Melatonin Suppression by Illumination of Upper and Lower Visual Fields

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Abstract As a guide to optimizing the geometry of bright light treatment, 12 healthy subjects were studied three times in the laboratory from 11 p.m. to 2 a.m. On three evenings, in counterbalanced orders, subjects received 500 lux in the upper visual field, 500 lux in the lower visual field, or 5 lux while watching television. In the upper visual field, 500 lux significantly suppressed melatonin, as compared to 500 lux in the lower visual field or to 5 lux. In the lower visual field, 500 lux produced intermediate suppression of borderline significance. The results suggest that bright light treatment of depression or circadian phase disorders might be most effective when applied in the upper visual field.

Key words light, melatonin, visual field, retina, suppression, eye

INTRODUCTION

Bright light treatment has become accepted for treatment of seasonal affective disorder and is indicated for nonseasonal depression and a variety of sleep disorders (Depression Guideline Panel, 1993; Rosenthal, 1995; Terman, 1995; Kripke, 1998).

Many questions have not yet been answered about the most effective way in which to give bright light treatments. The most popular and successful mode of light treatment has been with special fluorescent lighting panels, but little is known about how such panels are best oriented. Some evidence suggests that light boxes are most effective when placed a bit above the eyes (in the upper visual field) and tilted down (Terman et al., 1990), but that study confounded orientation with the distance and consequent illumination levels produced by the treatment devices. On the other hand, superiority over placebo has not been demonstrated with light visors, which seem to administer bright light from a similar part of the upper visual field (Teicher et al., 1995). Knowledge of the most effective areas of the visual field is important to guide the placement of treatment lights.

Most researchers assume that the receptive elements for light treatment are in the retinas, although the experimental evidence is limited (Wehr et al., 1987). The receptors that mediate effective light treatment have not been identified, and they might not be the recognized rods and cones (Brainard et al., 1997). Indeed, because light treatment is active through closed eyelids (Avery et al., (1994), and even light to the back of the knee has been claimed to influence the circadian system (Campbell and Murphy, 1998), it is not entirely certain that the only receptive elements are in the eye.

Although the light intensity required for circadian phase shifting is quite different from that which produces melatonin suppression (Hashimoto et al., 1996), both responses are mediated through projections of the retinohypothalamic tract to the suprachiasmatic nuclei. It seems plausible that the antidepressant effects of bright light might be mediated through the same receptive elements and retinohypothalamic pathways that affect melatonin secretion, so that the receptive field for treatment effects might resemble that for melatonin suppression. Gaddy et al. (1992) demonstrated that full retinal illumination causes

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greater melatonin suppression than does partial illumination, suggesting that the receptors are widely distributed in the peripheral retina, as is the cases of cats and rats (Groos et al., 1983). Adler et al. (1992) showed that melatonin suppression in humans is equivalent using either central or lateral peripheral illumination. The present study was designed to determine whether melatonin suppression is equivalent using illumination of either the upper or lower visual field.

MATERIALS AND METHODS

A total of 12 paid subjects (6 male and 6 female) between 24 and 38 years of age (mean age 28) were recruited for excellent general health and use of no medications other than oral contraceptives. Subjects were asked to sleep regularly from 11 p.m. to 7 a.m. for a 6-week period and were tested at the ends of Weeks 2, 4, and 6. They were asked to refrain from ingestion of alcohol and caffeine for 5 h prior to each test and to avoid any use of nonsteroidal anti-inflammatories for 24 h before each test because such drugs might influence melatonin secretion. Each subject received three treatments in counterbalanced orders: bright light (500 lux) in the upper visual field, bright light (500 lux) in the lower visual field, and dim light (5 lux). Illumination of 500 lux was selected prospectively, in hopes of obtaining partial (not complete) suppression, to avoid ceiling effects in comparing treatments. Treatments also were counterbalanced according to menstrual cycle phase for the female subjects because of possible menstrual cycle modulation of melatonin secretion.

On arriving at the laboratory at 11 p.m. for an evening test, subjects were seated in darkened rooms and asked to watch entertainment videos until 2 a.m. In each room, 2 subjects were seated side by side, 1.8 m from an eye-level television screen, which produced less than 5 lux illumination when measured from the eye in the direction of gaze. In a similar experiment, it was found that subjects directed their gazes to the video screen an average of 98% of the time (Adler et al., 1992). On one night, a 30 × 60 cm Apollo cool white fluorescent light box with diffuser was placed with its center 76 cm (23°) above the center of the television, illuminated from midnight to 2 a.m. On another night, the light box was placed 76 cm (23°) below the center of the television and illuminated from midnight to 2 a.m. On a third night, no light box illumination was used. Whether above or below the television, the light

boxes produced about 500 lux of illumination, measured hourly with the photometer at eye level and directed toward the television. Subjects verified that the light boxes were entirely visible in the upper or lower peripheral vision while maintaining their gazes on the television screen.

Saliva samples were obtained at midnight (after 1 h of 5 lux), at 1 a.m., and at 2 a.m. to indicate the effects of the first and second hours of counterbalanced treatments. The saliva melatonin radioimmunoassay was performed by Diagnostech International (Osceola, WI), using its Melatonin Direct (MEL100) assay kit. The antibody has been validated against gas chromatography–mass spectroscopy melatonin and has a minimal detectable concentration in saliva of 1.0 pg/ml (CV 5.6%). Samples for this study ranged from 6.7 to 59.1 pg/ml.

Because the subjects displayed a wide range of melatonin concentrations in saliva, concentrations at 1 and 2 a.m. for each sample were calculated as percent change from the midnight sample (baseline) concentration. Changes from baseline were then compared for the three treatments, using Friedman's nonparametric test for related samples. It was prospectively assumed that 500 lux illumination would result in lower melatonin concentrations than would dimmer illumination, but no prediction was made of the relative effectiveness between upper and lower field illuminations. Post hoc pairwise comparisons subsequently were computed using the Wilcoxon signed ranks test. Friedman's test also was used to examine any effects of treatment order that might be independent of treatment type.

RESULTS

As shown in Fig. 1, relative melatonin levels in the 5 lux condition were progressively higher at 1 and 2 a.m. than at midnight, as would be expected from the usual pattern of melatonin secretion. Illumination of 500 lux in the upper visual field prevented this expected rise, and the rise with 500 lux in the lower visual field was intermediate.

Friedman's test showed that the three treatments were significantly different at 1 a.m. ($p < .01$) and at 2 a.m. ($p < .03$). Pairwise tests showed that at 1 a.m., 500 lux in the upper visual field produced melatonin concentrations significantly different from 5 lux ($p = .005$) and from 500 lux in the lower visual field ($p < .03$), but 500 lux in the lower visual field produced melatonin
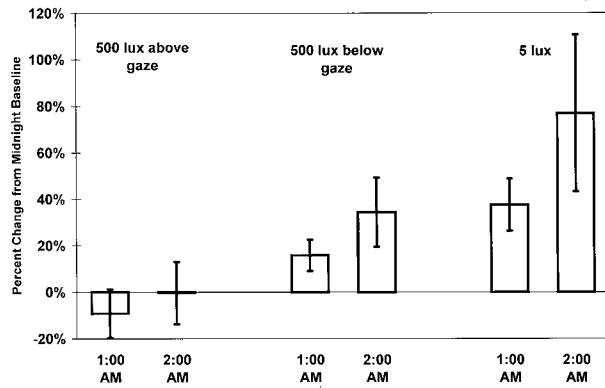
Figure 1.   Percentage changes of saliva melatonin concentrations from midnight baseline for three illumination conditions. Means ± *SEM* (*n* = 12).

concentrations only equivocally different from 5 lux (*p* = .06, two-tailed). At 2 a.m., 500 lux in the upper visual field produced melatonin concentrations significantly different from 5 lux (*p* = .01) and from 500 lux in the lower visual field (*p* < .05), but 500 lux in the lower visual field produced concentrations only equivocally different from 5 lux (*p* < .10, two-tailed). There were no significant effects of chronological order of weeks.

DISCUSSION

Robust evidence was obtained that 500 lux in the upper visual field suppressed melatonin, as contrasted with dim 5 lux illumination, and that suppression was greater with illumination in the upper visual field, as contrasted with the lower visual field. This might suggest a relative concentration of the retinohypothalamic neurons in the lower half of the human retina. However, other factors might mediate differential responsivity such as differences in pupillary response between upper and lower visual fields. Melatonin suppression from 500 lux in the lower visual field was weak but might be considered statistically significant with one-tailed tests because the direction of the effect was prospectively predicted. Because complete counterbalancing was employed and there were no order effects detected, it is highly unlikely that interactions of treatment and order contaminated the crossover design.

Visser et al. (1999 [this issue]) also studied light suppression by illumination of different areas of the retina. They also found greater suppression when the lower retina (upper visual field) was illuminated, al-

though in their 8 subjects, the difference did not achieve significance. Attempting the difficult task of correcting for shadowing and reflections from the nose, they found that illumination of the nasal retina produced more suppression than did illumination of the lateral retina. Because light stimulating the nasal retina of one eye normally will stimulate the lateral retina of the other eye, this distinction can be practically relevant only when special lighting devices are mounted on the head.

The daily light treatments used to produce clinical benefits have generally produced an order of magnitude more photons than is needed for melatonin suppression, so it is uncertain in what ways treatment responses and melatonin suppression might be related. If the assumption is correct that melatonin suppression and light treatment use the same visual receptors and retinohypothalamic pathways, then these data would suggest that light treatment will be most efficient when applied to the upper visual field. Nevertheless, because light visor treatment has been shown to suppress melatonin but has not been shown to be clinically more effective than placebo (Teicher et al., 1995), we must reserve judgment as to whether the implications are referable to the clinical setting. Current knowledge might suggest that it is prudent to place light treatment devices above the level of the eyes, but actual clinical trials are needed to confirm that light in the upper visual field is more clinically effective.

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