An Oral Lipid Challenge and Acute Intake of Caffeinated Coffee Additively Decrease Glucose Tolerance in Healthy Men1–3
Marie-Soleil Beaudoin, Lindsay E. Robinson, and Terry E. Graham*

Department of Human Health and Nutritional Sciences, University of Guelph, Guelph, Ontario N1G 2W1, Canada

Abstract
Lipid-induced insulin resistance has been investigated primarily with i.v. infusions, and caffeine-induced insulin resistance, with alkaloid caffeine. The effects of orally consumed lipids and coffee have not been established and to our knowledge have never been simultaneously investigated. The goals of this study were to determine whether an oral lipid challenge and caffeinated coffee would disrupt glucose homeostasis and to characterize their respective incretin responses. It was hypothesized that oral ingestion of saturated lipids would impair glucose tolerance and that caffeinated coffee would further hinder glucose management. Ten young, healthy males participated in 5 trials in a randomized, cross-over design. At time 0 h, they underwent an oral fat tolerance test (OFTT: 1 g lipid/kg body weight) or consumed water, followed 5 h later by caffeinated (5 mg/kg) coffee, decaffeinated coffee, or water. At 6 h, volunteers underwent an oral glucose tolerance test (OGTT). Consumption of the OFTT increased glucose concentrations (P < 0.05) after a subsequent OGTT. At 7 h, caffeinated coffee produced the highest glucose concentrations (P < 0.05). Glucagon-like peptide-1 active (GLP-1α) and glucose-dependent insulinotropic polypeptide (GIP) were both increased for up to 6 h in all OFTT trials (P < 0.05). Compared to all other treatments, caffeinated and decaffeinated coffee produced higher GLP-1α response at 6.25 h (P < 0.05), whereas only caffeinated coffee increased GIP secretion (P < 0.05). These results show that oral consumption of lipids and caffeinated coffee can independently and additively decrease glucose tolerance. Incretin hormones could explain at least in part this impaired glucose homeostasis.


Introduction
Acute administration of alkaloid caffeine impairs glucose homeostasis in healthy (1–4) and obese (5,6) individuals as well as in diabetic patients (6–8). Consumption of caffeine before an oral glucose tolerance test (OGTT) has consistently been shown to reduce the insulin sensitivity index (ISI) by 20–30% (2,5,7,9) and to decrease the glucose infusion rate during a euglycemic-hyperinsulinemic clamp by a similar extent (3,6,9–12). Caffeine’s detrimental effects on glucose management are generally attributed to adenosine receptor antagonism (9,13,14) and epinephrine action on skeletal muscle (9,11,12).

Caffeine is often consumed in beverage form, notably as caffeinated coffee. The effects of caffeine cannot be readily generalized to coffee, as caffeine only represents 2% of coffee’s compounds (15). Acutely, caffeinated coffee induces a similar impairment, albeit of lesser magnitude, on glucose management (1,2,16,17). In marked contrast, regular and long-term coffee consumption is associated with a decreased risk for type 2 diabetes in a dose-dependent fashion (18–22).

I.v. infusion of lipids is associated with an elevation in plasma FFA and a reduction in insulin-stimulated glucose uptake by 20–50% in healthy volunteers (23–31), diabetics (32), offspring of diabetic patients (33), and in both sexes (24,28). This whole-body effect is predominantly attributed to an impairment in skeletal muscle metabolism (24,25,28,30,31) and to a lesser extent to lipids’ actions on the liver (24,28–30,34). The lipid-induced impairment of glucose management may be exacerbated by SFA, which have been suggested to be more deleterious than unsaturated fatty acids both in vitro (35–39) and in vivo (40–42).

I.v. lipid infusions would exclude possible responses in intestine-derived incretin hormones, which have been demonstrated to play an important role in whole-body glucose...
tolerance. Carbohydrates (43), lipids (44–46), and coffee (16) all potentiate the release of glucose-dependent insulinoctrop peptide (GIP) and glucagon-like peptide-1 (GLP-1). The metabolic impact of the incretins may include both pancreatic and extra-pancreatic actions [especially on skeletal muscle (47) and on gastric emptying (48)].

We hypothesized that consumption of an oral lipid load would impair glucose tolerance in a subsequent OGTT. We also postulated that caffeinated coffee would further disrupt glucose homeostasis during the postprandial lipid challenge. The incretin responses to this combination of dietary challenges were also characterized to establish if they might account for any alterations in carbohydrate homeostasis.

Materials and Methods

Participants. Eleven nonsmoking and recreationally active men were recruited from the University of Guelph community by poster and Web site advertisements. Prior to the study, volunteers were screened by a questionnaire for medical conditions and height and weight were recorded. All participants gave written informed consent to participate in the experimental procedures after the potential risks were explained to them. One participant withdrew from the study due to coffee intolerance. The study was approved by the University of Guelph Research Ethics Board.

Experimental design. Each participant came into the laboratory on 5 different occasions, separated by at least 7 d. Volunteers were instructed to withdraw from exercise, caffeine-containing products, and alcohol 48 h prior to each trial. In addition, they received a standardized meal to consume before 2000 h as their last meal before each trial (2008 kJ; 62 ± 1% of energy carbohydrate, 16 ± 1% of energy fat, 22 ± 1% of energy protein). On the day of the experiment, participants reported to the laboratory at 0800 h after a 12-h fast. Upon their arrival at the laboratory, a venous catheter was placed into an antecubital vein and was kept patent by a saline solution infusion. On the first trial day, body composition was determined by bioimpedance analysis (BodyStat 1500). Throughout the day, volunteers sat quietly (read, watched movies, used a computer, etc.).

At the beginning of the experiment (time 0 h), in 4 of the 5 trials (Supplemental Table 1), the participants were given enough oral fat beverage (described below) to provide 1 g of lipid/kg body weight or the equivalent weight of water (control OGTT). After 5 h, they received either caffeinated coffee (OFTT/CAF) providing 5 mg caffeine/kg body weight, the equivalent volume of decaffeinated coffee (OFTT/DECAF), or water (control COFTT, control OGTT, OFTT/-). One hour later, at 6 h, volunteers received 75 g of dextrose in solution (OFTT/CAF, OFTT/DECAF, OFTT/-, control OGTT) (OGTT: Trutol 75, NERL Diagnostics), except on one occasion when the 5-h water ingestion was then followed with water ingestion at 6 h (control OFTT) (Supplemental Table 1). In the one trial in which the fat beverage was not ingested, water was ingested at time 0 and 5 h, and at 6 h, 75 g of dextrose was consumed. Thus, in the control OFTT treatment, participants did not receive a coffee beverage or OGTT; in the control OGTT, they did not receive OFTT; and in the OFTT/- treatment, they received both the OFTT and OGTT but did not consume a coffee beverage. The treatments were designed to administer the OGTT 1 h after coffee consumption and after at least 3 h of elevated plasma FFA, because this timing has been shown sufficient to induce caffeine- (1,2,5–7) and lipid-mediated (23,26) insulin resistance. The order of treatment administration was randomized. Water was allowed ad libitum during the day.

To determine whether the consumption of the oral lipid load would disrupt glucose homeostasis, we compared the 6–8 h data from the control OGTT treatment to those of the OFTT/-, because these 2 treatments differed only in the ingestion of the lipid drink at time 0 h. We included the control OFTT treatment to allow baseline measurements (without OGTT) between 6 and 8 h. To examine whether caffeinated coffee would further disrupt glucose tolerance in a context of postpran-
Energy intake and macronutrient composition were assessed using The Food Processor SQL Nutritional Analysis Software (2002–2003 ESHA Research), and analyzed for day and treatment effects by 2-way repeated-measures ANOVA (SigmaStat Statistical Software, 2004).

**Statistical analysis.** All time-based data were analyzed for time and treatment effects by repeated-measure 2-way ANOVA (SigmaStat Statistical Software, 2004). When appropriate, a Tukey test was used for multiple comparison analysis. The AUC were calculated using the trapezoid method (Graph Pad Prism, 2004) over the 8-h experimental period. In addition, glucose, insulin, C-peptide, GLP-1a, and GIP AUC were also assessed during the 2-h OGTT, using data from time 6 h as baseline. The ISI was calculated based on Matsuda and DeFronzo’s formula (53). For this calculation, fasting whole-blood glucose and serum insulin concentrations were taken from time 0 h, and mean glucose and insulin represented the mean concentrations between 6–8 h. Differences between treatments for AUC and ISI were analyzed by repeated-measures 1-way ANOVA. All data are presented as mean ± SEM. Statistical differences were accepted at α = 0.05.

**Results**

**Lipids.** The participants’ baseline characteristics were within the normal range (Table 1). Consumption of the OFTT elevated plasma FFA between 5 and 7 h above the water control (P < 0.05; Fig. 1A). Similarly, all OFTT treatments, except for OFTT/DECAF, elevated FFA 8 h AUC (P < 0.05; Table 2). Concurrently, TG were increased in the OFTT/– and control OFTT treatments between 3 and 5 h compared to the water control (P < 0.05; Fig. 1B). In addition, all 4 treatments involving an OFTT increased the TG AUC above that of the control OGTT (P < 0.05; Table 2).

Circulating glucose, insulin, and C-peptide concentrations. Fasting whole-blood glucose concentrations were normal and comparable for each treatment (~4.4 mmol/L). In all 5 treatments, glucose remained at fasting levels during the first 6 h, reflecting that the test beverage did not contain carbohydrates (Supplemental Table 3). In all treatments except the control OFTT, glucose levels increased rapidly at 6 h, upon initiation of the OGTT, and were elevated (P < 0.05) compared to the control OFTT treatment between 6.5 and 8 h (Fig. 2A). At 7 h, blood glucose in the OFTT/CAF trial reached 10.7 ± 0.4 mmol/L, which was higher (P < 0.05) than OFTT/DECAF, OFTT/–, and control OGTT. In addition, OFTT/DECAF and OFTT/– both induced intermediate glucose levels that were higher (P < 0.05) than control OGTT (Fig. 2A). AUC analysis during the OGTT period (6–8 h) showed that all 4 treatments involving the OGTT increased blood glucose AUC above that of control OFTT. In addition, compared to the control OGTT treatment, glucose AUC was elevated in OFTT/– (32%; P = 0.097), OFTT/DECAF (46%; P < 0.05), and OFTT/CAF (65%; P < 0.05) (Table 3).

Plasma insulin responses mirrored the blood glucose responses (Fig. 2B) and remained at fasting level up to 6 h (Supplemental Table 4). Between 6.25 and 8 h, the consumption of the OGTT increased insulin levels beyond the OFTT control (P < 0.05). Moreover, the OFTT/CAF treatment resulted in elevated insulin concentrations (P < 0.05 vs. OGTT between 6.5 and 7.5 h; Fig. 2B). In addition, the OFTT/CAF insulin concentration was also elevated compared to OFTT/– at 7 h and OFTT/DECAF at 7.5 h (P < 0.05; Fig. 2B). Between 6 and 8 h, insulin AUC for the OGTT treatments were greater than that of the OFTT control (P < 0.05). In addition, OFTT/CAF produced higher insulin AUC than the OGTT control (56%; P < 0.05) (Table 3).

In agreement with the insulin and glucose data, serum C-peptide concentrations for all 5 treatments remained at baseline levels (~0.2 nmol/L) during the first 6 h of the experiment, with no differences between treatments (data not shown). C-peptide concentrations for OFTT control did not differ from fasting

---

**TABLE 1** Baseline characteristics of and fasting whole-blood measurements for 10 healthy men

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mean values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>22.9 ± 0.4</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.8 ± 0.03</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>78.9 ± 4.8</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.7 ± 0.8</td>
</tr>
<tr>
<td>Body fat, %</td>
<td>16.5 ± 1.4</td>
</tr>
<tr>
<td>TC, mmol/L</td>
<td>3.8 ± 0.2</td>
</tr>
<tr>
<td>HDL-C, mmol/L</td>
<td>1.2 ± 0.1</td>
</tr>
<tr>
<td>TG, mmol/L</td>
<td>1.1 ± 0.1</td>
</tr>
<tr>
<td>LDL-cholesterol, mmol/L</td>
<td>2.2 ± 0.2</td>
</tr>
<tr>
<td>TCHDL-C</td>
<td>3.4 ± 0.3</td>
</tr>
<tr>
<td>Exercise, activities/wk</td>
<td>3.2 ± 0.5</td>
</tr>
</tbody>
</table>

1 Values are presented as means ± SEM, n = 10.
2 TC, total cholesterol; HDL-C, HDL cholesterol.
3 Activities: one session of moderate aerobic or resistance exercise.

---
values at any point during the protocol. In contrast, compared to the OFTT control, C-peptide was elevated ($P < 0.05$) between 6.5 and 8 h for OFTT/CAF, between 7 and 8 h for OFTT/DECAF and control OGTT. C-peptide concentrations were also greater in OFTT/DECAF and OFTT/– compared to the OGTT control at 8 h ($P < 0.05$; data not shown). From 6 to 8 h, the C-peptide AUC data for OFTT/CAF, OFTT/DECAF, and OFTT/– were all greater than those of OFTT control ($P < 0.05$; Table 3).

The ISI for the OGTT period was 5.9, 6.2, 7.6, and 7.5 for OFTT/CAF, OFTT/DECAF, OFTT/–, and OGTT control, respectively. Although OFTT/CAF ISI was 22% lower than the value for the OGTT control, the treatments did not differ.

**Incretins: plasma GLP-1a and GIP.** Consumption of the lipid test beverage elevated ($P < 0.05$) plasma GLP-1a (2–6 h; Fig. 3A) and GIP (30 min–6 h; Fig. 4A) above the water control. At 6 h, consumption of 75 g of dextrose transiently ($P < 0.05$) increased GLP-1a above baseline levels at 6.25 h in the OGTT treatment, whereas in the OFTT/– treatment, the GLP-1a concentration did not differ between 6 and 6.25 h ($P = 0.83$). Consequently, there were no differences in GLP-1a concentrations between OFTT/– and the OGTT control at 6.25 h. In contrast, both OFTT/CAF and OFTT/DECAF treatments considerably increased ($P < 0.05$) GLP-1a, compared to the OFTT control (6.25–6.5 h), OFTT/– (6.25 h), and OGTT control (6.25–6.5 h) (Fig. 3B).

The consumption of the OGTT alone also increased GIP levels above baseline values ($P < 0.05$) and this increase was sustained throughout the last 2 h of the protocol. In contrast to GLP-1a responses, only the OFTT/CAF treatment elevated the GIP concentration compared to all other treatments at 6.25 h ($P < 0.05$). At 6.5 h, OFTT/CAF GIP levels were still higher than both OGTT and OFTT controls ($P < 0.05$) and tended to be higher than OFTT/DECAF ($P = 0.06$) (Fig. 4B).

The analysis of the whole protocol (0–8 h) compared to the 6- to 8-h period led to very different findings regarding the incretins. The AUC analysis for the entire experimental period (0–8 h) revealed that OFTT control, OFTT/CAF, OFTT/DECAF, and OFTT/– produced larger ($P < 0.05$) GLP-1a AUC than the OGTT control (Table 2). In contrast, the AUC analysis for the OGTT period (6–8 h) showed that the OGTT control treatment triggered the largest GLP-1a response, which was greater than that of OFTT/CAF ($P < 0.05$) and OFTT/DECAF ($P < 0.05$) and also elevated 9.5- and 11-fold compared to the OFTT control ($P = 0.12$) and OFTT/– ($P = 0.10$), respectively (Table 3). The GIP AUC computed between 0 and 8 h was elevated 4-fold in OFTT control, OFTT/CAF, OFTT/DECAF, and OFTT/– treatments compared to OGTT control ($P < 0.05$; Table 2). On the other hand, the GIP AUC analysis during the 2-h OGTT revealed that OFTT/CAF, OFTT/DECAF, and OGTT control produced higher responses than the OFTT control ($P < 0.05$; Table 3).

**Discussion**

This experiment was undertaken to examine whether an oral load of saturated lipids and/or ingestion of caffeinated coffee would disrupt glucose homeostasis in healthy men and to characterize the incretin responses to these stimuli. We hypothesized that the acute consumption of an oral load of lipids and caffeinated coffee would independently and additively impair glucose management during a subsequent OGTT. The main

---

**TABLE 2** AUC for circulating glucose, insulin, C-peptide, GLP-1a, and GIP in men during the 8-h protocol following OFTT control, OFTT/CAF, OFTT/DECAF, OFTT/–, and OGTT control treatments

<table>
<thead>
<tr>
<th></th>
<th>OFTT control</th>
<th>OFTT/CAF</th>
<th>OFTT/DECAF</th>
<th>OFTT/–</th>
<th>OGTT control</th>
</tr>
</thead>
<tbody>
<tr>
<td>FFA, mmol/L: 8 h</td>
<td>$1.7 \pm 0.3^a$</td>
<td>$1.7 \pm 0.2^a$</td>
<td>$1.2 \pm 0.3^b$</td>
<td>$1.7 \pm 0.2^a$</td>
<td>$0.7 \pm 0.2^a$</td>
</tr>
<tr>
<td>TG, mmol/L: 8 h</td>
<td>$3.7 \pm 0.2^b$</td>
<td>$2.7 \pm 0.2^b$</td>
<td>$1.6 \pm 0.6^b$</td>
<td>$2.6 \pm 0.6^b$</td>
<td>$–0.8 \pm 0.4^b$</td>
</tr>
<tr>
<td>Glucose, mmol/L: 8 h</td>
<td>$–1.6 \pm 0.7^a$</td>
<td>$8.4 \pm 0.5^b$</td>
<td>$5.7 \pm 1.0^b$</td>
<td>$6.2 \pm 1.1^b$</td>
<td>$4.4 \pm 0.7^b$</td>
</tr>
<tr>
<td>Insulin, pmol/L: 8 h</td>
<td>$32 \pm 2^a$</td>
<td>$721 \pm 11^b$</td>
<td>$547 \pm 8^b$</td>
<td>$509 \pm 10^b$</td>
<td>$426 \pm 8^b$</td>
</tr>
<tr>
<td>C-peptide, pmol/L: 8 h</td>
<td>$–0.6 \pm 0.2^a$</td>
<td>$1.5 \pm 0.4^b$</td>
<td>$1.3 \pm 0.3^b$</td>
<td>$1.2 \pm 0.4^b$</td>
<td>$1.1 \pm 0.3^b$</td>
</tr>
<tr>
<td>GLP-1a, pmol/L: 8 h</td>
<td>$70 \pm 12^b$</td>
<td>$77 \pm 12^b$</td>
<td>$88 \pm 22^b$</td>
<td>$76 \pm 14^b$</td>
<td>$8 \pm 5^b$</td>
</tr>
<tr>
<td>GIP, pmol/L: 8h</td>
<td>$181 \pm 24^b$</td>
<td>$202 \pm 16^b$</td>
<td>$181 \pm 21^b$</td>
<td>$204 \pm 27^b$</td>
<td>$37 \pm 6^b$</td>
</tr>
</tbody>
</table>

1 Values are means $\pm$ SEM, $n = 10$. Means in a row with superscripts without a common letter differ, $P < 0.05$. 

**FIGURE 2** Time course for whole-blood glucose (A) and plasma insulin (B) concentrations in men throughout the last 3 h of the protocol for OFTT control, OFTT/CAF, OFTT/DECAF, OFTT/–, and OGTT control. Data are means $\pm$ SEM, $n = 10$. Means at a time without a common letter differ, $P < 0.05$. 

Lipids, coffee, and carbohydrate homeostasis 577
findings were that ingestion of lipids and caffeinated coffee independently and additively increased the blood glucose concentration and that both GLP-1a and GIP responses were dampened during an OGTT if preceded by an oral lipid challenge.

**Consumption of oral lipids disrupts glucose homeostasis.** The present findings suggest that the consumption of an oral lipid load decreased glucose tolerance in healthy men. The lipid drink provided ~80 g of lipids, which increased plasma FFA to 0.72–0.84 mmol/L after 6 h, a level comparable to the concentrations reached with either lipid and heparin infusions (24,54) and similar to postprandial lipemia in diabetic patients (24). This lipid increase was sufficient to elicit exaggerated blood glucose responses during an OGTT in all OFTT treatments (OFTT/CAF, OFTT/DECAF, and OFTT/−) compared to the OGTT control (Table 3; Fig. 2B). These elevated glucose concentrations were present despite similar insulin responses among OFTT/CAF, OFTT/DECAF, and OGTT control treatments, suggesting that insulin action was disrupted following lipid ingestion (Fig. 2B).

Disrupted glucose management in the present study is also illustrated by the fact that the glucose AUC reported here are far greater than what was previously reported from our laboratory for comparable healthy volunteers. In fact, compared to the mean values we have reported for healthy men [159 mmol/L–120 min (1,2,9)], glucose AUC for OFTT/− and OGTT control were elevated 2.7- and 2.1-fold, respectively. In addition, in the present investigation, the ISI in both the OGTT control and OFTT/− trials were reduced by 31% compared to similar studies in healthy males (1,2,9). There is no reason to think that differences in participants’ fitness or adiposity can explain these glucose AUC discrepancies (Table 1). Rather, the increases in FFA and/or TG through prolonged fasting (OGTT control) or oral lipid consumption (OFTT/−) probably explain the higher glucose AUC and decreased ISI in the current investigation.

Notably, in the OGTT control treatment, dextrose was ingested 6 h after the start of the protocol, i.e. after at least 18 h of fasting, in order to match the treatments chronologically. However, this prolonged fasting resulted in increases in FFA (Fig. 1A) that likely negatively affected glucose tolerance. It is impressive that despite this apparent blunted glucose tolerance in the OGTT control treatment, there was still evidence that consumption of the OFTT further disrupted glucose homeostasis. Thus, the current protocol probably portrays a conservative image of the glucose intolerance induced by the oral lipid beverage.

**Consumption of caffeinated coffee impairs glucose management in healthy men.** It has been extensively reported that alkaloid caffeine (3,9–12,55,56) and caffeinated coffee (2,16,17) induce insulin resistance. This action is usually attributed to the antagonism of the adenosine A1 receptor, but elevated FFA have also been considered as a complementary mechanism. The present study is the first to our knowledge to characterize this effect in the context of postprandial lipid challenge. The consumption of caffeinated coffee 5 h after an oral load of lipid increased glucose and insulin levels beyond those of lipids only or lipids and decaffeinated coffee (Fig. 2A,B). The concurrent increases in insulin and glucose responses suggest that insulin action, and not insulin secretion, is impaired with the combined action of lipids and caffeinated coffee, a situation that is further supported by the C-peptide data. The glucose AUC for the OFTT/CAF treatment was elevated by 65% compared to the OGTT control, whereas OFTT/− and OFTT/DECAF only increased AUC by 32 and 46%, respectively. Taken together, these data support the interpretation that caffeinated coffee and lipids disrupt glucose tolerance in an additive manner. At the level of skeletal muscle, lipid-induced insulin resistance is thought to be mediated by the disruption of phosphoinositide

### Table 3

AUC for circulating glucose, insulin, C-peptide, GLP-1a, and GIP in men during the 2-h OGTT following OFTT control, OFTT/CAF, OFTT/DECAF, OFTT/−, and OGTT control treatments

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Glucose (mmol/L 120 min)</th>
<th>Insulin (pmol/L 120 min)</th>
<th>C-peptide (nmol/L 120 min)</th>
<th>GLP-1a (pmol/L 120 min)</th>
<th>GIP (pmol/L 120 min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OFTT control</td>
<td>−15 ± 8</td>
<td>543 ± 41</td>
<td>0 ± 1</td>
<td>51 ± 239</td>
<td>85 ± 396</td>
</tr>
<tr>
<td>OFTT/CAF</td>
<td>481 ± 34</td>
<td>433 ± 68</td>
<td>97 ± 28</td>
<td>−73 ± 148</td>
<td>1710 ± 448</td>
</tr>
<tr>
<td>OFTT/DECAF</td>
<td>348 ± 10</td>
<td>433 ± 68</td>
<td>92 ± 16</td>
<td>−87 ± 132</td>
<td>1750 ± 269</td>
</tr>
<tr>
<td>OFTT/−</td>
<td>433 ± 68</td>
<td>433 ± 68</td>
<td>92 ± 26</td>
<td>62 ± 197</td>
<td>1420 ± 371</td>
</tr>
<tr>
<td>OGTT control</td>
<td>433 ± 68</td>
<td>433 ± 68</td>
<td>92 ± 26</td>
<td>62 ± 197</td>
<td>2580 ± 297</td>
</tr>
</tbody>
</table>

1 Values are means ± SEM, n = 10. Means in a row with superscripts without a common letter differ, P < 0.05.
consumption in Western societies. Similarly, participants ingested ~80 g of lipids, which can be achieved with a single fast-food meal. Therefore, the metabolic challenges in the current study are relevant to the Western diet.

**Lipids, coffee, and caffeine mediate incretin release from the intestine.** The ingestion of the lipid drink was sufficient to induce the secretion of GLP-1a (3-fold) and GIP (6-fold) for up to 6 h. While GLP-1a has previously been shown to respond to lipids as well as carbohydrates (44), the current study expands these findings to GIP, showing that this hormone is also responsive to lipids. Moreover, to our knowledge, the present study is the first to document that consumption of oral lipids decreases incretin responses to a subsequent glucose challenge. As expected, the OGTT control produced large and rapid increases in both GLP-1a and GIP at 6.25 h upon consumption of dextrose. In contrast, after consumption of the lipid load, glucose did not induce incretin secretion (Figs. 3B, 4B, Table 3). In fact, between 6.25 and 8 h, GLP-1a and GIP concentrations in the OFTT/− treatment never differed from those of the OFTT or OGTT controls. The fact that 75 g of glucose failed to increase incretin secretion after a lipid challenge is a novel finding and is consistent with the knowledge that GLP-1 secretion is blunted in type 2 diabetic patients (59). The lack of incretin responses in the present study could partly mediate the blunted glucose tolerance described after lipid ingestion. Therefore, a high-fat diet and/or elevated circulating FFA, often characteristic of obesity and diabetic states, could lead to metabolic issues based on interference with the regulation incretin secretion and/or action.

In addition, the present findings suggest that coffee can independently modulate incretin responses. During the OGTT, the ingestion of both caffeinated and decaffeinated coffee increased the GLP-1a concentration above that of OFTT/−, a treatment that differed only by the consumption of water instead of coffee. Moreover, only caffeinated, but not decaffeinated coffee, elevated the GIP concentration at 6.25 and 6.5 h. These results are comparable with those of Johnson et al. (16), who showed that GIP, but not GLP-1a, was higher after ingestion of caffeinated compared to decaffeinated coffee (0.1 < P < 0.05).

Taken together, these findings suggest that caffeine itself may be a potent stimulus for GIP secretion, whereas GLP-1a could be responsive to other coffee compounds. Chlorogenic compounds (60,61) and quinides (62) are 2 classes of substances present in coffee that were associated with improved glucose tolerance. It is possible that action of these bioactive compounds in the gastrointestinal tract mediates GLP-1a release. Furthermore, the association among coffee, caffeine, and incretin secretion may explain at least in part the negative correlation between long-term coffee consumption and type 2 diabetes risks (18,19).

Admittedly, several other gastrointestinal factors may have responded to coffee and/or lipids in the present study. However, we are confident that this study examined 2 of the most bioactive gastrointestinal molecules, GLP-1a and GIP, and that they played an important role in the present results. In addition, our results are consistent with previous reports, suggesting that the insulin resistance described here is a direct effect of coffee and lipids and not secondary to the modulation of gastric emptying, intestinal transit time, or other gastrointestinal factors.

In conclusion, the present study documents that the ingestion of an oral lipid load and caffeinated coffee can, independently and additively, blunt glucose tolerance in healthy men. We not only confirmed that caffeine has a negative effect on glucose homeostasis, but also demonstrated for the first time to our knowledge that this impairment is still evident in a postprandial state.
lipid context. In addition, the modulation of incretins by lipids and coffee could explain at least in part their respective effects on glucose metabolism during the OGTT. That the combination of saturated lipids and caffeine is effective, 2 common items in Western diets, has such a profound effect on glucose tolerance and insulin action even in young, lean, active adults is highly relevant for the prevention and control of insulin resistance and type 2 diabetes.

Acknowledgments

We thank Premila Sathasivam and Mehrnoosh Kashani for excellent technical assistance. M-S.B., L.E.R., and T.E.G. designed the study; M-S.B. conducted research and analyzed data; M-S.B., L.E.R., and T.E.G. interpreted the results; and M-S.B. and T.E.G. wrote the paper. All authors read and approved the final manuscript.

Literature Cited

10. Greer F, Hudson R, Ross R, Graham TE. Caffeine ingestion decreases glucose disposal during a hyperinsulinemic-euglycemic clamp in seden-


