Effect of dihydrocapsiate on resting metabolic rate in humans[1–3]

Jose E Galgani and Eric Ravussin

ABSTRACT

Background: Dihydrocapsiate is a capsinoid found in chili peppers. Dihydrocapsiate is similar to capsaicin, which is known for its thermogenic properties.

Objective: The objective was to determine the acute and chronic effect of dihydrocapsiate on resting metabolic rate (RMR).

Design: Seventy-eight healthy subjects in a double-blind, parallel-arm trial were randomly assigned to 3 groups receiving 0 (placebo), 3, or 9 mg dihydrocapsiate/d for 28 d. After a 10-h overnight fast, RMR was measured by indirect calorimetry for 30 min before and 120 min after ingestion of dihydrocapsiate.

Results: RMR was similar in the 3 groups before dosing on day 1 [1714 ± 41 kcal/d (0 mg), 1760 ± 41 kcal/d (3 mg), and 1694 ± 38 kcal/d (9 mg)] and after acute dosing (41 ± 17, 55 ± 17, and 3 ± 24 kcal/d for 3-mg, 9-mg, and placebo groups, respectively). When the chronic effect of dihydrocapsiate on RMR was calculated from the average 2-h RMR on day 28 minus the 30-min preingestion RMR at baseline, a borderline effect in subjects receiving 3 mg dihydrocapsiate/d compared with placebo was observed (61 ± 24 kcal/d compared with −1 ± 12 kcal/d, $P = 0.054$), whereas no significant increase in RMR in comparison with placebo was noted for the 9-mg/d dose (48 ± 23 kcal/d compared with −1 ± 12 kcal/d, $P = 0.12$). When data from both groups were combined, the thermic effect of dihydrocapsiate reached significance (53 ± 9 kcal/d compared with −1 ± 12 kcal/d in the placebo group, $P = 0.04$). Fat oxidation was unaffected by dihydrocapsiate.

Conclusion: After 1 mo of supplementation, dihydrocapsiate had a small thermogenic effect of ≈50 kcal/d, which is in the range of day-to-day RMR variability. This trial was registered at clinicaltrials.gov as NCT00999297. *Am J Clin Nutr* 2010;92:1089–93.

INTRODUCTION

The prevalence of obesity continues to increase in developed and developing countries (1). At present, energy restriction and increased physical activity are advocated in most weight control programs; however, sustained changes in diet and physical activity are difficult to achieve. There is growing interest in finding natural substances or extracts that modify energy balance. Capsaicin is naturally present in chili peppers. Capsaicin has been shown to increase energy expenditure (2) and fat oxidation (2, 3) probably via an increase in the activity of the sympathetic nervous system (4) or cathecolamine secretion (2, 5, 6). However, given its strong pungency, not all people can consume capsaicin. Capsinoids are much less pungent (7, 8) and have a thermogenic effect in mice (9, 10). In humans, we recently showed no effect of single doses of 1, 3, 6, or 12 mg of encapsulated capsinoids on metabolic rate (11). However, other studies have reported thermogenic properties including increased metabolic rate or fat oxidation after chronic consumption of encapsulated capsinoids (12, 13), thus suggesting that a prolonged consumption may be necessary to achieve efficacy on metabolic rate in humans.

Dihydrocapsiate, one of the compounds from the capsinoids family, has been synthesized (7) and may become beneficial as a food ingredient. In vivo and in vitro electrophysiologic experiments showed dihydrocapsiate to have almost similar potency compared with other capsinoids (14). We investigated in a double-blind randomized clinical trial the acute and chronic effect of 0, 3, or 9 mg of dihydrocapsiate per day for 28 d on metabolic rate and fat oxidation. In addition, changes in body weight and body composition were evaluated.

SUBJECTS AND METHODS

Subjects

Seventy-eight nonsmoking men (25–28 subjects per group) were recruited by advertising in local newspapers, television, and the Pennington Biomedical Research Center website. Participants were healthy as indicated by physical examination and routine medical laboratory tests and their body weight was stable over the past month. None of them exercised more than twice a week for the past 6 mo, and none participated in regular resistance exercise. Other exclusion criteria were attempt to diet to increase or decrease body weight; allergy to chili peppers; consumption of >2 cups tea or coffee/d, >4 cans caffeinated soft drink/d, or >3 standard alcoholic drinks/d; and use of weight-loss drugs, drugs affecting energy metabolism, and drugs for depression. Subjects' characteristics are shown in **Table 1**. The protocol was approved by the Pennington Biomedical Research Center Institutional Review Board, and all subjects provided written informed consent.

[1] From the Pennington Biomedical Research Center, Baton Rouge, LA.

[2] Supported by Ajinomoto Co, Inc (Tokyo, Japan). This work was also partially supported by a Nutrition Obesity Research Center grant 1P30 DK072476 "Nutritional Programming: Environmental and Molecular Interactions" sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases. JEG was supported by a fellowship from The International Nutrition Foundation/Ellison Medical Foundation.

[3] Address correspondence to E Ravussin, Pennington Biomedical Research Center, 6400 Perkins Road, Baton Rouge, LA 70808. E-mail: eric.ravussin@pbrc.edu.

Received June 25, 2010. Accepted for publication August 19, 2010.

First published online September 8, 2010; doi: 10.3945/ajcn.2010.30036.

TABLE 1
Characteristics of subjects at baseline[1]

		Dihydrocapsiate	
	Placebo	3 mg	9 mg
White/AA/other (*n*)	16/9/3	15/9/1	19/4/2
Age (y)	39.0 ± 2.0[2]	33.4 ± 1.9	37.6 ± 2.6
Body weight (kg)	91.0 ± 2.7	92.4 ± 2.0	90.9 ± 2.2
Body fat (%)	25.3 ± 1.0	24.6 ± 1.0	26.2 ± 0.9
BMI (kg/m^2)	29.3 ± 0.6	29.5 ± 0.5	29.3 ± 0.6

[1] There were no significant differences between groups. AA, African American.
[2] Mean ± SE (all such values).

Experimental design

This study was a double-blind, placebo-controlled, single center, randomized, parallel arm clinical trial. After completing the screening process, on days 0 and 27, participants reported at 1800 to our inpatient unit. At 1830 they received a standardized dinner and, at 2000, a snack providing 50% of resting energy requirement (15) with 50% from carbohydrates, 30% from fat, and 20% from protein. On the next day (days 1 and 28), a symptoms' checklist questionnaire was collected to assess the previous 24 h. While subjects remained in their beds, resting metabolic rate (RMR) was measured for 45 min (baseline) before and 120 min after ingestion of 9 gel capsules of placebo or dihydrocapsiate. Doses (placebo, 3 or 9 mg of dihydrocapsiate) were randomly assigned. On waking up, urine was collected after the 165-min RMR measurement of nitrogen excretion. Blood pressure and body temperature were measured before and 2 h after ingestion of the capsules. The symptoms' checklist (16) was again collected after the metabolic rate measurement.

Total body fat content was then measured by dual-energy X-ray absorptiometry scan (Hologic Dual Energy X-ray Absorptiometer—QDR 4500; Hologic, Waltham, MA). Finally, 72 h after the last testing day, subjects were contacted by phone and interviewed for the presence of symptoms and adverse events. Physical activity and consumption of tea, coffee, and alcohol were not permitted during the week preceding the metabolic evaluation. One (day 8) and 2 wk (day 15) after the measures of metabolic rate, body weight, vital signs, drug compliance, and symptoms' checklist for the past 24 h were completed.

Dihydrocapsiate capsules

Dihydrocapsiate was enzymatically synthesized with vanillyl alcohol and 8-methylnonanoic acid through esterification, filtration, extraction, and evaporation. Refined rapeseed oil was used to dilute dihydrocapsiate at a concentration of 0.5%. Capsules were then made with 1 mg dihydrocapsiate. The placebo capsules were prepared in the same manner.

With the aim of providing the same amount of capsules every day, different proportions of capsules containing placebo or dihydrocapsiate were provided. Subjects were instructed to take 3 capsules before each meal time with 100 mL of tap water. On the testing metabolic rate day (days 1 and 28), the same daily dihydrocapsiate dose (9 capsules) was given with 150 mL of tap water at room temperature.

Indirect calorimetry and fuel oxidation

RMR was measured in the participant's bed in fasting conditions. The subject was in supine position, awake, and in a quiet environment (soft music was permitted) in a room at 22°C. RMR was measured from gas exchange by using a Deltatrac II metabolic cart (Datex-Ohmeda, Helsinki, Finland). The analyzer was calibrated before each study with standardized gases containing 5% CO_2 and 95% O_2. A transparent plastic hood connected to the device was placed over the head of the participant. VO_2 and VCO_2 were calculated from continuous measurements of CO_2 and O_2 concentrations in inspired and expired air diluted in a constant airflow of ≈40 L/min. Oxygen consumption, CO_2 production, and energy expenditure standardized for temperature, pressure, and moisture were calculated at 1-min intervals. Energy substrate oxidation was calculated taking into account urinary nitrogen excretion rate (17).

Symptoms and adverse events

Assessment of adverse events was done by using a validated symptom questionnaire (16). This questionnaire assessed 34 different symptoms (eg, energetic, tired, hungry, fresh, alert, sleepy, and so forth) in 4 different intensities: not at all, slightly, moderately, or greatly. The questionnaire was administered before baseline RMR and 2 h after the ingestion of the capsules.

Statistical analysis

RMR measured under standard conditions has an intra-individual variability of <5% (11). With this in mind, our sample size allowed us to detect a difference between placebo and dihydrocapsiate groups of 75 kcal/d with type I and II errors of 5% and 10%, respectively. All statistical analyses were performed by using SAS software version 9.1.3 (SAS Institute, Cary, NC). Data were analyzed by using covariance analysis (PROC MIXED) with dose (0, 3, and 9 mg), acute consumption (before/after pill), chronic consumption (days 1 and 28) and their interactions as the fixed effects. Each subject was nested within dose as a random effect. The chronic effect of dihydrocapsiate on RMR was also assessed by comparing the changes in RMR calculated as the difference between the 2-h (1–30, 31–60, 61–90, 91–120 min) RMR at day 28 minus the 30-min RMR before dihydrocapsiate ingestion at baseline. The statistical significance for multiple comparisons was adjusted by using the Tukey-Kramer method. Race distribution and frequency of presence or absence of symptoms among groups were tested by using chi-square analyses. $P < 0.05$ was considered statistically significant. Data are expressed as means ± SEs.

RESULTS

Compliance in use of capsules was high and not different between groups [placebo (97 ± 1%), 3 mg dihydrocapsiate (96 ± 1%), and 9 mg dihydrocapsiate (95 ± 2%); $P = 0.50$]. After 28 d of placebo or dihydrocapsiate treatment, a significant increase in fat mass was detected (0.34 ± 0.11 kg; $P = 0.002$), while a borderline increase in fat-free mass was observed after 28 d (0.23 ± 0.12 kg; $P = 0.07$). None of these changes were

TABLE 2
Body composition and resting metabolic rate (RMR) before and after 28 d of placebo or dihydrocapsiate ingestion[1]

	Placebo (n = 28)		3 mg dihydrocapsiate (n = 25)		9 mg dihydrocapsiate (n = 25)		Effect (P value)		
	Day 0	Day 28	Day 0	Day 28	Day 0	Day 28	Acute	Chronic	Dose
Fat-free mass (kg)	67.6 ± 1.8	67.7 ± 1.8	69.5 ± 1.5	69.9 ± 1.5	66.8 ± 1.4	67.1 ± 1.4	—	0.07	0.47
Fat mass (kg)	23.4 ± 1.4	23.7 ± 1.4	22.9 ± 1.2	23.2 ± 1.1	24.0 ± 1.3	24.4 ± 1.3	—	0.002	0.81
RMR									
Before pill ingestion (kcal/d)	1714 ± 41	1700 ± 43	1760 ± 41	1792 ± 39	1694 ± 38	1723 ± 35	0.003	0.19	0.22
After pill ingestion (kcal/d)	1717 ± 40	1716 ± 37	1800 ± 39	1817 ± 42	1749 ± 31	1755 ± 39			
Acute thermogenic effect (kcal/d)	3 ± 24	17 ± 19	41 ± 17	25 ± 21	55 ± 17	31 ± 16	—	0.56	0.27
Total AUC (kcal × min/d)	205,654 ± 4713	205,637 ± 4511	215,481 ± 4670	217,217 ± 4952	207,931 ± 4079	210,107 ± 4535	—	0.43	0.21
Nonprotein RQ									
Before pill ingestion	0.84 ± 0.01	0.85 ± 0.01	0.83 ± 0.01	0.85 ± 0.01	0.83 ± 0.01	0.85 ± 0.01	<0.001	<0.0001	0.73
After pill ingestion	0.83 ± 0.01	0.84 ± 0.01	0.82 ± 0.01	0.84 ± 0.01	0.83 ± 0.01	0.83 ± 0.01			
Total AUC (min)	100 ± 1	101 ± 1	99 ± 1	101 ± 1	99 ± 1	100 ± 1	—	0.005	0.79
Fat oxidation (g/d)									
Before pill ingestion	68 ± 5	60 ± 5	72 ± 5	67 ± 6	68 ± 7	65 ± 6	<0.001	0.002	0.44
After pill ingestion	74 ± 4	69 ± 5	83 ± 5	75 ± 5	76 ± 5	77 ± 5			
Total AUC (g × min/d)	8831 ± 482	8189 ± 539	9854 ± 563	8876 ± 634	8749 ± 604	9077 ± 613	—	0.20	0.47

[1] All values are means ± SEs. RQ, respiratory quotient; AUC, area under the curve after pill ingestion. Metabolic variables were analyzed with the mixed model. Data were analyzed by using covariance analysis (PROC MIXED; SAS Institute, Cary, NC) with dose (0, 3, and 9 mg), acute consumption (before or after taking pill), and chronic consumption (days 1 and 28) and their interactions as fixed effects, whereas the subject nested within dose was the random effect. Fat and fat-free masses used similar analyses without acute effect.

affected by treatment ($P > 0.47$) or its interaction with time ($P > 0.74$) (**Table 2**).

Symptoms and adverse events

In general, dihydrocapsiate capsules were well tolerated and only a few differences in symptoms and adverse events between groups were observed. On day 1 and after pill ingestion, 32% of the individuals in the placebo group reported dry mouth, whereas 44% and 66% of the subjects taking 9 and 3 mg dihydrocapsiate/d, respectively, reported that same symptom ($P = 0.04$). On day 28 and before pill ingestion, 12% of the subjects taking 9 mg dihydrocapsiate/d reported leg cramps compared with none of the individuals taking 3 mg dihydrocapsiate/d or placebo ($P = 0.04$).

Energy metabolism

Metabolic rate, nonprotein respiratory quotient, and fat oxidation before and after pill ingestion on days 1 and 28 are shown in Table 2. Metabolic rate measured over 2 h after pill ingestion was higher than values observed before pill ingestion ($P = 0.003$). No differences in metabolic rate were detected when values on days 1 and 28 were compared ($P = 0.19$). Similarly, no effect of dihydrocapsiate was observed on metabolic rate when compared with placebo ($P = 0.22$). In addition, metabolic rate assessed by the total area under the curve remained similar across doses ($P = 0.21$) and days ($P = 0.43$). Fat oxidation was higher after pill ingestion ($P < 0.0001$) and lower after 28 d of intervention ($P = 0.002$). However, no dose effect on fat oxidation was noted ($P = 0.44$). When the total area under the curve was analyzed, no differences between days ($P = 0.20$) and doses ($P = 0.47$) were detected.

To evaluate the chronic effect of dihydrocapsiate on energy metabolism, we performed further analysis by comparing the changes in RMR from the differences between each 30-min period after 28 d minus RMR before pill ingestion at baseline (**Figure 1**). This thermogenic effect was almost significant in subjects receiving 3 mg dihydrocapsiate/d compared with placebo (61 ± 24 kcal/d compared with -1 ± 12 kcal/d, respectively; $P = 0.054$) but not in those receiving 9 mg/d (48.1 ± 23.4 kcal/d; $P = 0.12$). This chronic effect of dihydrocapsiate reached statistical significance only after combining the active groups (3 and 9 mg): 53 ± 9 kcal/d compared with -1 ± 12 kcal/d in the placebo group ($P = 0.04$).

Because small but significant differences in body size and composition were detected after 28 d of intervention (Table 2), we repeated all the analyses after adjusting for fat-free mass. Results were virtually identical when compared with unadjusted results (data not shown).

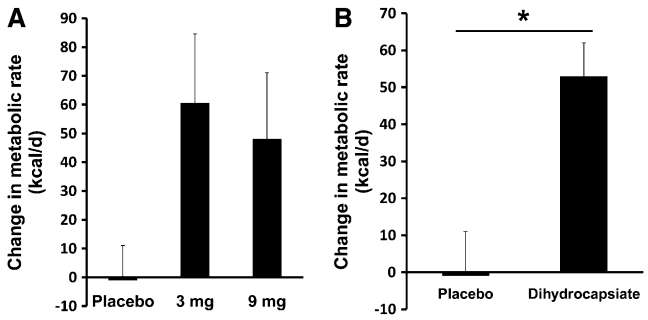

FIGURE 1. Change in metabolic rate after 28 d of placebo or dihydrocapsiate ingestion. Change in metabolic rate calculated as 2.5-h resting metabolic rate on day 28 minus resting metabolic rate before pill ingestion on day 1. A: Difference calculated in each group (placebo, 3 and 9 mg dihydrocapsiate/d). B: Difference calculated after combining groups receiving dihydrocapsiate (3 and 9 mg) compared with placebo. Data were analyzed by using covariance analysis (PROC MIXED; SAS Institute, Cary, NC) with dose (0, 3, and 9 mg). Statistical significance for multiple comparisons was adjusted by using the Tukey-Kramer method. $*P < 0.05$

DISCUSSION

In this study, we observed no significant increase in metabolic rate after acute consumption of dihydrocapsiate. However, only after combining the 2 dihydrocapsiate groups (3 and 9 mg), we did observe an ≈50-kcal/d increase in metabolic rate, which might be encouraging enough to pursue its utility during weight-loss intervention.

This study was originally designed to detect a statistically and biologically meaningful increase in RMR of 75 kcal/d at the 9-mg dose when compared with placebo. We set up this cutoff because the day-to-day variability in RMR is ≈5% (11, 18). Thus, we failed to show such an effect with 9 mg of daily ingestion of dihydrocapsiate. However, our 50-kcal/d increase in metabolic rate in the combined group is in agreement with another study by using chronic treatment of natural capsinoids extract (13). Furthermore, such a small energy imbalance should be kept in the context of the general increase in body weight observed in the United States over the past 2–3 decades, which may have been triggered by a persistent positive energy imbalance of as little as 50 kcal/d (19). One can also make the case that a small but consistent increase in energy expenditure will help individuals maintain body weight if not lose weight. Whether this small thermogenic effect may affect body weight in the long term cannot be answered from our study. However, the concept that small changes in energy homeostasis can modify body mass has been vigorously challenged by us and others (20–22).

In our previous human study, by using a single-dose crossover acute study we observed no thermogenic impact of a natural capsinoids extract (11). On the basis of this observation and the previous findings of increased oxygen consumption with increasing uncoupling proteins following 2-wk capsinoid treatment in animal studies (9, 10), we had predicted the possibility that a longer exposure to dihydrocapsiate would increase metabolic rate. The findings of the metabolic rate from the present study could, at least partly support this prediction.

A main limitation in our study design is the short period of metabolic assessment (≈2.5 h). A more physiologic, integrative, and comprehensive approach would be to include 24-h energy expenditure measurements. This method is more accurate and reproducible than RMR measurements (23). Further investigation by using this method is needed to confirm our original hypothesis. Changes in body mass and composition may offer an appropriate alternative to assess long-term energy homeostasis. Unless compensatory changes in energy intake and/or physical activity occur, an increase in energy expenditure and/or fat oxidation should lead to a reduction in body weight and/or fat mass. We did not observe changes in body weight or body composition between the placebo and dihydrocapsiate groups. These are not unlikely responses because it is known that energy

homeostasis is tightly regulated by complex and still-not-so-well-understood mechanisms (24). Because the present study focused on energy metabolism rather than body weight or composition, the subjects were not advised to modify their lifestyle. Surprisingly, Snitker et al (13) reported that increases in metabolic rate and fat oxidation in response to capsinoids were not accompanied by enhanced whole-body fat mass loss despite some abdominal fat mass loss. A potential explanation for such a tissue-specific fat mass reduction may be that tissues such as visceral adipose tissue have higher β-adrenergic receptor density and adrenergic sensitivity (25, 26) and therefore more visceral lipolysis. This idea highlights the potential influence of brown adipose tissue, another highly β-adrenergic receptor dense tissue, in modulating the effect of capsinoids on energy metabolism in humans. The recent discovery of variable amounts of brown adipose tissue in adult humans (27–29) supports this hypothesis.

In conclusion, this study showed that dihydrocapsiate ingestion does not stimulate acutely metabolic rate measured under resting fasting conditions. After 4 wk of exposure to the compound and only when the participants from both groups on dihydrocapsiate were combined, there was a small but significant effect on RMR, which was within the range of the day-to-day variability in RMR. Only well-controlled, long-term studies will provide insight into the physiologic relevance of small alterations in energy balance by dihydrocapsiate ingestion on weight management. In addition, the role of dihydrocapsiate in combination with meals or exercise on metabolic rate should also be explored.

The authors' responsibilities were as follows—ER: participated in study design, data analysis, and preparation of the manuscript; and JEG: participated in study design, data collection, analysis and preparation of the manuscript. Ajinomoto Co, Inc, did not have influence in the subjects' recruitment nor in data collection, analysis, interpretation, or the decision to publish this study. Neither author had any conflicts of interest to declare.

REFERENCES

1. Nishida C, Uauy R, Kumanyika S, Shetty P. The joint WHO/FAO expert consultation on diet, nutrition and the prevention of chronic diseases: process, product and policy implications. Public Health Nutr 2004;7:245–50.
2. Kawada T, Watanabe T, Takaishi T, Tanaka T, Iwai K. Capsaicin-induced beta-adrenergic action on energy metabolism in rats: influence of capsaicin on oxygen consumption, the respiratory quotient, and substrate utilization. Proc Soc Exp Biol Med 1986;183:250–6.
3. Lejeune MP, Kovacs EM, Westerterp-Plantenga MS. Effect of capsaicin on substrate oxidation and weight maintenance after modest body-weight loss in human subjects. Br J Nutr 2003;90:651–9.
4. Watanabe T, Kawada T, Kurosawa M, Sato A, Iwai K. Adrenal sympathetic efferent nerve and catecholamine secretion excitation caused by capsaicin in rats. Am J Physiol 1988;255:E23–7.
5. Kawada T, Sakabe S, Watanabe T, Yamamoto M, Iwai K. Some pungent principles of spices cause the adrenal medulla to secrete catecholamine in anesthetized rats. Proc Soc Exp Biol Med 1988;188:229–33.
6. Watanabe T, Kawada T, Yamamoto M, Iwai K. Capsaicin, a pungent principle of hot red pepper, evokes catecholamine secretion from the adrenal medulla of anesthetized rats. Biochem Biophys Res Commun 1987;142:259–64.
7. Kobata K, Sutoh K, Todo T, Yazawa S, Iwai K, Watanabe T. Nordihydrocapsiate, a new capsinoid from the fruits of a nonpungent pepper, capsicum annuum. J Nat Prod 1999;62:335–6.
8. Iida T, Moriyama T, Kobata K, et al. TRPV1 activation and induction of nociceptive response by a non-pungent capsaicin-like compound, capsiate. Neuropharmacology 2003;44:958–67.
9. Masuda Y, Haramizu S, Oki K, et al. Upregulation of uncoupling proteins by oral administration of capsiate, a nonpungent capsaicin analog. J Appl Physiol 2003;95:2408–15.
10. Ohnuki K, Haramizu S, Oki K, Watanabe T, Yazawa S, Fushiki T. Administration of capsiate, a non-pungent capsaicin analog, promotes energy metabolism and suppresses body fat accumulation in mice. Biosci Biotechnol Biochem 2001;65:2735–40.
11. Galgani JE, Ryan DH, Ravussin E. Effect of capsinoids on energy metabolism in human subjects. Br J Nutr 2010;103:38–42.
12. Inoue N, Matsunaga Y, Satoh H, Takahashi M. Enhanced energy expenditure and fat oxidation in humans with high BMI scores by the ingestion of novel and non-pungent capsaicin analogues (capsinoids). Biosci Biotechnol Biochem 2007;71:380–9.
13. Snitker S, Fujishima Y, Shen H, et al. Effects of novel capsinoid treatment on fatness and energy metabolism in humans: possible pharmacogenetic implications. Am J Clin Nutr 2009;89:45–50.
14. Sasahara I, Furuhata Y, Iwasaki Y, et al. Assessment of the biological similarity of three capsaicin analogs (Capsinoids) found in non-pungent chili pepper (CH-19 Sweet) fruits. Biosci Biotechnol Biochem 2010;74:274–8.
15. Shetty P. Energy requirements of adults. Public Health Nutrition 2005;8(7A):994–1009.
16. Wadden TA, Stunkard AJ, Day SC, Gould RA, Rubin CJ. Less food, less hunger: reports of appetite and symptoms in a controlled study of a protein-sparing modified fast. Int J Obes 1987;11:239–49.
17. Jequier E, Acheson K, Schutz Y. Assessment of energy expenditure and fuel utilization in man. Annu Rev Nutr 1987;7:187–208.
18. Adriaens MP, Schoffelen PF, Westerterp KR. Intra-individual variation of basal metabolic rate and the influence of daily habitual physical activity before testing. Br J Nutr 2003;90:419–23.
19. Hill JO. Understanding and addressing the epidemic of obesity: an energy balance perspective. Endocr Rev 2006;27:750–61.
20. Butte NF, Ellis KJ. Comment on "Obesity and the environment: where do we go from here?". Science 2003;301:598 (author reply).
21. Swinburn BA, Jolley D, Kremer PJ, Salbe AD, Ravussin E. Estimating the effects of energy imbalance on changes in body weight in children. Am J Clin Nutr 2006;83:859–63.
22. Weinsier RL, Bracco D, Schutz Y. Predicted effects of small decreases in energy expenditure on weight gain in adult women. Int J Obes Relat Metab Disord 1993;17:693–700.
23. Ravussin E, Lillioja S, Anderson TE, Christin L, Bogardus C. Determinants of 24-hour energy expenditure in man. Methods and results using a respiratory chamber. J Clin Invest 1986;78:1568–78.
24. Galgani J, Ravussin E. Energy metabolism, fuel selection and body weight regulation. Int J Obes (Lond) 2008;32:S109–19.
25. Hellmer J, Marcus C, Sonnenfeld T, Arner P. Mechanisms for differences in lipolysis between human subcutaneous and omental fat cells. J Clin Endocrinol Metab 1992;75:15–20.
26. Krief S, Lonnqvist F, Raimbault S, et al. Tissue distribution of beta 3-adrenergic receptor mRNA in man. J Clin Invest 1993;91:344–9.
27. Cypess AM, Lehman S, Williams G, et al. Identification and importance of brown adipose tissue in adult humans. N Engl J Med 2009;360:1509–17.
28. van Marken Lichtenbelt WD, Vanhommerig JW, Smulders NM, et al. Cold-activated brown adipose tissue in healthy men. N Engl J Med 2009;360:1500–8.
29. Virtanen KA, Lidell ME, Orava J, et al. Functional brown adipose tissue in healthy adults. N Engl J Med 2009;360:1518–25.