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Effectiveness of evening phototherapy for insomnia is reduced by bright daytime light exposure

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Abstract

Objective—To examine the affect of ambulatory daytime light exposure on phase delays and advances produced by timed exposure to bright evening or morning light.

Methods—As a subset of a larger study, 32 older (63.0 ± 6.43 years) adults with primary insomnia were randomized to an at-home, single-blind, twelve-week, parallel-group study entailing daily exposure to 45 minutes of scheduled evening or morning bright (~4000 lux) light. Light exposure patterns during baseline and the last week of treatment were monitored using actigraphs with built-in illuminance detectors. Circadian phase was determined through analysis of in-laboratory collected plasma melatonin.

Results—Less daytime light exposure during the last week of treatment was significantly associated with larger phase delays in response to evening light ($r's > 0.78$). Less daytime light exposure during the last week of treatment was also associated with a significant delay in wake time ($r's > -0.75$). There were no such relationships between light exposure history and phase advances in response to morning light.

Conclusions—Greater light exposure during the daytime may decrease the ability of evening light, but not morning light, exposure to engender meaningful changes of circadian phase.

Keywords

Sleep Initiation and Maintenance Disorders; Sleep; Phototherapy; Circadian Rhythm Disorders; Sleep Phase Chronotherapy; Humans; Aging

Introduction

Light is the strongest zeitgeber (Gm., time giver) for the human circadian timing system as it is the primary means by which the internal clock remains synchronized with the external, geophysical day. Light has been used therapeutically to treat older individuals with advanced sleep phase disorder, with the theory being that evening light will delay the timing of sleep to a more socially desirable hour. While theoretically sound, this therapy has had only minor success [1].

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The manner in which the circadian system responds to light can be defined by both the time at which the light is administered and the intensity of the light. Light exposure in the evening engenders delays in the timing of the clock while light exposure in the early morning engenders advances in the timing of the clock [2]. Exposure at either time exhibits an intensity-dependent responsivity; increasing intensity leads to greater phase shifts and such relationships are sigmoidal [3,4]. The intensity-dependence of the circadian system has been determined in laboratory settings that use dim background lighting. Recent evidence, however, indicates that the human circadian system may not respond to *absolute* intensities of light but rather to *relative* intensities of light [5,6,7,8]. In other words, the response to 1000 lux of light may be very different on a dim background of 10 lux as compared to a room light background of 150 lux. We previously examined morning and evening phototherapy in a group of older individuals with primary insomnia [9]. We report below on the influence of the proximal history of daytime light exposure on the magnitude of the light-induced phase shifts in these individuals.

Methods

For detailed methodology of the entire clinical trial, we direct the reader to our previous publication [9]. In brief, healthy older individuals with primary insomnia were recruited from the general community. Subjects were empanelled into one of four lighting conditions (dim morning, bright morning, dim evening, bright evening) with a ratio of 2-to-1 into the bright (2) and dim (1) treatment conditions. For the purposes of these analyses, we report only on the subjects who received bright light. Subjects received 45 minutes of bright light (~4000 lux) for 12 weeks, with the exposure starting 15 minutes after wake time (morning conditions) or one hour before scheduled bedtime (evening conditions). Experimental light was administered using SADelite Lamps (Northern Light Technologies, Montreal, Canada) that were pre-configured in subjects' homes. Illuminance was assessed and confirmed at multiple time points in the protocol [9]. All subjects also received general sleep hygiene instructions [10], which encouraged a midday (following morning bright light) or afternoon (preceding evening bright light) walk outdoors.

Circadian phase was assessed on a pre-treatment baseline night and on a night during the last week of treatment. Phase assessments were done at the Stanford Hospital General Clinical Research Center. Under conditions of dim light or darkness, blood was collected via an indwelling intravenous catheter from 17:00 until 09:00. Plasma concentrations of melatonin were later determined using a commercially available radioimmunoassay (Bühlmann Laboratories, Allschwil Switzerland) with an assay sensitivity limit of 0.5 pg/mL. Circadian phase was calculated as the midpoint between the times at which plasma melatonin concentrations rose above and fell below the 16-hour mean [11]. The use of a variable threshold for melatonin phase determination is critical since some older individuals have normal rhythmicity of plasma melatonin, but at a low amplitude [11].

During the pre-treatment baseline and during the last week of treatment, ambulatory light exposure was assessed using actigraphs with built-in illuminance detectors (Actiwatch-L, MiniMitter, Bend OR). Light data were analyzed and the following variables quantitated: average illuminance (lux), maximum illumination (lux), integrated illuminance (lux minutes), and time spent in bright (>1000 lux) light (minutes). Data were averaged within subjects over a week of data collection. In one subject (bright evening light condition), illuminance data were not available during the baseline week; this subject was removed from all further analyses. For comparisons of light with other factors (see text), the *relative*

change in light was calculated as $\frac{(EndTx - BL)}{BL}$, such that *BL* was the measurement taken during the pre-treatment baseline and *EndTx* was the measurement taken during the last

week of treatment. This normalization was done to remove some of the behavioral variation that can influence absolute illuminance measurements. Concomitant with actigraphic collection of light information, the timing of sleep and wake were captured using sleep logs; sleep log data were confirmed by visual analysis of actigraph-collected movement data.

Data are presented as mean $\pm$ SD. Associations between data sets were examined using linear regression analyses (OriginPro8, OriginLab Corporation, Northampton MA). Other statistical comparisons are noted within the text. All procedures were approved by the Stanford University Institutional Review Board. All aspects of the study conform to the principles outlined in the Declaration of Helsinki.

Results

We had complete data for 18 subjects who were exposed to bright morning light (3 males, 15 females; 63.1 ± 7.17 years old) and 13 subjects who were exposed to bright evening light (3 males, 10 females; 63.5 ± 5.44 years old). There was no difference in the age ($p=0.84$, unpaired t -test) or sex ratio ($p=0.68$, Fisher Exact test) between the two groups.

The baseline (one week) illumination pattern of subjects who would later be exposed to bright morning light did not differ from that of those who would later be exposed to bright evening light (Table 1). During the last week of light treatment, the illumination pattern of subjects who were being exposed to bright morning light also did not significantly differ from that of those who were being exposed to bright evening light (Table 1). As we have previously reported [9], there was no difference in these parameters of light exposure between baseline and the end of treatment in either those exposed to the bright morning ($p's > 0.14$, paired t -tests) or bright evening ($p's > 0.24$, paired t -tests) light.

As reported in our earlier manuscript [9], subjects receiving bright morning light exhibited significant phase advances (0.49 ± 0.66 hrs) and those receiving bright evening light exhibited significant phase delays (0.53 ± 0.97 hrs). All measures of daytime light exposure (average illuminance, maximum illuminance, integrated illuminance, time spent in bright light) were inversely associated with phase delays such that less light exposure was correlated with larger phase delays ($r's > 0.76$, $p's < 0.01$). In other words, at least 57% of the variance in subjects' responses to the evening light exposure could be attributed to differences in daytime light exposure. All measures of daytime light exposure were also negatively associated with the time at which subjects who received bright evening light got out of bed in the morning ($r's < -0.67$, $p's < 0.02$), such that individuals who had less daytime light exposure and larger phase delays also got out of bed later. There were no associations between daytime light exposure and the time at which subjects got into bed ($r's > -0.48$, $p's > 0.10$).

In contrast to phase delays engendered by evening light exposure, phase advances caused by experimental morning light exposure were not associated with any measure of daytime light exposure ($r's < -0.33$, $p's > 0.18$). Daytime light exposure in these subjects was also not associated with either the time at which they got into bed ($r's < 0.19$, $p's > 0.45$) or the time at which they got out of bed ($r's < 0.20$, $p's > 0.42$).

Discussion

Our data indicate that daytime light exposure can influence the effects of nighttime light exposure on the timing of the human circadian pacemaker in older individuals experimentally treated for insomnia. When subjects were exposed to greater illuminance during the daytime, the effectiveness of nighttime phototherapy in inducing phase delays of the circadian system was diminished. This implies that as opposed to responding to absolute

levels of light, the circadian pacemaker has some type of “memory” that can compare historical to current light exposure. Because there was no relationship between light exposure history and phase advances in response to morning phototherapy, this “memory” may be limited in duration. All subjects receiving morning phototherapy had approximately eight hours of darkness (during sleep) prior to phototherapy. Thus, the circadian clock may be using eight or fewer hours as a reference illuminance.

As most laboratory-based studies examining the responsivity of the circadian system to light (*e.g.*, references 2–8) are performed such that the “background” light is very dim (<15 lux), care must be taken in extrapolating the results of these studies to “real world” situations. These laboratory studies examine the *capacity* of the human circadian system to respond to light rather than its *functional* sensitivity. Future studies should examine the effects of changing daytime light exposure when administering phototherapy for clinical purposes. The present results would in themselves caution against the sleep hygiene guideline of increasing daytime light exposure in individuals in whom a phototherapy-induced phase delay of the circadian system is the desired clinical outcome.

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References

1. Forbes D, Culum I, Lischka AR, Morgan DG, Peacock S, Forbes J, et al. Light therapy for managing cognitive, sleep, functional, behavioural, or psychiatric disturbances in dementia. *Cochrane Database Syst Rev.* 2009;CD003946. [PubMed: 19821317]
2. Khalsa SBS, Jewett ME, Cajochen C, Czeisler CA. A phase-response curve to single bright light pulses in human subjects. *J Physiol.* 2003; 549:945–952. [PubMed: 12717008]
3. Zeitzer JM, Dijk D-J, Kronauer RE, Brown EN, Czeisler CA. Sensitivity of the human circadian pacemaker to nocturnal light: melatonin phase resetting and suppression. *J Physiol.* 2000; 526:695–702. [PubMed: 10922269]
4. Zeitzer JM, Khalsa SBS, Duffy JF, Boivin DB, Shanahan TL, Kronauer RE, et al. Dose-dependent response of the human circadian system to photic stimulation during the late biological night. *Am J Physiol.* 2005; 289:R839–R844.
5. Hébert M, Martin SK, Lee C, Eastman CI. The effects of prior light history on the suppression of melatonin by light in humans. *J Pineal Res.* 2002; 33:198–203. [PubMed: 12390501]
6. Smith KA, Schoen MW, Czeisler CA. Adaptation of human pineal melatonin suppression by recent photic history. *J Clin Endocrinol Metab.* 2004; 89:3610–3614. [PubMed: 15240654]
7. Smith MR, Eastman CI. Phase delaying the human circadian clock with blue-enriched polychromatic light. *Chronobiol Intl.* 2009; 26:709–725.
8. Chang AM, Scheer FA, Czeisler CA. The human circadian system adapts to prior photic history. *J Physiol.* online January 10, 2011. 10.1113/jphysiol.2010.201194
9. Friedman L, Zeitzer JM, Kushida CA, Zhdanova IV, Noda A, Lee T, et al. Scheduled bright light for treatment of insomnia in older adults. *J Am Geriatr Soc.* 2009; 57:441–452. [PubMed: 19187411]
10. Guilleminault C, Clerk A, Black J, Labanowski M, Pelayo R, Claman D. Nondrug treatment trials in psychophysiologic insomnia. *Arch Intern Med.* Apr 24.1995 155:838–844. [PubMed: 7717792]
11. Zeitzer JM, Daniels JE, Duffy JF, Klerman EB, Shanahan TL, Dijk D-J, et al. Plasma melatonin concentration: does it decline with age? *Amer J Med.* 1999; 107:432–436. [PubMed: 10569297]

Table 1

Light data from taken at baseline and the end of treatment. Data are shown as average (SD).

	Baseline			End of Treatment		
	Bright Morning	Bright Evening	p-value	Bright Morning	Bright Evening	p-value
Average Illuminance (lux)	1089 (749.7)	1395 (1024)	0.34	1522 (1127)	1857 (1590)	0.50
Maximum Illuminance (lux)	80480 (44970)	90650 (49470)	0.56	98040 (42000)	105200 (45100)	0.65
Integrated Illuminance (lux min.)	1444000 (983500)	1824000 (1404000)	0.38	2077000 (1541000)	2364000 (2036000)	0.66
Time in Bright Light (min.)	101.4 (50.79)	128.0 (0.27)	0.27	133.9 (79.00)	164.9 (76.89)	0.28