Caffeine Can Decrease Insulin Sensitivity in Humans

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OBJECTIVE — Caffeine is a central stimulant that increases the release of catecholamines. As a component of popular beverages, caffeine is widely used around the world. Its pharmacological effects are predominantly due to adenosine receptor antagonism and include release of catecholamines. We hypothesized that caffeine reduces insulin sensitivity, either due to catecholamines and/or as a result of blocking adenosine-mediated stimulation of peripheral glucose uptake.

RESEARCH DESIGN AND METHODS — Hyperinsulinemic-euglycemic glucose clamps were used to assess insulin sensitivity. Caffeine or placebo was administered intravenously to 12 healthy volunteers in a randomized, double-blind, crossover design. Measurements included plasma levels of insulin, catecholamines, free fatty acids (FFAs), and hemodynamic parameters. Insulin sensitivity was calculated as whole-body glucose uptake corrected for the insulin concentration. In a second study, the adenosine reuptake inhibitor dipyridamole was tested using an identical protocol in 10 healthy subjects.

RESULTS — Caffeine decreased insulin sensitivity by 15% ($P < 0.05$ vs. placebo). After caffeine administration, plasma FFAs increased ($P < 0.05$) and remained higher than during placebo. Plasma epinephrine increased fivefold ($P < 0.0005$), and smaller increases were recorded in plasma norepinephrine ($P < 0.02$) and blood pressure ($P < 0.001$). Dipyridamole did not alter insulin sensitivity and only increased plasma norepinephrine ($P < 0.01$).

CONCLUSIONS — Caffeine can decrease insulin sensitivity in healthy humans, possibly as a result of elevated plasma epinephrine levels. Because dipyridamole did not affect glucose uptake, peripheral adenosine receptor antagonism does not appear to contribute to this effect.

Caffeine is one of the most widely consumed "drugs" in the world. The average daily intake per capita in the western world is ~300 mg (1), and most of it comes from dietary sources such as coffee, tea, cola drinks, and chocolate. Caffeine is a methylxanthine derivative and a potent adenosine receptor antagonist that exerts its effects both centrally and peripherally because it crosses the blood-brain barrier. Systemic effects of caffeine include an increase in blood pressure and stimulation of the release of cat-echolamines, particularly epinephrine (2). Local effects of caffeine stem from interaction with interstitial adenosine (3).

Data from animal studies have indicated that methylxanthines are involved in insulin-mediated glucose handling and insulin responsiveness in adipose and muscular tissue. In obese Zucker rats, the caffeine-related adenosine receptor antagonist 1,3 dipropyl-8-(acrylic) phenylxanthine was found to inhibit glucose uptake in adipose tissue, whereas the reverse was observed in skeletal muscle (4).

Both effects were attributed to adenosine receptor antagonism at the tissue site because the compound does not cross the blood-brain barrier. Studies showing that adenosine or adenosine agonists increase insulin sensitivity in adipose tissue (5) and cardiac muscle (6,7) and decrease insulin sensitivity in skeletal muscle (8) are consistent with these observations. Consequently, the ultimate effect of adenosine receptor antagonism on whole-body glucose uptake is the sum total of all effects combined and depends on the relative amount of muscle and fat tissue and the degree of insulin sensitivity. Tissue-specific effects may explain why adenosine receptor blockade causes an increase in whole-body glucose uptake, or insulin sensitivity, in obese animals and a decrease in lean animals (4).

Apart from peripheral adenosine receptor blockade, methylxanthines that penetrate the blood-brain barrier, such as caffeine, also enhance the release of catecholamines. Especially epinephrine exerts insulin-antagonistic activity, including inhibition of peripheral glucose uptake (9). Which of these effects prevail in response to systemic use of caffeine is unknown. In vivo studies have demonstrated that caffeine (10,11) and aminophylline (12) decrease glucose tolerance, so that a reduction in insulin sensitivity can be anticipated. However, direct evidence for negative effects of caffeine on insulin sensitivity in humans in vivo is still lacking. The purpose of this study was to test the hypothesis that systemic caffeine reduces insulin sensitivity in humans. We conducted a randomized, placebo-controlled, double-blind study using the euglycemic-hyperinsulinemic clamp technique. To ascertain whether the effect of caffeine was mediated by peripheral adenosine antagonism, we also evaluated the effect of dipyridamole. Dipyridamole, an adenosine reuptake inhibitor, acts opposite to caffeine but is unable to cross the blood-brain barrier. In an in vivo study of humans, we have previously shown that dipyridamole-induced effects are completely based on adenosine receptor stimulation (13).

RESEARCH DESIGN AND METHODS

The study group consisted of 21 nonsmoking, lean (mean BMI ± SD, 21.9 ± 2.7 kg/m²), normotensive, healthy volunteers. Eleven subjects (six women and five men, mean age 22.6 ± 2.0 years) participated in the caffeine study, nine subjects participated in the dipyridamole study (six women and three men, mean age 21.7 ± 3.1 years), and one male subject (28 years of age) participated in both studies. All participants were studied on two occasions, except for the subject volunteering in both studies, who was tested four times. The experiments were separated by at least 3 weeks and took place in random order. Female subjects were tested at 4- or 8-week intervals to ensure that the experiments were performed during corresponding periods of the menstrual cycle. The experimental protocols were approved by the hospital ethics committee, and written informed consent was obtained before participation.

Caffeine study

On the morning of each experiment, subjects arrived at the test location at 8:00 A.M. after an overnight fast and having abstained from caffeine-containing substances for 72 h to render them caffeine naive. Under local anesthesia (Xylocaine 2%), the left (nondominant) brachial artery was cannulated (Angiocath 20-gauge; Beckton Dickinson, Sandy, UT) for blood sampling and hemodynamic monitoring. The antecubital vein in the contralateral arm was cannulated for administration of glucose 20%, insulin (Actrapid; Novo Nordisk, Bagsvaerd, Denmark), and test substances (caffeine, dipyridamole, or placebo).

Arterial cannulation was followed by an equilibration period of 30 min, and then baseline variables were obtained at −20 min. Subsequently, a caffeine-loading dose (3 mg/kg) or a comparable volume of placebo solution (NaCl 0.9%) was administered intravenously over 15 min in a randomized, double-blind manner. This was followed by continuous infusion of $0.6 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ caffeine (or placebo) for the remainder of the study period, aiming at a stable caffeine concentration of 5–10 mg/l during caffeine experiments (2).

After the caffeine/placebo loading dose (at 0 min), a hyperinsulinemic (60 $\text{mU} \cdot \text{m}^{-2} \cdot \text{min}^{-1}$)-euglycemic glucose clamp procedure was initiated and continued for 120 min (14). To maintain plasma glucose at 5 mmol/l with coefficients of variation (CVs) <5%, arterial plasma glucose levels were measured in duplicate at 5-min intervals. At −20, 0, 90, and 120 min, forearm blood flow (FBF) measurements were performed, and arterial blood was sampled for determination of catecholamines, cortisol, free fatty acids (FFAs), insulin, and caffeine. FBF was recorded in both forearms by venous occlusion plethysmography using mercury-in-silastic strain gauges (Hokanson EC4; Hokanson, Washington, DC), as previously described (15).

Dipyridamole study

In the dipyridamole study, a loading dose of 0.05 mg/kg dipyridamole (or placebo) was intravenously administered over 4 min, followed by continuous infusion of $0.2 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$ (or placebo), to increase peripheral adenosine concentrations (16). Thereafter, the studies were concurrent with the caffeine studies.

Analytical methods

Plasma glucose was measured in duplicate by the glucose oxidation method (Beckman Glucose Analyzer II; Beckman, Fullerton, CA) in arterial blood samples and immediately centrifuged. Blood samples for catecholamine measurements were collected in prechilled tubes containing glutathione (0.2 mol/l) and EGTA (0.25 mol/l) and immediately stored on ice. Blood samples for measurements of cortisol, caffeine, insulin, and FFAs were collected in lithium-containing heparin tubes and stored on ice. Plasma caffeine concentration was analyzed with a reversed-phase high-performance liquid chromatography (HPLC) method (limit of detection 0.2 mg/l). Plasma catecholamine levels were measured by HPLC with fluorometric detection, as previously described (17). Plasma insulin was assessed by radioimmunoassay using 125I-labeled human insulin and anti-human insulin antiserum raised in guinea pig. Bound and free tracer were separated by sheep anti–guinea pig antiserum; human insulin (Novo Biolabs, Danbury, CT) was used for standards. The interassay CV for insulin measurements was 10.3% at a level of 20.7 mU/l. Plasma cortisol was measured using the TDx batch analyzer of Abbott Laboratories (Abbott Diagnostics, Hoofddorp, The Netherlands) (interassay CV 5 and 8% at cortisol concentrations of 0.22 and 1.06 μmol/l, respectively). Plasma FFA levels were determined with a commercially available ACS-ACOD method (Wako NEFA C test; Wako Chemicals, Neuss, Germany).

Statistical methods and calculations

For statistical analyses, the following tests were performed. The effect of caffeine and dipyridamole on glucose infusion rates (GIRs) and hormonal and cardiovascular responses were tested with analysis of variance. As a modification of a previously described method (18), whole-body insulin sensitivity was calculated as the GIR divided by the plasma insulin concentration during the final 30 min of the study and expressed in $\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ per mU/l. Area under the insulin sensitivity curve (AUC_{IS}) was calculated and compared using Student's *t* test. All statistical analyses were performed using the SPSS personal computer software package (Version 9.0). Data are presented as means ± SEM, unless otherwise specified, and $P < 0.05$ was considered statistically significant.

RESULTS

During the clamp, plasma insulin levels increased to 99 ± 5 mU/l during caffeine and to 98 ± 5 mU/l during placebo ($P = $ NS). Insulin levels in the dipyridamole study were 90 ± 4 and 97 ± 3 mU/l during dipyridamole and placebo infusions, respectively ($P = $ NS). Caffeine levels were undetectable before the start of either of the four study arms.

Effects of hyperinsulinemia alone

For this purpose, data of all placebo studies ($n = 21$) were pooled. Mean whole-body insulin sensitivity was 0.47 ± 0.03 $\mu\text{mol} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ per mU/l. Hyperinsulinemia alone induced modest increases in systolic blood pressure, heart rate, FBF, epinephrine, and norepinephrine and almost completely suppressed plasma FFA levels (Table 1). These data reflect systemic vasodilation and sympathetic activation, both of which have been previously described as a consequence of hyperinsulinemia (19).

Reponses to caffeine alone

Plasma caffeine concentrations increased to 8.6 ± 0.7 mg/l directly after the caffeine bolus infusion and remained at 6.5 ± 0.4 mg/l during the maintenance

Table 1—*Responses to hyperinsulinemia in 21 subjects*

	Baseline (−30 min)	During clamp (90 min)	End of study (120 min)
Epinephrine (nmol/l)	0.19 ± 0.03	0.22 ± 0.03	0.28 ± 0.04*
Norepinephrine (nmol/l)	0.81 ± 0.09	1.00 ± 0.07	1.01 ± 0.06*
Cortisol (μmol/l)	0.58 ± 0.06	0.41 ± 0.03	0.40 ± 0.03*
FFAs (mmol/l)	0.40 ± 0.04	0.04 ± 0.00	0.03 ± 0.00*
Systolic BP (mmHg)	126 ± 2	131 ± 2	131 ± 3*
Diastolic BP (mmHg)	66 ± 1	68 ± 1	68 ± 1
Heart rate (bpm)	61 ± 2	65 ± 2	66 ± 2*
FBF (ml·dl^{-1}·min^{-1})	2.30 ± 0.19	2.49 ± 0.24	2.70 ± 0.27*

Data are means ± SEM. *$P < 0.05$ for trend. BP, blood pressure.

infusion. Before initiation of the hyperinsulinemic clamp, caffeine significantly stimulated the release of epinephrine ($P < 0.0005$), norepinephrine ($P = 0.010$), and FFA ($P = 0.047$) when compared with placebo (Fig. 1). Caffeine increased systolic and diastolic blood pressure ($P < 0.001$ for both) and modestly increased FBF ($P = 0.013$) but did not affect heart rate (Table 2).

Responses to caffeine and insulin

Glucose and insulin levels and GIR during the clamps are depicted in Fig. 2. During the first hour, GIR was roughly the same in caffeine and placebo arms. Thereafter, the curves diverted significantly, with an upward drift in the placebo studies that was absent with caffeine ($P < 0.0005$). The calculated whole-body insulin sensitivity during caffeine administration was 0.39 ± 0.04 compared with 0.46 ± 0.04 μmol·kg^{-1}·min^{-1} per mU/l in the placebo arm ($P = 0.043$ for difference in AUC$_{IS}$), equaling a decrease in insulin sensitivity of ~15%.
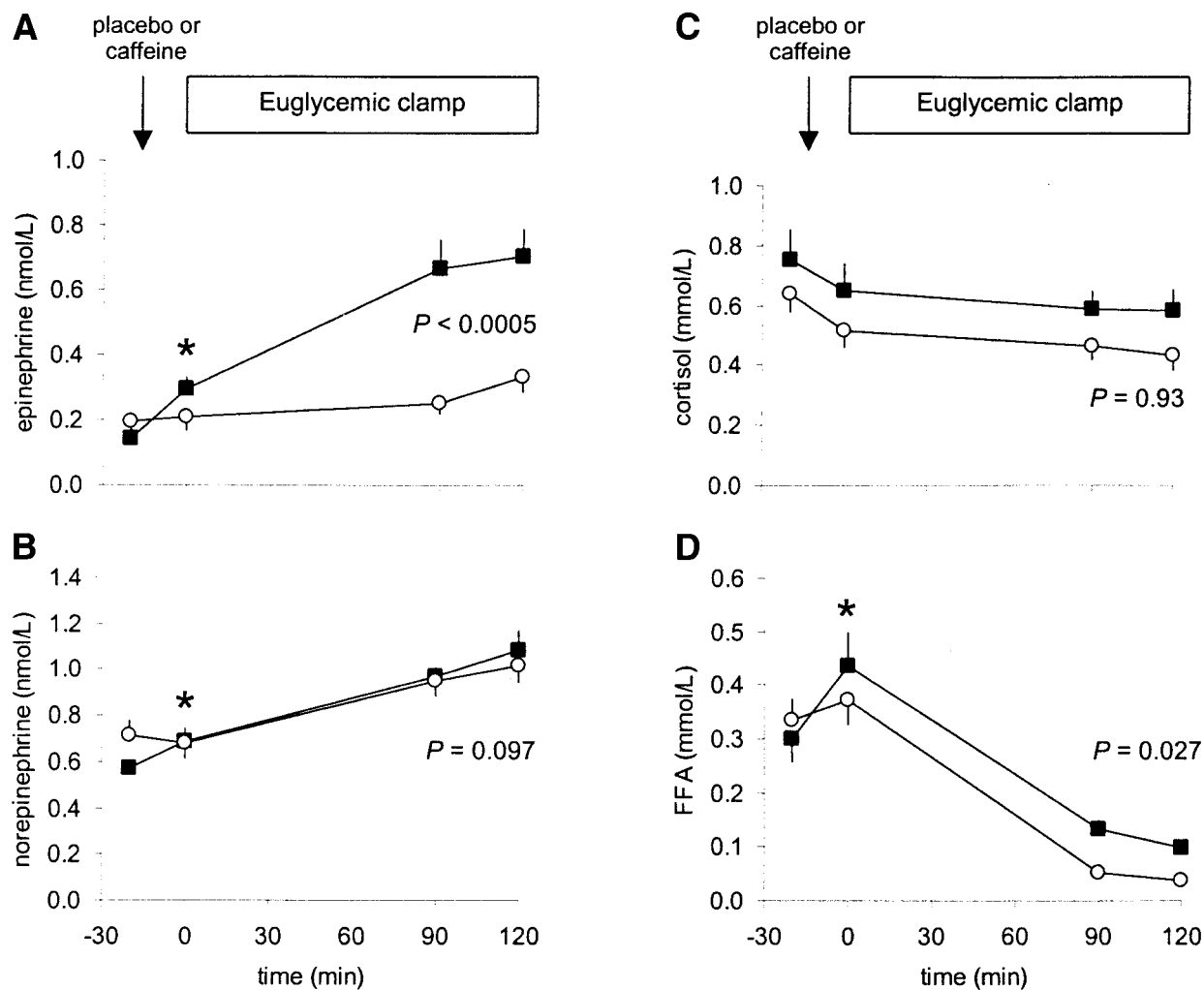
Plasma FFA levels decreased in both

Figure 1—*Responses of plasma epinephrine* (A), *norepinephrine* (B), *cortisol* (C), *and FFA* (D) *to caffeine* (■) *and placebo* (○). *Arrows denote start of caffeine or placebo infusions.* P *values are given for differences between caffeine and placebo studies.* *P < 0.05 *for change fom baseline between caffeine and placebo (reflecting effect of caffeine alone).*

Table 2—*Responses of metabolic and hemodynamic parameters*

	Baseline (−30 min)	After loading dose (0 min)	During clamp (90 min)	End of study (120 min)
Systolic BP (mmHg)				
Placebo	127 ± 2	128 ± 3	131 ± 3	133 ± 4*
Caffeine	122 ± 2	129 ± 2†	134 ± 2	134 ± 2*‡
Diastolic BP (mmHg)				
Placebo	68 ± 2	68 ± 2	69 ± 2	70 ± 2
Caffeine	64 ± 1	70 ± 1†	69 ± 1	69 ± 1*‡
Heart rate (bpm)				
Placebo	65 ± 3	65 ± 3	68 ± 3	69 ± 3*
Caffeine	59 ± 2	59 ± 2	64 ± 3	65 ± 3*
FBF ($ml \cdot dl^{-1} \cdot min^{-1}$)				
Placebo	2.25 ± 0.22	2.17 ± 0.20	2.75 ± 0.31	3.07 ± 0.38*
Caffeine	2.26 ± 0.40	2.60 ± 0.36	3.75 ± 0.85	4.64 ± 1.19*

Data are means ± SEM. *$P < 0.05$ for trend; †$P < 0.05$ vs. baseline; ‡$P < 0.05$ caffeine vs. placebo for trend. BP, blood pressure.

studies as a result of insulin but remained higher in the presence of caffeine ($P = 0.001$). Arterial plasma epinephrine levels increased significantly more with caffeine than placebo ($P = 0.001$) (Fig. 1). The increase in plasma norepinephrine levels and the decrease in plasma cortisol were not statistically different between caffeine and placebo. During the clamps, increases in systolic blood pressure, heart rate, and FBF did not differ significantly between caffeine and placebo, whereas diastolic blood pressure remained stable in either group (Table 2).

Responses to dipyridamole
Dipyridamole had no effect on insulin sensitivity compared with placebo ($0.49 ± 0.04$ vs. $0.50 ± 0.04$ $\mu mol \cdot kg^{-1} \cdot min^{-1}$ per mU/l, $P = NS$). Apart from a significant increase in plasma norepinephrine levels during the dipyridamole study that did not occur with placebo ($0.37 ± 0.05$ vs. $0.00 ± 0.13$ nmol/l, $P = 0.009$), all metabolic and hemodynamic responses were comparable during the dipyridamole and placebo studies.

CONCLUSIONS — The major finding of our study is that caffeine, in a dose that equals moderate consumption, decreased insulin sensitivity in healthy volunteers. Caffeine increased plasma catecholamines, plasma FFAs, and systolic and diastolic blood pressure. In contrast, dipyridamole had no effects on insulin sensitivity and only increased plasma norepinephrine levels. The decrease in insulin sensitivity we documented as result of caffeine ingestion is close to the magnitude of the increase in insulin sensitivity that can be achieved with glucose-lowering agents, such as metformin (20) and thiazolidinedione derivatives (21), and is therefore clinically relevant. Our finding may have serious health implications, especially when superimposed on already-disturbed glucose tolerance or established (type 2) diabetes.

The following factors probably contributed to the caffeine-induced fall in insulin sensitivity. Firstly, there was a fivefold increase in arterial plasma epinephrine levels compared with placebo. The effects of epinephrine on glucose metabolism are diametrical to insulin and include promotion of hepatic glucose production and inhibition of glucose uptake in muscle and fat. Using the euglycemic clamp technique, Deibert and DeFronzo (9) showed that epinephrine infusion reduced tissue sensitivity to insulin by ~50%. Effects of epinephrine were characterized by an inability of insulin to stimulate peripheral glucose disposal and to suppress hepatic glucose production. Because the epinephrine level attained in that study was fourfold higher than that in our study, the 15% fall in insulin sensitivity we observed may be comparable with data reported by Deibert and DeFronzo. The observation that caffeine does not affect either glucose or insulin levels in the absence of significant epinephrine release is consistent with this hypothesis (22). Secondly, caffeine stimulated FFA production, either as a consequence of epinephrine-mediated lipolysis or by inhibiting adenosine-induced suppression of lipolysis (23). Plasma FFA may decrease hepatic and peripheral glucose uptake and correlates negatively with insulin sensitivity (24). Also, in essential hypertension (25) and lipid disorders (26), insulin resistance has been, in part, attributed to elevated FFAs. Plasma norepinephrine was probably of minor relevance because it was only mildly elevated with caffeine, and the increase with dipyridamole was not associated with a change in insulin sensitivity. The fall in insulin sensitivity can also not be explained by reduced glucose delivery because we did not observe any vasoconstrictor effect of caffeine. On the contrary, caffeine increased both blood pressure and FBF—effects that can be largely attributed to caffeine-induced release of plasma catecholamines (27). The increase in FBF with caffeine is somewhat unexpected, as earlier studies reported no effects of caffeine on FBF (27,28). Mental stress experienced during the tests might explain this observation because caffeine is known to magnify vasodilator responses induced by mental stress (28,29).

Caffeine has two well-described molecular mechanisms of action; it is both an adenosine receptor antagonist and a phosphodiesterase inhibitor (30). In the periphery, interstitial adenosine may be involved in insulin-mediated glucose metabolism, although controversy exists as to whether adenosine exerts opposing effects in adipose tissue and skeletal muscle. Some studies have reported adenosine to increase insulin-mediated glucose metabolism in adipose tissue (5,31) and to decrease metabolism in skeletal muscle (32). Others have recorded decreased skeletal muscle glucose uptake with degradation or blocking of adenosine (33,34), indicating uniform effects of adenosine on (insulin-mediated) glucose metabolism in fat and muscle. In obese Zucker rats, blocking peripheral interstitial adenosine by systemic administration of a methylxanthine not entering the brain increased whole-body (insulin-mediated) glucose uptake, thus improving glucose tolerance (4). In contrast, a decrease in glucose uptake was observed in lean animals. To ascertain whether peripheral adenosine receptor antagonism was involved in caffeine effects on glucose disposal, the effect of increasing interstitial adenosine by dipyridamole was studied. Dipyridamole opposes caffeine only
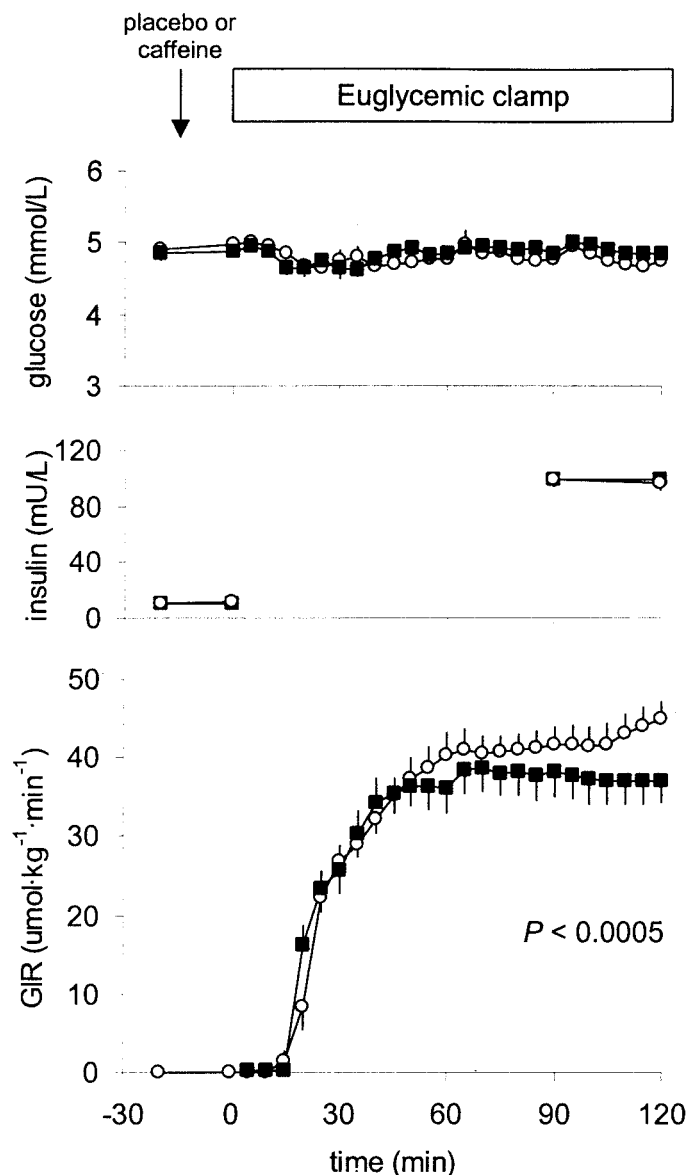
placebo or
caffeine

Euglycemic clamp

Figure 2—*Glucose and insulin levels and GIRs during clamp. The arrow denotes the start of caffeine or placebo infusions. ■, caffeine; ○, placebo.*

sor effects that are associated with acute ingestion (37), perhaps due to upregulation of adenosine receptors (38). The development of tolerance has been used to explain that large population-based studies have not identified a relation between coffee consumption and cardiovascular disease (39). When emergence of tolerance applies to the effect of caffeine on insulin sensitivity, decreases in insulin sensitivity may be expected to recover with chronic caffeine use. However, because emergence of tolerance is correlated to individual elimination half-lives of caffeine (40), tolerance may not develop in subjects with short caffeine half-lives. Also, not all caffeine effects appear to be subject to emergence of tolerance (41). Until these issues are resolved, considerations about environmental factors contributing to insulin resistance might include caffeine.

In conclusion, we demonstrate that acute administration of a moderate amount of caffeine decreases insulin sensitivity in healthy subjects. This effect may be explained by increased plasma epinephrine and FFA levels. Peripheral adenosine receptor antagonism is less likely to have played a role. Further investigation is required to elucidate whether this effect persists over time with chronic use of caffeine. Because tolerance may develop for the effects of caffeine, it is currently premature to advise against caffeine use in the management of insulin resistance.

in the periphery, as it does not penetrate the blood-brain barrier. Because dipyridamole had no effect on insulin sensitivity, a significant contribution of interstitial adenosine on glucose uptake is unlikely, although it is possible that opposing effects of adenosine antagonism on muscular and adipose tissue glucose uptake outweighed each other. These data are in accordance with those of Natali et al. (35), who found no effect of intrabrachial adenosine on local glucose uptake despite increased blood flow. Thus, in addition to tissue-specificity, adenosine effects may also be species-specific (36). Similarly,

the lack of effect of dipyridamole on insulin sensitivity almost excludes phosphodiesterase inhibition as a mechanism underlying the effect of caffeine because dipyridamole also inhibits phosphodiesterase activity. Indeed, plasma levels of caffeine achieved in this study are at least 10 times too low for phosphodiesterase to become significantly inhibited (30).

An important question is whether the present observations can be extrapolated to chronic use of caffeinated beverages. Chronic use of caffeine (and related methylxanthine derivatives) is known to result in attenuation of both humoral and pres-

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