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Luteinizing hormone following light exposure in healthy young men

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Abstract

Urinary luteinizing hormone (LH) and the melatonin metabolite (6-sulfatoxymelatonin; aMT6s) were measured in normal young men following early morning light exposure. Eleven young healthy men ages 19–30 years participated in this study. During separate weeks in counterbalanced order, each subject received both 5 days of bright light treatment (BL) and 5 days of placebo light treatment (PL) for 1 h (05:00–06:00). LH excretion was increased 69.5% after bright light exposure, but was not changed by placebo light exposure. The acrophases and offsets of aMT6s were advanced, but the duration of aMT6s excretion was not changed after BL. Light stimulation of LH could have interesting applications in psychiatry and reproductive endocrinology.

Keywords: Light; Luteinizing hormone; Melatonin; Sleep; Depression; Photoperiod

In some species, luteinizing hormone (LH) is strongly influenced by light or photoperiod. In hamsters, light at critical times of night produces massive increases in LH and growth of gonads [7]. In Japanese quail, a single light pulse induced a release of LH for several days [8]. However, few studies have examined the LH response of humans following light exposure, and results are inconsistent. Annual variations of LH secretion were reported in humans, with LH secretion increasing during summer time during a long photoperiod [14]. In a laboratory photoperiod study [18], there were no significant changes in LH from measurement after 1 week of 8 h nights to measurement after 4 weeks of 14 h nights, however, since only three blood samples were obtained on each occasion, and LH is both highly pulsatile and rather circadian, the sampling did not conclusively address the possibility of effects on LH. Determining LH levels after light exposure also has clinical implications in treating depressed patients. Decreased LH pulse frequency and decreased baseline LH secretion [4,13] have been reported in depression. Therefore, we wished to investigate whether light exposure, as a well-known treatment for depression [11], might increase LH levels.

With regard to photoperiodic responses, gonadotropin secretion may be regulated by the duration of melatonin secretion [9]. In mammals including humans, the duration of melatonin secretion is increased on short days and decreased on long days [19]. However, the relationship between gonadotropin secretion and the duration of melatonin secretion is quite different across species. In short-day breeders, such as rhesus monkeys and ewes, long duration of melatonin secretion stimulates gonadotropins and reproduction, but in long-day breeders such as hamsters, long duration of melatonin secretion inhibits gonadotropins and short duration of melatonin secretion stimulates gonadotropins and reproduction [9]. Investigating melatonin secretion and its relation with LH secretion after light exposure may provide further details regarding human photoperiodic responses. With these clinical and photoperiodic implications in mind, we examined the changes of LH and melatonin secretion in normal young men after 5 days of morning light exposure.

Eleven healthy young men ages 19–30 (23.8 ± 3.3 years; mean ± SD) participated in this study. Subjects had no endocrine or mental illnesses by physical and mental health history. This study was approved by the Institutional Review Board of the University of California, San Diego. Each subject gave written informed consent.

This study used a repeated-measures, cross-over design. Each subject received both bright light treatment (BL) and placebo light treatment (PL) at home in separate weeks. PL

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was done to control the effect of early morning awakening. The interval between BL and PL weeks was 13–15 days. Initially, ten subjects were assigned to take BL first, and nine subjects to take PL first, by a randomization table. Of completers whose data could be used, seven subjects received BL first and four subjects received PL first. Drop-out rates were not different between BL-first and PL-first group (χ^2 with Fisher's exact test, $P = 0.370$).

For the first 24–26 h baseline (BASE) of both BL and PL, from wake-up time to 09:00 the following day, subjects collected urine every 2 h during the daytime and any voidings during the sleep period. Neither bright light nor placebo light was administered on this first day. From the second day to the sixth day, subjects were exposed to bright light or placebo light for 1 h from 05:00–06:00. Light exposure at this time was reported to improve mood states in depressed patients [10]. Subjects sat in front of a light box with light intensity of 1000 lux during BL or a dim red light box with intensity <10 lux during PL. After these light exposures, subjects were allowed to sleep again to avoid sleep-deprivation. Urine was collected after the 1 h light exposure for 5 days. After completing the light treatment, on the 7th day urine was collected as during baseline for 24–26 hours to 09:00 the next day (POST). Subjects wore an Actiwatch Light® wrist monitor and recorded sleep logs for the entire 7 days of both BL and PL. The wrist monitor and sleep logs indicated sleep–wake rhythms and were used to detect subjects not compliant with the study protocol. Mood state changes after light exposure were also determined by recording a visual analog scale (VAS) for mood.

The total volume of each urine sample was recorded and aliquots frozen at -70 °C for assay. Urinary LH was estimated by a double antibody RIA with a sensitivity of 1.0 mIU/ml (Diagnostic Products Corporation, Los Angeles, CA) and intra- and interassay coefficients of variation of 9% and 12%, respectively. Urinary 6-sulphatoxymelatonin (aMT6s), the major metabolite of melatonin, was assayed with Bühlmann EIA kits (ALPCO, Ltd., Windham, NH). At a sample dilution of 1:200, the analytic sensitivity of this assay is 0.35 ng/ml, and intra- and interassay coefficients of variation are 4.7% and 7.3%, respectively.

Twenty-four hour averages of LH excretion (from 05:00 to the following 04:59) were compared between BASE and POST in both BL and PL. LH excretion was further analyzed by dividing 24 h into 6 h intervals, which were 05:00–10:59, 11:00–16:59, 17:00–22:59, and 23:00–04:59. For BL versus PL, 5 days' LH excretion between 05:00–06:00 was contrasted. Twenty-four hour cosine fits were applied to LH and aMT6s. Acrophases, amplitudes, and mesors (24 h cosine mean) were estimated from these 24 h cosine fits. The duration of aMT6s excretion was estimated from onsets and offsets interpolated from upward and downward crossings of the 24 h mesor. Among 11 subjects, we obtained satisfactory wrist motion data from nine subjects. Sleep times of the other two subjects were obtained from sleep diary. From Actiwatch scoring and sleep diaries, bedtime, wake-up time, time in bed (TIB), total sleep time (TST), and out-of bed napping were computed. Changes in bedtimes, wake-up times, TIB (including daytime napping), and TST (including daytime napping) following light treatment were compared between BL and PL. In analyzing 24 h averages of LH excretion, ANOVA with two levels of repeated measures was used to contrast time (BASE vs. POST) within treatment (PL vs. BL), and their interaction. In the analysis of the 6 h intervals of LH data, ANOVA with two levels of repeated measures was also used. The Rayleigh test of the acrophases of LH excretion was done to determine whether LH excretions showed a rhythmic pattern [3]. The significance criterion was defined at $P < 0.05$.

Fig. 1 displays the effect of bright light on the averaged 24 h LH excretion rate ($N = 11$). LH excretion rate was increased 69.5% after bright light exposure (93.8 ± 97.9 mIU/h, 156.0 ± 141.5 mIU/h, two-tailed paired t-test, $P < 0.05$), but was not increased after placebo light exposure (130.2 ± 109.9 mIU/h, 114.2 ± 101.1 mIU/h, $P = 0.335$). Baselines were not significantly different for the PL and BL weeks, nor were the baselines significantly different for the two orders. There was a significant interaction between treatment and time ($F(1, 10) = 9.800$, $P < 0.05$), but neither a treatment nor a time effect was observed ($F(1, 10) = 0.025$, $P = 0.878$, $F(1, 10) = 3.073$, $P = 0.110$, respectively). There was also a significant difference in BASE–POST change contrasting BL with PL (62.2 ± 67.4 mIU/h, -15.9 ± 52.2 mIU/h, two-tailed paired t-test, $P < 0.05$). No effect of treatment order on the change values was observed. In 6 h interval analysis of LH

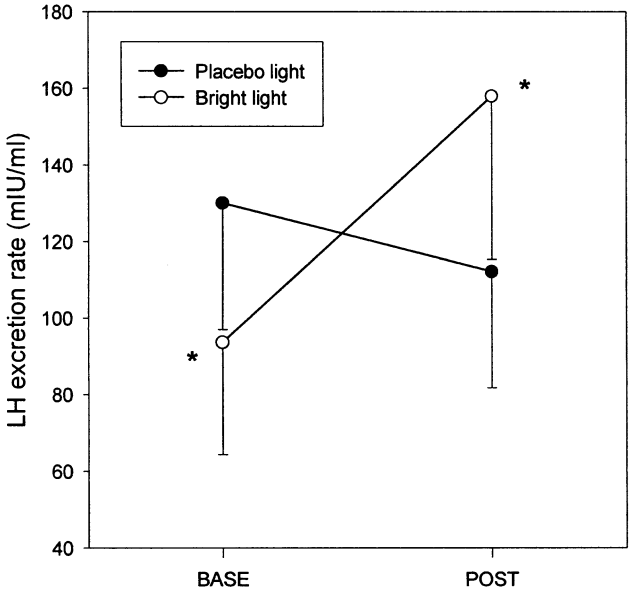

Fig. 1. LH excretion was increased after bright light exposure, but not changed after placebo light exposure. Vertical bars represent SEM ($N = 11$). *$P < 0.05$ between baseline and after-treatment in bright light exposure condition. There was a significant interaction between treatment and time ($F(1, 10) = 9.800$, $P < 0.05$). BASE, baseline; POST, after-treatment.

excretion rate in BL, a treatment effect was observed ($F(1, 10) = 9.353$, $P < 0.05$), but neither the time-of-day effect nor the interaction between treatment and time-of-day was significant. Repeated measures ANOVA of the 5 days' morning urines collected from 05:00–06:00 showed no significant treatment effect and no change over the 5 days.

Table 1 presents cosinor analyses of LH and aMT6s excretion. Cosine fitting to LH accounted for 66.34% of 24 h variance. In the Rayleigh test of the acrophases of LH excretions, the lengths of mean vector, r, were 0.7315 ($P = 0.002$), 0.7033 ($P = 0.003$), 0.6968 ($P = 0.003$), and 0.8291 ($P < 0.001$) in PL–BASE, PL–POST, BL–BASE, and BL–POST, respectively. At baseline, the LH acrophase was close to noon in both treatments. After treatment, the LH acrophase advanced by 82 min in BL, but this difference was not significant ($P < 0.055$) and there was no difference in the BASE–POST change in acrophases between BL and PL. After treatment, acrophases and offsets of aMT6s were advanced in BL (all $P < 0.05$, one-tailed tests), but onset and duration of aMT6s excretion were not changed. Comparing BL and PL, there were no differences in any aMT6s parameters. Duration, mesor, and amplitude of aMT6s excretion were also unchanged after treatment either in BL or PL. When BL and PL were combined, the onset, acrophase, and offset of aMT6s were significantly advanced after treatment (all $P < 0.05$, one-tailed tests). No correlations were observed between 24-hr parameters for aMT6s and LH excretion.

Neither bedtime nor wake-up time was advanced either in BL or PL. Neither change in TST nor TIB was different between BL and PL. Immediately after light exposure for 5 days, subjects reported more 'feeling good' on VAS both in BL and PL compared to before light exposure ($P < 0.001$, $P < 0.05$, respectively). This mood elevation was more prominent in BL than in PL ($P < 0.05$).

In summary, 24 h LH excretion was increased 69.5% after bright light exposure in the early morning. The acrophase and offset of aMT6s excretion were advanced after both bright light exposures in the early morning, but the duration and mesor of aMT6s were not changed. This finding suggest that in humans, in comparison to sheep and hamsters [2], the duration of melatonin secretion may be less important in mediating light effects on LH secretion. It is plausible that the suprachiasmatic nucleus (SCN), which receives light information through the retinohypothalamic tract, could be directly involved in LH secretion without the mediation of melatonin. Direct efferent pathways have been found from SCN to the anteroventral hypothalamic area, which possibly regulate sexual and reproductive behavior in humans or rodents [6,12]. However, the relationship between LH and melatonin secretion needs further investigation. A study with a larger sample size and saliva or blood melatonin measurements might lead to a better understanding of the relationship between LH and melatonin secretion. A limitation of the present study is that the circadian rhythm of aMT6s excretion were masked by room illumination [1]. Determination of 'unmasked' melatonin rhythms in a dim light condition might better reveal the underlying status of the SCN.

In the cosinor analysis of LH excretion, diurnal variations were confirmed by the Rayleigh test, and the acrophases were observed close to noon in baseline LH excretions. Circadian variation of LH secretion has been reported elsewhere [15,17]. The highest LH excretion around 1200 might be consistent with the previous finding that sleep stimulated LH secretion [5], if there is several hours delay in urinary elimination. The phase advance of aMT6s in combined BL and PL suggested that early morning awakening itself resulted in a phase advance. The present study also showed that mood states were improved by bright light exposure even within the normal range.

The encouraging result that LH excretion was increased after light exposure in the early morning might have research and clinical implications. Research on the photoperiodic responses of gonadotropins has been largely limited to animals, and not previously clarified in human photoperiodic studies [18]. However, more attention is being paid to human photoperiodic responses. Sexual dysfunctions such as loss of libido and decreased sexual activity are known to be not only depressive symptoms but also side effects of newly developed antidepressants. Based on reports that LH and testosterone levels were low in

Table 1
Cosinor analysis of LH and aMT6s excretion[a]

Parameters	Placebo Light (PL)			Bright Light (BL)		
	BASE	POST	*P*	BASE	POST	*P*
LH						
Acrophase	11:57 ± 3:05	12:01 ± 3:37	0.453	12:03 ± 3:26	10:41 ± 2:24	0.055
aMT6s						
Onset	0:43 ± 1:59	0:07 ± 1:44	0.086	0:54 ± 2:10	23:56 ± 2:05	0.096
Acrophase	5:13 ± 1:59	4:34 ± 1:41	0.08	5:31 ± 2:13	4:10 ± 1:51	<0.05
Offset	9:41 ± 2:58	8:32 ± 1:57	0.08	9:54 ± 2:33	8:27 ± 1:59	<0.05
Duration (h)	8.96 ± 1.30	8.43 ± 2.00	0.538	9.00 ± 1.18	8.52 ± 1.21	0.317

[a] Values are mean ± SD. Acrophase of LH and aMT6s, and onset and offset of aMT6s were compared by one-tailed tests, as advance was prospectively predicted. BASE, baseline; POST, after treatment. There were no significant contrasts comparing change values between BL and PL.

depressive males [4,20] and on the well-known fact that LH is involved in sexual functions of both men and women, it is theoretically possible that light exposure, which increases LH secretion, will alleviate sexual dysfunctions in depressed patients. Thus, the effects of light exposure on the LH secretion of normal volunteers should be replicated in depressed patients to elucidate the therapeutic effect of light exposure on the decreased LH levels and sexual dysfunctions of depression. Other applications deserve study, such as use of light for impotence or to trigger ovulation [16].

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References

[1] H. Aoki, N. Yamada, Y. Ozeki, H. Yamane, N. Kato, Minimum light intensity required to suppress nocturnal melatonin concentration in human saliva, Neurosci. Lett. 252 (1998) 91–94.
[2] T.J. Bartness, J.B. Powers, M.H. Hastings, E.L. Bittman, B.D. Goldman, The timed infusion paradigm for melatonin delivery: what has it taught us about the melatonin signal, its reception, and the photoperiodic control of seasonal responses?, J. Pineal Res. 15 (1993) 161–190.
[3] E. Batschelet, Circular statistics in biology, in: R. Sibson, J.E. Cohen (Eds.), Mathematics in Biology, Academic Press, New York, 1981, pp. 52–58.
[4] F. Brambilla, M. Maggioni, E. Ferrari, S. Scarone, M. Catalano, Tonic and dynamic gonadotropin secretion in depressive and normothymic phases of affective disorders, Psychiatry Res. 32 (1990) 229–239.
[5] C.A. Czeisler, E.B. Klerman, Circadian and sleep-dependent regulation of hormone release in humans, Recent. Prog. Horm. Res. 54 (1999) 97–132.
[6] J. Dai, D.F. Swaab, J. van der Vliet, R.M. Buijs, Postmortem tracing reveals the organization of hypothalamic projections of the suprachiasmatic nucleus in the human brain, J. Comp. Neurol. 400 (1998) 87–102.
[7] J.A. Elliott, Circadian rhythms and photoperiodic time measurement in mammals, Fed. Proc. 35 (1976) 2339–2346.
[8] B.K. Follett, R.G. Foster, T.J. Nicholls, Photoperiodism in birds, in: D. Evered, S. Clark (Eds.), Ciba Foundation Symposium 117: Photoperiodism, Melatonin and the Pineal, Pitman, London, 1985, pp. 93–115.
[9] B.D. Goldman, The circadian timing system and reproduction in mammals, Steroids 64 (1999) 679–685.
[10] D.F. Kripke, S.C. Risch, D. Janowsky, Bright white light alleviates depression, Psychiatry Res. 10 (1983) 105–112.
[11] D.F. Kripke, Light treatment for nonseasonal depression: speed, efficacy, and combined treatment, J. Affect. Disord. 49 (1998) 109–117.
[12] R.K. Leak, R.Y. Moore, Topographic organization of suprachiasmatic nucleus projection neurons, J. Comp. Neurol. 433 (2001) 312–334.
[13] W. Meller, P. Grambsh, C. Bingham, G. Tagatz, Hypothalamic pituitary gonadal axis dysregulation in depressed women, Psychoneuroendocrinology 26 (2001) 253–259.
[14] M.C. Merrigiola, E.A. Noonan, C.A. Paulsen, W.J. Bremnar, Annual patterns of luteinizing hormone, follicle stimulating hormone, testosterone and inhibin in normal men, Hum. Reprod. 11 (1996) 248–252.
[15] D.C. Parker, L.G. Rossman, D.F. Kripke, J.M. Hershman, W. Gibson, C. Davis, K. Wilson, E. Pekary, Endocrine rhythms across sleep–wake cycles in normal young men under basal state conditions, in: J. Orem, C.D. Barnes (Eds.), Physiology in Sleep, Academic Press, New York, 1980, pp. 145–179.
[16] A.A. Putilov, K.V. Danilenko, A.Y. Protopopova, D.F. Kripke, Menstrual phase response to nocturnal light, Biol. Rhythm Res. 33 (2002) 23–38.
[17] D.I. Spratt, L.S. O'Dea, D. Schoenfeld, J. Butler, P.N. Rao, W.F. Crowley Jr, Neuroendocrine-gonadal axis in men: frequent sampling of LH, FSH, and testosterone, Am. J. Physiol. 254 (1988) E658–E666.
[18] T.A. Wehr, D.E. Moul, G. Barbato, H.A. Giesen, J.A. Seidel, C. Barker, C. Bender, Conservation of photoperiod-responsive mechanisms in humans, Am. J. Physiol. 265 (1993) R846–R857.
[19] T.A. Wehr, Photoperiodism in humans and other primates: evidence and implications, J. Biol. Rhythms 16 (2001) 348–364.
[20] J.A. Yesavage, J. Davidson, L. Widrow, P.A. Berger, Plasma testosterone levels, depression, sexuality, and age, Biol. Psychiatry 20 (1985) 199–228.