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J Appl Physiol 110:619-626, 2011. First published 16 December 2010;
doi: 10.1152/japplphysiol.01413.2009

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Blue light from light-emitting diodes elicits a dose-dependent suppression of melatonin in humans

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Submitted 21 December 2009; accepted in final form 15 December 2010

West KE, Jablonski MR, Warfield B, Cecil KS, James M, Ayers MA, Maida J, Bowen C, Sliney DH, Rollag MD, Hanifin JP, Brainard GC. Blue light from light-emitting diodes elicits a dose-dependent suppression of melatonin in humans. *J Appl Physiol* 110: 619–626, 2011. First published December 16, 2010; doi:10.1152/japplphysiol.01413.2009.— Light suppresses melatonin in humans, with the strongest response occurring in the short-wavelength portion of the spectrum between 446 and 477 nm that appears blue. Blue monochromatic light has also been shown to be more effective than longer-wavelength light for enhancing alertness. Disturbed circadian rhythms and sleep loss have been described as risk factors for astronauts and NASA ground control workers, as well as civilians. Such disturbances can result in impaired alertness and diminished performance. Prior to exposing subjects to short-wavelength light from light-emitting diodes (LEDs) (peak λ = 469 nm; ½ peak bandwidth = 26 nm), the ocular safety exposure to the blue LED light was confirmed by an independent hazard analysis using the American Conference of Governmental Industrial Hygienists exposure limits. Subsequently, a fluence-response curve was developed for plasma melatonin suppression in healthy subjects (n = 8; mean age of 23.9 ± 0.5 years) exposed to a range of irradiances of blue LED light. Subjects with freely reactive pupils were exposed to light between 2:00 and 3:30 AM. Blood samples were collected before and after light exposures and quantified for melatonin. The results demonstrate that increasing irradiances of narrowband blue-appearing light can elicit increasing plasma melatonin suppression in healthy subjects ($P < 0.0001$). The data were fit to a sigmoidal fluence-response curve (R^2 = 0.99; ED_{50} = 14.19 $\mu W/cm^2$). A comparison of mean melatonin suppression with 40 $\mu W/cm^2$ from 4,000 K broadband white fluorescent light, currently used in most general lighting fixtures, suggests that narrow bandwidth blue LED light may be stronger than 4,000 K white fluorescent light for suppressing melatonin.

pineal; light-emitting diode

INFORMATION ABOUT ENVIRONMENTAL light is transmitted from initial exposure at the retina through the retinohypothalamic tract to the hypothalamic suprachiasmatic nuclei (SCN) (41). The SCN transmit information about lighting cues to the pineal gland, which responds by regulating the secretion of the hormone melatonin (33, 42). As a result, rhythmic patterns of light entrain the circadian production and secretion of melatonin. In mammals, this pattern results in higher levels of melatonin during dark, nighttime hours. In addition, exposure to light of sufficient intensity can suppress high nocturnal melatonin secretion (9, 36).

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Previous photobiological research has shown that exposing healthy male and female subjects to blue-appearing light within the short-wavelength portion of the spectrum, between 446 and 477 nm, results in melatonin suppression that is more than 3 times more potent than exposure to long-wavelength light above 530 nm (10, 57). Although quantification of melatonin suppression has been used extensively as a tool for elucidating the physiology of how the eye transduces light for neuroendocrine regulation (9), it is not necessarily a proxy for all circadian, neurobehavioral, and photoneural responses. It is notable, however, that a set of studies has confirmed that shorter-wavelength, monochromatic light is more potent than equal photon densities of longer-wavelength light for evoking circadian phase shifts, suppressing melatonin, enhancing subjective and objective correlates of alertness, increasing heart rate, increasing body temperature, and inducing expression of the circadian clock gene *Per2* in humans (12, 13, 37, 38, 50, 51).

Light therapy has been studied as a countermeasure for circadian disruption associated with intercontinental jet travel and shift work (7, 16, 49, 50). It is important to note that the efficacy of light as a therapeutic stimulus for any application depends on multiple factors, including the light intensity, spectrum, timing, duration, and spatial distribution relative to the eye. As detailed in the *Bioastronautics Roadmap* (39) and NASA's *Human Research Program Integrated Research Plan 2009* (44), known risk factors for the health and safety of astronauts and ground control workers include disturbed circadian rhythms and sleep loss. As a result of these disturbances, space program personnel may experience impaired alertness, loss of concentration, and diminished performance. In the Johnson and Kennedy Space Centers crew quarters, NASA currently uses relatively high illuminances of white fluorescent light at 7,000 to 10,000 lux as a prelaunch countermeasure for circadian disruption (17, 21, 55). In contrast, lighting specifications for supporting astronaut vision indicate much lower illuminances of white fluorescent light for interior illumination of both the Space Transportation System and the International Space Station (ISS). For example, general ISS illumination is specified as 108 lux, whereas lighting for food preparation is specified as 323 lux (43). Recently, actual illuminances in parts of the ISS were estimated to be lower than these specifications due to accelerated fluorescent lamp failures and blockage of light sources by equipment. The ISS, as well as future vehicles and habitats for space exploration, will be illuminated primarily by solid-state lighting. The primary solid-state technology for general visual stimulation will

be based on white-appearing light-emitting diodes (LEDs). There is additional interest in having adjustable lighting systems with narrow bandwidth and/or broad-bandwidth LEDs that can be controlled for changes in intensity, spectrum, and duration to better regulate circadian, neuroendocrine, or neurobehavioral physiology of astronauts.

Exposure to solid-state, LED panels emitting narrowband light in shorter wavelengths of the spectrum may provide a nonpharmacological countermeasure for disrupted sleep, desynchronized circadian rhythms, or diminished alertness. Commonly used fluorescent lighting fixtures emit white broadband light with a correlated color temperature around 4,000 K. Our primary hypothesis was that short-wavelength LED light in the blue-appearing portion of the spectrum (485–465 nm) would evoke an irradiance-dependent suppression of melatonin in humans. A secondary aim of the study was to test the hypothesis that this narrow bandwidth blue LED light would have increased efficacy for melatonin suppression compared with the relative efficacy of 4,000 K white fluorescent light. To accomplish these aims, a within-subject study tested melatonin suppression across eight irradiances of blue narrowband LED light, a single irradiance of 4,000 K white fluorescent light, and a dark control exposure.

LED technology is likely to become a greater presence in our homes, work, and general environment (53). With narrowbandwidth blue LEDs and blue-enriched white, broadband LEDs, there is some concern about the ocular safety with extended exposure to these light sources. Hence, an additional aim of this work was to assess the safety of these particular LED panels using national and international guidelines (3, 32). On the basis of these findings, our long-range goal is to develop a safe and effective lighting countermeasure that stimulates alertness in astronauts and ground control personnel during space exploration missions, as well as in domestic workers suffering from sleep or circadian disruption.

MATERIALS AND METHODS

Hazard analysis. An independent hazard analysis based on current guidelines set by the American Conference of Governmental Industrial Hygienists (ACGIH) was performed to ensure that study subjects were not at risk for photochemical retinal injury. Because blue light can induce damage to the eye when exposed to light within the range of 400 to 550 nm, an assessment of the blue LED lighting system was deemed necessary (2). The typical viewing distance was expected to be ~35 cm. Therefore, all measurements were taken at this distance from the panel. Additional UV hazard measurements were taken at the point of contact with the panel surface, and measurements of luminance and equivalent radiance measurements were taken up to 100 cm from the panel along the central axis of the highest irradiance output. Analysis was completed using a model 1400A radiometer/photometer (International Light, Peabody, MA), with three different detectors: *1*) a model SEL240 (no. 3682) detector with input optic T2ACT3 (#18613) that had been calibrated to read directly in terms of the ACGIH/ICNIRP UV-hazard-effective irradiance; *2*) a model SEL033 (no. 3805) detector (with input optic W#6874 and filter UVA#28245), which had been calibrated to measure near-ultraviolet (UV-A) radiation between ~315 and 400 nm; and *3*) a model SEL033 (no. 3805) detector with input optic W#6874 and filter F#14299, which had been calibrated to measure irradiance between 380 and 1,000 nm. A radiance hood, which limited the field of view of the detector to 0.45 steradians (sr), was used to directly measure the radiance of the sources. Spectral irradiance measurements were taken using a model FSHH 325–1075P FieldSpec hand-held spectroradiometer (Analytical Spectral Devices, Boulder, CO). In addition, a luminance meter (Konica Minolta, Ramsey, NJ) was used to measure the panel luminance as a check of the radiance measurements at 30–70 cm.

Results of the hazard analysis were evaluated against *NASA Constellation Program Human-Systems Integration Requirements Section 3.2.8.3.2* (45). This requirement uses the same B(λ) blue-light hazard weighting function and limits as the ACGIH, but the summation of visible spectral components in the ACGIH is scaled by a factor of 0.2 to reflect differences between NASA astronauts and the general population that includes children and individuals with either ocular disease or acute sensitivity. Although some spaceflight operations necessitate a relaxation of the more stringent ACGIH standards, the study reported here was predicated on meeting both the NASA and ACGIH standards.

Study design. A complete, within-subjects design was used for this study. Subjects were asked to come in one night a week, with at least 1 wk between study nights. Volunteers arrived at the laboratory by 11:45 PM on each study night, and blindfolds were placed over subjects' eyes at midnight. Subjects were awake and remained seated in a constant upright posture with feet placed on the floor. At 2:00 AM, while still blindfolded, a blood sample was taken by venipuncture of the antecubital vein. The blindfolds were then removed, and the subjects began a 90-min light exposure, during which subjects remained seated upright and with fixed gaze at a specified point on the light panel. Pupil measurements were taken for each subject every 30 min starting at 2:00 AM using a Neuroptics pupillometer (Neuroptics, Franklin Lakes, NJ). At 3:30 AM, a second blood sample was taken while subjects continued to gaze at the light. Each subject completed light exposure at eight different irradiances (ranging from 0.1 μW/cm^2 to 600 μW/cm^2) with the blue LED lamp, as well as one exposure of 40 μW/cm^2 with the 4,000 K lamp. On control nights, the 90-min light exposure was replaced with continued dark exposure, and both blood draws were taken while the subject was blindfolded. When possible, subjects had their dark exposure control night within the first two nights of their participation in the study. After that, on subsequent study nights, each subject was assigned a random exposure condition that he or she had not previously completed. Plasma samples were collected in 7-ml glass tubes with EDTA (K3, 12 mg). Melatonin content of plasma samples were determined by the original RIA technique developed by Rollag and Niswender (52). This assay employs R1055 antiserum and was later modified and optimized by Rollag for human plasma (10). The minimum detection limit of the assay is 0.5–2.0 pg/ml.

Subjects. The subjects consisted of eight healthy male ($n = 5$) and female ($n = 3$) subjects with a mean ± SE age of 23.9 ± 0.5 years. Potential subjects were assessed to ensure none were shift workers, planned long-distance travel in the upcoming 6 mo, reported irregular sleep patterns, and/or were taking medications that could interfere with their neurobehavioral physiology or neuroendocrine levels, including illegal drugs and excessive alcohol use. Before entering the study, each subject signed a consent form approved by the Institutional Review Board of Thomas Jefferson University. All subjects completed an eye exam prior to enrollment, and each subject demonstrated normal color vision as measured by the Ishihara and Farnsworth Munsell D-100 (FM 100) tests. The FM 100 tests were administered under a 50 W lamp (Model D65, GretagMacbeth, New Windsor, NY) at an average illuminance of 680 lux. Subjects completing the study had a mean Farnsworth Munsell score of 49.5 ± 5.9. For the length of the study, subjects were instructed to maintain a steady sleep schedule, abstain from alcohol on the day of the study and caffeine after noon on the day of the study, and to refrain from naps after 6:00 PM that day.

Light exposures and measurement. The narrowband, solid-state light exposure systems were constructed for this study by Apollo Health (part of Philips Home Healthcare Solutions, American Fork, UT). These lighting units consisted of an 122 × 122 cm blue LED array, composed of 5,776 LEDs, with a lens diffuser that results in a

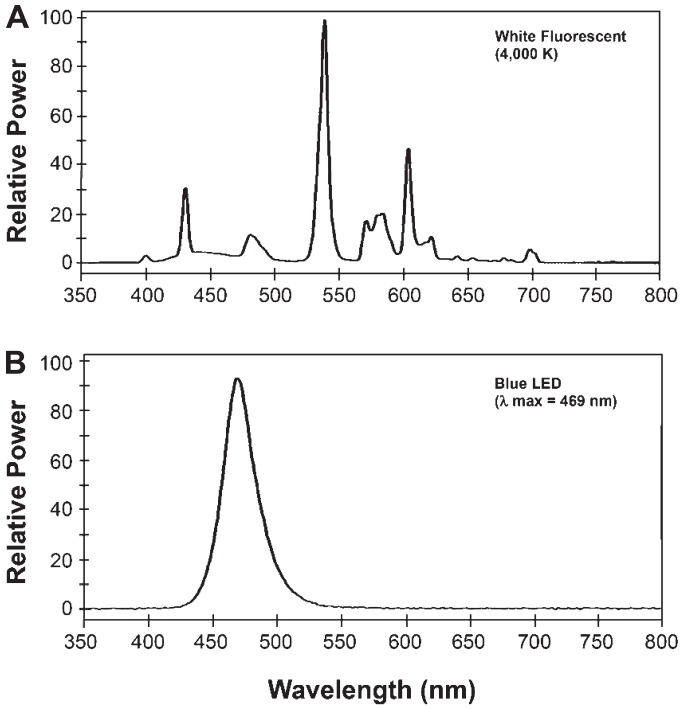

Fig. 1. *A*: spectral power distribution corresponding to the polychromatic white light source. These lamps have a correlated color temperature of 4,000 K. Polychromatic white fluorescent light is generally used for interior illumination, as well as for a prelaunch countermeasure for circadian disruption in astronaut crew quarters. *B*: spectral power distribution taken from one of the blue, narrowband LED panels used in the study. The peak wavelengths of the LEDs varied from 468 to 470 nm.

relatively even distribution of narrow bandwidth blue light (λ_{max} = 469 nm ± 1 nm; ½ peak bandwidth = 26 nm). Typical viewing distance is expected to be 35 cm. The spectral power distribution measurements, shown in Fig. 1, were taken using a model FSHH 325–1075P FieldSpec hand-held spectroradiometer (Analytical Spectral Devices, Boulder, CO). In addition, a broad-spectrum white fluorescent light (4,000 K) was used for one exposure night for each subject. The white fluorescent light was measured 122 × 122 cm and contained Master TL HO Eco 50 lamps (Philips Lighting B.V., Eindhoven, The Netherlands). Irradiance measurements for both lights were taken using an IL-1400BL radiometer/photometer (International Light Technologies, Peabody, MA). This meter had a model SEL033 (no. 3805) detector with input optic W#6874 and filter F#14299, which had been calibrated to measure irradiances between 380 and 1,000 nm. Irradiance output for both types of light panels was adjusted using a rheostat, at times combined with the use of acrylic neutral density filter panels fitted to sit in front of the diffusing panel. Neutral density (ND) filters are dark, but transparent, panels that uniformly reduce the amount of light transmission across the visible spectrum (Lee Filters, Burbank, CA). We used, singly or in combination, 0.3 ND (0.3 optical density; 50% transmittance), 0.6 ND (0.6 OD; 25% transmittance), and 0.9 ND (0.9 OD; 12.5% transmittance) panels. Each lighting unit was placed on a table 76 cm from the floor and supported by hooks built into the wall. Subjects were exposed to the lighting units, while being seated at these tables ~35 cm away from the light. All irradiance measurements were also taken at this distance, at eye level, and facing the light panel. Corneal irradiances and illuminances from both the LED and white fluorescent panels are presented in Table 1 along with mean pupillary diameters and calculated retinal irradiances. Retinal irradiance E_r was calculated using the equation: $E_r = 0.27 \cdot L \cdot \tau \cdot d_e^2$ where L is the calculated source radiance, d_e is pupil diameter, and τ is the transmittance of the ocular media (54).

Statistical methods. Two-tailed paired Student's *t*-tests were used to determine statistical significance of the change in raw melatonin levels from 2:00 to 3:30 AM. Next, change in melatonin levels and percent change were calculated for each subject using the data for subject plasma melatonin levels at 2:00 and 3:30 AM for each study night. The mean and the standard error of the mean were then calculated for each exposure setting. Percent change in melatonin data values were then normalized to percent control-adjusted change scores. This was done by subtracting percent change scores for each subject's control condition (no light exposure) from the percent melatonin change value for each condition for that same subject. This adjusts the plasma melatonin values to account for normal rise in melatonin levels during this time of night (9, 24). Each group of pre-exposure melatonin values was compared with its group of post-exposure values using paired, two-tailed *t*-tests. Pupillary diameters, pre-exposure melatonin values, percent melatonin change values, and percent control-adjusted melatonin change values for all eight subjects were analyzed using one-way, repeated-measures ANOVA and a post hoc Fisher paired least significant difference (PLSD) test, with α set at 0.05. The fluence-response curve for the LED blue light exposures was then calculated and fit using Origin 8.0 (OriginLab, Northhampton, MA). The curve was fit to an unconstrained parametric model in which the melatonin response (Y) to the corneal irradiance (X) is predicted by the following: a theoretical initial Y-response for the curve (A_1); the theoretical final Y-response ("infinite" dose) for the curve (A_2); the dose producing a response halfway between A_1 and A_2 (X_{50}); and the slope estimator for the slope of the curve between A_1 and A_2 (p). These compose the equation:

$$Y = \frac{A_1 - A_2}{1 + (X/X_{50})^p} + A_2$$

The curve was then tested for goodness-of-fit of the data by coefficient of correlation (R^2).

RESULTS

The hazard analysis found that the blue LED panel was safe for 8 h of continuous exposure, even for photosensitive individuals, on the basis of the ACGIH 2007 (2) and ICNIRP 1997 (32) criteria. The radiance measurements did not exceed the long-term limit of 10 mW/(cm^2·sr). A more detailed spectral weighting of the spectral power distribution provides the effective blue-light radiance. Spectral weighting of the spectral power distribution with the $B(\lambda)$ function provided a value of 61.7%, leading to a maximum effective blue-light radiance value of 0.67 mW/(cm^2·sr). Thus, the measured radiance of the

Table 1. *Corneal illuminance, pupil size, and calculated retinal irradiance of light stimuli*

Stimulus	Corneal Irradiance, μW/cm^2	Corneal Illuminance, lux	Mean Pupil Size, mm	Calculated Retinal Irradiance, μW/cm^2
469 nm LED	600	562	2.71	3.39
469 nm LED	300	281	2.76	1.76
469 nm LED	75	70.2	3.70	0.79
469 nm LED	20	18.7	4.04	0.25
469 nm LED	10	9.4	4.31	0.14
469 nm LED	2	1.87	5.18	0.04
469 nm LED	0.5	0.47	5.20	0.01
469 nm LED	0.1	0.09	5.15	0.002
4,000 K fluorescent	40	85.4	4.90	0.75

LED, light-emitting diode.

blue LED panel was less than 7% of the ACGIH and ICNIRP limits.

The National Aeronautics and Space Administration HSIR blue-light hazard evaluation method uses the same calculation method and $B(\lambda)$ weighting function as the ACGIH, but the resulting value is scaled down by 0.2 before comparing it with the ACGIH limit. Because the spectral power distribution of light from the LED panel meets the ACGIH limits, it also meets the less stringent HSIR requirements. Light stimuli characteristics (corneal irradiances and illuminances) are provided in Table 1, along with measured mean pupil sizes and calculated retinal irradiances.

ANOVA demonstrated a significant effect of the different light exposures on pupil diameter ($F = 15.6$, df = 8, $P < 0.0001$). Fisher's PLSD tests showed that pupil diameters were significantly larger when exposed to the lowest (0.1, 0.5, 2.0 $\mu W/cm^2$) LED irradiances vs. higher LED irradiances (10 through 600 $\mu W/cm^2$). Pupil diameters were significantly larger when exposed to intermediate irradiances of 10, 20, and 75 $\mu W/cm^2$ LED light compared with 300 and 600 $\mu W/cm^2$ LED light. Finally, when exposed to 40 $\mu W/cm^2$ of 4,000 K fluorescent light, pupil sizes were not significantly different compared with the lowest LED irradiances of 0.1, 0.5, and 2.0 $\mu W/cm^2$, but were significantly smaller compared with exposures to LED irradiances of 10 through 600 $\mu W/cm^2$.

Coefficient of variation calculated from control samples assayed as 25 pg/ml had 18.6% for intra-assay coefficient of variation. The inter-assay coefficient of variation from the 10 assays run for this experiment was 20.1%. The raw plasma melatonin data for pre-exposure and postlight exposure plasma melatonin levels were analyzed using paired, two-tailed *t*-tests. Figure 2 presents a comparison of the group means (+ SE) premelatonin and postmelatonin values for each study night. The figure shows that blue LED irradiance values at or above 20 $\mu W/cm^2$ significantly suppressed melatonin ($P < 0.05$ to $P < 0.005$). Neither the control condition (0), nor the groups of exposure nights to the lower irradiances of blue LED light (0.1, 0.5, 2, and 10 $\mu W/cm^2$) elicited a statistically significant change in plasma melatonin levels. Similarly, the 40 $\mu W/cm^2$ irradiance from the 4,000 K fluorescent light exposure did not significantly suppress melatonin ($P = 0.22$).

ANOVA demonstrated that there were no significant differences between mean pre-exposure melatonin values for each study night ($F = 1.1$, df = 9, $P = 0.38$). Mean percent changes in melatonin values exhibited increased suppression concurrent with increased irradiance of blue LED light. ANOVA indicated that the effect of the light irradiance on percent change scores was significant ($F = 10.7$, df = 9, $P < 0.0001$). Fisher's PLSD tests detected a significant difference between percent change in melatonin values for the control night and LED exposures at or above 10 $\mu W/cm^2$ of blue-appearing LED light. The 4,000 K exposure also elicited a stronger suppression compared with control. The mean percent change value for the 4,000 K fluorescent exposure is numerically similar to the mean 10 $\mu W/cm^2$ LED exposure value.

Percent control-adjusted melatonin change scores are presented in Fig. 3. ANOVA showed that there was a significant effect of light irradiance on melatonin suppression ($F = 9.4$, df = 8, $P < 0.0001$). Increasing irradiances of blue LED light exposure evoked progressively larger melatonin suppressions. Specifically, Fisher's PLSD tests showed that the higher corneal irradiances of blue LED light (600, 300, and 75 $\mu W/cm^2$) elicited a significantly stronger melatonin suppression than the lower irradiances (10, 2, 0.5, and 0.1 $\mu W/cm^2$). The corneal irradiance 20 $\mu W/cm^2$ of blue LED light elicited a significantly stronger melatonin suppression than the lower irradiances (2, 0.5, and 0.1 $\mu W/cm^2$), and 10 $\mu W/cm^2$ elicited a significantly stronger melatonin suppression than the lowest irradiance of 0.1 $\mu W/cm^2$. Finally, when exposed to 40 $\mu W/cm^2$ of 4,000 K fluorescent light, melatonin suppression was significantly less compared with the higher irradiances of 300 and 600 $\mu W/cm^2$ of blue LED light, significantly higher compared with the lowest blue LED irradiance of 0.1 $\mu W/cm^2$, and was not significantly different compared with the LED irradiances of 0.5 through 75 $\mu W/cm^2$.

Figure 4 illustrates a best-fit, sigmoidal fluence-response curve, which plots the melatonin percent control-adjusted

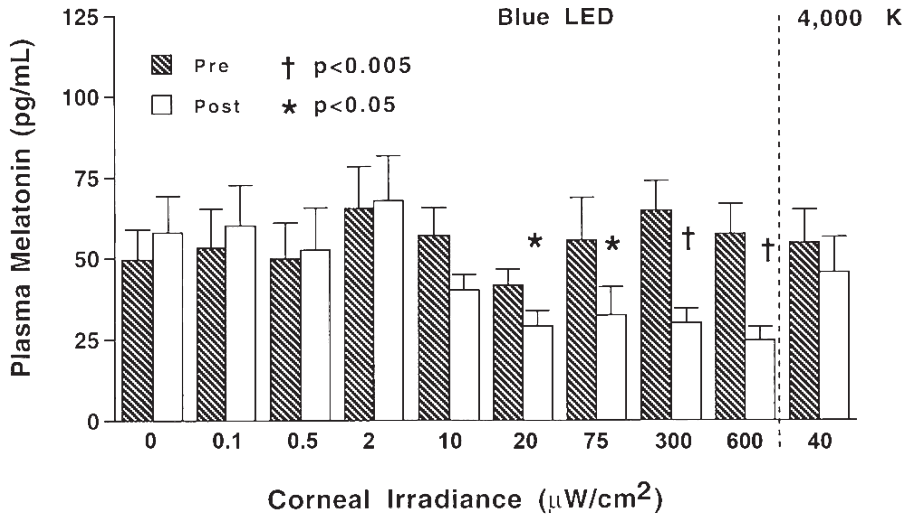

Fig. 2. In this graph, the bars represent group means + SE plasma melatonin values ($n = 8$) before and after eight irradiances on a blue LED panel, light exposure at 40 $\mu W/cm^2$ from a white fluorescent 4,000 K lamp and the control night (0 $\mu W/cm^2$). There were no significant variations across mean melatonin pre-exposure values ($F = 1.1$, df = 9, $P = 0.38$). Paired, two-tailed *t*-tests indicated which conditions elicited statistically significant melatonin suppression.

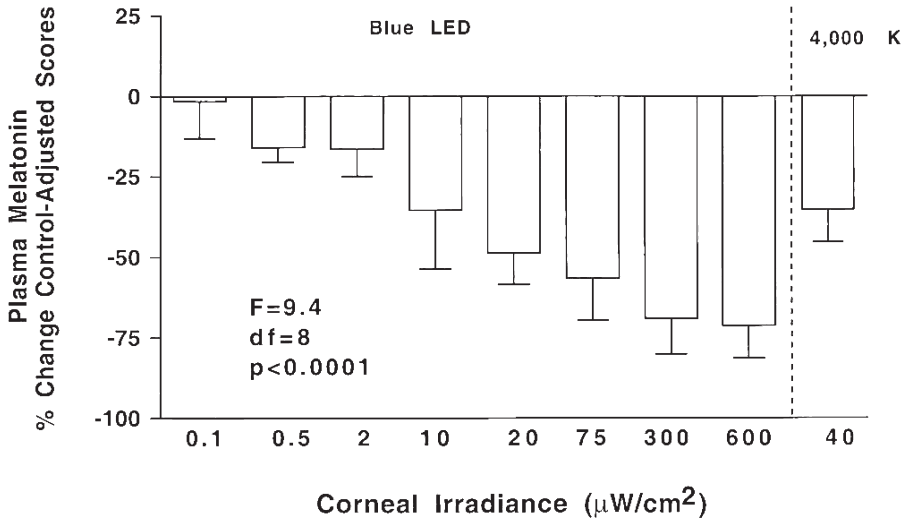

Fig. 3. This graph represents group means − SE percent control-adjusted melatonin change scores ($n = 8$) for control and eight irradiances on a narrow bandwidth blue LED panel, as well as the 40 μW/cm^2 with exposure to a fluorescent white 4,000 K lamp. Increases in the light irradiance produced an increased suppression of melatonin levels, compared with control melatonin values. The graph also demonstrates the mean percent change for a 40 μW/cm^2 exposure with a 4,000 K lamp is numerically very similar to suppression at 10 μW/cm^2 on the blue LED panel.

scores against corneal irradiance values for the blue LED panel. The curve is a best-fit line that follows the equation:

$$Y = \frac{(5.76 - 76.36)}{1 + (X/14.19)^{0.68}} + 76.36$$

DISCUSSION

The composite data from eight subjects exposed to eight irradiances of narrowband blue LED light demonstrated increased melatonin suppression with increased exposure irradiance. Those data have a strong fit to a sigmoidal fluence-response curve. A comparison of mean melatonin suppression with 40 μW/cm^2 from 4,000 K broadband white fluorescent light, currently used in most general lighting fixtures, suggests that narrow bandwidth blue LED light may be stronger than 4,000 K white fluorescent light for suppressing melatonin.

An initial action spectrum study on mice first identified peak sensitivity to light for circadian regulation in the short-wavelength portion of the spectrum, specifically at 480 nm (60). Later action spectra studies demonstrated that the blue-appearing portion (446–477 nm) was the most effective region of the spectrum for suppression of melatonin secretion from the pineal gland in humans (10, 57). Recent analytic action spectra have examined neuroendocrine, circadian, and neurobehavioral responses in humans, monkeys, and rodents. Specifically, all of those action spectra fit the data to opsin nomograms with relatively high coefficients of correlation. The action spectra predominantly indicate shorter-wavelength peak sensitivities in the blue-appearing region of the visible spectrum with calculated peak photosensitivities ranging from 459 nm to 484 nm (for review, see Ref. 8, 26, 61). The 469-nm blue LED used in this study was selected because its peak emission was in the

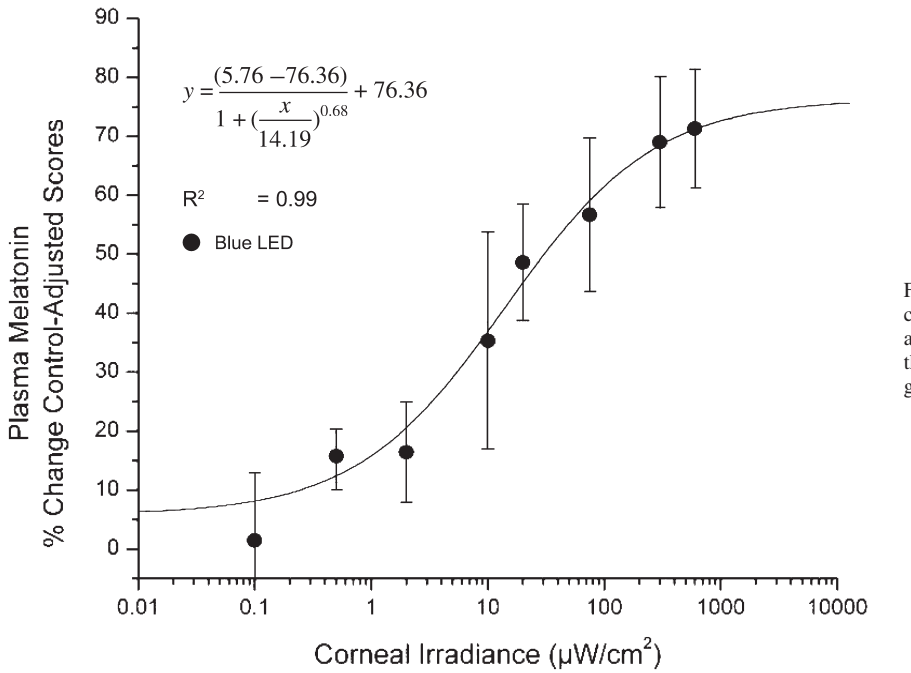

Fig. 4. This figure presents the fitted fluence-response curve for the plasma melatonin percent change control-adjusted scores ($n = 8$) relative to corneal irradiances on the blue LED lamp. Each data point represents one group mean ± SE.

range of the peak responsiveness for neurobehavioral regulation. It is important to note, however, that the light emitted from the blue LEDs had a half-maximum bandwidth of 26 nm. As with the emissions from most of the currently available narrow bandwidth LEDs, this stimulus is polychromatic. Hence, although the great majority of the emissions are in the spectral bandwidth (485–465 nm) that has the color appearance of blue, when considering the full bandwidth, the short- and long-wavelength emissions of this LED extend slightly into the spectral bandwidths (465–440 nm and 485–530 nm) that have a color appearance of indigo and green, respectively. In contrast, analytic action spectra are based on exposures to monochromatic light with half-maximum bandwidths of 15 nm or less (14, 30).

A limitation to this study is that the eight subjects were only exposed to white fluorescent light at 4,000 K at one irradiance compared with blue LED exposures at a full range of low to high intensities. The comparison remains useful, however, since a within-subjects study design was employed. As shown in Fig. 2, it is notable that 20 $\mu W/cm^2$ of the short-wavelength LED light elicited a significant melatonin suppression, whereas double the energy from the 4,000 K panel (40 $\mu W/cm^2$) did not evoke a significant melatonin suppression. As part of a more extensive project, a full fluence-response curve has been completed with a separate cohort of eight healthy subjects exposed to nine irradiances of 4,000 K white fluorescent light and a dark control exposure night (G. C. Brainard et al., unpublished data). Those preliminary data indicate an ED_{50} of ~94 $\mu W/cm^2$ (11). By comparison to the ED_{50} of 14.19 $\mu W/cm^2$ for the blue LEDs, narrow bandwidth blue light appears to be stronger than polychromatic 4,000 K white fluorescent light for melatonin suppression in healthy men and women.

There are a number of ways to predict the relative efficacy of a particular light stimulus in terms of its relative circadian, neuroendocrine, and neurobehavioral efficacy. For example, the opsin nomogram from the human melatonin suppression action spectrum (λ_{max} = 464 nm) predicts that the 469 nm blue LED stimulus would be significantly stronger than the 4,000 K fluorescent lamp stimulus for melatonin suppression (10). Similarly, a non-opsin model for "circadian photoreception photosensitivity" (λ_{max} = 480 nm) predicts that the 469-nm blue LED stimulus would be significantly stronger than the 4,000 K fluorescent lamp stimulus for melatonin suppression (46). These predictions match the data presented in this manuscript. Caution must be exercised, however, in relying on these and other models of circadian phototransduction (20, 25, 48). Ultimately, a functional mathematical model will evolve that is based on more extensive scientific background than currently available to the research community. Such a model will be codified by national and international consensus, as has been the case for the photopic (λ_{max} = 555 nm) and scotopic (λ_{max} = 507 nm) visual functions (47). Meanwhile, empirical verification of specific light stimuli will remain the most accurate way to determine the potency of light sources.

The discovery of the ipRGCs is relatively recent, and their detailed anatomy, physiology, photochemistry, and neural integration with the classical visual photoreceptor systems is still emergent. It is uncertain, for example, whether this photoreceptor system detects and transduces monochromatic and polychromatic light stimuli in an equivalent fashion for circadian, neuroendocrine, and neurobehavioral regulation. Using immunohistochemistry, Berson et al. (6) have elegantly described murine ipRGC anatomy and have identified two main types of melanopsin-containing RGCs (M1 and M2), which have differing locations, dendritic processes, and cell bodies. The relative insensitivity of ipRGCs to lower levels of light intensity suggests that classical photoreceptors must provide input to the ipRGCs (40). In fact, it is clear from studies on genetically manipulated rodents (1, 34), normal monkeys (18), and humans (28), that the visual rod and cone photoreceptors integrate into this physiology. Cellular recording studies from nonhuman primate retinas have demonstrated that rod and cone cells can directly activate ipRGCs (18). Using mice where cone or rod photoreceptors were destroyed, Altimus et al. (1) found that rods operated in two distinct retinal circuits to provide circadian photoentrainment over an extensive range of light intensities (1). Using mice in which human red cone opsin was expressed, Lall et al. (34) showed that rods drive circadian responses at very low irradiances, and some circadian responses can be rod driven at even higher light intensities. In humans, interestingly, cones appear to contribute substantially to circadian phase-shifting at lower intensities and at the initiation of light exposure (28). The relative contribution of the three classical retinal photoreceptors in detecting and transducing light stimuli for circadian, neuroendocrine, and neurobehavioral regulation remains an area of intense research.

In general, the spectral power distributions are very different between broad and narrow bandwidth LED and fluorescent light sources. Several other studies have compared the efficacy of light emitted from LEDs vs. fluorescent lamps for neuroendocrine, circadian, and neurobehavioral regulation. An early study with rats found no significant differences in melatonin suppression between broad-spectrum white LEDs and cool white fluorescent lamps across five different illuminances (29). A human study compared 2,000 lux light emitted by broad-spectrum white LEDs, blue/green LEDs, and white fluorescent lamps. The results showed no significant differences between light from white LEDs and light from white fluorescent lamps for acute melatonin suppression and phase delay of the melatonin rhythm, but broad-spectrum blue/green light appeared to have a stronger effect than both white light sources (58). In a follow up to that finding, it was shown that 65 $\mu W/cm^2$ of narrow-bandwidth LED light with peaks at 470, 495, and 525 nm could phase advance human circadian rhythms, but longer-wavelength peaks of LED light at 595 and 660 nm had no effect at this same irradiance (59). A different study with healthy human subjects showed that narrow bandwidth blue LED exposure was stronger than clear mercury vapor lamps for melatonin suppression (22). Further, an experiment with seven subjects tested with four illuminances of narrow bandwidth blue LED light peaking at 470 nm showed that increased illuminances evoked increased acute alertness in volunteers in both objective and subjective assessments (23). Finally, a study on 12 young male subjects suggests that a short exposure to illuminances of 0.22 and 1.25 lux of indirect light from 465 nm blue LEDs (25 nm half-peak bandwidth) did not suppress salivary melatonin (35). This emergent literature on the biological and behavioral efficacy of light emitted by LED sources has led to clinical trials showing the effectiveness of LED light as a therapeutic stimulus for treating jet lag and winter depression (4, 7, 27, 19, 56).

Currently, NASA's space vehicles and ground control facilities are illuminated by white fluorescent lighting. White LED lighting fixtures are being developed at this time for the CEV, which will replace the Space Shuttle, as well as for the vehicles and habitats being developed for lunar exploration. In addition, the ISS may be retrofitted with white broad-spectrum LED arrays. These new lighting technologies are principally intended to provide proper visual illumination for NASA astronauts to navigate their environment and accomplish their work. There is interest, however, in the strategic use of light as a nonpharmacological stimulus to help overcome the sleep and circadian disruption that some astronauts experience during space flight as documented in NASA's *Bioastronautics Roadmap* (39) and *Human Research Program Integrated Research Plan* 2009 (44). The neuroendocrine data reported here provide an important step toward the development of an in-flight LED lighting countermeasure for space exploration. Additional work is needed to quantify the circadian and neurobehavioral efficacy of both narrow and broad-bandwidth LED lighting in humans and specific luminaire configurations that may be effective for space flight applications. Elimination of competing light sources and maximization of light source exposure were primary goals in designing this experiment to quantify the neuroendocrine potency of the stimuli. During spaceflight or in everyday settings on Earth, however, full visual field exposures would not be replicated to such a high degree, and other ambient white light sources, such as overhead fluorescent or incandescent task lighting might be present simultaneously if a narrow bandwidth stimulus was being used to shift circadian rhythms or evoke acute alerting responses.

As with lighting applications for space exploration, the transition from fluorescent lamps to LED illumination sources also has advantages for domestic applications (53). Compared with current fluorescent and incandescent luminaries, LED lighting tends to be more durable, compact, versatile, and energy-efficient (5). It is estimated that if light usage does not change, solid-state lighting could cut electricity use in half, as LEDs only consume one-tenth of the power that is used by incandescent lighting (53). Currently, domestic use of broad-spectrum, white LED lighting is principally being considered for the traditional values of architectural lighting, providing illumination that *1*) is optimum for visual performance; *2*) is visually comfortable; *3*) permits aesthetic appreciation of the space; and *4*) conserves energy (47). Extensive biomedical research, however, demonstrates that light can have potent biological and behavioral effects on humans (15, 31). The data presented here show that such effects can be quantified for a narrow-bandwidth LED light source and compared with a conventional fluorescent light source. Such findings may open the door to new lighting designs that are optimum for humans in terms of visual stimulation, physiological health, and ecological impact.

ACKNOWLEDGMENTS

We are grateful for the generosity of Apollo Health, part of Philips Home Healthcare Solutions, for providing LED units for the purposes of this study and for the extensive support of Kent Savage and technical assistance and support of Scott Wheelhouse and his associates. We are also grateful to Philips Lighting, B.V. for providing the white fluorescent light system. We would also like to note that, after completion of the blue-light hazard analysis, Dr. David H. Sliney retired from his position at the U.S. Army Environmental Hygiene Agency. In addition, we would like to thank Bill Coyle, Karen White, Tyisha Vincent, Marianne Hamel, Kymberlee Milligan, Jessica Treadway, Ben Leiby, Alan Kubey, and Sylvia Holley for invaluable assistance in completing this research. A presentation at the 2008 NASA Human Research Program Investigators' Workshop showed some of the preliminary data from the full study provided in this manuscript.

GRANTS

This work is supported by the National Space Biomedical Research Institute through NASA NCC 9–58.

DISCLOSURES

Unrelated to the work presented in this manuscript, coauthor Dr. George Brainard is funded by the OSRAM-Sylvania Corporation and the Panasonic Corporation for other research projects. Additionally, he is coinventor on an issued patent "Photoreceptor System for Melatonin Regulation and Phototherapy" USPTO #09/853,428, and a pending patent "Method for Modifying or Resetting the Circadian Cycle Using Short-Wavelength Light" World PCT 2005/004948AZ. No companies have licensed either patent.

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