Chronobiology International, Early Online: 1–6, (2013)

ISSN: 0742-0528 print / 1525-6073 online
DOI: 10.3109/07420528.2013.854250

informa
healthcare

ORIGINAL ARTICLE

Extraocular light via the ear canal does not acutely affect human circadian physiology, alertness and psychomotor vigilance performance

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We aimed at testing potential effects of extraocular bright light via the ear canals on human evening melatonin levels, sleepiness and psychomotor vigilance performance. Twenty healthy young men and women (10/10) kept a regular sleep–wake cycle during the 2-week study. The volunteers reported to the laboratory on three evenings, 2 h 15 min before usual bedtime, on average at 21:45 h. They were exposed to three different light conditions, each lasting for 12 min: extraocular bright light via the ear canal, ocular bright light as an active control condition and a control condition (extraocular light therapy device with completely blacked out LEDs). The timing of exposure was on average from 22:48 to 23:00 h. During the 2-h protocol, saliva samples were collected in 15-min intervals for melatonin assays along with subjective sleepiness ratings, and the volunteers performed a 10-min visual psychomotor vigilance task (PVT) prior to and after each light condition. The evening melatonin rise was significantly attenuated after the 12-min ocular bright light exposure while no significant changes were observed after the extraocular bright light and sham light condition. Subjective sleepiness decreased immediately over a short period only after ocular light exposure. No significant differences were observed for mean reaction times and the number of lapses for the PVT between the three light conditions. We conclude that extraocular transcranial light exposure in the late evening does not suppress melatonin, reduce subjective sleepiness or improve performance, and therefore, does not acutely influence the human circadian timing system.

Keywords: Bright light therapy, extraocular transcranial light therapy, melatonin, psychomotor vigilance performance, sleepiness

INTRODUCTION

Specially conceived light therapy devices with daylight-like properties are used for the treatment of seasonal affective disorder, other affective disorders as well as circadian rhythm sleep disorders (Sack et al., 2007a,b; Terman & Terman, 2005). The beneficial effect of light comes about due to its synchronizing properties (i.e. Zeitgeber effect; Czeisler et al., 1980), but also by light's alerting (Cajochen, 2007) and antidepressant effects (Lewy et al., 1987). These non-visual light effects are all mediated via classical and non-classical photoreceptors in the retina through the retinohypothalamic tract to the suprachiasmatic nuclei, the central circadian clock, and from there to different efferent output systems (Hughes et al., 2012). Although, Campbell & Murphy (1998) have challenged the ''ocular view'' of non-visual light responses and reported evidence for extraocular circadian phototransduction in humans, none of the follow-up studies could replicate and confirm the results by Campbell and Murphy (Eastman et al., 2000; Hébert et al., 1999; Jean-Louis et al., 2000; Lushington et al., 2002; Lockley et al., 1998; Rogers et al., 1999; Rüger et al., 2003; Wright & Czeisler, 2002). Furthermore, extraocular light via the popliteal skin regions (i.e. behind the knees) has no antidepressant effects and did not exceed its placebo effect in patients suffering from seasonal affective disorders nor did it induce a phase shift of the circadian pacemaker (Koorengevel et al., 2001). In all of the above-mentioned studies, extraocular light was applied via the skin in the popliteal regions. Recently, a new device has appeared on the market, a LED (light emitting diodes) equipped headset that administers light via the ear canal. This so-called ''extraocular transcranial light therapy'' has been shown to be effective in the treatment of SAD. Ear light administered 8–12 min for 4–5 days per week during 4 weeks led to a significant improvement of depressive symptoms and even

Submitted August 22, 2013, Returned for revision September 24, 2013, Accepted October 8, 2013

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remission in 10 out of 13 patients (Timonen et al., 2012). However, the data were collected and published as uncontrolled preliminary results of a pilot study with no appropriate control groups as tested for extraocular light in the popliteal skin region (Koorengevel et al., 2001). A functional magnetic resonance imaging (fMRI) study pointed to an increased functional connectivity of the lateral visual cortex when 24 subjects were exposed to extraocular light compared to 26 subjects of the sham light control group (Starck et al., 2012). However, a comparison with ocular light exposure as an active control was not included in the study design. Whether extraocular transcranial light via the ear canal affects human circadian physiology has not been investigated so far. This is important, since the device supposedly projects directly to photosensitive regions of the brain through the ear canal (www.valkee.com).

Thus, we investigated whether extraocular transcranial administered light impacts acutely on human circadian physiology, alertness and cognitive performance. According to our knowledge about acute effects of ocular light, we hypothesized first, that 12-min extraocular light exposure 75 min before individual bed time suppresses melatonin secretion, second, that a 12-min extraocular light exposure 75 min before individual habitual bed time attenuates the evening increase in sleepiness (i.e. alerting response) and third, that 12-min extraocular light exposure 75 min before individual habitual bed time attenuates the evening decrease in psychomotor vigilance performance.

MATERIAL AND METHODS

Subjects

Twenty young men and women [10/10, 24.2 ± 3.4 years (mean ± SD), matched for age] were recruited in the area of Basel/Switzerland for participation in the study, which was carried out between October 2012 and April 2013. The volunteers were physically and mentally healthy and had no medication use and no drug or alcohol abuse as assessed by questionnaires and interviews by the co-author J.O. (cand. MD). All were good sleepers [Pittsburgh sleep quality index PSQI = 3.4 ± 1.5 (mean ± SD), range 0–5; Buysse et al., 1989] with a body mass index in the normal range [men: 23.4 ± 2.4, women: 21.2 ± 2.1 (mean ± SD)]. We excluded potential study volunteers who had done shift or night work within 2 month prior to the study and/or time zone travelling (>2 time zones) within 4 weeks prior to the study.

Study volunteers signed a consent form and were reimbursed for their participation. The study procedure was approved by the local Ethics Committee of Basel (EKBB), Switzerland, and all procedures conformed to the Declaration of Helsinki.

Ambulatory part – actimetry

Participants were requested to keep a regular sleep–wake cycle (bed- and rise-times within ±1 h) during the 2-week study protocol. They wore an Actiwatch (Cambridge Neurotechnology Ltd., UK) for rest-activity monitoring and kept a sleep diary in order to check compliance and to calculate individual bedtimes for the protocol of the in-lab part during study week 2.

Laboratory part

The volunteers reported to the laboratory on three evenings, 2 h 15 min before their usual bedtime. In the laboratory, the participants were sitting on a chair under controlled dim light (<8 lux) and temperature conditions (21°C) for 2 h. After sitting in dim light for 63 min, they were exposed to three different light conditions in a counterbalanced order, each lasting for 12 min (the maximally allowed exposure time for light via the ear canal per day according to the product information of Valkee Ltd.): (i) extraocular light exposure via the ear canal using a Valkee light therapy device NPT®1100, Valkee Ltd., Oulunsalo/Finland, with a light intensity of 3.5 lumen (i.e. =11 140 lux in an angle of radiation = 120° and at a distance of 1 cm as considered as the distance from the light source to possible receptors in the brain; according to *http://www.info-led.de/info/Visueller-Umrechner-fuer-Candela–Lumen–Lux–Abstrahlwinkel–Entfernung.html*); (ii) ocular light as an active control condition using a light therapy device (Daylight® therapy device, Uplift Technologies Inc., Canada; light intensity = ~10 000 lux in a distance of 20 cm from the eyes as applied in the experimental set-up and (iii) control condition using a Valkee light therapy device NPT®1100, Valkee Ltd., Oulunsalo/Finland, in which the light ray was completely blacked out by a black coat of lacquer.

Melatonin measures

During the entire protocol, nine saliva samples were collected in 15-min intervals using salivettes (Sarstedt AG, Switzerland) to determine evening melatonin levels. Melatonin was determined by a direct double-antibody radioimmunoassay (RIA) with an analytical sensitivity of 0.2 pg/ml and a functional least detectable dose of 0.65 pg/ml, an intra-assay coefficient of variation of 4.1% and an inter-assay coefficient of variation of 6.6% (Bühlmann Laboratories, Allschwil/Switzerland) (Weber et al., 1997).

Assessment of sleepiness and sustained attention

Concomitant to the saliva samples, subjective sleepiness was rated by the volunteers on the Karolinska sleepiness scale (KSS) (Akerstedt & Gillberg, 1990), the sleepiness symptoms check list (KSScl) and a visual analog scale (VAS) for sleepiness. A composite score of KSS, KSScl and VAS indicated in percentage of the highest possible

score of each questionnaire was used for analysis, thus each scale is equally weighted.

In addition, the participants performed a 10-min visual (PVT) to assess sustained attention 28 min prior to and 5 and 35 min after each of the three light conditions. The PVT is highly sensitive in measuring effects of sleepiness (Dinges et al., 1997). We considered the following variables on attentional failures in the analysis: mean reaction time (RT) in ms, 10% fastest RT (ms) and number of lapses. A response was considered valid if the RT was $\geq$100 ms. RTs shorter than 100 ms were counted as errors of commission and were excluded from the analysis. RTs $\geq$500 ms were classified as lapses and the statistical analysis was based on the median value of reaction time per subject and test session.

Statistical analysis

The statistical packages SAS (Version 9.1.3; SAS Institute, Inc.; Cary, NC) and Statistica (STATISTICA for windows, Version 8.0; StatSoft Inc., Tulsa, OK) were used. Three factors entered the analysis: ''light condition'', i.e. extraocular bright light, ocular bright light and extraocular light with completely blacked out LEDs as control condition, ''time of day'', i.e. melatonin values and subjective sleepiness scores in 15-min intervals, and outcome of the PVT performance of three trials per condition, and ''gender'' as a covariate. Melatonin profiles and subjective sleepiness were analyzed by general linear models (i.e. repeated-measures rANOVA) and p values were based on Huynh-Feldt corrected degrees of freedom. The Duncan's multiple range test was used for *post hoc* comparisons. Mixed model analyses of variance for repeated measures were used for mean reaction time and lapses of the PVT (PROC MIXED; SAS and p values were based on Kenward–Roger's corrected degrees of freedom). Contrasts were assessed with the LSMEANS statement and the respective level of significance was adjusted according to Tukey–Kramer. The alpha-criterion was set at a significance level of $p = 0.05$.

RESULTS

Salivary melatonin

In 4 out of 20 study volunteers, endogenous melatonin levels did not increase in the evening prior light exposure during all three evenings. Thus, data of these four volunteers were excluded from statistical analysis. In the remaining 16 participants (8 men, 8 women) no significant gender difference was found in the evening melatonin profiles (Table 1).

The factor time of day yielded significance [$F_{(8,112)} = 66.1$, $p < 0.001$], most likely due the increase of evening melatonin in all three conditions. Furthermore, a significant interaction light condition $\times$ time of day [$F_{(16,224)} = 3.5$, $p = 0.003$, Figure 1] indicated that this increase was significantly modulated by the light condition such that the 12-min ocular bright light exposure significantly attenuated the melatonin rise while no significant changes in melatonin levels were observed after the 12 min of extraocular bright light via the ear canals or after the control ear light condition. *Post hoc* comparisons yielded a significant difference between the control light condition (i.e. sham light) and ocular light condition for the time interval from 23:15 to 23:45 h (p at least 0.014) after light exposure as well as between extraocular and ocular light intervention for the time interval from 23:00 to 23:30 h (p at least 0.002) after light exposure. Melatonin levels did not significantly differ before light exposure between the three conditions, as well as between the control and extraocular light condition at all sampling times.

Subjective sleepiness

Subjective sleepiness levels increased significantly during all three evenings [effect of time of day: $F_{(88,144)} = 44.5$, $p < 0.001$]. This increase did not significantly differ between gender (time of day $\times$ gender: $p = 0.833$) and between the three light conditions (light condition: $p = 0.287$) (Table 1), when all nine sampling times were included in the statistical analysis. However, a short-time decrease in sleepiness immediately after ocular light exposure can be seen in Figure 2, but not after extraocular light via the ear canal or after the

TABLE 1. Main and interaction effects of gender, time of day and light condition on melatonin secretion, subjective sleepiness, subjective sleepiness with three points of time included in analysis (22:45–23:15) and mean reaction time as well as number of lapses of the psychomotor vigilance task.

Factor	Melatonin ($n = 16$)	Subjective sleepiness ($n = 20$)	Subjective sleepiness ($n = 20$; 3 points in time: 22:45–23:15)	Mean reaction time (PVT) ($n = 20$)	Mean number of lapses (PVT) ($n = 20$)
Gender	n.s.	n.s.	n.s.	n.s.	n.s.
Time of day	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$	$p < 0.001$
Light condition	n.s.	n.s.	n.s.	n.s.	n.s.
Time of day $\times$ gender	n.s.	n.s.	n.s.	n.s.	n.s.
Light condition $\times$ gender	n.s.	n.s.	n.s.	n.s.	n.s.
Time of day $\times$ light condition	$p = 0.003$	n.s.	$p = 0.007$	n.s.	n.s.
Time of day $\times$ light condition $\times$ gender	n.s.	n.s.	n.s.	n.s.	n.s.

n.s., nonsignificant, $p > 0.05$.

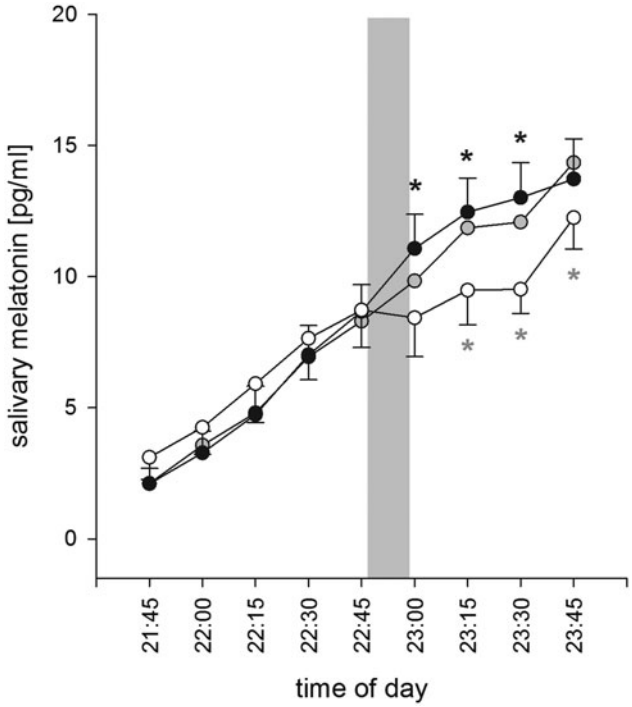

FIGURE 1. Salivary melatonin rise of 16 subjects (8 men, 8 women) in the laboratory on three evenings. 12 min of light exposure (grey bar) was applied either with sham light (control condition) (—◍—), with bright light via the ear canal (—●—) and ocular bright light (—○—). ✱ = significant difference between control condition and ocular light condition ($p < 0.015$), ★ = significant difference between extraocular light and ocular light condition ($p < 0.003$). The *x*-axis indicates mean sampling time of day.

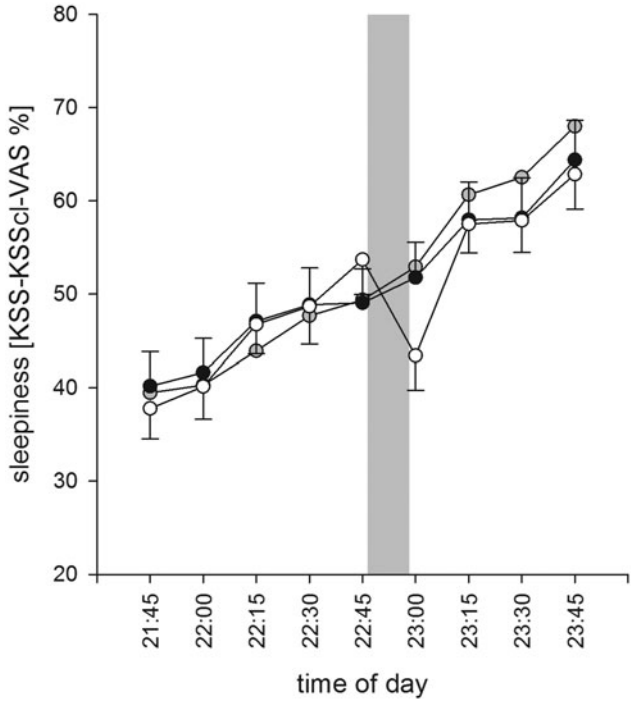

FIGURE 2. Evening increase in subjective sleepiness in 20 subjects (10 men, 10 women). 12 min of light exposure (grey bar) was applied either with sham light (control condition) (—◍—), with bright light via the ear canal (—●—) or ocular bright light (—○—). The *x*-axis indicates mean sampling time of day.

control condition. This decline in sleepiness reached significance when only three data points were included in the analysis (baseline/one sample immediately prior to light exposure and two samples after light exposure) [light condition × time of day: $F_{(4,72)} = 3.8$, $p = 0.008$]. Post hoc analysis yielded significant differences between the control and ocular light condition ($p = 0.003$) as well as between the extraocular and ocular light condition ($p = 0.007$).

PVT performance (sustained attention)

Mixed-model 3-way rANOVA for the PVT with the factors gender, light condition and time did not yield significant differences between gender ($p > 0.5$) for the mean reaction times (Table 1) and number of lapses between the three light conditions ($p > 0.6$ and $p > 0.4$, respectively). However, there was a significant effect of time of day ($p < 0.001$) with longer reaction times as time progressed in the evening (time 1 = 311.0 ms, time 2 = 319.5 ms, time 3 = 331.3 ms; time 1 < time 2 $p = 0.004$, time 2 < time 3 $p < 0.001$ and time 1 < time 3 $p < 0.001$) (Figure 3). Accordingly, the fastest 10% reaction times varied significantly over time as well ($p < 0.001$; time 1 = 271.5 ms, time 2 = 277.7 ms and time 3 = 285.6 ms) with significantly higher values in the third test session as compared with the previous test

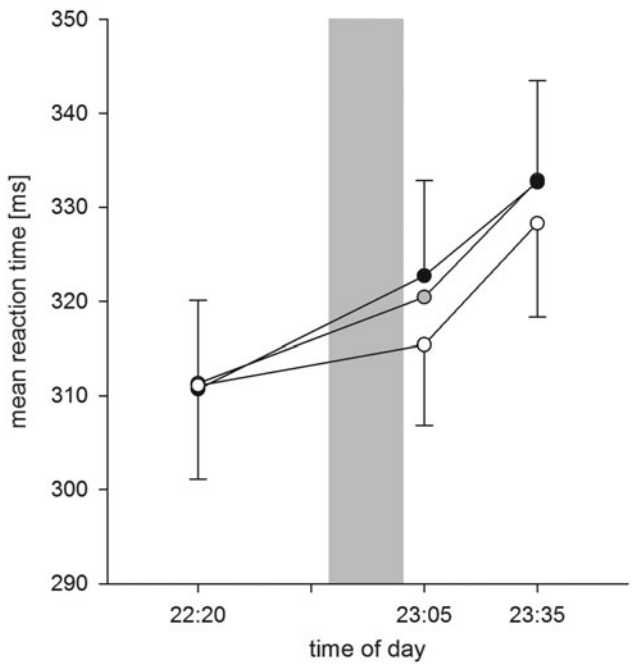

FIGURE 3. Reaction time (mean ± SE) as measured by the PVT of 20 subjects (10 men, 10 women). 12 min of light exposure (grey bar) was applied either with sham light (control condition) (—◍—), bright light with light via the ear canal (—●—) or ocular bright light (—○—). The *x*-axis indicates mean time of day of testing.

sessions 1 and 2 ($p<0.001$ and $p<0.001$, respectively). Additionally, number of lapses at the end of the evening (=4.9 lapses) were significantly higher than in the first two test sessions (time 1 = 2.5 and time 2 = 2.8 lapses; $p<0.001$; time 1 < time 3 $p=0.002$ and time 2 < time 3 $p=0.009$).

DISCUSSION

Our results do not provide evidence that a 12-min exposure of extraocular bright light via the ear canal in the evening acutely affects melatonin secretion, subjective sleepiness and sustained attention when compared to a sham light (no light) condition. On the other hand, a 12-min exposure of ocular bright light (i.e. active control condition) significantly attenuated the evening melatonin rise along with a short-term alerting effect when compared to the extraocular light and sham light condition. The latter is not surprising, since it is well known that light perceived by melanopsin-containing ganglion cells in the retina projects via the retinohypothalamic tract to the SCN (Berson et al., 2002; Hattar et al., 2002) and acutely suppresses melatonin secretion in the evening and during the night (Lewy et al., 1980). Moreover, ocular light has alerting properties and improves cognitive functioning (Cajochen, 2007; Chellappa et al., 2011; Lockley et al., 2006; Vandewalle et al., 2013). In the present study, the rather short-lasting (i.e. 12 min) exposure of ocular bright light of 10 000 lux led to an immediate reduction of subjective sleepiness of short duration. However, the 12 min of ocular light was not long enough to significantly improve sustained attention, as indexed by PVT mean reaction and PVT lapses. Results from functional magnetic resonance imaging (fMRI) studies indicate that alertness-related subcortical structures such as the brainstem, the hypothalamus and the dorsal and posterior parts of thalamus modulate light's impact on brain function (Vandewalle et al., 2009). Indirect projection from the SCN and the dorsal medial hypothalamus can elevate activity in the locus coeruleus in the brainstem and promote waking and alertness (Aston-Jones et al., 2001). It is not yet known whether these brain areas are photosensitive. If they were, a 12-min exposure to extraocular light via the ear canal may not have activated them, since we could not observe any alerting effect.

The idea of extraocular light perception in humans and its potential effect on the human circadian timing system has been around for >10 years but has been disproved in humans so far (Eastman et al., 2000; Hébert et al., 1999; Lockley et al., 1998; Rüger et al., 2003; Wright & Czeisler, 2002). However, there are findings showing extraocular phototransduction with effects on the circadian system in some vertebrates (Campbell et al., 2001), such as sparrows (Menaker et al., 1970). Studies of the effect of light via the ear canal in humans are based on the assumption that extraocular light is received by opsin proteins in the brain that convert light into neuronal reactions (cf. melanopsin in retinal ganglion cells). Particularly opsin 3 (Opn3, also known as encephalopsin or panopsin) shows high homology to vertebrate retinal and pineal opsins and has been found in different mammalian brain regions (Blackshaw & Snyder, 1999). Recent findings suggest, that homologs of vertebrate Opn3 might function as photoreceptors in various tissues (Koyanagi et al., 2013). However, the function of Opn3 and other opsins in the human brain are largely unexplored. According to the present knowledge, entrainment and phase shifts of the circadian rhythm by light in humans requires intact eyes or intact melanopsin-containing retinal ganglion cells, respectively, as shown in a few totally blind people (Czeisler et al., 1995), a patient group that shows a high incidence of desynchronized circadian rhythms (Sack et al., 1992). Extraocular light from the environment seems not to work as synchronizing agent in blind people.

In sum, here we report absence of melatonin suppression and alerting response to extraocular bright light via the ear canal. Although we only tested acute and short-term effects, we assume that extraocular bright light via the ear canals may also not elicit circadian phase shifts. Thus, based on our results we are skeptical whether extraocular transcranial light therapy has beneficial effects for the treatment of circadian rhythm sleep disorders. More research is needed to investigate the long-term effects of extraocular transcranial light therapy on the circadian system.

ACKNOWLEDGEMENTS

The authors thank Claudia Renz and Bühlmann Laboratories, Allschwil, Switzerland, for the melatonin assays, and the study volunteers for their participation.

DECLARATION OF INTEREST

The study was financially supported by the Centre for Chronobiology, Psychiatric Hospital of the University of Basel, Switzerland. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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