Chronobiology

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RESEARCH ARCHIVES

Treating Chronobiologic Sleep and Mood Disorders with BrightLight

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The study of circadian rhythms involves measuring the temporal relationships between bodily functions.

Treatment of mood disorders with bright light is one of the more promising non-pharmacological treatments of psychiatric disorders. The study of circadian rhythms and their effects on biological functions and mood have provided fascinating insights into the understanding of mental illness.

The study of circadian rhythms involves measuring the temporal relationships between bodily functions. Bodily functions frequently follow daily cycles with high and low points which are useful markers in identifying the timing of rhythms. It is then possible to compare relative phases of different rhythms to determine whether a peak or crest of the curve has occurred earlier (phase advanced) or later (phase delayed) than other conditions. For example, a body temperature minimum that occurs at 4 AM is phase delayed (i.e., occurs later) with respect to a body temperature minimum occurring at 2 AM. Conversely, the 2 AM minimum is phase advanced (i.e., occurs earlier) with respect to the 4 AM minimum. In other words, a phase advanced rhythm is one that is shifted to an earlier time and a phase delayed rhythm is one that is shifted to a later time.

The period of rhythm refers to how often it repeats. Circadian rhythms recur approximately every 24 hours. These rhythms recur precisely every 24 hours in the presence of 24-hour environmental cues (zeitgebers), particularly the 24-hour light-dark cycle. Under zeitgeber-free conditions, human circadian rhythms free-run with an average period of approximately 25 hours.[1] Studies have shown that the period of the melatonin production circadian rhythm in some blind people is approx-imately 25 hours.[2]

BRIGHT LIGHT SETS HUMAN CIRCADIAN RHYTHMS

Until recently, chrono-biologists agreed that social cues were the main zeitgebers for human circadian rhythms and that the light-dark cycle, which is the most important zeitgeber for animals, was relatively unimportant for humans.[1] This view changed radically, however, after the discovery that exposure to bright light suppresses nighttime melatonin production, whereas ordinary room light is not sufficiently intense to be effective.[3] One implication of these findings was that exposure to sunlight, which is generally 20 to 200 times as bright as indoor light, could synchronize human biological rhythms that remain unaffected by indoor light. A second implication was that bright artificial light could be used experimentally, and perhaps therapeutically, to manipulate biological rhythms in humans.

Studies conducted by Wever,[4] Eastman,[5] and Czeisler,[6] have confirmed that bright light is a potent zeitgeber for human circadian rhythms. Czeisler and colleagues[6] have recently modified their mathematical model based on the results of these studies and now support the single oscillator model proposed by Daan et al[7] and Eastman.[8] This model presents a single oscillator entrained directly and primarily by light. In other words, most scientists agree that one master clock probably drives all circadian rhythms.

TREATMENT OF DEPRESSION WITH BRIGHT LIGHT

Our own work has proceeded along both basic and clinical lines. In 1980,

we treated our first patient with bright light.[9] This patient had a 13-year history of winter depression that remitted spontaneously in the spring. Our first approach was to lengthen the winter days by exposure to bright light between 6 and 9 AM and between 4 and 7 PM. (Animals are aware of day length by the interval between the light pulses at dawn and dusk; light exposure during the middle of the day is relatively unimportant for cueing biological rhythms.) Following the first successful treatment, nine patients were treated the next year with bright light and dim light exposure at these times.[10] Lengthening the day with bright light was an effective antidepressant; dim light had no effect.

HUMAN CIRCADIAN RHYTHMS AND USE OF MELATONIN

We next became interested in how bright light might affect human circadian rhythms. Our work is based on the hypothesis that humans have a phase response curve (PRC) similar to those described for other animals.[11] PRCs are empirically derived from experiments in which animals free-run in constant dark and are briefly exposed to light pulses.[12-15] Depending on when the light pulse occurs, they shift their rhythms either in the advance direction (to an earlier time) or in the delay direction (to a later time). If the pulse of light occurs during subjective day (in constant darkness, subjective day is the activity phase of diurnal animals and the rest phase of nocturnal animals), there is a relatively small shift in rhythm. During subjective day, the re is a "dead zone" when light barely produces any shift at all. It is during subjective night that light pulses produce the greatest phase shifts. The closer to the middle of subjective night, the greater the magnitude of the phase shift. Phase delay shifts occur in the first part of subjective night; phase advance shifts occur in the second part of subjective night. In the middle of the night, there is an inflection point where only a few minutes separate a delay shift from an advance shift. In practice, this means that bright light exposure in the morning should advance circadian rhythms (shift them to an earlier time) and that bright light exposure in the evening should delay circadian rhythms (shift them to a later time.)

We first tested our hypothetical PRC by studying four normal volunteers in the summer who slept between 11 PM and 6 AM[16, 17] We measured their plasma melatonin levels the first day and then advanced dusk from about 9 PM to 4 PM by having them avoid bright light after this time. After a week of advanced dusk, we delayed dawn from about 6 AM to 9 AM by the same method for one week. After the first night of advanced dusk, the onset of melatonin production shifted to one hour earlier. Production remained stable for at least one more day. By the end of the week, onset of melatonin production advanced by another hour as did the offset. We interpret the end-of-the-week advance in both the onset and the offset of melatonin production as a result of removing illumination from the evening phase delay portion of our hypothesized PRC. However, the advance in the offset the first night of advanced dusk was probably due to removing a suppressant effect of light on melatonin production. (Phase shifting effects are usually produced over a few days, whereas the suppressant effect of light is an immediate one.)

It is during the subjective night that light pulses produce the greatest phase shifts.

Delaying dawn to 9 AM the second week caused a delay of about one hour in both the onset and the offset of melatonin production. There were no changes the first day. These data are consistent with the effect of removing illumination from the morning phase advance portion of our hypothesized PRC.

When sampling blood for melatonin onset, subjects should be kept away from bright light in the evening to avoid the suppressant effect of light on melatonin production. Thus, if subjects avoid bright light after 5 or 6 PM, nighttime melatonin onset ma y be an ideal marker for the phase shifting effects of light. The dim light melatonin onset (DLMO) has a number of advantages as a marker for circadian rhythms. First, it is the part of the melatonin curve that is least influenced by biochemical and physiological variables that might affect the amplitude of melatonin production. Second, subjects can leave after 11 PM. Third, sleep is not interrupted. Fourth, blood volume is conserved.

We have also demonstrated shifts in the melatonin rhythm as a result of adding bright light in the morning or evening. [18,19] We have found that, as predicted, bright light exposure in the evening delays circadian rhythms and bright light exposure in the morning advances circadian rhythms.[18-20]

DIAGNOSING ADVANCED OR DELAYED CIRCADIAN RHYTHMS IN DEPRESSED PATIENTS

In applying these findings to the clinical evaluation and treatment of patients with suspected chronobiologic sleep or mood disorders, we propose that such patients be "phase typed" into either the phase advanced or the phase delayed type.[18] If a patient 's sleep or mood disorder has a chronobiologic component that will respond to bright light therapy, the patient should respond to either bright light in the morning or bright light in the evening, depending on the phase type. Patients with phase advanced circadian rhythms should respond to evening light, which provides a corrective phase delay. Patients with phase delayed circadian rhythms should respond to morning light, which provides a corrective phase advance.

Previous psychiatric researchers hypothesized only a phase advanced type of chronobiologic disorder. [21,22] In the phase advance hypothesis of affective disorders, circadian rhythms

were thought to be abnormally advanced with respect to real time and to sleep. Advancing sleep in these patients, [21] as well as sleep deprivation in the second (but not first) half of the night,[23] was at least transiently helpful in some cases. Consequently, an internal phase angle disturbance was hypothesized, in which sleep was not as phase advanced as the other circadian rhythms. We have expanded upon this theory by describing a subgroup of depressed patients with phase delayed circadian rhythms.[18,19] We propose that these patients may have an internal phase angle disturbance, in which sleep is not as delayed as the other circadian rhythms.[19]

The cause of depression may be due to sleep not being as phase shifted as other circadian rhythms.

SLEEP AS A MARKER FOR DIAGNOSING ADVANCED OR DELAYED CIRCADIAN RHYTHMS

The most accessible, and therefore clinically useful, marker for circadian phase type may be sleep (sleep offset is more reliable than sleep onset). Paradoxically, however, the cause of depression may be due to sleep not being as phase shifted as other circadian rhythms. Sleep is shifted in the same direction as the other circadian rhythms but not shifted sufficiently to correct the phase angle disturbance. Furthermore, a shift in sleep superimposes its structure upon the light-dark cycle which, in turn, perpetuates an even greater shift in the other circadian rhythms. Previous studies on advancing sleep in depressed patients and delaying sleep in patients with delayed sleep phase syndrome did not specifically take into account the resulting effect on the perceived light-dark cycle.[21,24]

Delayed sleep phase syndrome, characterized by an inability to fall asleep at a reasonable time, has been treated by chronotherapy (successively delaying sleep 1 to 2 hours per day for several days until the desired bedtime is reached).[24] Sleep is delayed because these patients are unable to advance their sleep schedules. However, we have been able to help these patients fall asleep several hours earlier by exposing them to bright light in the morning (immediately upon awakening).[11]

TREATMENT OF ADVANCED OR DELAYED SLEEP SYNDROME

We have also successfully treated patients with advanced sleep phase syndrome, characterized by early evening fatigue and early morning awakening, by exposing them to bright light in the evening.[25] Sleep disorders may not have an internal phase angle disturbance because in these disorders all circadian rhythms, including sleep, may be phase shifted to the same extent.

Patients with advanced and delayed sleep phase syndrome must cooperate with these schedules and must therefore be motivated to change. However, they can be reassured that bright light exposure will help them to initiate and maintain the phase shift. One problem with chronotherapy is that patients frequently relapse. Chrono-therapy is also unwieldy. Consequently, bright light exposure will probably become the treatment of choice for patients with advanced and delayed sleep phase syndrome.

OTHER VARIABLES AFFECTING TREATMENT RESPONSE TO LIGHT

In addition to phase typing, we propose that there are three critical parameters for light to be chrono-biologically active in humans: intensity, wavelength, and timing.[26] In a study done a few years ago, we showed that the optimum wavelengths for melatonin suppression are around 509 nm.[27] This wavelength is representative of most white light sources.

Timing is still a somewhat controversial issue, at least with regard to the treatment of winter depression (or seasonal affective disorder, as it is sometimes called). The Bethesda group has stated that the timing of bright light is not critical, only its intensity and duration.[28-30] They call this the photon counting hypothesis because only the number of photons is important. They arrived at this hypothesis after testing and then rejecting their melatonin suppression hypothesis for seasonal affective disorder.[31] Their thinking was based on studies that suggested that lengthening the photo period at both ends was not critical[30] and that evening bright light was effective in treating this disorder.[28,29,32]

Although there is general agreement that lengthening the photo period at both ends is not critical, we disagree with the Bethesda group when they discount the importance of timing. First, photo period length is not the only aspect of timing; its effect on shifting the phase of circadian rhythms is also important. Second, many of the Bethesda group's studies were either not properly controlled or were in some other way methodologically suboptimal.[31] In brief, any study intended to demonstrate a mechanism of action should:

1) Optimize the antidepressant efficacy of light treatment,

2) Control sleep time and bright light exposure around dawn and dusk, and

3) Take into account the phase shift hypothesis. With regard to this latter point, bright light in the late morning or early afternoon might cause some amount of phase advance, since we do not know the precise boundaries of the "dead zone" of the PRC, either in normal controls or patients.

TREATMENT OF SEASONAL AFFECTIVE DISORDER (WINTER DEPRESSION)

Most of our thinking regarding the phase shift hypothesis has been the result of work with winter depressive patients. Preliminary data collected in 1981 to 1983 suggested that these patients were phase delayed and would

respond preferentially to morning bright light exposure.[16] During the winter of 1984-1985 we studied 14 winter depressed patients (eight as outpatients and six as inpatients) and seven normal controls at home.[18,19] Throughout the study subjects were not permitted to sleep between 6 AM and 10 PM. They remained indoors shielded from bright light exposure between 5 PM and 8 AM (The inpatients were also exposed to bright light between 8 and 8:15 AM and between 4:45 and 5 PM.) The first week served to establish a baseline. The second week half of the subjects were randomly assigned to either bright light exposure in the morning (6 to 8 AM) or in the evening (8 to 10 PM). The third week their exposure time was changed to the other lighting condition. The outpatients and the volunteers were studied for a fourth week during which they were exposed to bright light both in the morning and in the evening.

The patients preferentially responded to morning light. Hamilton depression ratings were significantly lower at the end of the week of morning light compared with the baseline week or the week of evening light. Ratings for the week of morning plus evening light were intermediate between those at the end of the week of morning or evening light alone. It is difficult to find any explanation for these results other than that the light is phase advancing the circadian rhythms of these patients. This would explain not only why the morning light was more effective than the evening light, but also why the combination had an intermediate effect: evening light, which would be expected to cause a phase delay in circadian rhythms, could be counteracting the phase advance induced by the morning light.

We were further convinced of this phase shift explanation after examining the circadian rhythms of our subjects. As a marker for circadian phase position, we used the dim light melatonin onset (DLMO). Many other circadian rhythm markers, such as temperature and cortisol, are affected by locomotor activity or sleep.

Compared with the normal controls, the DLMOs of the patients were significantly delayed at the end of the baseline week. This may represent an abnormality in the circadian system of the patients, i.e., abnormally phase delayed circadian rhythms. Morning light, which caused a remission, was associated with a normalization of the DLMO. The combination of morning plus evening light caused the patients' DLMOs to shift to intermediate phase positions, as if the morning and evening light when given together were counteracting each other.

Melatonin production does not appear to be affected by acute changes in locomotor activity or sleep.

During the winter of 1985-1986, we asked the following question: how much morning light is needed to treat patients with seasonal affective disorder?[33] Patients were exposed to bright light upon awakening between 6 and 6:30 AM and were crossed over to exposure between 6 and 8 AM with withdrawal weeks in between (to enhance the double-blind nature of the study, half of the patients started on a baseline week and half were started on light exposure). On average, the two light exposures had the same antidepressant effect. However, there appeared to be subgroups. One fourth of the patients appeared to respond better to two hours of bright light exposure and one fourth of the patients appeared to respond better to the one half hour exposure. We hypothesized that for the latter group two hours of morning light caused too much of a phase advance. In both our studies described here, patients' DLMOs advanced more than did those of normal controls in response to morning light exposure, suggesting that the PRCs of the patients are more delayed than are those of the normal controls.

In the final week of the 1985-1986 study, we tested the same morning light exposure used during the first or second week. When given during the last week of the study, a particular light exposure had a much more antidepressant effect than when given during the first week. We anticipated that the antidepressant response to morning light might take longer than a week because the patients had to advance their sleep to accommodate the morning light exposure and thus retard closure of the phase angle between sleep and the other circadian rhythms. To test this idea further, we found that while holding the circadian rhythms of three winter depressive patients constant with late-morning light, delaying their sleep caused a remission in their depressive symptoms.[33] Therefore, winter depression appears to be the result of circadian rhythms that are phase delayed with respect to sleep. These patients respond either to advancing their circadian rhythms (holding their sleep time constant) or delaying their sleep (holding their circadian rhythms constant). Guidelines for the practical treatment of patients with seasonal affective disorder are provided in the Figure.

CONCLUSION

We hope that these guidelines will be useful to the clinician in evaluating putative chronobiologic sleep and mood disorders and in testing the effects of appropriately timed bright light exposure. More research is necessary, particularly in the identification of useful circadian phase markers that might help to phase type patients. Either baseline time of melatonin onset or its phase shift response to morning and to evening light may be useful for phase typing and for evaluating the phase shifting effects of light. It seems probable that appropriately timed bright light exposure will have important treatment applications for chrono-biologic sleep and mood disorders and may also be used to help people with problems adjusting to shift work and air travel .[34]

Treatment Guidelines for Patients with Seasonal Affective Disorder*

1. If patients do not have early morning awakening, schedule 1-2 hours of 2500 lux exposure immediately upon awakening. (Author's Note: More recent studies have shown that 10,000 lux can reduce this time to 1/2 hour.)
2. If patients begin treatment on the weekend, they may not have to arise earlier to accommodate the morning light exposure; early rising may retard the response for a few days.
3. The response begins 2-4 days after beginning light therapy and is usually complete within 2 weeks.
4. These patients should minimize any advance in their sleep time and should avoid bright light in the evening.
5. If patients do not respond to treatment, they may need a longer duration of morning light.
6. If patients respond only transiently or begin to complain of early morning awakening or severe fatigue in the evening, they may be becoming overly phase advanced due to too much morning light. The duration of morning should be reduced but still begun immediately upon awakening or some late evening light exposure could be added.
7. Some patients may respond to an immediate "energizing" effect of bright light exposure (this may be a placebo effect), which if not administered too late in the evening might be helpful.
8. Once a response has been achieved, the duration and frequency of light exposures can be reduced. Always begin light exposure immediately upon awakening or a little later if patients become overly phase advanced.
9. If there is still no response, a trial of evening bright light (7-9 PM) may be necessary. These patients should minimize any delay in their sleep time and should avoid bright light in the morning.
10. Appropriate precautions should be taken to avoid any possibility of eye discomfort or injury (e.g., an eye history and exam if indicated, instructions never to stare at the sun, use of safe artificial light sources, recommendation of follow-up check-ups).

*These guidelines can be applied in the treatment of delayed and advanced sleep phase syndromes, with the modification that sleep is held constant only after it achieves a normal phase position. In the treatment of phase advanced sleep or mood disorders, evening bright light should be used and bright light should be avoided in the morning.

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