Metabolic effects of caffeine in humans: lipid oxidation or futile cycling?1–3

Kevin J Acheson, Gérard Gremaud, Isabelle Meirim, Franck Montigon, Yves Krebs, Laurent B Fay, Louis-Jean Gay, Philippe Schneiter, Charles Schindler, and Luc Tappy

ABSTRACT

Background: Caffeine ingestion stimulates both lipolysis and energy expenditure.

Objectives: Our objectives were to determine whether the lipolytic effect of caffeine is associated with increased lipid oxidation or futile cycling between triacylglycerol and free fatty acids (FFAs) and whether the effects of caffeine are mediated via the sympathetic nervous system.

Design: Respiratory exchange and [1-13C]palmitate were used to trace lipid oxidation and FFA turnover in 8 healthy, young men for 90 min before and 240 min after ingestion of placebo, caffeine (10 mg/kg), or caffeine during β-adrenoceptor blockade.

Results: During fasting conditions, there were few differences in measured variables between the 3 tests. During steady state conditions (last hour of the test) after ingestion of caffeine, lipid turnover increased 2-fold ($P < 0.005$), and the mean ($\pm$SEM) thermic effect was $13.3 \pm 2.2\%$ ($P < 0.001$), both of which were greater than after ingestion of placebo or caffeine during β-adrenoceptor blockade. After ingestion of caffeine, oxidative FFA disposal increased 44% ($236 \pm 21$ to $340 \pm 16 \mu$mol/min), whereas nonoxidative FFA disposal increased 2.3-fold ($455 \pm 66$ to $1054 \pm 242 \mu$mol/min; $P < 0.01$). In postabsorptive conditions, 34% of lipids were oxidized and 66% were recycled. Caffeine ingestion increased energy expenditure 13% and doubled the turnover of lipids, of which 24% were oxidized and 76% were recycled. β-Adrenoceptor blockade decreased, but did not inhibit, these variables.

Conclusions: Many, but not all, of the effects of caffeine are mediated via the sympathetic nervous system. The effect of caffeine on lipid mobilization in resting conditions can be interpreted in 2 ways: lipid mobilization alone is insufficient to drive lipid oxidation, or large increments in lipid turnover result in small increments in lipid oxidation. Am J Clin Nutr 2004;79:40–6.

KEY WORDS Paraxanthine, slow-release caffeine, thermic effect, lipid turnover, oxidative lipid disposal, nonoxidative lipid disposal

INTRODUCTION

For many years it has been known that caffeine and coffee can stimulate energy expenditure to varying degrees (1–3), and the use of caffeine alone (3) or in combination with ephedrine (4–8) has been proposed for the treatment of obesity. Although acute studies using caffeine alone showed that lipolysis and lipid oxidation increased in lean subjects, increases were not obvious in obese subjects (1). However, Bracco et al (9) observed that, compared with lean women, obese women had increased but blunted lipid oxidation the day after caffeine ingestion. Astrup et al (4) also observed increased fat oxidation in obese women who consumed a restricted diet and a mixture of ephedrine and caffeine over an 8-wk period.

The increase in energy expenditure and changes in plasma substrates after caffeine ingestion resemble those caused by increased activity of the sympathetic nervous system (SNS). Bellet et al (10) observed increased plasma free fatty acid (FFA) concentrations and increased urinary catecholamine excretion (11) after caffeine or coffee ingestion and suggested that increased lipolysis was, in part, due to increased catecholamine release. However, other studies performed during the same period showed that caffeine also increases lipolysis by inhibiting the cyclic nucleotide phosphodiesterase (12), which is responsible for catalyzing the conversion of cyclic AMP to AMP. The resulting high tissue concentrations of cyclic AMP activate inactive hormone-sensitive lipase and promote lipolysis. The authors of these studies showed that in the presence of lipolytic hormones, such as adrenaline, caffeine acts synergistically and causes an increase in cyclic AMP concentrations that is greater than that caused by the hormones alone (12). Thus, there is evidence that caffeine stimulates not only resting energy expenditure but lipid mobilization and fat oxidation as well.

To investigate the metabolic effects of caffeine further, we used a combination of slow-release caffeine and normal caffeine to obtain and maintain high plasma caffeine concentrations that is greater than that caused by the hormones alone (12). Hence, it is evident that caffeine stimulates not only resting energy expenditure but lipid mobilization and fat oxidation as well.

To investigate the metabolic effects of caffeine further, we used a combination of slow-release caffeine and normal caffeine to obtain and maintain high plasma caffeine concentrations that is greater than that caused by the hormones alone (12). Hence, it is evident that caffeine stimulates not only resting energy expenditure but lipid mobilization and fat oxidation as well.

1 From the Nestlé Research Center, Lausanne, Switzerland (KJA, GG, IM, FM, YK, and LBF); the Physiology Institute, Lausanne, Switzerland (L-JG, PS, and LT); and the Central Pharmacy, Lausanne University Hospital, Lausanne, Switzerland (CS).

2 Supported by Nestec SA, Switzerland.

3 Address reprint requests to KJ Acheson, Nestlé Research Center, PO Box 44, Vers-chez-les-Blanc, CH-1000 Lausanne 26, Switzerland. E-mail: kevin.acheson@rdls.nestle.com.

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TABLE 1
Physical characteristics of the male volunteers £

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
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</thead>
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<tr>
<td>Age (y)</td>
<td>23.1 ± 2.6</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>77.1 ± 7.4</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>174.4 ± 6.0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.5 ± 3.1</td>
</tr>
<tr>
<td>Fat: (% by wt)</td>
<td>14.5 ± 2.8</td>
</tr>
<tr>
<td>Lean body mass (kg)</td>
<td>65.8 ± 4.9</td>
</tr>
</tbody>
</table>

£ X ± SD; n = 8.

SUBJECTS AND METHODS

Subjects
Eight healthy male volunteers, whose physical characteristics are shown in Table 1, were recruited. The protocol, which had previously been submitted to and approved by the ethical committee of the Faculty of Medicine, Lausanne University, contained a simplified but detailed account of all of the experimental procedures. The subjects were accepted into the study after being fully informed about the protocol and giving their signed consent.

Protocol
Each subject underwent 4 experiments during which either caffeine or 500 mg lactose placebo was ingested to investigate energy expenditure, lipid turnover, and fat oxidation. In the third experiment, the influence of the SNS on energy expenditure and lipid turnover induced by caffeine ingestion was investigated by using the β-adrenoceptor antagonist propranolol (Inderal; AstraZeneca, Macclesfield, United Kingdom). Because labeled [1-13C]palmitate was infused and oxidized, thereby producing 13CO2, a fourth experiment in which caffeine was administered during a continuous infusion of [1-13C]acetate was also performed to measure 13CO2 recovery during the actual conditions of the test. The subjects participated in the experiments in random order, and each experiment was separated by a period of 1 wk.

Each subject consumed his habitual diet before each test and refrained from consuming caffeine-containing beverages and foods during the 24 h before each test. Before the test, the evening meal was consumed no later than 1900. After arriving at the Physiology Institute at 0630, overnight urine was collected, and minimal ablutions were performed. The subject was transferred to the test room and positioned comfortably in a semirecumbent position, and 2 venous catheters were inserted: one into an antecubital vein of one arm for the infusion of labeled substrates and the other retrogradely into the wrist vein of the other arm for blood sampling. The hand on the latter arm was placed in a warming pump (IMED, Abingdon, United Kingdom) for the whole duration of the experiment. After 1 h of tracer baseline measurements (time 0), either caffeine or a placebo (lactose) prepared in gelatin capsules was swallowed by the subject, and respiratory exchange measurements were continued for a further 4 h. The above protocol was also used for the test in which the contribution of the SNS was investigated. Propranolol (100 μg/kg bolus and 1 μg·kg⁻¹·min⁻¹) was infused continuously starting 60 min before ingestion of the caffeine capsules and for a further 210 min. Propranolol infusion was stopped 30 min before the respiratory exchange measurements ended at 240 min.

During the [1-13C]acetate labeled-carbon recovery test (13), respiratory exchange measurements were performed for 6 h. After collection of a baseline breath sample, sodium bicarbonate was given as a bolus (480 μmol), and an infusion of [1-13C]acetate (prime: 150 μmol; continuous: 6 μmol/min) was started at the same time. Three hours later, the subjects ingested gelatin capsules containing caffeine (5 mg slow-release caffeine/kg + 5 mg caffeine/kg), and measurements were continued for a further 3 h. Breath samples were collected every hour until the end of the test.

Stable isotopes, caffeine, and respiratory exchange measurements
All stable isotopes were purchased from MassTrace Inc (Woburn, MA). [1-13C]Palmitate was bound to albumin as previously described (14) and was infused at a continuous rate of 0.04 μmol·kg⁻¹·min⁻¹. The exact infusion rate was calculated by measuring the concentration of labeled palmitate in the infusate and multiplying it by the calibration factor of the infusion pump. Sodium bicarbonate was given as a bolus providing 2 μmol/kg.

The caffeine ingested by the subjects was of 2 types: normal pharmacologic grade and slow release. Both types were obtained from Eurand France SA (Nogent sur Oise, France), and the subjects received 5 mg of either type/kg. Respiratory exchange measurements were performed by using an open-circuit indirect calorimeter with a ventilated hood as described previously (15).

Blood and urine samples
Blood samples were taken at −90, −30, −20, −10, and 0 min. After caffeine or placebo administration, samples were taken at 30-min intervals until 3 h, and then a final sample was taken at 4 h. Urine was collected before, during (when necessary), and at the end of the experiment.

Analyses

Plasma samples
All samples were analyzed for concentrations of glucose (Beckman Instruments, Fullerton, CA), palmitate, and FFAs (see below). Blood urea in samples obtained at 0 and 240 min was measured by using a Beckman autoanalyzer. Insulin was measured by using radioimmunoassay with a kit from Medgenix (Brussels). Caffeine and paraxanthine were measured as follows. β-Hydroxyethyl theophylline was added to plasma samples as an internal standard, and caffeine and paraxanthine were extracted with chloroform/isopropanol. After centrifugation for 5 min at 1300 × g and 4 °C, the supernatant fluid was removed and discarded. The remainder was evaporated to dryness at 37 °C under nitrogen, resuspended in 0.05% (by vol)
aqueous acetic acid, and analyzed in triplicate by using HPLC (16).

**Urine samples**

Total nitrogen was measured in all urine samples by using the Kjeldahl method. Caffeine and paraxanthine were extracted in the same way as for plasma samples and were then analyzed in triplicate by using HPLC with β-hydroxyethyl theophylline as the internal standard (16).

**Breath samples**

Three breath samples were collected during the baseline period before infusion of labeled [1-13C]palmitate; 2 samples were collected before caffeine or placebo ingestion, and additional samples were taken thereafter at 30-min intervals until the end of the test.

**Stable-isotope analysis**

For measurement of FFAs, [4-13C]palmitate and [4-13C]octanoate were added as internal standards to each plasma sample, and the samples were incubated with ice-cold methanol. The protein precipitate was centrifuged for 15 min at 4000 × g and 4 °C, and the supernatant fluid was removed and dried under nitrogen. The dry residue was redissolved in acetonitrile:chloroform (3:1, by vol), and the FFAs were separated by thin-layer chromatography. After visualization and location with rhodanine G6 and ultraviolet light, the FFA band was removed, and the FFAs were converted into their methyl esters. FFAs were measured by gas chromatography–mass spectrometry (model 6890 gas chromatograph and model 5972 mass spectrometer; Hewlett-Packard, Palo Alto, CA) with electron impact ionization (70 eV). Ions were selectively monitored at mass-to-charge ratios (m/e) of 270, 271, and 274 to quantify isotopic enrichment in the plasma resulting from [1-13C]palmitate infusion (m/e of 271) and to determine the palmitate concentration by using the in vitro addition of the internal standard [4-13C]palmitate (m/e of 274). Ions with an m/e of 158 and 162 were used to calculate the concentration of octanoate, and ions with an m/e of 74 (nonspecific, abundant ions) were used to calculate the concentrations of FFAs having higher masses. Standard curves were prepared for FFA and palmitate concentrations and palmitate enrichment.

**Calculations**

Protein oxidation in the fasting postabsorptive state was calculated from total urinary nitrogen in the overnight urine sample. For each test, urinary nitrogen excretion was corrected for any changes observed in the serum urea nitrogen pool between 0 and 240 min (17). Energy expenditure and carbohydrate and lipid oxidation rates were calculated from respiratory exchange data as previously described by using the equations of Livesey and Elia (18). Mean values were calculated during the last half hour of baseline measurements and compared with the mean plateau values recorded during the last hour of the experiment, ie, 180–240 min. The rate of appearance of palmitate was calculated as described by Wolfe et al (19) by using Steele’s steady state equations.

**Statistics**

Results are expressed as means ± SEMs, unless stated otherwise, and were analyzed by using repeated-measures analysis of variance. The variables used were condition (baseline or stimulated state), treatment [placebo, caffeine, or caffeine during β-adrenoceptor blockade (caffeine + βB)], and subject (subjects 1–8). Significant differences between tests were further analyzed by using Bonferroni multiple comparison tests and NUMBER CRUNCHER STATISTICAL SYSTEMS software (NCSS Statistical Software, Kaysville, UT) to calculate pairwise differences between the means. P values for analysis of variance and Bonferroni-adjusted P values are reported in the text. P < 0.05 was considered significant.

**RESULTS**

**Blood variables**

Plasma caffeine and paraxanthine concentrations during the different experiments are shown in Figure 1. Baseline caffeine concentrations were ≤0.2 µg/mL, which confirmed that caffeine-containing products had not been ingested during the 24 h before the test, and caffeine concentrations were unchanged after placebo ingestion. After caffeine ingestion (with or without propranolol), plasma caffeine concentrations increased rapidly to 9.8–10 µg/mL at 60 min and remained in the range of 9.0–10 µg/mL for the next 3 h. Paraxanthine concentrations were not detectable during fasting conditions or during the placebo experiment, but they increased progressively throughout each experiment after caffeine ingestion and reached a maximum value of 3.0 ± 0.3 µg/mL at 4 h.

Other plasma concentrations are shown in Figure 2. FFA concentrations in the placebo, caffeine, and caffeine + βB
experiments were 108 ± 12, 125 ± 17, and 106 ± 16 mg/L, respectively, in the postabsorptive state and increased to 136 ± 8, 230 ± 23, and 211 ± 24 mg/L, respectively, during the last hour of the test. Glucose concentrations during fasting conditions did not differ significantly between the 3 experiments (93–95 mg/dL). Although no significant changes were observed after placebo and caffeine ingestion, glucose concentrations during the caffeine + βB experiment increased to 100 mg/dL at 90 min and plateaued at this value until 240 min.

Baseline insulin concentrations in the placebo, caffeine, and caffeine + βB experiments were 5.4 ± 0.8, 6.0 ± 1.0, and 5.2 ± 1.0 μU/mL, respectively. During the experiments, the concentrations fluctuated around the baseline values but did not change significantly.

Heart rate

There were significant treatment effects (P < 0.001) and significant treatment-by-condition interactions (P < 0.01) (Figure 3). In the postabsorptive fasting state, the heart rates in the placebo and the caffeine experiments did not differ significantly from one another (58 ± 3 and 60 ± 4 beats/min, respectively), but both differed significantly from the heart rate during fasting conditions in the caffeine + βB experiment (54 ± 3 beats/min; P < 0.02 and P < 0.001, respectively). The heart rates during the last hour of the 3 experiments did not differ significantly from their respective baseline values but did differ significantly from one another (P < 0.02).

Energy expenditure

There were significant treatment (P < 0.001) and condition (P < 0.001) effects and significant treatment-by-condition interactions (P < 0.001) for energy expenditure (Figure 4). Postabsorptive energy expenditure did not differ between the 3 experiments immediately before administration of placebo, caffeine, or caffeine + βB (1.37 ± 0.036, 1.37 ± 0.039, and 1.32 ± 0.035 kcal/min, respectively). Although, β-blockade before caffeine administration in the caffeine + βB experiment caused a decrease in energy expenditure (1.37 ± 0.037 to 1.32 ± 0.035 kcal/min), this change was not significant. After caffeine administration, energy expenditure increased significantly (P < 0.001) and reached a value of 1.55 ± 0.038 kcal/min during the last hour of the test, which was significantly higher than the corresponding values obtained after administration of either placebo (1.40 ± 0.04 kcal/min; P < 0.001) or caffeine + βB (1.41 ± 0.044 kcal/min; P < 0.001).
The thermic effect of caffeine, i.e., the mean energy expenditure during the last hour of the test expressed as a percentage of fasting energy expenditure, was 13.3 ± 2.2%, which was greater than the thermic effect of placebo (2.0 ± 0.5%; P < 0.001) or caffeine + βB (6.4 ± 1.2%; P < 0.02) (Figure 4).

**DISCUSSION**

In agreement with the results of previous studies (1, 20), the present study showed that caffeine ingestion increased energy expenditure (≈13%) and lipid turnover and oxidation. However, the contribution of nonoxidative lipid disposal was much greater (76%) than that of lipid oxidation (24%). β-Adrenoceptor blockade with propranolol decreased caffeine-stimulated energy expenditure and lipid turnover, which indicates that some of the metabolic effects of caffeine are mediated by the SNS. Because the dose of propranolol may not have blocked all β-adrenergic receptors, i.e., β1 receptors (21), the present results

![FIGURE 5. Mean (±SEM) total free fatty acid (FFA) turnover and mean (±SEM) values of its components, oxidative fatty acid disposal and nonoxidative fatty acid disposal or recycling, during postabsorptive fasting conditions (PA) and the last hour of experiments in which either a lactose placebo, caffeine (5 mg slow-release caffeine/kg + 5 mg caffeine/kg), or caffeine during β-adrenoceptor blockade with propranolol (βB) was administered (n = 8). For total FFA turnover, repeated-measures ANOVA showed significant treatment (P < 0.01) and condition (P < 0.001) effects and significant treatment-by-condition interactions (P < 0.02). The letters a and b above the bars refer to total FFA turnover. Bars with different letters are significantly different by at least P < 0.05 (Bonferroni multiple comparison test). For oxidative FFA disposal, repeated-measures ANOVA showed a significant condition effect (P < 0.001). For nonoxidative FFA disposal, repeated-measures ANOVA showed significant condition (P < 0.01) and condition (P < 0.01) effects and significant treatment-by-condition interactions (P < 0.02). The letters e and f inside the shaded bars refer to nonoxidative FFA disposal. Bars with different letters are significantly different by at least P < 0.01 (Bonferroni multiple comparison test).](https://doi.org/10.1093/ajcn/91.1.230)
indicate that the SNS accounts for ≥50% of the energy expenditure and 60% of the lipid turnover induced by caffeine ingestion. At the dose of propranolol used, the observed effect would not be mediated by β₁ receptors, but it could be argued that the remaining effects would be. If the decrease in fasting energy expenditure with propranolol were not taken into account when calculating the thermic effect of caffeine + βB, the thermic effect would be 2.1 ± 2.6% (NS compared with placebo). In this case, all of the metabolic effects of caffeine would be mediated via the SNS. We believe, however, that caffeine did stimulate thermogenesis during β-adrenergocceptor blockade, as indicated by the similar, almost parallel increases in energy expenditure observed during the first hour after caffeine ingestion (Figure 4).

In vitro, caffeine acts synergistically in the presence of adrenaline to promote lipolytic activity (12), which suggests that the effect of caffeine on lipolysis occurs via mechanisms other than stimulation of the SNS. In vivo, it has been observed that many of the metabolic effects of caffeine are very similar to those of increased SNS activity, such as increased heart rate, blood pressure (22), plasma adrenaline (22), urinary catecholamine excretion (11), and plasma FFAs (10, 22). Similarly, caffeine has been observed to potentiate the effects of ephedrine, a sympathomimetic agent that is capable of increasing energy expenditure (5, 7, 8) and promoting the loss of body fat. This result further supports the view that mechanisms other than SNS stimulation are involved in the metabolic effects of caffeine.

In postabsorptive fasting conditions, FFA turnover in the present study was similar to that observed by Arciero et al (20). Of the FFAs released, 67%, 66%, and 61% were reesterified (nonoxidative lipid disposal) during the placebo, caffeine, and caffeine + βB experiments, respectively, and these values are consistent with previously reported values during fasting conditions (23–25). The slightly lower turnover rate observed in the placebo group during fasting conditions with β-adrenergocceptor blockade has been observed before (26), which shows either that baseline sympathetic tone has an effect on fasting lipolysis or that β-adrenergic stimulation already contributes to lipolysis after a short-term overnight fast (26). This may also explain the slight decrease in baseline energy expenditure during propranolol infusion and should be taken into account when the thermic effect of caffeine + β-adrenergocceptor blockade is calculated.

FFA turnover doubled after caffeine ingestion because of a 44% increase in fatty acid oxidation and a much greater increase in fatty acid recycling (130%). During the placebo experiment, the small increase in FFA turnover was entirely due to an increase in fatty acid oxidation. Although it is well known that the effect of caffeine on energy expenditure and β-adrenergocceptors is dose dependent, extrapolation of the present observations to other caffeine doses remains to be performed. The results of the present study support those of previous studies showing that plasma FFAs influence their own oxidation in humans (23, 24); however, in resting conditions, large increments in lipid turnover are apparently necessary to induce a relatively small increase in lipid oxidation.

Adrenergic control of lipolysis occurs via the effects of a dual mechanism involving stimulatory β-adrenergocceptors and inhibitory α₂-adrenergocceptors on adenylyl cyclase (27). The adenosine receptor also inhibits lipolysis via adenylyl cyclase; thus, by virtue of its adenosine antagonist properties, caffeine stimulates lipolysis in vitro and in vivo (28). The large increase in FFA turnover after caffeine ingestion was probably due to the combined effects of caffeine on β-adrenergic lipolytic stimulation and on antagonism of the anti-lipolytic effects of adenosine. β-Adrenergocceptor blockade has also been shown to significantly decrease triacylglycerol–fatty acid cycling in patients with burn injuries (29). During β-adrenergocceptor blockade in the present study, a small but significant increase in plasma glucose concentrations occurred. A similar phenomenon, in which fructosuria increased during propranolol infusion, was observed previously (30) and was attributed to decreased hepatic blood flow (31, 32) and clearance (31, 33).

The mechanisms underlying the thermic effect of caffeine remain unknown. The effect may involve stimulation of futile cycling, particularly triacylglycerol–fatty acid and glucose-lactate cycles, or activation of uncoupling proteins. These 2 processes have indeed been observed to be responsive to sympathetic stimulation or catecholamine administration. It is also possible that other, yet unknown mechanisms are involved.

After β-blockade the thermic effect of caffeine was still 6.4%, which shows that caffeine probably has nonadrenergic thermogenic mechanisms. Caffeine is known to be an agonist of the ryanodine receptor (34), the calcium ion release channel of sarcoplasmic reticulum in skeletal muscle. Ryanodine receptor stimulation increases intramyocellular calcium flux, muscle contraction, heat production, glycolysis, ATP turnover, and mitochondrial pyruvate oxidation (35). In the inherited pathophysiological condition “malignant hyperthermia,” volatile anesthetics cause excessive calcium mobilization, muscle calcification, hyperthermia, cell lysis, and death (36). It is, therefore, possible that caffeine influences whole-body thermogenesis via changes in intracellular calcium trafficking. Indeed, Astrup et al (37, 38) proposed that the principal thermogenic tissue in humans is skeletal muscle, albeit in response to SNS stimulation, and Zurlo et al (39) showed that differences in resting muscle metabolism can explain some of the variance in metabolic rate between persons.

Although caffeine caused a 2-fold increase in fatty acid turnover, lipid oxidation increased by only 44%, which indicates that most mobilized fatty acids are reesterified in resting conditions. This is in contrast with exercise, which causes an increase in the turnover of fatty acids, of which 70-80% are oxidized (24). However, it is likely that muscle energy requirements during exercise are roughly balanced by a coordinated stimulation of adipose tissue lipolysis that is attained through activation of the SNS. Caffeine administration, in contrast, produces a much greater effect on adipose tissue lipolysis than on energy expenditure and thus represents a pharmacologic model of stimulated lipolysis. Under such conditions, only a small fraction of the fatty acids released from adipocytes are oxidized, and this fraction would be even smaller if caffeine did not simultaneously increase energy expenditure. This clearly indicates that stimulation of lipolysis per se is not a major factor in the regulation of lipid oxidation or energy expenditure and casts doubts on strategies aimed primarily at stimulating lipolysis to control body weight. Consequently, combining stimulation of lipolysis by caffeine administration and stimulation of energy expenditure by exercise may prove more effective than giving caffeine alone.

In conclusion, the results of the present study show not only that caffeine stimulates resting energy expenditure but that this
increased cellular thermogenesis is accompanied by an increase in fatty acid turnover and lipid oxidation. However, the increase in nonoxidative lipid turnover (triacylglycerol hydrolysis and reesterification) is far greater than the increase in oxidative lipid disposal, which indicates that a large increase in turnover rate is necessary to cause a small increase in lipid oxidation. The effect of caffeine on lipid and energy metabolism appears to have both sympathetic and nonsympathetic components.

All the authors were involved in the development of the study protocol and the experimental design. The stable-isotope infusates were prepared and tested under the supervision of CS. Experiments were performed by KJA, LT, PS, and L-JG. Samples were analyzed by IM, GG, FM, LBF, and YK. Data were analyzed by KJA, LT, and PS. KJA wrote the draft manuscript with contributions from LT, CS, PS, IM, GG, FM, LBF, and YK. All the authors read, commented on, and contributed to the submitted and revised manuscripts. KJA, GG, IM, FM, YK, and LBF are employees of Nestec SA, an affiliate of Nestlé SA, Switzerland. LIG, PS, CS, and LT had no personal interests in, and were not affiliated with, Nestec SA or any other company.

REFERENCES


