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Effects of a chronic reduction of short-wavelength light input on melatonin and sleep patterns in humans: Evidence for adaptation

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Light is an important environmental stimulus for the entrainment of the circadian clock and for increasing alertness. The intrinsically photosensitive ganglion cells in the retina play an important role in transferring this light information to the circadian system and they are elicited in particular by short-wavelength light. Exposure to short wavelengths is reduced, for instance, in elderly people due to yellowing of the ocular lenses. This reduction may be involved in the disrupted circadian rhythms observed in aged subjects. Here, we tested the effects of reduced blue light exposure in young healthy subjects (n = 15) by using soft orange contact lenses (SOCL). We showed (as expected) that a reduction in the melatonin suppressing effect of light is observed when subjects wear the SOCL. However, after chronic exposure to reduced (short wavelength) light for two consecutive weeks we observed an increase in sensitivity of the melatonin suppression response. The response normalized as if it took place under a polychromatic light pulse. No differences were found in the dim light melatonin onset or in the amplitude of the melatonin rhythms after chronic reduced blue light exposure. The effects on sleep parameters were limited. Our results demonstrate that the non-visual light system of healthy young subjects is capable of adapting to changes in the spectral composition of environmental light exposure. The present results emphasize the importance of considering not only the short-term effects of changes in environmental light characteristics.

Keywords: Adaptation, human, melatonin rhythms, short-wavelength light, sleep rhythms

INTRODUCTION

Light has a large impact on our everyday life. It does not only allow for vision but also for non-image-forming responses. Light is the environmental cue primarily responsible for the entrainment of the biological clock, i.e. the synchronization of our physiological and psychological rhythms to the 24-h rhythm of the environment. Impaired entrainment can lead to discomfort and higher risks for diseases (Pritchett et al., 2012; Rajaratnam & Arendt, 2001; Rüger & Scheer, 2009). Light also has activating effects (Cajochen, 2007; Rüger et al., 2006) and can acutely suppress the production of melatonin (Levy et al., 1980).

In the late 1990s, a new photoreceptor with a key role in transferring light information for non-image-forming responses was discovered (Freedman et al., 1999; Lucas et al., 1999). This is the intrinsically photosensitive retinal ganglion cell (ipRGC) containing the photopigment melanopsin with a sensitivity peak at around 480 nm (Berson et al., 2002; Hattar et al., 2002; Provencio et al., 2000, 1998). A similar sensitivity peak for non-visual responses was also observed in many human studies (Brainard et al., 2001; Cajochen et al., 2005; Lockley et al., 2003, 2006; Revell et al., 2005; Thapan et al., 2001; Warman et al., 2003).

Aging is a natural process by which input of especially short wavelengths is reduced as a consequence of a denser ocular lens (Giménez et al., 2010; Van Norren & Vos, 1974; Weale, 1988). Whether the weak and/or disturbed circadian rhythms observed in the elderly (e.g. fragmented sleep, early awakening and lower melatonin levels) (Van Someren, 2000) can be explained by this reduction in (short wavelength) light input needs further research.

The present study investigates the effects of a reduction in short wavelengths light input at the level of the ocular lens on melatonin and sleep rhythms and on suppression of nocturnal melatonin in healthy human subjects.
subjects. By means of soft orange contact lenses (SOCL) we mimicked, to a certain extent, the aging effects of the lens in healthy young subjects. This allowed us to assess the effects of exposure to short wavelengths in a realistic natural scenario as well as to separate the effects of altered lens transmittance from other aging effects. We hypothesized that reduced (short wavelength) light input would result in a less stable activity–rest cycle (see review Dijk et al., 2000), in a reduction in the nocturnal melatonin secretion (see review Skene & Swaab, 2003) as well as in a reduction in the suppression of nocturnal melatonin by light (Brainard et al., 1997; Duffy et al., 2007; Herljevic et al., 2005). Knowledge about the response to changes in environmental light exposure will be relevant for understanding rhythm disturbances in the elderly. It will also increase our understanding of the impact of changing the light environment in everyday life, a topic that is of interest to an interdisciplinary audience of health specialists, light industry and architects (Fournier & Wirz-Justice, 2010).

MATERIALS AND METHODS

Subjects
Fifty subjects started the selection procedure for the study. Only those between 18 and 30 years who were healthy, non-smoker, non-color blind (Ishihara test) and of an intermediate chronotype (midsleep on free days between 3.7 and 6.3 a.m. according to the Munich Chronotype Questionnaire, Roenneberg et al., 2003) were selected to participate. Subjects who had worked on night shifts or traveled across more than two time zones during the two weeks prior to the study were excluded.

The study required participants to wear in the experimental condition the SOCL during 2 consecutive weeks 24 h per day. To assess participants’ eyes health condition a check-up by a contact lens specialist (coauthor M.L. vd L.) was conducted at the University Medical Center of Groningen (UMCG), the Netherlands. After screening, 22 subjects were selected of whom 15 completed the study (7m: 8f, mean age ± sd: 23.5 ± 4.6 years). Most dropouts were due to irritations in one or both eyes and some due to discomfort. Special care was taken in order to exclude subjects who did not feel comfortable after wearing the SOCL for 24–48 h.

The experimental protocol conformed to international ethical standards (Portaluppi et al., 2008) and was approved by the Medical Ethics Committee of the UMCG, the Netherlands, all subjects signed a written informed consent form prior to their participation. All subjects were financially compensated for their participation.

Soft orange contact lenses
The SOCL (CE: 0120, with UV protection) were supplied by Ultravision International Ltd., UK. These lenses are normally used for medical purposes and are designed so that they can be continuously worn (24 h/day) for up to three consecutive months. The lenses reduce the overall light intensity in particular of short wavelengths. Light transmittance in the visible range of the spectrum (from 420 to 700 nm) was reduced by 37%. In the short wavelengths range (420–500 nm), the reduction in transmittance was 53% and 57% when considering the melanopsin sensitivity peak (480 nm). Figure 1 compares the relative light transmittance per wavelength (400–700 nm) of an average 25-year-old healthy subject without (Van de Kraats & Van Norren, 2007) and with the SOCL (dashed black line), in comparison with an average cataractous eye (n = 14 patients) (gray line from Giménez et al., 2010).

Experimental design
In randomized sequence, a control condition (13 subjects wore their own contact lenses and 2 subjects no lenses) and an experimental condition (all subjects wore the SOCL) were assigned to each of 15 subjects (8 subjects started with the control and 7 subjects started with the SOCL condition). The SOCL were adjusted according to the subjects’ needs for visual corrections. Each condition lasted 16 days. They were timed at least two weeks apart to avoid potential carry-over effects. For each subject both conditions started on the same day of the week (this differed between subjects) in order to control for the possible pattern of behavior throughout the week within each subject.

Subjects came to the lab for two consecutive nights on days 15 and 16. Melatonin profiles were assessed on night 15. Subjects arrived at the lab at 18:00 h. Light levels were dimmed (<5 lux). Saliva samples were taken using cotton swabs (Sarstedt BV, Etten-Leur, the Netherlands) every hour from 19:00 to 00:00 h, then every half hour until 2:00 h and every 2 h from 2:00 to 5:00 h. Subjects were financially compensated for their participation.
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classifies that as sleep end. Sleep onset, midsleep and sleep offset were used to describe sleep timing. All timing variables are shown for work and days off. We further investigated sleep efficiency (percentage of time spent asleep while in bed), the average activity of the least active 5 h, and the average activity of the 10 most active hours (Van Someren et al., 1999; Witting et al., 1990). The analysis of the sleep parameters is based on the first 14 days of each condition. The last two nights spent in the lab were excluded since sleep disturbances were introduced during the sampling of melatonin.

Light analysis 5 software (Cambridge Neurotech Ltd, Cambridge, UK) was used to calculate the average light intensity (lux), the maximum intensity (lux) and the time spent above 1000 lux.

The effects of the SOCL on the melatonin suppression response, on DLMO and on the amplitude of the melatonin profile were tested by means of paired t-test. A two-way analysis of variance (ANOVA) was used to test the effects of the SOCL on sleep for the factors: condition (control vs. SOCL), day of the week (work days vs. days off), and the interaction effect. For the analysis on the effects of the SOCL on KSS a repeated measures ANOVA was conducted for the factors: condition (control vs. SOCL), time (waking up 12, 16, 20 h and bed time), and for the interaction effects. A paired t-test was used to evaluate the differences in light exposure during the two weeks control and the SOCL condition.

RESULTS

Melatonin suppression by light

The course of melatonin in the evening and the percentage of melatonin suppression during the light pulse relative to control melatonin profile can be seen from Figure 3(A) and (B). The melatonin suppression 30 min after placing the SOCL (300-SOCL) was significantly less (average ± SEM: 17% ± 9%) than the suppression in the control (SC) condition (average ± SEM: 30% ± 9%) (t = −2.65, p < 0.05). This result shows that the SOCL indeed filtered the light reaching the retina enough to reduce the suppression of melatonin. After wearing the SOCL for 16 days (16 d-SOCL) no differences were found in the suppression of melatonin when compared with the SC condition (average ± SEM: 33% ± 6%, t = 0.15, p = 0.88). The suppression of melatonin in the 300-SOCL condition was significantly less than in the 16 d-SOCL condition (t = −2.37, p < 0.05). Two out of the 15 subjects showed no suppression of the nocturnal melatonin level to light at all in the control condition.

Melatonin profile

No significant differences were found in the timing of the DLMO between the control and the SOCL condition after 16 days (average ± SD: control: 21:50 ± 1:03 h; SOCL: 21:37 ± 1:35 h, t = 0.831, p = 0.42).

No significant differences were observed in the amplitude of the melatonin rhythm (average ± SD: control: 95.4% ± 3.7%; SOCL: 100.7% ± 23%, t = 0.852, p = 0.41).

Sleep characteristics

Sleep timing and sleep characteristics for work and days off are summarized in Table 1. Wearing the SOCL for 14 days had no significant effect neither in the timing of sleep nor on its efficiency or subjective quality. A main effect of day of the week was observed for all timing variables (all p < 0.01) except for sleep onset latency and for subjective sleep quality. No interaction effect between condition and type of day of the week was observed. A tendency of sleep onset latency being slightly shortened in the SOCL as compared with the control condition was observed. While no differences were observed in the average activity during the least 5 active hours (L5) (average ± SD: control: 11.1 ± 3.2, SOCL: 11.8 ± 3.9, t = −0.84, p = 0.41) a small but significant (t = 2.3, p < 0.05) reduction in the average activity of the
10 most active hours (M10) was shown in subjects wearing the SOCL (average ± SD: 54.9 ± 3.2) in comparison to the control condition (average ± SD: 55.9 ± 2).

KSS scores were analyzed to test whether condition had an effect in addition to the well-known effect of the time of day (a U-shaped curve with higher, more sleepy, values at waking up and before bedtime). No effect of the SOCL was found on the KSS scores (average ± SD: control: 4.7 ± 1.2; SOCL: 4.8 ± 1.1, \( F(1, 14) = 0.01, p = 0.94 \)). Only time-of-day contributed significantly to the explained variance (pattern over time: \( F = 21.138 \) (4, 11), \( p < 0.001 \), data not shown).

### Light exposure

No differences in the average light exposure, neither in the maximum nor on the average light exposure duration above 1000 lux were observed between conditions (Table 2).

#### DISCUSSION

The aim of the present study was to investigate the acute but also the chronic effects of exposure to diminished short-wavelength light throughout the day as it occurs, for instance, in the elderly population, on the suppression of the nocturnal melatonin by light and on melatonin and sleep–wake rhythms. The study yields three primary conclusions. (1) We found that melatonin suppression by light is sharply reduced when subjects wear the SOCL during the test (+30 min before). (2) This reduction disappears when subjects have worn the SOCL continuously for 16 days. (3) After two weeks, the use of the SOCL had no effect on circadian rhythms of sleep and melatonin. In view of these conclusions, the implications of reduced exposure to blue light in the elderly population and in society in general are discussed.

### Melatonin suppression by light

Light of short wavelength has been shown to have a larger suppressing effect on melatonin concentrations when compared with longer wavelengths (Brainard et al., 2001; Cajochen et al., 2005; Thapan et al., 2001). Studies where short wavelengths were blocked by means of goggles during a simulated night shift in bright light conditions found nocturnal melatonin levels similar to those observed under dim light conditions (i.e. no significant suppression of the nocturnal melatonin) (Kayumov, 2005; Sasseville et al., 2006). Our results are consistent with these studies in showing that melatonin concentrations in subjects wearing the SOCL during the 600-lux light pulse from midnight until 2 a.m. are not significantly different from the dim light melatonin values. A complete blockage of short wavelengths is most likely not needed to achieve this result since our lenses cut down the irradiance in the short wavelengths range by about 50%.

In order to understand the effect of exposure to a reduction in short wavelength light in a situation such as in the elderly another approach is needed. Here, this reduction due to yellowing of their lenses is continuously present, 24 h a day, and the long-term effects of this reduction need to be assessed. The results of this manipulation are discussed in the following sections.

#### TABLE 1. Sleep characteristics. Sleep timing, efficiency and subjective quality obtained by a combination of sleep diaries and actiwatch data.

<table>
<thead>
<tr>
<th></th>
<th>Work days</th>
<th>Days off</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
<td>16-day OL</td>
</tr>
<tr>
<td></td>
<td>Bed time(^a)</td>
<td>00:25 ± 40 min</td>
</tr>
<tr>
<td></td>
<td>Sleep onset(^a)</td>
<td>00:39 ± 40 min</td>
</tr>
<tr>
<td></td>
<td>Sleep offset(^a)</td>
<td>7:46 ± 54 min</td>
</tr>
<tr>
<td></td>
<td>Sleep onset latency (min)(^b)</td>
<td>14.4 ± 9</td>
</tr>
<tr>
<td></td>
<td>Midsleep(^a)</td>
<td>4:13 ± 39 min</td>
</tr>
<tr>
<td></td>
<td>Sleep efficiency (%):(^a)</td>
<td>81.1 ± 4.4</td>
</tr>
<tr>
<td></td>
<td>Subjective sleep quality(^a)</td>
<td>6.4 ± 0.8</td>
</tr>
</tbody>
</table>

Data are shown as average ± SD.

\(^a\)Significant main effect of day of the week (\( p < 0.01 \)).

\(^b\)Main effect of condition \( p = 0.06 \).

No significant effect of interaction between condition and day of the week was observed (0.7 < \( p > 0.1 \)).

#### TABLE 2. Light exposure characteristics. Average light intensity, average maximum intensity and average time spent above 1000 lux as obtained from actiwatch data.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>16-day OL</th>
<th>( T )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average light intensity (lux)</td>
<td>552 ± 335</td>
<td>515 ± 340</td>
<td>0.41</td>
<td>0.69</td>
</tr>
<tr>
<td>Average max. light intensity (lux)</td>
<td>16945 ± 7860</td>
<td>15687 ± 7848</td>
<td>0.82</td>
<td>0.42</td>
</tr>
<tr>
<td>Average time spent above 1000 lux</td>
<td>2 h 19 min ± 1 h 19 min</td>
<td>2 h 1 min ± 1 h 17 min</td>
<td>1.04</td>
<td>0.31</td>
</tr>
</tbody>
</table>

Data are shown as average ± SD.

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Adaptation to reduced (short wavelength) light exposure

After wearing the SOCL for 24 h a day for two consecutive weeks, the suppression of the nocturnal melatonin by light was as large as the suppression observed in the control condition (without the SOCL). Previous studies have shown that light history has a large impact on non-image-forming responses. In time frames ranging from hours up to a week exposures to dimmer light conditions have lead to an increase in sensitivity of the biological clock system as measured by means of melatonin suppression (Hébert et al., 2002; Jasser et al., 2006; Owen & Arendt, 1992; Smith et al., 2004). Our findings do not only imply an increase in sensitivity but rather a restoration/normalization of the response to the levels of the control condition. We further found that after wearing the SOCL for two weeks neither DLMO nor the amplitude of the melatonin rhythm differed significantly from the control condition. This also means that light exposure for the assessment of the suppression response occurred on average at the same circadian phase. In conclusion, these findings suggest that during these two weeks adaptation to the changes in the spectral composition of light occurred. Adaptation is the process that potentially compensates for light intensity differences. One could argue that differential exposure to light could have lead to the observed results. Subjects would have had to naturally, but systematically, expose themselves to just enough more light in order to compensate for the difference between the control and the SOCL condition to restore melatonin suppression values to those observed in the control condition. Our light exposure data reveal no differences between both conditions, allowing us to discard differential light exposure as a key factor for our findings.

Neither the previous studies nor the present one were designed to precisely assess the temporal characteristics of adaptation. It would be valuable to develop an adaptation curve to changes in the spectral composition during the day (i.e. after how many hours/days of selective exposure to certain wavelengths during daytime is the melatonin suppression response restored to reach dim light melatonin levels again). Restoration after exposure to darkness should be considered. In mice circadian phase responses to light are reduced rapidly by prior light exposure and fully restored by prolonged (18 h) dark exposure (Comas et al., 2007). If the lenses have caused “dark adaptation”, this would enhance sensitivity to entraining light stimuli and thus compensate for the reduced penetration of blue light to the ipRGCs. Alternatively, redistribution of sensitivity across photoreceptors could explain our observations. It is reasonable to surmise the occurrence of compensatory processes under the constant presence of relatively small changes in light intensity and spectral composition. Data collection at intermediate time points would allow to quantify more accurately the rate of adaptation. Such experiments are critical to gain an insight in sensitzation and desensitization of the non-image forming system by light and darkness.

Effects of SOCL on circadian rhythms of melatonin and sleep

We observed no differences in the timing of sleep or melatonin rhythms after wearing the SOCL for two weeks in comparison to the control condition. Only slight changes in sleep onset latency and in the activity during the 10 most active hours were found. The slight tendency to a shorter sleep onset latency and the reduction in M10 shown in the SOCL condition could indicate an increased tiredness and/or less alerting/activating effects of light as expected after exposure to less light (Cajochen, 2007; Rüger et al., 2006). Studies in humans have shown that complete absence of short-wavelength light before bedtime improves sleep (Burkhart & Phelps, 2009; Santhi et al., 2012), while its presence leads to the opposite effect (Münch et al., 2006; Santhi et al., 2012) in a blue-amount-dependent manner (Santhi et al., 2012). The use of orange goggles during the morning hours (from awakening until ~15:00 h) lead to a phase delay of the DLMO (Figueiro & Rea, 2010). These studies tested the effect of (lack of) blue light at specific times of the day. Our study shows that sleep and melatonin rhythms after two weeks of continuous partial absence of blue light are not different from sleep and melatonin rhythms after two weeks of unfiltered light exposure.

It could be argued that the reduction of light exposure due to the SOCL was not large enough to induce sleep disturbances or a shift in phase in these young people. However, the melatonin suppression data indicate that there is a reduction in lens transmission that leads to a reduction in melatonin suppression after wearing the lenses for 30 min. If changes in melatonin suppression are achieved by means of the SOCL it is expected that those changes in light input are also capable of inducing a shift in phase (Zeitger et al., 2000). In this sense, adaptation to the new light environmental conditions seems a plausible explanation for the lack of effects observed after wearing the SOCL for two consecutive weeks.

Thus, neither the melatonin profile nor the sleep characteristics suggest that entrainment of the circadian system is compromised by the relatively long-term application of SOCL. The reduction we achieved by means of the SOCL is relatively similar to that of a cataractous eye at about 480 nm at which the sensitivity of the ipRGCs peak (Panda et al., 2005; Provencio et al., 2002). At shorter wavelengths the discrepancy becomes larger. If, as in young subjects very short wavelengths lead to increased alerting effects (Revell et al., 2006) in the elderly, this could, in the long term, have implications for the timing of sleep. The present study
does not support the idea that the general circadian characteristics of the elderly can be explained by the age-related reduction in (short wavelength) light transmittance only. The effects observed in the present study were marginal and probably of a transitional nature, whereas in the elderly the impaired circadian output remains. In agreement with our observations, a recent study shows that the increased lens filtering that occurs with aging does not lead to a proportional change in the response of the non-image forming system (Najjar et al., 2014). Najjar et al. suggest that compensatory mechanisms might take place in healthy elderly. Their comparisons are of a between (young vs. elderly) and not within (elderly with and without blue input) nature. Healthy young subjects might have a more plastic non-visual system than elderly people. With pathological aging the plasticity might become less and may lose its capability to fully adapt to changing situations. Still, exposure to bright light, exercise and melatonin can promote restoration of diminished-non-visual responses in elderly subjects (for review see (Van Someren et al., 2002). These improvements are mainly based on studies conducted in institutionalized subjects where light conditions are far from being optimal. Further studies are needed in order to gain an insight in the mechanisms of adaptation/compensation to reduced short-wavelength light input in the young and elderly.

CONCLUSION

In this study, exposure to light was exclusively modified by using contact lenses that absorb some of the, mainly, short wavelengths. There were no behavioral restrictions whatsoever. In this way, the study approaches the effects of light history on sensitivity of the circadian system in a rather realistic manner: the altered lens transmittance is continuously present, as it is, for instance, in elderly people. Our observation that the system in healthy young people is able to adapt to the spectral composition of the light is remarkable. Apparently, the circadian system continues to function as a time keeping mechanism: it regulates entrainment and alertness as if nothing had changed. Such adaptations are likely to serve important functions. They may help healthy humans to adjust to different life styles, such as living indoors or outdoors, and to seasonal and/or latitudinal changes. Whether similar adaptations still occur in healthy aged individuals and no longer in subjects suffering from severe cataract remains to be investigated.

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DECLARATION OF INTEREST

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