The Reduction in Postprandial Lipemia After Exercise Is Independent of the Relative Contributions of Fat and Carbohydrate to Energy Metabolism During Exercise

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A single session of exercise several hours before a high-fat meal reduces postprandial lipemia. The purpose of the present study was to test the hypothesis that this effect is independent of substrate metabolism during exercise. Twelve men aged 21 to 36 years underwent three oral fat tolerance tests with intervals of at least 1 week. On one occasion, only activities of daily living were allowed the preceding day (control). On the other two occasions, subjects ran on a treadmill for 90 minutes on the afternoon preceding the fat tolerance test; 90 minutes before running, they ingested either acipimox, an inhibitor of lipolysis in adipose tissue, or placebo. Acipimox abolished the increase in the nonesterified fatty acid (NEFA) concentration observed during the run after placebo and reduced lipid oxidation (placebo, 37 ± 7 g; acipimox, 21 ± 3 g; $P < .05$, mean ± SEM), but had no effect on gross energy expenditure (placebo, 4.86 ± 0.20 MJ; acipimox, 4.83 ± 0.18 MJ). Before each of the three fat tolerance tests, subjects reported to the laboratory after an overnight fast. Blood samples were obtained in the fasted state and for 6 hours after consumption of a high-fat meal (per kilogram of body mass: 1.2 g fat, 1.2 g carbohydrate, and 61 kJ energy). Plasma concentrations of NEFA were higher postprandially with acipimox, compared with control and placebo ($P < .05$), as were glucose concentrations measured over the first 4 hours. The insulin response to the meal was lower in placebo compared with control and acipimox ($P < .05$). Despite these counterregulatory responses, postprandial lipemia was reduced to the same degree (compared with control, $P < .05$) by exercise preceded by acipimox and by exercise preceded by placebo (area under the plasma triacylglycerol concentration *v* time curve: control, 8.77 ± 1.17 mmol/L · 6 h; placebo, 6.95 ± 0.97 mmol/L · 6 h; acipimox, 6.81 ± 0.81 mmol/L · 6 h). These findings suggest that some factor other than the nature of the metabolic substrate used during exercise determines the attenuating effect of prior exercise on postprandial lipemia.

THE METABOLIC SYNDROME—also called the insulin resistance syndrome—is a constellation of risk factors for atherosclerotic disease. Five major abnormalities are commonly identified, ie, hypertension, insulin resistance, glucose intolerance, dyslipidemia (fasting hypertriglyceridemia and low high-density lipoprotein [HDL] cholesterol), and obesity.[1] Recently, impaired postprandial triacylglycerol (TAG) clearance has been added to this list.[2] When the clearance of TAG-rich lipoproteins is poor, their residence time in the circulation is increased, increasing the opportunity for the reciprocal transfer of TAG and cholesterol between TAG-rich lipoproteins and cholesterol-rich lipoproteins, ie, HDL and low-density lipoprotein (LDL). This not only impairs the passage of TAG-rich lipoproteins through the lipolytic cascade, but also leads to the formation of small dense HDL and LDL[3]—modifications that probably increase the atherogenic stimulus.

The magnitude of postprandial lipemia can be attenuated by prior exercise. For example, it is reported to be as much as 30% lower following a single prolonged session of exercise.[4] This probably reflects an enhanced TAG removal rate[5] mediated through a delayed increase in lipoprotein lipase (LPL) activity in the exercised muscle,[6] and may constitute a mechanism for replenishing intramuscular TAG reduced by the exercise.[7] However, exercise sessions of comparable energy expenditure but contrasting duration and intensity—and therefore relying to differing degrees on intramuscular and blood-borne substrates[8]—have been reported to cause similar reductions in postprandial lipemia.[9] One interpretation of this finding is that the energy expended in exercise, or some proxy for this, is the most important determinant of its effect on postprandial disposal of TAG.

Exercise is increasingly emphasized as part of a preventive strategy against the metabolic syndrome,[10] and study of the factors that determine its effects on disturbances in lipoprotein metabolism during the postprandial period may help to define effective patterns of physical activity. Therefore, the purpose of the present study was to test the hypothesis that the reduction in postprandial lipemia by prior exercise is independent of substrate metabolism during the exercise session. Acipimox, a nicotinic acid analog that is a powerful inhibitor of lipolysis in adipose tissue,[11] was used to reduce fat oxidation during exercise. When plasma concentrations of nonesterified fatty acid (NEFA) are low, exercising muscle relies more heavily on glycogen[12] and, during moderate exercise, speculatively also on intramuscular TAG.[13,14]

SUBJECTS AND METHODS

Subjects

Twelve healthy men aged 21 to 36 years, with a body mass index of 24.0 ± 2.5 kg/m^2 (mean ± SD) and a maximal oxygen uptake (V_{O_2}max) of 58.6 ± 6.5 mL/kg/min volunteered to participate in the study, which had the approval of the University's Ethical Advisory Committee. They provided written informed consent after being informed of the risks involved. All subjects were normolipidemic, with plasma concentrations in the fasted state of 4.09 ± 0.79 mmol/L for total cholesterol, 1.13 ± 0.21 mmol/L for HDL cholesterol, and 0.92 ± 0.46 mmol/L for TAG. They were all nonsmokers without a clinical

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history of bleeding or coagulation disorders or physician-diagnosed cardiovascular or metabolic disease. None were taking pharmacotherapeutic medications known to affect lipid or carbohydrate metabolism. All were physically active: two trained regularly and 10 engaged in two or three sessions per week of moderate-intensity recreational activity.

Study Design

Each subject underwent three oral fat tolerance tests in a fully balanced design with intervals of 1 week. On two occasions, subjects ran on a treadmill for 90 minutes during the afternoon of the preceding day. On the third occasion, no exercise was performed (control). Before each run, subjects ingested (in a blind fashion) a capsule containing either acipimox (Olbetam; Farmitalia Carlo Erba, Milton Keynes, UK) or 15 mg fructose as a placebo. The acipimox dose (1.7 mg/kg body mass) and timing of administration were selected on the basis of its pharmacokinetics (at doses ≥80 mg, plasma NEFA concentrations were suppressed for ≥4 hours[11]) and pilot studies.

Other than the treadmill runs, subjects did not exercise during the 3 days preceding each fat tolerance test. (Only activities of daily living and slow walking or cycling for personal transport over short distances were permitted.) Subjects weighed and recorded all food and drink consumed during the 2 days before each test, replicating this prior to subsequent tests. Subjects refrained from drinking alcohol for 24 hours before each test.

Preliminary Exercise Tests

Two preliminary exercise tests were conducted to find the speed to elicit 60% of $\dot{V}O_2$max for each individual. In the first, $\dot{V}O_2$max was determined during uphill running at a constant speed (range, 3.2 to 4.5 m/s). In the second, the steady-state relationship between submaximal $\dot{V}O_2$ and treadmill speed was established.

Treadmill Runs

Subjects ate a light lunch at noon, standardized between trials. This contained 103 ± 52 g carbohydrate, 16 ± 8 g fat, 31 ± 13 g protein, and 2.49 ± 0.87 MJ energy. After lunch, subjects either left the laboratory (control) or rested until the start of the run; prior to each run, 45 minutes after lunch, a cannula was inserted into a forearm or antecubital vein. After an interval of 10 minutes, a baseline blood sample was obtained before ingestion of the capsule containing either acipimox (mean, 131 mg; range, 104 to 156) or placebo. Subjects began running 1.5 hours later, ie, 2.5 hours after lunch, at 60% of $\dot{V}O_2$max.

Further venous blood samples were obtained immediately before the run, every 30 minutes during the run, and 15 minutes and 30 minutes after the run. On each occasion, 10 mL was collected into EDTA tubes and 5 mL into heparinized tubes to which 75 μL EGTA was added as a preservative. The cannula was kept patent by flushing with nonheparinized saline (9 g/L). Expired-air samples were collected every 15 minutes using Douglas bag techniques. These were analyzed for oxygen using a paramagnetic analyzer (model 570A; Taylor-Servomex, Crowborough, UK) and for carbon dioxide using an infrared analyzer (Lira MSA model 303; Mines Safety Appliances Britain, Coatbridge, Scotland). Gas volumes were measured using a dry gas meter (Harvard Apparatus, Edenbridge, Kent, UK), and oxygen uptake and carbon dioxide production were calculated using the Haldane transformation. The heart rate was monitored using short-range telemetry (SPORT-TESTER; Polar Electro, Tampere, Finland) and ratings of perceived exertion using the Borg scale.[15] Water was provided ad libitum, and the volume consumed was recorded. Approximately 3 hours after each run (and at the corresponding time on the control trial), subjects ate an evening meal. The food items consumed in this meal were recorded on the first occasion and replicated on subsequent occasions.

Fat Tolerance Tests

Subjects reported to the laboratory at 8 AM after a 12-hour fast. After a cannula was placed in a forearm or antecubital vein, they rested for 10 minutes before baseline blood samples were obtained (9 mL into EDTA tubes and 4 mL into plain tubes). The test meal was prepared by the researchers and consisted of cereal, coconut, nuts, chocolate, fruit, and whipping cream (per kilogram of body mass: 1.2 g fat, 1.2 g carbohydrate, and 61 kJ energy). Subjects ingested the meal (92 ± 14 g fat, 92 ± 14 g carbohydrate, 15 ± 2 g protein, and 4.64 ± 0.72 MJ energy) within 15 minutes. The cannula was kept patent by flushing with nonheparinized saline, and further blood samples were obtained 0.5, 1, 2, 3, 4, 5, and 6 hours after the meal. Subjects rested or worked quietly throughout and consumed only water, the volume of which was recorded during the first test and replicated during subsequent tests. Blood samples were obtained after the subject rested in a supine position for at least 10 minutes.

Analytical Methods

The hemoglobin concentration and hematocrit were measured for estimation of changes in plasma volume.[16] Before each run and at 30-minute intervals during the run, duplicate 20-μL aliquots of blood were deproteinized in 2.5% perchloric acid for analysis of lactate. Blood samples in plain tubes were allowed to clot for 1 hour at room temperature before the serum was separated. Serum was analyzed for insulin by radioimmunassay (COAT-A-COUNT; Diagnostic Products, Los Angeles, CA). Blood samples containing anticoagulant were separated at 4°C, and the plasma was divided into aliquots. All samples were stored at −20°C until analysis. Plasma concentrations of total cholesterol, HDL cholesterol, TAG, glucose (all Boehringer Mannheim, Lewes, UK) and NEFA (Wako, Neuss, Germany) were determined with enzymatic colorimetric methods using a centrifugal analyzer (Cobas-Bio; Roche, Basel, Switzerland). Catecholamines were determined in EGTA plasma by high-performance liquid chromatography with electrochemical detection.[17] Samples from one subject were always analyzed in the same batch. Within-batch coefficients of variation were as follows: total cholesterol 1.9%, HDL cholesterol 3.1%, TAG 1.2%, glucose 1.2%, NEFA 1.3%, insulin 4.2%, epinephrine 6.0%, and norepinephrine 4.0%. The accuracy of lipid analyses was maintained using quality-control sera (Boehringer Mannheim and Roche).

Analysis of Weighed Food Intake Records

A computerized version (COMP-EAT; Nutrition Systems, London, UK) of food composition tables[18] was used to analyze the weighed food intake records to provide data describing the intake of energy and major nutrients.

Calculations and Statistics

Rates of whole-body lipid and carbohydrate oxidation and energy expenditure during running were calculated using indirect calorimetry. Postprandial lipemia and insulinemia were quantified using the respective concentration versus time curves: the total response was the whole area under a curve over 6 hours, and the incremental response was the area above the fasting level. Responses during running were compared using paired t tests. Data describing postprandial lipemia (our main outcome measure) were not normally distributed, so all comparisons of responses to the test meal were made using Friedman's ANOVA by rank, with the Wilcoxon signed-rank test post hoc. A 5% level of confidence was used throughout, and data are presented as the mean ± SEM unless otherwise stated.

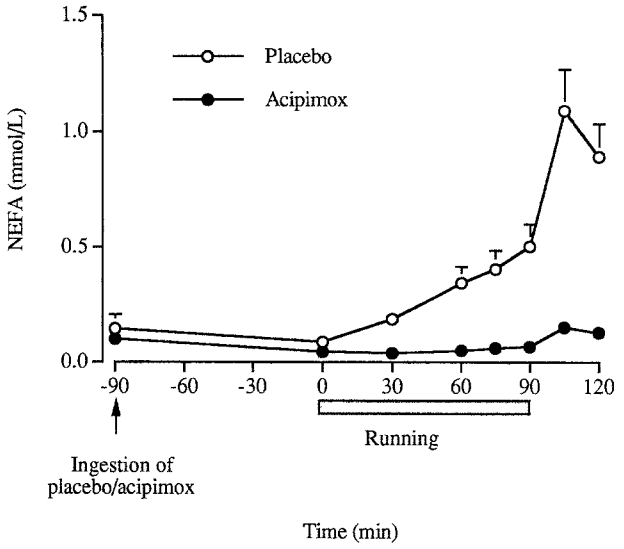

Fig 1. Plasma NEFA concentration before ingestion of acipimox or placebo (−90 minutes), immediately before (0 minutes), during (0-90 minutes), and after a 90-minute treadmill run at 60% $\dot{V}O_2$max. Values are the mean ± SEM for 12 men. Concentrations were significantly different between trials before, during, and after exercise ($P < .05$).

RESULTS

Effect of Acipimox on Responses During Running

The main side effect of acipimox, facial flushing, was observed transiently in one subject, but this disappeared quickly and his skin color was normal during the run. Plasma volume was similar before each run (difference, 1.0% ± 0.5%), and changes during running were small (placebo, 2.6% ± 0.4%; acipimox, 3.1% ± 0.3%). Plasma concentrations therefore were not adjusted.

Plasma NEFA concentrations did not differ significantly before ingestion of acipimox or placebo (placebo, 0.15 ± 0.06 mmol/L; acipimox, 0.10 ± 0.02 mmol/L), but acipimox reduced NEFA levels before, during, and after exercise (Fig 1). Changes in plasma glucose and lactate concentrations during running were small and not significantly affected by acipimox (Table 1), although the glucose concentration was lower at the end of the run preceded by acipimox ingestion ($P = .06$).

Subjects ran at a mean of 60% ± 1% $\dot{V}O_2$max after placebo and 59% ± 1% $\dot{V}O_2$max after acipimox (NS). Acipimox did not influence the ratings of perceived exertion (placebo, 12.0 ± 0.5; acipimox, 12.0 ± 0.4). Figure 2 shows the estimates of gross energy expenditure and fat and carbohydrate oxidation during running. Ingestion of acipimox increased carbohydrate oxidation (placebo, 203 ± 13 g; acipimox, 235 ± 9 g; $P < .05$) with a complementary decrease in fat oxidation (placebo, 37 ± 7 g; acipimox, 21 ± 3 g; $P < 0.05$), but did not affect gross energy expenditure (placebo, 4.86 ± 0.20 MJ; acipimox, 4.83 ± 0.18 MJ). Consequently, the proportion of energy derived from fat during running was lower ($P < .05$) after acipimox (16% ± 2%) versus placebo (28% ± 4%) and the proportion from carbohydrate was correspondingly greater (placebo, 72% ± 4%; acipimox, 84% ± 2%; $P < .05$).

Plasma epinephrine and norepinephrine concentrations increased during exercise and then decreased rapidly (Table 2). The norepinephrine response did not differ between the two runs, but the concentration of epinephrine at 30 minutes postexercise was higher ($P < .05$) after acipimox.

Effect of Prior Running and of Prior Running After Ingestion of Acipimox on Responses to the Oral Fat Tolerance Test

During the 6-hour observation period, plasma volume changed by 0.1% ± 0.8%, −0.5% ± 0.7%, and 0.3% ± 0.7% (control, placebo, and acipimox, respectively). Relative to the control, plasma volume was 0.5% ± 0.7% higher in the placebo condition and 0.1% ± 0.8% lower in the acipimox condition. No adjustments were made to the measured concentrations of plasma or serum constituents.

Plasma TAG concentrations are shown in Fig 3. In the fasted state, there were no significant differences in TAG concentration between tests in the three different conditions. Compared with control, the total lipemic response was 18% ± 7% lower in placebo and 19% ± 5% lower in acipimox. The incremental lipemic response was lower than the control by 22% ± 12% in placebo and 28% ± 14% in acipimox. Neither index of lipemia

Table 1. $\dot{V}O_2$, Heart Rate, Respiratory Exchange Ratio, and Concentrations of Blood Lactate and Plasma Glucose During a 90-Minute Treadmill Run at 60% $\dot{V}O_2$max 90 Minutes After Ingestion of Either Placebo or Acipimox (mean ± SEM for 12 men)

	Pre-run, 0 min		30 min		60 min		75 min		90 min	
Parameter	Placebo	Acipimox	Placebo	Acipimox	Placebo	Acipimox	Placebo	Acipimox	Placebo	Acipimox
$\dot{V}O_2$ (mL/kg/min)	—	—	31.7 ± 1.2	31.4 ± 1.2	35.2 ± 1.0	34.3 ± 1.1	35.5 ± 1.2	34.6 ± 1.2	36.3 ± 1.2	35.6 ± 1.3
Heart rate (beats/min)	—	—	137 ± 4	139 ± 4	156 ± 5	156 ± 5	157 ± 5	158 ± 5	161 ± 5	162 ± 6
Respiratory exchange ratio*	—	—	0.84 ± 0.02	0 85 ± 0.01	0.92 ± 0.02	0.95 ± 0.01	0.90 ± 0.01	0.96 ± 0.01	0.90 ± 0.02	0.95 ± 0.01
Plasma glucose (mmol/L)	4.23 ± 0.16	3.99 ± 0.15	4.33 ± 0.18	4.49 ± 0.21	4.61 ± 0.16	4.50 ± 0.20	4.59 ± 0.20	4.36 ± 0.18	4.59 ± 0.16	4.29 ± 0.21
Blood lactate (mmol/L)	0.86 ± 0.13	0.78 ± 0.10	1.10 ± 0.18	1.09 ± 0.14	1.19 ± 0.18	1.01 ± 0.13	1.20 ± 0.20	1.25 ± 0.19	1.24 ± 0.25	1.29 ± 0.23

*n = 11, mean values significantly different between placebo and acipimox (placebo, 0.91 ± 0.01; acipimox, 0.94 ± 0.01; $P < .05$).

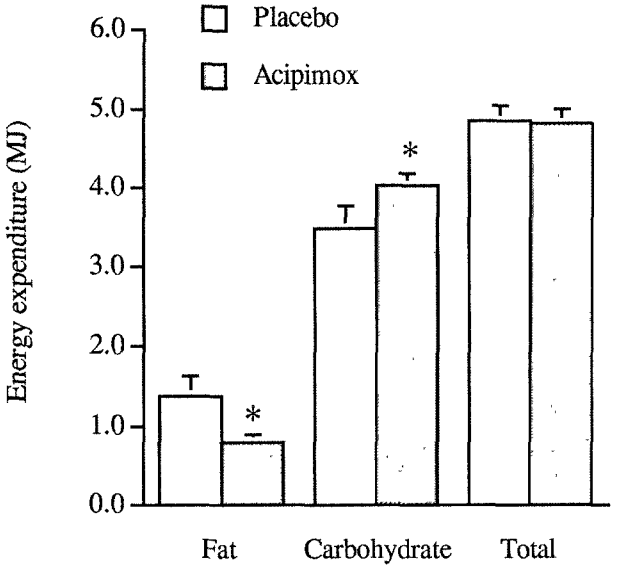

Fig 2. Gross energy expenditure during the 90-minute run at 60% $\dot{V}O_2$max. Values are the mean ± SEM for 11 men. *$P < .05$ *v* placebo.

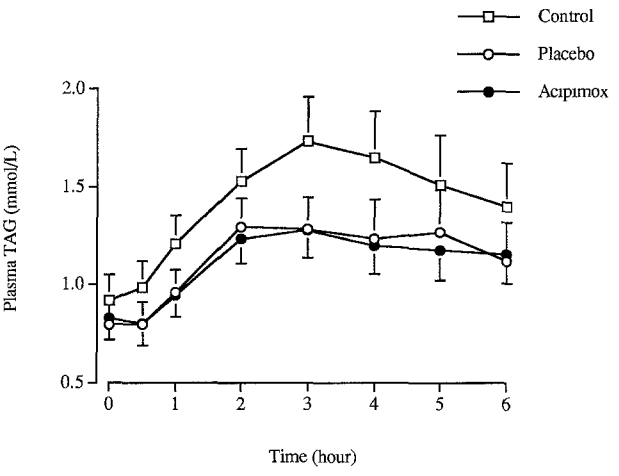

Fig 3. Plasma TAG concentration in the fasted state and for 6 hours after ingestion of a high-fat mixed meal in 3 conditions, control, placebo, and acipimox. Values are the mean ± SEM for 12 men.

differed significantly between placebo and acipimox conditions (Table 3).

The response of plasma glucose, plasma NEFA, and serum insulin is shown in Fig 4. There were no differences in the glucose concentration in the fasted state, but there were indications of differences postprandially. During the early part of the observation period, plasma glucose was higher in the acipimox condition ($P < .05$ *v* both control and placebo; values during the first 4 hours: control, 4.6 ± 0.1 mmol/L; placebo, 4.6 ± 0.1 mmol/L; acipimox, 4.9 ± 0.1 mmol/L).

In the fasted state, there were no differences in the serum insulin concentration. The total insulinemic response was lower in the placebo versus the other two conditions (Table 3), with most of this difference evident during the first 4 hours (Fig 4). There were no significant differences in the incremental insulinemic response. Plasma NEFA concentrations in the fasted state were significantly higher than control levels ($P < .05$) on the morning after running irrespective of whether the run was preceded by ingestion of placebo or acipimox (Fig 4). In the acipimox condition, the total area under the plasma NEFA concentration versus time curve (3.22 ± 0.16 mmol/L × 6 h) was significantly higher than in the placebo (2.78 ± 0.18 mmol/L × 6 h) and control (2.58 ± 0.17 mmol/L × 6 h) conditions (both $P < .05$).

Food Intake

There were no significant differences in the mean intake of energy or major nutrients during the 2 days preceding the oral fat tolerance tests or in the evening meal eaten after exercise on the evening before these tests (Table 4).

DISCUSSION

Our main finding is that moderate-intensity exercise expending about 5 MJ gross energy decreased by nearly 20% the lipemic response to a high-fat mixed meal consumed 16 hours afterward, irrespective of the relative contribution of fat and carbohydrate to energy metabolism during exercise. This confirms the efficacy of exercise as a means to attenuate postprandial lipemia[4,19,20] and provides support for the proposition[9] that the magnitude of fat metabolism during exercise is probably not the major determinant of this effect.

Acipimox, an antilipolytic agent, reduced preexercise concentrations of NEFA and prevented the normal increase of NEFA during exercise. As reported in prior studies, fat oxidation during exercise was reduced, with a compensatory increase in carbohydrate oxidation.[13,14] We administered less than a single therapeutic dose of acipimox, ie, between 104 and 156 mg. This was less than half the dose given in prior exercise studies,[14,21,22] and was selected so that, although lipolysis would be inhibited before and during running,[11] the drug would be eliminated from the circulation before the start of the fat tolerance test the following morning. This was particularly important because of the report that in addition to its inhibitory effects on hormone-sensitive lipase in adipose tissue, acipimox has a stimulatory effect on LPL activity in this tissue.[23]

Acipimox is not significantly metabolized by the body. It is eliminated in the urine, with greater than 90% of a 250-mg dose being excreted within 12 hours and 93% within 24 hours.[11] After a single dose administered when food is present in the

Table 2. Plasma Concentrations of Catecholamines Before Ingestion of Placebo or Acipimox, Immediately Before the Start of the 90-Minute Treadmill Run, at the End of the Run, and 30 Minutes After the Run (mean ± SEM for 11 men)

	Preingestion, −90 min		Pre-run, 0 min		End-run, 90 min		Post-run, 120 min	
Parameter	Placebo	Acipimox	Placebo	Acipimox	Placebo	Acipimox	Placebo	Acipimox
Epinephrine (nmol/L)	0.19 ± 0.04	0.14 ± 0.03	0.14 ± 0.03	0.15 ± 0.04	1.97 ± 0.47	2.49 ± 0.91	0.33 ± 0.07	0.63 ± 0.19*
Norepinephrine (nmol/L)	1.43 ± 0.21	1.83 ± 0.24	2.18 ± 0.49	2.38 ± 0.40	8.86 ± 0.98	8.62 ± 1.20	1.73 ± 0.31	2.01 ± 0.36

*$P < .05$ *v* placebo.

Table 3. Indices of Lipemia and Insulinemia Measured During Fat Tolerance Tests in Three Different Conditions: The Morning After a Day With Only Activities of Daily Living (control), the Morning After a 90-Minute Run Preceded by Ingestion of Placebo, and the Morning After a 90-Minute Run Preceded by Ingestion of Acipimox (mean ± SEM for 12 men)

Index	Control	Placebo	Acipimox
Lipemic response (mmol/L · 6 h)			
Total	8.77 ± 1.17	6.95 ± 0.97*	6.81 ± 0.81*
Incremental	3.25 ± 0.56	2.19 ± 0.47*	1.84 ± 0.24*
Insulinemic response (μJU/mL · 6 h)			
Total	128 ± 9	110 ± 9*†	130 ± 10
Incremental	63 ± 7	52 ± 6	59 ± 8

*$P < .05$ *v* control.
†$P < .05$ *v* acipimox.

gastrointestinal tract—as in our study—plasma concentrations reach a peak in about 3 hours. The first phase of the ensuing decline is rapid, with a half-life of about 2 hours; the second is slow, with a half-life of between 12 and 24 hours.[24] Thus, our subjects' responses to the test meal, consumed about 17 hours after they ingested acipimox, would not have been directly affected by the drug. In confirmation of this reasoning, plasma concentrations of NEFA were not depressed on the morning after acipimox ingestion (Fig 4).

Our subjects exercised at 60% $\dot{V}O_2max$, with fat oxidation contributing nearly 30% of energy metabolism during running after placebo. This was reduced by half when the same exercise was performed after acipimox. During sustained exercise, one important factor limiting fat oxidation is the supply of NEFA from adipose tissue,[25] and this was suppressed by acipimox. An isoform of hormone-sensitive lipase is also found in muscle, and experimental findings indicate that hydrolysis of the intramuscular TAG pool is under hormonal control.[26] Acipimox may therefore inhibit hormone-induced lipolysis in muscle[11] as it does in adipose tissue, although we are not aware of any evidence for this. However, our data show that fat oxidation contributed 16% of energy expenditure during exercise even after acipimox, which fits with the suggestion that muscle TAG degradation is also under nonhormonal control that may involve exercise-induced alterations inside the muscle cell.[26] Intramuscular TAG is therefore likely to have been the predominant source of fatty acids for oxidation after acipimox, although the extent to which this would have been from TAG droplets within fibers or from TAG in adipocytes between fibers cannot be stated.

The compensatory increase in carbohydrate oxidation when NEFA mobilization was suppressed probably reflected mainly a greater rate of muscle glycogen degradation.[27] Plasma glucose concentrations at the end of the run were lower after acipimox as reported previously,[22] and this could reflect an increased utilization of blood glucose. However, the availability of glycerol, an important gluconeogenic precursor, would have been limited after acipimox, so the lower glucose concentration after acipimox may have equally reflected reduced hepatic glucose production.

During the period immediately after exercise, the effect of acipimox on substrate metabolism may be even greater than observed during exercise.[14] Normally, NEFA concentrations remain elevated after exercise, probably for at least 2 hours,[28] and glucose oxidation is decreased, with an increase in nonoxidative glucose disposal that reflects glycogen resynthesis in the previously exercised muscles.[29] We have no direct evidence as

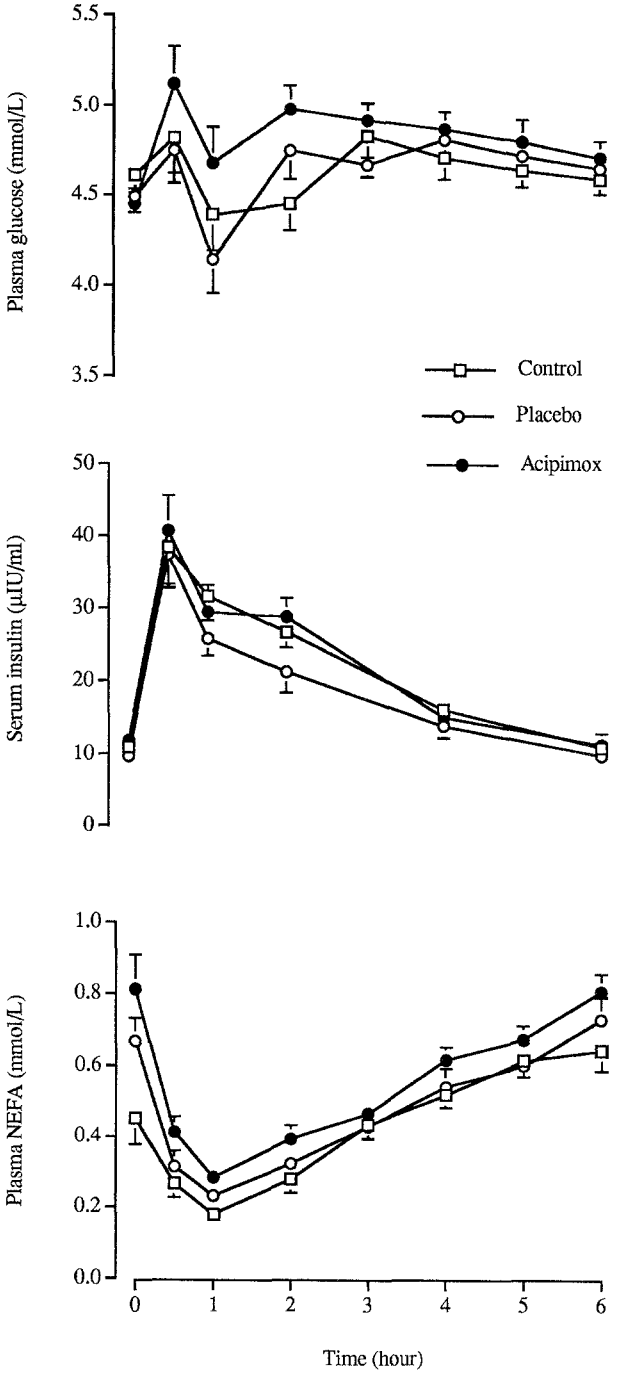

Fig 4. Concentrations of plasma glucose, serum insulin, and plasma NEFA in the fasted state and for 6 hours after ingestion of a high-fat mixed meal in 3 conditions, control, placebo, and acipimox. Values are the mean ± SEM for 12 men. Concentrations of NEFA in the fasted state for acipimox and placebo were both significantly different *v* control ($P < .05$).

Table 4. Dietary Intake of Energy and Macronutrients During the 2 Days Prior to the Oral Fat Tolerance Tests (mean ± SEM for 12 men)

Parameter	Control	Placebo/Run	Acipimox/Run
Mean over 2 days preceding fat tolerance test			
Energy (MJ)	11.87 ± 0.86	11.68 ± 0.99	11.41 ± 0.91
Carbohydrate (g)	464 ± 58	455 ± 64	459 ± 63
Fat (g)	70 ± 9	65 ± 6	62 ± 8
Protein (g)	93 ± 4	94 ± 6	92 ± 6
Meal after exercise on evening before fat tolerance test			
Energy (MJ)	3.44 ± 0.37	3.23 ± 0.27	3.27 ± 0.45
Carbohydrate (g)	157 ± 22	148 ± 17	153 ± 25
Fat (g)	11 ± 3	11 ± 3	10 ± 3
Protein (g)	27 ± 5	27 ± 5	26 ± 5

NOTE. Data for the meal the evening before are included in the mean over 2 days and also shown separately.

to the duration of the suppressive effect of acipimox on NEFA in our study, but based on the pharmacokinetics,[24] this probably would have lasted for at least 2 hours after the end of the run. Postexercise oxidation of carbohydrate would be increased, inhibiting glycogen resynthesis during the period when this is normally facilitated most, at least in muscle.[30] Two hormonal effects of acipimox would also oppose glycogen synthesis: first, the higher epinephrine concentration during the early postexercise period (Table 2); and second, the marked increase in human growth hormone that persists for at least 1 hour after exercise.[14] Growth hormone exerts an anti-insulin effect in muscle,[31] and this would reduce the nonoxidative disposal of carbohydrate ingested in the subject's evening meal. Therefore, relative to the placebo condition, postexercise replenishment of glycogen was probably impaired by acipimox.

A low muscle glycogen concentration in muscle results in an increase of NEFA concentrations,[32] so the high plasma NEFA concentrations on the morning after acipimox may reflect lower glycogen levels. Another reason may be the enhanced human growth hormone response after acipimox; the potent lipolytic effect of this hormone develops slowly over several hours.[33]

Despite the qualitative differences in the metabolic demands of exercise (including recovery) attributable to acipimox, postprandial lipemia was strikingly similar in two fat tolerance tests preceded by running (Fig 3); in both cases, this was nearly 20% lower than in the control condition. The most plausible explanation for the lower response after exercise is an enhanced rate of TAG removal. Exercise has been reported to stimulate a marked increase in LPL transcription in skeletal muscle over a time scale that ties in persuasively with the present findings[6] (increase in mRNA for LPL after 4 hours and increase in LPL mass after 8 hours), with no effect on the activity of this enzyme in adipose tissue[34]—the other major site of uptake. Muscle is therefore likely to be the site of enhanced uptake of TAG after exercise, although (to our knowledge) this has not been studied directly. However, it should be noted that our methodology does not permit exogenous and endogenous TAG-rich particles to be distinguished, and their contributions to the similar postprandial response of plasma total TAG could have differed between the two exercise trials. For example, the higher plasma NEFA concentrations during the fat tolerance test after acipimox may have stimulated an increase in hepatic production of very–low-density lipoproteins,[35] and this would obscure a difference in the TAG removal rate between placebo and acipimox conditions.

Although acipimox ingestion did not influence the exercise attenuation of the plasma TAG response to the high-fat meal, there were clear effects on other responses; plasma concentrations of NEFA and glucose were higher on the morning after the single dose of acipimox than on the other two test occasions, and in addition, acipimox abolished the exercise-induced reduction in the insulin response. These differences must reflect either the indirect effects of the drug administration or—because we have no data on the effect of the drug in the absence of exercise—the interaction of these effects with exercise.

Running diminished the insulin response to the test meal, presumably indicating the improved insulin sensitivity typically found 12 to 15 hours after exercise,[36] but this effect was not evident when acipimox was ingested prior to running. In the acipimox condition, glucose concentrations were higher than in the placebo condition, and this was associated with a higher insulin response that matched the control response. One explanation may be the higher plasma NEFA levels after acipimox. Increasing the NEFA concentration impairs glucose tolerance in normal subjects,[37] because this diminishes insulin's ability to suppress hepatic glucose output.[38] This effect is greatest during the first hour of a glucose tolerance test, which is in accordance with our observations of higher glucose concentrations in the acipimox condition during the early postprandial period. Indeed, the responses of our subjects in this condition, ie, higher responses of NEFA, glucose, and insulin by comparison to the placebo condition, mimic on a smaller scale the disturbances of non–insulin-dependent diabetes mellitus. Higher NEFA concentrations during the fat tolerance test after acipimox may also contribute to higher glucose concentrations by inhibiting glucose uptake, ie, via the classic glucose–fatty acid cycle.[39] However, this would not account for the similarity of the glucose response in control and placebo conditions.

Whatever the explanation(s) for the altered NEFA, insulin, and glucose responses to the test meal, some counterregulatory response was triggered that was linked to the ingestion of acipimox about 24 hours earlier. A conclusion concerning which aspects may be "cause" and which may be "effect" cannot be reached from our data. Indeed, these responses are so intimately interrelated that to attempt this is probably unwise.

In summary, our findings indicate that the mechanisms by which prior exercise attenuates postprandial lipemia are not influenced by manipulation of the relative contributions of fat and carbohydrate to energy metabolism. This is consistent with the proposition that contractile activity is the primary stimulus for synthesis of LPL when muscle nutrient status is reduced by exercise.[6] Thus, exercise regimens based on a variety of different combinations of intensity and duration—provided the exercise sessions are frequent[19]—may have equivalent potential to maintain low levels of postprandial lipemia.

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