Nonpungent capsaicin analogs (capsinoids) increase energy expenditure through the activation of brown adipose tissue in humans[1–3]

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ABSTRACT

Background: Capsinoids—nonpungent capsaicin analogs—are known to activate brown adipose tissue (BAT) thermogenesis and whole-body energy expenditure (EE) in small rodents. BAT activity can be assessed by [^{18}F]fluorodeoxyglucose–positron emission tomography (FDG-PET) in humans.

Objectives: The aims of the current study were to examine the acute effects of capsinoid ingestion on EE and to analyze its relation to BAT activity in humans.

Design: Eighteen healthy men aged 20–32 y underwent FDG-PET after 2 h of cold exposure (19°C) while wearing light clothing. Whole-body EE and skin temperature, after oral ingestion of capsinoids (9 mg), were measured for 2 h under warm conditions (27°C) in a single-blind, randomized, placebo-controlled, crossover design.

Results: When exposed to cold, 10 subjects showed marked FDG uptake into adipose tissue of the supraclavicular and paraspinal regions (BAT-positive group), whereas the remaining 8 subjects (BAT-negative group) showed no detectable uptake. Under warm conditions (27°C), the mean (±SEM) resting EE was 6114 ± 226 kJ/d in the BAT-positive group and 6307 ± 156 kJ/d in the BAT-negative group (NS). EE increased by 15.2 ± 2.6 kJ/h in 1 h in the BAT-positive group and by 1.7 ± 3.8 kJ/h in the BAT-negative group after oral ingestion of capsinoids ($P < 0.01$). Placebo ingestion produced no significant change in either group. Neither capsinoids nor placebo changed the skin temperature in various regions, including regions close to BAT deposits.

Conclusion: Capsinoid ingestion increases EE through the activation of BAT in humans. This trial was registered at http://www.umin.ac.jp/ctr/ as UMIN 000006073. *Am J Clin Nutr* 2012;95:845–50.

INTRODUCTION

The global increase in obesity and associated comorbidities stresses the need for effective treatments. Obesity can be treated by reducing energy intake and/or increasing EE[4]. Whereas increased physical activity is usually recommended to increase EE, specific food components and/or natural substances have also been the subject of focus. One of these food substances is capsaicin—the pungent principle of hot pepper, which is known to increase EE and fat oxidation through the activation of the adrenosympathetic nervous system and to reduce body fat in rats (1–4). The thermogenic effect of red pepper was also reported in human subjects (5). However, because of its pungency, many people cannot ingest it in large quantities, and the effects observed in small rodents are less convincing in humans (6, 7). Capsinoids (capsiate, dihydrocapsiate, and nordihydrocapsiate) are capsaicin-like compounds found in a nonpungent type of red pepper, "CH-19 Sweet" (8, 9). Although capsinoids are much less pungent than capsaicin, they are as potent as capsaicin at increasing sympathetic nerve activity, thermogenesis, EE, and fat oxidation and in reducing body fat both in small rodents and humans (10–16).

Reports in small rodents suggest a role of BAT in the thermic effect of capsaicin and capsinoids. BAT is the major site of sympathetically activated thermogenesis during cold exposure and spontaneous hyperphagia and thereby controls whole-body EE and adiposity (17, 18). Intragastric administration of capsinoids produces a rapid rise in BAT temperature, which is followed by an elevation of rectal temperature in mice (19). These responses are much attenuated in mice deficient in TRPV1, a receptor for capsaicin and capsinoids. Moreover, daily treatment of rats with capsiate upregulates uncoupling protein 1—a key molecule of BAT thermogenesis (20). Collectively, it seems likely that capsinoids increase EE through the activation of the pathway of TRPV1, the sympathetic nervous system, and BAT. However, despite these observations in small rodents, the possible contribution of BAT in humans has not been reported on.

BAT has long been believed to be absent or negligible in adult humans, but recent studies using FDG-PET showed the existence of metabolically active BAT in healthy adult humans (21–23). We have shown that human BAT is involved in cold-induced increases in whole-body EE (24) and thereby, in the control of

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[2] Supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of Japan (22590227) and a Special Research Grant from Tenshi College. The capsinoids and placebo capsules were provided from Ajinomoto Co Inc, Tokyo, Japan.

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[4] Abbreviations used: BAT, brown adipose tissue; CT, computed tomography; EE, energy expenditure; FDG, fluorodeoxyglucose; PET, positron emission tomography; SUVmax, maximal standardized uptake value; TRPV1, transient receptor potential channel V1.

Received April 20, 2011. Accepted for publication January 18, 2012.

First published online February 29, 2012; doi: 10.3945/ajcn.111.018606.

adiposity (25). In the current study, we examined the effects of capsinoid ingestion on EE in healthy adult volunteers and analyzed its relation to BAT activity assessed by FDG-PET. Change in skin temperature was also monitored in various regions, including those close to BAT.

SUBJECTS AND METHODS

Subjects

Eighteen healthy men aged 20–32 y who had been living in Sapporo for >3 y were recruited. The participants were carefully instructed regarding the study and gave their informed consent to participate. They underwent a standardized health examination and FDG-PET/CT between January and March of 2010 or 2011. The protocol was approved by the institutional review boards of Tenshi College.

FDG-PET/CT

After fasting for 6 to 12 h, the subjects entered an air-conditioned room at 19°C while wearing light clothing (usually a T-shirt and underwear) and placed their feet on an ice block wrapped in cloth intermittently (usually for 4 min every 5 min). After 1 h under this cold condition, the subjects were given an intravenous injection of [^{18}F]FDG (1.66–5.18 MBq/kg body wt) and continued under the same cold conditions. One hour after the [^{18}F]FDG injection, PET/CT scans were performed by using a PET/CT system (Aquiduo; Toshiba Medical Systems) in a room at 24°C. With the CT parameters of 120 kV and real-exposure control, unenhanced low-dose spiral axial 2-mm collimated images were obtained. This was used for PET attenuation correction and for anatomic localization. Subsequently, full-ring PET was performed in 6 incremental table positions, each ~15 cm in thickness. The total time for these scans was ~30 min.

PET and CT images were co-registered and analyzed by using a VOX-BASE workstation (J-MAC System). Two experienced, blinded observers assessed FDG uptake, particularly on both sides of the neck and paravertebral regions, by visually judging the presence (BAT-positive) or absence (BAT-negative) of radioactivity greater than that of the background. BAT activity in the neck region was quantified by calculating SUVmax, defined as the radioactivity per milliliter within the region of interest divided by the injected dose in megabecquerels per gram of body weight. In our previous study, SUVmax in 162 healthy subjects visually judged as BAT-positive was 2.1–42.7 (mean ± SEM: 6.8 ± 0.8) (25). Thus, the cutoff value of SUVmax for dividing subjects into BAT-positive and BAT-negative groups was 2.0, which was also applied in other retrospective clinical studies (26, 27).

Test substances

Capsinoids and placebo capsules were provided from Ajinomoto Co Inc (Tokyo, Japan). Capsinoids were extracted from pepper fruit variety CH-19 Sweet (*Capsicum anuum L.*), purified, and encapsulated as described previously (12). Each capsule contained no (placebo) or 1.5 mg capsinoids, which consisted of capsiate, dihidrocapsiate, and nordihydrocapsiate in a 7:2:1 ratio and 199 mg of a mixture of rapeseed oil and medium-chain triglycerides.

Indirect calorimetry and skin temperature measurement

Within 4 wk after the FDG-PET/CT examination, the responses of whole-body EE and skin temperature to oral ingestion of either capsinoids or placebo were tested in a single-blind, randomized, crossover design with the BAT-positive and BAT-negative groups. The 2 tests were conducted 1–3 wk apart.

Whole-body EE was estimated by means of a respiratory gas analyzer connected to a ventilated hood (O-Jiro; Alko System). In brief, after fasting for 6 to 12 h, the subjects relaxed on a bed while wearing light clothing in a room at 27°C, and oxygen consumption and carbon dioxide production were continuously recorded for 30 min. The stable value of the last 10-min period was used to calculate the resting energy expenditure and respiratory quotient. Then, the subjects ingested a total of 6 capsinoid-containing or placebo capsules (a total dose of 9 or 0 mg, respectively) with 100 mL water in 1 min. After 15, 45, 75, and 105 min, respiratory gas parameters were recorded for 20 min, and the energy expenditure and respiratory quotient during the last 10-min period were calculated.

In parallel with respiratory gas analysis, the skin temperature was monitored continuously by using a small disc-type temperature data logger (Thermochron G; KN Laboratories), which was put in 4 positions as described previously (24): a supraclavicular region (A), which is expected to be closest to the shoulder BAT deposits; a subclavicular region, which is the middle position between A and a nipple; the forehead; and the dorsal surface of the leg at the middle position between the knee and ankle. The temperature of the eardrum was also monitored by using an ear-temperature data logger (Techno Science).

Data analysis

Data are expressed as means ± SEMs and were analyzed by either *t* tests or 3-factor ANOVA for repeated measures on 2 between-subject factors (time and capsinoids/placebo) and one within-subject factor (BAT-positive/BAT-negative) with post hoc testing by Tukey's test with IBM SPSS Statistics 18.0 (IBM Japan). Values were considered to be statistically significant if $P < 0.05$.

RESULTS

Before the measurement of EE, 18 subjects fasted overnight and underwent FDG-PET/CT examination after being kept at 19°C for 2 h in light clothing and intermittently using an ice-cooled footrest. Some subjects showed a clear and intense FDG uptake in adipose tissue in the supraclavicular region, whereas others showed no detectable FDG uptake into adipose tissue. After the FDG uptake was assessed visually and quantitatively by calculating SUVmax, the subjects were divided into 2 groups: those with undetectable FDG uptake (BAT-negative; $n = 8$) and those with detectable FDG uptake with SUVmax >2 (BAT-positive; $n = 10$). No significant difference in age, basal EE, or anthropometric measurements was found between the 2 groups (**Table 1**).

Within 4 wk after the FDG-PET/CT examination, BAT-positive and BAT-negative subjects fasted overnight and underwent

TABLE 1
Characteristics of the subjects[1]

	All (n = 18)	BAT-positive (n = 10)	BAT-negative (n = 8)
Age (y)	22.8 ± 0.7 (20–32)	22.8 ± 0.8 (20–27)	22.8 ± 1.4 (20–32)
Height (cm)	170.8 ± 1.3 (160.0–181.5)	169.6 ± 1.4 (160.0–174.5)	172.3 ± 1.4 (165.0–181.5)
Weight (kg)	62.3 ± 1.6 (51.6–72.4)	61.3 ± 2.3 (51.6–72.1)	63.6 ± 2.1 (53.2–72.4)
BMI (kg/m^2)[2]	21.3 ± 0.4 (18.7–24.3)	21.3 ± 0.6 (18.7–24.0)	21.4 ± 0.6 (19.4–24.3)
REE before capsinoid ingestion (kJ/d)	6200 ± 142 (5161–7343)	6114 ± 226 (5161–7343)	6307 ± 156 (5595–7000)
REE before placebo ingestion (kJ/d)	6173 ± 208 (4233–8085)	6115 ± 207 (4896–7162)	6246 ± 407 (4233–8085)

[1] All values are means ± SEMs; ranges in parentheses. Student's t test showed no significant differences between the BAT-positive and BAT-negative groups. BAT, brown adipose tissue; REE, resting energy expenditure.

[2] BMI was calculated as body weight (in kg) divided by the square of height (in m).

respiratory gas analysis after oral ingestion of either capsinoids (9 mg) or placebo for 2 h. Under the resting condition before ingestion of capsinoids, the mean EE calculated from oxygen consumption and carbon dioxide production was 6114 ± 226 kJ/d in the BAT-positive group, which was not significantly different from that in the BAT-negative group (6307 ± 156 kJ/d) (Table 1). The effects of capsinoid ingestion and BAT on EE were analyzed by 3-factor ANOVA for repeated measures on 2 between-subjects factors (time and capsinoids/placebo) and one within-subject factor (BAT-positive/BAT-negative). Significant effects of time ($P < 0.001$), capsinoids × BAT ($P < 0.05$), and time × capsinoids × BAT ($P < 0.05$) were found. In the BAT-positive group, EE had increased significantly 0.5–2 h after ingestion of capsinoids (maximal increase of 502 ± 81 kJ/d at 1 h), whereas it changed little after placebo ingestion (**Figure 1**). In contrast, in the BAT-negative group, no notable change was observed after ingestion of either capsinoids or placebo for ≥2 h. When the data of the 2 groups were combined, the mean EE was 6200 ± 142 kJ/d under the resting condition and did not change significantly after ingestion of capsinoids or placebo. The significant interaction of time × capsinoids × BAT implies that the difference in the EE responses to capsinoids and placebo was larger in the BAT-positive group than in the BAT-negative group. Collectively, EE was significantly higher in response to capsinoids than in response to placebo (0.5 and 1 h) in the BAT-positive group and was higher than in the BAT-negative group (0.5, 1, and 2 h).

The EE response to capsinoids during the 1-h period, expressed as area under the curve, was 15.2 ± 2.6 kJ/h in the BAT-positive group, which was significantly greater than that in

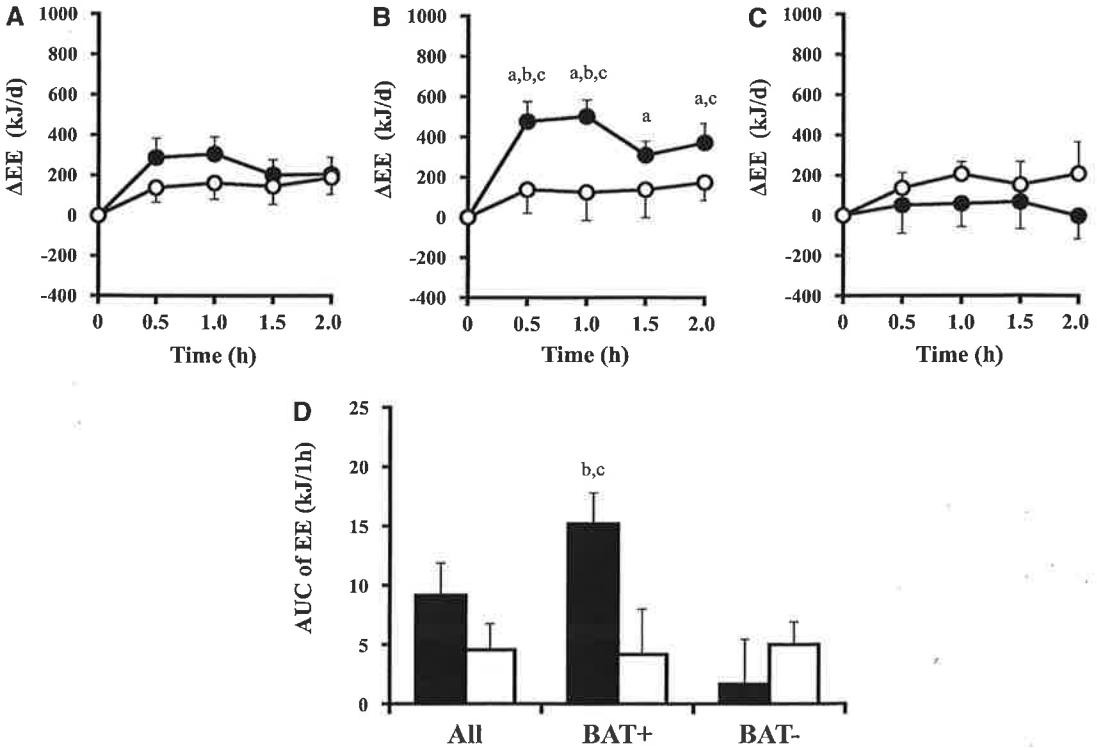

FIGURE 1. Mean (±SEM) ΔEE before (0 h) and after oral ingestion of 9 mg capsinoids (●) and placebo (○) in all subjects (A; n = 18), in BAT-positive subjects (B; n = 10), and in BAT-negative subjects (C; n = 8) and ΔEE during a 1-h period after ingestion of capsinoids (D; closed columns) and placebo (open columns), calculated as the AUC between 0 and 1 h. ANOVA showed significant effects of time ($P < 0.001$), capsinoids × BAT ($P = 0.03$), and time × capsinoids × BAT ($P = 0.046$) in B and C. [a]Significantly different from 0 h, $P < 0.05$. [b]Significantly different from placebo, $P < 0.05$. [c]Significantly different from BAT-negative group given capsinoids, $P < 0.05$. BAT, brown adipose tissue; BAT+, BAT-positive; BAT–, BAT-negative; EE, energy expenditure; ΔEE, change in energy expenditure.

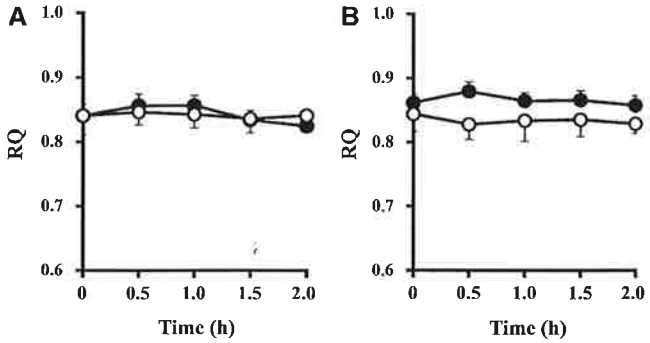

FIGURE 2. Mean (±SEM) RQ after ingestion of capsinoids (●) and placebo (○) in BAT-positive (A; n = 10) and BAT-negative (B; n = 8) subjects. ANOVA showed no significant effects. BAT; brown adipose tissue; RQ, respiratory quotient.

the BAT-negative group (1.7 ± 3.8 kJ/h; $P < 0.01$) and was also significantly greater than the response to placebo ingestion (4.2 ± 3.8 kJ/h; $P < 0.05$). When all data for the BAT-positive and BAT-negative groups were combined, no significant difference was found between capsinoid (9.2 ± 2.7 kJ/h) and placebo (4.5 ± 2.2 kJ/h) ingestion. Thus, the EE response to capsinoids was dependent on the presence of metabolically active BAT assessed by FDG-PET. Respiratory quotient was also calculated, from oxygen consumption and carbon dioxide production (**Figure 2**), and was found not to be changed after capsinoid or placebo ingestion, at least during the 2-h period.

In parallel with calorimetric measurement, the skin temperature of various regions was also monitored. As shown in **Figure 3**, ingestion of capsinoids and placebo resulted in no notable changes in the temperature of the eardrum or in some skin regions between the BAT-positive and BAT-negative groups.

DISCUSSION

In this study, we used FDG-PET/CT to determine the presence or absence of metabolically active BAT in young healthy men after 2 h of cold exposure. We then divided the subjects into BAT-positive and BAT-negative groups and examined the responses of EE and skin temperature to oral ingestion of capsinoids for 2 h. The major findings were as follows: *1*) the 2 groups showed comparable EE under a basal condition; *2*) the BAT-positive group showed an increase in EE after capsinoid, but not after placebo, ingestion; *3*) the BAT-negative group showed no notable change in EE after either capsinoid or placebo ingestion; *4*) the difference in the EE responses to capsinoids and placebo was larger in the BAT-positive group than in the BAT-negative group; and *5*) neither capsinoid nor placebo ingestion changed the skin temperature.

As reported previously (21), the metabolic activity of BAT can be assessed by performing FDG-PET/CT after acute cold exposure at 19°C. In the current study, we used this method to detect BAT in young men and divided them into 2 groups: those with undetectable BAT (BAT-negative) and those with metabolically active BAT (BAT-positive). Consistent with our previous results (21, 24, 25), cold-activated BAT was detected in ~50% of the subjects. Compared with the BAT-negative group, the BAT-positive group had comparable anthropometric measurements, including BMI and resting EE. This allowed comparison of EE and skin

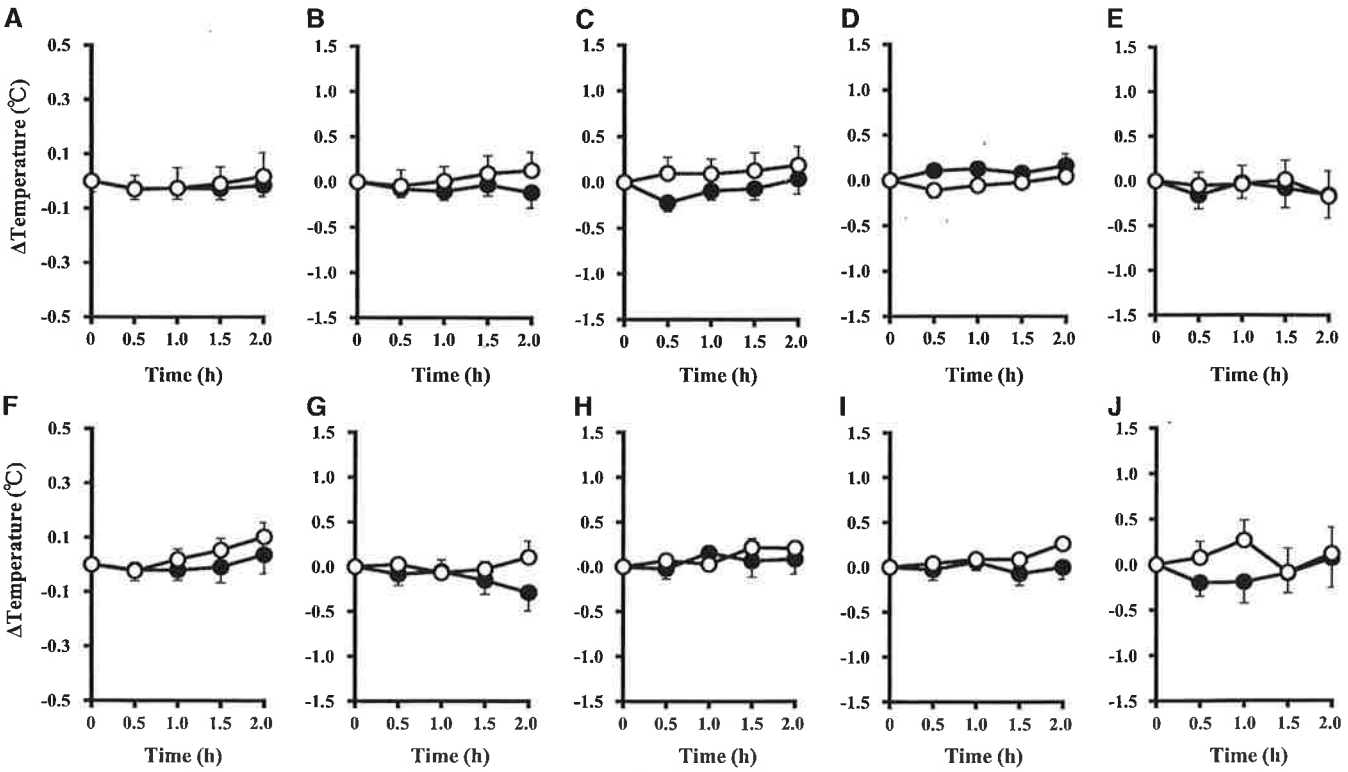

FIGURE 3. Mean (±SEM) changes in eardrum and skin temperature after ingestion of capsinoids (●) and placebo (○) in BAT-positive (A–E; n = 10) and BAT-negative (F–J; n = 8) subjects. A, F: eardrum temperature; B, G: supraclavicular region skin temperature; C, H: chest region skin temperature; D, I: forehead skin temperature; and E, J: leg skin temperature. ANOVA showed no significant effects. BAT; brown adipose tissue; Δ, change.

temperature responses without having to take into consideration the possible effects of adiposity on the responses.

The current results indicate that capsinoid ingestion elicited a slight but significant increase in EE in the BAT-positive group, whereas placebo ingestion showed no notable change. In contrast, neither capsinoid nor placebo ingestion changed EE in the BAT-negative group. Moreover, the effect of capsinoids was larger in the BAT-positive group than in the BAT-negative group. These results indicate that BAT is involved in the capsinoid-induced increase in EE, as proposed in small rodents (19, 20). It is well known that TRPV1 is the primary perceptive site of capsaicin (28). Recently, Kawabata et al (19) showed in mice that capsaicin and capsinoids activated BAT thermogenesis and increased EE through the activation of TRPV1 in the gastrointestinal tract. It is thus likely in humans, as in small rodents, that orally ingested capsinoids activate BAT via gastrointestinal TRPV1 and increase EE.

In contrast with the findings of studies in small rodents, some conflicting results have been reported about the acute effects of capsinoids on EE in humans. Galgani et al (29) reported in healthy young subjects that ingestion of 1 to 13 mg capsinoids had no influence on EE, blood pressure, or axillary temperature for $\geq$2 h. In contrast, Ohnuki et al (11) showed slightly but significantly higher EE 40 min after ingestion of CH-19 Sweet than after ingestion of California-Wandar, which contained neither capsaicin nor capsiate. In the current study, we showed that the apparent thermic effect of capsinoids was detected in BAT-positive subjects, but not in BAT-negative subjects or when the data of all subjects were combined. Thus, one of the reasons for the discrepant results reported thus far may be individual differences in BAT activity, although it was not assessed in previous studies.

Previous studies have shown a significant reduction in adiposity after prolonged ingestion of capsinoids in humans (12, 13). Our results indicate that the stimulatory effect of capsinoids on EE is largely attributable to the activation of BAT, which suggests that BAT is the site responsible for the antiobesity effect of capsinoids. This implies that capsinoids are effective in people with BAT, but not in those without detectable BAT. However, note that BAT can be recruited after chronic activation of the sympathetic nervous system. For example, prolonged cold exposure or treatment with β3-adrenoceptor agonists produces hyperplasia of BAT and ectopic induction of brown-like adipocytes in white fat pads in small rodents and dogs (17, 30–33). Increased uncoupling protein 1 expression was also shown in rats treated with capsinoids for 2 wk (20). Moreover, we reported in humans that BAT activity was increased in winter in individuals who showed undetectable activities in summer (21). Collectively, it seems possible that prolonged treatment with capsinoids and some sympathomimetic agents recruits BAT, even in individuals losing BAT. Snitker et al (13) reported a significant reduction in adiposity and an elevation of EE after a 12-wk treatment with capsinoids in middle-aged and slightly obese human subjects. A small but significant increase in EE was also confirmed when dihydrocapsiate was given for 28 d (14). Although no information about the BAT activity of their subjects was available, most of these subjects may have lost BAT activity before the treatment, given our finding that the prevalence of BAT decreases with age and that BAT is present in <30% of individuals in their forties (25). Thus, the antiobesity effects of capsinoids can best be explained by their recruitment after prolonged capsinoid treatment. Additional studies are needed to test this intriguing idea.

Capsinoid ingestion produced no notable change in the temperature of the eardrum or in some skin regions in the BAT-positive and BAT-negative groups, consistent with previous reports (29, 34). We showed previously that acute cold exposure produced a higher EE response of 1717 kJ/d and a smaller decrease in skin temperature (0.4°C) in the BAT-positive than in the BAT-negative group (24), which suggests a significant contribution of BAT to body temperature regulation during cold exposure. In the current study, the capsinoid-induced rise in EE was only 502 $\pm$ 81 kJ/d, which was significantly smaller than that after cold exposure (1717 $\pm$ 501 kJ/d) and may be insufficient to produce a detectable temperature change.

In conclusion, our results indicate the involvement of BAT in the capsinoid-induced EE in healthy men. This finding contributes to a better understanding of the underlying mechanisms of the antiobesity effects of capsaicin, capsinoids, and probably of other natural substances acting on TRPV1 and related receptors.

We thank the study participants and Ajinomoto Co Inc (Tokyo, Japan), for providing the capsinoid and placebo capsules.

The authors' responsibilities were as follows—TY and MS: designed the research; TY, SA, and YK: conducted the research; TY, TI, and MS: analyzed the data; and MS: wrote the manuscript and had primary responsibility for the final content. All authors read and approved the final manuscript. Ajinomoto Co Inc did not have any influence in the study. None of the authors had any conflicts of interest to declare.

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