Endurance exercise training does not alter lipolytic or adipose tissue blood flow sensitivity to epinephrine

JEFFREY F. HOROWITZ, RENATA J. BRAUDY, WADE H. MARTIN III, AND SAMUEL KLEIN

Department of Internal Medicine, Washington University
School of Medicine, St. Louis, Missouri 63110

Endurance exercise training does not alter lipolytic or adipose tissue blood flow sensitivity to epinephrine. Am. J. Physiol. 277 (Endocrinol. Metab. 40): E325–E331, 1999.—We evaluated the relationship between lipolysis and adipose tissue blood flow (ATBF) in response to epinephrine and the effect of endurance exercise training on these responses. Five healthy untrained men underwent a four-stage incremental epinephrine infusion (0.00125, 0.005, 0.0125, and 0.025 µg · kg fat free mass⁻¹ · min⁻¹) plus hormonal clamp before and after 16 wk of cycle ergometry exercise training. Whole body glycerol and free fatty acid (FFA) rates of appearance (Rₐ) in plasma were determined by stable isotope methodology, and ATBF was assessed by ¹³³Xe clearance. After each training session, subjects were fed the approximate number of calories expended during exercise to prevent changes in body weight. Glycerol Rₐ, FFA Rₐ, and ATBF increased when plasma epinephrine concentration reached 0.8 nM, but at plasma epinephrine concentrations >1.6 nM ATBF plateaued, whereas lipolysis continued to increase. Exercise training increased peak oxygen uptake by 24% (2.9 ± 0.2 vs. 3.6 ± 0.1 l/min; P < 0.05) but did not alter body weight [70.5 ± 3.8 vs. 72.0 ± 3.8 kg; P = nonsignificant (NS)] or percent body fat (18.4 ± 1.6 vs. 17.8 ± 1.9%; P = NS). Lipolytic and ATBF responses to epinephrine were also the same before and after training. We conclude that the lipolytic and ATBF responses to epinephrine are coordinated when plasma epinephrine concentration is ≤1.6 nM, but that at higher epinephrine concentrations, lipolysis continues to increase while ATBF remains constant. Endurance exercise training does not change lipolytic or ATBF sensitivity to epinephrine infusion in vivo during resting conditions.

lipolysis; triglycerides; catecholamines; stable isotopes; pancreatic clamp

ADIPOSE TISSUE TRIGLYCERIDES are the largest energy store in the human body and provide an important source of fuel during endurance exercise (18). The use of adipose tissue as fuel requires hydrolysis of triglycerides and delivery of released fatty acids to working muscles. This process involves catecholamine-mediated lipolysis (1) and an exercise-induced increase in both adipose tissue and skeletal muscle blood flows. During prolonged moderate-intensity exercise, performed at 40–50% of maximum oxygen consumption (Vₒ₂max), there is a sixfold rise in whole body lipolytic rate (15), a threefold increase in adipose tissue blood flow (ATBF) (2), and a 5- to 10-fold elevation in skeletal muscle blood flow (25).

Endurance exercise training increases the use of fat as a fuel during exercise (10). However, the effect of endurance training on the ability to mobilize endogenous triglycerides is controversial because of conflicting results from different investigations. Indirect evidence from studies performed in vivo (22) and direct evidence from those carried out in vitro (5, 23) suggest that the lipolytic response to epinephrine is enhanced by exercise training. In a longitudinal training study, Phillips et al. (22) found that plasma epinephrine concentration during exercise was >50% lower after training than before training. However, glycerol rate of appearance (Rₐ) in plasma, an index of whole body lipolytic rate, was similar before and after training. Several studies have reported that the lipolytic response to epinephrine was more than twofold greater in adipocytes obtained from endurance-trained compared with untrained subjects (5, 23). In contrast, in a cross-sectional study of elite athletes and sedentary volunteers, Stallknecht et al. (29) found that epinephrine-stimulated lipolysis of abdominal subcutaneous adipose tissue in situ was the same in both groups. The reason for these discrepancies is not clear but may be related to differences in study design, study subjects, or methods for measuring lipolytic activity.

As a result of the regulation of hormones that control lipolysis and the delivery of FFA carrier proteins (i.e., albumin) that facilitate intravascular transport of FFA, the coordination between ATBF and lipolysis is particularly important during endurance exercise, when there is an increased requirement for mobilization and transport of FFA from adipose tissue to skeletal muscle. Therefore, it is logical that the catecholamine response to exercise stimulates β-adrenergic receptors, which increase both ATBF (21) and lipolysis of adipose tissue triglycerides (1). However, the precise relationship between ATBF and lipolysis during β-adrenergic stimulation and the effect of endurance training on this relationship are not known.

The aims of the present study were to evaluate the relationship between ATBF and lipolysis in response to epinephrine in vivo and to determine the effect of endurance exercise training on these responses. Whole body glycerol and FFA kinetics and ATBF were determined during a multistage epinephrine infusion before and after 16 wk of endurance training. The rates of epinephrine infusion were chosen to achieve plasma concentrations that span the physiological range observed during low-, moderate-, and high-intensity endurance exercise. Plasma insulin concentration was...
controlled by using the pancreatic hormonal clamp technique (17) to avoid the confounding effects of epinephrine-induced alterations in plasma insulin concentration.

**METHODS**

**Subjects.** Five lean healthy men (age 26 ± 3 yr) participated in this study (Table 1). All subjects were considered to be in good health after a comprehensive medical examination, which included a history and physical examination, blood tests, an electrocardiogram, and an exercise stress test. No subjects were taking regular medication or smoked tobacco, and all had been sedentary for ≥6 mo before the study. Written informed consent was obtained before participation in the study, which was approved by the Institutional Review Board and the General Clinical Research Center (GCRC) Scientific Advisory Committee of Washington University School of Medicine.

Preliminary testing. Peak aerobic capacity and body composition were measured before and after 16 wk of exercise training. Peak oxygen consumption (VO₂peak) was measured during cycle ergometer exercise to assess cardiorespiratory fitness. The protocol consisted of a 4-min warm-up, after which the work rate was progressively increased every minute until volitional fatigue (achieved within 7–10 min). Fat mass and fat-free mass (FFM) were determined by dual-energy X-ray absorptiometry (Hologic QDR 1000W, Waltham, MA).

Experimental protocol. Subjects were admitted to the GCRC at Washington University School of Medicine on two occasions: once before training (PRE) and once after 16 wk of endurance exercise training (POST). The POST trial was performed exactly 3 days after the final exercise training bout. At 1900 on the day of admission to the GCRC, subjects ingested a standard meal containing 12 kcal/kg body weight (55% carbohydrate, 30% fat, and 15% protein). At 2230, subjects ingested a liquid formula snack containing 80 g carbohydrate, 12.2 g fat, and 17.6 g protein (Ensure, Ross Laboratories, Columbus, OH). After this snack, the subjects fasted until completion of the protocol the following day.

The following morning, a stable isotope infusion protocol was performed to evaluate lipolytic rates under basal conditions and during a 4-stage epinephrine infusion with hormonal clamp (Fig. 1). Catheters were inserted into a forearm vein of each arm for isotope and hormone infusion and into a radial artery for blood sampling. At ~0800 (~240 min), a primed (1.5 µmol/kg, constant infusion (0.10 µmol·kg⁻¹·min⁻¹) of [1,1,2,3,3-²H]glycerol [99% atoms percent excess (APE); Cambridge Isotopes, Andover, MA] was started and continued for the next 240 min by use of a calibrated syringe pump (Harvard Apparatus, Natick, MA) to assess glycerol kinetics. At ~210 min, a constant infusion (0.04 µmol·kg⁻¹·min⁻¹) of [2,2-³H]palmitate (98% APE, Cambridge Isotopes) bound to human albumin (Centeon LLC; Kankakee, IL) was started and continued for the next 60 min to assess basal plasma FFA kinetics. Palmitate tracer infusion was restarted at ~60 min and continued throughout the remainder of the study.

Hormonal clamp. At ~150 min of the study, a hormonal clamp was initiated by infusing somatostatin (0.17 µg·kg⁻¹·min⁻¹; BACHEM Farchemicals; Bubendorf, Switzerland), insulin (0.08 mU·kg⁻¹·min⁻¹; Novo Nordisk Pharmaceuticals, Princeton, NJ), and growth hormone (0.00375 µg·kg⁻¹·min⁻¹; Genentech, San Francisco, CA) (Fig. 1). Plasma glucose concentration was monitored every 10 min between ~150 min and ~15 min, and 20% dextrose was infused as needed between ~150 min and ~60 min to maintain baseline blood glucose concentration. By ~60 min, euglycemia was maintained in all subjects without infusing dextrose. Therefore, dextrose was not infused during the last 4.5 h of the hormonal clamp.

Epinephrine infusion. At 0 min, a 4-stage epinephrine infusion was started. Epinephrine (Lederle Laboratories, Chicago, IL) was infused for 30 min at 0.00125 µg·kg⁻¹·min⁻¹ (Epi-1), 0.005 µg·kg⁻¹·min⁻¹ (Epi-2), 0.0125 µg·kg⁻¹·min⁻¹ (Epi-3), and 0.025 µg·kg⁻¹·min⁻¹ (Epi-4) in four discrete stages, separated by a 30-min period without epinephrine infusion to reestablish basal epinephrine concentration and lipolytic rates (Fig. 1). Ascorbic acid (0.5 mg/ml; Abbott Laboratories, Chicago, IL) was added to the epinephrine infusate to improve the stability of epinephrine at room temperature.

Blood sampling. Blood samples were obtained at ~165, ~160, ~155, and ~150 min (basal), at ~15, ~10, ~5, and 0 min (pre-Epi), and every 5 min during each 30-min epinephrine infusion stage (Epi-1, Epi-2, Epi-3, and Epi-4; Fig. 1). These samples were used to assess lipid kinetics and plasma hormone concentrations during basal conditions, the hormonal clamp baseline period (pre-Epi), and each stage of epinephrine infusion.

ATBF measurement. Abdominal subcutaneous ATBF was measured by the ¹³³Xe clearance technique (19). At least 60 min before the first epinephrine infusion (during the hormonal clamp), ~100 µCi of ¹³³Xe dissolved in 0.15 ml of normal saline were slowly injected over 60 s into subcutaneous adipose tissue 3 cm lateral to the umbilicus. A cesium iodide detector (Oakfield Instruments, Eynsham, UK) was placed directly over the site of injection and secured to the skin by tape. The decline in ¹³³Xe was determined by collecting 10-s counts (26) beginning 15 min before Epi-1 and throughout each epinephrine infusion (Fig. 1).

Exercise training. After the PRE experimental trial was completed, all subjects participated in an endurance training program, which consisted of cycling on an ergometer for 35–45 min 4 days/wk for 16 wk, under direct supervision. Exercise intensity was based on the percentage of each subject's maximal heart rate (HRmax) determined during the initial aerobic capacity test. Exercise intensity was increased progressively from 70 to 85% HRmax during the first 8 wk of the training period. To prevent weight loss during the 16-wk training period, energy balance was maintained by feeding the subjects a defined liquid formula diet (ENSURE, Ross Laboratories, Columbus, OH) at the end of each training session to replace the calories expended during exercise.

Analytic procedures. Plasma insulin (9) and C-peptide (8) concentrations were measured by radioimmunoassay. Plasma catecholamine concentrations were determined by a radioenzymatic method (28).

Glycerol and palmitate tracer-to-tracee (tracer/tracee) ratios in plasma were determined by gas chromatography-mass spectrometry by use of an MSD 5971 system (Hewlett-

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Table 1. Characteristics of study subjects

<table>
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<th>Pretraining</th>
<th>Posttraining</th>
<th>P Value</th>
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<td>Body mass index, kg/m²</td>
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<tr>
<td>Fat-free mass, kg</td>
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<td>58.9±1.9</td>
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<tr>
<td>VO₂peak, l/min</td>
<td>2.9±0.2</td>
<td>3.6±0.1*</td>
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</tbody>
</table>

Values are means ± SE of 5 subjects. VO₂peak, peak oxygen consumption. *Significantly different from pretraining value, P < 0.05.
Packard, Palo Alto, CA) with capillary column (16). An internal standard ([2-13C]glycerol) was added to each plasma sample to determine glycerol concentration. Acetone was used to precipitate plasma proteins, and hexane was used to extract plasma lipids. The aqueous phase was dried by speed-vac centrifugation (Savant Instruments, Farmingdale, NY). Heptafluorobutyric (HFB) anhydride was used to form an HFB derivative of glycerol, and ions were produced by electron impact ionization. Glycerol tracer/tracee ratios were determined by selectively monitoring ions at mass-to-charge ratios (m/z) 253, 254, and 257. FFA were isolated from plasma and converted to their methyl esters. Ions at m/z 270.2 and 272.2, representing labeled and unlabeled palmitate produced by electron impact ionization, were selectively monitored.

Calculations. A plateau in substrate concentration and isotopic enrichment was achieved during basal, pre-Epi, and the final 10 min of each epinephrine infusion period. Therefore, glycerol and FFA Ra values during the basal and pre-Epi periods and peak glycerol and FFA Ra values during each stage of epinephrine infusion were calculated using Steele’s equation for steady-state conditions (31)

$$ R_a = \frac{F}{TTR} $$

Where F is the isotope infusion rate, and TTR is the tracer/tracee ratio. Total glycerol and FFA Ra values during each 30-min epinephrine infusion were calculated as the area under the Ra vs. time curve (AUC) by use of the non-steady-state equation of Steele (31)

$$ R_a = F - \frac{V_d[(C_2 + C_1)/2] \cdot (dTTR/dt)}{(TTR_1 + TTR_2)/2} $$

where $V_d$ is the effective volume of distribution (estimated to be 240 ml/kg for glycerol and 50 ml/kg for palmitate); $C_1$ and $C_2$ are the plasma concentrations of tracee at times 1 and 2, respectively; $dTTR/dt$ is the change in TTR with respect to time; and TTR1 and TTR2 are the tracer/tracee ratios at times 1 and 2, respectively. The TTR and concentration data were smoothed by spline fitting (33).

Subcutaneous ATBF was calculated from $^{133}$Xe clearance (19)

$$ ATBF = -k \cdot \lambda \cdot 100 \ (ml \cdot 100 \ g \ adipose \ tissue^{-1} \cdot \min^{-1}) $$

where k is the rate constant of the $^{133}$Xe monoeXponential washout curve, and $\lambda$ is the adipose tissue-to-blood partition coefficient for xenon. Values for k were determined experimentally as $\ln(y_2 - y_1)/(t_2 - t_1)$, where $y_1$ and $y_2$ were the counting rates at times $t_1$ and $t_2$, respectively. The value for $\lambda$ was assumed to be 1.0 ml/g (34).

Statistical analysis. A power analysis was performed on the basis of data reported by Divertie et al. (7), who evaluated palmitate Ra during a similar epinephrine infusion and hormonal clamp procedure in normal volunteers and in subjects with diabetes. Our analysis suggested that five subjects would be needed to detect a 30% increase in peak FFA Ra at our highest rate of epinephrine infusion, with an expected SD equal to 60% of the change, an a-value of 0.05, and a power of 0.79.

A two-way ANOVA (training × epinephrine dose) with Tukey post hoc analysis was used to test significance for lipid kinetics, plasma hormone concentrations, and ATBF. A Student’s t-test for paired samples was used to test the significance of differences in body composition and VO2peak between PRE and POST trials. Ra and ATBF data from the PRE and POST trials were combined because exercise training did not alter lipid kinetics or ATBF. A value of P < 0.05 was considered to be statistically significant. All data are expressed as means ± SE.

RESULTS

Body composition and aerobic fitness. Body weight and body composition were not altered by 16 wk of exercise training (Table 1). Although FFM tended (P = 0.09) to increase after training, this increase (3 ± 1%) did not reach statistical significance. VO2peak increased by 24 ± 7% (P < 0.05).

Plasma hormone concentration. The graded epinephrine infusion resulted in a progressive increase in plasma epinephrine concentration without alteration.
of plasma insulin concentration (Fig. 2). Plasma epinephrine and insulin concentrations were identical during the PRE and POST trials. Plasma norepinephrine was not affected by epinephrine infusion or exercise training and remained at basal levels throughout the study during both PRE and POST trials (0.87 ± 0.05 and 1.01 ± 0.1 nmol/l, respectively). Somatostatin infusion reduced plasma C-peptide concentration to values below baseline during both PRE and POST trials (from 1.7 ± 0.1 to 0.3 ± 0.1 ng/ml and from 1.5 ± 0.4 to 0.2 ± 0.1 ng/ml, respectively; both P < 0.05).

Plasma glycerol and fatty acid kinetics. Glycerol Ra and FFA Ra during the PRE and POST trials are shown in Figs. 3 and 4. During both trials, a small increase in plasma epinephrine concentration (from 0.1 nM to 0.4 nM) did not alter either glycerol or FFA Ra. However, further increases in plasma epinephrine concentration (≥0.8 nM) elicited a progressive increase in both peak and total glycerol and FFA Ra (main effect for plasma epinephrine concentration: all P < 0.001; Figs. 3 and 4). Endurance training did not affect either peak or total glycerol Ra (main effect for training: P = 0.42 for peak and P = 0.37 for total glycerol Ra) or FFA Ra (P = 0.73 for peak and P = 0.50 for total FFA Ra) during the epinephrine infusion. In addition, there were no interaction effects between glycerol Ra or FFA Ra and plasma epinephrine concentration (all P > 0.58). The apparent trend toward an increase in glycerol Ra during epinephrine infusion after training was due to one subject who had higher values in the POST compared with the PRE trial. This difference was likely due to lower plasma insulin concentrations achieved during this subject’s POST trial than in his PRE trial clamp protocol (5 ± 1 vs. 9 ± 1 µU/ml, respectively) rather than to the effect of exercise training.

ATBF. Endurance training did not affect ATBF (P = 0.79). During both trials, increasing plasma epinephrine concentration from −0.1 nM to 0.4 nM did not alter ATBF (Fig. 5). A progressive increase in ATBF was observed when plasma epinephrine concentration was increased from 0.4 nM to 1.6 nM (P < 0.05 vs. pre-Epi). However, increasing plasma epinephrine concentration beyond 1.6 nM did not result in a further increase in ATBF.

DISCUSSION

The present study represents the first longitudinal study to evaluate the effect of endurance exercise training on the lipolytic and adipose tissue blood flow responses to epinephrine in vivo. Our data demonstrate that 16 wk of endurance exercise training, resulting in nearly a 25% increase in aerobic capacity, did not alter glycerol Ra, FFA Ra, or ATBF in response to a physiolog-
cal range of plasma epinephrine concentrations. In addition, we found that the lipolytic and ATBF responses to epinephrine infusion were coordinated at plasma epinephrine concentrations \( \approx 1.6 \, \text{nM} \) but that at higher epinephrine concentrations, lipolysis continued to increase while ATBF remained the same. This study was specifically designed to eliminate potential factors that could have influenced the lipolytic sensitivity to epinephrine. The hormonal clamp technique (17) was used to prevent epinephrine-induced hyperinsulinemia (4) and to avoid possible training-induced alterations in plasma insulin concentration. In addition, we prevented changes in body composition, which can influence lipolytic sensitivity, by feeding our subjects the calories they expended during exercise after each training session.

Although we found lipolytic sensitivity to epinephrine in vivo was unchanged after training, in vitro studies have found that endurance training enhances the lipolytic response of adipocytes to epinephrine (5, 23). However, it is only at high epinephrine concentrations (\( \geq 10^{-6} \, \text{M} \)) that lipolysis in adipocytes obtained from endurance-trained subjects is greater than that in adipocytes from untrained subjects (5, 23). Within the physiological range of plasma epinephrine concentration (\( 10^{-9} \, \text{M} \)), these studies indicate that the lipolytic response to epinephrine is similar in trained and untrained persons (5, 23). Therefore, the data from studies performed in isolated adipocytes are consistent with the in vivo findings of the present study. Our findings are also consistent with in situ data in which abdominal subcutaneous adipose tissue lipolysis (measured by microdialysis) was not different in sedentary men compared with elite athletes (29). Because lipolytic regulation is heterogeneous among different adipose tissue depots (13), the present findings extend those of Stallknecht et al. (29) indicating that epinephrine-stimulated glycerol and FFA R\(_a\) are unchanged after endurance training.

Although whole body lipolytic sensitivity to epinephrine during hormonal control at rest was not affected by exercise training, we cannot rule out the possibility that training increases lipolytic sensitivity during other physiological conditions. It is still possible that training-induced changes in fat cell size and fat mass, which were prevented by diet control in the present study, enhance adipose tissue lipolytic sensitivity to epinephrine. It is also possible that training increases lipolytic sensitivity to catecholamines in adipose tissue or other fat depots during exercise when there are marked alterations in plasma hormone concentrations. Several studies suggest that endurance exercise training increases the use of intramuscular triglycerides (IMTG) during exercise (11, 12, 20, 22). However, the effect of exercise training on the contribution of IMTG as a fuel during exercise is controversial because of conflicting results from other studies (14, 30). The proximity of IMTG to skeletal muscle mitochondria facilitates their use as a fuel during exercise, because the released FFA do not require transport from a peripheral TG depot. The factors that regulate IMTG lipolysis are not clear but presumably involve the adrenergic system, because IMTG depletion during exercise is inhibited by \( \beta_2 \)-adrenergic blockade (3). However, the threshold for \( \beta \)-adrenergic stimulation of IMTG lipolysis and the effect of exercise training on this threshold have not been investigated. The method used to evaluate lipoly-
sis in the present study, intravenous infusion of glycerol and fatty acid tracers, may not be able to detect differences in lipolytic sensitivity of IMTG because some glycerol and fatty acids released during lipolysis of IMTG could be metabolized locally within the muscle and never enter the systemic circulation.

The major function of adipose tissue is to provide a source of energy for other tissues. Therefore, coordination between adipose tissue lipolysis and blood flow is important. In the present study, we found that both ATBF and lipolytic rate (glycerol Ra and FFA Ra) increase when plasma epinephrine concentration reaches 0.8 nM. This coordinated stimulation of ATBF and lipolysis may be useful for increasing the mobilization and export of FFA from adipose tissue. In contrast, at high plasma epinephrine concentrations, there was a discordance between ATBF and lipolytic activity; maximum ATBF was achieved at a plasma epinephrine concentration of ~1.6 nM, whereas glycerol Ra and FFA Ra continued to increase. This plateau in ATBF may contribute to the decline in FFA transport into the circulation observed when both plasma epinephrine concentration and lipolytic rate are high, such as during high-intensity exercise.

Our observation that endurance exercise training did not alter basal ATBF differs from the data reported by Stallknecht et al. (29), who found that basal ATBF was two- to threefold greater in elite athletes compared with sedentary subjects. It is possible that differences in training intensity and duration, as well as genetic differences between elite athletes and recently trained volunteers, may be responsible for the differences in blood flow responses between the studies. In addition, differences in fat cell size between subjects may have contributed to the discrepancy between these two studies. In a dog model, DiGirolamo et al. (6) found that ATBF is inversely related to fat cell volume. Therefore, blood flow expressed per 100 g of adipose tissue is higher in adipose tissue containing smaller compared with larger fat cells. Endurance athletes have a smaller fat cell volume than sedentary persons (5, 23), which may explain the greater ATBF in trained compared with untrained subjects observed by Stallknecht et al. It is unlikely that our endurance training program altered fat cell size, because total body fat mass did not change.

To minimize any potential influence of acute exercise on the lipolytic response to epinephrine, all subjects performed their POST trial 3 days after their final exercise training bout. Although exercise may enhance the lipolytic response to epinephrine, this effect is probably short-lived. Data from in vitro studies indicate that the lipolytic response of isolated adipose tissue cells to pharmacological concentrations of catecholamines is enhanced immediately after moderate-intensity exercise (27, 32). However, we have previously found that an exercise bout performed 90 min before epinephrine infusion did not augment the whole body lipolytic response to epinephrine (16). Therefore, it is likely that 3 days of rest were sufficient to avoid any influence of a prior exercise bout on the lipolytic response to epinephrine.

The small number of subjects participating in our study raises the possibility that we failed to detect an effect of endurance training because of a type II statistical error. However, power calculations based on our measured values for glycerol Ra and FFA Ra indicate that a large number of subjects would need to be studied to demonstrate that the small differences we observed in lipid kinetics before and after training were statistically significant (more than 125 subjects to detect a difference in glycerol Ra and more than 1,000 subjects to detect a difference in FFA Ra). Therefore, it is unlikely that our study missed an important effect of endurance training on fat metabolism or that our conclusions would change if we studied more subjects.

In summary, epinephrine infusion simultaneously stimulates adipose tissue lipolysis and blood flow. The coordinated increase in lipolysis and ATBF at plasma epinephrine concentrations <1.6 nM may be beneficial by increasing FFA export from adipose tissue. However, at higher plasma epinephrine concentrations (>1.6 nM), ATBF remains constant while lipolysis continues to increase. Endurance exercise training did not alter in vivo lipolytic or adipose tissue blood flow sensitivity to epinephrine.

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Address for correspondence and reprint requests: S. Klein, Washington Univ. School of Medicine, 660 S. Euclid Ave., Box 8127, St. Louis, MO 63110–1093 (E-mail: sklein@mgate.wustl.edu).

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