Normal caffeine consumption: influence on thermogenesis and daily energy expenditure in lean and postobese human volunteers[1-4]

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ABSTRACT Single-dose oral administration of 100 mg caffeine increased the resting metabolic rate of both lean and postobese human volunteers by 3–4% ($p < 0.02$) over 150 min and improved the defective diet-induced thermogenesis observed in the postobese subjects. Measurements of energy expenditure (EE) in a room respirometer indicate that repeated caffeine administration (100 mg) at 2-h intervals over a 12-h day period increased the EE of both subject groups by 8–11% ($p < 0.01$) during that period but had no influence on the subsequent 12-h night EE. The net effect was a significant increase ($p < 0.02$) in daily EE of 150 kcal in the lean volunteers and 79 kcal in the postobese subjects. Caffeine at commonly consumed doses can have a significant influence on energy balance and may promote thermogenesis in the treatment of obesity. *Am J Clin Nutr* 1989;49:44–50.

KEY WORDS Obesity, thermogenesis, caffeine, energy expenditure

Introduction

The widespread use of caffeine in drinks, food, and numerous pharmaceutical preparations, such as muscle relaxants, decongestants, and allergy drugs, has generated much interest in elucidating the multitude of effects and mechanisms of action of this drug of everyday life. With increasing evidence pointing to a thermogenic defect as being contributory to the etiology of obesity (1), nutritionists are particularly interested in caffeine's effects on energy expenditure (EE), not only as an apparently safe thermogenic drug but also as a pharmacological tool to elucidate the mechanisms of thermogenesis and metabolic differences between lean and obese people.

Although the stimulatory effect of caffeine on metabolic rate in man is well established and was demonstrated both in subjects who fasted (2–7) and in those who did not (5, 6), most of these studies focused on caffeine's acute thermogenic effects when administered at relatively large doses. There is little information about caffeine's influence on daily EE and the thermogenic effects of caffeine in amounts that are generally consumed at any one time (as in a cup of coffee or in preparations usually containing $\leq$ 100 mg caffeine).

We conducted studies in lean and postobese human volunteers that examined the effect of commonly consumed doses of caffeine on the resting metabolic rate (RMR), diet-induced thermogenesis, and 24-h energy expenditure.

Methods

Subjects

Eighteen healthy volunteers were selected from students and staff of King's College, London University and were allocated to two groups by the ease with which they maintained a relatively lean body weight. One group (lean group; $n = 9$, six females, 3 males) consisted of lean subjects who claimed to maintain body weight without effort. The other group (postobese group; $n = 9$, six females, three males) comprised subjects who admitted to a weight problem and were previously overweight with grade I (mild to moderate) obesity; their Quetelet index (wt/ht^2) ranged from 26.1 to 29.6 with a mean value of 27.3 $\pm$ 0.5 SEM. The various grades of obesity based on the Quetelet Index (or body mass index) were described by Garrow (8). These obese subjects can only maintain a normal body weight by restricting their food intake, otherwise they would become overweight again within a few months. Although they are predisposed to obesity, they had maintained a normal body weight for at least 5–6 mo before the study began.

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At the outset of the study, body weight and height were measured in both subject groups and the degree of obesity (if any) was reevaluated by using the Queletet index and by estimating the percentage body fat. Percentage body fat was assessed by the method of Durnin and Womersley (9) from measurements of skinfold thicknesses with a Harpenden skinfold caliper (Holtain Ltd, Dyfed, Wales, UK). Lean body mass was calculated by subtracting body fat from body weight. Food was weighed and intake was recorded for 7 d immediately before the study; energy content was expressed as daily means. Analysis of nutrient composition showed no difference between the two groups in the proportion of metabolizable energy intake ($\bar{x} \pm$ SEM) derived from protein (lean subjects, 17 ± 1%; postobese subjects, 16 ± 1%), fat (lean subjects, 32 ± 3%; postobese subjects, 34 ± 2%), and carbohydrate (lean subjects, 51 ± 2%; postobese subjects, 50 ± 2%). Methylxanthine intake (eg, caffeine, theophylline) from beverages (coffee, tea, hot chocolate, and coke) ranged from 250 to 500 mg/d. All subjects were thus classified as mild to moderate consumers of methylxanthines. None of the subjects had a familial history of diabetes and none engaged in physical training, regular exercise, or sport activities.

The study was carried out in accordance with the regulations of the Ethical Committee for Human Experimentation of King's College, University of London.

Acute metabolic-rate studies

The subjects' metabolic rate while fasting and not fasting was measured by open-circuit indirect calorimetry using 100 L capacity Douglas bags and mouthpiece connections with respiratory valves. Details of these measurements were described previously (10) and involved measurements of oxygen consumption rates and calculations of heat production using the Weir formula (11).

All subjects were given four randomized treatments on four different days and with at least a 2-d interval between treatments. The four treatments were *1*) a 100-mg tablet of anhydrous caffeine (Pro-plus, Boots Ltd, Nottingham, UK); *2*) a 300-kcal liquid meal (Complan®, Glaxo, Devon, UK) made up to 200 mL with water; *3*) a 300-kcal liquid meal plus a 100-mg tablet of caffeine; and *4*) a 200-mL glass of H_2O. The complan powder contained (per/kg) 180 g protein, 470 g carbohydrate, and 330 g fat with an energy value of 4.4 kcal/g dry wt.

The subjects arrived at the university department at 0800 after an overnight 12-h fast. They had traveled either by automobile or by public transportation. They were requested to walk casually, to use elevators rather than stairs, and to avoid any burst of physical activity on the way to the laboratory. On arrival a subject was seated in a comfortable armchair and spent the duration of this acute study either reading or relaxing. The pretreatment phase consisted of at least 30 min of relaxation followed by three or four measurements of base-line RMR, each lasting 5 min with a 5–10 min interval between measurements. After each treatment was administered, measurements of metabolic rate were performed over the next 150 min, each lasting 5 min with intervals of 10–15 min between measurements.

To ensure steady-state breathing the subjects breathed for a few minutes through the mouth piece and tubing system with the tap for expired air closed to the Douglas bag but open to ambient air. The tap to the bag was then opened and expired air was collected for the next 5 min. All subjects were familiar with this technique for measuring metabolic rate and felt no discomfort during the study.

Daily energy expenditure

Five lean (three females, two males) and six postobese (three females, three males) subjects participated in this study. EE was measured for 24 h in a human respirometer (10) on two separate occasions for each subject. One measurement determined base-line (control) EE in the absence of any methylxanthine and the other measurement determined EE during the administration of caffeine. At least a 1-wk interval was allowed between these 2 d of measurements, which were carried out in a randomized order for all subjects. All subjects were requested to ensure that their activity and food consumption patterns were normal (with no unusual excesses in either direction) for at least 2 d before the measurements were taken.

On each measurement day the subject reported to the laboratory between 0800 and 0830 after an overnight fast. After at least 30 min of rest and relaxation in a comfortable armchair, the subject entered the respirometer at 0900 and left at 0900 the next day. While inside the respirometer, the subject spent time reading, studying, lying in bed, listening to the radio, or watching television. The subject kept an activity diary (duration to the nearest minute) describing position and activity throughout the 24 h. No methylxanthine-containing food or beverages were provided on either day, but subjects were provided with meals and drinks with an energy content similar to their mean customary energy intakes. On the treatment day each subject ingested six caffeine tablets (100 mg/tablet), one tablet every 2 h for 12 h as follows: 0900 with breakfast, 1100, 1300 with lunch, 1500, 1700, and 1900 with dinner.

Statistics

Data were analyzed by Student's *t* test and by two-way analysis of variance with repeated measures. Posthoc comparison between pairs of treatments were performed with the Newman-Keul's multiple sample comparison test after analysis of variance had established significant differences between treatments (12). All results are presented as mean ± SEM.

Results

The physical characteristics of the subjects are outlined in **Table 1.** Height was similar in both groups but the mean value for body weight was ~9% higher in postobese subjects than in lean subjects; this difference was not statistically significant. The mean value for age was also slightly higher (NS) in the postobese group (range 20–46 y) than in the lean group (range 18–35 y). The Quetelet Index, ranging from 18.5 to 23.4 in the lean group and from 19.5 to 24.9 in the postobese group, indicates that none of the subjects could be classified as obese at the start of the study. The percentage body fat was similar in both groups whereas lean body mass was 8% higher (NS) in the postobese group. Food intake, measured for 1 wk, was significantly lower in the postobese group than in the lean group by ~25% in absolute terms ($p < 0.01$) and by 30% per kilogram body weight ($p < 0.001$). The postobese group maintained their weight on a mean energy intake of 1600 kcal, which was 500 kcal less than that of the lean group.

Acute metabolic-rate studies

Table 1 shows the pretreatment RMR computed over the measurement days after an overnight 12-h fast. The

TABLE 1
Physical characteristics, customary food intake, and pretreatment resting metabolic rate (RMR) of subject groups*

	Age	Height	Body weight	Body fat	Quetelet index	Lean body mass	Daily food intake	Food intake by weight	Pretreatment RMR	Daily pretreatment RMR
	y	*cm*	*kg*	*%*	*kg/cm²*	*kg*	*kcal/d*	*kcal·kg⁻¹·d⁻¹*	*kcal/min*	*kcal·kg⁻¹·d⁻¹*
Lean subjects	24.8 ± 1.6	169 ± 3	58.3 ± 3.1	22.1 ± 2.6	20.6 ± 0.5	45.8 ± 3.8	2105 ± 117	37.5 ± 2.4	1.046 ± 0.069	25.8 ± 0.96
Postobese subjects	28.2 ± 2.6	168 ± 2	63.5 ± 3.1	21.9 ± 1.3	22.2 ± 0.7	49.5 ± 3.1	1592 ± 91	25.6 ± 1.4	1.036 ± 0.039	23.6 ± 0.7

* $\bar{x}$ ± SEM, n = 9 per group; six females, three males per group.

within-subject coefficient of variation ($\bar{x}$ ± SD) during the measurement days ranged from 1.4 ± 1.0 to 2.7 ± 1.5% in the lean group and from 1.6 ± 1.3 to 1.8 ± 1.4% in the postobese group. The between-day coefficient of variation ($\bar{x}$ ± SD) was 2.4 ± 2.5% in the lean group and 2.6 ± 2.1% in the postobese group. The RMR in absolute terms was not different between the two subject groups but when the data were expressed per unit body weight to account for both between-group as well as within-group variations in body weight, RMR was 8% lower in the postobese group than in the lean group. This difference nearly achieved statistical significance (p = 0.056). Similarly, the RMR per unit lean body mass was 8% lower (p = 0.06) in the postobese group than in the lean group.

The values for metabolic rate before and after treatment are shown in **Table 2** and the data for the total thermogenic response (both absolute and percentage increases) over the 150-min posttreatment period are presented in **Table 3.** The thermogenic response curves, expressed as a percentage of the base-line (pretreatment) RMR, are shown in **Figure 1** for both lean and postobese groups. The control water treatment had no effect on the RMR of either group (Fig 1). In contrast, ingestion of 100 mg caffeine with a similar volume of H_2O increased metabolic rate in both groups. Metabolic rates reached peak values within 20 to 40 min after treatment and decreased gradually toward base-line levels. At the end of the study, the metabolic rate in both groups was not significantly different from base-line values.

The thermogenic response curve followed a similar pattern in both the lean and the postobese subjects, and the total thermogenic response integrated over the entire 150-min study period (Table 3) was increased by 3–4% in both subject groups. This posttreatment increase in metabolic rate was statistically significant when compared with either the corresponding pretreatment RMR or the posttreatment RMR assessed during the control day.

Ingestion of a 300 kcal liquid meal caused a sharp rise in metabolic rate that reached peak levels in 30–60 min in both subject groups. The peak increase in metabolic rate was significantly greater ($p < 0.001$) in lean subjects (+25%) than in postobese subjects (+15%). Both groups maintained peak metabolic rate for about another hour, after which the metabolic rate declined at a faster rate in the postobese group than in the lean group. At the end of the 150 min, the metabolic rate of the lean group was still ~17% above base-line RMR ($p < 0.001$) whereas that of the postobese group was only 5% higher (NS). As shown in Tables 2 and 3, the overall thermogenic response of the postobese subjects to the 300 kcal meal was only half of that measured in the lean subjects.

Administration of a 100-mg caffeine tablet in the lean group produced a small additional (+12%, NS) stimulatory effect on their thermogenic response to food. In the postobese group, caffeine was more effective in augmenting the thermogenic effect of the meal; both the peak metabolic rate and the total thermogenic response (integrated over 150 min) were 25–30% higher after caffeine and a meal than after the meal alone. The 50% reduction in diet-induced thermogenesis (DIT) observed in the

TABLE 2
Metabolic rate before and after treatment with 100 mg caffeine and/or a 300-kcal liquid meal in lean and postobese subjects*

	Caffeine		Meal		Meal + caffeine	
	Before	After	Before	After	Before	After
	kcal/min					
Lean subjects	1.055 ± 0.071	1.095 ± 0.063†	1.025 ± 0.064	1.236 ± 0.077‡	1.055 ± 0.075	1.292 ± 0.087‡
Postobese subjects	1.026 ± 0.043	1.059 ± 0.045§	1.039 ± 0.038	1.164 ± 0.052‡	1.047 ± 0.034	1.213 ± 0.045‡

* $\bar{x}$ ± SEM, n = 9 per group; six females, three males per group.
† $p < 0.02$.
‡ $p < 0.001$.
§ $p < 0.01$.

TABLE 3
Increases in metabolic rate over 150 min in response to 100 mg caffeine and/or a 300-kcal liquid meal in lean and postobese subjects

	Absolute increase				Percentage increase			
	Caffeine [1]	Meal [2]	Meal + caffeine [3]	Posthoc comparison	Caffeine [1]	Meal [2]	Meal + caffeine [3]	Posthoc comparison
	kcal/min				%			
Lean subjects	0.040 ± 0.016	0.210 ± 0.015	0.236 ± 0.014	1 vs 2, 3 $p < 0.001$ 2 vs 3 NS	4.38 ± 1.8	20.6 ± 0.9	22.7 ± 1.1	1 vs 2, 3 $p < 0.001$ 2 vs 3 NS
Postobese subjects	0.032 ± 0.009	0.125 ± 0.018	0.165 ± 0.015	1 vs 2, 3 $p < 0.001$ 2 vs 3 $p < 0.05$	3.16 ± 0.87	11.8 ± 1.4	15.7 ± 1.3	1 vs 2, 3 $p < 0.001$ 2 vs 3 $p < 0.05$
Significance of F between treatments				$p < 0.001$	Significance of F between treatments			$p < 0.001$
between groups				$p < 0.001$	between groups			$p < 0.001$

* $\bar{x}$ ± SEM, n = 9 per groups; six females, three males per group.

postobese group was ameliorated to an extent that their thermogenic response to food with caffeine was only 25% below that of the lean group. Thus the subnormal DIT of the postobese group was partially corrected by the administration of caffeine. However, the thermogenic responses in both subject groups after a meal were not measured until the study ended and were thus underestimated.

Daily energy expenditure

The data on 24-h EE measured in the respirometer were divided into two 12-h periods (**Fig 2, Tables 4 and 5**): the 12-h day period (0–12 h EE) during which the caffeine tablets were administered, followed by a second 12-h night period (12–24 h EE) when no caffeine was ingested. The mean EE (MJ/person) was 8–10% lower in the postobese group than in the lean group (Fig 2) but these differences were not statistically significant. However, analysis of variance (Table 4) shows that during the control study and also during treatment with caffeine, EE expressed per unit body weight was significantly lower by 13–18% in the postobese group than in the lean group for 0–12-h EE, 12–24-h EE, and total 24-h EE. Administration of caffeine increased the 0–12-h EE in

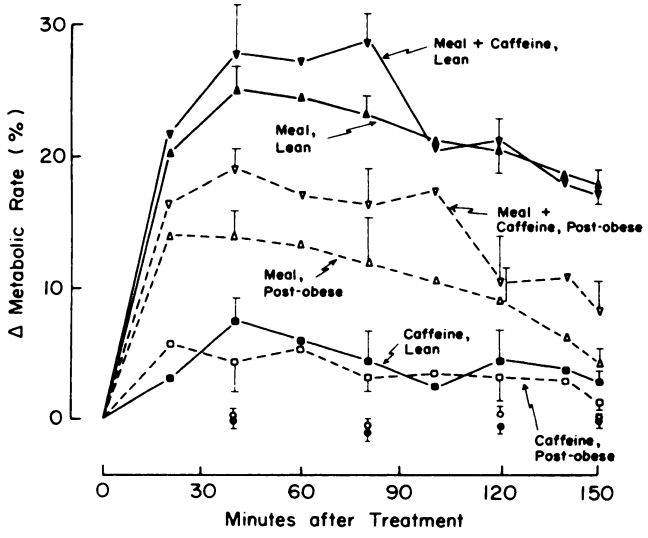

FIG 1. Thermogenic response of lean and postobese subjects to a 100-mg caffeine tablet administered after fasting, to a 300 kcal mixed meal, or to a combination of caffeine and a meal. The effect of the control water load is also shown for the lean (closed circles) and for the postobese subjects (open circles). Vertical bars represent the SEM n = 9).

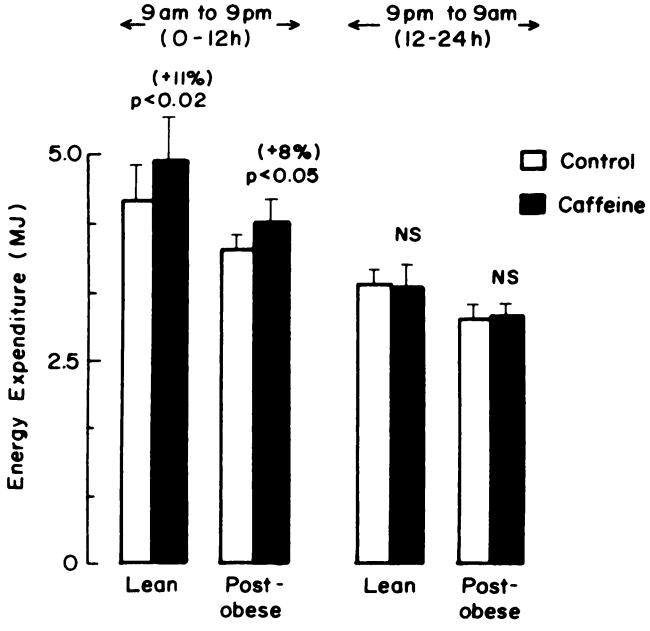

FIG 2. Energy expenditure compartmented into the first 12-h d period (0–12 h) and the subsequent 12-h night period (12–24 h) in lean (n = 5) and postobese (n = 6) subjects during a control study (open bars) and during administration of caffeine. Vertical bars represent the SEM values. The probability level for significant differences is for paired data. MJ values can be converted to kcal by multiplying them by 239.

TABLE 4
Energy expenditure (kcal/kg) in respirometer during base-line (control) study and during treatment with caffeine

	0–12 h		12–24 h		0–24 h	
	Control	Caffeine	Control	Caffeine	Control	Caffeine
Lean subjects†	17.2 ± 0.8	19.2 ± 0.9	13.4 ± 0.6	13.2 ± 0.4	30.6 ± 0.9	32.3 ± 0.9
Postobese subjects‡	14.5 ± 0.8	15.7 ± 0.8	11.3 ± 0.4	11.5 ± 0.5	25.8 ± 0.9	27.2 ± 1.2
Significance of F						
between treatments	$p < 0.01$		NS		$p < 0.01$	
between groups	$p < 0.025$		$p < 0.02$		$p < 0.01$	

* $\bar{x} \pm$ SEM.
† $n = 5$; three females, two males.
‡ $n = 6$; three females, three males.

the lean and postobese groups to a similar extent but had no significant effect on the subsequent 12–24-h EE in either subject group (Fig 2, Table 5). Thus, the total 24-h EE was significantly increased in both groups.

The data on activity levels measured within the respirometer were analyzed by computing the amount of time spent on various activities. Activities were categorized as sleeping, lying, sitting quietly (ie, minimal action, such as reading, watching television, etc), sitting actively (eg, eating, writing, knitting, etc), and pottering or fidgeting (eg, moving around the room to collect meals, performing personal toilets, etc). In the respirometer there were no differences in activity patterns between subject groups or between treatments.

Discussion

Effect of caffeine on resting metabolic rate and diet-induced thermogenesis

This study demonstrates that caffeine increased the RMR by 3–4% over 2.5 h at doses as low as 100 mg. Because early studies (13, 14) indicated that RMR was unaltered by lower doses of caffeine, it is likely that the amount of caffeine administered in our study represents the minimum (or near minimum) dose that would allow a demonstrable stimulatory effect on RMR. In addition, it seems that the thermogenic effect of caffeine in man is dose dependent because the present data and the results of other studies (2–7, 14) indicate that the magnitude of response increases almost linearly with higher doses: over 2–2.5 h the thermogenic responses to doses of 100, 200–250, and 400–450 mg were 4–5, 10–12, and 16%, respectively.

The current data also indicate that after fasting both the lean and the postobese subjects show similar increases in metabolic rate after caffeine is ingested. These findings are compatible with a previous study (6) in which no difference was observed between lean and obese groups but are in direct conflict with another report (7) in which the thermogenic response of the postobese subjects to caffeine is one-third less than that in lean subjects. These discrepancies could be because in the latter study (7) both groups received the same amount of caffeine even though the postobese subjects weighed about one-third more than the lean subjects and therefore received a smaller dose of caffeine per unit body weight. This explanation is supported by data from the same study that indicated a lower plasma caffeine level in postobese subjects than in lean subjects. In the present study the mean body weight and lean body mass

TABLE 5
Changes in energy expenditure measured in a respirometer during administration of caffeine*

	Absolute changes			Percentage changes		
	0–12 h	12–24 h	0–24 h	0–12 h	12–24 h	0–24 h
	kcal			%		
Lean subjects†	120 ± 36	−11 ± 25	109 ± 50	11.4 ± 3.1	−1.8 ± 3.3	5.5 ± 2.3
Postobese subjects‡	74 ± 31	6 ± 24	78 ± 34	7.9 ± 3.4	1.5 ± 3.5	4.9 ± 1.8
Significance of F						
between treatments	$p < 0.01$	NS	$p < 0.02$	$p < 0.01$	NS	$p < 0.02$
between groups	NS	NS	NS	NS	NS	NS

* $\bar{x} \pm$ SEM.
† $n = 5$; three females, two males.
‡ $n = 6$; three females, three males.

of the postobese group and the lean group did not differ significantly and a similar increase in RMR resulted from the administration of the same dose of caffeine; this suggests that under fasting conditions both groups show similar sensitivity in thermogenic response to caffeine.

In contrast, the thermogenic response to a mixed meal differed considerably between the two subject groups. The response of the postobese group was only half as much as that of the lean group. These findings provide further evidence for a subnormal thermogenic response to food in those with a predisposition to obesity. Their defective DIT was improved by caffeine, its thermogenic effect being additive to that of the food. However, caffeine produced only a small additional stimulatory effect on DIT in the lean group. This apparently greater thermogenic response in the postobese group, at least at this relatively low dose, suggests that the postobese group is more sensitive to caffeine than the lean group but only when caffeine is taken with food. Similar greater thermogenic responses of postobese subjects than the lean subjects in the fed state were reported during single-dose administration of a sympathomimetic mixture of ephedrine and methylxanthines, although both groups also showed identical thermogenic responses to the drugs in the fasted state (10).

Influence of caffeine on daily energy expenditure

Although this study focuses primarily on the thermogenic responses of lean and postobese subjects to caffeine rather than on a comparison of their absolute metabolic rates, it nevertheless demonstrates that in addition to a subnormal DIT the RMR and 24-h EE of the postobese group were lower than in the lean group. These differences are statistically significant when the metabolic-rate data are corrected for intergroup and intragroup variations in body weight. Similar differences ($p < 0.02$) are also apparent if the data are expressed per lean body mass. Therefore, these findings support previous reports (15–17) that postobese subjects tend to have a lower energy requirement for weight maintenance than do lean subjects.

Repeated administration of caffeine increased the EE of both subject groups but only during the period of drug administration (ie, the first 12-h day period). The lack of any residual thermogenic effect in the second 12-h night period is probably because any residual plasma caffeine level would have been cleared given its relatively short half-life of 3–3.5 h. However, the similar increase in 0–12-h EE in both subject groups contrasts with the findings of the single-dose study indicating that caffeine had a much smaller stimulatory effect on DIT in the lean group than in the postobese group. There are two explanations for this apparent discrepancy. It is possible that after repeated caffeine intake the additive effect of caffeine and food on thermogenesis in the postobese group was not sustained and that the increase in 0–12-h EE resulted mostly from the stimulatory effect of caffeine on the other components of EE. Alternatively, it is plausible to suggest that repeated administration of caffeine, resulting in a higher plasma level of caffeine than that achieved with a single dose, stimulated DIT to a similar extent in both the postobese group and the lean group. This agrees with previous studies in lean subjects (5, 6) indicating that administration of higher doses of caffeine produced an effect additive to that of food on thermogenesis. Therefore, the current findings and previous studies (5, 6) imply that people with a predisposition to obesity may differ from lean people in sensitivity but not in capacity to the stimulatory effect of caffeine on DIT and on daily EE.

Caffeine and weight control

A main implication of this study concerns the potential use of caffeine as an apparently safe thermogenic agent for weight control. The effect of caffeine on appetite is unknown in man, but if it is assumed that there is no compensatory increase in food intake, the increase of ~5% in 24-h EE after caffeine would represent an energy deficit of 75–110 kcal/d. These changes may be small but over several months could accumulate and lead to substantial changes in body weight. A long-term human study of the effects of caffeine on body fat content is long overdue but studies in animals demonstrated that caffeine and other methylxanthines, albeit at high doses, reduced body weight and body fat by both anorectic and thermogenic effects (18). Although caffeine and other methylxanthines were ineffective in altering EE when administered at low doses, they can markedly potentiate the thermogenic effects of ephedrine (a sympathomimetic agent) and lead to a reversal or prevention of obesity in some animal models (19–21). In man, administration of methylxanthines in doses (80 mg) similar to those administered in this study (100 mg) doubles the thermogenic effect of ephedrine, and such mixtures completely normalize the defective DIT found in postobese subjects to those levels found in lean subjects (10). The ability of commonly consumed amounts of caffeine to increase daily EE, as demonstrated in the present investigation, coupled with caffeine's ability to augment the thermogenic effects of certain sympathetic stimulants (10, 19–22) may have contributed to reported weight losses in obese humans (23). The potential use of caffeine as a promoter of thermogenesis during the treatment of obesity warrants further study.

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