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Effects of light on human circadian rhythms

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Abstract — Blind subjects with defective retinal processing provide a good model to study the effects of light (or absence of light) on the human circadian system. The circadian rhythms (melatonin, cortisol, timing of sleep/wake) of individuals with different degrees of light perception ($n = 67$) have been studied. Blind subjects with some degree of light perception (LP) mainly have normally entrained circadian rhythms, whereas subjects with no conscious light perception (NPL) are more likely to exhibit disturbed circadian rhythms. All subjects who were bilaterally enucleated showed free running melatonin and cortisol rhythms. Studies assessing the light-induced suppression of melatonin show the response to be intensity and wavelength dependent. In contrast to ocular light exposure, extra-ocular light failed to suppress night-time melatonin. Thus, ocular light appears to be the predominant time cue and major determinant of circadian rhythm type. Optimisation of the light for entrainment (intensity, duration, wavelength, time of administration) requires further study. © Inra/Elsevier, Paris

circadian rhythms / light / melatonin / human / blindness

Résumé — Effets de la lumière sur les rythmes circadiens humains. Des sujets aveugles avec un défaut d'intégration rétinienne constituent un bon modèle pour étudier les effets de la lumière (ou de l'absence de lumière) sur le système circadien humain. Les rythmes circadiens (mélatonine, cortisol, veille/sommeil) d'individus caractérisés par des degrés différents de perception lumineuse ont été étudiés ($n = 67$). Les sujets aveugles avec un certain degré de perception lumineuse (LP) ont généralement des rythmes circadiens normalement entraînés alors que les sujets sans conscience de perception lumineuse (NPL) ont plus de chance d'avoir des rythmes circadiens perturbés. Tous les sujets avec une énucléation bilatérale ont montré des rythmes de mélatonine et de cortisol en libre cours. L'estimation de l'inhibition de la sécrétion de mélatonine induite par la lumière indique que la réponse dépend de l'intensité et de la longueur d'onde. Contrairement à l'exposition oculaire à la lumière, la lumière extra-oculaire n'induit pas de suppression de la mélatonine nocturne. La lumière perçue par l'œil semble donc être le synchroniseur prédominant et le déterminant majeur du type de rythme circadien. L'optimisation de la lumière en tant que synchroniseur (intensité, durée, longueur d'onde, moment de traitement) exige des études additionnelles. © Inra/Elsevier, Paris

rythmes circadiens / lumière / mélatonine / humain / cécité

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1. INTRODUCTION

Circadian rhythms are endogenously generated by the pacemaker localised in the hypothalamic suprachiasmatic nuclei (SCN). The SCN generate a rhythm that is approximately (circa) 24 h. Environmental light acting via retinal photoreceptors and the retinohypothalamic tract (RHT), entrains SCN activity to the 24-h day. This photic entrainment pathway is anatomically distinct from the pathway that is responsible for image formation. In addition to entrainment, light exposure at night causes acute suppression of melatonin production.

Numerous questions remain regarding the effects of light on the human circadian clock. With respect to entrainment, what is the minimum amount of light (intensity/duration) required? What are the optimum light conditions (time of light administration, spectral quality)? What is the contribution of non-photic time cues? With respect to the circadian entrainment pathway, which photoreceptors (rods and/or cones and/or novel photopigments) are involved? What are their spectral characteristics and their retinal distribution? What is the role of extraocular light?

In order to study the effects of light on the human circadian system and the neural mechanisms involved, we have employed two model systems: 1) assessment of circadian rhythms (melatonin, cortisol, temperature, sleep/wake cycle) in blind subjects with varying degrees of visual loss; 2) light-induced suppression of melatonin in sighted and blind subjects. The present review summarises the results of these studies. The reader is referred to our recent publications for more detail [4, 17–20, 30–32, 35].

2. CIRCADIAN RHYTHMS IN THE BLIND

Blind people provide the ideal model system to study the effects of ocular light on the circadian system. In the absence of photic entrainment, circadian rhythms in blind individuals would be expected to exhibit a non-24-h (i.e. free running) pattern. Past studies of blind subjects have confirmed the presence of disrupted rhythms of melatonin [2, 3, 10, 16, 24, 29, 33], cortisol [5, 11, 13, 23–26, 29, 36], core body temperature [10, 24, 34] and the sleep/wake cycle [14, 21, 22, 24]. However, there has been no systematic attempt to assess the relationship between the degree of visual loss (amount of light perception/visual disease/visual field loss) and the type of circadian rhythm disorder observed. Studying blind subjects with different visual pathologies (for example, rod dysfunction, cone loss, bilateral enucleation) may also help to determine the retinal processes involved in circadian entrainment in humans.

Thus, the circadian rhythms of blind individuals with different degrees of visual loss have been assessed. In our initial epidemiological study of 388 registered blind individuals, subjects with no light perception (NPL) were found to have a higher incidence and more severe sleep disturbance than subjects with some degree of light perception (LP) [30, 35]. To examine the relationship between the degree of light perception and circadian rhythm disorders further, a field study of 49 blind subjects with different causes of visual loss (LP, $n = 19$; NPL, $n = 30$) was conducted. The full details of these subjects are published in Lockley et al. [17]. Since then 18 more blind subjects have been studied. Below we describe the overall findings for the total population ($n = 67$).

2.1. Subjects and methods

Registered blind subjects were classified according to the severity of their visual loss into those with some degree of light perception (LP) or better (at least 3/60 Snellen visual acuity, $n = 15$; ability to count fingers (CF), $n = 7$; see hand movements

(HMO), $n = 4$; or perceive light only (PL), $n = 4$); and those with no conscious light perception (NPL). NPL subjects ($n = 37$) were further subdivided into those with two eyes present (2E), $n = 17$; one eye present (1E), $n = 7$; or no eyes present (0E), $n = 13$.

The subjects ranged in age from 19–74 years (mean ± SD = 47 ± 13 years). The majority were male (48 males; 19 females). Most of the subjects (82 %) complained of a sleep disorder as assessed by the Pittsburgh Sleep Quality Index (PSQI) questionnaire [8], PSQI scores of 5 or more being indicative of a sleep disorder. During the study no attempt was made to alter the subjects' lifestyles. Most (81 %) lived with a partner and/or family and 59 % were employed full time with conventional working hours.

Ophthalmological examination and a structured interview revealed that the subjects suffered from a range of diseases and that their duration and rapidity of onset of blindness varied. Most of the subjects (81 %) had acquired blindness and had been blind for a range of years (1–72 years). Only 13 individuals were blind from birth. The majority of subjects (63 %) had both peripheral and central loss of vision. The largest diagnostic category was retinal dystrophy which included 16 subjects with retinitis pigmentosa (RP). The second largest diagnostic category was the bilaterally enucleated group ($n = 13$), followed by other retinal diseases which included eight subjects with retinal detachment.

Each subject was studied for at least four consecutive weeks in the field. Daily sleep and nap diaries were kept. The subjects wore activity monitors (Ambulatory Monitoring, USA) throughout the study period (to provide information about the activity rhythm as well as an objective measure of the sleep/wake cycle). For 48 h each week, subjects collected urine approximately every 4 h whilst awake as well as an overnight collection. Samples were stored at –20 °C until analysis of the major urinary metabolite of melatonin, 6-sulphatoxymelatonin (aMT6s) and cortisol.

Urinary aMT6s concentrations were measured by radioimmunoassay (RIA) [1]. Antiserum and radiolabel were supplied by Stockgrand Ltd (University of Surrey, Guildford, UK). The limit of sensitivity of the assay was 0.5 $ng \cdot mL^{-1}$. For cortisol determinations urine samples were extracted with dichloromethane and cortisol was measured in the extract by RIA [27] using an antiserum raised in sheep (anti-cortisol-3-O-(carboxymethyl)oxime-bovine albumin conjugate, Scottish Antiserum Production Unit) and an iodinated radiolabel (Amersham International, UK). The limit of detection for the assay was 6 $nmol \cdot L^{-1}$.

Output for each sequential urine collection period (aMT6s $ng \cdot mL^{-1}$; cortisol $nmol \cdot L^{-1}$) was converted to $ng \cdot h^{-1}$ (aMT6s) and $nmol \cdot h^{-1}$ (cortisol) and subjected to cosinor analysis to determine the peak time (acrophase or phi (φ)) of the rhythm. The period (tau) of the rhythm was calculated by fitting regression lines through the acrophases (tau = 24 h + slope of regression line). A rhythm was considered free running (FR) if the slope and its 95 % confidence limits did not cross 0 (i.e. 24.00 h). A rhythm was considered entrained if the regression analysis was not significantly different from 24.00 h. Subjects were classified as abnormally entrained (AE) if the mean aMT6s acrophase time was outside the range for sighted individuals (aMT6s range; mean ± 2 SD, 4.2 ± 2.9 h; $n = 80$, English and Arendt, unpublished results).

2.2. Results

2.2.1. 6-Sulphatoxymelatonin (aMT6s) rhythms

Of the 30 LP individuals (19 men, 11 women; aged 19–61 years), most (23 of 30, 77 %) had normally entrained (NE) aMT6s rhythms (*figure 1*). Four individuals (13 %) showed abnormally entrained (AE) aMT6s rhythms with mean acrophase times outside the normal range (8.90, 9.00,

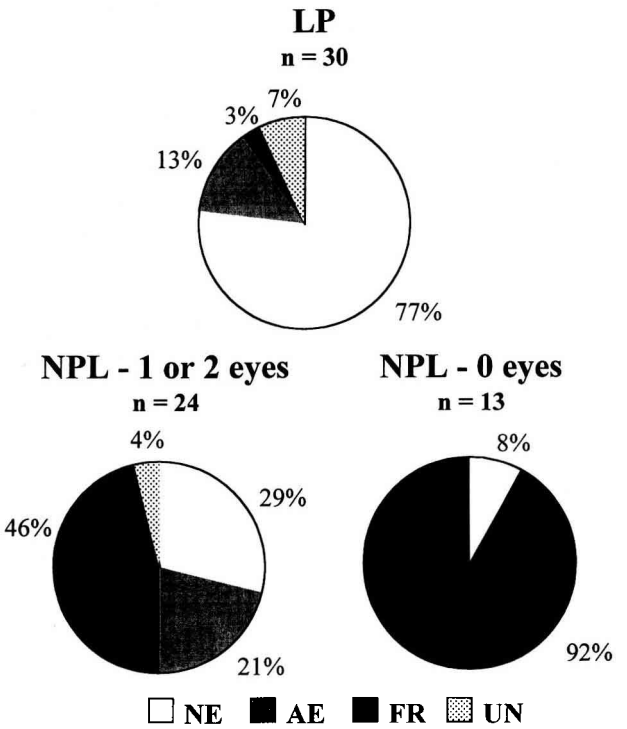

Figure 1. Distribution of circadian rhythm types (NE, normally entrained; AE, abnormally entrained; FR, free running; UN, unclassified) in blind subjects with light perception or better (LP) and in those with no conscious light perception (NPL) divided according to the presence (one or two eyes) or absence of intact eyes.

21.20 and 1.03 h). Two subjects did not show any significant rhythm and were defined as unclassified. One subject with light perception only (PL) in one eye exhibited a free running aMT6s rhythm (tau 24.62 h). Decreasing visual loss within the LP group, i.e. CF, HMO, PL did not appear to be related to the type of aMT6s rhythm observed.

In contrast to the LP subjects, the majority of NPL subjects (28 of 37, 76 %) had abnormal aMT6s rhythms (either abnormally entrained or free running). In the NPL group with either one or both eyes intact (n = 24), there was a range of circadian rhythm patterns (*figure 1*). Eleven individuals (46 %) had FR aMT6s rhythms (tau range of 23.92–24.79 h), five (21 %) had AE aMT6s rhythms (three abnormally advanced; two abnormally delayed) and seven (29 %) had NE aMT6s rhythms. One subject had no significant rhythm and was defined as unclassified.

Thirteen NPL subjects had no eyes present. All but one (= 92 %) had FR aMT6s rhythms with taus ranging from 24.13 to 24.81 h. These 12 subjects with FR aMT6s rhythms had all been bilaterally enucleated. In contrast, the one subject with an entrained aMT6s rhythm had not been enucleated but was diagnosed at birth as being anophthalmic (i.e. no eyes). There is the possibility that the subject has a very slow free running rhythm (with a tau close to 24 h) that was not able to be observed in our 4-week

protocol. However, repeated sampling of this subject over the past year has confirmed an entrained aMT6s and cortisol rhythm. Ultrasound recordings reveal the presence of small vestigial eyes (cryptophthalmos). Whether these eyes are capable of photic entrainment is currently being investigated.

Abnormally entrained aMT6s rhythms were seen in both LP (13 %) and NPL (14 %) subjects. An AE rhythm may be a slow free running rhythm with a period close to 24 h that, owing to the restricted length of the study period, appeared abnormally entrained. However, repeated sampling over intervals of several months has confirmed the AE rhythms in three of the NPL subjects. The ability of light to entrain/suppress these AE rhythms is currently being investigated. Preliminary results in two NPL subjects with AE rhythms show that white light (2 250 lux, 1 440 $\mu W/cm^2$) was unable to suppress the peak melatonin concentrations. Although it is feasible that higher intensity light may suppress melatonin, the present data point to light subsensitivity in these AE subjects compared to sighted subjects. The role of light in entraining these subjects' circadian rhythms is thus not straightforward.

2.2.2. Cortisol rhythms

Urinary cortisol rhythms have also been measured in the original cohort of 49 blind subjects [31]. Three subjects were excluded from the analysis of urinary cortisol rhythms because of drugs interfering with their cortisol determinations. In the remaining subjects (n = 46), those (n = 20) with NE aMT6s rhythms (mean acrophase ± SD 4.2 ± 1.2 h) had NE (9.9 ± 1.8 h) cortisol rhythms. Individuals with delayed AE aMT6s rhythms (acrophase range 7.2–14.3 h) and advanced AE aMT6s rhythms (acrophase range 20.3–1.0 h) also exhibited delayed (13.0–20.0 h) and advanced (5.0–7.5 h) AE cortisol rhythms, respectively. In these entrained subjects (both NE and AE), there was a significant correlation between the time of the aMT6s and cortisol acrophases ($r = 0.81$, $P < 0.000\ 1$).

Subjects with FR aMT6s rhythms (mean tau ± SD 24.52 ± 0.21 h) also had FR cortisol rhythms (mean tau ± SD 24.55 ± 0.28 h). In these subjects there was also a significant correlation between the period lengths (or tau) of the aMT6s and cortisol rhythms ($r = 0.81$, $P < 0.001$).

The urinary cortisol rhythms thus paralleled the aMT6s rhythms, irrespective of the type of circadian rhythm, i.e. entrained or free running. This correlation between the aMT6s and cortisol rhythms supports the idea that the circadian rhythm type observed (NE, AE, FR) reflects the underlying circadian oscillator.

2.2.3. Sleep/wake cycle

Daily sleep and nap diaries provided measurements of sleep latency, onset, offset, duration, number and duration of night awakenings, sleep quality and the number and duration of daytime naps. Cosinor analysis of the activity data provided the acrophase of the activity rhythm. Analysis of the sleep/wake patterns in our blind population has been published in detail [18, 20].

Briefly, subjects with NE aMT6s rhythms had significantly fewer naps of a shorter duration than subjects with AE or FR aMT6s rhythms. The timing of the naps was not random, significantly more naps occurred within a 5-h range before and after the aMT6s peak. Individuals with aMT6s rhythms that free ran through a normal (24.00–06.00 h) and abnormal (06.00–24.00 h) phase had significantly more naps of a longer duration during the abnormal phase compared to the normal phase. In order to evaluate the duration and timing of sleep at each phase of the circadian cycle, subjects (n = 6) who free ran through a full circadian cycle were examined. Overall night sleep duration, sleep timing, number and duration of daytime naps and timing of peak activity changed with circadian phase.

Increased night sleep duration and reduced number and duration of daytime naps was associated with a normal aMT6s phase. The timing of sleep and activity paralleled aMT6s timing, with sleep onset, offset and activity being relatively advanced when the aMT6s acrophase was in an advanced phase position. Conversely, when the aMT6s acrophase was in a delayed phase position, sleep timing and activity were relatively delayed.

Our results show that daytime napping is a sensitive indicator of a disordered circadian rhythm. To a lesser extent, changes in sleep (timing and duration) and activity rhythms also reflect changes in circadian phase.

3. LIGHT-INDUCED SUPPRESSION OF MELATONIN

3.1. Ocular exposure

Since the first report of Lewy and coworkers [15] numerous researchers have studied the ability of ocular light to cause acute suppression of nocturnal plasma melatonin in a variety of patient groups. In summary, melatonin suppression has been shown to depend on the light parameters (intensity, duration, wavelength, time of administration) and other factors (individual susceptibility, season, experimental design).

In humans the neural pathway mediating light-induced melatonin suppression is presumed to be the retina–RHT–SCN–pineal gland pathway. Light is unable to suppress plasma melatonin in blindfolded subjects or in subjects who have been bilaterally enucleated [10]. The so-called 'melatonin suppression test' has thus been used as an indirect way to assess the integrity of the retina–RHT–SCN pathway in subjectively blind subjects. In addition, melatonin suppression can be used to indirectly determine the characteristics of the photoreceptors that mediate circadian photoreception (for a review, see [7]).

Our early work showed that, in addition to bright light (2 500 lux), light of low intensity (300 lux) was also capable of suppressing plasma melatonin [6]. In a crude attempt to decipher the photoreceptors involved, red–green colour blind subjects were subsequently studied [28]. Suppression did not appear to differ between the colour blind and normal subjects suggesting that an intact trichromatic visual system was not essential for melatonin suppression. However, in order to precisely determine the spectral characteristics of the photoreceptor(s) involved in transmitting photic information to the clock, an action spectrum needs to be determined. As this involves numerous suppression tests over a long period of time in a large number of individuals, a controlled light delivery system and a protocol that minimises the factors capable of affecting the melatonin rhythm are essential. Below we describe our protocol and preliminary results.

3.1.1. Methods

Light generated by a metal halide arc lamp is delivered via a fibre optic cable to the input port of an integrating sphere. The wavelength and intensity of the light can be changed by interference and neutral density filters, respectively. The sphere, coated with high quality reflectance paint, provides a uniform light source illuminating the entire visual field of the subject. Dilation of the subjects' pupils (Tropicamide 0.5 %) eliminates their pupillary reflex as a confounding factor.

Subjects (five males, three females; mean age ± SD 24 ± 4 years) are studied on two to three consecutive nights, where night 1 is the baseline, no light treatment night. The baseline night controls for short- (e.g. posture, pupil dilation) and long-term factors (stage of menstrual cycle, season, changes in circadian phase) which may affect the melatonin rhythm. Melatonin suppression on nights 2 and 3 are expressed in relation to the baseline night. Possible phase shifts of the

circadian clock (another confounding factor) are minimised by controlling the subjects' sleep/wake cycle and monitoring their light exposure for at least 3 days before the baseline study night. Prior to the study, subjects collect sequential 4 hourly (8 h overnight) urine samples for 48 h for measurement of aMT6s. Light administration on nights 2 and 3 is timed to occur on the rising phase of the subjects' endogenous melatonin rhythm (predicted from aMT6s data). Environmental light and posture is controlled between 21.00 and 07.00 hours and is identical between nights. Blood samples are taken at 15-min intervals from 15 min before to 120 min after lights on, and at 23.00 and 07.00 hours. Plasma melatonin was measured by RIA [12].

3.1.2. Results

Using the above experimental design, white light of 91 $\mu W/cm^2$ (120 lux) for 30 min produced a statistically significant suppression of melatonin compared to the baseline night ($n = 8$, $P < 0.0005$). Intra-individual reproducibility of this melatonin suppression was also assessed by studying four subjects on two separate occasions. There was no significant difference in the subjects' melatonin suppression in both tests. The effect of the pupil dilator on the melatonin profile was also assessed. There was no significant difference in the subjects' melatonin rhythm in the presence and absence of the pupil dilator.

The equipment and protocol is presently being used to assess the ability of light of different wavelengths to suppress melatonin. Irradiance response curves using monochromatic light of λ_{max} 480 nm, 535 nm and 560 nm (at 10-nm half-peak bandwidth) are being established. Preliminary results show that light-induced suppression of melatonin not only depends on the number of photons delivered but also depends on the wavelength of light, short wavelengths (480–535 nm) being more effective than longer wavelengths (560 nm).

3.2. Extraocular exposure

The recent demonstration by Campbell and Murphy [9] that extraocular light exposure was capable of producing phase shifts of the circadian clock prompted us to investigate whether extraocular light could suppress nocturnal plasma melatonin.

3.2.1. Methods

A fibre optic light ring was strapped behind each subjects' knee (popliteal region). Light of two intensities (14 000 lux = 9 000 $\mu W/cm^2$ and 67 500 lux = 43 000 $\mu W/cm^2$, measured 2 mm from the light rings) was administered for 180 min between 24.00 and 03.00 hours on night 2. For full details of the experiments see Lockley et al. [19].

3.2.2. Results

Compared with the baseline night 1, there was no evidence of melatonin suppression in any of the study subjects following extraocular exposure (*figure 2*). In contrast, 30 min of ocular exposure (2 250 lux = 1 440 $\mu W/cm^2$) using the same light source resulted in a significant suppression of nighttime plasma melatonin.

4. CONCLUSIONS

The studies in the blind show that whether a subject has light perception or not plays a large part in determining the expressed circadian rhythm, thus supporting the view that light is a major time cue in the human circadian system. The inability of high intensity extraocular light exposure to suppress melatonin by inference suggests that it is ocular light acting via the retina–RHT pathway that entrains the SCN oscillator. The characteristics of the light needed for entrainment (intensity, duration, wavelength, time of administration) require further study.

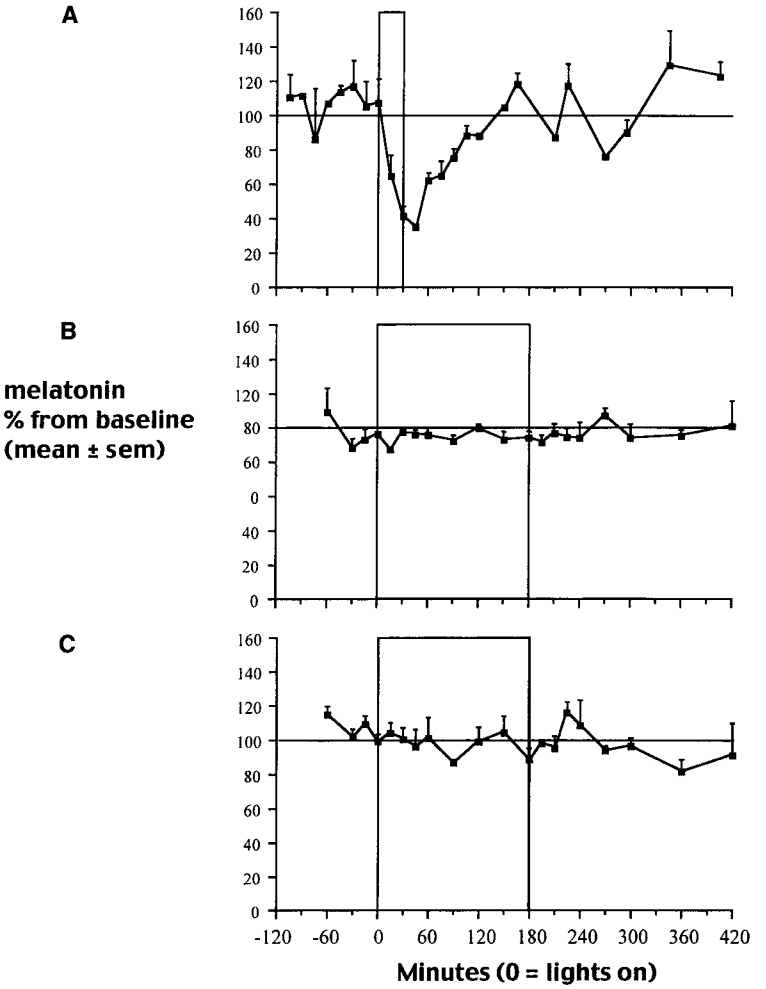

Figure 2. Melatonin levels (mean ± SEM) during light treatment night (N2) expressed as a percentage of the baseline night (N1). The X-axis is plotted in relation to the time of lights on (time 0) and the duration of light treatment is shown by the block. Melatonin levels were significantly suppressed following 30 min of 2 250 lux ocular light exposure (**A**; $n = 3$) but were not suppressed following 180 min of extraocular light exposure of 14 000 lux (**B**; $n = 4$) and 67 500 lux (**C**; $n = 3$).

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