

Green tea extract ingestion, fat oxidation, and glucose tolerance in healthy humans^{1,2}

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ABSTRACT

Background: Green tea consumption is reportedly associated with various health-promoting properties. For example, it has been shown to promote fat oxidation in humans at rest and to prevent obesity and improve insulin sensitivity in mice.

Objective: We investigated the effects of acute ingestion of green tea extract (GTE) on glucose tolerance and fat oxidation during moderate-intensity exercise in humans.

Design: Two studies were performed, both with a counter-balanced crossover design. In study A, 12 healthy men performed a 30-min cycling exercise at 60% of maximal oxygen consumption ($\dot{V}O_{2\max}$) before and after supplementation. In study B, 11 healthy men took an oral-glucose-tolerance test before and after supplementation. In the 24-h period before the experimental trials, participants ingested 3 capsules containing either GTE (total: 890 ± 13 mg polyphenols and 366 ± 5 mg EGCG) or a corn-flour placebo (total: 1729 ± 22 mg).

Results: Average fat oxidation rates were 17% higher after ingestion of GTE than after ingestion of placebo (0.41 ± 0.03 and 0.35 ± 0.03 g/min, respectively; $P < 0.05$). Moreover, the contribution of fat oxidation to total energy expenditure was also significantly higher, by a similar percentage, after GTE supplementation. The insulin area under the curve decreased in both the GTE and placebo trials (3612 ± 301 and 4280 ± 309 $\mu\text{IU/dL} \cdot 120$ min, respectively; $P < 0.01$), and there was a concomitant increase of 13% in insulin sensitivity.

Conclusions: Acute GTE ingestion can increase fat oxidation during moderate-intensity exercise and can improve insulin sensitivity and glucose tolerance in healthy young men. *Am J Clin Nutr* 2008;87:778–84.

KEY WORDS Tea catechins, substrate metabolism, oral-glucose-tolerance test, moderate-intensity exercise, men

INTRODUCTION

The prevalence of obesity is reaching epidemic proportions in many Western countries, with recently published data suggesting that, in some states in the United States, the prevalence of obesity is $>30\%$. Because obesity and insulin resistance are major risk factors for the development of type 2 diabetes mellitus and cardiovascular disease, any potential treatment can have far-reaching economic and medical implications.

Green tea contains a class of polyphenolic flavonoids known as catechins, which comprise epigallocatechin gallate (EGCG), epicatechin gallate, and gallic catechin gallate; EGCG is thought to be the most pharmacologically active of the catechins. Several experimental studies have indicated that chronic consumption of

green tea extract (GTE) can improve exercise performance, increase fat oxidation, and prevent obesity in C57BL/6J mice (1–4). It has been suggested that GTE exerts these effects through its action on the sympathetic nervous system, more specifically on the breakdown of the catecholamine noradrenaline. EGCG is a known inhibitor of the enzyme catechol *O*-methyltransferase (5), which degrades noradrenaline, and therefore EGCG can exert a regulatory effect on sympathetic activation and lipolysis.

Although most studies with green tea have been performed in animal models, Dulloo et al (6) showed that, in healthy young men, a similar effect can be observed with acute GTE ingestion. In their study, resting 24-h energy expenditure (EE) and the contribution of fat oxidation to total EE were elevated.

During moderate-intensity exercise, EE is several times higher than that during rest, and absolute rates of lipolysis and fat oxidation also are higher (7, 8). To date, it remains unclear whether EGCG can elevate fat oxidation and lipolysis during exercise when fatty acid (FA) metabolism is already stimulated.

In addition to effects on fat metabolism, GTE may have an effect on glucose tolerance and insulin sensitivity. When Sprague-Dawley rats were fed a diet including 148 mg green tea catechins/d for 12 d, fasting plasma glucose and insulin concentrations and the insulin response to an oral glucose load (2 g glucose/kg body wt) were significantly reduced (9). In addition, when spontaneously hypertensive rats, which are often used as a genetic model of the metabolic syndrome, were fed a diet supplemented with 200 mg EGCG \cdot kg⁻¹ \cdot d⁻¹ for 3 wk, insulin sensitivity increased (10).

The first study presented in this report (study A) investigated whether acute ingestion of GTE can increase fat oxidation rates during moderate-intensity exercise. The second study (study B) investigated the effects of acute ingestion of GTE on glucose tolerance as assessed by a 2-h oral-glucose-tolerance test (OGTT). We hypothesized that the acute intake of GTE will increase fat oxidation during exercise and will improve glucose tolerance in healthy young men.

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SUBJECTS AND METHODS

Participants

Twelve male participants [$\bar{x} \pm SD$ age: 26 ± 2 y; weight: 75.1 ± 3.2 kg; body mass index (BMI; in kg/m^2): 23.9 ± 0.8 ; maximal oxygen consumption ($\dot{V}\text{O}_2\text{max}$): 50.9 ± 2.1 $\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$] were recruited for study A. An additional 11 male participants (age: 23 ± 2 y; weight: 77.7 ± 4.5 kg; BMI: 24.1 ± 1.1 ; $\dot{V}\text{O}_2\text{max}$: 52.0 ± 2.8 $\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$) were recruited for study B. All participants were healthy according to results of a general health questionnaire.

All participants gave written informed consent to participate in the study. Both study A and study B were approved by the Ethics Subcommittee of the School of Sport and Exercise Sciences at the University of Birmingham.

Preliminary testing

At least 1 wk before the first experimental trial, all participants undertook an incremental exercise test, on an electronically braked cycle ergometer (Lode Excalibur Sport, Groningen, Netherlands), to volitional exhaustion. Participants started by cycling at 95W for 3 min and increased their effort by incremental steps of 35W every 3 min until they reached exhaustion. The W_{max} was calculated by using the following equation (11):

$$W_{\text{max}} = W_{\text{out}} + [(t/180) \times 35] \quad (1)$$

where W_{out} is the power output of the last completed stage, and t is the time (in s) spent in the final stage. W_{max} values were used to determine the workload (50% W_{max}) used in the later experimental trials for study A. Respiratory gas measurements were made by using the Douglas bag technique; oxygen consumption ($\dot{V}\text{O}_2$) and carbon dioxide production were calculated by using standard equations (12). Heart rate (HR) was measured continuously by using telemetry and an HR monitor (Polar S625X; Polar Electro Oy, Kempele, Finland). $\dot{V}\text{O}_2$ was considered to be maximal if 2 of the 3 following conditions were met: 1) a leveling off of $\dot{V}\text{O}_2$ with further increasing workloads (an increase of ≤ 2 $\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$); 2) an HR within 10 beats/min of the age-predicted maximum ($220 \text{ bpm} - \text{age}$); and 3) a respiratory exchange ratio of >1.05 .

General study designs

In a counter-balanced crossover design, each participant completed 2 trial days separated by ≥ 1 wk. In study A, each participant completed 30 min of cycling exercise at 50% of their previously determined W_{max} ; in study B, each participant underwent 2 OGTTs.

Diet and capsule content

In the 24-h period before the first trial, the participants were asked to produce a food diary; this was replicated before the second trial. During this 24-h period, participants ingested 3 capsules containing either GTE or a corn-flour placebo. The capsules were ingested with lunch and dinner on the day before the trial and in the morning, ≥ 1 h before the trial.

The GTE (Healthspan, St Peter Port, United Kingdom) consisted of a standardized GTE (total of 340 mg polyphenols and 136 mg EGCG), maltodextrin, microcrystalline cellulose, sodium croscarmellose, stearic acid, silicon dioxide, magnesium

stearate (vegetable origin), hydroxypropylmethyl cellulose coating, and glycerine (vegetable origin). The capsule does not contain caffeine. The amount of GTE contained in each capsule is equivalent to ≈ 3.5 cups green tea. The placebo capsule contained 1517 ± 48 mg of a gluten-free corn flour (Whitworths Ltd, Wellingborough, United Kingdom).

Experimental protocol

Study A

All participants reported to the Human Performance Laboratory between 0700 and 0900 after a 10-h overnight fast and having avoided strenuous exercise, alcohol, and caffeinated beverages for the preceding 24 h. On their arrival, standard measures of height and weight (Seca Alpha, Hamburg, Germany) were taken. A flexible 20-gauge Teflon catheter (Venflon; Becton Dickinson, Plymouth, United Kingdom) was then inserted into an antecubital vein. A 3-way stopcock (PVB Medizintechnik, Kirchseean, Germany) was attached to the catheter to allow repeated blood sampling during the test period. The participants then mounted the cycle ergometer, and a resting blood sample (5 mL) was collected in EDTA-containing tubes (Becton Dickinson) and stored on ice for later centrifugation. Additional blood samples, expiratory breath samples (2 min), and ratings of perceived exertion were collected at 10-min intervals throughout the exercise period. We kept the catheter patent by flushing it with 2–3 mL isotonic saline (0.9%; Baxter, Norfolk, United Kingdom) after each blood sample collection. HR was recorded continuously by telemetry with the use of a Polar S625X HR monitor, and averages were taken of the final 5 min of each 10-min interval.

Study B

All participants reported to the Human Performance Laboratory between 0700 and 0900 after a 10-h overnight fast and having avoided strenuous exercise, alcohol, and caffeinated beverages for the preceding 24 h. On their arrival, standard measures of height and weight (Seca Alpha) were taken. A flexible 20-gauge Teflon catheter (Venflon; Becton Dickinson) was then inserted into an antecubital vein. A 3-way stopcock (PVB Medizintechnik) was attached to the catheter to allow repeated blood sampling during the test period. A resting blood sample (5 mL) was taken, immediately after which the participants ingested a 25% glucose beverage consisting of 75 g glucose made up with water to a volume of 300 mL (Meritose-200; Amylum UK Ltd, London, United Kingdom). Further blood samples (5 mL) were collected at 15, 30, 45, 60, 90, and 120 min while the participants were seated. We kept the catheter patent by flushing it with 2–3 mL isotonic saline (0.9%; Baxter) after each blood sample collection and at 75 and 105 min. Of the 5-mL blood sample, 3 mL was collected into chilled EDTA-containing tubes (Becton Dickinson) and stored on ice; 2 mL was collected into serum tubes and left to clot at room temperature.

Blood variables

All tubes were centrifuged at $1700 \times g$ for 10 min at 4°C . Aliquots of plasma and serum were immediately frozen in liquid nitrogen and stored at -80°C for later analysis. Where appropriate, plasma glucose (Glucose HK; ABX Diagnostics, Chicksands, United Kingdom), free FAs [(FFA) NEFA-C; Wako Chemicals, Neuss, Germany], and glycerol (Raisio Diagnostics



UK Ltd, Worksop, United Kingdom) were analyzed on a CO-BAS MIRA semi-automatic analyzer (La Roche, Basel, Switzerland). Serum insulin was analyzed by using an enzyme-linked immunosorbent assay (DX EIA-2935 ELISA; IDS Ltd, Bolden, United Kingdom).

Calculations

Study A

From the rate of carbon dioxide production and $\dot{V}O_2$ (L/min), total carbohydrate and fat oxidation rates (g/min) were calculated by using the following stoichiometric equations of Jeukendrup and Wallis (13), working under the assumption that protein oxidation during exercise is negligible:

$$\text{Carbohydrate oxidation} = 4.210 \dot{V}CO_2 - 2.962 \dot{V}O_2 \quad (2)$$

and

$$\text{Fat oxidation} = 1.695 \dot{V}O_2 - 1.701 \dot{V}CO_2 \quad (3)$$

Study B

From plasma glucose and serum insulin concentrations during the 2-h OGTT, the whole-body insulin sensitivity index (ISI) was calculated by using the following equation of Matsuda and DeFronzo (14):

$$ISI = 1000/$$

$$\sqrt{\frac{(FPG \times FPI) \times (\text{mean OGTT insulin concentration})}{\text{mean OGTT glucose concentration}}} \quad (4)$$

where FPG is the fasting plasma glucose concentration, FPI is the fasting serum insulin concentration, and 10 000 represents a constant that allows numbers ranging between 1 and 12 to be obtained. The square root conversion is used to correct the nonlinear distribution of values.

Statistical analysis

Data analysis was performed by using SPSS for WINDOWS software (version 12.0.1; SPSS Inc, Chicago, IL). Data are expressed as means \pm SEs unless otherwise stated. Blood variables over the course of the experimental trials were compared by using a 2-factor (time \times trial) repeated-measures analysis of variance. Paired-sample *t* tests compared the contribution of substrate to total EE, the areas under the curve (AUCs) for glucose and insulin, and the ISI in the different trials. Significance was set at $P < 0.05$.

RESULTS

Study A

Workload and exercise intensities

The workload of 50% W_{max} ($133 \pm 7W$) used during the 30-min exercise trials elicited an average absolute $\dot{V}O_2$ of 2300 ± 99 and 2351 ± 94 mL/min for the placebo and GTE trials, respectively. Consequently, the average relative exercise intensity ($61 \pm 1\%$ and $62 \pm 1\%$ $\dot{V}O_{2max}$) and EE (11.35 ± 0.48 and 11.57 ± 0.45 kcal/min) between trials in the placebo and GTE trials, respectively, did not differ significantly. In addition, there were no significant differences in HR (134 ± 4 and 136 ± 4 bpm), rate of perceived exertion (12 ± 1 and 12 ± 1), or self-selected cadence (85 ± 2 and 87 ± 3 rpm) between trials in the placebo and GTE trials, respectively.

Carbohydrate and fat oxidation

The ingestion of GTE increased whole-body fat oxidation significantly more than did that of the placebo trial (0.41 ± 0.03 and 0.35 ± 0.03 g/min, respectively; $P < 0.01$ for main effect of trial; **Figure 1A**). The relative contribution of substrates to total EE can be seen in Figure 1B. Fat oxidation contributed 30% in the

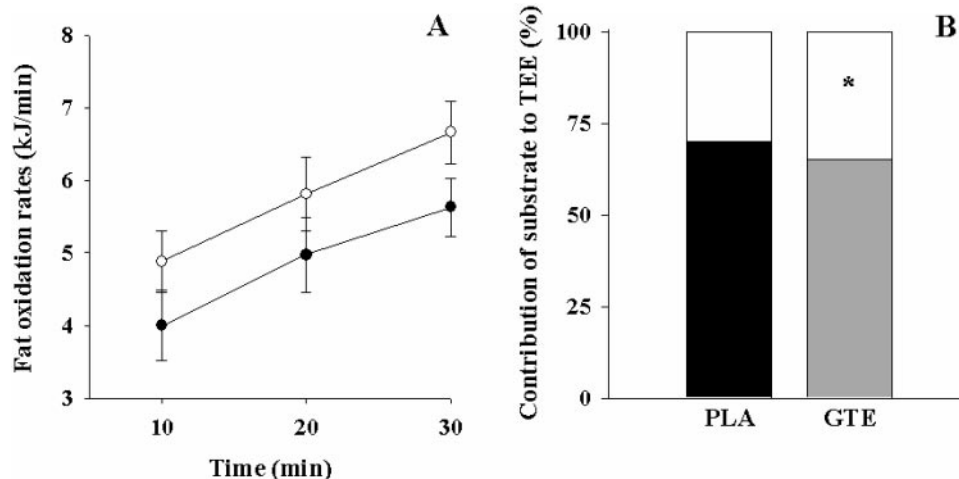


FIGURE 1. Mean (\pm SEM) fat oxidation measured every 10 min in the placebo (PLA) (●) and green tea extract (GTE) (○) trials (A) and contribution of substrate (□, fat; ■, carbohydrate) to total energy expenditure over the course of the 30-min period in the PLA and GTE exercise trials (B). $n = 12$. Differences between trials were determined by using repeated-measures ANOVA (A) and a paired-sample *t* test (B). * $P < 0.05$. Figure 1A indicates that there was a main effect of the trial; ie, the GTE trial had significantly ($P < 0.01$) higher fat oxidation rates than did the PLA trial.

placebo trial and 35% in the GTE trial, which represents a significant ($P < 0.05$) increase of 17%. Correspondingly, the contribution of carbohydrate was decreased by 17% after GTE ingestion ($P < 0.05$).

Plasma metabolites and insulin

The effects of time and supplementation with or without GTE on plasma glucose, insulin, FFAs, and glycerol can be seen in **Figure 2**. Plasma glucose concentration was unaffected by GTE, although there was a decrease with time in both trials (Figure 2A; $P < 0.05$). Plasma insulin concentrations displayed a similar pattern, being unaffected by GTE but decreasing over time (Figure 2B; $P < 0.05$). Plasma FFA concentrations after GTE ingestion were elevated, but the change was not significant ($P = 0.06$ for main effect of trial; Figure 2C). GTE ingestion elicited significantly higher plasma glycerol concentrations than did placebo ingestion ($P < 0.05$ for main effect of trial; Figure 2D).

Study B

There were no significant differences in fasting plasma glucose (5.04 ± 0.08 and 5.12 ± 0.08 mmol/L) or serum insulin (8.16 ± 1.53 and 7.93 ± 1.40 μ IU/mL) concentrations between

trials in the placebo and GTE trials, respectively. However there was a significant time effect on plasma glucose ($P < 0.01$; **Figure 3A**) and also time and trial effects on serum insulin ($P < 0.01$ for both), such that the GTE trial had lower serum insulin concentrations than the did placebo trial during the 2-h OGTT (Figure 3B).

The AUCs for plasma glucose (Figure 3C) did not differ between trials; however, the AUC for serum insulin was $15 \pm 4\%$ smaller during the GTE trial than during the placebo trial (3612 ± 301 and 4280 ± 309 μ IU/mL \cdot 120 min, respectively; $P < 0.01$; Figure 3D). When the ISI of Matsuda and DeFronzo was used, ISI was $13 \pm 4\%$ greater during the GTE trial than during the placebo trial (7.24 ± 0.61 and 6.52 ± 0.60 , respectively; $P < 0.05$; **Figure 4**).

DISCUSSION

The study reported here is the first to show that GTE can increase fat oxidation during moderate-intensity cycling exercise in healthy young men. It also observed that the acute ingestion of GTE significantly reduced the insulin AUC during a 2-h OGTT and improved insulin sensitivity. The study observed a 17%

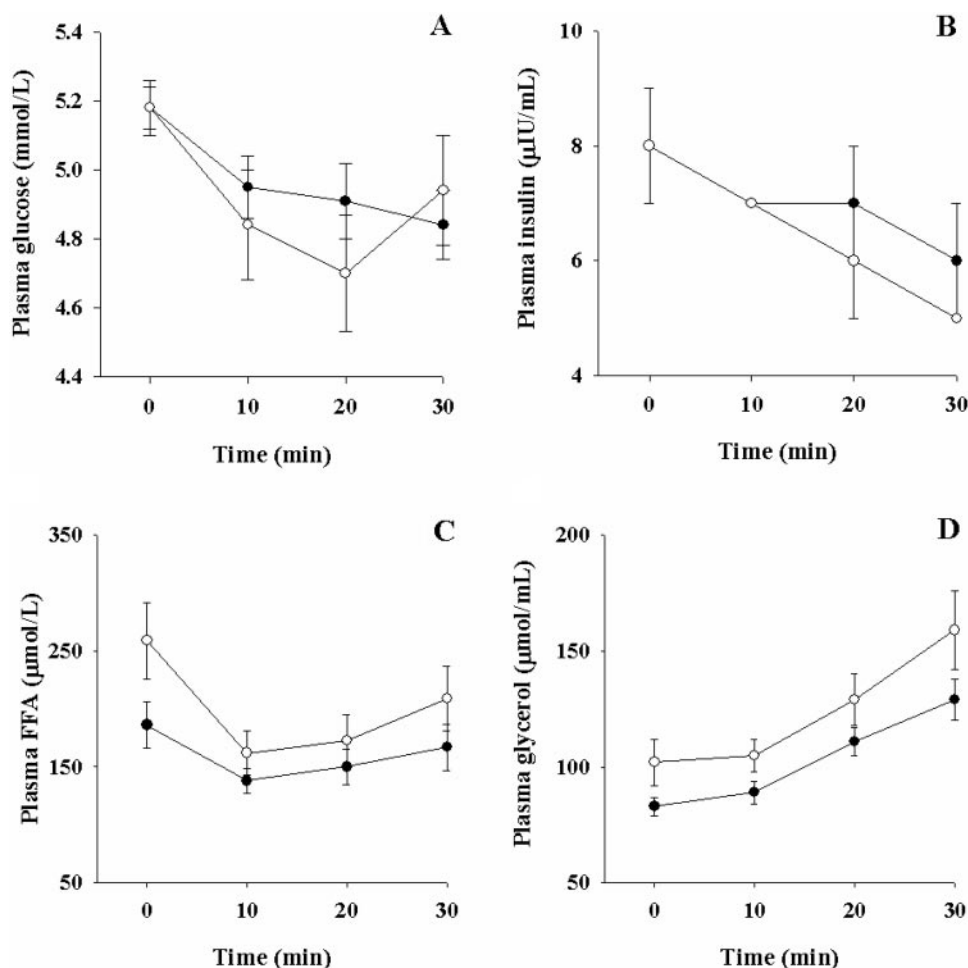


FIGURE 2. Mean (\pm SEM) plasma concentrations of glucose (A), insulin (B), free fatty acids (FFA) (C), and glycerol (D) over the course of the 30-min period in both the placebo (●) and green tea extract (○) exercise trials. $n = 12$. Differences between trials were determined by using repeated-measures ANOVA. Figure 2D indicates that there was a main effect of trial; ie, the plasma glycerol concentrations were significantly ($P < 0.05$) higher in the green tea extract trial than in the placebo trial.

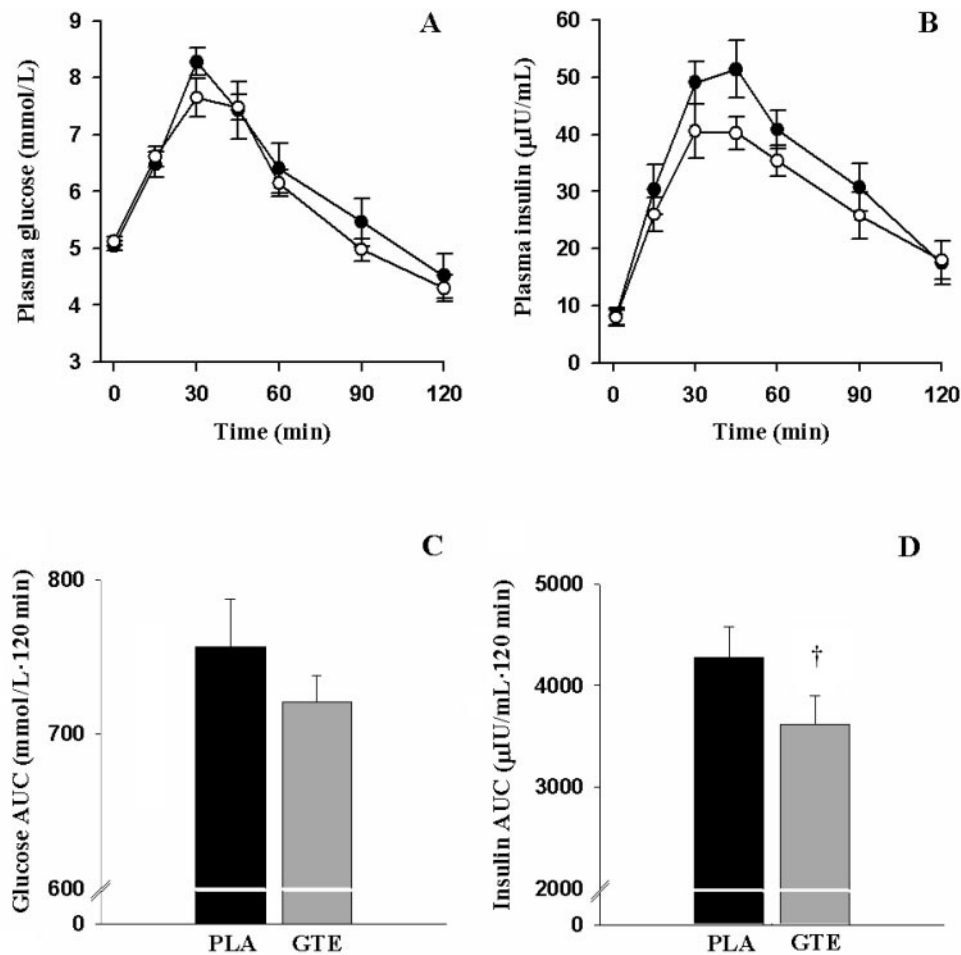


FIGURE 3. Mean (\pm SEM) plasma glucose (A) and insulin (B) concentrations in the placebo (PLA) (\circ) and green tea extract (GTE) (\circ) trials and the area under the curve (AUC) for glucose (C) and insulin (D) over the course of a 2-h oral-glucose-tolerance test in the 2 trials. $n = 11$. Differences between trials were determined by using repeated-measures ANOVA (A and B) and paired-sample t tests (C and D). $^{\dagger}P < 0.01$. Figure 3B indicates that there was a main effect of trial: ie, the serum insulin concentrations were significantly ($P < 0.01$) lower in the GTE trial than in the PLA trial.

greater fat contribution to total EE during moderate-intensity exercise when GTE was ingested than when placebo was ingested. This increase is in agreement with, yet not as great as, the 31% increase observed at rest by Dulloo et al (6). Several factors

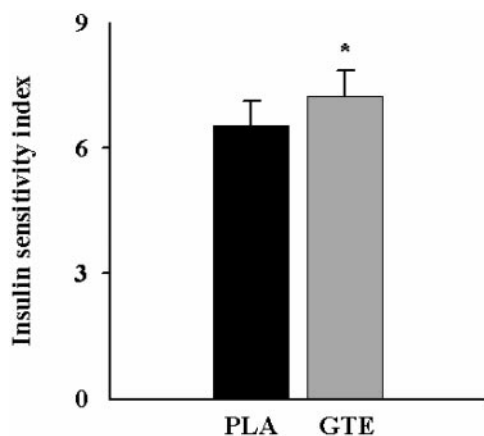


FIGURE 4. Mean (\pm SEM) insulin sensitivity index in the placebo (PLA) and green tea extract (GTE) trials. $n = 11$. Differences between trials were determined by using paired-sample t tests. $^*P < 0.05$.

may explain this difference; first, the GTE used in the study by Dulloo et al contained 150 mg caffeine, a quantity that they observed to be sufficient to increase EE and the fat contribution to total EE by 7%. Second, evidence suggests that, during exercise in the fasted state, caffeine can increase fat oxidation (15, 16). Third, the present study investigated the effect of GTE on fat oxidation during exercise, rather than during rest, and it is known that, during moderate-intensity exercise, both lipolysis and fat oxidation already show marked increases compared with the values during rest (8, 17–19). The present study therefore shows that, even under conditions of elevated lipolysis and fat oxidation seen during moderate-intensity exercise, GTE can increase fat metabolism.

It is believed that GTE exerts its effects on fat oxidation through the inhibition of catechol *O*-methyltransferase (5, 6), an enzyme that degrades noradrenaline. This reduction in noradrenaline degradation could potentially prolong adrenergic drive and increase lipolysis. The higher plasma glycerol concentrations seen during the GTE trial than during the placebo trial in the present study have shown, albeit indirectly, that GTE can increase lipolysis.

In addition to adrenergic drive, insulin is a well-known regulator (ie, inhibitor) of lipolysis (20), and it could be conceived



that, during the placebo trial, the corn flour may have elevated plasma glucose, which resulted in insulin release and which ultimately inhibited lipolysis. The difference between the 2 trials, therefore, is due to a lower rate of lipolysis in the placebo trial, rather than to a higher rate in the GTE trial. Thus, we rule out this potential mechanism, because the amount of corn flour ingested was minimal (1.5 g), and neither fasted glucose nor insulin concentrations differed significantly between trials.

Lipolysis during low-intensity exercise of this nature is not thought to limit fat oxidation (21), and it could be that GTE has additional effects on lipid metabolism. Chronic feeding of GTE to mice has been shown to elevate the mRNA content of important proteins involved in lipid transport and oxidation such as FA translocase/CD36 and medium-chain acyl-CoA dehydrogenase (1). In a similar study, GTE also reduced the content of malonyl CoA (2), and, thus, it could relieve the inhibition on and increase the activity of carnitine palmitoyl transferase². Whether this can occur with acute GTE feeding, either through a direct regulatory action of GTE or due to the transient increase in FA, remains to be seen. However, dietary manipulations that elevate plasma FA can up-regulate many genes encoding for proteins involved in fat metabolism (22). In addition, Watanabe et al (23) incubated 3T3-L1 adipocytes in a medium containing various concentrations of EGCG for 15 min and observed an inhibition in the enzyme acetyl CoA-carboxylase. EGCG could therefore alter the partitioning of lipid in such a way that lipid is directed away from storage and toward oxidation.

The present study also showed that GTE ingestion can increase insulin sensitivity by 13% and, therefore, can reduce the insulin response to a glucose load by 15%. Fructose-fed Sprague-Dawley rats exhibit insulin resistance and hypertension, pathologic conditions that resemble type 2 diabetes mellitus in humans. When these rats were supplemented with GTE in addition to fructose for 12 wk, they became more insulin sensitive. Fasting plasma glucose and insulin concentrations were reduced to control concentrations, and plasma insulin concentrations during the OGTT were significantly lower than those in the rats fed fructose only at all time-points. In parallel with this, increases in adipocyte insulin-receptor binding and membrane GLUT 4 protein content were observed (9, 24). EGCG can also mimic insulin by increasing the tyrosine phosphorylation of both the insulin receptor and insulin receptor substrate-1 (25)—the first stage of insulin-stimulated glucose uptake.

A further mechanism by which GTE could enhance glucose tolerance may be the partitioning of lipid toward oxidation rather than storage. The present study has shown an increase in fat oxidation during moderate-intensity exercise, which could reduce the build-up of FA metabolites within the muscle. Such metabolites are known to interfere with the insulin-signaling cascade via the activation of novel isoforms of protein kinase C (nPKC β and θ) (26, 27). A reduction in the build-up of such metabolites could therefore relieve the inhibition of the signaling cascade and increase insulin-stimulated glucose uptake within the skeletal muscle.

In conclusion, acute ingestion of green tea can increase fat oxidation during moderate-intensity exercise, possibly through an increase in lipolysis and therefore an increased availability of fat as a fuel. Green tea ingestion can also improve glycemic control after an oral glucose load and could have the potential to reduce the risk of type 2 diabetes mellitus.

The authors' responsibilities were as follows—MCV: study design, data collection and analysis, and writing of the manuscript; CJH: data collection and critical review of the manuscript; HRC: data collection; and AEJ: study design and critical review of the manuscript. None of the authors had a personal or financial conflict of interest.

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