Increase in the Thermic Effect of Food in Women by Adrenergic Amines Extracted from Citrus Aurantium

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Abstract

GOUGEON, RÉJEANNE, KATHY HARRIGAN, JEAN-FRANÇOIS TREMBLAY, PHILIP HEDREI, MARIE LAMARCHE, AND JOSÉ A. MORAIS. Increase in the thermic effect of food in women by adrenergic amines extracted from citrus aurantium. *Obes Res.* 2005;13: 1187–1194.

Objective: To compare the thermic response to a meal between men and women of varied body composition and to determine whether adrenergic amines extracted from citrus aurantium (CA) induce an increase in metabolic rate and enhance the thermic response to the meal.

Research Methods and Procedures: In 30 healthy weight-stable subjects (17 women, 13 men; BMI: 20 to 42 kg/m^2), body composition was determined by bioimpedance analysis followed by resting energy expenditure for 20 minutes, and the thermic effect of food (TEF) of a 1.7-MJ, 30-gram protein meal was determined intermittently for 300 minutes by indirect calorimetry. In a subset of 22 subjects, the TEFs of CA alone and when added to the same 1.7-MJ meal were determined. Blood pressure and pulse before and throughout the studies and catecholamine excretion were determined.

Results: TEF was significantly lower in women than men (152 ± 7 vs. 190 ± 12 kJ and 8.8 ± 0.4% vs. 11.0 ± 0.7% of meal), independently of age and magnitude of adiposity. The thermic response to CA alone was higher in men, but, when added to the meal, CA increased TEF only in women and to values no longer different from men. CA had no effect on blood pressure and pulse rate but increased epinephrine excretion by 2.4-fold.

Discussion: A 20% lower TEF in women suggests a diminished sympathetic nervous system response to meals, because with CA, TEF increased by 29% only in women. However, this acute response may not translate into a chronic effect or a clinically significant weight loss over time.

Key words: diet-induced thermogenesis, sex, synephrine

Introduction

Obesity has reached epidemic proportions in North America (1,2) partly because of genetic abnormalities leading to a reduced energy expenditure (3). Energy expenditure comprises resting energy expenditure (REE),[1] the thermic effect of food (TEF), and exercise. A reduction in TEF has been identified as a contributor to lower expenditure, a positive energy balance, and weight gain over time (4). TEF is defined as the acute increase in energy expenditure over REE (oxygen uptake) after macronutrient intake (5–7) and represents ~10% of total energy expenditure (8). TEF and its relationship to obesity have been the focus of studies that have attempted to determine whether TEF is affected by obesity in general (4), by abnormal glucose tolerance (9) and insulin resistance (10), by distribution (11) or location of fat stores, or by type of stored fat (12). There is a lack of consensus in the literature regarding the presence of a defect in TEF in obese individuals (4,13); of the many factors that could explain this controversy, sex has not been mentioned (13). However, in their reappraisal of the methodology used to measure diet-induced thermogenesis, Westrate (14) showed significantly lower TEF in women as percent of

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[1] Nonstandard abbreviations: REE, resting energy expenditure; TEF, thermic effect of food; SNS, sympathetic nervous system; CA, citrus aurantium; FFM, fat-free mass; RQ, respiratory quotient.

energy content of a test meal (6.5 ± 0.3% vs. 7.9 ± 0.4%) and in absolute value, but the authors did not address these sex differences. Leenen et al. (15), in their study of 78 obese (40 women and 38 men) subjects, showed sex differences in TEF but addressed only the differences in the associations between visceral fat and the thermic response to a mixed meal: only in women did higher visceral fat relate to higher TEF, concurrently with higher fasting insulin levels.

One abnormality reported to cause a lower TEF may be found in components of facultative thermogenesis, namely alterations in the sympathetic nervous system (SNS). Decreased SNS activity and/or responsiveness of various tissues to SNS activity (16,17), concentrated at the β-adrenoreceptors that mediate lipolysis, thermogenesis, and glycogenolysis, have been reported (18,19). A reduced SNS response to feeding has been proposed, along with insulin resistance (19,20), as a contributing factor to the blunted TEF reported in obesity (4). However, the importance of the role of SNS in TEF in humans has been questioned (21), as indicated by the absence of effect of β-adrenergic blockade on the thermogenic response to a meal (22) but not to glucose (6).

An increase in energy expenditure through the mediation of thermogenesis to create a negative energy balance has been considered in the treatment of obesity. β-Adrenergic drugs targeting the SNS to increase the rate of thermogenesis (23) without negative effects on heart rate and blood pressure have included ephedrine and ephedrine-like substances (24). Citrus aurantium (CA) is a natural herbal extract containing the essential oils of the Seville orange. It contains a family of indirect-acting β-sympathicomimetics that include synephrine, hordenine, octopamine, tyramine, and *N*-methyltyramine and is said to work primarily at the β_3 receptor; therefore, it is not associated with undesirable side effects on heart rate, blood pressure, or the central nervous system (25) (ZhiThin; Fyto Research, Lachine, Canada). However, selective β_3-adrenergic receptor agonists have been shown to lack chronic effects on energy balance (26) and thermogenic responses in humans (25) and not to affect body weight or body composition (26,27). The inability of β_3-agonists to induce weight loss with long-term use has been explained by the fact that their primary target tissue is brown adipose tissue, a tissue found in limited amounts in adult humans and with questionable functional capacity (26). CA may have the potential to increase total energy expenditure and TEF when consumed with meals if it stimulates β_2-adrenergic receptors, which are shown to increase metabolic rate in humans (25).

The purpose of this study was to dissect the effects of sex and adiposity on the thermogenic response to a mixed meal consumed by healthy men and women varying in body composition. Furthermore, we hypothesized that alkaloids extracted from CA would induce a notable increase in metabolic rate when taken orally in capsule form with water and would potentiate the TEF when taken with a meal.

Research Methods and Procedures

Subjects and Interventions

Thirty subjects (17 women and 13 men) were recruited in response to an advertisement in local newspapers or on the Royal Victoria Hospital bulletin boards. Subjects were informed of the study protocol, the implications of their participation, and the potential risks, and consent was obtained according to the hospital's Human Ethics Committee. The study population consisted of healthy non-smoking obese (BMI $>$ 30 kg/m^2; waist circumference $>$102 cm in men and $>$85 cm in women) and non-obese people between the ages of 18 and 60 who had been weight stable for the past 6 months. Their clinical characteristics are shown in Table 1. Subjects were required to have a complete medical history and exam by a physician including, among laboratory tests, tests for HIV, hepatitis B and C, and an electrocardiogram. Subjects on medications, those with major complications of hepatic, cardiovascular, renal, pulmonary dysfunction, or diabetes, and those consuming atypical diets were excluded. Thyroid function in all subjects was normal. To control for the confounding effect of changes in SNS activity and metabolic rate during the menstrual cycle (28), the studies in women who undertook more than one study were done within the same phase.

Height (centimeters), weight (kilograms), and waist and hip circumferences (centimeters) were measured in the fasted state after voiding. Subjects were in light clothing without shoes. Waist circumference was assessed at the smallest point between the lower rib and iliac crest. Hip circumference was measured at the widest point in the greater trochanter and buttocks area. Waist-to-hip ratio was calculated to assess the distribution of body fat. Fat-free mass (FFM) and percent body fat were measured by the bioelectrical impedance analysis method using a four-terminal bioimpedance analyzer (BIA-101A; RJL Systems, Detroit, MI), with procedures, anatomical sites, and equations used as described by Lukaski et al. (29).

Subjects reported to the McGill Crabtree Laboratory at the Royal Victoria Hospital after an overnight fast (12 hours of water only), were instructed to avoid strenuous activity before arrival at the laboratory, and were asked to rest for 30 minutes on arrival. All were assigned a 1.7-MJ mixed meal composed of two chocolate-flavored food bars with energy derived as follows: 53% from carbohydrates, 29% from protein, and 18% from fat (Power 8; Bariatrix International, Lachine, Canada). Of the 30 subjects recruited, a subset of 11 men and 11 women was studied a second time after ingesting five CA capsules (ZhiThin; Fyto Research) with the same 1.7-MJ mixed meal. For comparison purposes, 12 women and 8 men of the same subset were studied a third

Table 1. Clinical characteristics of subjects

	Women	Men	*p*
N	17	13	
Age (years)	34.9 ± 3.3	24.4 ± 1.9	<0.001
Weight (kg)	72.3 ± 4.7 (43 to 104)	77.0 ± 4.5 (50 to 100)	NS
Height (cm)	160.5 ± 2.0	172.0 ± 2.1	<0.001
BMI (kg/m^2)	28.3 ± 2.1 (19 to 42)	26.0 ± 1.5 (20 to 38)	NS
Waist circumference (cm)	88.2 ± 5.1 (60 to 120)	89.0 ± 4.7 (71 to 119)	NS
Hip circumference (cm)	108.8 ± 4.1 (84 to 127)	99.8 ± 4.1 (83 to 124)	NS
Waist-to-hip ratio	0.80 ± 0.02 (0.70 to 0.99)	0.89 ± 0.02 (0.80 to 1.00)	<0.01
FFM (kg)	45.4 ± 1.4	58.0 ± 2.2	<0.001
Fat mass (kg)	28.0 ± 3.9	19.0 ± 3.2	NS
Percent body fat	35.3 ± 3.1 (15 to 52)	23.2 ± 2.7 (10 to 43)	0.007
REE (kJ/d)	5820 ± 197	7017 ± 289	0.001
REE (kcal/d)	1391 ± 47	1677 ± 69	0.001
REE/FFM (kJ/kg)	129 ± 3	121 ± 3	NS

Values are means ± SE (range).
NS, not significant.

time and received CA capsules alone with 240 mL of water. The capsules provided 26 mg synephrine, 4 mg octopamine, 3.6 mg *N*-methyltyramine, and 2.9 mg tyramine and hordenine. Multiple studies performed on the same subjects were done with a time interval of 2 to 7 days between repeated measurements. Two subjects were studied for 4 hours after being given 750 mL of water only to confirm that, in our laboratory, there was constancy in REE with time (29).

TEF

After resting, initial REE was measured in a thermally neutral and quiet environment, as described elsewhere (20), using a ventilated-hood indirect calorimeter (Deltatrac Metabolic Monitor; Sensormedics, Yorba Linda, CA). Subjects were asked to breathe under the plastic canopy for 20 minutes, and the average of the data collected during the last 15 minutes was used to calculate the 24-hour REE according to the de Weir equation (30). Then the subjects consumed the meal, CA with water, or meal + CA. A 25-minute period was allowed for the intake of the meal. Energy expenditure and respiratory quotient (RQ) were measured for 300 minutes using the indirect calorimeter continuously for 40 minutes, with a 20-minute break per hour to allow voiding; otherwise, subjects remained in a semisupine position. Values were extrapolated from data collected before and after the break to give a smoothing adjustment. The subjects remained awake in a semisupine position at all times. The TEF was defined as the absolute increase of energy expenditure after the meal under the assumption that the basal REE measured before the test meal would not change if a meal was not consumed, and calculated from the area under the curve above resting values. Non-protein RQ was calculated based on estimated nitrogen excretion from protein intake. At baseline and after ingestion of meals and/or CA, brachial blood pressure (systolic and diastolic) measurements were obtained with a manual sphygmomanometer every 60 minutes for 5 hours. Heart rate was also measured at the same periods by palpating the radial pulse. On the day of the study of CA with water, overnight urine and urine during the study were collected to compare catecholamine excretion.

Statistical Analysis

Statistical analyses were carried out with the SPSS/PC statistical package version 10 (SPSS, Chicago, IL). The data were obtained by calculating the surface area under the curve of the REE graph and subtracting it from the area of the TEF curve for 300 minutes. Between-group analyses were done by ANOVA using repeated measures design; between-group comparisons of increments as percent above REE, percent energy content of meal, and in absolute values over time were performed using unpaired Student's *t* test. Univariate ANOVAs were used to assess effects of sex, age, BMI, FFM, and percent body fat on the TEF responses. Paired Student's *t* tests were done to identify the significant differences of the values obtained with or without CA.

Results in text, figures, and tables are reported as means ± SE and were considered statistically significant if p values were <0.05.

Results

The thermic response to a 1.7-MJ (405 kcal), 30-gram protein meal is shown in Figure 1 for the 30 subjects. TEF was significantly lower in women than in men in absolute values (152 ± 7 compared with 190 ± 12 kJ per 300 minutes, $p = 0.009$) and as percent of the energy content of meal (8.8 ± 0.4% compared with 11.0 ± 0.7%, $p = 0.005$), adjusting for age and BMI or waist circumference. There was no sex difference when expressed as percent increment above REE (12.8 ± 0.7% compared with 13.3 ± 1.0%, not significant). Indices of obesity (weight, percent body fat, BMI, waist and hip circumferences) had no significant effect on the thermic response of meals (9.1 ± 0.5% vs. 10.2 ± 0.6% of energy content of meal in obese and non-obese subjects, respectively, not significant) or when the groups of men and women were assessed separately (data not shown).

Figure 2A compares the thermic response obtained in a subset of 22 subjects (11 women and 11 men) after consumption of the meal alone or with CA. TEF remained significantly lower ($p < 0.05$) in women compared with men as percent of energy content of meal and in kilojoules per 300 minutes. With CA, a greater increase in TEF was seen in women only: as % above REE (16.0 ± 1.1 vs. 12.3 ± 0.8), as % of energy content of meal (11.2 ± 0.5 vs. 8.7 ± 0.4), and in absolute values (196 ± 9 vs. 152 ± 8 kJ per 300 minutes). The latter values no longer differed from those of men (Figure 2A), in whom the addition of CA did not significantly affect TEF.

Figure 3 shows the energy expenditure above REE after consumption of the five capsules of CA with 240 mL water

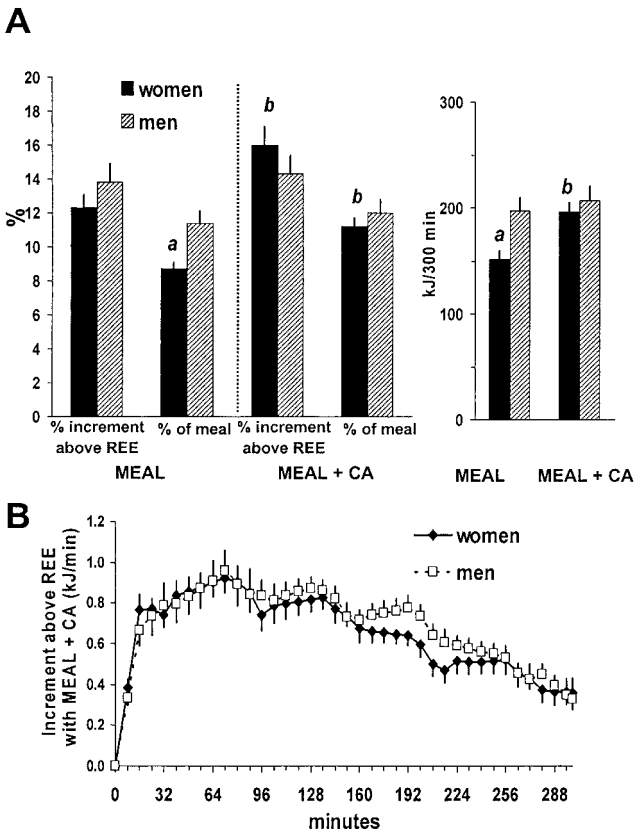

Figure 2: TEF of a mixed meal in women ($n = 11$) and in men ($n = 11$) with and without CA (A) as percent increment above REE, percent of energy content of meal, and in kilojoules per 300 minutes. (B) Increments above REE in kilojoules per minute after mixed meal with CA. Data presented as in Figure 1. [a]$p < 0.05$ vs. men during same treatment, with age and BMI as covariates. [b]$p < 0.005$ vs. meal without CA in women.

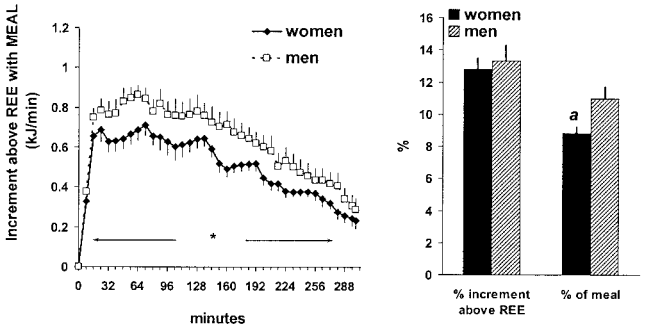

Figure 1: TEF of a mixed meal in women ($n = 17$) and men ($n = 13$) in kilojoules per minute, percent increments above REE, and percentage of energy content of the meal over 300 minutes. Data are presented as mean ± SE; *$p = 0.007$ between groups; [a]$p < 0.005$ vs. men.

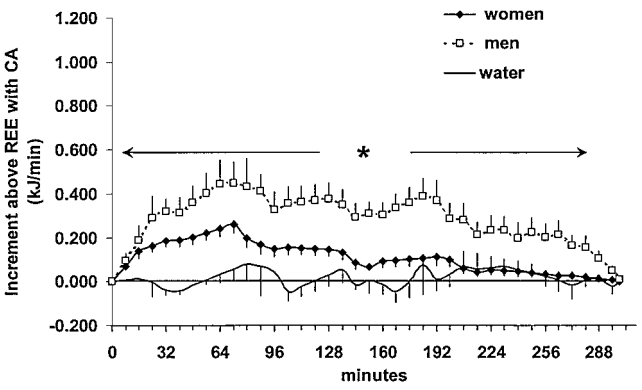

Figure 3: Increments above REE in response to intake of water ($n = 2$ women) and of CA ($n = 12$ women and 8 men). Data presented as in Figure 1. *$p < 0.05$ between men and women.

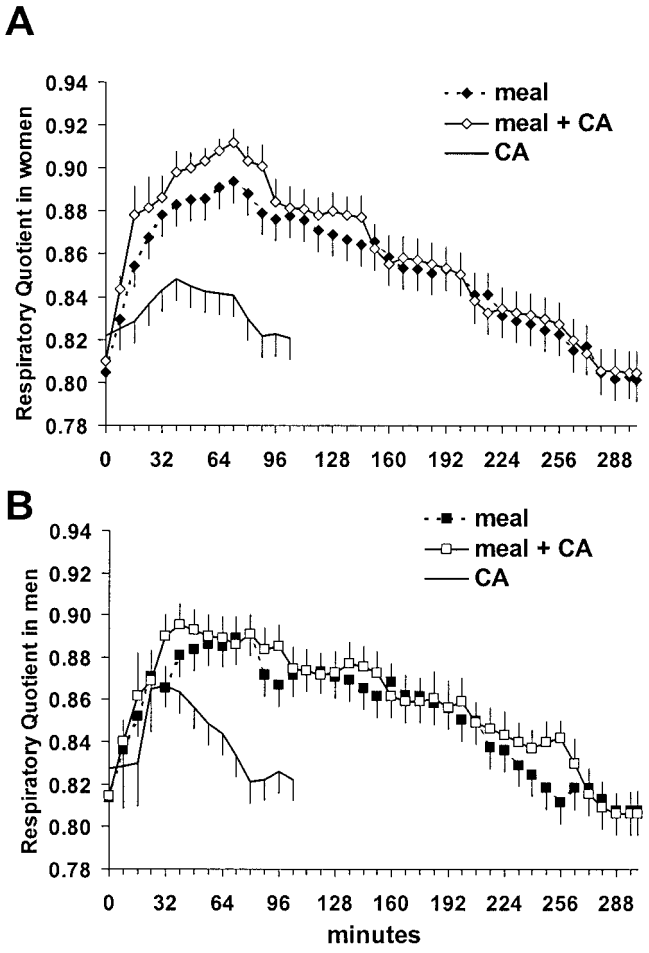

Figure 4: The RQ response to CA alone (n = 12 women and 8 men) and to mixed meals with or without CA (n = 11 women and 11 men). Results for women (A) and men (B).

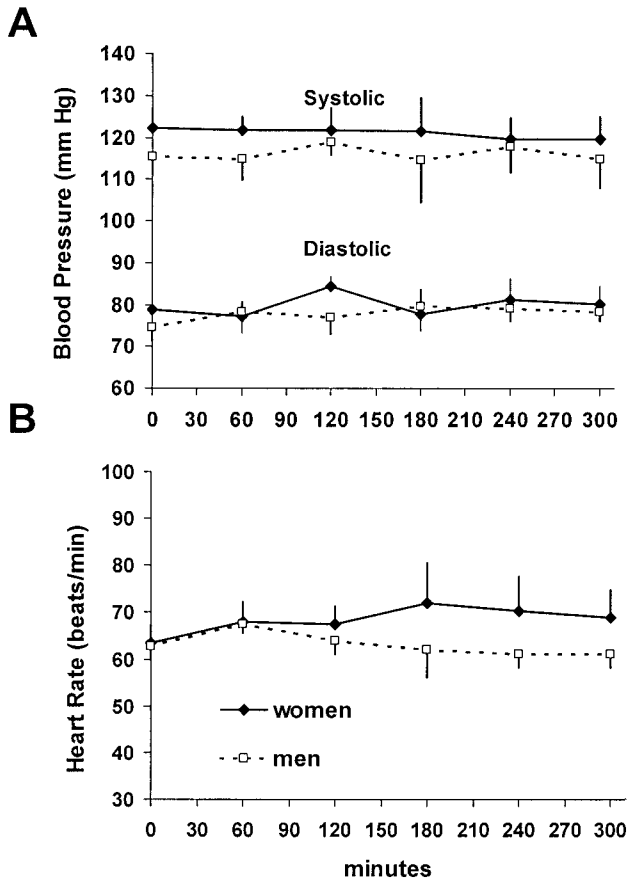

Figure 5: Systolic and diastolic pressure (A) and heart rate (B) taken every 60 minutes during 300 minutes after consumption of a mixed meal with CA by women (n = 11) and men (n = 11). Data are presented as mean ± SE. There was no effect of time or group.

by 12 women and 8 men compared with that of consuming 750 mL of water by 2 women. Water had no significant effect on energy expenditure with time; however, CA increased energy expenditure compared with baseline and with water consumption in both groups but significantly more in men (42 kJ in women compared with 94 kJ in men per 300 minutes, $p = 0.002$ and $p = 0.043$, respectively, when correcting for BMI). There was no significant difference between groups when comparing the responses between lean and obese subjects.

The RQs per minute in response to CA alone for 100 minutes and to meals with or without CA for 300 minutes are shown for women (Figure 4A) and men (Figure 4B). Baseline RQ did not differ among studies done in the same subjects (data not shown) and did not differ between sexes when correcting for adiposity. It was significantly higher in obese compared with lean subjects (0.84 vs. 0.80, $p = 0.033$). There was a significant increase in RQ after consumption of CA alone that did not differ between groups. RQ increased ($p < 0.001$) with meals in both groups in a comparable manner, whether meals were taken with CA or not. However, in women, the RQ response to meals with CA was significantly higher from minutes 64 to 88 ($p = 0.045$) compared with meals without CA; it did not differ in men.

The hemodynamic effects of consuming the mixed meal with CA are shown in Figure 5. There was no significant change in systolic and diastolic pressures (Figure 5A) or pulse rates (Figure 5B) with CA in women and men compared with baseline values. Overnight fasting urinary epinephrine was lower in women than in men (0.7 ± 0.2 vs. 1.9 ± 0.6 nmol/h, $p < 0.05$) and remained lower in women with CA, although it increased by ~2.4-fold in both groups.

Discussion

Data from this study provide evidence that there is a sex effect in the thermic response to food. Heat increment was

25% higher in men compared with women. Sex effects on energy expenditure have been shown mainly on REE and explained partly by differences in body composition; men have more active tissue, which is usually defined as FFM. In our study, REE was 21% higher in men (Table 1), a value similar to the 23% difference reported by Arciero et al. (31). In their well-designed study that used strict procedures, body composition did not explain all of the sex differences; REE remained 3% lower in women after adjustment for FFM, fat mass, and peak $V\text{O}_2$. In our study, contrary to their results, sex effect was no longer significant when we adjusted REE for FFM whether in a univariate analysis using FFM as covariate or as a mathematical ratio (in Table 1); this may result from our smaller sample size, although others have also failed to detect a sex difference when adjusting for FFM (32,33). In studies reporting higher REE in elderly men after adjustment for FFM, higher sympathetic nervous system activity, related to greater waist circumference compared with women, explained the results (34). Higher muscle sympathetic nerve activity has been associated with a higher waist-to-hip ratio in younger men compared with age-matched women (35). We found that TEF, in kilocalories per 300 minutes, tended ($p = 0.06$) to correlate with waist-to-hip ratio but not with waist or hip circumferences. Waist-to-hip ratio has been considered an index of abdominal adiposity that characterizes men preferentially (15); women have greater lower body adiposity whether they are obese or not. Lower body adipocytes have been shown to have greater α_2-adrenergic receptors and may respond less to stimuli (36). It is conceivable that the sex effect on TEF in our study may be secondary to lower meal-induced increases in catecholamines or alterations in the responses to catecholamines.

Reported sex differences in sympatho-adrenal activity have included lower urinary epinephrine in women (37). The adrenergic response to stimuli such as hypoglycemia has also been shown to be lower (38), and systolic blood pressure has been shown to increase less and diastolic blood pressure to fall less with incremental infusions of adrenaline (39) in women. The increment in metabolic rate after ingestion of CA lasted longer in male subjects (Figure 3). Webber and Macdonald (39) found that the rise in metabolic rate with continuous adrenaline infusions lasted longer before reaching optimal values in men. CA ingestion was associated with an increase in RQ, indicating a switch to glucose as fuel, a substrate known to be associated with increases in plasma norepinephrine (40). Because 30% of TEF has been linked to postprandial sympatho-adrenal activity, likely mediated by insulin, a blunted TEF response in women could be secondary to less SNS activity, although no direct relationship has been shown between postprandial sympathetic nervous activation and thermogenesis (41). TEF has been shown to be reduced by the presence of insulin resistance (9), and no difference in thermogenesis between insulin sensitive lean and obese female subjects was found after a glucose challenge (42) or after intragastric or intravenous feeding (43). The protein content of our meal was high and proportionately may have stimulated more oxygen uptake in the splanchnic organs (44), masking any effect of the variation in insulin sensitivity of skeletal muscle in our study. Oxygen uptake by the splanchnic tissues has been shown to account for 50% of amino acid–induced thermogenesis (45). Segal et al. (10) reported that the thermic effect of infused glucose during hyperinsulinemic euglycemic clamp was blunted in insulin resistant lean and obese men. However, because less nutrient was infused in the insulin-resistant subjects, the difference between groups would no longer be significant if TEF was corrected for the rate of glucose infused; in the insulin sensitive men, in whom the rate of glucose infusion did not differ, the thermic response to glucose was not affected by obesity. In Segal et al.'s study, food ingested orally was associated with impaired TEF in both obese and insulin-resistant subjects matched for FFM. Although in our study women were characterized by lower FFM, the sex effect remained significant when adjusting for FFM. Furthermore, within the group of women, FFM differed between the obese and the lean subjects, but TEF did not; in contrast, within the group of men, FFM did not differ between lean and obese, nor did TEF. Thus, FFM did not affect our results even though the absolute mass of lean tissue has been regarded as a confounding variable (10) for facultative thermogenesis induced by carbohydrate (16).

Glucose-induced thermogenesis, found to be higher and more prolonged in women with abdominal obesity compared with gluteal-femoral obesity, has been attributed to higher insulin levels, activating the sympathetic nervous system to a greater extent in the latter (46). Greater visceral fat has been associated with higher TEF in women (15). These studies suggest a relation between fat distribution and TEF, possibly attributed to differences in sex steroid concentrations. Some evidence for a role for estradiol in energy expenditure has been shown (47). These results support our findings of a greater TEF in men, whose waist-to-hip ratio was greater and whose thermic response to CA was also greater compared with women.

Although the women in our study were older than the men, the effect of sex remained significant after adjusting for age. TEF in women has been shown not to diminish with age (48). In elderly men, a decrease of 20% in TEF was no longer significant when adjusted for body composition, and TEF related negatively with fat mass and percent body fat (48). The blunted TEF with age has been explained by a possible resistance to β-sympathetic stimulation in the elderly (49). In a study by Visser et al. (48), young women had a lower TEF after consuming a 1.33-MJ mixed meal than young men (115 ± 25 vs. 154 ± 34 kJ/180 minutes, $p < 0.001$), but the authors did not address the sex differences.

As reported by others (50), in the doses given, CA did not affect pulse rates or blood pressure. The dose given somewhat exceeded the single dose of 20 mg considered safe for synephrine (or phenylephrine) for over-the-counter use (51). Although it was below the accepted daily dose of 60 mg, the potential safety of chronic use remains to be shown (51). It increased energy expenditure by 44 kJ (29%) and corrected the blunted TEF in women, indicating an additive effect with the meal. No response in men suggests that TEF may have been optimal with the meal. CA alone increased thermogenesis, on average, by 4% (52), a response that is statistically significant but not necessarily clinically significant, representing an average 1 kg over 6 months. Our study does not provide the mechanisms explaining an acute thermogenic response to CA. Furthermore, clinical studies on long-term use would be indicated to assess bioavailability, adaptation, metabolic effects, and energy expenditure.

In conclusion, we found a lower TEF in women, a factor that may contribute to their higher prevalence of obesity (53) and to the controversy regarding the effect of obesity on TEF, because studies have not always matched groups of obese and lean subjects for sex (54). Adding CA extracts with 26 mg of synephrine corrected the blunted TEF in women without any cardiovascular effects.

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