Weak relationships between suppression of melatonin and suppression of sleepiness/fatigue in response to light exposure

Ruger, M; Gordijn, Margaretha; Beersma, DGM; de Vries, Bontje; Daan, S

Published in:
Journal of Sleep Research

Publication date:
2005

J. Sleep Res. (2005) **14,** 221–227

Weak relationships between suppression of melatonin and suppression of sleepiness/fatigue in response to light exposure

MELANIE RÜGER, MARIJKE C. M. GORDIJN, DOMIEN G. M. BEERSMA, BONNIE DE VRIES and SERGE DAAN
Department of Chronobiology, University of Groningen, Groningen, The Netherlands

Accepted in revised form 11 March 2005; received 23 August 2004

SUMMARY In this paper we examine the relationship between melatonin suppression and reduction of sleepiness through light by comparing three different data sets. In total 36 subjects participated in three studies and received 4 h of bright light either from midnight till 4:00 hours (experiments A and B) or from noon till 16:00 hours (experiment C). In experiment A (night-time light, *partial illumination of the retina, pupil dilated*) subjects were exposed to either 100 lx of ocular light on the temporal, 100 lx on the nasal part of the retina, or <10 lx of dim light on the whole retina. In experiments B (night-time light, *whole retina, pupil not dilated*) and C (daytime light, *whole retina, pupil not dilated*) subjects were exposed either to bright (5000 lx) or to dim light (<10 lx). Subjective sleepiness/fatigue and melatonin concentrations in saliva were assessed hourly in all three experiments. For experiment A, a significant suppression of melatonin due to nasal and temporal illumination of the retina was found, that was not accompanied by a detectable reduction of subjective sleepiness/fatigue. For experiment B we found a suppression of melatonin that was paralleled with a significant reduction in subjective sleepiness, but not in fatigue. During experiment C we found no melatonin suppression but a reduction of subjective sleepiness, but also no effect on fatigue. From these data we conclude that the effects of light on sleepiness/fatigue are not mediated by melatonin and that the influence of endogenous melatonin concentration on sleepiness/fatigue is restricted.

KEYWORDS bright light, melatonin, night time and daytime exposure, subjective sleepiness

INTRODUCTION

Bright light exposure at night-time is known to suppress melatonin in humans immediately (Lewy *et al*., 1980). Several studies showed that the bright light induced melatonin suppression is accompanied by a reduction of subjective sleepiness (Cajochen *et al*., 2000; Campbell *et al*., 1995; Rüger *et al*., 2003), an enhancement of alertness (Badia *et al*., 1990, 1991; Campbell and Dawson, 1990; Dawson and Campbell, 1991; Myers and Badia, 1993), and an improvement of mood and performance in healthy subjects (Daurat *et al*., 1993; Foret *et al*., 1998; Partonen and Lonnqvist, 2000). Exogenously administered melatonin enhances sleepiness (Cajochen *et al*., 2003; Dollins *et al*., 1994; Graw *et al*., 2001; Rogers *et al*., 2003), impairs performance (Graw *et al*., 2001; Rogers *et al*., 2003), and blocks the elevation of body temperature in response to bright light exposure (Strassman *et al*., 1991). The soporific effects of exogenous melatonin administration seem to be dose-dependent as two studies by van den Heuvel *et al*. (1998, 1999) have shown. Low doses of exogenous melatonin during daytime (i.e. in the range of nocturnal melatonin production) reduced the daytime rise in core body temperature significantly, but had no effect on subjective sleepiness. Supra-physiological levels of melatonin during daytime on the other hand resulted in attenuation of core body temperature and in increase in sleepiness. Using comparable doses of melatonin Singer *et al*., (2003) failed to show a soporific effect of melatonin in a group of Alzheimer patients.

Correspondence: Melanie Rüger, Department of Chronobiology, University of Groningen, PO Box 14, 9750 AA Haren, The Netherlands. Tel.: 0031-(0)50-363-2061; fax: 0031-(0)50-363-2148; e-mail: m.rueger@rug.nl

Although these data suggest that endogenous melatonin is a primary causal factor in determining sleepiness and fatigue, either by itself or via its effect on body temperature (Badia *et al*., 1993; Gilbert *et al*., 1999), this can certainly not be the whole story. The sleepiness and fatigue reducing effects of light are not solely regulated by melatonin suppression or by changes in body temperature, as light exposure during daytime (i.e. when melatonin is not secreted and body temperature does not seem to be influenced by light) does lead to reduced subjective sleepiness and improved performance (Phipps-Nelson *et al*., 2003; Rüger *et al*., 2002). Sleepiness and performance changes over the 24-h cycle are known to be dependent on both the duration of waketime and of circadian phase (Dijk *et al*., 1992) independent of the presence of melatonin. In nocturnal animals activity even occurs during the night when melatonin is high and sleep during the day when melatonin is low.

In this paper we investigated the nature of the relationship between melatonin suppression and reduction of sleepiness/fatigue by using three different data sets obtained in light exposure experiments published earlier (Rüger *et al*., 2002, 2003, 2005). In total 36 subjects participated in the three studies and they were exposed to various light stimuli, ranging from 100 lx of partial retinal illumination to 5000 lx whole retinal illumination between midnight and 4:00 hours or noon till 16:00 hours respectively.

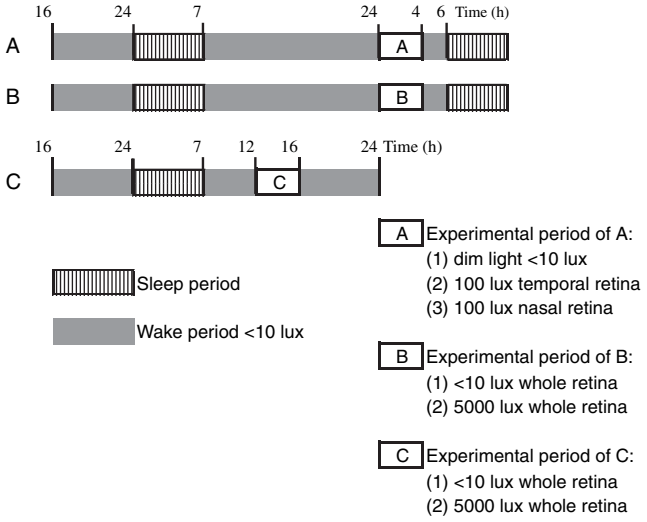

Figure 1. Experimental design of the three experiments. Upper part of the figure: night-time experiments, lower part daytime bright light experiment. Wake periods in dim light (< 10 lx) are indicated by grey bars, sleeping periods by hatched bars and periods of light exposure by white bars.

METHODS

Subjects

A total number of 36 subjects (29 males and seven females, mean age 21.91 years, SD = 2.03) participated in the experiments, 12 in each of them. Subjects were screened using a general health questionnaire and a Morningness–Eveningness Questionnaire (MEQ: Horne and Östberg, 1976). Only healthy, non-smoking, non-extreme morning or evening types (i.e. only MEQ scores between 31 and 69 were accepted) without eye problems such as far- or short-sightedness, history of glaucoma or cataract, colour-blindness and night blindness were included. Subjects had to be without current medication, history of psychiatric illness and must not have travelled more than one time zone within the month preceding the experiment. Female subjects not using oral contraceptives were tested in the luteal phase of their menstrual cycle, whereas female subjects taking oral contraceptives were tested during the phases they took a contraceptive by which a stable hormone concentration ensues. All subjects signed informed consent and were paid for their participation. The medical ethics committee of the University of Groningen approved the protocol.

Experimental protocol

The experimental designs of the three experiments are summarized in Fig. 1. All three experiments took place in the Time Isolation Facility of the University of Groningen, where neither clock information nor daylight is present. For a detailed description of the facility see Rüger *et al*. (2003). Experiment A (Rüger *et al*., 2005) consisted of an adaptation night (day 0), followed by a period of 23 h of sustained wakefulness, starting at 7:00 hours on day 1. The first testing period started at 18:00 hours and lasted till 5:00 hours the next morning (day 2). It included the hourly collection of saliva samples to determine melatonin concentration and hourly tests on the computer, including the questionnaires to assess sleepiness and fatigue. Within the testing period, subjects received either 100 lx of ocular light on the nasal part of both retinas, 100 lx of ocular light on the temporal part of both retinas, or < 10 lx on the whole retina (control condition) from midnight till 4:00 hours. Experiment B (see Rüger *et al*., 2003) also consisted of an adaptation night (day 0) at the laboratory, followed by a period of 26-h of sustained wakefulness. The first testing period with hourly measurements (including saliva samples and test battery) started at 18:00 hours on day 1 and lasted until 9:00 hours on day 2. During this period subjects received either 5000 lx of bright white light or dim light (< 10 lx, control condition) from midnight till 4:00 hours. In experiment C the first testing period (including saliva samples and test battery) started at 18:00 hours on day 0, followed by an adaptation night. Subjects woke at 7:00 hours the following day (day 1) and the second testing period started at 09:00 hours, lasting till midnight. Within this period, subjects received either 5000 lx of bright light or < 10 lx of dim light from noon till 4:00 hours. In all three experiments, during the periods they had to stay awake, subjects were monitored closely by cameras to ensure they were not falling asleep.

Light exposure

Except for the periods of light exposure and sleep (0 lx) the level of illumination was < 10 lx throughout all three experiments. We used Bright Light® boxes (Philips, Eindhoven, The Netherlands) for the light exposure in all three experiments. Figure 2 shows the spectral distribution of this light source.

In experiments B and C the light boxes were placed in front of the subject vertically next to a computer screen. Subjects remained seated in front of the computer screen during the 4 h of the light exposure. Luminance was 5000 lx at eye level, measured in the direction of gaze. During the time of light exposure, subjects had to complete a test battery hourly. In the intervals between tests they were allowed to read in front of the computer. They were not allowed to use the computer except for the test batteries. In experiment A, subjects were seated in a comfortable chair with a headrest in front of a video monitor at a distance of 5 m and watched videos, thus keeping their eyes fixed towards the middle of the TV screen. Two Bright Light® boxes were placed at an angle of 30 ° at the left and at the right relative to the direction of gaze of the subjects. To ensure that either the *temporal* or the *nasal* part of both retinas was illuminated exclusively, subjects wore helmets with black shields attached. In the *temporal* condition shields of black cardboard were attached to the left and right side of the helmet ensuring that light of the left Bright Light® box only entered the right eye of the subject and vice versa. For the *nasal* condition the shield was placed between the eyes and above and along the nose, so that the light of the left lamp only entered the left eye and the light of the right lamp only entered the right eye (for details see Rüger *et al*., 2005; Visser *et al*., 1999). In the dim light condition subjects wore the helmets without shields. In all three conditions of experiment A the pupils were dilated during light exposure by administering two droplets of cyclopentolate beforehand.

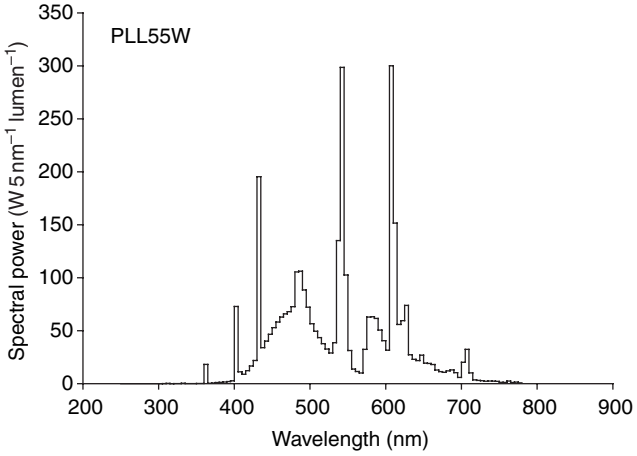

Figure 2. Spectral distribution of the light TL tubes PL55W used in the Bright Light® boxes.

Melatonin

Melatonin concentration was measured in saliva. Every hour the subjects gave a sample before filling in the questionnaires on the computer. The 15 min prior to each sample, subjects had to remain seated in front of the test computer, as posture is known to influence hormonal concentrations (Deacon and Arendt, 1994). No consumptions were allowed in the 45-min interval prior to the saliva samples. After each consumption the subjects had to rinse their mouth with water to prevent contamination of the next saliva sample. Saliva was collected using Sarstedt Salivettes® (Sarstedt BV, Etten-Leur, The Netherlands) with a polyester swab. Samples were centrifuged immediately and stored at −20 °C. Melatonin concentration was determined by means of a radioimmunoassay (RIA) (Rabbit antibody supplied by Stockgrand Ltd., Guildford Surrey, UK; SAC-Cel anti-Rabbit by Lucron Bioproducts, Gennep, The Netherlands; 2-[125] Iodomelatonin by Amersham Biosciences, Roosendaal, The Netherlands).

The limit of detection for the RIA in the three experiments was 0.39 pg ml^{-1} with an intra-assay variation between 11% and 14.5% at a low concentration (5 pg ml^{-1}) and varying between 9% and 13.7% at a high concentration (92 pg ml^{-1}). Interassay covariance varied from 11.9% to 17% at a low melatonin concentration (4.7 pg ml^{-1}) and between 12.2% and 16% at a high melatonin concentration (63 pg ml^{-1}).

Sleepiness and fatigue

Subjective sleepiness and fatigue were assessed hourly with the help of two questionnaires, the Karolinska Sleepiness Scale (KSS; Åkerstedt and Gillberg, 1990) and the Visual Analogue Scale for fatigue (VAS-f; Lee *et al*., 1991). We used these two questionnaires to capture the different aspects resulting from the sustained wakefulness our subjects were undergoing. The questionnaires were presented electronically on a computer screen.

Statistical analyses

The immediate effects of the various light treatments on the KSS and the VAS-f scores, and the melatonin concentration were tested with a paired *t*-test (including statistical powers and effect sizes (Cohen's *d* of the comparisons; Cohen, 1988), comparing the mean values during light exposure (1:00, 2:00 and 3:00 hours for the two night-time bright light experiments and 13:00, 14:00 and 15:00 hours for the daytime bright light experiment) with the mean values during the control condition (dim light). The midnight and 4:00 hours or 16:00 hours measurements, respectively, were not taken into account because the lights had just been switched on or off respectively. As the elimination half-life of melatonin is about 40 min (Cavallo and Ritschel, 1996; Dawson *et al*., 1996) this means that after 1 h of light exposure most of the melatonin circulating in prior dim light is eliminated.

To test whether a suppression of melatonin is associated with a reduction of sleepiness and fatigue we calculated the Spearman rank order correlation coefficient. Sleepiness, fatigue scores, and melatonin concentrations were expressed as differences between the mean values during the light and the control condition for experiments A and B. For the suppression of sleepiness and fatigue absolute differences were used. For melatonin suppression, however, the large interindividual variation prompted us to express the differences as a fraction of the corresponding value of the dim light condition. Due to the fact that there are very low melatonin concentrations during daytime, no correlations could be calculated for experiment C.

RESULTS

Figure 3 gives an overview of the light responses in experiments A, B and C. From top to bottom the results for the KSS, the Visual Analogue Scale for fatigue (VAS-f), and melatonin concentration for experiment A are presented. The upper left panel shows that there was no difference between KSS scores in the three conditions, independent of which part of the retina was illuminated (dim versus temporal: t (1,11) = 1.167, $P = 0.268$, dim versus nasal: t (1,11) = 1.856, $P = 0.090$). The middle left panel shows that neither temporal illumination (t (1,11) = 1.598, $P = 0.138$) nor nasal illumination did reduce the subjective fatigue ratings compared with the dim light condition (t (1,11) = 0.786, $P = 0.448$). The lower left panel of the first column shows the melatonin concentration in the three conditions. There was a significant reduction of melatonin concentration under temporal illumination compared with dim light (t (1,11) = 3.943, $P = 0.002$, $d = 0.64$, power = 0.32), as well as under nasal illumination compared with dim light (t (1,11) = 6.993, $P = 0.000$, $d = 2.04$, power > 0.99). Also, nasal and temporal illumination yielded a significantly different suppression of melatonin (t (1,11) = 4.630, $P = 0.001$).

The middle column of Fig. 3 shows the results on KSS, VAS-f and melatonin for experiment B. There was a significant reduction of subjective sleepiness under ocular light compared with the dim light condition (t (1,11) = 2.529, $P = 0.028$, $d = 0.94$, power = 0.59). This reduction was not found for the fatigue ratings on the VAS-f (t (1,11) = 1.650, $P = 0.127$).

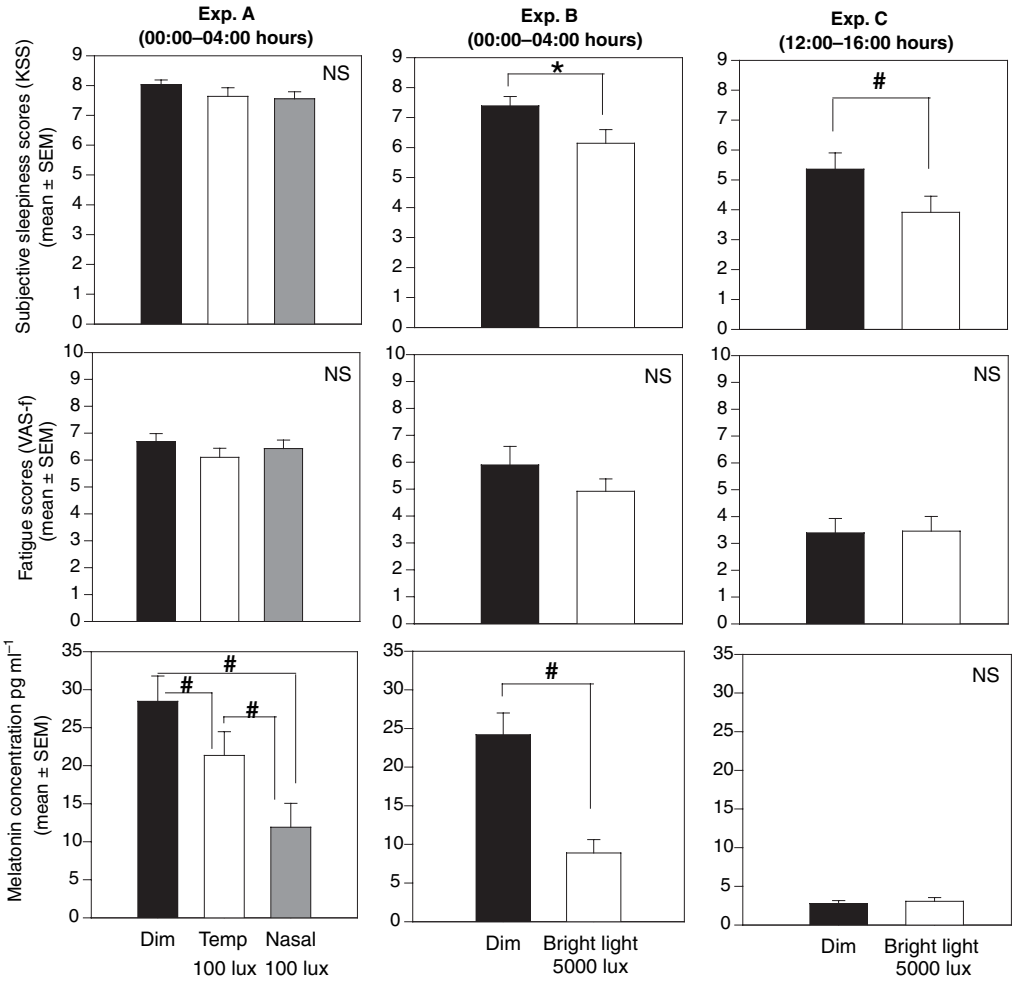

Figure 3. Mean ± SEM values for KSS, VAS-f, and melatonin during light exposure compared with control conditions (experiments A and B: 1, 2 and 3:00 hours; experiment C: 13:00, 14:00 15:00 hours). *$P < 0.05$, #$P < 0.01$.

Yet, there was a significant reduction of melatonin under ocular light compared with the dim light condition (t (1,11) = 5.554, $P = 0.000$, $d = 1.96$, power > 0.99). The third and last column of Fig. 3 shows the results of experiment C. The upper panel shows a significant reduction of subjective sleepiness under bright ocular light compared with the dim light condition (t (1,11) = 3.533, $P = 0.005$, $d = 0.78$, power = 0.44). This reduction of sleepiness was not accompanied by a similar reduction in the fatigue ratings of the VAS-f (t (1,11) = −0.132, $P = 0.897$). There was also no significant difference between the melatonin concentrations under bright and dim light during the day (t (1,11) = −0.629, $P = 0.542$).

Combining two studies in one analysis we analysed whether a monotonous correlation exists between the suppression of melatonin and the suppression of sleepiness or fatigue by ocular light. Experiment C was left out because no suppression of melatonin could be measured because of the very low melatonin levels at daytime. The left panel of Fig. 4 shows that there was no significant interindividual correlation (Spearman) between the change in sleepiness (KSS scores) and the change in melatonin concentration during light exposure ($n = 36$, $r_s = ,-0.085$ $P = 0.623$) for experiments A and B. The right panel of Fig. 4 shows no significant correlation (Spearman) between the change in fatigue (VAS-f scores) and the change in melatonin concentrations ($n = 36$, $r_s = -0.062$, $P = 0.720$).

DISCUSSION

In this paper we examined the relationship between the suppressive effects of light on (endogenous) melatonin concentration and on sleepiness/fatigue. For this reason we compared three different data sets from experiments published elsewhere (Rüger *et al.*, 2002, 2003, 2005) which varied in stimulus intensity (< 10, 100 and 5000 lx), time of exposure (midnight till 4:00 hours versus noon till 16:00 hours) and retinal area exposed to the stimulus (whole retinal versus partial illumination). A 4-h pulse of 5000 lx of bright light on the whole retina significantly reduced subjective sleepiness during night-time, when initial melatonin levels were high, as well as during the day, when melatonin levels were low. At night partial illumination of the retina also suppressed melatonin but such partial retinal light exposure had no significant effect on sleepiness/fatigue.

If we look closely at the two night-time light experiments, there is no significant correlation between either the suppression of sleepiness or the suppression of fatigue and the suppression of melatonin. This is true if we combine experiments A and B (Fig. 4), but also if we treat them separately (data not shown).

It is clear that it is impossible to expose subjects to bright light without them being aware of the exposure. This leaves ample space for placebo effects. To minimize such effects subjects were not informed about our interest in the relationship between subjective sleepiness and physiological measures, and they were given no feedback on their scores. If expectancy effects would have accounted for the results we would have expected to see an effect also for the Visual Analogue Scale and not only for the KSS. Furthermore, we would have expected to see this effect right at the start, but in fact it takes at least about 1 h of light exposure to see a reduction of sleepiness on the KSS (Rüger *et al.*, 2002, 2003). Therefore placebo effects and expectations are unlikely to have had a major impact on the observed relationship between melatonin suppression and sleepiness score.

The significant suppression of sleepiness in experiment C in response to light exposure in the middle of the day (when

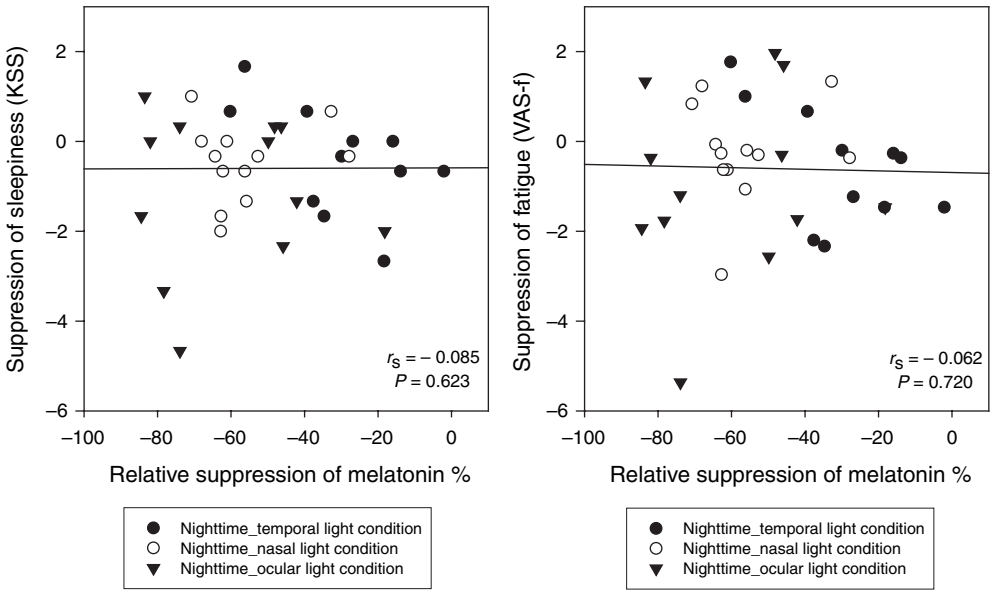

Figure 4. Correlation (Spearman) between mean melatonin suppression (relative values) and mean sleepiness suppression (absolute values) (left panel), and fatigue suppression (absolute values), respectively (right panel) for the last 3 h of the 4-h light exposure.

endogenous melatonin levels are very low and not suppressed by light), is in accordance with the results of Phipps-Nelson *et al*. (2003). In their daytime bright light exposure study they also showed a decreases of sleepiness and no effect on salivary melatonin. They sleep deprived their subjects with a sleep restriction regimen (5 h) for two nights and then exposed them to 5 h of 1000 lx of light from noon till 17:00 hours. As in our study, they used the KSS to assess sleepiness and collected saliva to determine melatonin concentration. Furthermore, they assessed performance with the psychomotor vigilance test (PVT) and found an improvement of the PVT performance under bright light compared with the dim light condition (< 5 lx). Both, our results and those of Phipps-Nelson *et al*. (2003), show that other factors than melatonin suppression obviously influence the control of sleepiness.

Evidence for that comes from neuroanatomical animal studies and neuroimaging studies in humans. Aston-Jones *et al*. (2001) were able to show in rats a neural circuit between the suprachiasmatic nucleus (SCN) and the locus coeruleus (LC) with the dorsomedial nucleus of the hypothalamus (DMH) functioning as a relay in between. The LC is a brain area that is strongly associated with arousal and sleep–wake functions (Lu *et al*., 1999, 2000). Using anterograde and retrograde labelling techniques theses authors were able to show that the SCN send indirect projections to the LC via the DMH. Furthermore they showed circadian rhythmicity in LC impulse activity. They confirmed functionality of the SCN–DMH–LC circuit by lesions of the DMH. Their results tie in with the findings of Deurveilher and Semba (2005). These authors showed in the rat that the DMH, the medial preoptic area, and the subparaventricular zone (SPVZ) are possible relay nuclei for indirect projections from the SCN to brain regions involved in sleep–wake regulation, the ventrolateral and median preoptic nuclei. In humans, Perrin *et al*. (2004) measured regional cerebral blood flow (PET scans) to relate this to the alerting effects of bright light exposure during the night. They found suppression of melatonin and an attenuation of the decline of alertness over the night, accompanied by a significantly higher activation in brain regions that were part of an occipito-parietal attention network. The activation was proportional to the duration of light exposure before the scans, whereas activity in the hypothalamus decreased proportional to the bright light exposure, especially in the suprachiasmatic region. Because of the limited resolution of PET scans, the authors could not specify the nuclei in this deactivated area. Based on the literature, they surmise that possible candiate regions for the involved nuclei to project to are the SCN and structures like the SPVZ or the ventro-lateral preoptic area (VLPO). The SPVZ and the VLPO are also target regions for the projections from intrinsically photosensitive retinal ganglion cells, which contribute to circadian entrainment, pupillary light reflex and the regulation of sleep–wake states (Gooley *et al*., 2003).

Both our studies on light exposure at night have induced a wide range of changes in subjective sleepiness together with a wide range of suppressions of melatonin concentration. Yet, the induced changes in sleepiness were not related to the changes in melatonin concentration. We conclude therefore, that even at night, endogenous melatonin plays only a very minor role in the mechanism by which light reduces sleepiness and therefore the indirect projections from the SCN to brain areas strongly associated with the regulation of sleep-wake, like the VLPO, are more likely to be responsible.

ACKNOWLEDGEMENTS

We thank Marjan Alssema, Annegriet Diever, Els Møst, Marij Zuidersma, Elisabeth Pomp and Sander Berends for their help in collecting the data and the colleagues of the eye clinic of the Groningen Hospital for generously supervising and providing us with the cyclopentolate. This research was financially supported by the Dutch Technology Foundation (STW), the applied science division of NWO, and the Ministry of Economic Affairs, Philips Domestic Appliances and Personal Care and Philips Lighting.

REFERENCES

Åkerstedt, T. and Gillberg, M. Subjective and objective sleepiness in the active individual. *Int. J. Neurosci*., 1990, 52: 29–37.

Aston-Jones, G., Chen, S., Zhu, Y. and Oshinsky, M. L. A neural circuit for circadian regulation of arousal. *Nat. Neurosci*., 2001, 4: 732–738.

Badia, P., Culpepper, J., Myers, B., Boecker, M. and Harsh, J. Psychophysiological and behavioral effects of bright and dim light. *Sleep Res*., 1990, 19: 387.

Badia, P., Myers, B., Boecker, M., Culpepper, J. and Harsh, J. R. Bright light effects on body temperature, alertness, EEG and behavior. *Physiol. Behav*., 1991, 50: 583–588.

Badia, P., Myers, B. and Murphy, P. Melatonin and thermoregulation. In: R. Reiter and H.-S. Yu (Eds) *Melatonin: Biosynthesis, Physiological Effects, and Clinical Applications*. CRC Press, Boca Raton, FL, 1993.

Cajochen, C., Zeitzer, J. M., Czeisler, C. A. and Dijk, D. J. Dose–response relationship for light intensity and ocular and electroencephalographic correlates of human alertness. *Behav. Brain Res*., 2000, 115: 75–83.

Cajochen, C., Krauchi, K. and Wirz-Justice, A. Role of melatonin in the regulation of human circadian rhythms and sleep. *J. Neuroendocrinol*., 2003, 15: 432–437.

Campbell, S. S. and Dawson, D. Enhancement of nighttime alertness and performance with bright ambient light. *Physiol. Behav*., 1990, 48: 317–320.

Campbell, S. S., Dijk, D. J., Boulos, Z., Eastman, C. I., Lewy, A. J. and Terman, M. Light treatment for sleep disorders: consensus report. III. Alerting and activating effects. *J. Biol. Rhythms*, 1995, 10: 129–132.

Cavallo, A. and Ritschel, W. A. Pharmacokinetics of melatonin in human sexual maturation. *J. Clin. Endocrinol. Metab*., 1996, 81: 1882–1886.

Cohen, J. *Statistical Power Analysis for the Behavioral Sciences*, 2nd edn. Erlbaum, Hillsdale, NJ, 1988.

Daurat, A., Aguirre, A., Foret, J., Gonnet, P., Keromes, A. and Benoit, O. Bright light affects alertness and performance rhythms during a 24-h constant routine. *Physiol. Behav*., 1993, 53: 929–936.

Dawson, D. and Campbell, S. S. Timed exposure to bright light improves sleep and alertness during simulated night shifts. *Sleep*, 1991, 14: 511–516.

Dawson, D., Gibbon, S. and Singh, P. The hypothermic effect of melatonin on core body temperature: is more better? *J. Pineal Res.*, 1996, 20: 192–197.

Deacon, S. and Arendt, J. Posture influences melatonin concentrations in plasma and saliva in humans. *Neurosci. Lett.*, 1994, 167: 191–194.

Deurveilher, S. and Semba, K. Indirect projections from the suprachiasmatic nucleus to major arousal-promoting cell groups in rat: implications for the circadian control of behavioural state. *Neuroscience*, 2005, 130: 165–183.

Dijk, D. J., Duffy, J. F. and Czeisler, C. A. Circadian and sleep/wake dependent aspects of subjective alertness and cognitive performance. *J. Sleep Res.*, 1992, 1: 112–117.

Dollins, A. B., Zhdanova, I. V., Wurtman, R. J., Lynch, H. J. and Deng, M. H. Effect of inducing nocturnal serum melatonin concentrations in daytime on sleep, mood, body temperature, and performance. *Proc. Natl Acad. Sci. USA*, 1994, 91: 1824–1828.

Foret, J., Daurat, A. and Tirilly, G. Effect of bright light at night on core temperature, subjective alertness and performance as a function of exposure time. *Scand. J. Work Environ. Health*, 1998, 24 (Suppl. 3): 115–120.

Gilbert, S. S., Van Den Heuvel, C. J. and Dawson, D. Daytime melatonin and temazepam in young adult humans: equivalent effects on sleep latency and body temperatures. *J. Physiol.*, 1999, 514: 905–914.

Gooley, J. J., Lu, J., Fischer, D. and Saper, C. B. A broad role for melanopsin in nonvisual photoreception. *J. Neurosci.*, 2003, 23: 7093–7106.

Graw, P., Werth, E., Krauchi, K., Gutzwiller, F., Cajochen, C. and Wirz-Justice, A. Early morning melatonin administration impairs psychomotor vigilance. *Behav. Brain Res.*, 2001, 121: 167–172.

Horne, J. A. and Östberg, O. A self-assessment questionnaire to determine morningness- eveningness in human circadian rhythms. *Int. J. Chronobiol.*, 1976, 4: 97–110.

Lee, K. A., Hicks, G. and Nino-Murcia, G. Validity and reliability of a scale to assess fatigue. *Psychiatry Res.*, 1991, 36: 291–298.

Lewy, A. J., Wehr, T. A., Goodwin, F. K., Newsome, D. A. and Markey, S. P. Light suppresses melatonin secretion in humans. *Science*, 1980, 210: 1267–1269.

Lu, J., Shiromani, P. and Saper, C. B. Retinal input to the sleep-active ventrolateral preoptic nucleus in the rat. *Neuroscience*, 1999, 93: 209–214.

Lu, J., Greco, M. A., Shiromani, P. and Saper, C. B. Effect of lesions of the ventrolateral preoptic nucleus on NREM and REM sleep. *J. Neurosci.*, 2000, 20: 3830–3842.

Myers, B. L. and Badia, P. Immediate effects of different light intensities on body temperature and alertness. *Physiol. Behav.*, 1993, 54: 199–202.

Partonen, T. and Lonnqvist, J. Bright light improves vitality and alleviates distress in healthy people. *J. Affect. Disord.*, 2000, 57: 55–61.

Perrin, F., Peigneux, P., Fuchs, S., Verhaeghe, S., Laureys, S., Middleton, B., Degueldre, C., Del, F. G., Vandewalle, G., Balteau, E., Poirrier, R., Moreau, V., Luxen, A., Maquet, P. and Dijk, D. J. Nonvisual responses to light exposure in the human brain during the circadian night. *Curr. Biol.*, 2004, 14: 1842–1846.

Phipps-Nelson, J., Redman, J. R., Dijk, D. J. and Rajaratnam, S. M. Daytime exposure to bright light, as compared to dim light, decreases sleepiness and improves psychomotor vigilance performance. *Sleep*, 2003, 26: 695–700.

Rogers, N. L., Kennaway, D. J. and Dawson, D. Neurobehavioural performance effects of daytime melatonin and temazepam administration. *J. Sleep Res.*, 2003, 12: 207–212.

Rüger, M., Gordijn, M. C., Beersma, D. G., de Vries, B. and Daan, S. Bright light effects at night and day on various measures of sleepiness. In: A. L. Van Bemmel, D. G. Beersma, W. F. Hofman, G. S. F. Ruigt, P. J. E. Vos (Eds) *Sleep-Wake Research in the Netherlands*. 2002: 95–99.

Rüger, M., Gordijn, M. C., Beersma, D. G., de Vries, B. and Daan, S. Acute and phase-shifting effects of ocular and extraocular light in human circadian physiology. *J. Biol. Rhythms*, 2003, 18: 409–419.

Rüger, M., Gordijn, M. C., Beersma, D. G., de Vries, B. and Daan, S. Nasal versus temporal illumination of the human retina: effects on core body temperature, melatonin, and circadian phase. *J. Biol. Rhythms*, 2005, 20: 60–70.

Singer, C., Tractenberg, R. E., Kaye, J., Schafer, K., Gamst, A., Grundman, M., Thomas, R. and Thal, L. J. A multicenter, placebo-controlled trial of melatonin for sleep disturbance in Alzheimer's disease. *Sleep*, 2003, 26: 893–901.

Strassman, R. J., Qualls, C. R., Lisansky, E. J. and Peake, G. T. Elevated rectal temperature produced by all-night bright light is reversed by melatonin infusion in men. *J. Appl. Physiol.*, 1991, 71: 2178–2182.

Van Den Heuvel, C. J., Kennaway, D. J. and Dawson, D. Effects of daytime melatonin infusion in young adults. *Am. J. Physiol.*, 1998, 275: E19–E26.

Van Den Heuvel, C. J., Kennaway, D. J. and Dawson, D. Thermoregulatory and soporific effects of very low dose melatonin injection. *Am. J. Physiol.*, 1999, 276: E249–E254.

Visser, E. K., Beersma, D. G. and Daan, S. Melatonin suppression by light in humans is maximal when the nasal part of the retina is illuminated. *J. Biol. Rhythms*, 1999, 14: 116–121.