleep/wake cycle and its evoked rhythms, and therefore that any shift to an earlier sleep time should be held to a minimum. We also expressed concern about the possibility that too much morning light could overly phase advance these rhythms (34). Finally, we pointed out that there might be a small group of SAD patients who cued to dusk rather than dawn, and for whom evening bright light would be most antidepressant, producing a corrective phase delay (34). We also proposed an elaboration of the phase shift hypothesis (PSH): Typical patients are phase delayed, but not necessarily compared to normal controls, in that the phase delay could be ipsative (35); that is, we expected typical patients to be delayed when depressed in the winter compared to when they were euthymic. According to the nomenclature, if SAD patients are thought to have relatively long intrinsic circadian periods, they should have a relatively late dim light melatonin onset (DLMO) given either as clock time or as zeitgeber time (ZT) (that is, delayed relative to wake time). Indeed, as mentioned, it is thought that the DLMO of most SAD patients is delayed relative to the sleep/wake cycle (and therefore the ambient light/dark cycle).

Although some investigators were quick to embrace the PSH (such as David Avery, who underscored the significance of morning hypersomnia as a predictor of response to morning light) (36), many distinguished experts in the field advanced other ways of conceptualizing SAD. For example, the NIMH group published a paper in 1985 recommending 5 to 6 hours of 2,000 to 2,500 lux light in the evening (37). According to their "photon counting" hypothesis, light at any time of day should be antidepressant, as long as light of sufficient duration and intensity was used (38). Because people with SAD do not like to get up any earlier than they have to in the morning, evening was proposed to be the most convenient time for light treatment.

Both hypotheses received help from a review by the Terman group (39). Morning light was shown to be more antidepressant than evening light; however, evening bright light was shown to be more effective than evening dim light. It should be noted, though, that there was no control for the dim evening light condition; therefore, evening dim light could have been eliciting purely a placebo response. Significantly, the Terman group made the important suggestion that 10,000 lux could be used for a shorter duration than the 2,000- to 2,500-lux light that had been the previous standard.

Morning Versus Evening Light

Support for the PSH depends on the superiority of morning light for most patients. Some studies have shown that morning light is more effective than evening light (40,41); whereas other studies showed that they are equally effective (42). The former studies used a crossover design, whereas the latter studies used parallel groups. Critics of the PSH pointed out the advantages of the latter type of study design, whereas advocates of the PSH pointed out the advantages of the former compared to the latter. Some critics of the PSH also proposed that exposure to morning light prevented an antidepressant response to subsequent treatment with evening light (43). The Terman group also proposed a corollary to the PSH that could be construed as quite different from the original hypothesis: Light at any time of day should be antidepressant for SAD, as long as it does not produce a phase delay (44).

With the publication of three large studies by independent groups in 1998 (45–47), there is now general agreement that morning light is more antidepressant than evening light in the treatment of SAD. An "order" effect (43) does not seem to confound these studies, and morning light has been shown to be more effective than evening light in both parallel (45–47) and crossover comparisons (40,41, 46). Morning light does not seem to prevent an antidepressant response to evening light (47). Moreover, evening light does not seem to be more antidepressant than a credible placebo control (45).

However, the superiority of morning light does not prove the PSH, because people could simply have a greater overall sensitivity to light at that time of day. This seemed to us to be an unlikely explanation, given that patients become more depressed when switched from morning to evening light, even after they have responded. Recently, however, the Terman group (48) as well as our group (49) found that the antidepressant response to morning light correlates with the amount of phase advance. We had previously shown this relationship with patients exposed to 30 minutes versus 120 minutes of morning light (50), which has the obvious disadvantage that patients would expect light of a

greater duration to be more antidepressant. The PSH continues to remain the most viable hypothesis for explaining why patients with SAD become depressed in the winter and for explaining how light is antidepressant in these patients.

It should be mentioned that even if the PSH is ultimately shown to be correct, it might explain only part of the response to light. As Charmane Eastman has shown, the placebo response is a major component to light treatment (51). Whether or not a specific mechanism for this can be found (e.g., an energizing effect) (52) remains to be determined.

Other Chronobiologic Hypotheses

Finally, four other chronobiologic hypotheses for SAD should be mentioned, none of which are mutually exclusive with the PSH. Martin Teicher has proposed that SAD patients are not stably entrained to the light/dark cycle (53), which in many respects is similar to the PSH. Domien Beersma has proposed that people with SAD are supersensitive to light (54). Accordingly, these people might delay in the winter in response to ordinary-intensity room light in the evening that would not be sufficiently bright to phase delay normal controls. The jury remains out on this hypothesis, which, in any event, is not inconsistent with the PSH. Also, Thomas Wehr has found that the melatonin duration (the time interval between the melatonin onset and the melatonin synthesis offset, or SynOff) expands in the winter in SAD patients but not normal controls (55); however, he also finds an overall delay in the melatonin rhythm in SAD patients in the winter compared to the summer, particularly in the SynOff. A third hypothesis, suggested by Charles Czeisler, is that SAD patients have diminished circadian amplitude when depressed in the winter (56). Czeisler has not done much testing of his hypothesis, and other investigators have not found much support for it (57,58).

The DLMO as a Marker for Circadian Phase Position

History

In the early 1980s, we thought that plasma melatonin sampled every 30 to 60 minutes might be able to show differences in circadian phase position between individuals and to monitor the phase-shifting effects of bright light (31,32). We further proposed that only one night of sampling is needed, indeed, only during the evening, so as to determine the time when melatonin levels begin to increase. We recommended that subjects be studied under dim light, so as not to suppress the rise in melatonin levels. The DLMO continues to be a useful marker for circadian phase position (59–61). We have also recommended that the time when melatonin levels begin to fall, the synthesis offset, or SynOff, is another useful marker for the ECP (Fig. 129.2) (61); however, the SynOff requires sample collection during sleep.

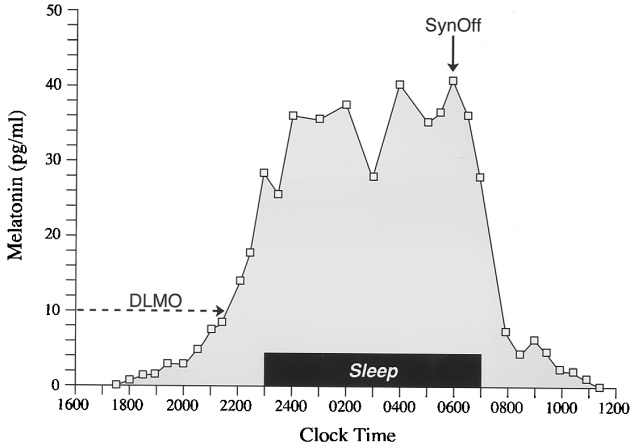

FIGURE 129.2. Representative overnight endogenous melatonin profile, showing the dim light melatonin onset (DLMO), the threshold when melatonin levels cross 10 pg/mL and continues to rise, and the melatonin synthesis offset (SynOff), indicating the beginning of the end of melatonin production.

Current Recommendations

Currently, we are suggesting that the light be so dim that subjects are not able to read without the aid of small book lamps. We further suggest that dim light begin 1 hour before blood sampling (61). The same recommendations apply to salivary collections. It is important not to put the subject in absolute darkness too early in the day, because this might cause a significant phase advance in the ECP (62).

The DLMO is now being employed extensively in research labs, and the salivary DLMO is beginning to be used in clinical settings as well (63,64). The DLMO has several advantages. It appears to be relatively free of noise and is easily obtained compared to other techniques for assessing circadian phase position. Outpatient determination of the DLMO usually does not interfere very much with sleep. Saliva can be collected at home.

Low Melatonin Producers

There are a couple of caveats to keep in mind. Very low or very high producers of melatonin may have an artifactually late or early DLMO, respectively (61). When there is a large range in melatonin amplitude between individuals, the DLMO can be adjusted algorithmically, or a lower threshold than the usual 10 pg/mL can be used (the 2 pg/mL DLMO is minimally affected by amplitude). Thomas Wehr has recently shown that the melatonin duration does not change across the year in normal subjects (55); however, in

SAD patients he has reported a greater delay in the SynOff than in the melatonin onset in the winter compared to the summer. Thus, we may be underestimating the amount of delay in SAD patients when just using the DLMO; therefore, for studies of circadian phase, measuring the DLMO may miss a finding that can be demonstrated using the rest of the melatonin profile. However, in most situations, measurement of the DLMO should suffice.

Circadian Amplitude

It is not clear if the overnight melatonin profile is a good marker for the amplitude of its endogenous circadian pacemaker. Furthermore, it is not clear if circadian amplitude is as important as circadian phase, in that an amplitude disturbance has yet to be shown. Moreover, no technique has been shown to enhance circadian amplitude or to reliably diminish it. The jury is out over whether or not suppressing amplitude is important for bright light to cause phase shifts (65,66).

The Melatonin Phase Response Curve

Blindness and Constant Dark Conditions

In 1983, Redmond, Armstrong, and Ng showed that a free-running mammal (in this case, rats) could be entrained to a daily dose of melatonin (67). We had been interested in the possibility of using melatonin to entrain the free-running rhythms of totally blind people. There appear to be at least three types of blind people: normally entrained, entrained at an abnormal phase, and free-running [blind free-runners (BFRs)] (68,69). BRFs are usually without any light perception, subjective or objective. Of the million or so legally blind in the United States, about 200,000 are totally blind. At least half of them are probably BFRs (70). BFRs generally have a recurrent sleep disorder that occurs when their sleep propensity rhythm drifts 12 hours out of phase with their preferred sleep time. On these days, they have insomnia and have to fight hard to resist urge to sleep during the day.

The technique we use to determine the free-running period of BFRs is to determine the melatonin onset on multiple occasions. We call this the multiple melatonin onset test (MMOT). In a typical BFR, the melatonin onset will be several minutes later each day and several hours later over a few weeks.

Although we were the first group to give melatonin to the blind (71), other investigators preceded us in giving melatonin to sighted people. Jo Arendt was the first to use melatonin in the treatment of jet lag (72); she also was the first to study its phase-shifting effects on the endogenous melatonin rhythm (73). Bruno Claustrat's group (74) also did some early work this area.

Another reason why we started with blind people is that we were concerned that the light/dark cycle would prevent melatonin's phase-shifting effects. The data on sighted subjects were intriguing, but were neither robust nor consistent (75). However, in the blind we were able to demonstrate quite reliable phase shifts using a dose of 5 mg of melatonin (71,76,77); thus encouraged, we were then ready to study sighted people, even though we had not yet achieved our goal of reliably entraining blind people to a daily dose of melatonin.

Sighted People

In sighted people, we reduced the dose to .5 mg, which produces melatonin levels of the same order of magnitude that occur physiologically. As opposed to previous studies of melatonin (which used higher doses and gave melatonin in the late afternoon or evening), we administered melatonin at different times. In each trial we gave melatonin on four consecutive days, and the results were the first unequivocal demonstration of both phase delays and phase advances, as well as the first description of the melatonin phase response curve (PRC) in humans (78–82). The melatonin PRC has now been replicated, by us (83) and two other groups (84,85); the earlier melatonin is given in the advance zone, the greater is the phase advance (however, less is known about the delay zone).

The melatonin PRC appears to have an advance zone of about 12 hours' duration, a delay zone of about 12 hours' duration, and it appears to be about 12 hours out of phase with the light PRC. That melatonin causes phase shifts opposite to those of light should not be surprising, because melatonin appears to be a chemical signal for darkness.

Circadian Time

Internal body clock time can be assessed using a variety of marker rhythms. We prefer the DLMO. On average, the DLMO occurs 14 hours after wake time. Because "lights on" is, by tradition, designated circadian time (CT) 0, we use the DLMO as CT 14. That is, no matter what clock time the DLMO occurs, its circadian time is CT 14.

On average the crossover times of the melatonin PRC appear to be at about 1 PM and about 1 AM. In circadian time, these are CT 6 and CT 18, respectively (83). That is, advance responses are obtained when melatonin is given between CT 6 and CT 18, and delay responses are obtained when melatonin is given between CT 18 and CT 6. When comparing the phase of the melatonin PRC to the light PRC, we use the beginning of the stimulus. Accordingly, the Czeisler PRC (which uses 5 hours of bright light) places the crossover times in the middle of the day at CT 6 and in the middle of the night at CT 18, according to these same conventions recommended by the PRC Atlas (86,87). This can be confusing, because the light PRC's crossover time in the middle of the night is also thought to occur at

the temperature minimum (86,88–91), which is usually just a few hours before wake time (CT 0).

Phase Relationship between the Light and Melatonin PRCs

In any event, light exposure during the interval between CT 6 and CT 18 causes phase delays, and during the interval between CT 18 and CT 6 causes phase advances; therefore, the light and melatonin PRCs are 12 hours out of phase with each other (Figs. 129.3 and 129.4). If the midpoint of the stimulus is used as the phase reference instead, the melatonin and light PRCs are still about 12 hours out of phase with each other. The times are given both as average clock times and as CTs. CT is more accurate if it can be calculated using an internal phase marker, such as the DLMO, which is designated CT 14. CT can be more easily but more roughly estimated using sleep onset as CT 16, or preferably, sleep offset as CT 0. The clock times in the figures below are averages, based on the presumption of a habitual wake time of 7 AM. The crossover times could be a few hours later or earlier, depending on how much the habitual wake time (not the wake time on a particular day) differs from 7 AM. For example, a person who habitually awakens at 6 AM will likely have crossover times at noon and midnight, instead of 1 PM and 1 AM.

Circadian Time and Zeitgeber Time

A somewhat confusing issue is how to use the DLMO as a marker for internal body clock time. When scheduling bright light and melatonin using the light and melatonin PRCs, we use the CT, which as mentioned in the preceding, is designated CT 14. Therefore, the advance zone of the melatonin PRC begins 8 hours before the DLMO and ends 4 hours after the DLMO. Also mentioned, the DLMO occurs on average 14 hours after wake time. However, if a person has a relatively short intrinsic circadian period, he or she will be entrained by the light/dark cycle in a relatively advanced phase position, and if a person has a relatively long intrinsic circadian period, he or she will be entrained by the light/dark cycle in a relatively delayed phase position. When using the DLMO to provide information about the intrinsic period of the ECP, we speak of the zeitgeber time (ZT) of the DLMO. For example, if a person has a DLMO that is 13 hours after wake time (or the time of first light exposure, the main entraining agent of the ECP), the phase angle of entrainment, or zeitgeber time of the DLMO, is ZT 13. A person with a DLMO of ZT 13 probably has a relatively short intrinsic period. However, the CT of the DLMO (when operationally defined as the crossing of the 10 pg/mL plasma melatonin threshold) is always designated CT 14. In other words, the same DLMO clock time may be ZT 13 and CT 14. This is discussed further in the section on advanced and delayed sleep phase syndromes.

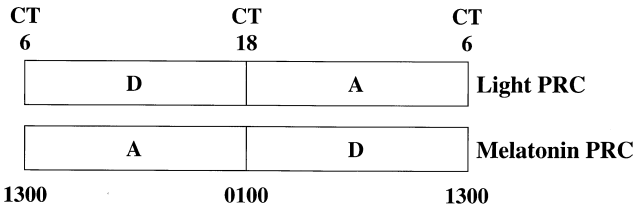

FIGURE 129.3. Schematic diagram of the light and melatonin phase response curves (PRCs). The melatonin PRC appears to be about 12 hours out of phase with the light PRC. The crossover times separating the advance (A) and delay (D) zones appear to be at about CT 6 and CT 18, on average about 1 PM and 1 AM, respectively, for people who awaken at 7 AM. The endogenous melatonin profile usually extends from about CT 14 to about CT 1. Adapted with permission from Lewy AJ, Bauer VK, Ahmed S, et al. The human phase response curve (PRC) to melatonin is about 12 hours out of phase with the PRC to light. *Chronobiol Int* 1998; 15:71–83.

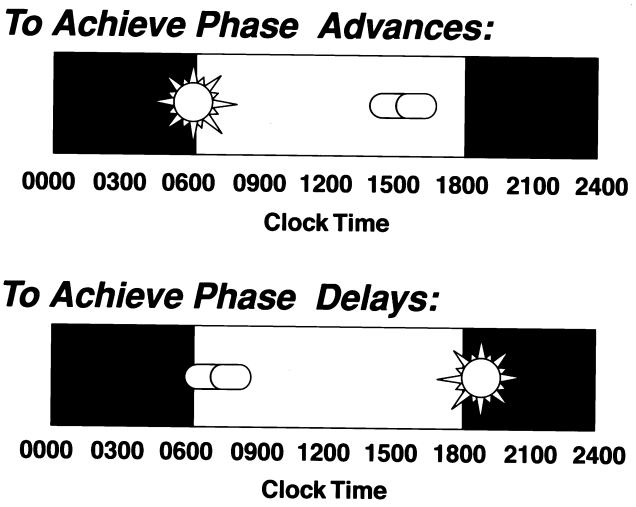

FIGURE 129.4. Phase-shifting effects of light and exogenous melatonin, assuming a normal circadian phase. To cause a phase advance, light should be administered in the morning and melatonin in the afternoon/evening. To cause a phase delay, light should be given in the evening and melatonin should be taken in the morning. The timing of light and melatonin administration is best done with reference to circadian time rather than clock time. Adapted with permission from Lewy A, Sack R. The role of melatonin and light in the human circadian system. In: Buijs R, Kalsbeek A, Romijn H, et al, eds. *Progress in brain research, vol. 111. Hypothalamic integration of circadian rhythms.* Amsterdam: Elsevier, 1996:205–216.

SAD UPDATE

Confirmation of the PSH for SAD?

The use of melatonin has allowed us to conduct a further test of the PSH for winter depression in order to answer

the following question: Does the correlation between the antidepressant response and the phase-advancing effect of morning light indicate a causal relationship? First, we did a pilot study. Five patients were given placebo in the afternoon and five were given melatonin, which was administered in two divided doses of .125 mg at CT 8 and CT 12. After 2 weeks, there was a significant improvement in the melatonin group compared to the placebo group (92).

These findings led to the study of 81 patients, divided into three groups. One group received low doses of melatonin in the afternoon and evening for 3 weeks. A second group received the same dosing regimen in the morning. There is also a placebo group. Interestingly, the antidepressant response appears to be related to the amount of phase advance (49). Therefore, the phase advance in the ECP appears to be the best-defined mechanism of action for the antidepressant effect of morning light in winter depression.

Clinical Implications of the PSH

We have cautioned (34) that it is possible to overly phase advance the body clock. A phase advance of about 1.5 hours relative to the sleep/wake cycle seems to be the optimal amount (48). Although the duration can be reduced after the patient has responded in 1 or 2 weeks, some patients will not comply with the 1 to 2 hours of bright light exposure immediately on awakening, because they do not want to get up too early. Furthermore, any advance in sleep time should be minimized, since this will retard the antidepressant response to advancing the ECP, because—according to the PSH—the ECP needs to be advanced with respect to the timing of the sleep bout (93,94).

Administration of melatonin (.5 mg) in the afternoon will cause a phase advance (82). This can be achieved while minimizing its soporific side effect, by using very low doses (.75 to 1.25 mg) given three or four times every 2 to 3 hours beginning 7 to 8 hours after habitual wake time. The addition of melatonin will reduce the need for an inconveniently long duration of morning bright light exposure by providing some additional phase advance. Those patients who do not get sleepy on melatonin may be able to take a sufficient dose of melatonin so that they do not require any morning bright light. Many patients with SAD seem to be unusually sensitive to the soporific effect of melatonin and will require bright light in combination with melatonin to achieve a therapeutic phase advance.

It takes less of a phase-resetting agent to maintain a certain circadian phase position than to initiate it. Hence, once a patient has responded, the duration of bright light and/or the dose of melatonin can be reduced. Patients will need to be treated until the photoperiod lengthens in the spring. When the patient's habitual wake time is occurring about 30 minutes past dawn, obtaining 15 to 30 minutes of outdoor light immediately on awakening is sufficiently therapeutic. At this time of the year, he or she is probably beginning to spontaneously remit. By the way, another way to cause a phase advance with respect to sleep time is to use a dawn simulator set to start slowly increasing light intensity a few hours before awakening (95,96). According to the light PRC, even relatively low intensity of light (diminished further because of closed eyelids) can cause a phase advance if given in the middle of the night.

TABLE 129.2. PHASE SHIFTS WITH BRIGHT LIGHT AND MELATONIN ADMINISTRATION

	Phase Advances (Hours ±)	Phase Delays (Hours ±)
Bright light	1.40 (± 0.21)	1.12 (± 0.16)
Melatonin	1.03 (± 0.14)	0.20 (± 0.12)

In order to compare the phase-shifting effects of light and melatonin, ideally each treatment should be optimized. Absent this, we compared 2 weeks of 2,500 lux light at 6 AM to 8 AM or 7 PM to 9 PM in our largest light treatment of winter depression study (46). Phase shifts owing to light were of the same order of magnitude as phase shifts after 3 weeks of a divided dose of .225 to .3 mg of melatonin (which produces high but physiologic levels) used in our ongoing melatonin-treatment study described in the preceding (Table 129.2).

We think it unlikely that a third week of treatment substantially increases the phase shift. This table indicates the phase-shifting effects of light and melatonin are of the same order of magnitude, although each treatment should be optimized for the most useful comparison.

OTHER CIRCADIAN PHASE DISORDERS

Shift Workers

The magnitude of the phase shifts in the melatonin PRC are smaller than those of the light PRC. However, subjects in the light PRCs studies had their sleep/wake cycles either shifted 12 hours before bright light exposure was scheduled or free to shift at will (86,88–90). In the melatonin PRC study, the sleep/wake cycle was held constant, and hence the ambient light/dark cycle also was held constant (82,83).

When we gave .5 mg of melatonin just before bedtime to night workers whose sleep/wake cycles were shifted about 12 hours, we found phase shifts of the same order of magnitude as those obtained with bright light (97). Apparently, holding the light/dark cycle constant diminishes the phase-shifting effects of melatonin (as it does light). Nevertheless, bright light seems to be a somewhat more robust phase-resetting agent than melatonin, although melatonin is of course much more convenient. In all likelihood, greater

phase shifts can be achieved in sighted people when melatonin and bright light are combined.

Jet Lag

The first use of melatonin in humans was to treat jet lag (98). There are surprisingly few studies in this area, however. Sunlight exposure at destination can be scheduled according to the nomogram we published in 1984 (99) (Fig. 129.5). This applies to obtaining (and in some cases avoiding) bright light for the day of arrival. The schedule for subsequent days can be arrived at by assuming a 2- to 3-hour phase shift per day and looking up the instructions for a crossing of the number of time zones. For example, if you have flown to Israel from Portland, OR, follow the directions for 10 time zones on the first day in Israel. For the second day in Israel, follow the directions for crossing eight time zones. Melatonin can also be helpful in the treatment of jet lag. We are currently developing guidelines for the optimal use of melatonin in the treatment of jet lag.

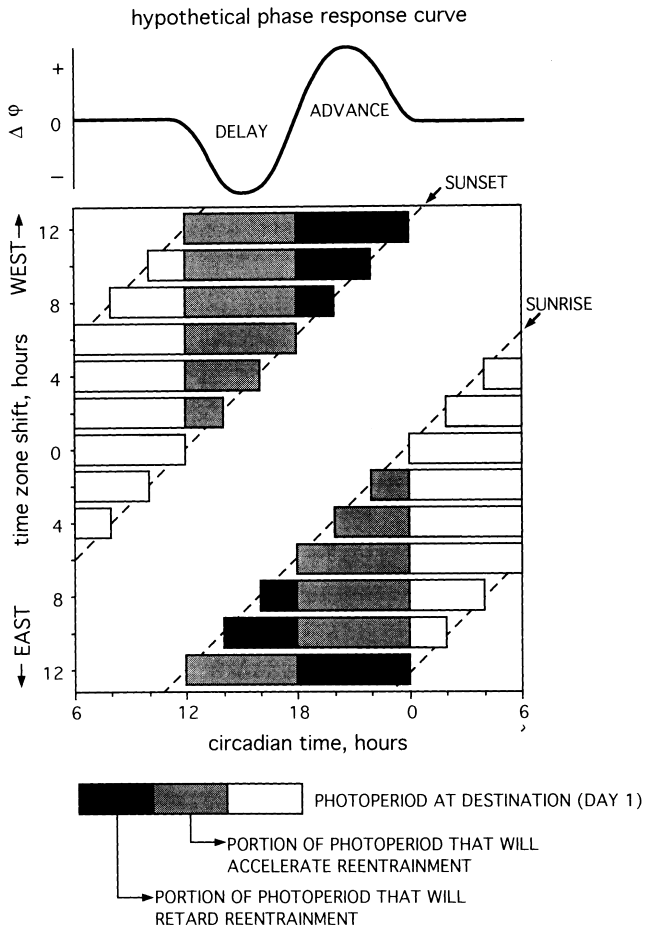

FIGURE 129.5. Proposed times for when bright light exposure should occur and when bright light exposure should be avoided the first few days after transmeridional flight. For example, after a 2-hour west-to-east trip, bright light exposure should begin at dawn and should be (optimally) 2 hours in duration. In another example, after a 10-hour west-to-east trip, however, bright light exposure should be *avoided* until 4 hours after sunrise and should occur (optimally) for 6 hours. From Daan S, Lewy AJ. Scheduled exposure to daylight: a potential strategy to reduce ''jet lag'' following transmeridian flight. *Psychopharmacol Bull* 1984;20: 566–568, with permission.

Entrainment of BFRs

Following the first demonstration of phase shifting the ECP of a BFR (71), others and our group have found cases of varying degrees of certainty in which a daily dose of melatonin appeared to cause entrainment (100–102). In some instances, only the sleep/wake cycle appeared to be entrained (103–105).

We estimate that there are at least 100,000 totally blind people in the United States who have periodic insomnia. We have recently discovered a way to entrain most of these people (101,106). A dose of 10 mg given within an hour of preferred bedtime should in all likelihood eventually entrain most of them. Entrainment occurs in just a few days or a few weeks by initiating treatment when the MO is occurring around bedtime. Once the free-running clock of the blind person has been ''captured,'' the maintenance dose can be decreased to as low as .5 mg. Ongoing work in our laboratory is investigating the possibility of moving the melatonin dose earlier, to 7 to 13 hours after habitual wake time, so as to provide a typical phase angle of entrainment. In three BFRs who had pretreatment circadian periods less than 24.4 hours, we were able to capture their circadian rhythms with a *de novo* bedtime dose of .5 mg. Therefore, it may be possible to entrain people initially with .5 mg, particularly if their free-running periods are not much greater than 24 hours. Indeed, the only person who failed to entrain to the 10-mg dose had the longest free-running period of our group (24.9 hours).

BFRs are perhaps ideally suited for phenotyping people according to their intrinsic circadian period for clock gene studies, particularly bilaterally enucleated people in whom there is no chance for ocularly mediated effects of light on the circadian system. Of course, this presupposes minimal, if any influence of behaviorally related zeitgebers (BRZs) (107,108) or nonocular light (109). If these other possible modes of entrainment are shown to be negligible, then entrained BFRs with one or two eyes are probably still sensitive to the ocularly mediated light zeitgeber, even though they have no conscious light perception or any objective sign of light response, such as the melatonin suppression test, which we developed in sighted people (23,110–114) and has also been recommended for blind people (107). However, until we have ruled out entrainment by ocularly mediated light in what are thought to be totally blind people, we do not recommend the use of the melatonin suppression test, which we recently have come to think may risk desensitizing the few remaining photoreceptors that may have been suffi-

ciently sensitive to mediate entrainment. Furthermore, the melatonin suppression test does not seem to be very useful clinically, because it does not discriminate BFRs from entrained blind people very well. These issues cannot be resolved until the entrainment effects of BRZs (107,108,115) or nonocular light (109) are established or ruled out.

Are Nonseasonal Affective Disorders Chronobiologic?

Daniel Kripke has done more work in this area than anyone else (24). We do not think that bright light has the same robust antidepressant effect in nonseasonal depression as it has in SAD, and the jury is out as to whether it works better than placebo. However, if a patient has a circadian rhythm component to his or her affective disorder, such as early morning awakening or morning hypersomnia, then melatonin and/or bright light can be used to shift sleep to a more desirable time. Whether or not correcting the phase disturbance improves the remaining symptoms is not known at the present time.

Melatonin in Young and Elderly People

There are anecdotal and testimonial reports that melatonin improves the sleep of children with ADHD and adults with Alzheimer disease. A study has been done in elderly people indicating that benzodiazepines can be reduced or eliminated with concomitant melatonin administration (116). Although we might want to use lower doses of melatonin in young and elderly people, melatonin appears to be reasonably safe in these populations as long as a physician is monitoring them. Indeed, to date I know of no reports published in the scientific literature of serious irreversible side effects as the result of taking melatonin, and certainly millions of people have been doing so for the past several years. Nevertheless, there is a continued need for physician monitoring of melatonin usage, particularly when taken every day. However, we do not expect this to be a very common effect of melatonin, given the fact that melatonin can have either progondal or antigonadal effects, depending on whether the species is a fall or spring breeder (6,117) and the fact that there is only a very slight seasonal rhythm in human fertility (118,119).

Advanced and Delayed Sleep Phase Syndromes

Appropriately timed bright light exposure and melatonin administration can be used to treat other circadian phase disorders. These include advanced sleep phase syndrome (ASPS) and delayed sleep phase syndrome (DSPS). Light treatment of these disorders has already been summarized (120), and we are currently developing recommendations for melatonin treatment. A remarkable report was published recently concerning a family with advanced sleep phase syndrome (121). The clock time of the DLMO was quite early, even with respect to sleep; that is, the ZT of the DLMO (the number of hours after wake time) can be calculated as 13.3. The intrinsic period of one of these subjects was studied in temporal isolation and was found to be 23.3 hours, one of the shortest, if not the shortest, ever recorded. Therefore, if the wake time and DLMO time are known, their interval should predict intrinsic period, and perhaps obviate the need for an arduous study under temporal isolation conditions. This should be of interest to those interested in phenotyping sighted people for clock gene studies.

MELATONIN AND CIRCADIAN PHASE DISORDERS: PAST, PRESENT, AND FUTURE

Past Skepticism about Melatonin

The melatonin fad of a few years ago has stimulated a number of scientists to make skeptical comments. Many of these concerns are well taken. There is no clinical evidence that melatonin is useful for anything other than phase shifting and sleep; however, some investigators have expressed skepticism even for these well-documented uses.

Charles Czeisler has perhaps most comprehensively articulated these criticisms (122). Czeisler contends that our melatonin PRC was not conducted under sufficiently controlled conditions, namely, that subjects were studied at home and under a variety of light intensities. However, we view this as a strength of the methodology: because the subjects lived mainly at home, the findings can be more directly applied to real-life situations. Furthermore, despite "noise" owing to uncontrolled light intensities, the data clearly describe a well-defined PRC, perhaps because of the large number of data points. Moreover, it is difficult to imagine a systematic confound in the study owing to melatonin's soporific side effect (particularly because naps in the middle of the day do not cause phase shifts) (123); waking up at night to take a placebo capsule causes phase shifts, if any, opposite to those of melatonin (Lewy, in preparation).

Czeisler is also concerned that the Claustrat replication PRC is slightly different from ours. Claustrat used a 3-hour intravenous infusion of melatonin, whereas our .5-mg oral dose kept blood levels elevated for several hours (84). We have speculated that melatonin's phase-shifting effects are optimal if the exogenous dose overlaps with the endogenous melatonin profile (75). This might explain why the intravenous dose given in the evening produced more of a phase advance than the one given in the afternoon, in that the afternoon dose did not overlap with the endogenous melatonin profile. Our PRC shows that melatonin's phase-advancing effects increase as it is given earlier in the afternoon: even at this time, the .5-mg oral dose raises blood levels through the time of the melatonin onset.

However, Czeisler's main problem with melatonin as a useful phase-resetting agent has been the difficulty demonstrating its ability to entrain BFRs. This issue is now moot, given the definitive findings of two independent groups (102,106).

We agree with Czeisler that light is the most powerful phase-resetting agent. However, Czeisler thinks that light is an order of magnitude more powerful than light, whereas as indicated in the preceding (Table 129.2) we think that there is not that much difference between the two zeitgebers. In any event, melatonin is much more convenient than using light as a phase-resetting agent. Although our group has concentrated on melatonin as a secondary zeitgeber in humans, Czeisler and his co-workers have continued to pursue a longstanding interest in the activity/rest cycle, first as a primary (124,125), and then as a secondary (107,108), zeitgeber. The jury is out as to the strength of the activity/rest zeitgeber in humans.

The Function of Endogenous Melatonin Production

In many animals, the duration of nighttime melatonin production appears to be critically involved in the regulation of seasonal rhythms. However, this does not appear to be the case in SAD, although Tom Wehr has some intriguing data on this point (55). Although seasonal rhythms are not very robust in humans (118,119), we have most of the circadian rhythms found in other animals, and melatonin may play a role, however humble, in helping the light/dark cycle entrain the ECP. This function for melatonin is critically dependent on suppression of melatonin by bright light.

Light entrains the ECP (located in the SCN), which regulates all overt circadian rhythms, including the nightly increase in pineal melatonin production. As mentioned in the beginning of this chapter, melatonin feeds back onto the SCN and stimulates receptors causing phase shifts opposite to those of light (126–128). Sufficiently bright light at the twilight transitions suppresses melatonin production, causing the endogenous melatonin onset to occur later and the endogenous melatonin offset to occur earlier. Thus, melatonin is prevented from stimulating parts of the melatonin PRC that might counteract the phase shift resulting from light (Fig. 129.6). In this way, the phase-shifting effect of light is augmented by an indirect effect of light acting on suppressing melatonin production. For example, if a person who normally gets up at 7 AM goes outdoors at 5 AM during the summer, earlier sunlight exposure will stimulate more of the advance zone of the light PRC, so as to cause a phase advance. Simultaneously, the melatonin offset will occur 2 hours earlier, reducing stimulation of the delay zone of the melatonin PRC. The same thinking can be applied to changes in bright exposure in the evening.

Clearly, light is the major zeitgeber for entraining circadian rhythms. In most mammals, melatonin is used for conveying the time of the year (primarily for seasonal breeding and other photoperiodic effects) and not necessarily the time of day (6). The acute suppressant effect of light (23) is important in truncating the endogenous melatonin profile, and humans have retained the suppressant effect of light but are not really seasonal breeders. It may be that melatonin is primarily used for either circadian or seasonal time keeping, and that this difference might distinguish humans from nonhuman primates. In other words, perhaps primates use melatonin either for telling the time of the year or the time of the day, but not both. For example, in a species of primates that has a seasonal breeding cycle, melatonin has not been shown to have circadian phase-shifting effects (129). Interestingly, activity is an effective zeitgeber in at least one species of primates, which has a seasonal breeding cycle (130). A corollary of this hypothesis is that a species that does not use melatonin for telling time of the day uses activity as the secondary circadian zeitgeber. Humans, who do not appear to use activity as the secondary zeitgeber, use melatonin as one. In other words, light is the primary zeitgeber, and either melatonin or activity is the secondary zeitgeber, depending on whether or not melatonin is used for cueing seasonal rhythms.

Once again, there is no question that light is the primary zeitgeber. Light regulates the melatonin circadian rhythm

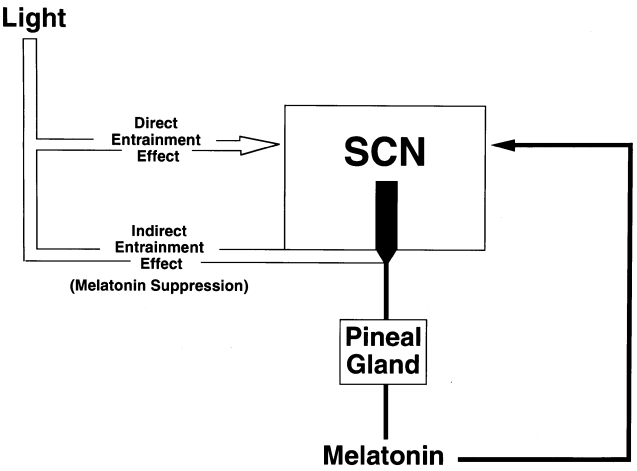

FIGURE 129.6. Schematic diagram of some of the relationships between nighttime melatonin production by the pineal gland, the light/dark cycle and the endogenous circadian pacemaker thought to be located in the hypothalamic suprachiasmatic nuclei (SCN). Acting on the SCN as described by the melatonin phase response curve (PRC) at any given time of the day or night, melatonin causes phase shifts opposite to those that light would cause *(opposing arrows).* However, the suppressant effect of light pares the margins of the nighttime melatonin profile *(tapered vertical arrow)* and reduces endogenous melatonin's stimulation of the melatonin PRC at the day–night transitions. This second pathway for entrainment by light is particularly significant during shifts of the light/dark cycle. From Lewy AJ, Ahmed S, Jackson JML et al. Melatonin shifts circadian rhythms according to a phase-response curve. *Chronobiol Int* 1992;9:380–392, with permission.

in two ways: Light entrains the SCN and acutely suppresses melatonin production. However, in humans melatonin appears to feed back onto the SCN to act as a secondary zeitgeber.

FUTURE DIRECTIONS

Optimal dosing of melatonin will depend on minimizing its soporific side effect, while maximizing its phase-shifting effects. This may entail using a low-dose sustained-release formulation to smooth out any sharp spikes in melatonin levels that appear to cause sleepiness in some people. The sustained-release formulation also has the advantage of providing continuity between exogenous levels from a low dose and the endogenous melatonin profile.

Another useful product that we might look forward to is a delayed-release sustained-release formulation that can be taken at bedtime to conveniently produce increases in melatonin throughout the night, beginning shortly after CT 18, so as to selectively stimulate the delay zone of the melatonin PRC. It may also be desirable to continue a low level of melatonin until the early afternoon in order to enhance a phase delay.

Clearly, shifting the sleep/wake (and consequently the ambient light/dark) cycle enhances the phase-shifting effects of melatonin. We have also speculated that placing a person in darkness when exogenous melatonin levels are increased may also enhance melatonin's phase-shifting effects. This needs to be more extensively tested.

Finally, we need more field studies of melatonin, not just in jet lag but with shift workers as well. One attempt at this was star-crossed (131). Our advice was not taken in its entirety, and the study design had several serious flaws in experimental design, for example, a failure to induce much jet lag in the placebo group after the first night's sleep at destination (most subjects expected to be an active treatment) and an absence of a circadian phase marker.

In some people, melatonin may be used as a mild sleep-promoting agent. The prospects for using melatonin and bright light to treat circadian phase disorders are even better. Most circadian phase disorders are relatively straightforward, and their treatment is based on the light and melatonin PRCs.

SAD is more complicated, although it is far and away the disorder most often treated with portable bright light fixtures. There appear to be two types of SAD patients (31): The typical patient with SAD is phase delayed (and complains of morning hypersomnia); the atypical patient is phase advanced (these people often report a history of getting up early year round, even on the week-ends, and often wanting to go to bed much earlier in the winter than summer). The phase disturbance in SAD is with respect to sleep as well as with respect to clock time. Therefore, there is an internal phase-angle disturbance in SAD. Sleep time should be held constant in these patients while their other circadian rhythms are shifted into the correct relative phase position with sleep. Even a confirmed PSH, however, raises new questions:

1. Which circadian rhythms tightly coupled to the ECP must be out of phase with which processes tied to sleep in order to trigger a depression each winter?
2. Does light have a specific antidepressant effect other than phase shifting?
3. How can we apply what we have learned about SAD to other affective disorders?

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