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Systemic administration of [6]-gingerol, a pungent constituent of ginger, induces hypothermia in rats via an inhibitory effect on metabolic rate

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Abstract

We investigated the effects of systemic administrations of ginger (*Zingiber officinale* Roscoe, Zingiberaceae) or its pungent constituent, [6]-gingerol, on resting body temperature in rats. Rats given ginger-containing rat chow for 5 days showed no changes in their day–night cycle of body temperature or physical activity. However, a single intraperitoneal (i.p.) injection of [6]-gingerol (2.5 or 25 mg/kg) induced a rapid, marked drop in body temperature in a dose-related manner, with no change in physical activity. A significant decrease in metabolic rate was observed immediately after an i.p. injection of [6]-gingerol (25 mg/kg), although heat-loss responses underwent no alteration (versus vehicle). These results suggest that in rats: (a) a decrease in metabolic rate is responsible for the [6]-gingerol-induced hypothermia, and (b) [6]-gingerol modulates or interferes with the mechanisms underlying body temperature regulation, while other bioactive constituents of ginger may counteract the hypothermic effect of [6]-gingerol.

Keywords: Body temperature; Ginger; Gingerol; Heat-loss; Metabolic rate

1. Introduction

Ginger (*Zingiber officinale* Roscoe, Zingiberaceae) has been utilized in traditional oriental medicine to relieve such conditions as headache, nausea, and colds (Grant and Lutz, 2000). However, no scientific reports are available to show whether ginger has any effect on fever, a major symptom of colds, and moreover oral administration of ginger has been found to have no significant effect on resting body temperature in rats (Kano et al., 1991). One of the major pungent constituents of ginger, [6]-gingerol, has been shown to have many interesting pharmacological effects: for example, anti-oxidant, anti-tumor promoting, and anti-inflammatory effects (Kim et al., 2005; Surh, 2002; Young et al., 2005). Among these, a potent suppressive effect on fever (an inflammatory response) has been demonstrated for [6]-gingerol (Suekawa et al., 1984), although its effect on resting body temperature has never been investigated. In addition, there are conflicting reports concerning the effects of [6]-gingerol/ginger on thermogenesis (Westerterp-Plantenga et al., 2006): one study revealed a [6]-gingerol-induced increase in oxygen consumption in the perfused rat hindlimb (Eldershaw et al., 1992), while another detected no change in metabolic rate in humans eating ginger (Henry and Piggott, 1987). Thus, collectively, previous studies have not provided clear answers to the question: "How do [6]-gingerol and ginger affect body temperature and thermogenesis?".

In the present study, we investigated the effects of ginger and [6]-gingerol on resting body temperature, thermogenesis, and heat-loss activities in rats. The results suggest that in this species, an i.p. injection of [6]-gingerol elicits a marked decrease in metabolic rate, which in turn induces a drop in body temperature.

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2. Methods

2.1. Animals

The animals used in this study were male Wistar rats, weighing 250–350 g. They were housed in individual plastic cages [40 × 25 × 20 cm; (length × width × depth)] with wood-chip bedding in a room maintained at 26 ± 1 °C, a temperature near the lower limit of the thermoneutral zone for rats. They experienced a photoperiod of 12 h light:12 h dark, lights coming on at 0700. All animals had *ad libitum* access to drink and standard laboratory rat chow. The protocols were reviewed by the Committee on the Ethics of Animal Experiments in Tottori University Faculty of Medicine, and the experiments were carried out in accordance both with the Guidelines for Animal Experiments at Tottori University Faculty of Medicine and with the Federal Law (no. 221) and Notification (no. 6) issued by the Japanese Government.

This study comprised four experiments (Experiments 1–4), all on freely moving rats. Each rat took part in only one experiment. Details of the experimental protocols are given below.

2.2. Surgery

Body temperature was measured using a biotelemetry system (Data Science, Inc., St Paul, MN, USA; Lange et al., 1991) in Experiments 1 and 2 (see below). In brief, rats were anaesthetized with sodium pentobarbitone (50 mg/kg, i.p.), and a battery-operated transmitter (model TA10TA-F40) was implanted i.p. The output of the transmitter was monitored by antennae mounted in a receiver board (model CTR86) placed under each animal's cage. The data were fed into a peripheral processor (matrix model BCM100) connected to an IBM 6587-JC3 computer. This implantation was performed at least 10 days before the measurement of body temperature.

All rats were handled for 5 min each day for at least 5 days to accustom them to the experimenters.

2.3. Drugs

Normal rat chow was purchased from CLEA Japan, Inc. (CE-2; Tokyo, Japan). Ginger-containing (2%) rat chow, which was produced by Oriental Yeast Co., Ltd. (Tokyo, Japan), was made by adding ginger powder (provided by Yawata Co., Yonago, Japan) to the normal rat chow (CE-2). [6]-gingerol (WAKO, Japan) was suspended in olive oil (WAKO, Japan). The doses injected in each experimental group are given below.

2.4. Experimental protocols

2.4.1. Experiment 1

Free-moving rats ate the rat chow containing ginger (2%) to allow us to observe any changes induced in the day–night cycle of resting body temperature and/or physical activity. The normal chow was given for the first 3 days, followed by presentation of the ginger-containing chow for the next 5 days, then by a return to the normal chow for another 3 days. Switching from one to the other kind of chow was performed at 09:00. The concentration of ginger (2%) selected for this study is the highest that rats will normally eat (Iwami et al., 2003).

Each rat was gently picked up and its transmitter switched on with a magnet at 18 h before the start of the experiment. From the next day (i.e., day 1) onwards, we measured body temperature and physical activity at an ambient temperature of 26 ± 1 °C for 11 days (see above).

The amount of chow taken by the individual rats on each day (from 09:00 to 09:00) and their body weight (at 09:00 on each day) were measured, too.

2.4.2. Experiment 2

The effect of an i.p. injection of one of two doses of [6]-gingerol (2.5 or 25 mg/kg) or its vehicle (olive oil) was investigated on resting body temperature and physical activity in rats. An i.p. injection of [6]-gingerol (25–100 mg/kg) reportedly has analgesic and anti-inflammatory activities (Young et al., 2005). Furthermore, *intravenous* administration of [6]-gingerol (at 1.75–3.5 mg/kg) has antipyretic effects (Suekawa et al., 1984). Therefore, we selected doses of 2.5 and 25 mg/kg i.p. for this study. To minimize the influence of the rat's own circadian rhythm, [6]-gingerol was always given between 11:00 and 12:00 h. We measured the changes in body temperature and physical activity for 5 h after the [6]-gingerol injection. The other procedures were essentially the same as those described for Experiment 1.

Table 1
Foldagram analysis of the body temperature and activity data shown in Fig. 1

	Time of day							
	07:30	10:30	13:30	16:30	19:30	22:30	01:30	04:30
ΔBody temperature (°C)								
Days 1–3	0.02±0.06	−0.06±0.11	−0.16±0.11	−0.19±0.11	0.44±0.10	0.90±0.12	0.83±0.09	0.96±0.11
Days 4–8 (ginger period)	0.02±0.08	−0.12±0.10	−0.15±0.11	−0.05±0.11	0.69±0.11	0.94±0.14	0.91±0.12	0.95±0.14
Days 9–11	0.01±0.09	−0.20±0.11	−0.27±0.09	0.003±0.07	0.68±0.10	0.93±0.14	0.84±0.12	0.93±0.13
Activity (counts/min)								
Days 1–3	2.31±0.60	1.08±0.32	0.62±0.11	1.19±0.38	2.30±0.39	3.02±0.45	2.39±0.60	4.38±0.81
Days 4–8 (ginger period)	1.61±0.42	1.03±0.34	0.42±0.10	0.69±0.12	2.76±0.43	2.80±0.40	2.49±0.70	4.34±0.65
Days 9–11	1.50±0.37	0.95±0.33	0.57±0.11	0.59±0.13	3.00±0.53	2.89±0.44	2.66±0.53	4.33±0.54

Mean values (±S.E.M.; $n = 6$ rats) obtained in a "foldagram" analysis of data for change in body temperature (°C) and absolute activity level (counts/min) of rats eating normal (days 1–3 and days 9–11) or ginger-containing (days 4–8) rat chow.

Table 2
Daily values for body weight and intake of rat chow (ginger-containing for 5 consecutive days, following and followed by 3-day periods on normal chow)

	Time (day)										
	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10	Day 11
						g					
Intake of chow	21.2±0.6	21.3±0.6	21.7±0.6	6.3±0.7[a]	19.8±1.0	28.4±0.5[a]	16.7±1.1[a]	22.4±1.1	25.1±0.6[a]	23.7±0.6[a]	23.5±1.4
Body weight	308.8±3.6	312.4±2.2	315.1±4.0	313.0±3.5	319.7±4.0	321.6±2.5	327.0±3.1	328.3±3.5	332.5±2.7	339.5±3.8	341.5±4.2
					Ginger						

Mean values (±S.E.M.; $n=6$ rats) obtained for intake (g) of normal or ginger-containing rat chow and body weight (g).
White bar at bottom indicates "ginger" period. [a]$P<0.05$ vs. day 1 (intake of chow).

2.4.3. Experiment 3

We examined changes in metabolic rate for 5 h after an i.p. injection of [6]-gingerol (25 mg/kg). To this end, we used an open-flow indirect calorimetry system for the measurement of oxygen consumption, as previously described by Shido et al. (1995). In brief, the oxygen analyser of this system was calibrated before use by means of a certified mixture of gases (20.00% O_2 and 80.00% N_2). Then, a rat was placed in the metabolic chamber (25×30×25 cm), the wall temperature of which was set at 26±1 °C. Fresh air was introduced into the chamber at a constant rate of 1.5 l/min. Air samples passing from the metabolic chamber to the oxygen analyser were dehydrated using silica gel. A fraction of the air (100 ml/min) withdrawn from the chamber was passed into a Zirconia oxygen analyser (LC 700E; Toray, Tokyo) and oxygen consumption was calculated from measurements of oxygen content. Metabolic heat production was then calculated by multiplying the oxygen consumption by the caloric equivalent for oxygen (Dawson et al., 1970), as follows:

$$M\ (\mathrm{W}/100\ \mathrm{g}) = 0.06973 \times 4.825\ (\mathrm{cal/ml}) \times \dot{\mathrm{V}}\mathrm{O}_2\ (\mathrm{ml/min})/\mathrm{body\ weight}\ (\mathrm{g})/100$$

where M is metabolic rate; 0.06973 is a factor to convert from calories per min to W (Joule/second); 4.825 is the caloric equivalent; $\dot{V}O_2$ is oxygen consumption.

2.4.4. Experiment 4

For 5 h after the injection of [6]-gingerol (25 mg/kg i.p.), the heat-loss response was assessed in rats. This was done using a calorimeter (BCD-200; Densikagaku Co. Ltd., Tokyo, Japan) designed for the measurement of heat-loss in small animals such as mice or rats. In brief, the animal was placed in a temperature-controlled chamber (26±1 °C) and the amount of heat radiated from the animal was measured as the heat-flow through thermo-modules embedded in the walls of the chamber.

2.5. Statistical analysis

All results are expressed as mean±S.E.M.

Data from Experiments 2–4 (see Figs. 2 and 3) were analysed for statistical significance by means of a repeated-measures ANOVA, followed by Fisher's PLSD test (post hoc test) (Macintosh, StatView 4.0). A one-way ANOVA, followed by Fisher's PLSD test (post hoc test) was used for the values obtained in our modified "foldagram" analysis of data for body temperature and activity in Experiment 1 (see Table 1). In the case of body temperature, for each rat we first calculated delta changes [at 3-h intervals throughout the experiment (days 1–11)] from the baseline value obtained at time 0 (i.e. 07:00 on day 1). Then, the data for the first experimental time-point (07:30) was averaged to yield one "07:30" data-point for the group of rats for each of the three experimental periods (i.e. days 1–3, 4–8 and 9–11). This

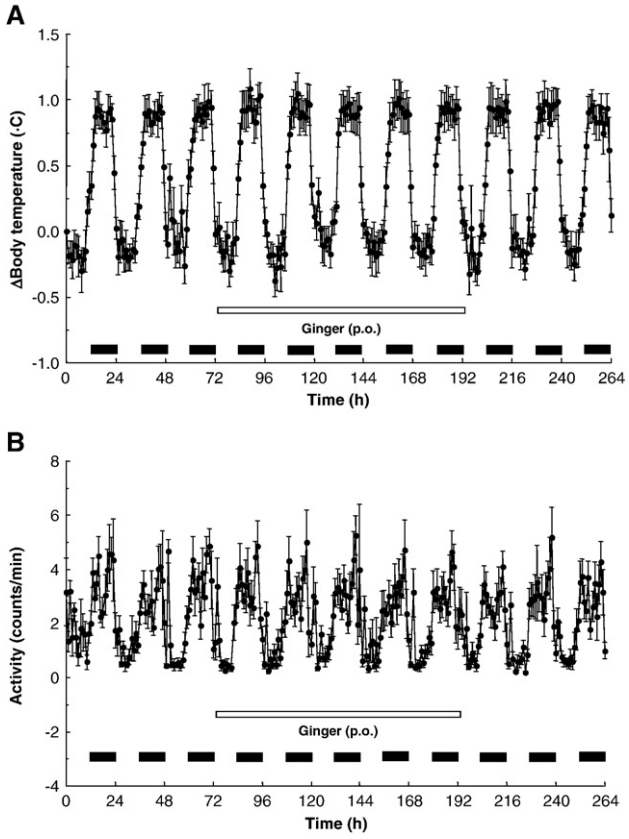

Fig. 1. Diurnal changes in body temperature and physical activity in rats given ginger-containing rat chow. Values (mean±S.E.M.) for body temperature (A; delta changes relative to baseline values) and physical activity (B; absolute values) in rats given ginger-containing (2%) rat chow over a 5-day period. Rats ate normal rat chow for 3 days before and 3 days after the "ginger" period (white bar). Mean values obtained for baseline body temperature (±S.E.M.) and physical activity levels (±S.E.M.) at time 0 [namely, at the start of the experiment (at 0700 on day 1)] were 37.11±0.08 °C and 3.17±1.24 counts/min, respectively. The black bars at the bottom indicate the periods of darkness. Each parameter was measured at 60-min intervals.

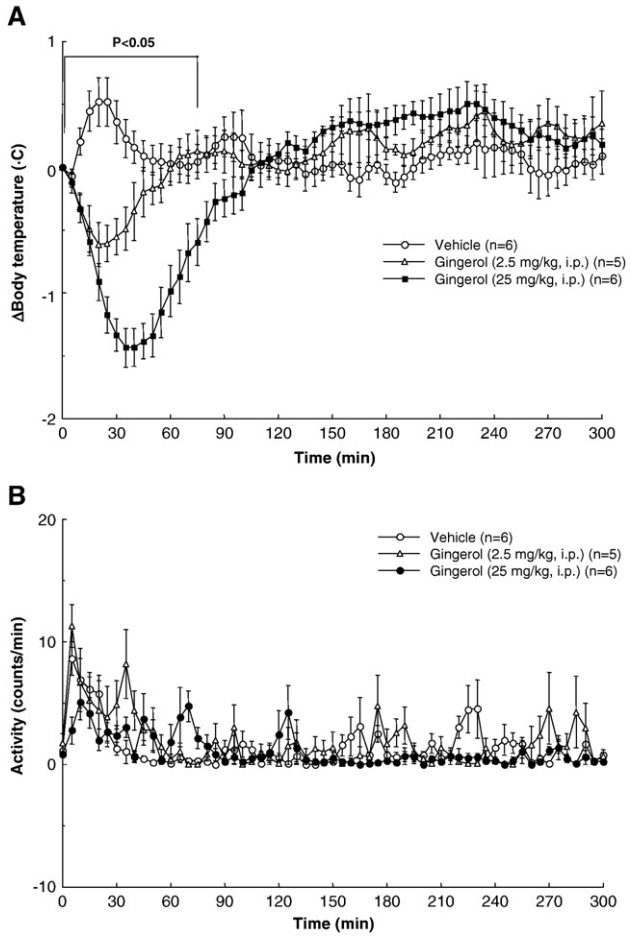

Fig. 2. Effect of intraperitoneal (i.p.) injection of [6]-gingerol on resting body temperature and physical activity in rats. Values (mean±S.E.M.) for body temperature (A; delta changes relative to baseline values) and physical activity (B; absolute values) in rats after i.p. injection of one of two doses of [6]-gingerol (2.5 or 25 mg/kg) or its vehicle. Mean values obtained for baseline body temperature (±S.E.M.) at time 0 (the time of the injection of 2.5 or 25 mg/kg of gingerol or vehicle) were 37.03±0.16 °C, 37.14±0.09 °C, and 36.93±0.13 °C, respectively. Mean baseline physical activity levels (±S.E.M.) at time 0 (the time of injection of 2.5 or 25 mg/kg of gingerol or vehicle) were 1.76±0.71 counts/min, 0.85±0.24 counts/min, and 1.17±0.46 counts/min, respectively. Each parameter was measured at 5-min intervals.

process was repeated for each of the subsequent time-points (i.e. 10:30, 13:30, etc.) throughout the 24 h, creating a new series of 8 data-points for each of the three experimental periods. In the case of activity values, the process was similar, except that absolute values (not changes) were used. Each of the food consumption values for days 2–11 (Experiment 1; see Table 2) was compared with that obtained for day 1 by means of a paired *t*-test (Macintosh, StatView 4.0). Differences were considered significant at $P<0.05$.

3. Results

3.1. Effect of oral treatment with ginger on resting body temperature and physical activity in rats (Experiment 1)

Fig. 1 shows day–night variations in resting body temperature and physical activity in rats given ginger-containing rat chow. As depicted in Fig. 1A and B, oral treatment with ginger appeared to have no effect on the diurnal changes in body temperature or physical activity. Indeed, our "foldagram" analysis (DSI Software LabPro; Data Science, Inc., St Paul, MN, USA) revealed no significant differences in either body temperature or activity between the normal chow (days 1–3 and days 9–11) and ginger (days 4–8) periods (Table 1).

As compared with the amount of normal chow that the rats had taken on day 1 (control rate), they ate little chow on the first day of the ginger period (i.e., day 4), probably because this was their first experience of the pungent taste. Afterwards, they ate ginger-containing chow irregularly — at above the control rate on day 6, below it on day 7, and at a rate equal to it on days 5 and 8 (see Table 2). On 2 days of the normal chow period (viz. on days 9 and 10), rats took the normal chow at above the control rate. A decrease in body weight (versus on the previous day) was observed only on the first day of ginger treatment (i.e. day 4), this being the day on which the profound reduction in food consumption mentioned above was detected.

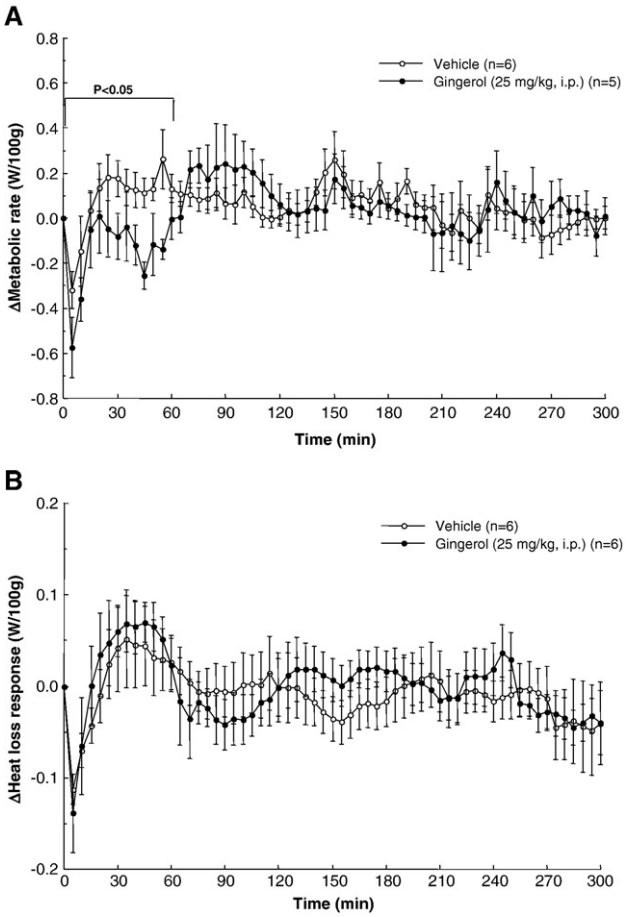

Fig. 3. Effect of intraperitoneal (i.p.) injection of [6]-gingerol on metabolic rate and heat-loss in rats. Delta changes (mean±S.E.M.; relative to baseline values) in metabolic rate (A) and heat-loss (B) in rats after i.p. injection of [6]-gingerol (25 mg/kg) or its vehicle. Mean values obtained for baseline metabolic rate (±S.E.M.) at time 0 (the time of injection of [6]-gingerol or its vehicle) were 0.50±0.03 W/100 g and 0.46±0.04 W/100 g, respectively. Mean values for baseline heat-loss (±S.E.M.) at time 0 (the time of injection of [6]-gingerol or its vehicle) were 0.48±0.02 W/100 g and 0.49±0.02 W/100 g, respectively. Each parameter was measured at 5-min intervals.

3.2. Effect of i.p. treatment with [6]-gingerol on resting body temperature and physical activity in rats (Experiment 2)

As shown in Fig. 2, i.p. injection of [6]-gingerol (2.5 or 25 mg/kg) induced a rapid and significant decrease in resting body temperature in a dose-related manner (at 0–75 min), but there were no significant changes in physical activities during the same period (versus vehicle). It can also be seen in Fig. 2A that the vehicle for [6]-gingerol, olive oil, induced no change in body temperature after its i.p. injection — except for a small increase (~0.5 °C) immediately after the injection (this represents an injection-stress-induced hyperthermia) — indicating that the vehicle *per se* had no effect on body-core temperature.

3.3. Effect of i.p. treatment with [6]-gingerol on resting metabolic rate and heat-loss response in rats (Experiments 3 and 4)

Fig. 3A shows that the metabolic rate was significantly lower ($P<0.05$) in [6]-gingerol (25 mg/kg)-injected rats than in vehicle-injected control animals from 0 to 60 min. In contrast, the heat-loss response did not differ between [6]-gingerol and vehicle injection (Fig. 3B).

The apparent falls in metabolic rate and heat-loss immediately after these injections (seen at time 0 in Fig. 3) were caused by the rat's chamber needing to be opened for us to give the injection.

4. Discussion

The present results show that i.p. injections of [6]-gingerol induce rapid, dose-related decreases in body temperature in rats. Since such injections led to no changes in the rats' physical activity, the [6]-gingerol-induced hypothermia seemed not to be due to a decrease in activity. It therefore seemed likely that [6]-gingerol induced hypothermia by actually modulating thermoregulatory mechanisms. Indeed, decreases in metabolic rate were observed after our i.p. injections of [6]-gingerol. Since the heat-loss response did not differ between [6]-gingerol and vehicle, it is likely that the decrease in metabolic rate was responsible for the [6]-gingerol-induced hypothermia. Thus, [6]-gingerol would seem to modulate or interfere with the mechanisms underlying body temperature regulation in rats. In contrast, in this study oral administration of ginger itself had no effects on the diurnal changes in body temperature. This observation seems to indicate that some component(s) of ginger other than [6]-gingerol (such as shogaol, zingerone, hexahydrocurcumin, and/or desmethylhexahydrocurcumin) may have activities opposing those of [6]-gingerol, thus counteracting the hypothermia-inducing effect of [6]-gingerol. This possibility should be examined in the near future.

Exactly how [6]-gingerol evokes changes in thermoregulatory responses, leading to hypothermia, is an interesting question. One point to be considered is the rapidity of the drop in body temperature (~5 min) after the injection of [6]-gingerol. This makes it likely that [6]-gingerol exerted its effects via the neuronal system rather than the hormonal one. It has repeatedly been reported that peripheral afferent nerves, such as the vagus, play important roles in the development of the initial upward changes in body temperature (i.e., fever) induced by systemic administration of either lipopolysaccharide or the pyrogenic cytokine, interleukin-1 (Blatteis et al., 2005; Romanovsky et al., 2005). Thus, it is possible that [6]-gingerol, by acting on afferent endings somewhere in the body, causes signals promoting hypothermia (another change in body temperature) to be sent to the brain, leading to modification of the activities of the thermoregulatory centre in the hypothalamus. Alternatively, [6]-gingerol may enter the brain and act directly on the hypothalamic thermoregulatory centre to induce hypothermia (providing [6]-gingerol administered i.p. can cross the blood–brain barrier in rats, which is yet to be determined). It should also be mentioned that in rodents, brown adipose tissue is the main organ responsible for thermogenesis, and brown adipose tissue relies on sympathetic nerves for its stimulation. Hence, [6]-gingerol could conceivably act on the efferent sympathetic innervation of brown adipose tissue to inhibit thermogenesis in rats. The above ideas will need to be tested in the not-too-distant future.

The literature contains one report showing a [6]-gingerol-induced increase in oxygen consumption in the perfused rat hindlimb (Eldershaw et al., 1992). This is inconsistent with our results, but the apparent discrepancy could be explained if we focus on the experimental conditions used. We measured oxygen consumption from freely moving rats given [6]-gingerol systemically, while the previous authors (Eldershaw et al., 1992; see above) used anaesthetized rats and measured the local oxygen consumption of a perfused hindlimb preparation. In other words, Eldershaw et al. (1992) did not examine the effects of [6]-gingerol on the whole body (including the main thermogenic organ, brown adipose tissue), and moreover the influence of anaesthesia on their results cannot be ruled out. Another of our findings, namely that oral administration of ginger had no effect on resting body temperature, is supported by previous reports indicating no significant change in the rat's body temperature after oral administration of ginger (Kano et al., 1991) and no change in the metabolic rate of humans eating ginger (Henry and Piggott, 1987). In our study, although the rats ate ginger-containing chow irregularly, we are certain that they actually took the ginger during the experimental period. Since on day 4 the food intake was very low, with the consequent decrease in body weight observed in our study, some alteration in the circadian body temperature changes might have been expected. Indeed, a hypothermic effect of food-deprivation has been reported during 4 days of food-deprivation (Yoda et al., 2000). However, a starvation-induced hypothermia was not apparent during the first day of the deprivation in that previous study, and our rats took a reduced amount of chow for only one day. Although, in our study, the resting body temperature appeared not to be altered by ginger treatment, it is possible that use of longer baseline and/or experimental periods might enable us to detect subtle effects of ginger consumption. This idea should be tested in future studies.

In summary, the present results represent the first evidence that systemic injection of [6]-gingerol in rats induces a rapid drop in resting body temperature together with an immediate decrease in metabolic rate. A previous report indicated that [6]-gingerol has

antipyretic activity (Suekawa et al., 1984). A reasonable inference is that the hypothermia-inducing effect of [6]-gingerol is responsible for its reported inhibitory effect on febrile responses. Be that as it may, the hypothermia-producing activity of [6]-gingerol could prove to be a useful tool not only for the treatment of febrile patients suffering from various forms of infectious diseases, but perhaps also for the induction of hypothermia in patients who need a lowered body temperature, such as those with a subarachnoid hemorrhage (hypothermia treatment). Actually, agents other than gingerol have been shown to evoke regulated hypothermia in experimental animals, and such an effect can be elicited in brain-damaged humans, too; indeed, such regulated hypothermia seems to be the best way to treat such patients (Gordon, 2001). Finally, we have to keep in mind the possibility that the [6]-gingerol-induced hypothermia could be an acute toxic effect. Indeed, acute administration of any of a variety of toxicants and drugs results in a regulated hypothermic response together with a reduction in oxygen consumption (Gordon, 2005; Gordon et al., 1988; Watanabe and Suzuki, 1986).

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