Effect of Short-Term Exercise Training on Leptin and Insulin Action

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The purpose of the study was to determine the effect of short-term exercise training (7 consecutive days for 60 min/d at 75% maximal oxygen consumption [$\dot{V}O_2$ max]), which did not change body mass on fasting plasma leptin concentration and insulin action. Young, lean subjects (n = 16; age, 21.9 ± 0.6 years; body fat, 17.5% ± 1.5%) and older subjects with relatively more adipose tissue (n = 14; age, 58.6 ± 1.4 years; body fat, 28.3% ± 1.3%) were studied (mean ± SE). Fasting plasma leptin was significantly ($P < .05$) related to adiposity (fat mass, $r = .58$; % body fat, $r = .76$) in this population. Body mass did not change ($P < .05$) in any of the groups with training (71.8 ± 2.5 *v* 71.9 ± 2.5 kg). The insulin sensitivity index (S_I determined from an intravenous glucose tolerance test (IVGTT) improved significantly ($P < .05$) in both the young group (4.8 ± 0.6 *v* 6.9 ± 0.8 × 10^{-4}/min (μU/mL) and the older group (3.2 ± 0.6 *v* 5.9 ± 1.0 × 10^{-4}/min (μU/mL)). Fasting leptin did not change with training in either group (10.4 ± 1.6 *v* 9.2 ± 1.0 ng/mL). These findings suggest that exercise does not independently affect the fasting plasma leptin concentration and the improvement in insulin action with exercise is not associated with an alteration in fasting leptin in healthy sedentary lean and relatively lean subjects.

LEPTIN is a hormone secreted by adipose tissue that may signal the relative size of the fat depot and control body mass.[1-3] In support of this relationship, fasting induces a pronounced reduction in leptin[4,5] whereas overfeeding can increase plasma leptin.[6] Weight loss and weight gain are also associated with a reduction and an increase in plasma leptin, respectively.[4,6,7] Such findings suggest that leptin is responsive to changes in energy balance.

If leptin is reflective of energy balance, it is conceivable that an increase in energy expenditure, ie, physical activity, may also modulate plasma leptin. In support of this association, in rodents, a single bout of exercise or exercise training elicits a reduction in plasma leptin and *ob* mRNA.[8-11] However, in humans, the effect of exercise on plasma leptin is not as definitive. Either a reduction[12-16] or no change[17-19] have been reported following a single exercise bout. Repeated daily exercise bouts (ie, exercise training) have also been reported either to decrease[18,20-22] or not to alter[20,23] plasma leptin. It is thus difficult to discern if the increase in energy expenditure with exercise recruits leptin as a possible signal to control body mass, even in healthy, relatively lean individuals.

The effect of exercise training on leptin is also potentially important in relation to insulin action. Leptin has been demonstrated to induce insulin resistance.[24] Segal et al[25] also reported that insulin resistance is independently associated with an elevated plasma leptin concentration in males. It is thus conceivable that the reduction in plasma leptin with exercise training[18,20-22] may improve insulin action. On the other hand, any reduction in leptin may simply reflect the decrease in body mass with exercise training rather than serving as a means to regulate insulin action.

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The purpose of this study was to discern if exercise training, which improves insulin action but does not change body mass, is linked with a change in the fasting plasma leptin concentration. Several groups have reported that 7 consecutive days of exercise training improves insulin action without changing body mass or composition.[26-29] We thus used this model to determine the effect of exercise on the plasma leptin concentration, body mass, and insulin action in young lean and older subjects with relatively more fat mass. These groups were compared since there is evidence that exercise may affect plasma leptin differently according to the degree of adiposity[8,21] and that aging may alter the leptin–fat mass relationship.[30]

SUBJECTS AND METHODS

Study Design

Two groups of subjects were examined: (1) young lean individuals (n = 16, 9 women and 7 men) and (2) older individuals with relatively more adipose tissue (n = 14, 8 women and 6 men). The rationale for examining these groups was to provide a comparison of a potential exercise effect between individuals with initially different plasma leptin concentrations and adiposity. Subjects were screened for body composition and cardiovascular fitness level. A pretraining insulin sensitivity index (S_I) was determined with an intravenous glucose tolerance test (IVGTT). Subjects then underwent 7 consecutive days of supervised exercise training. A posttraining IVGTT was performed 15 to 17 hours after the final training bout. A fasting sample from the IVGTT was used to determine the plasma leptin concentration.

Subjects

The subjects were volunteers who were not active in an exercise program for at least the previous 2 years. They were also questioned concerning their normal daily activities, and only those with a relatively sedentary life-style were included. Other inclusion criteria were no smoking, no use of medications that alter insulin action, and no evidence of coronary artery disease, hypertension, or orthopedic injuries that would inhibit exercise training. All of the older women were postmenopausal, and 5 of these women were on estrogen replacement therapy. There were no initial differences in insulin action or the plasma leptin concentration with estrogen replacement versus nonmedication, in agreement with other data[21]; the responses to exercise also did not differ. The data were thus combined in the older women. The young women were tested in the follicular phase of the menstrual cycle based on a recall of their previous menses.

Insulin Action and Plasma Leptin

An insulin sensitivity index (S_I) was determined with an IVGTT as described by Bergman et al.[31] The S_I is a composite measure that includes the effect of insulin on glucose disappearance and reducing hepatic glucose production. Subjects reported to the laboratory in the morning after a 12-hour fast and had consumed at least 250 g carbohydrate per day for the previous 3 days. They were instructed to record and consume the same foods for 24 hours prior to each IVGTT. The pretraining IVGTT was performed in the sedentary condition, and the posttraining test was performed 15 to 17 hours after the final exercise bout. Two to 3 hours after the final exercise bout, the subjects consumed a meal and then fasted overnight (12 hours). Briefly, the IVGTT procedure consisted of 4 baseline samples before the intravenous injection of glucose (1.7 mmol/kg) at time 0 and insulin (150 pmol/kg) 20 minutes later. Twenty-five samples were obtained between 0 and 180 minutes and subsequently analyzed by spectrophotometry for glucose (procedure HK 16-UV; Sigma, St Louis, MO) and microparticle enzyme immunoassay for insulin (IMx; Abbott, Chicago, IL). The S_I was calculated with the minimal model of insulin action (MINMOD version 3.0[31]). The leptin concentration was determined with a commercial radioimmunoassay (Linco Research, St Louis, MO). Each sample was analyzed in duplicate, and the coefficient of variation was less than 4%.

Cardiovascular Fitness and Body Composition

Maximal oxygen consumption ($\dot{V}O_2$max) was measured during incremental exercise on an electrically braked cycle ergometer (Lode; Diversified, Brea, CA). In the younger, leaner subjects, the initial workload was 50 W with an increase of 25 W every 2 minutes. In the older subjects with relatively more body fat, the initial workload was 25 W with an increment of 25 W every 2 minutes until voluntary exhaustion was achieved. For a valid test, 2 of the following criteria had to be fulfilled: (1) respiratory exchange ratio greater than 1.0, (2) heart rate at least 15 bpm less than the age-predicted maximal heart rate, or (3) maintenance of oxygen consumption within 2 mL/kg/min despite an increase in workload. Oxygen consumption was measured with open-circuit spirometry using a metabolic cart (model 2900; Sensor Medics, Anaheim, CA). A 12-lead electrocardiogram (EKG) recorded the heart rate and EKG tracings. The maximal exercise test was used (1) to screen for potential heart disease and (2) to determine the heart rate and oxygen consumption required to elicit the desired exercise intensity (70% to 75% $\dot{V}O_2$max) during 7 days of training. A physician was present during the maximal testing of all older subjects and interpreted the exercise EKGs. The percent body fat, fat mass, and fat-free mass were determined with the 7-site skinfold method.[32]

Exercise Training

The subjects exercised 1 h/d for 7 consecutive days on a cycle ergometer. Exercise intensity was adjusted to achieve 70% to 75% $\dot{V}O_2$max as determined from Douglas bags collected at minute 5 and every subsequent 15 minutes of exercise. All subjects exercised continuously for 1 hour during the 7 days of training. They were instructed to consume their normal diet during the exercise training period with the addition of approximately 450 kcal, which represented the energy expended daily with exercise.

Statistics

Data were compared with a 2 (group) $\times$ 2 (treatment before and after exercise training) repeated-measures ANOVA. Contrast comparisons were used to determine specific differences when a significant interaction or group effect ($P < .05$) was obtained. Descriptive data (age, body composition, and exercise variables) were compared between the groups with an independent *t* test ($P < .05$).

RESULTS

Anthropometric and Exercise Data

Age, anthropometric, and exercise data for the groups are presented in Table 1. The older group had significantly ($P < .05$) more adipose tissue (% body fat, fat mass, and body mass index [BMI]) and body mass than the younger group. $\dot{V}O_2$max was significantly ($P < .05$) lower in the older group. All groups exercised at approximately 75% $\dot{V}O_2$max. Body mass did not change ($P < .05$) in any of the groups with the 7 days of training (mean for pooled data, 71.8 $\pm$ 2.5 *v* 71.9 $\pm$ 2.5 kg).

Insulin Action

There was a significant ($P < .05$) treatment effect with no significant interaction for an improvement in insulin action (S_I) with age (Fig 1). There were no significant ($P > .05$) differences in initial or posttraining S_I between the 2 groups. The insulin action data were pooled to further compare the response to training. There was a significant treatment (training) effect ($P < .0001$) for increasing S_I (4.1 $\pm$ 0.4 *v* 6.5 $\pm$ 0.6 $\times 10^{-4}$/min μU/mL). There was a trend for elevated fasting insulin ($P = .06$) and glucose ($P = .07$) in the older group. However, fasting blood glucose and insulin were within normal values and did not change with exercise in either group (Table 2). This is in agreement with other 7-day training studies in which fasting insulin and glucose did not change in obese patients[28] or patients with mild type 2 diabetes[29] despite enhanced insulin sensitivity with exercise.

Plasma Leptin Concentration

The fasting plasma leptin concentration for each of the groups is presented in Fig 2. It was significantly elevated in the older group compared with their younger counterparts ($P < .05$). Plasma leptin was significantly related to fat mass ($r = .58$, $P < .001$) and percent body fat ($r = .76$, $p < .0001$) in this population. Plasma leptin values did not change ($P = .29$ for treatment effect and $P = .13$ for interaction effect) with training despite an improvement in insulin action with 7 days of exercise in both groups (Figs 1 and 2). Values for the young group were 7.1 $\pm$ 1.3 versus 7.6 $\pm$ 1.3 ng/mL and values for the older group were 14.2 $\pm$ 2.7 versus 11.0 $\pm$ 1.3 ng/mL pretraining versus posttraining, respectively. There was also no change in plasma leptin with training when all subjects were combined (10.4 $\pm$ 1.6 *v* 9.2 $\pm$ 1.0 ng/mL before *v* after training, respectively). There were no differences in the response to exercise when the groups were classified according to gender (ie, young *v* older women

Table 1. Age, Anthropometric, and Exercise Data for the Young and Older Groups (mean $\pm$ SE)

Variable	Young	Older	*P*
Age (yr)	21.9 $\pm$ 0.6	58.6 $\pm$ 1.4*	<.001
Body fat (%)	17.5 $\pm$ 1.5	28.3 $\pm$ 1.3*	<.001
BMI (kg/m^2)	23.4 $\pm$ 0.5	26.9 $\pm$ 1.1*	<.01
Body mass (kg)	66.9 $\pm$ 1.9	77.5 $\pm$ 4.6*	<.05
Fat mass (kg)	11.5 $\pm$ 0.9	21.9 $\pm$ 1.6*	<.001
$\dot{V}O_2$max (mL/kg/min)	35.8 $\pm$ 2.0	23.2 $\pm$ 1.8*	<.001
Training %$\dot{V}O_2$max	74.9 $\pm$ 0.1	75.0 $\pm$ 0.5	.92

*$P < .05$ *v* young.

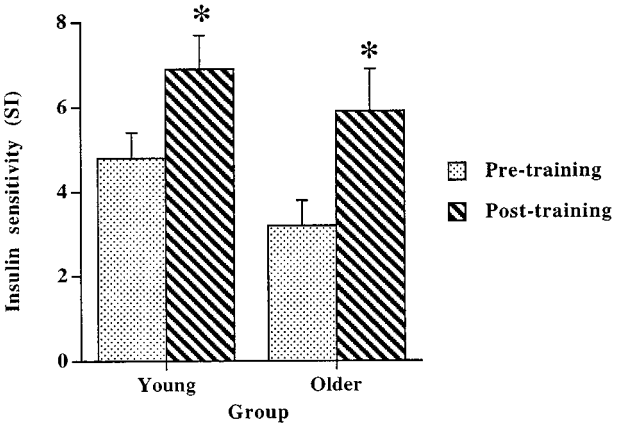

Fig 1. Insulin sensitivity (×10⁻⁴/min (μU/mL)) determined from an IVGTT in the young and older groups. *Significant ($P < .05$) improvement with training.

and men). Changes in insulin sensitivity did not correlate with changes in plasma leptin.

DISCUSSION

The main finding of the present study is that exercise training which did not alter body mass also did not change the fasting plasma leptin concentration in young or older individuals. These data suggest that exercise training does not independently regulate fasting plasma leptin. In support of this premise, other studies have reported little or no reduction in fasting leptin with exercise training after statistical correction for a decrease in fat mass.[18,21] However, the design of the current study allowed us to directly assess the exercise/leptin relationship since body mass was not altered after the week of training. The current findings imply that the exercise-induced negative energy balance that produces a loss of fat mass is the primary factor in controlling the fasting plasma leptin concentration with exercise training rather than the exercise per se.

Additional insight into the exercise/leptin relationship may be gathered from studies examining the effect of a single exercise bout. Several reports have noted a reduction in plasma leptin following physical activity.[12,13] However, the exercise was somewhat extreme, ie, a 26-mile[13] or 101-mile[12] footrace. A study by van Aggel-Leijssen et al[16] examined hourly to bihourly plasma leptin concentrations following a single 2-hour bout of exercise. They reported that the leptin concentration over a 24-hour period decreased after exercise when energy balance was maintained as compared with energy balance with no exercise. Studies examining a single shorter-duration exercise bout similar to that used in the current study (ie, 30 to 60 minutes) in sedentary individuals observed no alterations in the postexercise or fasting plasma leptin concentration.[18,19,23] The current findings are in agreement with these latter data and extend these findings to short-term exercise training that does not alter body mass.

Table 2. Fasting Insulin and Glucose Data for the Young and Older Groups Before and After 7 Days of Exercise Training (mean ± SE)

Variable	Before	After
Young group		
Fasting insulin (μU/mL)	5.8 ± 0.5	5.7 ± 0.8
Fasting glucose (mg/dL)	87.8 ± 3.1	84.2 ± 3.0
Older group		
Fasting insulin (μU/mL)	8.5 ± 1.2	8.3 ± 1.5
Fasting glucose (mg/dL)	93.9 ± 4.6	94.8 ± 4.1

In the current study, insulin action improved with the exercise stimulus despite a lack of change in fasting leptin (Figs 1 and 2). In humans, an elevated leptin concentration may be linked with insulin resistance.[24,25] The reduction in leptin reported with exercise training[18,20,21] may thus be potentially important for regulating insulin action, particularly in individuals in whom leptin is initially elevated such as the older subjects of our study (Fig 2). However, it is not evident if the reduction in plasma leptin with exercise training is secondary to a reduction in body mass, rather than serving as a modulator for insulin action. The current findings suggest that the improvement in insulin action with exercise training is not associated with a decrease in plasma leptin, as insulin action was enhanced while the fasting plasma leptin concentration was not altered (Figs 1 and 2). This association was evident even in older subjects with a relatively high fat mass and fasting plasma leptin concentration (Table 1 and Fig 2).

One purpose of the current study was to compare the response to exercise training in a lean young group and older individuals with relatively more adipose tissue. This is a potentially important comparison, as Pagano et al[8] report that leptin decreased in lean animals after a single exercise bout but was unaltered in obese animals. However, Kohrt et al[21] reported that exercise training reduced fasting leptin disproprotionally more in a subgroup of women with high adiposity compared with leaner women. There is thus the potential that individuals with a larger fat mass respond differently to exercise versus leaner subjects in terms of plasma leptin. In addition, the fat mass–leptin relationship may be altered with age such that there is a leptin deficiency relative to the fat mass.[30] However, despite these potential differences between the groups in terms of leptin regulation, there was no significant difference in the response to exercise, regardless of the fact that the older group had a greater fat mass and a higher fasting plasma leptin level (Table 1 and

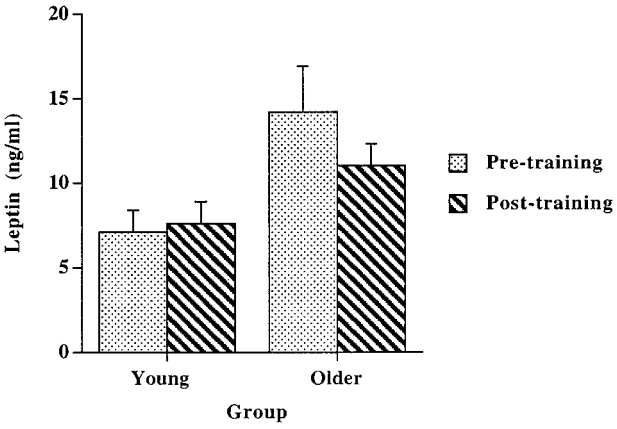

Fig 2. Plasma leptin in the young and older groups before and after 7 days of exercise training. There was a significant ($P < .05$) group effect, with older subjects having higher leptin levels.

Fig 2). The relatively greater reduction in plasma leptin in more obese individuals with exercise training[21] may thus only become evident when there is a loss of fat mass. In agreement with other reports,[17,21,33] we observed a positive relationship between adiposity and the plasma leptin concentration.

In summary, 7 consecutive days of exercise training (60 min/d, at 75% $\dot{V}O_2$max) did not alter the fasting plasma leptin concentration in young and older men and women despite enhanced insulin action. Exercise training did not alter the body mass. These data suggest that exercise per se does not independently regulate fasting plasma leptin. The improvement in insulin action with exercise training also may not be associated with an alteration in fasting leptin.

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