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Effect of Systemic Estradiol Administration on Circadian Body Temperature and Activity Rhythms in Female Rats

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Abstract

The estrus cycle affects the circadian body temperature (T_b) and activity rhythms, and progesterone is related to these alterations. However, it is not clear whether estrogen (E_2) influences it. The present study examined whether E_2 affects the circadian T_b and activity rhythm. Ovariectomized rats were implanted with a silastic plate with or without E_2 underneath the dorsal skin (E_2(-) and E_2(+)), and these along with sham operated rats (SH) were measured for T_b and activity for 2 weeks. The mean T_b was lower, and mean activity was higher in E_2(+) than that in E_2(-) in the day. In the dark phase, the slope of the relationship between the mean T_b and activity in E_2(-) was the greatest. The slope in E_2(+) and SH was greater in the light phase than that in the dark phase. The daily peak of T_b and activity was lower in E_2(+) than that in E_2(-). The appearance of the nadir in T_b was later in E_2(+) and SH than that in E_2(-). The appearance of the peak in T_b and activity was earlier in E_2(+) and SH than that in E_2(-). Thus, E_2 may modulate the circadian T_b and activity rhythm in female rats.

Keywords: Estradiol; Body temperature; Activity; Circadian

Introduction

It is reported that in an environment of thermo-neutral range [1], where autonomic thermoregulatory responses are minimum, the estrus cycle affects circadian body temperature (T_b) rhythm in women [2-9] and in female rats [10-12]. In women, the change of the rhythm is characterized as the increased mean T_b and decreased circadian amplitude in the luteal phase [7,12]. The estrus cycle in female rats generally lasts 4-5 days, consisting of four phases; two days of diestrus, followed by the proestrus and estrus phases. In the proestrus phase, the mean T_b in the light phase decreases [12]. Moreover, in the proestrus phase, the tail surface temperature (T_{tail}) decreases in the dark phase [13], and spontaneous activity increases [14,15], compared with that in the other phases. The peak in the activity appears earlier in the proestrus rather than on the first day of diestrus [11]. An increase in the mean, peak, and nadir of T_b and a decrease in the amplitude of T_b were observed in the luteal phase, which shows a higher progesterone level compared with that in the follicular phase in women [5]. However, the mechanism involved in the changes of the rhythms remains unclear.

It has been speculated that progesterone, the level of which changes with the estrus cycle, affects the circadian T_b rhythm [2,5,16] in a thermoneutral environment. Progesterone administration suppressed activity in female rats [17]. In contrast to the influence of progesterone on the circadian T_b rhythm, the role of estradiol (E_2) still remains controversial. E_2 did not alter the circadian T_b rhythm in rats [13] and in women [2,3,5]; however, some reports showed that E_2 decreased the T_{tail} in the dark phase in rats [13]. E_2 influences the circadian rhythm of activity in mice [18-21] and hamsters [22,23] but not in rats [14,24]. Thus, we hypothesized that E_2 might modulate the circadian rhythm of T_b and activity.

In the present study, we compared T_b and activity between sham operated rats, ovariectomized rats, and rats administered E_2 externally, to determine the effect of E_2 on the circadian rhythm of T_b and activity.

Methods

Animals

Female Wistar rats (n=24; 224 ± 2 g; age, 8 weeks; Takasugi, Saitama, Japan) were used in the present study. They were individually housed in cages (45 cm × 25 cm × 20 cm) at an ambient temperature (T_a) of 27 ± 0.5°C with a lighting schedule of 12-h light and 12-h complete darkness (lights on at 0700 h, 300 lux at their eye level). All experimental protocols were approved by the Institutional Animal Care and Use Committee of Waseda University.

Surgery

Under inhalation anesthesia with 2% sevoflurane, a radio transmitter (26 mm × 8 mm, 2.2 g; PDT-4000 HR E-Mitter®, Starr Life Sciences Corp., Oakmont, PA, USA) for measuring T_b and spontaneous activity was placed in the peritoneal cavity. Bilateral ovariectomy or sham (SH group; n=8) surgery was conducted through a dorsal skin incision. Silastic plates (5 mm × 25 mm × 15 mm; Silpot134, 0.2 ml; Silpot catalyst 184, 20 µl; Dow Corning Toray Co., Ltd, Tokyo, Japan) with and without 17β-estradiol (Sigma, St. Louis, MO, USA) were prepared. One plate was placed under the right dorsal skin. Eight rats were implanted with an E_2 plate (E_2(+) group) and eight other animals had a control plate without E_2 (E_2(-) group). The placement of the estradiol-containing plate results in a constant E_2 level in the plasma at least for 7 days [25]. We set a pharmacological level of E_2 to determine the definitive effect of E_2. Plasma E_2 concentration was kept at a high level in the E_2(+) group (1208 ± 85 pg/ml) for 26 days. After the surgery, the rats were injected sc with

penicillin G (1,000 U, Meiji Pharmaceutical, Tokyo, Japan) to prevent post-surgical infection, and were placed in the cage at 27°C.

Experimental protocols

Before the surgery, body weight, food intake, and water intake were estimated at 0830-0900 for 5 days. Then, the entry to animal room was restricted for 2 weeks to avoid a time cue effect by the touches and sounds of experimenters during the T_b and activity measurements. After a non-contact period, the same measurements were again performed for 5 days. The signals from the radio transmitter were obtained through a receiver board ER-4000 Energizer/Receiver, Starr Life Sciences Corp.) Every 5 min, and were stored in a personal computer with a data-logging program (VitalView; Starr Life Sciences Corp.). The accuracy of the value of T_b was ± 0.1°C.

Statistics

The T_b and activity on each day were averaged every 30 min, and also for the light and dark phases and the entire day. The mean, nadir, and peak of the circadian T_b and activity rhythms and the difference between the maximum and minimum (amplitude) were estimated for each day of the 2-week measurement period, and the values were averaged. Differences in these values were assessed by two-way ANOVA with R language (R version 3.1.2, The R Foundation for Statistical Computing). Tukey-Kramer's test was used to identify the significant differences at specific time points of T_b and activity. The null hypothesis was rejected at the level of $P<0.05$.

Results

The circadian T_b and activity rhythms in a day are shown in Figure 1A and 1B. T_b in the E_2(-) group was lower than that in the SH group at 0-2, 9-10, and 15-23 hours. T_b in the E_2(+) group was lower than that in the SH group at 2-4 and 9-23 hours (Figure 1A). T_b in E_2(+) was lower than that in E_2(-) at 2-16 and 21-24 hours. Activity was lower in the E_2(-) group than that in the SH group at 0-3 and 10-23 hours. Activity was lower in the E_2(+) group than that in the SH group at 7-8, 11-12, and 21-23 hours. Activity was higher in the E_2(+) group than that in the E_2(-) group at 1-3, 10-11, and 12-23 hours (Figure 1B).

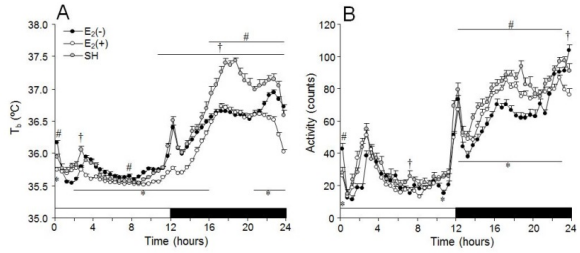

Figure 1: Body temperature (T_b) and activity in a day (A and B) in the E_2(-), E_2(+), and SH groups. Values are mean ± SE (n=8 per group). Significant difference between E_2(-) and E_2(+) (*), E_2(-) and SH (#), and E_2(+) and SH (†), $P<0.05$.

Figure 2A and 2B show the relationship between T_b and activity during the light and dark phases. Table 1 shows the slope of the regression line between T_b and activity in the light and dark phases. The slope in the light phase was not different among groups; however, in the dark phase, the slope in the E_2(-) group was the greatest among the three groups. There was no difference in the slope in the E_2(-) group between the light and dark phases; however, in the E_2(+) and SH groups, the slope was greater in the light phase than that in the dark phase.

Slope of the regression line between T_b and activity in light and dark phases in the E_2(-), E_2(+), and SH groups.

	E_2(-)	E_2(+)	SH
Light Phase	55.2 ± 2.8	64.4 ± 6.4 §	52.0 ± 4.3 §
Dark Phase	53.8 ± 2.9*,#	28.4 ± 2.3	24.9 ± 0.9

Table 1: Slope of the regression line between body temperature (T_b) and activity in the light and dark phases in the E_2(-), E_2(+), and SH groups. Values are mean ± SE (n=8 per group). Significant difference between E_2(-) and E_2(+) (*), E_2(-) and SH (#), and light and dark phases (§), $P<0.05$.

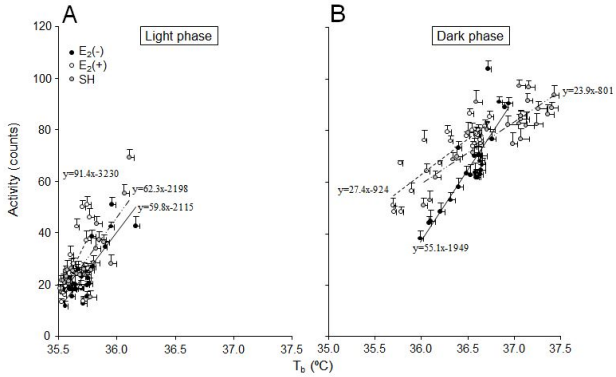

Figure 2: Relationship between T_b and activity in the light (A) and dark (B) phases in the E_2(-), E_2(+), and SH groups. Values are mean ± SE (n=8 per group).

Table 2 shows the mean in the day, light, and dark phase, the amplitude, the nadir, and the peak of T_b (°C) and activity (counts). The mean in a day of T_b in SH was the greatest among all groups. The value was not different between the E_2(+) and E_2(-) groups. The mean in the light phase of T_b was not different among the groups. On the other hand, the mean in the dark phase and the amplitude of Tb in the SH group were greater than those in the E_2(-) group, and did not differ from those in the E_2(+) group. The values in the E_2(+) group were lower than those in the E_2(-) group. The nadir of T_b was not different among groups; however, the peak of T_b in the SH group was greatest among the groups; the value in the E_2(+) group was greater than that in the E_2(-) group. The mean of activity in the SH group was greater than that in the E_2(-) group, and was not different from that in the E_2(+) group. The mean in the light phase of activity in the SH group was the greatest among groups; however, the value was not different between the E_2(-) and E_2(+) groups. The mean in the dark phase of activity in the SH group was greater than that in the E_2(-) group, and was not different from that in the E_2(+) group. The value in the E_2(+) group was greater than that in the E_2(-) group. The peak and amplitude of activity in the SH group was not different from that in the E_2(-) group, and was greater than that in the E_2(+) group. The value in the

E_2(+) group was greater than that in the E_2(-) group. The nadir of activity was not different among groups.

Mean in the day, light, and dark phase, amplitude, nadir, and peak of T_b (°C) and activity (counts) in the E_2(-), E_2(+), and SH groups				
		E_2(-)	E_2(+)	SH
T_b(°C)	Mean in a day	36.1 ± 0.0*	36.0 ± 0.0	36.3 ± 0.0 $^{\dagger,\#}$
	Mean in the light phase	35.7 ± 0.0*	35.6 ± 0.0	35.7 ± 0.0 †
	Mean in the dark phase	36.5 ± 0.0*,§	36.3 ± 0.0 §	36.9 ± 0.0 §
	Amplitude	1.5 ± 0.0*	1.4 ± 0.0	2.2 ± 0.1
	Nadir	35.5 ± 0.0*	35.5 ± 0.0	35.4 ± 0.0
	Peak	37.0 ± 0.0*	36.8 ± 0.0	37.6 ± 0.0 $^{\dagger,\#}$
Activity (counts)	Mean in a day	45 ± 1	49 ± 1*	55 ± 1$^{\#}$
	Mean in the light phase	24 ± 1	26 ± 1	29 ± 1 $^{\dagger\#}$
	Mean in the dark phase	67 ± 1 §	73 ± 3*,§	80 ± 2$^{\#,\S}$
	Amplitude	99 ± 3*	85 ± 2	97 ± 3 †
	Nadir	7 ± 1	8 ± 1	10 ± 1
	Peak	106 ± 3*	93 ± 2	106 ± 2 †

Table 2: Mean in the day, light, and dark phase, amplitude, nadir, and peak of Tb (°C) and activity (counts) in the E_2(-), E_2(+), and SH groups. Values are mean ± SE (n=8 per group). Significant difference between E_2(-) and E_2(+) (*), E_2(-) and SH ($^{\#}$), E_2(+) and SH (†), and light and dark phases (§), P<0.05.

Table 3 shows the appearance time of the nadir and the peak of T_b and activity. The appearance time of the amplitude in T_b for the SH group was earlier than that in the E_2(-) group, and was not different from that in the E_2(+) group. The value in the E_2(+) group was earlier than that in the E_2(-) group. The appearance time of the nadir in T_b in the SH group was later than that in the E_2(-) group, and was not different from that in the E_2(+) group. The value in the E_2(+) group was later than that in the E_2(-) group. The appearance time of the peak in T_b in the SH group was earlier than that in the E_2(-) group, and was not different from that in the E_2(+) group. The value in the E_2(+) group was earlier than that in the E_2(-) group. The appearance time of the amplitude in activity in the SH group was not different from that in the E_2(-) and E_2(+) groups. The value in the E_2(+) group was earlier than that in the E_2(-) group. The appearance time of the nadir in activity was not different among groups. The appearance time of the peak in activity in the SH group was earlier than that in the E_2(-) group, and was not different from that in the E_2(+) group. The appearance time of the peak in activity in the E_2(+) group was earlier than that in the E_2(-) group.

Appearance time of the nadir, peak of T_b and activity, and the amplitude in the E_2(-), E_2(+), and SH groups				
		E_2(-)	E_2(+)	SH
Appearance time of T_b (hours)	Amplitude	17.3 ± 0.8$^{*,\#}$	10.6 ± 0.6	11.7 ± 0.7
	Nadir	4.3 ± 0.6	8.0 ± 0.4*	6.9 ± 0.5$^{\#}$
Appearance time of activity (hours)	Peak	21.6 ± 0.4$^{*,\#}$	18.6 ± 0.4	18.7 ± 0.4
	Amplitude	19.3 ± 1.0*	15.4 ± 0.9	16.4 ± 1.4
	Nadir	3.8 ± 0.9	4.8 ± 0.8	4.1 ± 0.8
	Peak	23.1 ± 0.2$^{*,\#}$	20.02 ± 0.7	20.5 ± 0.9

Table 3: The amplitude, nadir, and peak of the appearance time of T_b and activity in the E_2(-), E_2(+), and SH groups. Values are mean ± SE (n=8 per group). Significant difference between E_2(-) and E_2(+) (*), E_2(-) and SH ($^{\#}$), E_2(+) and SH (†), P<0.05.

The body weight, food intake, and water intake are shown in Figure 3A-3C, respectively. Pre-surgery body weight was not different among the groups; however, post-surgery body weight in the SH group was greater than that in the E_2(-) group. The value in the E_2(+) group was

lower than that in the E_2(-) group (Figure 3A). Pre- and post-surgery food intake and water intake were not different among groups (Figure 3B and 3C). Post-surgery food intake decreased from the pre-surgery food intake in all groups (Figure 3B). Water intake showed no difference between the pre- and post-surgery (Figure 3C). Plasma estradiol concentration in the E_2(+) group was higher than that in the E_2(-) and SH groups (62 ± 6 and 201 ± 60 pg/ml, respectively).

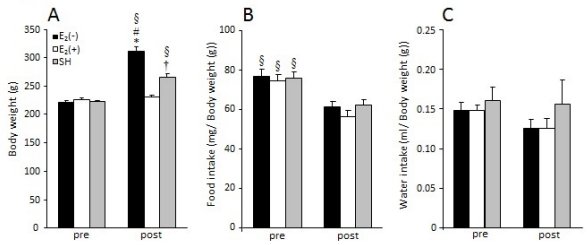

Figure 3: Body weight, food intake, and water intake (A, B, and C). Values are mean ± SE (n=8 per group). Significant difference between E_2(-) and E_2(+) (*), E_2(-) and SH ($^{\#}$), E_2(+) and SH (†), and pre-surgery vs. post-surgery (§), P<0.05.

Discussion

The present study showed that E_2 decreased the mean of T_b, and increased the mean of activity in the dark phase. E_2 affected the time-dependent relationship between T_b and activity. E_2 decreased the peak of T_b and activity, and delayed its appearance; however, E_2 did not influence the nadir of T_b and activity, but delayed their appearance. Thus, E_2 may modulate circadian rhythm of T_b and activity in female rats.

E_2 did not affect T_b in the light phase. This result coincides with those of a previous study showing that E_2 did not affect T_b in the light and dark phases [13]. Activity in the dark phase was decreased in ovariectomized mice [26] and rats [27]. The effect of E_2 on activity in the dark phase is controversial; E_2 increased it in the dark phase in mice [18,19], but did not influence it in the light and dark phases in rats [14,28]. The increased activity in the dark phase by E_2 coincided partly with the results of the previous studies.

In the E_2(+) group, the dependence of T_b on activity in the dark phase was lower than that in the light phase; however, it was not observed in the E_2(-) group (Table 1). Thus, E_2 may decrease the dependence of T_b on activity specifically in the dark phase. In literature, T_b is mainly determined by skin vasomotion and activity in rats at thermoneutral environments. E_2 decreased the T_{tail} in the dark phase at the thermoneutral range [14,28]. Vasoconstrictors like plasma adrenaline and arginine vasopressin have a circadian rhythm; higher in the light [29] and dark [30] phases, respectively. E_2 did not affect these [31,32]. Plasma renin activity and angiotensin related to the synthesis of vasoconstrictor angiotensin II were higher in the light phase in a day [33]. The influence of E_2 on angiotensin II is controversial as E_2 increased [34] or did not affect [35] it. Thus, it is difficult to assume that the vasoconstrictors induced the decreased T_{tail} by E_2 in the dark phase.

The circadian rhythm of peripheral vasodilators like endothelium-derived hyperpolarizing factor (EDHF) and endogenous hydrogen sulfide (H2S) is unknown yet. In the light phase, E_2 affected EDHF in the mesenteric artery in female rats [36,37] and H2S production in the mesenteric artery in ewes [38]. Thus, E_2 may contribute to peripheral vasodilation rather than vasoconstriction through EDHF and H2S in the light phase; however, the effect in the dark phase is unclear. E_2 is considered to affect sympathetic nerves because plasma norepinephrine fluctuated along with the estrus cycle in females [39]. E_2 may modulate the skin vasomotor circadian rhythm through vasodilators and sympathetic nerves. In summary, it was speculated that the dependence of T_b on activity was decreased due to strong skin vasomotion in the dark phase in the E_2(+) group.

The effect of E_2 on circadian T_b and activity rhythm is controversial; E_2 did not influence the circadian rhythm of T_b in female rats [28] and women [40], but increased the activity and amplitude, delayed their peaks, and advanced their onset [18]. E_2 decreased the peak of T_b and activity, advanced its appearance, and delayed the appearance of the nadir in T_b. The circadian rhythm of activity in mice administered with E_2 was similar to that in mice administered with E_2 α and β receptors agonists [18]. It was speculated that the E_2 α and β receptors are related to the alteration in T_b by E_2 in the present study, though a mechanism yet unknown.

The decreased body weight by E_2 coincided with that observed in previous studies [41-43]. E_2 administration did not affect the food intake per body weight. E_2 administration in ovariectomized rats decreased the food intake in a day [44] and in the light phase [41,42,45]. Food intake in previous studies was not calculated per body weight. This may influence a difference in the results between the present and previous studies.

The estrus cycle affects water intake and drinking behavior. Drinking behavior in the estrus phase was lesser than that in other phases [46]. Isoprenaline-induced water intake in the proestrus and estrus phases was lower than that in the other phases [47]. Ovariectomy in rats resulted in increased water intake [48]. E_2 administration decreased the water intake in female rats after water deprivation [49]. E_2 administration prolonged the onset of drinking behavior in female rats administrated with NaCl solution [50]. Our result that E_2 decreased water intake coincided that of with previous studies. The result that E_2 did not influence water intake per body weight or food intake could not be compared with previous studies, because they were not calculated previously. The apparent water intake seemed to decrease due to the decreased body weight by E_2.

The present study showed that E_2 affected the time-dependent relationship between T_b and activity, and modulated the circadian rhythm of T_b and activity in female rats.

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Author Contributions

KN supervised the entire project. YU and KN designed the study and wrote the manuscript. YU, SM and KT performed experiments.

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