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Cinnamaldehyde application decreases tail temperature in ovariectomized rats with and without estradiol administration

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ABSTRACT

The aim of this study was to examine the effect of estradiol (E_2) on the thermoregulatory responses induced by cinnamaldehyde, a component extracted from cinnamon at 16 °C or 27 °C. The thermoneutral and subneutral experiments were performed to evaluate the augmented effect of cinnamaldehyde by cold exposure and the effect of cinnamaldehyde itself. Ovariectomized rats were implanted with a silastic tube with or without E_2 ($E_2(+)$ and $E_2(-)$ groups), and data loggers into the peritoneal cavity. After the application of 30% cinnamaldehyde or vehicle into the skin of the whole trunk of rats, the rats were exposed to 16 °C or 27 °C for 2 h. Body temperature (T_b) and tail temperature (T_{tail}) were measured using a data logger and thermography. After exposure, blood samples were obtained, and plasma catecholamine concentration were measured by high-performance liquid chromatography. In the $E_2(-)$ group exposed to 27 °C, the change in T_b in rats applied cinnamaldehyde was significantly lower than that of rats applied vehicle. The change in T_{tail} in rats applied cinnamaldehyde was significantly lower than that of rats applied vehicle in both $E_2(-)$ and $E_2(+)$ groups at 27 °C and 16 °C. Plasma catecholamine concentration at 27 °C was not different among the groups. E_2 might not affect thermoregulatory responses induced by cinnamaldehyde application; however, it decreased T_{tail} in female rats.

1. Introduction

Homeothermic animals maintain body temperature (T_b) by autonomic and behavioral thermoregulatory responses. Female hormones, such as estradiol (E_2) and progesterone, affect various physiological phenomena in female animals. E_2 administration to ovariectomized rats decreased tail skin temperature (T_{tail}) (Kobayashi et al., 2000). The local administration of E_2 to the medial preoptic area in the hypothalamus of ovariectomized rats increased T_b, and decreased T_{tail} in the cold (Uchida et al., 2010). These results indicated that E_2 affected the autonomic thermoregulatory responses in female rats.

We reported a new thermoregulatory behavior of rats exposed to cold environments, including tail-hiding behavior where rats hide their tail underneath their bodies in the cold (Uchida et al., 2012). Previous studies used the thermal gradient system (Lin et al., 2012) and operant system (Adair, 1971; Hori et al., 1987) for the quantification of behavioral thermoregulatory responses in animals. Animals choose the preferred temperature in thermal gradient system; however, the temperature itself affects their T_b. The operant behavior in the system is not natural thermoregulatory behavior, because animals must be trained to use the system. Thus, tail-hiding behavior is useful for an indicator of natural thermoregulatory behavior in the cold. E_2 administration to ovariectomized rats increased the duration of tail-hiding behavior in the cold associated with the suppression of insula activation in the brain (Uchida et al., 2017) These results indicated that E_2 facilitates thermoregulatory behavior in female rats. E_2 affects the autonomic and behavioral thermoregulatory responses in the cold; however, it is still unknown if E_2 affects peripheral cold sensitivity in the skin.

We focused on TRPA1, which was one of cold receptors in sensory nerve in the skin, and activated under 17 °C in vitro (Story et al., 2003), because we exposed the rats in the cold (ambient temperature (T_a) of 16 °C) in the previous study (Uchida et al., 2017). The rat TRPA1 is activated by stepwise cold stimulus from 24 °C to 8 °C (Chen et al., 2013). In vivo, the gastric administration of TRPA1 agonists, cinnamaldehyde and allyl isothiocyanate, increased T_b and decreased T_{tail} in mice (Masamoto et al., 2009). These results indicated that TRPA1 is a cold receptor in rodents. In contrast, the result that administration of TRPA1 antagonist, A967079, did not affect coronal temperature and T_{tail} in male rats during cold exposure (Ondicova and Mravec, 2010) indicated that TRPA1 was not related to autonomic thermoregulation in the cold. It is still being debated if TRPA1 is the cold receptor; however, based on the evidences (Story et al., 2003; Chen et al., 2013), we regarded TRPA1 as the cold receptor in sensory nerve that contributed peripheral cold sensitivity, and used cinnamaldehyde, a component of

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cinnamon and a TRPA1 agonist (Premkumar and Abooj, 2013).

The aim of the present study was to validate the hypothesis that the E_2 decreased T_{tail} and increased the duration of tail-hiding behavior in ovariectomized rats applied cinnamaldehyde. The T_b, T_{tail}, the duration of tail-hiding behavior, and plasma catecholamine concentrations related to thermoregulatory responses were assessed.

2. Methods

2.1. Animals

Virgin female Wistar rats (n = 72; body weight 163.6 ± 1.3 g; age, 9 weeks; Japan SLC, Hamamatsu, Japan) were used. They were individually housed in cages (37 × 21 × 19 cm) at T_a of 26 ± 1 °C in 12:12-h light-dark cycle (light on at 07:00 h) and allowed free access to food and water. The institutional Animal Care and use Committee of Nara Women's University (Nara, Japan) approved all experimental protocols.

2.2. Surgery

The rats underwent surgery under inhalation anesthesia with isoflurane (Pfizer Japan, Tokyo, Japan). After a medial skin incision, a temperature sensor with a built-in data logger (Thermochron SL type, KN Laboratories, Osaka, Japan) for measuring T_b was implanted into the peritoneal cavity. Bilateral ovariectomy was conducted via a dorsal skin incision. A silastic tube (Dow Corning Toray Co., Ltd, Tokyo, Japan) with 22.3 mg 17β-estradiol ($E_2(+)$; Sigma- Aldrich, St. Louis, MO, USA; n = 38) or not ($E_2(-)$; n = 37) was placed underneath the right dorsal skin. The implanted E_2 tube maintained a constant E_2 concentration (75 pg/ml) in plasma (Shima et al., 2003) at levels comparable to what is observed during the proestrus phase of the estrous cycle of the rat (Butcher et al., 1974). Rats were injected with s.c. penicillin G (1000 U, Meiji Seika Pharma Co., Ltd., Tokyo, Japan) to prevent post-surgical infection.

2.3. Exposure protocols and measurements

At 1 week after surgery, each rat was transferred to a polyethylene box (19.8 × 30.3 × 48.5 cm) and moved to a climatic chamber (Program Incubator IN804, Yamato Scientific, Tokyo, Japan) maintained at 27 °C for 2 h (08:00–10:00 h). At 10:00, each rat was lightly anesthetized with isoflurane, applied 2.4 ml of vehicle (ethanol, FUJIFILM Wako Pure Chemical Corporation, Osaka, Japan) or 30% cinnamaldehyde (Sigma-Aldrich, Saint Louis, MO; solvent, ethanol) to the skin of whole trunk of rat using a piece of tissue paper (Kimwipe 10 × 12 cm). Skin hair was not shaved. Head, limbs, and tail were free from the chemicals. After recovery from anesthesia, rat was moved to a polyethylene box, exposed to 16 °C or 27 °C for following 2 h (10:00–12:00 h) during the light phase. Rat did not have access to food and water during cinnamaldehyde or vehicle application and exposure. T_a reached at the level within 30 min, and was maintained within ± 0.5 °C of each set temperature. T_a was measured at 1-min intervals by a data logger placed 5 cm above the bottom of a polyethylene box. T_{tail} and tail-hiding behavior and tail position were monitored by infrared thermography (Thermo GEAR G100, Nippon Avionics Co., Ltd, Tokyo, Japan) at 1-min intervals. Infrared thermography placed 68 cm above rat, and the accuracy was ± 0.06 °C. Based on the thermograms, T_{tail} was analyzed at two points (one-third of the tail length from the tail tip and root) and then averaged. T_{tail} value was calibrated by a compensation formula taken from a calibration experiment with thermocouple. Duration of tail-hiding behavior and each tail position were calculated as the total duration that the behavior was observed during 90 min (from 30 min to 120 min during the exposure).

After the measurements, the rats were killed via i.p. injection of an overdose of pentobarbital Na+ (50 mg/100 g bw; Somnopentil, Kyoritsu Seiyaku, Tokyo, Japan). A.

2-ml blood sample was taken from the left ventricular cavity and centrifuged at 4 °C, and the plasma was stored at −80 °C. The plasma level of catecholamine was determined by catecholamine kit in duplicate (CA test TOSOH; Tosoh Corporation, Tokyo, Japan) at SRL, Inc (Tokyo, Japan); however, the blood samples at 16 °C could not measure because the amount of the samples were not enough.

2.4. Statistical analysis

Data are presented as the mean ± standard error. The baseline value (the mean for the 30 min before 16 °C or 27 °C exposure), change in T_b and T_{tail} from the baseline levels were calculated. Values for change in T_b and T_{tail} were averaged every 30 min. Differences between $E_2(-)$ and $E_2(+)$, and vehicle and cinnamaldehyde were assessed by two-way ANOVA with SPSS Statistics 21 software (IBM Corp., Armonk, NY). The Tukey-Kramer method was performed to identify significant differences at specific time points in the change in T_b (ΔT_b) and change in T_{tail} (ΔT_{tail}), and the duration of the behavior of six patterns in the tail. The null hypothesis was rejected at the level of $P < 0.05$.

3. Results

3.1. Change in body temperature (ΔT_b) and change in tail skin temperature (ΔT_{tail})

Fig. 1 showed that the ΔT_b and ΔT_{tail} from the baseline at 27 °C (A and C) and 16 °C (B and D). At 27 °C, the baseline of T_b was not different among the groups (Vehicle/$E_2(-)$, 37.6 ± 0.1 °C; Vehicle/$E_2(+)$, 37.9 ± 0.1 °C; Cinnamaldehyde/$E_2(-)$, 37.7 ± 0.1 °C; Cinnamaldehyde/$E_2(+)$, 37.6 ± 0.1 °C). Two-way ANOVA indicated a significant main effect of time [$F(3,96) = 25.73$, $p < 0.01$] and a significant interaction between time and group on ΔT_b [$F(9,96) = 2.57$, $p < 0.05$] at 27 °C. The ΔT_b in Cinnamaldehyde/$E_2(-)$ group was lower than that in Vehicle/$E_2(-)$ group at 90 and 120 min [$p < 0.01$]. (Fig. 1A).

At 16 °C, the baseline of T_b was not different among the groups (Vehicle/$E_2(-)$, 37.7 ± 0.1 °C; Vehicle/$E_2(+)$, 37.8 ± 0.1 °C; Cinnamaldehyde/$E_2(-)$, 37.6 ± 0.1 °C; Cinnamaldehyde/$E_2(+)$, 37.7 ± 0.1 °C). Two-way ANOVA indicated a significant main effect of time [$F(2,87) = 77.10$, $p < 0.01$] and a significant interaction between time and group on ΔT_b [$F(8,87) = 2.70$, $p < 0.05$] at 16 °C. The ΔT_b in Vehicle/$E_2(+)$ group was lower than in that in Cinnamaldehyde/$E_2(+)$ group at 30 min [$p < 0.01$] (Fig. 1B).

At 27 °C, the baseline of T_{tail} was not different among the groups (Vehicle/$E_2(-)$, 28.5 ± 0.4 °C; Vehicle/$E_2(+)$, 27.8 ± 0.4 °C; Cinnamaldehyde/$E_2(-)$, 28.5 ± 0.4 °C; Cinnamaldehyde/$E_2(+)$, 27.9 ± 0.4 °C). Two-way ANOVA indicated a significant main effect of time [$F(2,88) = 28.13$, $p < 0.01$] and a significant interaction between time and group on ΔT_{tail} [$F(8,88) = 4.03$, $p < 0.01$] at 27 °C. The ΔT_{tail} in Cinnamaldehyde/$E_2(-)$ group was lower than that in Vehicle/$E_2(-)$ group at 60, 90, 120 min [$p < 0.05$; $p < 0.01$; $p < 0.01$]. The ΔT_{tail} in Cinnamaldehyde/$E_2(+)$ group was lower than that in Vehicle/$E_2(+)$ group at 90, 120 min [$p < 0.05$] (Fig. 1C).

At 16 °C, the baseline of T_{tail} was not different among the groups (Vehicle/$E_2(-)$, 28.2 ± 0.4 °C; Vehicle/$E_2(+)$, 27.9 ± 0.4 °C; Cinnamaldehyde/$E_2(-)$, 28.0 ± 0.3 °C; Cinnamaldehyde/$E_2(+)$, 28.0 ± 0.5 °C). Two-way ANOVA indicated a significant main effect of time [$F(3,96) = 1237.77$, $p < 0.01$] and a significant interaction between time and group on ΔT_{tail} [$F(9.02,96.24) = 5.75$, $p < 0.01$] at 16 °C. The ΔT_{tail} in Cinnamaldehyde/$E_2(-)$ group was lower than that in Vehicle/$E_2(-)$ group at 90 and 120 min [$p < 0.05$; $p < 0.01$]. The ΔT_{tail} in Cinnamaldehyde/$E_2(+)$ group was lower than that in Vehicle/$E_2(+)$ group at 90 and 120 min [$p < 0.05$; $p < 0.01$] (Fig. 1D).

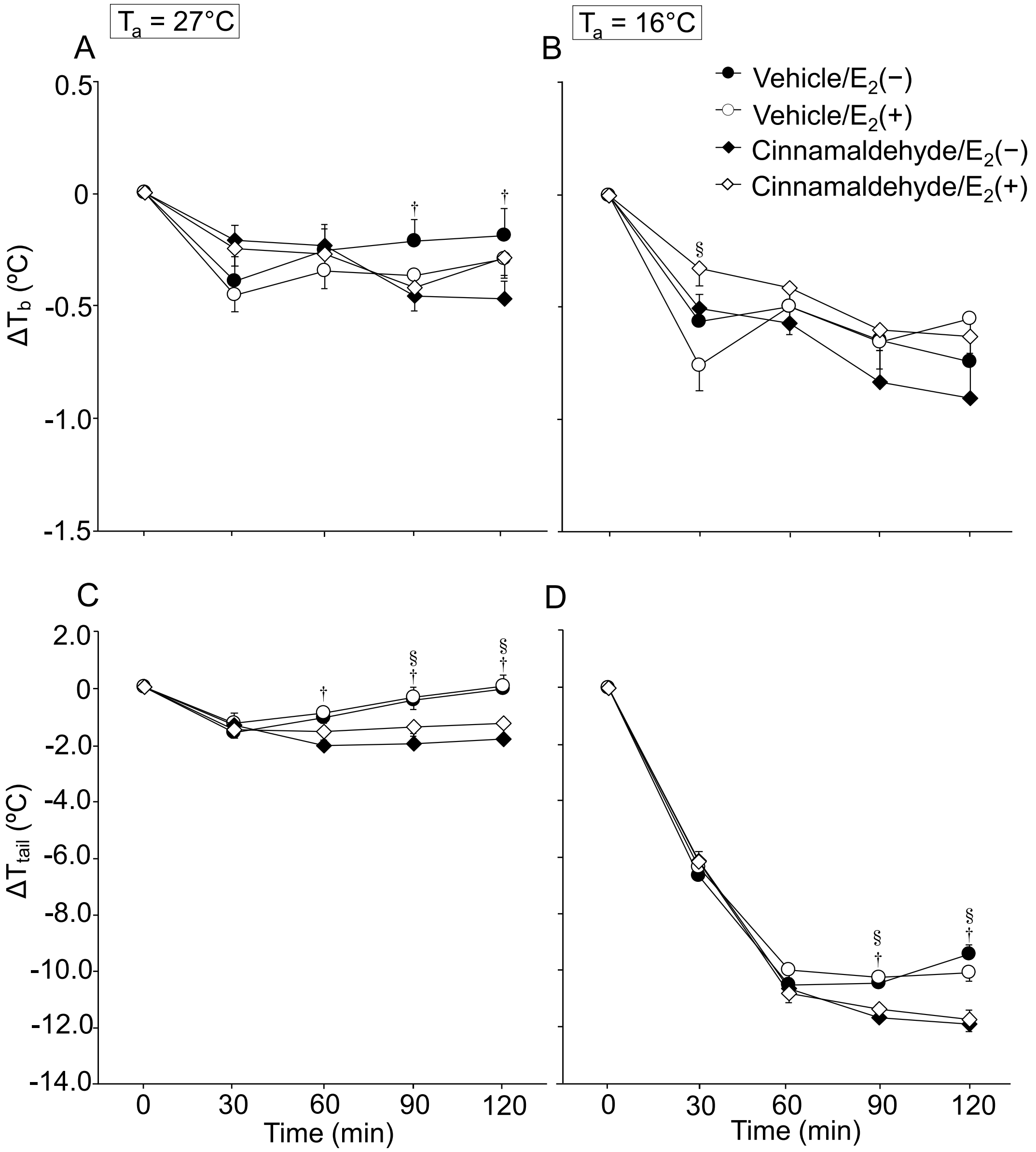

Fig. 1. Change in body temperature (T_b) and tail skin temperature (T_{tail}) from the baseline at 27 °C (A and C) and 16 °C (B and D). Values are presented as the mean ± standard error (n = 9/group). Significant difference between Vehicle/E$_2$(−) and Cinnamaldehyde/E$_2$(−) groups (†), and Vehicle/E$_2$(+) and Cinnamaldehyde/E$_2$(+) groups (§), $P < 0.05$.

3.2. Plasma noradrenaline, adrenaline, and dopamine concentrations

Fig. 2 showed plasma levels of adrenaline (A), noradrenaline (B), and dopamine (C) concentrations at 27 °C. No significant difference was observed in plasma adrenaline, noradrenaline, and dopamine concentrations among all groups.

3.3. The tail placement classification and the duration of the behavior of six patterns in the tail

Fig. 3A illustrated that the tail placement classification; whole tail (a), tail position which tip part is hidden (b), tip part of tail (c), middle part of tail at side of body trunk (d), little part of tip of tail (e), tail-hiding behavior (f). Fig. 3B showed that the duration of the behavior of six patterns in the tail at 27 °C and 16 °C. At 27 °C, two-way ANOVA indicated a significant main effect of cinnamaldehyde [F(1,32) = 56.22, $p < 0.01$] on the duration of behavior (a). The duration of behavior (a) in Cinnamaldehyde/E$_2$(−) group was greater than that in Vehicle/E$_2$(−) group [$p < 0.01$]. The duration of behavior (a) in Cinnamaldehyde/E$_2$(+) group was greater than that in Vehicle/E$_2$(+) group [$p < 0.01$]. Two-way ANOVA indicated a significant main effect of cinnamaldehyde [F(1,32) = 15.16, $p < 0.01$] on the duration of behavior (b). The duration of behavior (b) in Cinnamaldehyde/E$_2$(−) group was shorter than that in Vehicle/E$_2$(−) group [$p < 0.01$]. Two-way ANOVA indicated a significant main effect of cinnamaldehyde [F(1,32) = 4.81, $p < 0.01$] on the duration of behavior (c). The duration of behavior (c) in Cinnamaldehyde/E$_2$(+) group was shorter than that in Vehicle/E$_2$(+) group [$p < 0.05$]. Two-way ANOVA indicated a significant main effect of cinnamaldehyde [F(1,32) = 23.05, $p < 0.01$] on the duration of behavior (d). The duration of behavior (d) in Cinnamaldehyde/E$_2$(−) group was shorter than that in Vehicle/E$_2$(−) group [$p < 0.01$]. The duration of behavior (d) in Cinnamaldehyde/E$_2$(+) group was shorter than that in Vehicle/E$_2$(+) group [$p < 0.01$]. Two-way ANOVA indicated a significant main effect of cinnamaldehyde [F(1,32) = 11.43, $p < 0.01$] on the duration of behavior (e). The duration of behavior (e) in

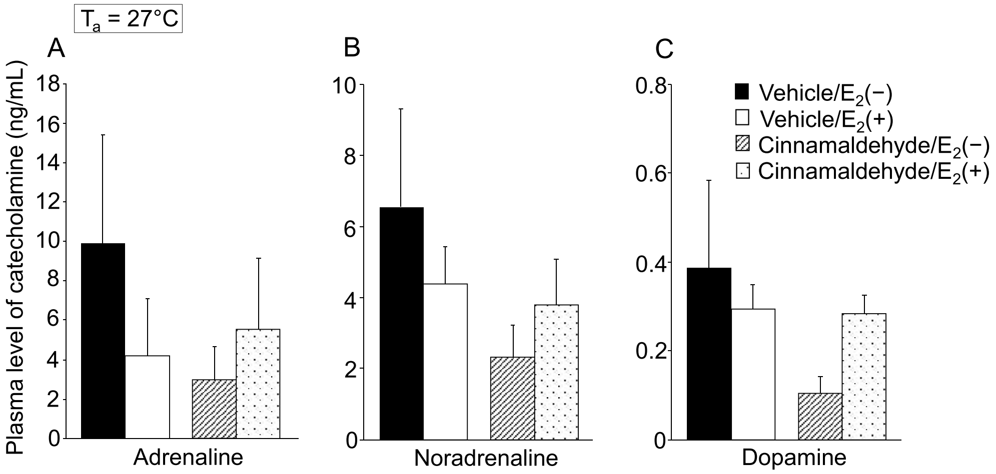

Fig. 2. Plasma levels of adrenaline (A), noradrenaline (B) and dopamine (C) concentration at 27 °C. Values are presented as the mean ± standard error (n = 7/group).

Cinnamaldehyde/$E_2(+)$ group was shorter than that in Vehicle/$E_2(+)$ group [$p < 0.01$]. Two-way ANOVA indicated a significant main effect of cinnamaldehyde [$F(1,32) = 6.31$, $p < 0.05$] on the duration of behavior (f). The duration of behavior (f) in Cinnamaldehyde/$E_2(+)$ group was shorter than that in Vehicle/$E_2(+)$ group [$p < 0.05$] (Fig. 3B–a).

At 16 °C, two-way ANOVA indicated a significant main effect of cinnamaldehyde [$F(1,32) = 42.83$, $p < 0.01$] on the duration of behavior (a). The duration of behavior (a) in Cinnamaldehyde/$E_2(-)$ group was greater than that in Vehicle/$E_2(-)$ group [$p < 0.01$]. The duration of behavior (a) in Cinnamaldehyde/$E_2(+)$ group was greater than that in Vehicle/$E_2(+)$ group [$p < 0.01$]. Two-way ANOVA indicated a significant main effect of cinnamaldehyde [$F(1,32) = 6.04$, $p < 0.05$] on the duration of behavior (b). The duration of behavior (b) in Cinnamaldehyde/$E_2(-)$ group was shorter than that in Vehicle/$E_2(-)$ group [$p < 0.05$]. Two-way ANOVA indicated a significant main effect of cinnamaldehyde [$F(1,32) = 7.94$, $p < 0.01$] on the duration of behavior (c). The duration of behavior (c) in

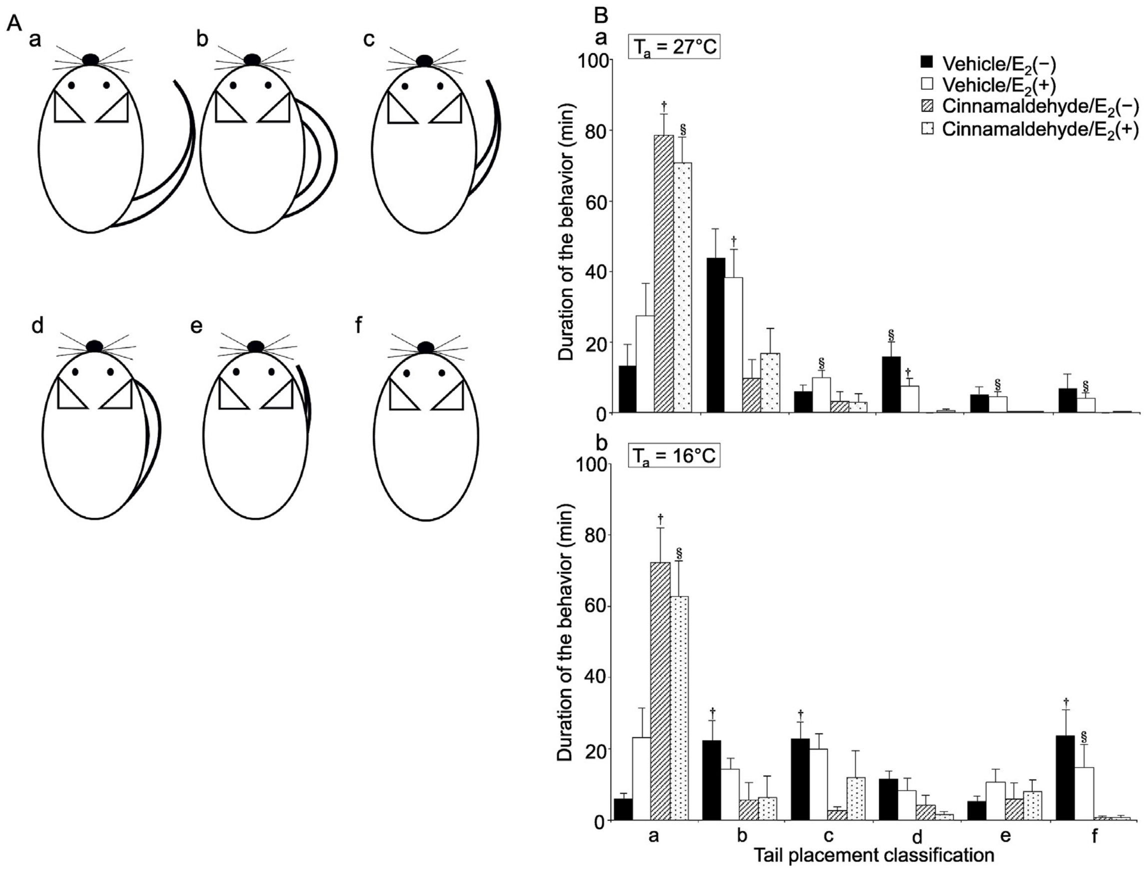

Fig. 3. Tail placement classification; whole tail (a), tail position which tip part is hidden (b), tip part of tail (c), middle part of tail at side of body trunk (d), little part of tip of tail (e), tail-hiding behavior (f). This picture was cited from a previous study (Uchida et al., 2018) (A). The duration for which each tail position was observed at 27 °C and 16 °C (B). Values are presented as the mean ± standard error (n = 9/group). Significant difference between Vehicle/$E_2(-)$ and Cinnamaldehyde/$E_2(-)$ groups (†), and Vehicle/$E_2(+)$ and Cinnamaldehyde/$E_2(+)$ groups (§), P < 0.05.

Cinnamaldehyde/$E_2(-)$ group was shorter than that in Vehicle/$E_2(-)$ group [$p < 0.01$]. Two-way ANOVA indicated a significant main effect of cinnamaldehyde [$F(1,32) = 14.13$, $p < 0.01$] on the duration of behavior (f). The duration of behavior (f) in Cinnamaldehyde/$E_2(-)$ group was shorter than that in Vehicle/$E_2(-)$ group [$p < 0.01$]. The duration of behavior (f) in Cinnamaldehyde/$E_2(+)$ group was shorter than that in Vehicle/$E_2(+)$ group [$p < 0.05$] (Fig. 3B–b).

4. Discussion

The present study revealed that cinnamaldehyde application decreased T_{tail} in ovariectomized rats exposed to 27 °C and 16 °C in the presence and absence of E_2. E_2 did not affect T_b, T_{tail}, the duration of tail-hiding behaviors, and plasma catecholamine concentration in rats treated with cinnamaldehyde. These results were not coincident with our hypothesis.

In rats exposed to 27 °C and 16 °C, E_2 did not affect a change in T_b in ovariectomized rats after application of vehicle or cinnamaldehyde. The results from ovariectomized vehicle-treated rats were consistent with results from previous studies: systemic E_2 administration did not affect T_b in ovariectomized rats in thermoneutral and subneutral conditions (Uchida et al., 2017; Hosono et al., 2001). At 27 °C, cinnamaldehyde decreased T_b in ovariectomized rats without E_2, but not with $E_{2.}$ The effect of cinnamaldehyde on T_b is controversial; i.p. cinnamaldehyde administration to male mice decreased rectal temperature (Gentry et al., 2015); however, the gastric administration of cinnamaldehyde in male mice increased coronal temperature (Masamoto et al., 2009). Additionally, the oral administration of the TRPA1 agonist, allyl isothiocyanate, did not affect T_b in humans (Langeveld et al., 2017). The differences in administration method, experimental object, and TRPA1 agonist might have yielded the different results for T_b. At 16 °C, cinnamaldehyde did not affect T_b in ovariectomized rats without E_2, but caused a slight increase in T_b in ovariectomized rats with E_2; however, the increased T_b did not persist. The results of previous study showed that oral administration of cinnamaldehyde (250 mg/kg for 7 days) did not affect T_b in male rats during cold exposure (Pandit and Anilakumar, 2017), were consistent with our results in ovariectomized rats without $E_{2.}$ These results showed that E_2 did not affect T_b in ovariectomized rats applied cinnamaldehyde in thermoneutral and subneutral conditions.

At 27 °C and 16 °C, E_2 did not affect a change in T_{tail} in ovariectomized rats treated with vehicle or cinnamaldehyde. The response of T_{tail} in ovariectomized rats treated with vehicle was consistent with the results that E_2 did not affect T_{tail} in ovariectomized rats at 27 °C and 16 °C (Uchida et al., 2017). Our results indicated that cinnamaldehyde decreased T_{tail} in ovariectomized rats with and without $E_{2,}$ exposed to 27 °C and 16 °C, was consistent with the results that the gastric administration of cinnamaldehyde in male mice decreased T_{tail} (Masamoto et al., 2009). These results showed that cinnamaldehyde decreased T_{tail} in female rats exposed to thermoneutral and subneutral conditions. We performed the thermoneutral and subneutral experiments to evaluate the effect of cinnamaldehyde itself and the augmented effect of cinnamaldehyde by cold exposure. The effect to decrease T_{tail} by cinnamaldehyde application might be attenuated or cancelled in the supraneutral due to both hot stimulus by air and cold stimulus by cinnamaldehyde. We regarded that it was not appropriate to evaluate the effect of E_2 on thermoregulatory responses by cinnamaldehyde application at supraneutral. Thus, we did not perform the experiment. It was speculated that E_2 did not affect thermoregulatory responses by cinnamaldehyde application in the supraneutral.

Tail placement classification was performed in accordance with a previous study (Uchida et al., 2018). At 27 °C and 16 °C, E_2 did not affect the duration of tail-hiding behavior in ovariectomized rats treated with vehicle, which was consistent with the results obtained from the same experimental protocol in the previous study (Uchida et al., 2018). In contrast, E_2 facilitated tail-hiding behavior in ovariectomized rats in the cold (Uchida et al., 2017). These differences may have resulted from differences in the vehicle applied. We used ethanol as the vehicle in the present study; however, the ovariectomized rats in the previous study (Uchida et al., 2017) were not treated with ethanol. Ethanol application to male mice temporarily increases oxygen consumption (Tajino et al., 2007). The heat production induced by ethanol may affect these differences. These results showed that E_2 did not affect tail-hiding behavior in ovariectomized rats treated with cinnamaldehyde. At 16 °C, T_b was maintained same level in both vehicle and cinnamaldehyde groups. The rats in vehicle group might maintain T_b by the increase of tail-hiding behavior, because the T_{tail} was greater compared with cinnamaldehyde group. In contrast, the rats in cinnamaldehyde group might maintain T_b by the decrease of T_{tail}, because the duration of tail-hiding behavior was short compared with vehicle group. Thus, cinnamaldehyde application might augment autonomic, but not behavioral thermoregulatory response to maintain T_b at 16 °C.

Catecholamine affects thermoregulatory responses; noradrenalin and adrenaline induced tail vasoconstriction in rats, respectively (Ootsuka and Tanaka, 2015; Wade and Beilin, 1970), and dopamine decreased rectal temperature in rats (Cox and Lee, 1977). E_2 and cinnamaldehyde did not affect plasma catecholamine concentration. Adrenaline concentration was increased by the intravenous administration of cinnamaldehyde (10 mg/kg) in male rats (Iwasaki et al., 2008). The oral administration of cinnamaldehyde (250 mg/kg, 7 days) did not affect plasma noradrenalin concentration in male rats exposed to the cold (Pandit and Anilakumar, 2017). The differences in the administration method and dose of cinnamaldehyde may be the reason for these different results. These results indicated that plasma catecholamine did not affect the decrease in T_{tail} caused by cinnamaldehyde. Possible reasons for the decreased T_{tail} could be central activation (e.g., the paraventricular nucleus that is the sympathetic center (Ondicova and Mravec, 2010), or medullary raphe that facilitate sympathetic nerve activity of tail (Tanaka et al., 2007)) and axon reflex by cinnamaldehyde.

In conclusion, the present study revealed that cinnamaldehyde application decreased T_{tail} in ovariectomized rats with and without E_2; however, E_2 did not affect the thermoregulatory responses induced by cinnamaldehyde. The mechanism responsible for the decrease in T_{tail} induced by cinnamaldehyde in female rats is still unknown.

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