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Combined Influences of Gradual Changes in Room Temperature and Light around Dusk and Dawn on Circadian Rhythms of Core Temperature, Urinary 6-Hydroxymelatonin Sulfate and Waking Sensation Just after Rising

Masayuki Kondo[1], Hiromi Tokura[2], Tomoko Wakamura[3], Ki-Ja Hyun[4], Satoshi Tamotsu[4], Takeshi Morita[5] and Tadashi Oishi[4]

[1] Heart-ful Living R&D Institute, Comprehensive Housing R&D Institute, Sekisui House Ltd., Kyoto, Japan
[2] Institute of Textiles & Clothing, The Hong Kong Polytechnic University, Kowloon, Hong Kong, China
[3] School of Health Sciences, Faculty of Medicine, Kyoto University, Kyoto, Japan
[4] Graduate School of Humanities and Sciences, Nara Women's University, Nara, Japan
[5] Department of Living Environmental Science, Fukuoka Women's University, Fukuoka, Japan

ABSTRACT

The present experiment aimed at knowing how a gradual changes of room temperature (T_a) and light in the evening and early morning could influence circadian rhythms of core temperature (T_{core}), skin temperatures, urinary 6-hydroxymelatonin sulfate and waking sensation just after rising in humans. Two kinds of room environment were provided for each participant: 1) Constant room temperature (T_a) of 27 °C over the 24 h and LD-rectangular light change with abrupt decreasing from 3,000 lx to100 lx at 1800,abrupt increasing from 0 lx to 3,000 lx at 0700. 2) Cyclic changes of T_a and with gradual decrease from 3,000 lx to 100 lx onset at 1700 (twilight period about 2 h), with gradual increasing from 0 lx to 3,000 lx onset at 0500 (about 2 h). Main results are summarized as follows: 1) Circadian rhythms of nadir in the core temperature (T_{core}) significantly advanced earlier under the influence of gradual changes of T_a and light than no gradual changes of T_a and light. 2) Nocturnal fall of T_{core} and morning rise of T_{core} were greater and quicker, respectively, under the influence of gradual changes of T_a and light than no gradual changes of T_a and light. 3) Urinary 6-hydroxymelatonin sulfate during nocturnal sleep was significantly greater under the influence of gradual changes of T_a and light. 4) Waking sensation just after rising was significantly better under the influence of gradual changes of T_a and light. We discussed these findings in terms of circadian and thermoregulatory physiology.

Key words: *circadian rhythms, core temperature, skin temperatures, urinary 6-hydroxymelatonin, waking sensation*

Introduction

According to Kondo et al. (unpublished data), room temperature cycles (T_a) (gradual decrease from 27 °C to 24 °C between 1800 and 2200 h and gradual increase from 24 °C to 27 °C between 0300 and 0700 h) around the dusk and dawn advanced significantly the circadian nadir of core temperature (T_{core}) and raised significantly the nocturnal concentration of 6-hydroxymelatonin sulfate in the urine during nocturnal sleep, compared with constant room T_a of 27 °C for 24 h. Furthermore, Kondo et al. (unpublished data) disclosed that the nadir time of the circadian rhythms in the core temperature phase-advanced significantly and the nocturnal concentration of 6-hydroxymelatonin sulfate in the urine during nocturnal sleep was raised significantly under the influence of light-dark cycle with twilight of gradual decrease from 3,000 lx to 100 lx starting at 1700 h, and with gradual in-

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crease from 0 lx to 3,000 lx starting at 0500 h, compared with light-dark rectangular change with abrupt decrease from 3,000 lx to 100 lx at 1800 h and abrupt increase from 0 lx to 3,000 lx at 0700 h. However, it remains to be studied what might happen concerning core temperature rhythm and 6-hydroxymelatonin sulfate under the influence of concurrent occurrence of gradual changes of T_a and light. Mankind has evolved over millions of years, being always surrounded by dusk and dawn, and cyclic T_a in the evening and early morning. With these in mind, it is tempting to know how circadian rhythms of core temperature and 6-hydromelatonin sulfate would react under combined conditions of gradual changes of T_a and light in the evening and the morning.

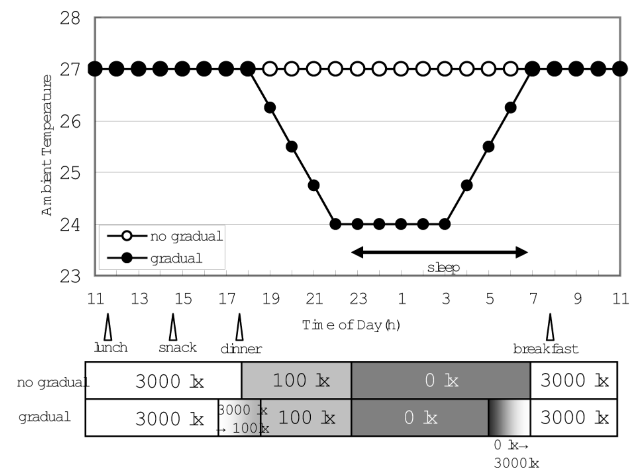

Fig. 1. Experimental protocol. Open circles: no gradual (constant T_a and light-dark cycle with rectangular light to dark change and vice versa). Closed circles: gradual (cyclic T_a and light-dark cycle with twilight light to dark change and vice versa). Relative humidity: 60%. Arrows show times of the three meals and the snack.

Participants and Methods

Participants

Nine female and two male students served as participants, who were all physically and mentally in healthy conditions. The menstrual cycle phase in the female participants was checked by measuring oral temperature in bed every morning and they served as participants when they were in the follicular phase. Their physical characteristics were as follows: age, 21.1±0.4 (mean±SEM) yrs (range 19–23); stature, 1.63±0.02 m (range 1.57–1.77); body mass, 52.6±2.1 kg (range 45–66); body mass index, calculated by weight/height^2, 19.86±0.36 kg/m^2 (range 18.26–21.10); and body surface area, by the usage of weight$^{0.444}$×height$^{0.663}$×88.83 cm/kg, weight in kg and height in cm, 1.51±0.04 m^2 (range 1.38–1.77). Clothing without skin pressure was worn during the experiments. Isocaloric meals were provided at 0800, 1200 and 1800 h, and a light snack was served at 1500 h. All participants did not have any sleep disorders, at least for one month prior to the start of experiment. Experimental design was approved by the Ethics Committee at the Heart-ful Living R&D Institute, Sekisui House, Ltd. The purpose and risk of the experiment were fully explained to all participants. All of them agreed with their attendance by signature as participants. They could leave the experimental chamber at any time whenever they wanted. The honorarium for their attendance as participants was paid to them by SEKISUI HOUSE Ltd., Heart-ful Living R&D Institute for their attendance.

Experimental design

Figure 1 depicts the experimental design. A participant entered a bioclimatic chamber (size; 7.3 m in length, 3.8 m in width, controlled at 27 °C and a relative humidity of 60%) at 0930 h. Light intensity was controlled at eye level. A participant retired at 2300 h and rose at 0700 h. He or she was requested to sit on a chair and spend time as quietly as possible during the time of wakefulness, reading a book or listening to light taped music.

Two kinds of room temperature were provided for each participant: 1) Constant room temperature (T_a) of 27 °C over the 24 h and LD-rectangular light change with abrupt decreasing from 3,000 lx to 100 lx at 1800 h, abrupt increasing from 0 lx to 3,000 lx at 0700 h. 2) Gradual changes of T_a from 27 °C to 24 °C over 1800 to 2200 h, and from 24 °C to 27 °C over 0300 to 0700 h and light with gradual decrease from 3,000 lx to 100 lx onset at 1700 (twilight period about 2 h), with gradual increasing from 0 lx to 3,000 lx onset at 0500 h (about 2h) (Figure 1). The order of these two conditions was counterbalanced. A participant emptied his or her bladder on retiring at 2300 h and again on waking at 0700 h. The 6-hydroxymelatonin sulfate content of these overnight samples was analyzed at SRL Laboratory in Tokyo. The experiment was carried out in the Heart-ful Living R&D Institute, Sekisui House Ltd., Kyoto/Japan from October 22th, 2004 to Feburary 19th, 2005.

Physiological parameters measured

Rectal temperature (T_{core}) was measured every min by a logger (LT-8A, Gram, Japan) using a thermistor probe (LT-ST08-11, accuracy±0.01 °C, Gram, Japan) inserted 0.12 m beyond the anal sphincter. Skin temperatures were measured by thermistor sensors (LT-ST08-12, accuracy±0.01 °C, Gram, Japan) fixed to the skin surface at seven sites with thin, air-permeable adhesive surgical tape. The seven sites were mid-forehead ($T_{forehead}$), frontal chest (T_{chest}), right mid-thigh (T_{thigh}), right leg (T_{leg}), right instep of foot (T_{foot}), right forearm (T_{arm}) and right back of hand (T_{hand}).

Urinary 6-hydroxymelatonin sulfate concentration of the overnight urine sample was analyzed by an enzyme-linked immunosorbent assay (ELISA, IBL, Hamburg, Germany). For comparison of hormone levels between participants, the results were standardized as rates per milligram of creatinine.

Each morning at 0700 h, sleep was estimated with the Kansei-Gakuin Sleepiness Scale (KSS)[1]. KSS is a subjective rating scale of drowsiness that has been translated into Japanese, and which is based on the SSS (Stanford Sleepiness Scale).

Data analysis

Raw temperature data were inspected visually and segments that had been lost (due to slippage of the temperature sensor) were estimated by interpolation. Maximum and minimum values of rectal temperature of each participant were visually evaluated from raw data. Then raw data from each participant were averaged every 30 min. The times when acrophase and bathyphase occurred, were individually derived from cosine curve analysis of the raw data.

A comparison of values obtained between the two T_a conditions was made using a two–way analysis of variance (ANOVA) with repeated measures. The ANOVA was applied separately for five periods: 1200–1800, 1800–2300, 2300–0200, 0200–0600 and 0600–1000 h. Multiple comparisons of differences were performed with Dunnett's Multiple comparison test. Values for 6-hydroxymelatonin sulfate concentration and the sleepiness feeling were compared by paired Student t-tests. Data were generally expressed means±SEM. Statistical significance was assessed at 1% and 5% levels.

Results

The results of the circadian phase (as assessed by cosinor analysis) from all participants are summarized in Table 1. Mean nadir time with SEM was 0427±0020 h with gradual changes of T_a and light and 0523±0015 h with no gradual changes of T_a and light. The values were significantly different ($p<0.01$), suggesting that circadian phase of T_{core} significantly advanced earlier with gradual changes of T_a and light than with no gradual changes of T_a and light. Mesor was also significantly different ($p<0.01$). On the contrary, amplitude did not differ between two conditions.

The results of maximum and minimum time and their values were summarized in Table 2. The time of minimum temperatures was 0216±0033 h in gradual changes of T_a and light and 0448±0034 h in no gradual changes of T_a and light, which was significantly different ($p<0.01$). On the contrary, other parameters, such as minimum and maximum value, and time of maximum did not differ between the two conditions.

Figure 2 compares temporal changes of mean T_{core} (top), $T_{forehead}$ (middle) and T_{chest} (bottom) between no gradual changes of T_a and light (rectangular) and gradual changes of T_a and light. T_{core} fell more quickly and was significantly lower from 2300 to 0200 h ($p<0.01$), and it rose more quickly and was significantly higher from 0600 to 1000 h ($p<0.05$), with gradual changes of T_a and light. T_{core} was significantly higher with no gradual changes of T_a and light than gradual changes of T_a and light from 1200 to 1800 h ($p<0.01$). $T_{forehead}$ was significantly lower with gradual changes of T_a and light than with no gradual changes of T_a and light from 1800 to 0600 h ($p<0.05$, $p<0.01$), and significantly higher from 0600 to 1000 h ($P<0.05$). T_{chest} was significantly lower with gradual changes of T_a and light than no gradual changes of T_a and light from 2300 to 0200 h ($p<0.01$) and

TABLE 1
THE RESULTS OF THE CIRCADIAN PHASE

	Nadir time**		Amplitude		Mesor*	
	No gradual	Gradual	No gradual	Gradual	No gradual	Gradual
S-1	5:50	5:51	0.49	0.44	36.91	36.85
S-2	3:50	3:45	0.43	0.46	36.73	36.70
S-3	5:06	3:26	0.47	0.47	36.74	36.75
S-4	5:31	4:29	0.31	0.19	36.72	36.63
S-5	4:08	2:21	0.23	0.39	36.59	36.48
S-6	5:31	4:11	0.31	0.37	36.96	36.83
S-7	6:46	4:44	0.25	0.46	36.68	36.63
S-8	6:06	4:17	0.42	0.37	36.67	36.65
S-9	5:00	5:18	0.58	0.58	36.62	36.67
S-10	5:38	6:14	0.32	0.10	36.57	36.59
S-11	5:41	4:22	0.47	0.43	37.00	36.92
Ave	5:23	4:27	0.39	0.39	36.74	36.70
SEM	0:15	0:20	0.03	0.04	0.05	0.04

Individual bathyphase (nadir) times and amplitude, mesor of 24h T_{core} rhythm in no gradual and gradual conditions. Note the significant differences in nadir time and mesor T_{core}.

TABLE 2
THE RESULTS OF MAXIMUM AND MINIMUM TIME AND THEIR VALUES

	Maximum				Minimum			
	Value		Time		Value		Time**	
	No gradual	Gradual	No gradual	Gradual	No gradual	Gradual	No gradual	Gradual
S-1	37.50	37.32	21:39	20:58	36.38	36.36	5:45	5:51
S-2	37.19	37.06	18:16	20:30	36.10	35.96	1:37	1:34
S-3	37.32	37.31	16:49	18:26	36.19	36.06	1:14	0:24
S-4	37.13	37.00	22:32	22:41	36.24	36.07	3:31	3:25
S-5	36.88	36.83	19:44	18:25	36.19	35.67	4:21	0:29
S-6	37.49	37.44	23:05	20:36	36.32	36.29	6:04	5:14
S-7	37.12	37.20	19:21	20:37	36.19	35.94	6:29	1:00
S-8	37.16	37.05	23:00	21:30	36.01	36.08	6:23	2:02
S-9	37.23	37.37	23:00	21:23	35.66	35.76	5:21	2:00
S-10	36.88	37.00	19:13	22:54	35.84	36.31	5:13	1:18
S-11	37.50	37.47	17:40	17:22	36.26	36.20	6:48	1:11
Ave	37.22	37.19	20:23	20:29	36.13	36.06	4:48	2:16
SEM	0.07	0.06	0:42	0:35	0.06	0.07	0:34	0:33

Individual maximum and minimum values of 24h T_{core} rhythm in no gradual and gradual conditions. Note the significant differences in minimum time of T_{core}.
No gradual (constant T_a and light-dark change in rectangular), gradual (cyclic T_a and light – dark change in twilight). **$p<0.01$.

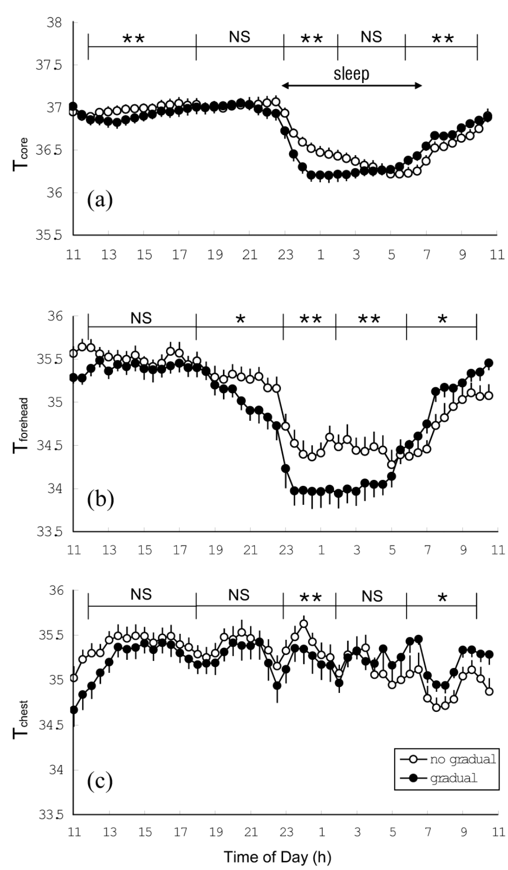

*Fig. 2. A comparison of temporal changes of mean T_{core} (a), $T_{forehead}$ (b), and T_{chest} (c) under the influence of either no gradual or gradual conditions. *p<0.05, **p<0.01. n=11. NS: Not significant. Abscissa: time of day (h). Ordinate: T_{core} (°C) (a), $T_{forehead}$ (°C) (b), and T_{chest} (°C) (c). Open circles: no gradual. Closed circles: gradual.*

significantly higher with gradual changes of T_a and light than no gradual changes of T_a and light from 0600 to 1000 h ($p<0.05$).

Figure 3 compares temporal changes of mean T_{thigh} (top of left column), T_{leg} (second of left column), T_{hand} (third of left column) and T_{foot} (bottom of left column), and ($T_{thigh}-T_a$) (top of right column), ($T_{leg}-T_a$) (second of right column), ($T_{hand}-T_a$) (third of right column) and ($T_{foot}-T_a$) (bottom of right column) between no gradual changes of T_a and light and gradual changes of T_a and light. As seen in the figure, it is generally observed that skin temperatures were lower with gradual changes of T_a and light than no gradual changes of T_a and light (left column), while (skin temperatures – T_a) were significantly higher with gradual changes of T_a and light, especially during the evening and night than no gradual changes of T_a and light (right column).

Figure 4 compares the two conditions, no gradual changes of T_a and light and gradual changes of T_a and light with regard to temporal changes of T_{core} between 1800 and 2200 h (top), 2200 and 0300 h (middle) and 0300 and 1000 h (bottom). There were no significant differences in the changes of T_{core} between 1800 and 2200 h (top), T_{core} fell significantly earlier ($p<0.05$) at 2300 h in gradual changes of T_a and light and to a greater extent in a gradual changes of T_a and light between 2200 and 0300 h, and T_{core} began to rise significantly earlier and to a higher value in gradual changes of T_a and light between 0300 and 1000 h.

Figure 5 compares urinary levels of 6-hydroxymelatonin sulfate during nocturnal sleep (2300 to 0700 h) between no gradual changes of T_a and light. All individuals (data shown in the top graph) had significantly higher

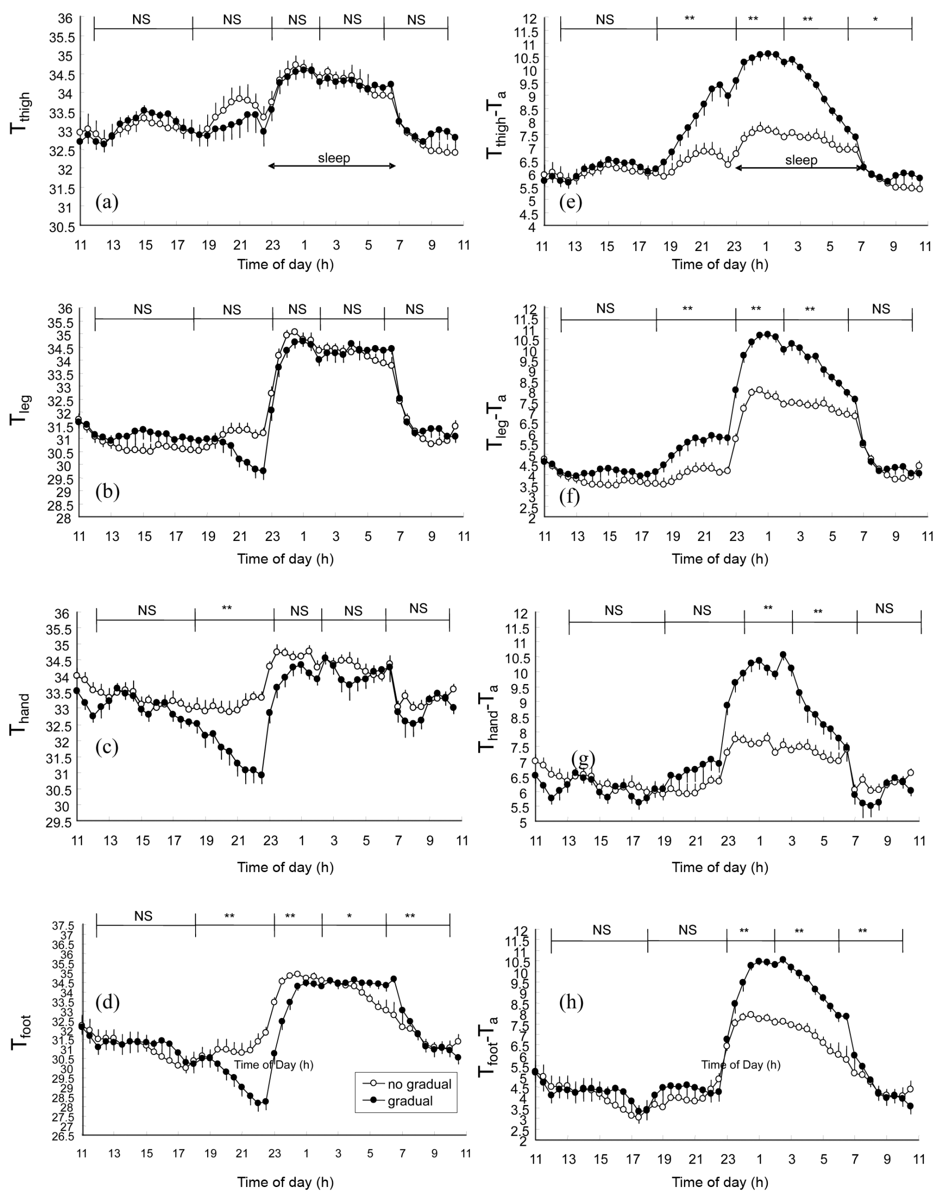

*Fig. 3. A comparison of temporal changes of mean T_{thigh} (a), T_{leg} (b), T_{hand} (c) and T_{foot} (d), and (T_{thigh}–T_a) (e), (T_{leg}–T_a) (f), (T_{hand}–T_a) (g) and (T_{foo}–T_a) (h) under no gradual vs. gradual conditions. *$p<0.05$, **$p<0.01$. n=11. NS: not significant. Abscissa: time of day (h). Open circles: no gradual. Closed circles: gradual.*

values ($p<0.05$) with gradual changes than no gradual changes of T_a and light. Mean urinary 6-hydroxymelatonin sulfate levels were 58.56±9.26 (ng/mgCRE) in no gradual changes and 73.11±8.32(ng/mgCRE) with gradual changes (bottom).

Figure 6 compares the results from the KSS questionnaire, which was carried out immediately after collecting urine as soon as the participants rose in the morning. The mean score was significantly lower with gradual changes of T_a and light than no gradual changes of T_a and light ($p<0.05$), suggesting that the participants woke up feeling better.

Discussion

Kondo et al. (unpublished data) found that the circadian nadir of T_{core} rhythm was significantly advanced earlier by 71 min under the influence of gradual changes of T_a and light than no gradual changes of T_a and light. Same group (unpublished data) also found that the circadian nadir of T_{core} rhythm was significantly advanced earlier by 49 min under the influence of gradual changes of light than no gradual changes of light. In our present experiment the circadian nadir of T_{core} was significantly advanced earlier by 56 min under the influence of gradual changes of T_a and light than of no gradual changes of T_a and light. Thus, the advance of nadir seemed to be

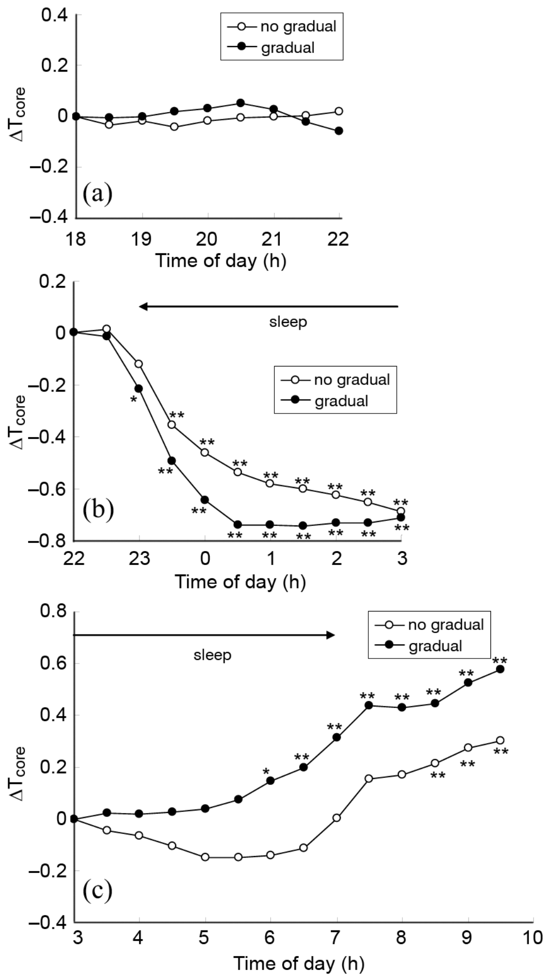

*Fig. 4. A comparison between no gradual and gradual conditions of temporal changes of T_{core} from 1800 to 2200 h (a), 2200 to 0300 h (b), and 0300 to 1000 h (c). Statistical differences from the beginning: *p<0.05, **p<0.01. Abscissa: time of day (h). Open circles: no gradual; Closed circles: gradual.*

suppressed under the influence of gradual changes of T_a and light, compared with gradual changes of only T_a, suggesting that gradual changes of light seem to have power to turn back advanced circadian phase. Wakamura and Tokura[2] compared circadian rhythm of nadir time of T_{core}. They found difference of nadir time between constant T_a and cyclic T_a was 35 min. The authors used cyclic light. This is a reason why phase advance was not great in their experiment. Also, we should notice that the insertion of gradual changes of T_a to gradual changes of light could advance the circadian nadir time. Physiological mechanisms why gradual changes of light could turn back the advanced circadian phase remains to be studied. However, its ecological significance is plausible, because if the nadir time would advance too early, T_{core} would start also to rise earlier, resulting in an earlier awakening and an inhibition of enough duration of sleep.

Why did T_{core} begin to fall more quickly from 2200 h and rise more earlier from 0300 h under the influence of

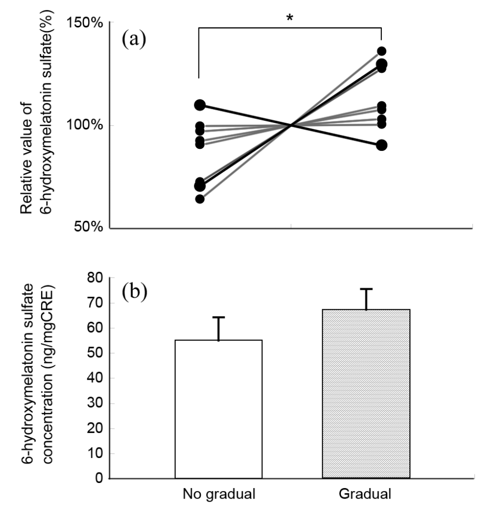

*Fig. 5. A comparison of 6-hydroxymelatonin sulfate levels during nocturnal sleep (2300 to 0700 h) under no gradual and gradual conditions. Urinary was sampled at 0700 h every morning. (a): Individual comparison of 6-hydroxymelatonin sulfate, expressed relatively. The mean of two data sets obtained from a participant exposed to two conditions was expressed as 100%. Deviations were then expressed relatively. (b), Shaded column: no gradual; Dark column: gradual. Data on urinary 6-hydroxymelatonin sulfate were expressed as per unit creatinine concentration to correct for urine volume. *p<0.05, n=10 (one participant was omitted, because failure to collect urine).*

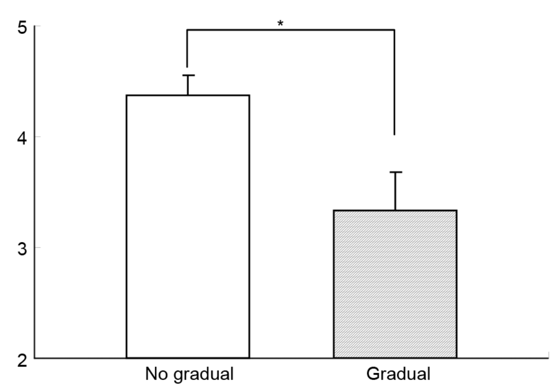

*Fig. 6. A comparison of the results from the KSS test, which was administered immediately after collecting urine, i.e., as soon as participants rose in the morning. Shaded column: no gradual. Dark column: gradual. *p<0.05. n=11.*

gradual changes of T_a and light than no gradual changes of T_a and light (Figure 4)? The reason for this is that (T_{thigh}–T_a), (T_{leg}–T_a), (T_{hand}–T_a) and (T_{foot}–T_a) were significantly greater in gradual changes of T_a and light than no gradual changes of T_a and light during nocturnal sleep. These suggest that dry heat loss from the extremities[3] was significantly higher in gradual changes of T_a and light. It should be noticed that these values between the extremities skin temperatures and surrounding air were also greater in gradual changes of T_{core} and light than in gradual changes of only T_a (Kondo et al., unpublished data). Why were these values between the extremities skin temperatures and surrounding air greater in gradual changes of T_a and light? It is because the extremities skin temperatures became higher under the influence of gradual changes of T_a and light. Evening twilight induced stronger vasodilatation during nocturnal sleep, resulting in higher skin temperatures in the extremities. According to Ki-Ja et al. (unpublished data), gradual changes of T_a and/or light induced reduction of catecholamine during nocturnal sleep, indicating an occurrence of relaxation[4] during nocturnal sleep under the influence of gradual changes of T_a and light in the evening and early morning. These findings are compatible with higher increase of the extremities skin temperatures in our present experiment.

Melatonin and catecholamine secretion may be inversely linked each other[5]. Higher level of urinary 6-hydroxymelatonin sulfate under the influence of gradual changes of T_a and light may reflect the reduced catecholamine during nocturnal sleep. The participants woke up feeling better (Figure 6), reflecting higher core temperature in the morning (Figure 4).

It is concluded that significant advance of circadian rhythms of T_{core}, quicker fall of T_{core} after retirement, faster rise of T_{core} towards morning, higher level of urinary 6-hydroxymelatonin sulfate in urine during nocturnal sleep, waking up with better feeling may occur under the influence of gradual changes of T_a and light in the evening and early morning.

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H. Tokura

Institute of Textiles & Clothing, The Hong Kong Polytechnic University, Hung Hom, Kowloon, Hong Kong
e-mail address: tchiromi@polyu.edu.hk

KOMBINIRANI UTJECAJ POSTUPNE PROMJENE TEMPERATURE ZRAKA I JAČINE SVJETLOSTI TIJEKOM ZORE I SUMRAKA NA CIRKADIJSKE RITMOVE UNUTARNJE TJELESNE TEMPERATURE I 6-HIDROKSIMELATONIN SULFATA U MOKRAĆI TE NA OSJET BUDNOSTI NETOM NAKON USTAJANJA

SAŽETAK

Cilj ovog istraživanja bio je ustanoviti kako postepene promjene temperature prostora (T_a) i jačine svjetlosti navečer i u rano jutro utječu na cirkadijske ritmove unutarnje (T_{core}) i periferne tjelesne temperature, 6-hidroksimelatonin sulfata u mokraći i osjet budnosti netom nakon ustajanja kod ljudi. Svaki ispitanik bio je podvrgnut dvama tipovima okolišnih uvjeta: 1) Stalna temperatura prostora (T_a) od 27°C tijekom 24 h i LD-pravokutna promjena jačine svjetlosti s naglim padom s 3,000 lx na100 lx u 18:00 te naglim porastom s 0 lx na 3,000 lx u 07:00. 2) Cikličke promjene T_a i postepeni pad jačine svjetlosti s 3,000 lx na 100 lx počevši u 17:00 (period sumraka od 2h) te postepeni porast s 0 lx na 3,000 lx počevši u 05:00 (ukupnog trajanja 2 h). Glavni rezultati su slijedeći: 1) Cirkadijski ritam unutarnje tjelesne temperature (T_{core}) bio je izraženiji pod utjecajem postupnih promjena T_a i svjetlosti, nego kod naglih promjena. 2) Noćni pad T_{core} i jutarnji porast bio je veći i brži pod utjecajem postupnih promjena T_a i svjetlosti nego kod naglih promjena. 3) Koncentracija 6-hidroksimelatonin sulfata u mokraći tijekom noćnog sna bila je znatno veća pod utjecajem postupnih promjena T_a i svjetlosti. 4) Osjet budnosti netom nakon ustajanja bio je znatno bolji pod utjecajem postupnih promjena T_a i svjetlosti. Objašnjavamo ove rezultate na temelju cirkadijske i termoregulacijske fiziologije.