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Blue blocker glasses impede the capacity of bright light to suppress melatonin production

Abstract: Blocking morning light exposure with dark goggles can contribute to the adjustment to night work but these glasses are incompatible with driving. Recently, it was discovered that the biological clock is most sensitive to short wavelengths (blue light). Therefore, we tested the hypothesis that cutting the blue portion of the light spectrum with orange lens glasses (blue blockers) would prevent the light-induced melatonin suppression, a test broadly used as an indirect assessment of the circadian clock sensitivity. Fourteen normal subjects were exposed at night to a 60 min bright light pulse (1300 lx behind filters) between 01:00 and 02:00 hr while wearing orange lens glasses (experimental condition) or grey lens glasses (control condition). The amount of salivary melatonin change observed during the light pulse was compared with a melatonin baseline obtained the night before. Although both glasses transmitted the same illuminance (1300 lx) but at an irradiance 25% higher for the orange lens (408 $\mu W/cm^2$) compared with the grey lens (327 $\mu W/cm^2$), a non-significant increase of 6% (95% CI, −20% to 9%) was observed with the orange lens whereas a significant ($P < 0.05$) reduction of 46% (95% CI, 35–57%) was observed with the grey lens. Blue blockers represent an elegant means to prevent the light-induced melatonin suppression. Further studies are needed to show that these glasses, which are suitable for driving, could facilitate adaptation to night work.

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Introduction

The circadian clock, located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus [1], is responsible for generating biological rhythms. In order to maintain a proper synchronization with the environment, the circadian clock is very sensitive to the 24 hr light/dark cycle, with morning light being the most powerful resetting cue. Melatonin, one of the key rhythms generated by the SCN, is also sensitive to light. The 24-hr cycle of melatonin production by the pineal gland [2, 3] can acutely be suppressed by nocturnal light exposure [4] and the effect appears to be mediated by the eye as suppression cannot be achieved with extraocular light exposure [5, 6] or in bilaterally enucleated subjects [7]. To induce this suppression, the efferent light signal originating from the retina has to transit first by the SCN before reaching the pineal gland through a complex multisynaptic neural pathway, composed of the hypothalamic subparaventricular nuclei, thoracic intermediolateral cell column and superior cervical ganglia [8, 9].

As melatonin suppression is dependent on the response of the SCN to the light stimulus, it has been broadly used as an indirect assessment of the biological clock sensitivity [10]. Studies have already demonstrated a dose–response relationship between light intensity or irradiance and melatonin suppression [11–14]. Others factors such as prior light history have also been demonstrated to impact sensitivity to melatonin suppression [15, 16]. More interestingly, it was recently demonstrated that melatonin suppression is wavelength dependent with a peak sensitivity in the 446–477 nm (blue light) portion of the visible spectrum [17, 18]. Accordingly, it may be possible to control the effect of light on the biological clock by blocking the blue portion of the visible light. Close inspection of the action spectra provided by Brainard et al. [17] reveals that, for the most part, suppression is achieved with wavelengths below 550 nm with minimal suppression occurring above 555 nm.

An objective of our research is to provide a means by which the undesired synchronizing effect of morning light, after a night shift, could be easily blocked. As argued by the Eastman's group [19], real shift-workers do not usually phase shift because morning light exposure after a night shift usually coincides with the phase-advance portion of the phase response curve, therefore, inhibiting circadian rhythms from phase delaying. Although it was shown that wearing dark goggles can facilitate re-entrainment to night work and day sleep [20], these glasses are incompatible with driving. However, cutting defined wavelengths may represent an effective means for this purpose. Importantly, to be safe for traffic light recognition while driving, sufficient yellow–green light (550 nm) must be allowed. The aim of this study was to determine if complete obstruction of wavelengths below 540 nm with orange lenses, also known as blue blockers (which are suitable for driving) that do

transmit 5% of light at 550 nm, would impede the capacity of bright white light to suppress melatonin production. In the present study, we investigated the capacity of blue blockers to prevent melatonin suppression during a 60-min light pulse at 4000 lx that is an intensity known to be sufficient to induce maximal melatonin suppression [13] and which can be encountered easily in the morning while driving home [21].

Methods

Study participants

Fourteen subjects (six females and eight males) [mean age (±S.D.) 23.1 (±1.2) yr] completed the study. The protocol was approved by the ethics committee and written informed consent was obtained prior to participation. All subjects were in good health, not taking medications and reported no history of sleep problems, night shifts or travelled through more than two time zones, 1 month prior to the experiment. Only women taking oral contraceptives were allowed as the natural hormonal cycle is known to impact melatonin production [22, 23]. Based on the Horne-Östberg Morningness-Eveningness Scale, we screened out subjects who were revealed to be at the extremity of the scale. Subjects completed the experiment between April and October of 2002 and 2003.

Study protocol

Three days before the experimentation, subjects maintained a sleep diary that showed a regular sleep and wake schedule and wore a wrist activity monitor (Actiwatch-Light, Mini Mitter Co. Inc., Bend, OR, USA) on the non-dominant wrist to record their activity and ambient light exposure. Subjects had to refrain from alcohol 48 hr prior to each laboratory night and not drink caffeine, eat bananas, cheese or turkey 12 hr before laboratory nights. Subjects were admitted to the laboratory for two consecutive nights (see protocol chart presented at Fig. 1). Night 1 served as baseline and night 2 served as the experimental night. During these nights, to minimize posture change, subjects were seated comfortably (La-Z-Boy) in a semireclined position and when needed, transported in a wheel chair to a nearby washroom while wearing dark sunglasses. Subjects were permitted only water, except for 10 min before each saliva sample. During each night in the laboratory, with the exception of night 2 in which a light pulse was presented between 01:00 and 02:00 hr, subjects stayed in dim light (5 lx) from 22:00 to 03:00 hr while watching a 21-inches TV (about 1 lx, included in the 5 lx total), positioned 214 cm away. After night 1, subjects were instructed to sleep in the laboratory before going home at 07:00 hr to ensure that all subjects would get their natural morning resetting light. On night 2, they were driven home after collection of the last saliva sample.

Light exposure

On night 2, a bright pulse of white light was presented between 01:00 and 02:00 hr. While exposed, subjects wore either orange lenses glasses (Solar Shield Ultra; Eschenbach

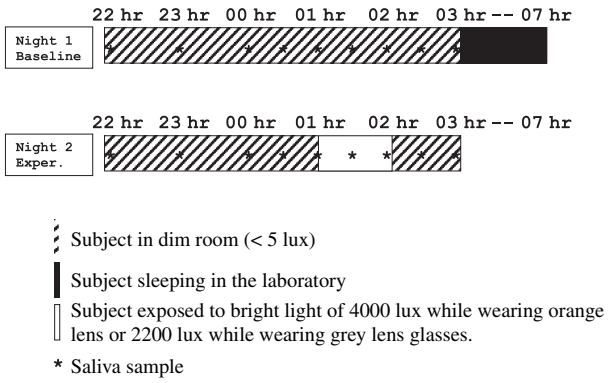

Fig. 1. Overview of the protocol design. On night 1, subjects passed 5 hr under < 5 lx and were then allowed to sleep 4 hr before going home. On night 2, after 3 hr under < 5 lx, subjects were exposed to a bright white light pulse for 60 min while wearing orange or grey lens glasses. Subsequently, subjects spent 1 hr under < 5 lx before being allowed to go home. The entire protocol was carried out under constant recline position. Saliva samples were collected at hourly intervals from 22:00 to 00:00 hr and then at every half an hour until 03:00 hr.

Optik of America, Ridgefield, CT, USA) or grey lens glasses depending of the experimental condition they were assigned first which was determined randomly. However, all subjects performed both conditions separated by at least a week. The grey lens glasses were made by replacing the orange lens of the Solar Shield Ultra by grey neutral density filters (2-stop; Rosco Canada, Markham Canada). Adjustments were made so that both the orange lenses (32% transmittance) and grey lens (52% transmittance) let 1300 lx of illuminance reaching the eyes. To achieve this illuminance, a light source of 4000 lx (1083 $\mu W/cm^2$) was needed for the orange lens glasses condition whereas only 2200 lx (540 $\mu W/cm^2$) was needed for the grey lens glasses condition. These intensities were achieved by seating subjects on average, 60 cm away from the light box when wearing the orange lens glasses and 74 cm away when wearing the grey lens glasses. However, due to the spectral characteristic of each lenses (Fig. 2), the irradiance trans-

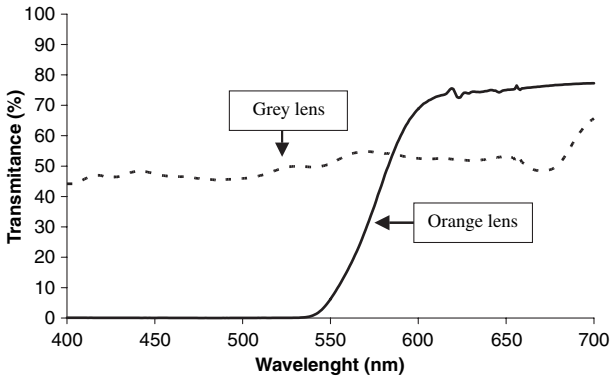

Fig. 2. Transmittance level of the two optical filters. The orange lenses (——) cut off all wavelengths of light below 540 nm. Above 600 nm the transmittance is approximately 70% whereas at 555 nm the transmittance it is about 11%. The grey lenses (- - - - -) have a mean transmittance level of about 50% in the visible range (400–700 nm).

mitted to the eyes was close to 25% higher with the orange lens (408 $\mu W/cm^2$) when compared with the grey lens (327 $\mu W/cm^2$; IL 1700 radiometer, International Light, Peabody, MA, USA). After the TV was turned off at 01:00 hr, subjects were required to stare directly at a $24'' \times 23.5''$ light box (The Sun Box Co., Gaithersburg, MD, USA) during the 60-min period. Light level was measured (in lx) every 20 min at the subject's forehead and if necessary, small adjustments were made.

Salivary melatonin

Saliva samples were collected every hour from 22:00 to 00:00 hr and then every half-hour until 03:00 hr using Salivettes (Sarstedt, Newton, NC, USA). Tubes were centrifuged after collection and frozen. Enzyme immunoassays were performed on all saliva samples in duplicate with ELISA kit (Direct saliva melatonin ELISA; ALPCO Diagnostics, Salem, NH, USA). The maximum intra-assay and interassay variabilities were 6.5% and 7% respectively. The lower limit of detection was at least 0.4 pg/mL throughout the study.

Data analysis

To assess the effect of condition on melatonin change during the light pulse and the same respective time during baseline, a one-way, repeated-measures ANOVA ($P < 0.05$) was performed and significant difference between conditions were assessed by Bonferroni post hoc selected pairs comparison. As a secondary analysis we also performed a gender comparison for the percent melatonin change scores observed in the orange lens and grey lens condition using unpaired two-tailed Student's *t*-tests ($P < 0.05$). Because light history may impact light-induced melatonin suppression [15, 16, 24], we also performed an analysis of light exposure that occurred before the test nights. Our interest was to detect the duration of time spent outside in natural light, which was defined arbitrarily as time spent above 500 lx, so as to take into account that measurements at wrist level are known to underestimate real exposure at the eye level. The averaged duration of light exposure above 500 lx for 3 days preceding the laboratory nights was compared between conditions using a paired two-tailed Student's *t*-tests ($P < 0.05$). Because of technical difficulties, complete light data were available for 10 subjects only.

Results

Table 1 presents the group mean raw melatonin concentration of samples pre and post for both the experimental and baseline nights in both conditions. From this table it can be seen that pre- and post-values were quite stable between conditions with the exception of the post-value in the grey lens condition where a decline in melatonin (of about 40%) is observed after the 1-hr pulse of 2200 lx. However, for statistical analysis we used the light-induced melatonin percent change that occurred during the experimental night, compared with the melatonin percent change that took place at the same respective time during the baseline night (which occurred the night before). This 'control-adjusted change scores' technique takes into account the individual natural rise or fall in melatonin levels [10, 17, 25]. However, to avoid confusion with the control condition (grey lens) we have termed the no-light condition 'baseline' in the following formula [(experimental post × 100/experimental pre) − (baseline post × 100/baseline pre)]. For a better understanding of the formula, the points of reference have been identified on the graph presented at Fig. 3A. The terms 'baseline pre' and 'experimental pre' refer to the mean value of melatonin observed at 00:30 and 01:00 hr, during the baseline and experimental nights respectively. These two points (00:30 and 01:00 hr) were averaged to improve accuracy. The terms 'baseline post' and 'experimental post' refer to the data point at 02:00 hr for the baseline and experimental nights respectively. Using this formula, positive numbers suggest melatonin suppression during the experimental night when compared with baseline.

Figure 3 shows the averaged melatonin profiles for both nights in both conditions. Melatonin suppression can be

Table 1. Raw melatonin mean values in both baseline and experimental nights while wearing the orange or the grey lens goggles

	Orange lens				Grey lens			
	Baseline pre (pg/mL)[a]	Baseline post (pg/mL)[b]	Experimental pre (pg/mL)[c]	Experimental post (pg/mL)[d]	Baseline pre (pg/mL)[a]	Baseline post (pg/mL)[b]	Experimental pre (pg/mL)[c]	Experimental post (pg/mL)[d]
Moyenne	28.7	26.6	29.1	26.9	29.3	30.7	28.2	17.0
S.D.	17.5	15.5	16.2	15.5	22.8	20.0	21.6	12.6
Lower 95% CI	18.4	17.7	19.5	18.0	16.1	19.1	15.7	9.7
Upper 95% CI	38.8	35.6	38.5	35.9	42.3	42.3	40.7	24.3

[a]Average of raw value of melatonin in pg/mL during baseline night observed before the respective time of the light pulse between 00:30 and 01:00 hr on the experimental night for the orange or the grey lens condition.
[b]Raw value of melatonin in pg/mL during baseline night observed at the end of the respective time of the light pulse at 02:00 hr on the experimental night for the orange or the grey lens condition.
[c]Average of raw value of melatonin in pg/mL observed before the light pulse between 00:30 and 01:00 hr during experimental night for the orange or the grey lens condition.
[d]Raw value of melatonin in pg/mL observed at the end of the light pulse at 02:00 hr during experimental night for the orange or the grey lens condition.

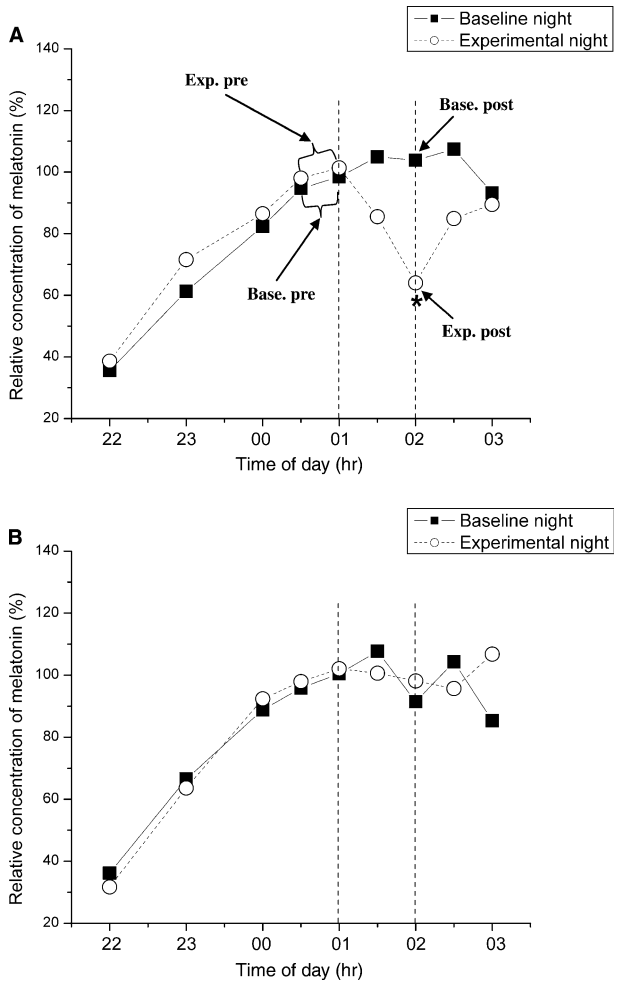

Fig. 3. Effect of a 60 min light exposure between 01:00 and 02:00 hr on salivary melatonin level (A) while wearing the grey lens goggles and (B) while wearing orange lens glasses. Melatonin profiles were converted into percentages of the mean value observed at 00:30 and 01:00 hr before group averaging. The (*) indicates where suppression was significant. In panel (A), reference points for the formula used to quantify the amount of melatonin change during the light pulse [experimental post versus experimental pre] and during the same respective time in baseline [baseline post versus baseline pre] are shown with arrows.

observed easily in the control condition (grey lens condition). Individual percent change in melatonin production during the experimental night and baseline night as well as the baseline-adjusted percent melatonin change scores are provided in Table 2 for both the orange lens and grey lens conditions. Looking at the baseline-adjusted scores column, it can be observed that while wearing the orange lens glasses, three subjects exhibited a decrease of 20–26% in melatonin production whereas four subjects showed an increase over 20%. In contrast, when wearing the grey lens all subjects showed a decrease (suppression) above 25% with nine of 14 showing melatonin suppression over 40%. The ANOVA performed on the percent melatonin change observed between the data points pre and post in the experimental and baseline nights showed a highly significant effect of conditions ($F_{3,13} = 8.588$; $P = 0.0002$). Post-tests revealed that the percent melatonin change scores between 01:00 and 02:00 hr was neither significant between the two baselines nights (one for each condition) nor was it significant for the experimental night in the orange lens condition when compared with its respective baseline. The only significant change was observed in the control grey lens condition, when compared with its respective baseline ($P < 0.001$). No gender difference was observed for the baseline-adjusted percent melatonin change observed in the grey light condition (mean ± S.D., women n = 6; 47 ± 13%; men n = 8; 46 ± 24%) or orange lens condition (0 ± 26% and −10 ± 25% respectively). For the 10 subjects with light data available, the amount of time spent above 500 lx 3 days before each condition was not significantly different between the orange (mean ± S.D.; 61 ± 106 min) and grey (75 ± 79 min) lens conditions respectively.

Discussion

Our data show that, irrespective of gender, orange lens glasses can effectively block the capacity, of a 1-hr light pulse of 1300 lx in the eye, to suppress melatonin production. In this study, we used the grey lens as a control condition to demonstrate the superiority of controlling distinctively the spectral quality of light for neuroendocrine and circadian regulation. But, in order to maintain a similar illuminance (1300 lx) at eye level (behind the filters) we had to lower by almost 50% the light intensity used to for the grey lens condition which yielded to an irradiance that was 25% higher for the orange glasses due to its spectral characteristics. In choosing to work with the same illuminance we wanted to make sure that we were stimulating the photopic visual system in a constant manner independently of the lens used. Although illuminance in lux is not recognized as a good measure of light, it does represent the best measure of the response of the photopic three-cone system which peaks at 555 nm. Therefore, our experiment represents an additional support to the fact that the three-cone system is not the main contributor to the biological effect of light at least, with the intensity used in the present study (1300 lx).

Our data are in agreement with previous reports using melatonin production as a biological marker which point to the existence of a novel non-visual circadian photoreceptor, melanopsin [26–29], particularly insensitive to longer narrow bandwidths wavelengths [17, 25, 30–35]. At present, there exists only one contradictory report. Zeitzer et al. [36] were able to induce a phase shift under certain strict conditions that is a 5-hr pulse of broadband red light (above 600 nm) presented for 3 days and centred 1.5 hr after the temperature nadir. However, it is still unclear if the effect observed by this group was due the significantly long exposition (5 hr) or to a red filter used in the study which let a small peak of transmission at 400 nm. If longer wavelengths (through standard photoreceptors) contribute to the melatonin suppression effect, as the orange lens glasses used in this study do transmit about 11% of the light between 550 and 560 nm, this may explain why some melatonin suppression could be observed (albeit never above 26%) in three of our subjects. But, aside from intersubject sensitivity to light, the suppression observed in

Table 2. Normalized melatonin levels change at 02:00 hr in both baseline and experimental nights and amount of suppression to a 1-hr light pulse (1300 lx behind the glasses) presented during the experimental night while wearing the orange or the grey lens goggles

	Orange lens			Grey lens		
Subject/ gender	Baseline melatonin change (%)[a]	Experimental melatonin change (%)[b]	Adjusted melatonin change (%)[c]	Baseline melatonin change (%)[a]	Experimental melatonin change (%)[b]	Adjusted melatonin change (%)[c]
1/M	141	154	−13	112	70	**42**
2/F	94	74	**20**	72	40	**32**
3/F	97	86	11	72	40	**32**
4/M	112	130	−18	115	90	**25**
5/F	53	92	−39	119	57	**62**
6/F	113	87	**26**	88	40	**48**
7/M	73	66	7	142	96	**46**
8/M	159	134	**25**	147	93	**54**
9/M	53	79	−26	100	57	**43**
10/F	139	132	7	102	45	**57**
11/F	48	74	−26	156	105	**51**
12/M	55	112	−57	130	31	**99**
13/M	139	132	7	104	77	**27**
14/M	68	72	−4	86	58	**28**
Mean	96	102	−6	110	64	**46**
S.D.	38	29	25	27	24	19
Lower 95% CI	74	85	−20	95	50	35
Upper 95% CI	118	119	9	126	78	57

[a]Baseline night percent melatonin change during the respective time of the light pulse in experimental night, calculated on individual raw values with formula: baseline post × 100/baseline pre (see Fig. 3).
[b]Experimental night percent melatonin change during light pulse, calculated on individual raw values with formula: experimental post × 100/experimental pre (see Fig. 3).
[c]Baseline adjusted melatonin percent change scores obtained by subtracting the baseline night percent melatonin change to the experimental night per cent melatonin change. Positive numbers refer to suppression. Suppressions above 20% are in bold.

three subjects could also be attributable to day-to-day variation in melatonin levels [24] since four subjects showed the opposite effect that is an increase (over 20%) in melatonin production while being exposed to bright light when wearing the orange lens glasses.

In addition, it was shown recently that the melanopsin photopigment does not seem to respond to narrowband light stimulation at 540 nm or higher [28], which suggest that our orange lens may be optimal to impede the capacity of bright light to affect the biological clock. Of interest, it was recently reported by another group that in 19 subjects, orange lens glasses cutting all wavelengths below 530 nm could also prevent the suppression of melatonin to a modestly bright light (800 lx) pulse but significantly longer presentation (20:00–08:00 hr) [37]. This group also showed that maintaining melatonin production when wearing the goggles did neither impair performance nor impact alertness and subjective sleepiness.

In this study, the exposition of 60 min at 4000 lx, was deemed to be compatible with the light that would be expected in the morning while driving home after a night shift. In support of this statement, we measured for four consecutive weeks light exposure in 10 permanent night shift workers using an Actiwatch wrist monitor and observed a mean morning light exposure of 1919 ± 1874 lx between the summer months of June and August in Quebec city (unpublished data, Herbert, M. H.). As stated earlier, light measured at the wrist level probably underestimating the real eye exposure. But, depending on the weather and season, light intensity is known to vary from 100 to 10,000 lx when the sun reached a 10° angle from the horizon [21] in the morning, so 4000 lx is not too far from the averaged morning light exposure that a night workers would expect. Although the amount of blue light in a natural environment varies depending on the time of the day (there is more in the morning) and on the reflecting surface such as snow, grass, water, sand or cement [38], blue blockers which are cutting all wavelengths below 540 nm should also be effective in naturalistic condition albeit that proper glasses' frame are made to cover all angles.

In conclusion, assuming that the biological clock shares the same sensitivity to wavelengths as melatonin (as demonstrated by others using phase-shifting protocols [25, 30–33], we propose that these glasses, when worn in the morning, should greatly impede resynchronization of the biological clock by light. Further studies, currently in progress in our laboratory, are necessary to confirm that these glasses have the potential to improve adaptation to night shifts.

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