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Blocking Low-Wavelength Light Prevents Nocturnal Melatonin Suppression with No Adverse Effect on Performance during Simulated Shift Work

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Decreases in melatonin production in human and animals are known to be caused by environmental lighting, especially short-wavelength lighting (between 470 and 525 nm). We investigated the novel hypothesis that the use of goggles with selective exclusion of all wavelengths less than 530 nm could prevent the suppression of melatonin in bright-light conditions during a simulated shift-work experiment. Salivary melatonin levels were measured under dim (<5 lux), bright (800 lux), and filtered (800 lux) light at hourly intervals between 2000 and 0800 h in 11 healthy young males and eight females (mean age, 24.7 ± 4.6 yr). The measurements were performed during three nonconsecutive nights over a 2-wk period. Subjective sleepiness was measured by self-report scales, whereas objective performance was assessed with the Continuous Performance Test. All subjects demonstrated preserved melatonin levels in filtered light similar to their dim-light secretion profile. Unfiltered bright light drastically suppressed melatonin production. Normalization of endogenous melatonin production while wearing goggles did not impair measures of performance, subjective sleepiness, or alertness. (*J Clin Endocrinol Metab* 90: 2755–2761, 2005)

MELATONIN, *N*-ACETYL-5-METHOXYTRYPTAMINE, is a neurohormone secreted by the mammalian pineal gland that synchronizes circadian rhythms in many vertebrates, including humans. This synthesis occurs in a diurnal pattern with its output peaking during the dark phase of the geophysical light-dark cycle. The light-dark cycle is the prominent Zeitgeber of the regulation of circadian timing system: in the presence of light, the output from the retino-hypothalamic tract inhibits the melatonin synthesis, whereas darkness stimulates it (1).

The melatonin rhythm is generated by an endogenous pacemaker located in the anterior hypothalamic suprachiasmatic nuclei. In humans, the circadian rhythm for the release of melatonin is closely synchronized with the habitual hours of sleep. Melatonin secretion increases soon after the onset of darkness, peaks in the middle of the night (between 0200 and 0400 h) and gradually falls during the second half of the night. However, the melatonin rhythm can be acutely interrupted by exposure to light (1, 2). Light exposure in the early subjective night delays the timing of the circadian clock, whereas light exposure in the late subjective night advances the timing of the clock. Exposure to light at either time suppresses melatonin secretion (3, 4). This suppression of melatonin production is common among shift workers who spend nighttime hours under artificial environmental lighting (5). Substantial research evidence is emerging to implicate potential long-term consequences of shift work-associated risk factors including cardiovascular disease, gastrointestinal disorders, and mood disorders and their associated morbidity and mortality (6–9).

Although it is beyond the scope of this study, the scientific literature suggests that shift workers may be at increased risk of developing various forms of cancer due to repetitive exposure to light at night. Recent studies have pointed to a link between night shift work and light-induced suppression of nocturnal melatonin with an increased risk of breast and colorectal cancers (10–12). These studies implicate the disruption of the normal melatonin rhythm as a causative factor for the higher malignancy rates in shift workers. However, some investigators deem this association in humans to be controversial and requiring prospective studies to further explore the relationship (13).

Animal studies have shown compelling evidence that constant exposure to light significantly promotes transplacental carcinogenesis (14). Furthermore, melatonin has been shown to be a free-radical scavenger and antioxidant, and conditions that involve free-radical damage may be aggravated by light-mediated suppression of melatonin levels (15).

Light of various wavelengths has been shown to have differential effect on melatonin output. Light of relatively short wavelength, between 470 and 525 nm, elicits a significant suppression of nocturnal melatonin (2, 16, 17). Therefore, blocking light of low wavelengths in bright-light conditions may prevent the suppression of melatonin. For this purpose, we have designed and purchased optical filter lenses (Offenhaueser+Berger, GmbH, Heidenheim, Ger-

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Abbreviations: CPT, Continuous Performance Test; CT, circadian time; DLMO, dim-light melatonin onset.

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many) allowing selective exclusion of all wavelengths less than 530 nm while maintaining relatively good color recognition and visual light transmittance of approximately 73%. We hypothesized that wearing of such light-filtering lenses could prevent the suppression of melatonin during night work in bright light.

Theoretically, preserving normal nocturnal levels of endogenous melatonin may reduce alertness; consequently, job performance might be affected if melatonin is secreted normally during the working period. Therefore, we have evaluated the effect of eliminating low-wavelength (<530 nm) light on several behavioral parameters. These included testing of subjective sleepiness, alertness, and fatigue as well as objective measures of performance [Continuous Performance Test (CPT)] (18).

Subjects and Methods

Experimental subjects

The study was conducted over 2 months during the summer and involved a total of 42 potential subjects who were screened for normal sleep patterns. All subjects initially underwent psychiatric and sleep assessments to rule out significant psychopathology and sleep disturbance. All subjects scored less than 7 on the Epworth Sleepiness Scale (19) and scored in the normal range on the Morningness-Eveningness questionnaire (20), a subjective measure of their circadian rhythm. Subjects were excluded if they had a history of sleep and circadian rhythm disorders, excessive daytime sleepiness, eye disease, depression, psychotic illness, a history of cancer, or shift work in the past year. After screening, 19 healthy subjects were selected for the study (11 males and eight females with mean age of 24.7 ± 4.6 yr). The relatively high number of screen failures was due to aberrant sleep-wake cycle related either to poor sleep hygiene or increased prevalence of Delayed Sleep Phase Syndrome symptoms, which are frequently seen in younger age groups (21).

To avoid the confounding effects of menstrual cycle phase on alertness, cognitive performance, and melatonin (22, 23), only those females who were using oral contraceptives were recruited. Additionally, they were matched for the day of the menstrual cycle.

The study protocol was approved by the Human Ethics Committee of the University Health Network, and written informed consent was obtained from all participants after the nature and possible consequences of the study were explained.

Methodology

Self-recorded sleep diaries were kept by the subjects at home during the 2-wk period before baseline laboratory parameters were measured. The diaries showed a mean lights-out time of 2300 h ± 45.0 min (number of hours and minutes). Subjective sleep onset latency was 18.5 ± 11.8 min. The mean subjective sleep offset time was at 0730 h ± 32.5 min. Before each study night, subjects completed a previous night sleep inventory to ensure adequate sleep quality and normal sleep duration (24). Subjects who reported poor sleep quality were excluded from the study participation.

During the study, all subjects were asked to stay awake overnight at the Sleep Research Clinic for three nonconsecutive nights over a 2-wk period. On the first night, melatonin production measured in saliva under dim-light (<5 lux) conditions established each individual's circadian profile of melatonin secretion, unaffected by light exposure. Previous research has supported high validity of saliva specimens, which provide a noninvasive and practical method for melatonin assessment (25).

The dim-light melatonin onset (DLMO) test was used as a marker of circadian phase (26) and was the time of the first saliva melatonin level to cross the DLMO threshold. The threshold was defined as the first 20% increase in melatonin concentration above 4 pg/ml (27, 28).

On all nights, we collected 13 saliva samples at regular 1-h intervals beginning at 2000 h. On the second and third nights, subjects were placed in a well-lit room (800 lux) designed to mimic a shift-work environment. The exact luminescence of the rooms was determined using a luxmeter (HD 8366 Light Level Measurement Instrument digital luxmeter; Hotek Technologies, Tacoma, WA). Saliva specimens were collected using the Sali-Saver (American Laboratory Products Company, Windham, NH). The Sali-Saver consists of a small cotton roll that is placed between the cheek and the gum for 3–5 min to collect a saliva specimen (up to 2 ml can be collected at a time). Saliva specimens were analyzed immediately after collection of the last sample. Saliva melatonin was determined by a Direct Saliva Melatonin ELISA kit from Buhlman Laboratories (Allschwil, Switzerland). Aliquots of at least 200 μl of centrifuged saliva from each collection time were used for the analysis. Saliva specimens from a given subject were run with the same assay kit; all kits used in this study were from the same lot. Quality control was assessed by using a low and high melatonin standard included in the kit. Assay functional sensitivity was 1.3 pg/ml, and the maximum intra- and interassay coefficients of variability were 6.5% (n = 12) and 11.3% (n =1 2), respectively (in the range of concentrations of melatonin between 1 and 81 pg/ml).

Subjects were asked to wear the low-wavelength-restricting goggles beginning on the second or third night of testing. The optical filter lenses, which were designed by our team, allowed selective exclusion of all wavelengths less than 530 nm while maintaining relatively good color recognition and a visual light transmittance of approximately 73% (Fig. 1).

The subjects spent 12 h awake, from 2000–0800 h, in the sleep laboratory while hourly data were collected. The results of the DLMO testing provided a baseline for comparison of melatonin levels during the other interventions. The subjects were randomly assigned to wear the optical filter lenses incorporated into goggles on either the second or third night. On the alternate night, the subjects were exposed to the bright light (800 lux) without wearing goggles. Due to individual variability in DLMO and acute phase shifting effects of light on melatonin secretion profiles, we converted clock time to circadian time (CT). For this purpose, we referenced the beginning of melatonin production by designating the baseline DLMO as CT 14 (29). This technique allowed us to compare the hormonal status of each individual at the same CT in three different conditions. Moreover, we assumed that darkness is an ideal environment for maximum melatonin production; therefore, we used relative values of melatonin in light conditions (with or without goggles) compared with designated 100% production in the dark. Another reason to use relative values was the large interindividual variability in absolute melatonin levels because it is well recognized that there are low and high melatonin secretors (30).

On both the second and third nights, subjects completed the Stanford Sleepiness Scale (31), Fatigue Severity Scale (32), and the Alertness Visual Analog Scale at 2-h intervals throughout the night. Testing was carried out while the subjects were exposed to the bright light while either wearing or not wearing light-filtering goggles. Concurrently with

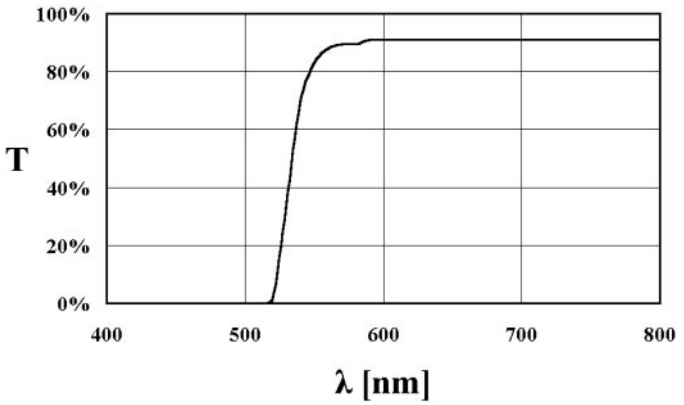

FIG. 1. Optical filter lenses. Technical characteristics: edge at ± 530 nm; all wavelengths shorter than 530 nm are filtered out; approximately 8% of wavelengths longer than 530 nm are filtered out; visual transmittance of approximately 73%; lenses appear yellow; good color recognition except for green.

the questionnaires, the CPT testing was administered (18). The CPT, which is a widely used test of performance measures, included errors of omission (*i.e.* failing to respond to target) and commission (responding to target inappropriately) along with the subjects' reaction time.

Data analysis

Differences between melatonin levels when the participants were wearing goggles and when they were exposed to bright light were tested using a multivariate split-plot ANOVA for the factors: CT (pre-DLMO/CT14/CT15/CT16/CT17/CT18/ CT19/CT20), condition (bright light/goggles), and gender. The same statistical model was applied to investigate differences between subjective measures of sleepiness, fatigue, alertness, and the continuous performance tasks measures. Statistically significant results detected by the multivariate ANOVA ($P < 0.05$) were further analyzed by using Bonferroni *post hoc* paired comparisons using the Statistical Package for the Social Sciences (SPSS version 11.5 for Windows; SPSS Inc., Chicago, IL).

Results

The study results showed that all subjects wearing the optical filter goggles exhibited a melatonin secretion profile similar to their dim-light pattern throughout the night. In contrast, bright light drastically suppressed melatonin production. Exposure to both bright and filtered light caused a phase delay in endogenous melatonin secretion, although wearing the optical filter goggles induced a less pronounced shift. The phase delay between the dim- and bright-light conditions was statistically significant ($P < 0.05$); however, delay between dim and filtered light was not statistically significant ($P > 0.05$). Figures 2 and 3 display characteristic effects of bright and filtered light on endogenous melatonin secretion in male and female subjects.

Conversion of the clock time into CT predictably reduced samples available for analysis (from 13 to eight): pre-DLMO baselines and CT14–CT20 melatonin levels. Summary of the analysis of melatonin values is presented in Table 1.

Suppression of melatonin levels did not occur at any of the data collection points (except at pre-DLMO) when the optical filter lenses blocking light of wavelengths less than 530 nm were worn. Table 2 summarizes the differences in endogenous melatonin levels at different times in subjects exposed to full-spectrum bright light directly or while being shielded from low-wavelength light.

Figure 4 illustrates relative values of melatonin secretion during dim light, exposure to bright light, and exposure to light protected by the optical filters for the entire group.

Contrary to our expectations, enhancement of endogenous melatonin production while wearing light-filtering goggles did not impair performance parameters and had no detectable effects on subjective sleepiness, alertness, or fatigue. There were no significant differences in performance on the CPT or in subjective scores between the two nights under different conditions (bright light/goggles). The Stanford Sleepiness Scale showed a normal circadian variation, with the sleepiest time between 0600 and 0800 h during both the filtered and normal lighting conditions ($F = 37.7$, $P = 0.0001$, df = 2.7; $F = 44.8$, $P = 0.0001$, df = 3.3, respectively). The same pattern was observed on the Fatigue Severity Scale in both conditions ($F = 38.3$, $P = 0.0001$, df = 2.7; $F = 43.7$, $P = 0.0001$, df = 3.4, respectively). The Alertness Visual Analog Scale had similar circadian profiles on both nights as well. The worst level of alertness was observed in the same time

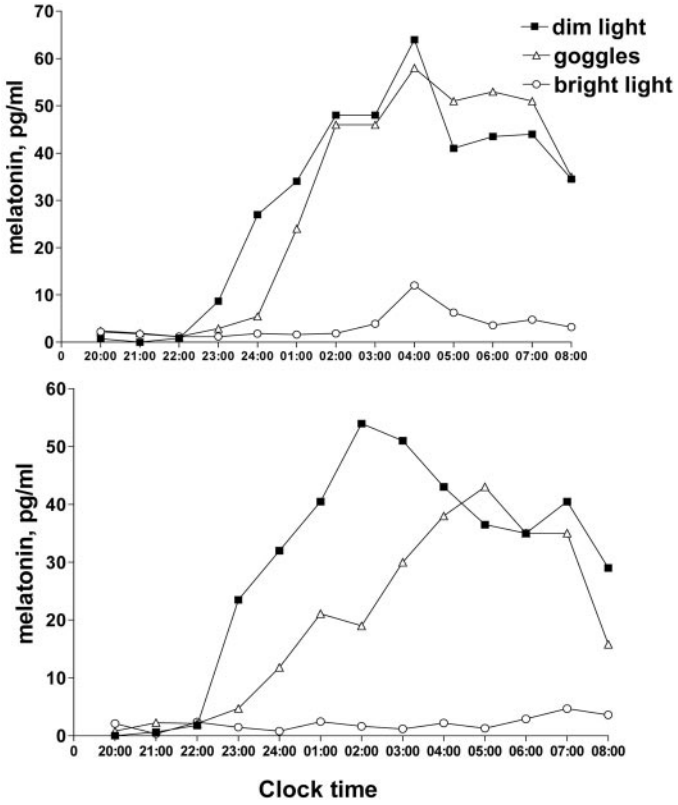

FIG. 2. Typical melatonin secretion profiles in two males exposed to dim-light, filtered, and bright-light conditions. The results under the dim-light condition represent normal melatonin production. Subjects demonstrated preserved melatonin secretion in filtered light similar to the profile obtained in dim light, although there was a noticeable phase delay under both light conditions.

interval on both nights ($F = 30.8$, $P = 0.0001$, df = 2.9; $F = 47.4$, $P = 0.0001$, df = 3.8, respectively). Interestingly, none of the CPT parameters revealed significant circadian variations throughout both nights, except for reaction time slowing toward the morning hours under filtered light ($F = 4.3$, $P < 0.01$, df = 2.6). However, reaction time did not significantly differ at any time interval between the two conditions. No gender differences were detected in any of the subjective scores or performance parameters between the two conditions.

Discussion

Our data strongly suggest that wearing the light-filtering goggles, which block wavelengths of less than 530 nm, results in close to normal melatonin onset and peak secretion in subjects during nighttime exposure to bright light. These findings complement numerous studies showing that exposure to short wavelengths in the interval 470–525 nm has the most robust melatonin suppression effects (2, 16, 17). The significant phase delay between dim- and bright-light conditions is also congruent with previous findings (2–4).

Implementing filters to eliminate the most energetic part of the visible spectrum appears to be a simple and elegant way to preserve normal levels of melatonin at night. One concern in the strategy of attempting to preserve normal nocturnal levels of melatonin is that the enhancement of

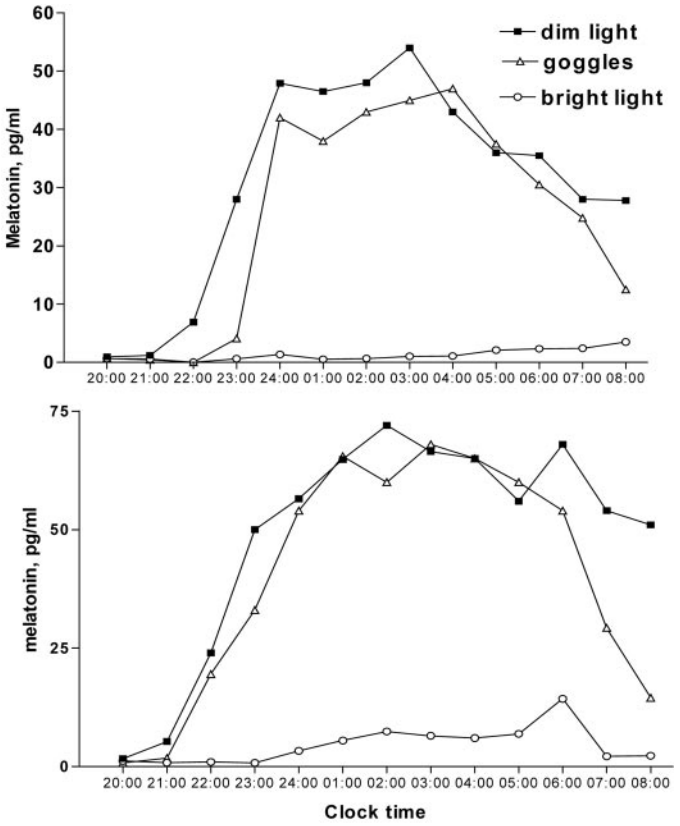

FIG. 3. Typical melatonin secretion profiles in two females exposed to dim-light, filtered, and bright-light conditions. Subjects demonstrated preserved melatonin secretion in filtered light similar to the profile obtained in dim light. Labels are the same as in Fig. 2.

melatonin production may increase the risks of on-the-job sleepiness, chronic fatigue, decreased alertness, and impaired job performance in night-shift workers. The consequences of these risks, apart from a reduction in productivity, are a distinct threat to workplace safety. It is well known that shift work is associated with a greater rate of accidents compared with those seen in daytime workers (33–35).

Our performance data (CPT) have demonstrated that the blocking of short-wavelength light does not interfere with attention span, concentration, or response accuracy. This evidence does not support the widely held view that melatonin is exclusively a sleep-promoting agent because our goggles helped maintain normal melatonin levels, and yet subjects showed no evidence of reduced performance. Melatonin is in fact a robust chronobiotic that primarily impacts the body's endogenous clock with phase-shifting properties (shifts all body cycles, not only sleep), although it does possess very mild and transient hypnotic properties. Consistent with this view is evidence from a recent study (36) that exogenous melatonin (6 mg) does not impair serial reaction time, logical reasoning, serial subtraction, or complex neuromotor functions (attention, reaction time, motor coordination). Thus, these findings suggest that strategies designed to preserve normal melatonin secretion produce few, if any, impairments in neurobehavioral functions and are unlikely to negatively affect on the job performance. In contrast, there is research evidence to support the hypothesis that shift work-related fatigue, sleepiness, and performance decrements occur as a result of failure to achieve adequate restorative sleep, in turn caused by a quantitative and qualitative sleep deficit and/or circadian rhythm sleep disorders (35, 37, 38). The cumulative effects of acute and chronic sleep deprivation are compounded by the misalignment of a person's desired sleep-wake schedule and circadian rhythm that leads to difficulty with sleep initiation or maintenance (39) during the daytime sleep period. A recent study reported that persistent sleep restriction leads to cumulative additional wakefulness beyond stable neurobehavioral functioning and results in cognitive performance deficits (40). Furthermore, accidents on the drive home after the night shift constitute a major risk for shift-worker safety (41, 42).

TABLE 1. Summary of multivariate ANOVA for melatonin levels by CT, condition, and gender (n = 19)

Effect	df	F	*P*
Gender (G)	1	0.16	0.70
S × Error within groups	17	(8642.63)	
Within subjects			
Condition (C)	1	44.12	<0.0005
C × G	1	0.27	0.61
S × error (C)	17	(6303.26)	
CT	7	1.30	0.10
CT × G	7	1.39	0.22
S × error (CT)	119	(2589.46)	
C × CT	7	1.59	0.15
C × CT × G	7	0.94	0.48
S × error (C × CT)	119	(2533.46)	

Values in *parentheses* represent mean square errors. *S*, Subjects. No gender differences were observed in melatonin production at any point of data collection.

One may argue that alterations in the melatonin rhythm with shift work may have an adaptive function, *i.e.* suppression of melatonin at night, and a subsequent rise in the daytime sleep period may be conducive to daytime sleep. However, shift workers, even those working permanent night duty, do not develop a consistently delayed pattern of melatonin secretion and other circadian rhythms (43), and complete circadian phase adjustment to night work is almost never found (44). Shift workers tend to return to night sleep and daytime activities on their days off in response to family and social obligations. Moreover, a significant proportion of shift workers have a chronic suppression of melatonin with a flattened distribution and no discernible rhythm of peaks and nadirs (45).

Light-filtering goggles, apart from maintaining the physiological rise in melatonin at night, have the potential for improving daytime sleep. Shift workers on their way home in the early morning are exposed to daylight, which is the most powerful Zeitgeiber, producing high levels of daytime alertness and preventing shift workers from obtaining the proper amount of sleep during the day (usually no more than 4–5 h of poor-quality sleep). Some studies (46, 47) have shown that dark goggles worn on the way home after a nighttime work shift prevent the body from going into an alertness phase, producing better subjective daytime sleep, less subjective fatigue, and better mood. However, dark goggles are not a feasible option due to safety issues of wearing such goggles while driving. The light-filtering goggles de-

TABLE 2. Summary of differences of relative melatonin levels between conditions at CT points (n = 19)

CT	Condition				*t*	*P*
	Goggles		Bright light			
	M	SD	M	SD		
Pre-DLMO	77.70	55.98	44.33	33.62	1.58	0.14
CT14	105.91	42.61	32.12	26.99	2.54	0.02
CT15	96.11	35.32	20.75	15.65	5.49	<0.0005
CT16	79.34	20.60	21.23	18.20	8.30	<0.0005
CT17	83.11	29.49	23.34	20.68	6.29	<0.0005
CT18	105.29	36.92	26.29	23.75	6.70	<0.0005
CT19	83.88	21.32	26.24	24.12	7.08	<0.0005
CT20	91.48	26.80	29.18	29.85	5.33	<0.0005

Post hoc Bonferroni *t* tests adjusting the type J error rate for the number of tests performed.

signed for the present study preserve good light transmission [73 *vs.* the 12% characteristic of dark goggles (47)] while also enabling wearers to retain their color discrimination ability, especially for traffic lights, and, therefore, should not impede their driving.

The use of these goggles may represent a noninvasive method for promoting other types of health benefits in which melatonin may be involved. There may be broader health benefits of maintaining normal circadian melatonin rhythm that goes far beyond improving quality of daytime sleep. The biological clock has been shown to modulate autonomic cardiovascular regulation, and melatonin has been implicated as having an important role in the prevention of essential hypertension (48). Furthermore, impaired nocturnal synthesis of melatonin has been found in patients with coronary artery disease (7), suggesting a possible role in the high incidence of cardiovascular disease in night-shift workers. Melatonin release has been shown to have a direct effect on many gastrointestinal tissues and has been implicated as having a protective function against developing ulcerative colitis, gastric ulcers, and irritable bowel syndrome (8).

Recent epidemiological studies suggested an association of night-shift work and an increase of breast and colorectal cancer (10–12). It has been hypothesized that decreased melatonin production under bright ambient light induces an increase in the level of reproductive hormones such as estrogens, thereby stimulating the growth of hormone-sensitive tumors in the breast (49, 50). Decreased risk of cancer in blind women with unaltered levels of melatonin further confirms the link between light, melatonin, and cancer (51).

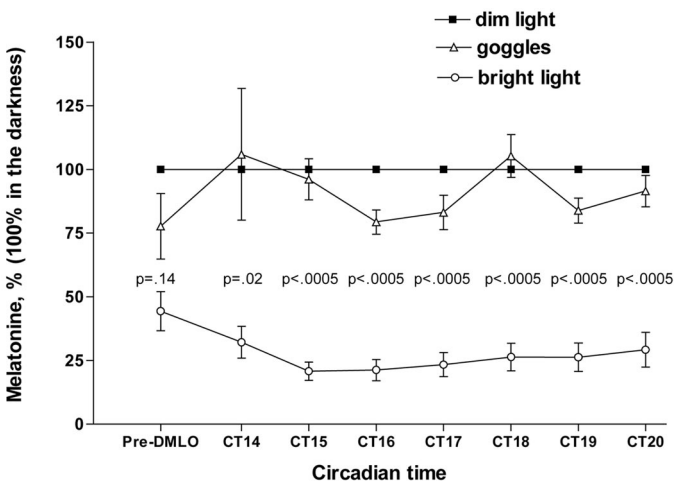

FIG. 4. Relative melatonin levels under dim-, bright-, and filtered-light conditions. Dim-light melatonin production was set arbitrarily at 100%. Filtered light preserved high levels of melatonin similar to the dim-light secretion profile.

The direct DNA protective action of melatonin has been demonstrated in experiments *in vivo* (52) and *in vitro* (53) in human lymphocytes in which DNA damage was induced by ionizing radiation. In addition, studies in animal models have supported the inference that melatonin has physiological antitumor activity (14, 15). Blask *et al.* (54, 55) provided experimental evidence that light exposure during darkness increases the risk of cancer progression via elimination of the nocturnal melatonin signal and its suppression of tumor fatty acid metabolism.

Other studies with human subjects have shown inconsistent results in relation to cancer risk. Travis *et al.* (13) found in women diagnosed with breast cancer that there were no differences in melatonin levels between normal controls and the affected group in women diagnosed with breast cancer. This absence of a difference in melatonin would be expected if the sample collection was performed during the day when melatonin levels are universally low. The question remains open about antitumor role of melatonin. For instance, Lissoni *et al.* (56) found in a study of lung cancer patients that regimen of standard chemotherapy combined with melatonin was superior to chemotherapy alone with increased survival rates at 5-yr follow-up.

In this preliminary investigation, an intentionally homogeneous sample was chosen for study. Young healthy males and females were selected because of their lack of any noteworthy pathology that might have confounded an intervention effect. As a consequence, an important subgroup, namely older workers, which might reasonably be found in shift-work employment, were not investigated. It is known that melatonin output is reduced in association with advancing age (57). One limitation of the study, therefore, is that its findings cannot be generalized to individuals not matching our sample's characteristics.

Another factor that remains to be explored in further investigations is whether ambient lighting, which is altered to restrict wavelengths of less than 530 nm, would have the same potentially protective effect against suppression of melatonin synthesis. Changes to ambient illumination as an alternative to the requirement that study subjects or employees

wear goggles for extended periods could increase the acceptability and convenience of this type of intervention.

Although further exploration of the intricate relationship among exposure to light at night, melatonin levels, and increased risk of a broad range of shift-work-related pathologies is necessary, this study provides a proof of concept in showing that preventing bright-light suppression of melatonin in a work environment at night is possible and might be beneficial. Although many questions remain unanswered after this preliminary study, we believe that use of short-wavelength-blocking goggles holds promise of having applicability in the work environment as well as for a broad range of pathologies.

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