Lighting up the clock
Rüger, Melanie

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Chapter 3

Blue light suppresses human sleepiness

Marijke C.M. Gordijn, Domien G.M. Beersma, Melanie Rüger, & Serge Daan

Manuscript
Abstract

Non-image forming effects of retinal light exposure in humans range from pupillary reflexes, and phase shifts of the circadian pacemaker, to increased alertness. A recently discovered network of blue-light sensitive retinal ganglion cells (iRGCs) is likely part of the input system for the physiological effects. To test whether the anti-somnolence effects of light are attributable to the blue rather than red component, two groups of subjects (n = 2*40) were exposed to either blue light or red light of equal photopic intensities from 6 pm until 2 am. The increase in sleepiness from 8 pm to 2 am is 1.4-fold larger under red than under blue light (p<0.02). Since the photopic light intensities were similar, the visual photoreceptive system of rods and cones is probably not responsible for this difference, although involvement of the S-cone cannot be excluded. The results are consistent with the hypothesis that a short-wavelength photoreceptor, probably the iRGCs, play a role in mediating the anti-somnolent effects of light.
Introduction

Non-image forming effects of retinal light exposure range from effects on physiological measures, e.g. suppression of melatonin, increase of body temperature, shifts of the circadian rhythms of melatonin and body temperature, to effects on psychological measures: high environmental light intensity increases alertness (Cajochen et al., 2000; Rüger et al., 2003). The mechanism by which light exerts these alerting effects is unknown. A recently discovered network of blue-light sensitive retinal ganglion cells (iRGCs) (Berson et al., 2002; Hattar et al., 2002) is likely part of the input system for the physiological effects. Both in animals (Boulos, 1995; Hattar et al., 2003) and in humans (Wright and Lack, 2001; Thapan et al., 2001; Brainard et al., 2001; Warman et al., 2003) suppression of melatonin and shifts of circadian rhythms are particularly sensitive to a short wavelength component of light ($\lambda_{\text{max}}$ in humans between 446-477 nm).

The iRGCs are intrinsically light sensitive ($\lambda_{\text{max}} \approx 484$ nm) and express the photopigment melanopsin (Berson et al., 2002; Hattar et al., 2002; Melyan et al., 2005). They also project to brain regions (Hattar et al., 2002; Gooley et al., 2003) including the suprachiasmatic nucleus (SCN) containing the circadian pacemaker and the ventrolateral preoptic nucleus (VLPO) involved in sleep regulation (Lu et al., 1999), suggesting that they might mediate the effect of light on sleepiness.

To explore the connection between the non-image forming light input system and somnolence, we performed an experiment on 80 students, split into groups subjected to either blue or red light.

Methods

To test consistency, the experiment was performed twice in consecutive years. Each year, the groups (University students, first group n = 35, second group n = 45) were split into two rooms, one lit with blue light (TLD36W/18, Philips, Eindhoven, The Netherlands. Emission spectrum in inset of Fig. 1A), the other with red light (TLD36W/54, Philips, Eindhoven, The Netherlands. Emission spectrum in inset of Fig. 1A). To provide equal intensities to the photopic visual system, light intensity in lux was balanced between rooms: blue light 99.5 ± 16.5 lux, red light 124.8 ± 59.5 lux, measured at the subjects’ desk in the direction of the light source. The groups of subjects exposed to blue light (n= 40, 17 in the first and 23 in the second group) and red light (n=40, 18 in the first and 22 in the second group) were balanced for gender, number of smokers, and for morningness-eveningness tendency based upon the
Morningness-Eveningness questionnaire (Horne and Östberg, 1976). Once every hour, starting at 8 pm, subjects collected sleepiness data by completing the Karolinska Sleepiness Scale, KSS (Åkerstedt and Gillberg, 1990) and produced a saliva sample to measure melatonin concentration.

Saliva was collected using Sarstedt Salivettes® (Sarstedt BV, Etten-Leur, The Netherlands) with a polyester swab. Samples were stored at –20 °C. Melatonin concentration was determined by means of a RIA immunoassay (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 was 0.39 pg/ml with an intra-assay variation between 11 and 14.5 % at a low concentration (5 pg/ml) and varying between 9 and 13.7 % at a high concentration (92 pg/ml). Inter-assay covariance varied from 11.9 % to 17 % at a low melatonin concentration (4.7 pg/ml) and between 12.2 % and 16 % at a high melatonin concentration (63 pg/ml).

Statistics was performed with a t-test for independent samples.

**Results**

Figure 1A shows the courses of the average hourly melatonin concentrations for the groups under blue light and under red light. Melatonin increased over the night, especially in the groups under red light. The melatonin increase in the evening was significantly suppressed under blue light as compared to red light. At 2 pm melatonin concentration under red light is 3.8 times higher than under blue light (p<0.01). In the first experiment the melatonin concentrations of each individual were analyzed separately and averaged per hour. In the second experiment, for technical reasons, from 9 pm until 1 am an amount of 100µl of saliva of each individual per hour was pooled before the analysis, and the melatonin concentration of this pooled sample was analyzed in duplicate samples. As can be observed, the data of the two experiments are very similar.

Sleepiness, as measured by the Karolinska Sleepiness Scale, increased over the evening both under red light and under blue light. The increase under red light was more steeply than under blue light (Figure 1B), from 8 p.m. to 2 a.m. is the increase in sleepiness is 1.4-fold larger under red than under blue light (p<0.02). The two experiments yielded a virtually identical result, both for the suppression of melatonin, and for the suppression of sleepiness, underscoring its robustness.
Figure 1. A. Course of salivary melatonin concentration; B. Course of sleepiness, measured by the Karolinska Sleepiness Scale; Open dots refer to 18, open triangles to 22 subjects exposed to red light (TLD36W/54, emission spectrum in inset); filled dots to 17, filled triangles to 23 subjects exposed to blue light (TLD36W/18, emission spectrum in inset).
Discussion

The higher suppression of melatonin under blue light compared to under red light is consistent with earlier studies in humans (Brainard et al., 2001; Wright and Lack, 2001). The finding that also a psychological parameter, *i.e.* sleepiness, is more affected by blue light than by red light is new, and only recently also reported in one other study (Cajochen et al., 2005). The difference in sleepiness (30% reduction under blue light) is substantial and comparable to other studies presenting the alerting effects of light (Cajochen et al., 2000; Rüger et al., 2003). Since the photopic light intensities were similar, the visual photoreceptive system of rods and cones is probably not responsible for this difference. If anything, the slightly higher intensity in the red room should have led to opposite results. The results are consistent with the hypothesis that a short-wavelength photoreceptor, probably the iRGCs, play a role in mediating the anti-somnolent effects of light, although involvement of the S-cone can not be excluded.

Although the study demonstrates a substantial reduction of subjective sleepiness and a suppression of melatonin under blue versus red light, the changes in alertness need not be caused by melatonin suppression. The alerting effect of light occurs also around noon, when melatonin is absent (Gordijn et al., 2002; Phipps-Nelson et al., 2003). Only quantification of the entire action spectrum can firmly establish whether the iRGCs are solely responsible for the light effects on alertness. Recently it was reported that blocking short-wavelength light by goggles prevented the nocturnal melatonin suppression without any adverse effects on performance during the night (Kayumov et al., 2005). This seems in contrast with our finding that red light did not block the nocturnal increase in sleepiness.

From the present study we conclude that modification of the wavelength of light sources can have a major impact on human alertness. This result can be exploited to maintain alertness and allow proper vision in different shift work situations and on-call duties. For each situation however, the spectral composition of environmental light should be considered separately, since other effects of short wavelength light, *i.e.* the induction of phase shifts of circadian rhythms, may not always be desirable.
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References


