Peripheral vision suppression of melatonin

Adler JS, Kripke DF, Loving RT, Berga SL. Peripheral vision suppression of melatonin. J. Pineal Res. 1992:12:49–52.

Joshua S. Adler,[1] Daniel F. Kripke,[2,3] Richard T. Loving,[3] and Sarah L. Berga[4]

[1]Department of Medicine, University of California, San Francisco, CA; [2]Department of Psychiatry, University of California, San Diego, La Jolla, CA; [3]Department of Psychiatry, Veterans Affairs Medical Center, San Diego, CA; [4]Department of Obstetrics and Gynecology and Psychiatry; The University of Pittsburgh Magee-Women's Hospital, Pittsburgh, PA, U.S.A.

Abstract: The suppression of melatonin by bright light is probably mediated by the suprachiasmatic nucleus (SCN) in humans. In animals, SCN cells have broad visual receptive fields, suggesting that peripheral bright light could be effective for melatonin suppression. Twelve healthy subjects were subjected to 1000 lux illumination for 2 hr from 0100 to 0300 on two occasions: once lighting the central visual field 5° from the center of gaze and once lighting the peripheral visual field 60° lateral to the direction of gaze. Six subjects were observed on a third occasion in dim light. The three conditions differed significantly, with less melatonin secreted in 1000 lux, but melatonin levels with central and peripheral illumination did not differ. This suggests that phototherapy using bright light in the visual periphery may be effective.

Key words: melatonon—phototherapy—light—vision—peripheral—circadian

Address reprint requests to Daniel F. Kripke, M.D., Department of Psychiatry, V-116-A, Veterans Affairs Medical Center, 3350 La Jolla Village Drive, San Diego, CA 92161, U.S.A.

Received September 28, 1990; accepted September 24, 1991.

Introduction

Direct control of melatonin secretion is mediated through an endogenous circadian pacemaker located in the suprachiasmatic nucleus (SCN) of the hypothalamus [Rusak, 1989]. Environmental photic information is transmitted to the SCN by the retinohypothalamic tract. In normal subjects, pineal gland melatonin secretion is maximal at night and almost completely suppressed during the day [Arendt et al., 1982; Wetterberg, 1983]. The secretion of melatonin is regulated by the environmental light:dark cycle [Arendt and Broadway, 1987]. Melatonin secretion may serve as an indicator of the state of the circadian system, including the SCN [Lewy et al., 1986].

Bright artificial light has been used to alter endogenous circadian rhythms in humans [Wever, 1989; Czeisler et al., 1989]. Bright light exposure at night also suppresses the nocturnal secretion of melatonin [Lewy et al., 1980]. The intensity of light may control the degree of suppression [Brainard et al., 1988]. This effect is presumably mediated by retinal stimulation, transmitted to the pineal gland via the SCN. The pathway may be similar to that which normally entrains melatonin to the environmental light:dark cycle. Bright light has been used to treat certain psychiatric disorders (e.g., seasonal affective disorder (SAD) and major depressive disorders) [Rosenthal and Blehar, 1989]. Some investigators hypothesize that these disorders are associated with abnormally delayed, or advanced, circadian rhythms, and that bright light treatment may function by resetting these rhythms to the proper phase [Lewy et al., 1989].

There has been considerable variation in practical approaches taken for light treatment. In some therapeutic bright light trials, subjects have been instructed to intermittently gaze directly at a bright light source. Thus, the angle of incidence of light was equal to the direction of gaze for an undetermined portion of the exposure. The duration and angle of light impinging upon the peripheral visual field of the subjects were not investigated. In other trials, gazing continuously toward the light source was not required. Therefore, the extent to which effects of bright light have been due to exposure in the center of the visual field, versus exposure in the peripheral visual field, has not been well established.

In mammals, SCN cells are known to have broad receptive fields for visual input; further retinal ganglion cells projecting to the SCN are distributed throughout the retina [Groos and Mason, 1980; Pickard, 1979]. Thus, it is possible that bright light impinging on the peripheral visual field in humans would be sufficient to suppress melatonin and to treat certain psychiatric disorders. In this study, we compared the suppression of nocturnal melatonin

secretion by bright light exposures in the center and in the periphery of the visual field.

Materials and methods

Twelve healthy male subjects (ages 20–29) with no history of psychiatric illness consented to participate in this study. After the nature of study was explained, informed consent was obtained from each subject. Subjects were then exposed to both central bright light and peripheral bright light on two separate nights at least 1 week apart. Orders of exposure were counterbalanced. For 48 hr prior to each trial, the subjects refrained from consuming alcohol, and 24 hr prior to each trial, the subjects refrained from consuming caffeine and chocolate, because these substances might affect circadian rhythms.

On trial nights, subjects arrived at the hospital at 2230. Dark glasses were used to reduce the illumination exposure, while an intravenous line was started. EDTA (1.5 mg/ml) was used as an anticoagulant because heparin may interfere with melatonin assays. Subjects were then allowed to read or watch television in dim light ($<$ 50 lux) until 0100. Subjects were then exposed to 2 hr of bright light (1000 lux measured at the subject's eye level) from 0100 to 0300. We used an Apollo Light Systems Brite Light with cool-white fluorescent bulbs as the light source.

An illumination of 1000 lux was chosen to suppress melatonin to an intermediate degree, so that any differences between peripheral and central exposure could be recognized. The illumination intensity was monitored using a UDT-351 photometer held 2 cm lateral to the subjects' eyes and directed at the light source. The photometer itself has a wide field of view. The subjects watched television during the light exposure in order to maintain a relatively constant direction of gaze. During the light exposures, the eyes of eight subjects were simultaneously videotaped. These videotapes were later scored to quantify the duration of time each subject was looking directly at the television. The nontelevision-directed gaze time could not be quantified with regard to the altered directions of gaze.

For the central visual field exposure, the Brite Lite was placed directly next to a television set, resulting in an angle of incidence of bright light averaging 5° from the direction of gaze. For the peripheral visual field exposure, the Brite Lite was placed to the side of the subject, at eye level, to create an angle of incidence averaging 60° lateral to the direction of gaze. Half of the subjects received light from the right side on both trials, while the other half received light from the left side.

Six of the subjects repeated the study with dim light exposure ($<$ 50 lux) from 0100 to 0300 to confirm if the bright light exposures suppressed melatonin.

Blood samples of 6 cc each were drawn every 15 min from midnight to 0300 each night. Samples were anticoagulated with EDTA (1.5 mg/cc) and centrifuged. Plasma was pipetted and immediately frozen on dry ice. Samples were stored at −20°C and subsequently assayed. Melatonin was measured directly without extraction using previously-described direct radioimmunoassay methods [Berga et al., 1988; Fraser et al., 1983; Webley et al., 1985]. Assay sensitivity was 10 pg/ml. All samples were analyzed in duplicate. Intra- and interassay coefficients of variation were 8.1% and 10.9%, respectively.

Results

The mean plasma melatonin levels for the three types of light exposure (bright peripheral, bright central, and dim) at each time are shown in Figure 1. In dim light, the normal increase in melatonin from midnight (2400) to 0200–0300 was observed, whereas after 0100, melatonin concentrations were lower in both the central and peripheral 1000 lux conditions. Comparing the mean of four samples before bright light exposure (1200–1245) with the mean of four samples at the end of exposure (0215–0300) in the central, peripheral, and dim groups with factorial repeated-measures ANOVA, we found a significant interaction of time (before or after 0100) and exposure group (ANOVA $F = 5.54$, $p = 0.024$, $DF = 10,2$). There was, however, no significant pair-wise difference between the central and peripheral 1000 lux groups at any time.

Analysis of the trends (slopes) in melatonin concentrations over time also showed no significant difference between the effects of central and peripheral light exposure.

When melatonin levels of blood collected over 3-hr periods were averaged (for each subject), the levels for central and peripheral illumination were correlated with $r = 0.899$ ($P < 0.025$).

Analyses of the videotapes showed that all eight subjects had their eyes directed toward the television for at least 96% of the 2-hr light exposure interval (mean = 98%).

Discussion

We found that peripheral bright light and central bright light suppress nocturnal melatonin secretion to a similar degree. Although melatonin suppression and circadian phase-shifting may have different

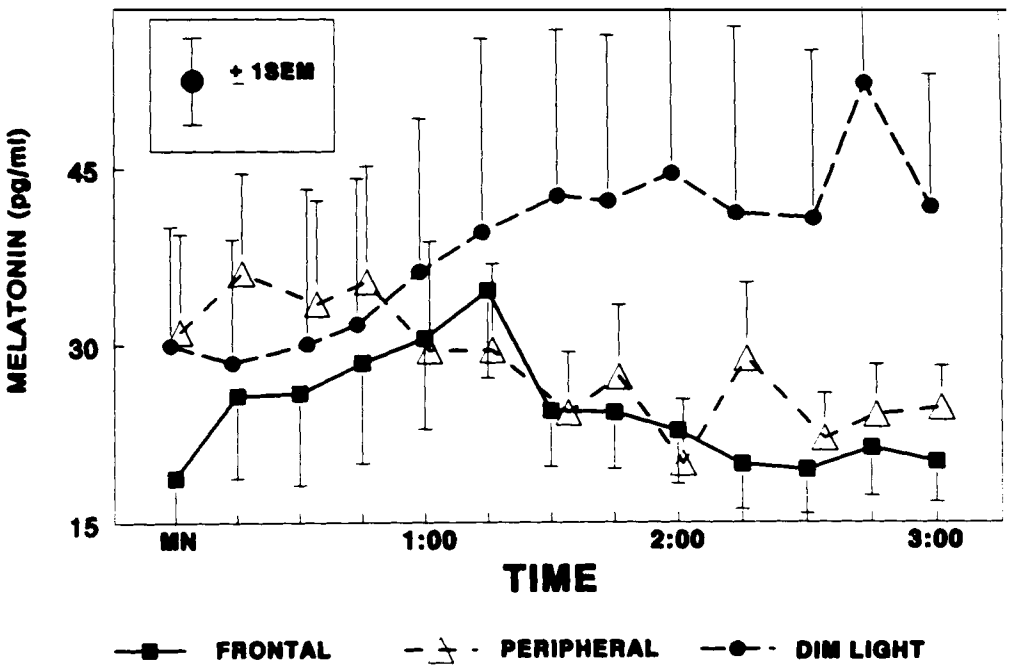

Fig. 1. Mean melatonin (pg/ml) for subjects exposed to diffuse dim light, 1000 lux peripheral light, and 1000 lux control light.

kinetics, the retinal mediation may be similar. Thus, the effects of peripheral bright light and central bright light on the circadian system could also be similar. The entire retina, or a substantial portion of it, may be involved in the normal daily entrainment of endogenous rhythms. Involvement of the peripheral retina in circadian rhythm entrainment is consistent with previous evidence that SCN cells have broad receptive fields for visual input [Groos and Mason, 1980].

These results suggest that peripheral bright light might be sufficient for treating certain psychiatric disorders. These findings support testing of peripheral bright light in future therapeutic trials. The possible advantages of peripheral bright light over central bright light are two-fold. First, bright light in the peripheral visual field is more comfortable than central bright light, and subjects may engage in other, more enjoyable activities during the exposure (e.g., watching television or reading). Second, although the adverse effects of bright light exposure are thought to be minimal, there is some evidence to suggest that the peripheral retina is less susceptible than the central retina to damage by bright light [Lawwill et al., 1980]. The correlation of mean melatonin concentrations after central and peripheral illumination is consistent with previous data suggesting that individual melatonin secretion patterns are rather stable from night to night.

Nevertheless, several surprising results require further reservation. Lin et al. [1990], Terman and Schlager [1990] and Avery et al. [1991] have reported that surprisingly low levels of illumination during sleep are biologically active through closed eyelids. Goggles at 60 lux also may produce unanticipated effects [Levitt et al., 1991]. If these results are confirmed, there may be important determinants of light efficacy apart from illumination intensity and angle of view.

Acknowledgements

NIMH RSDA MH00117, MH38822, HL07491, HD12303, GCRC RR-00827, and the Department of Veterans Affairs.

Literature cited

ARENDT, J., J. BROADWAY (1987) Light and melatonin as zeitgebers in man. Chronobiol. Intl. 4:273–82.

ARENDT, J., S. HAMPTON, J. ENGLISH, P. KWASOWSKI, V. MARKS (1982) 24-hour profiles of melatonin cortisol, insulin, c-peptide, and gip following a meal and subsequent fasting. Clin. Endocrinol. 16:89–95.

AVERY, D., M.A. BOLTE, M. WEYER, S. DAGER, L. WILSON, D. DUNNER, L. TAY, M. MILLET, G. COX (1991) Dawn simulation treatment of winter depression: A controlled study. Society for Light Treatment and Biological Rhythms. 3:9 (Abstract).

BERGA, S.L., J.F. MORTOLA, S.S.C. YEN (1988) Amplification of nocturnal melatonin secretion in women with functional amenorrhea. J. Clin. Endocrinol. Metab. 66:242–244 (Abstract).

BRAINARD, G.C., A.J. LEWY, M. MENAKER, R.H. FREDRICK-

SON, L.S. MILLER, R.G. WELEBER, V. CASSONE, D. HUDSON (1988) Dose-response relationship between light irradiance and the suppression of plasma melatonin in human volunteers. Brain Res. 454:212–218.

CZEISLER, C.A., R.E. KRONAUER, J.S. ALLAN, J.F. DUFFY, M.E. JEWETT, E.N. BROWN, J.M. RONDA (1989) Bright light induction of strong (type 0) resetting of the human circadian pacemaker. Science 244:1328–1332.

FRASER, S., P. COWEN, M. FRANKLIN, C. FRANEY, J. ARENDT (1983) Direct radioimmunoassay for melatonin in plasma. Clin. Chem. 29:396–397.

GROOS, G.A., R. MASON (1980) The visual properties of rat and cat suprachiasmatic neurones. J. Comp. Physiol. 135:349–56.

LAWWILL, T., R.S. CROCKETT, G. CURRIER (1980) The nature of chronic light damage to the retina. In: The Effects of Constant Light on Visual Processes. T.P. Williams, B.W. Baker, eds. Plenum Press, New York.

LEVITT, A.J., R.T. JOFFE, L.S. MARTIN, D.E. MOUL, R.W. LAM, M.H. TEICHER, B. LEBEGUE, D.A. OREN, A. BUCHANAN, C.A. GLOD, M.G. MURRAY, J. BROWN (1991) Light visor treatment of SAD. Society for Light Treatment and Biological Rhythms. 3:49 (Abstract).

LEWY, A.J., R.L. SACK, L.S. MILLER, T.M. HOBAN, C.M. SINGER, J.R. SAMPLES, G.L. KRAUSS (1986) The use of plasma melatonin levels and light in the assessment and treatment of chronobiologic sleep and mood disorders. J. Neural Transm. 21:311–322.

LEWY, A.J., R.L. SACK, C.M. SINGER, D.M. WHITE, T.M. HOBAN (1989) Winter depression: The phase angle between sleep and other circadian rhythms may be critical. In: Seasonal Affective Disorder. C. Thompson, T. Silverstone, eds. CNS Publishers, London, pp. 205–221.

LEWY, A.J., T.A. WEHR, F.K. GOODWIN, D.A. NEWSOME, S.P. MARKEY (1980) Light suppresses melatonin secretion in humans. Science 210:1267–1269.

LIN, M.C., D.F. KRIPKE, B.L. PARRY, S.L. BERGA (1990) Night light alters menstrual cycles. Psychiatry Res. 33:135-138.

PICKARD, G.E. (1979) Morphologic characteristics of retinal ganglion cells projecting to the suprachiasmatic nucleus: A horseradish peroxidase study. Brain Res. 183:458–465.

ROSENTHAL, N.E., M.C. BLEHAR (1989) Seasonal Affective Disorders and Phototherapy. Guilford Press, New York.

RUSAK, B. (1989) The Mammalian circadian system: Models and physiology. J. Biol. Rhythms. 4:121–134.

TERMAN, M., D.S. SCHLAGER (1990) Twilight therapeutics, winter depression, melatonin, and sleep. In: J. Montplaisir, Sleep and Biological Rhythms. R. Godbout, eds. Oxford University Press, New York, pp. 113–128.

WEBLEY, G.E., H. MEHL, K.P. WILLEY (1985) Validation of a sensitive direct assay for melatonin for investigation of circadian rhythms in different species. J. Endocrinol. 106:387–394.

WETTERBERG, L. (1983) Melatonin as a chronobiological marker in health and disease. In: The Pineal Gland and its Endocrine Role. J. Axelrod, F. Fraschini, G.P. Velo, eds. Plenum Press, New York, pp. 575–587.

WEVER, R.A. (1989) Light effects on human circadian rhythms: A review of recent Andechs experiments. J. Biol. Rhythms 4:161–185.