Differential Effects of Maximal- and Moderate-Intensity Runs on Plasma Leptin in Healthy Trained Subjects

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This study investigated the effect of different exercise bouts on plasma leptin response. Trained men (n = 9) performed a short duration, maximal intensity (MAX) bout and a 60-min endurance run at ~70% of maximal oxygen consumption (END). Blood was collected before, immediately after, 24 h after (24 h Post), and 48 h after exercise (48 h Post) for measurement of plasma leptin, insulin, and glucose. VO_2max and percent body fat were 57.8 ± 2.1 mL · kg^{-1} · min^{-1} and 10.8 ± 1.5% (mean ± SEM), respectively. Energy expenditure was 197.5 ± 11.8 and 882.7 ± 14.4 kcal for MAX and END, respectively. Plasma leptin levels did not differ between time points for the MAX run. Leptin was significantly lower 48 h Post (2.2 ± 0.3 ng/mL) versus before, immediately after, and 24 h Post exercise (3.1 ± 0.3, 3.0 ± 0.3, and 2.5 ± 0.4 ng/mL, respectively) for END. Leptin tended to be lower at 24 h Post than before or immediately after exercise (P = 0.10). Plasma insulin was lower 24 h Post- versus preexercise for the END, but was not correlated to changes in leptin levels. Plasma glucose levels did not change significantly during the endurance test. We found a delayed decrease in leptin at 48 h after an extended exercise session (900 kcal). Furthermore, this effect did not appear to be related to changes in insulin or glucose levels. Findings from this study address the effects of exercise on leptin, aiding in the evaluation of the impact of exercise and energy expenditure on plasma leptin concentrations in the prevention and treatment of obesity. *Nutrition* 2001;17:365–369. ©Elsevier Science Inc. 2001

KEY WORDS: leptin, insulin, exercise

INTRODUCTION

The cloning of the obese (ob) gene from genetically derived mice homozygous for the *ob* gene suggests that a signal from the periphery, more specifically the adipose tissue, is involved in energy balance.[1] Leptin is the protein hormone expressed by the *ob* gene, and it has a purported role in energy balance through control of appetite and energy expenditure. In animal models with a genetic defect in the *ob* gene, leptin administration has been shown to decrease appetite and increase energy expenditure, leading to a loss in body fat and body weight.[2] The hypothalamus appears to be the site of action for these responses. Plasma leptin concentration is highly correlated to indices of body fatness.[3–5] This relationship has been found in normal weight,[6] extremely underweight,[7] and obese individuals.[3,6] Studies indicate that the overwhelming majority of obese individuals are hyperleptinemic,[6,8] suggesting that obesity is a condition of leptin resistance. Mean serum leptin levels vary widely at a given body composition, but are approximately four times greater in obese (31.3 ± 24.1 ng/mL) compared with normal weight, healthy individuals (7.5 ± 9.3 ng/mL).[6] Other known factors that correlate with plasma leptin levels are age,[9] gender,[4,9,10] insulin production,[11] glucose levels,[11] dietary intake,[6] and fat distribution.[12]

The relationships between plasma leptin concentrations and insulin, glucose, and diet are complex. Generally, acute changes in glucose and insulin have minimal effects on plasma leptin,[13] whereas chronic, sustained hyperinsulinemia increases leptin production.[14] However, prolonged changes in energy intake are postulated to modulate leptin concentrations independent of fat mass by insulin-mediated glucose uptake by adipocytes.[15]

Although much research has been conducted investigating the effect of hormones and energy substrates on leptin production, relatively few studies have investigated the relationship of different energy expenditures on plasma leptin concentrations. Discrepant findings are present in regard to exercise and differing expenditures. Several studies have found that a single moderate bout of exercise has no significant effect on leptin levels in blood taken immediately after exercise[16–19] or several hours after exercise.[20] This result has been apparent using a variety of subjects and exercise bouts, including exercise-trained men completing an endurance bout at moderate intensity[16,18]; sedentary healthy men and women completing a short high-intensity exercise bout[17]; lean and obese men completing an endurance bout at mild intensity[19]; and in untrained men completing a maximal test and an endurance bout of mild intensity.[20]

A few studies have found that a single exercise bout does significantly decrease plasma leptin levels as a delayed response, with changes occurring as soon as 24 h and prolonging to at least 48 h or longer after the exercise session.[21,22] Van Aggel-Leijssen et al.[22] reported a 20% decrease in leptin levels 24 h after exercise (expenditure = 800 kcal) when energy balance was maintained. Essig et al.[21] found that trained, fasted men who expended 800 and 1500 kilocalories (kcal) during an exercise session had a significant reduction in leptin levels 24 h (1500 kcal) and 48 h postexercise (800 and 1500 kcal), but not immediately postexercise. Furthermore, evidence suggests that a more strenuous exercise may confer a more rapid decrease in leptin levels. Following a

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101-mile road race, leptin levels were 32% lower at 6 h postexercise compared with preexercise values.[18] These decreases in leptin levels were maintained for 18–24 h after the road race.

With the scarcity of data and conflicting results available on the effect of different exercise intensities on the delayed response of plasma leptin levels, we were interested in examining the effects of a short-term, maximal-intensity and a long-term, moderate-intensity exercise bout on plasma leptin levels. Secondly, we wanted to explore the possibility of acute changes in insulin and glucose levels during the two exercise bouts as possible factors contributing to the changes in leptin with exercise. We sought to examine the following hypotheses in this study: 1) a short-term maximal intensity test will not affect plasma leptin levels measured immediately postexercise, and 24 and 48 h postexercise; 2) a moderate-intensity bout of exercise will decrease plasma leptin levels in the 48 h after the exercise; and 3) plasma insulin and glucose levels will not be correlated to plasma leptin levels.

METHODS

Nine healthy male subjects (age range 22–33 y) were recruited to participate in the study based on current activity levels. Inclusion exercise criteria for the study was participation in a minimum of 1 h of moderate intensity physical activity 5–7 days a week. Before testing each subject signed an informed consent approved by the Institutional Review Board for Research with Human Subjects at Wake Forest University.

Each participant was asked to perform two treadmill tests with 1 week separating each test. The first test was a maximal graded exercise test (MAX) and the second test was a 1-h endurance (END) run. Both tests for each individual were conducted at the same time in the morning with all participants being tested during the morning hours between the times of 0700 and 1000 h to control for circadian rhythms of leptin. Participants reported to the laboratory for both exercise testing sessions and for subsequent blood draws in a 12-h fasted state at the same time of the day as their exercise tests. Throughout the duration of the experiment, participants were asked to maintain their normal exercise and diet routines to ensure that these confounding variables remained constant throughout the trial. Self-reported daily exercise and diet records, starting 1 day before the first treadmill test and ending with the last blood collection of the second treadmill test, were maintained by the participants to monitor these behaviors. Participants avoided strenuous exercise 2 days before and 2 days after the testing period. Dietary analysis was performed using Nutritionist IV software (First DataBank, Hearst Corp., San Bruno, CA). Average daily energy intake in kilocalories (kcal), carbohydrate intake (g and kcal), and fat intake (g and kcal) were calculated from the diet records.

In a separate laboratory visit before exercise testing, body density was determined for each subject by hydrostatic weighing. Residual lung volume was measured by the use of a whole-body plethysmograph computerized system (1085-D, Medical Graphics Corp., St. Paul, MN, USA). Body composition was calculated using the Siri equation. Body mass index (BMI) was determined from the body mass and stature for each subject.

The MAX run consisted of a graded exercise test on a motorized treadmill (Q-65, Quinton Instruments Co., Bothell, WA) with increases in work occurring in 2-min increments. The first three stages were at 0% grade with increasing speed until the desired speed was attained. This speed was chosen based on the individual's reported normal training pace. Once the desired running pace was achieved, increase in work intensity was obtained by increasing the treadmill grade. The completion of the test was at the participant's volitional exhaustion.

The endurance test was a 60-min run conducted on the treadmill at a workload corresponding to approximately 70% of the participant's maximal oxygen consumption, as determined by the MAX test. Grade was set at either 0% or 1% to elicit the desired intensity. For both MAX and END tests, respiratory gases were collected for the first 10 min of the exercise session and for 5 min at 25 and 55 min into the exercise session to assure a steady state condition. Oxygen consumption was approximately 70% of maximal oxygen uptake throughout the entire test. Respiratory gases were collected and analyzed for both exercise sessions with MedGraphics CPX-D metabolic cart (Medical Graphics Corp.). Total energy expenditure and carbohydrate and lipid oxidation rates for END were calculated by indirect calorimetry from oxygen consumed and carbon dioxide produced using standard tables, assuming the respiratory exchange ratio is equal to the non-protein respiratory quotient. The goal energy expenditure for the endurance run was 900 cal. Total energy expenditure from MAX was estimated by using the factor 5.0 kcal/L oxygen because this test was conducted at non–steady-state conditions.

For each running session, blood was drawn from an antecubital vein (and collected in two 7-mL heparinized vaccutainers) immediately before and immediately after exercise, and at 24 and 48 h postexercise. All subjects were asked to maintain a 12-h fast before each blood draw. Blood samples were centrifuged (4°C at 1700 × *g* for 12 min) and plasma was collected and frozen at −20°C until blood assays were conducted. Hematocrit and hemoglobin levels were measured to allow for corrections in hemoconcentration differences that may occur due to the exercise session.

Plasma leptin and insulin concentrations were measured using radioimmunoassay kits from Linco Research (St. Charles, MO, USA) and ICN Biomedicals (Costa Mesa, CA, USA), respectively. All samples were analyzed within the same assay for the hormones. Glucose concentration was measured from plasma at each blood draw by the use of a glucose analyzer (YSI Model 2300 STAT PLUS, Yellow Springs Instrument Inc., Yellow Springs, OH, USA).

One-way repeated-measures analyses of variance (ANOVA) were used to examine changes in leptin, insulin, and glucose across the 48-h period for each exercise test (SPSS version 7.0, SPSS Inc., Chicago, IL, USA). The level of significance for all analyses was set at $P \leq 0.05$. Pairwise comparisons with a Bonferroni adjustment were conducted to reveal differences within the ANOVA. Pearson product moment correlations were calculated between leptin, insulin, and glucose to determine the relationship between leptin versus insulin and glucose for both exercise tests at similar times. Correlations were also conducted for the END run between leptin and total energy expenditure (kcal), fat used during the exercise session (g), and carbohydrate used during the exercise session (g). A paired samples *t* test found no difference between preexercise leptin concentrations for the two exercise bouts ($P > 0.05$). Therefore, data for this time period were pooled and the values were correlated with BMI, percent body fat, body mass, total energy intake (kcal), fat intake (g), and carbohydrate intake (g).

RESULTS

Mean body composition for the participants was 10.8% ± 1.5% fat (mean ± standard error of mean), ranging between 4.5% and 19.4%. Body mass was 74.5 ± 1.9 kg, ranging between 66.8 and 86.1 kg. BMI was 24.2 ± 0.7, ranging between 20.9 and 27.2. Maximal oxygen consumption was 57.8 ± 2.1 $mL \cdot kg^{-1} \cdot min^{-1}$, ranging between 50.3 and 69.2 $mL \cdot kg^{-1} \cdot min^{-1}$. Average daily dietary intake and exercise energy expenditure during the exercise sessions are found in Table I. We observed that total energy and macronutrient dietary intake were similar for participants across the individual recording days (data not shown), therefore for simplicity each individual's mean energy and macronutrient intake across the recording days were determined and only these results are presented. Approximately 60% of the calories came from carbohydrate and 25% from fat. Exercise logs indicated that par-

TABLE I.

AVERAGE DAILY DIETARY INTAKE AND EXERCISE ENERGY EXPENDITURE

Variables	Mean (SEM)	Range
Daily energy intake (kcal)	2130 (166)	1628–3167
Carbohydrate (g)	324 (24)	243–477
Fat (g)	56 (5)	36–79
Exercise energy expenditure (kcal)		
Maximum test	197.5 (11.8)	151.4–266.9
Endurance test	871.2 (14.5)	809.6–942.6
Carbohydrate (g)	146.2 (5.9)	110.8–170.5
Fat (g)	27.3 (2.1)	17.4–36.6

SEM, standard error of the mean.

ticipants maintained their normal exercise routines with little variation from day to day throughout the duration of the testing period (data not shown).

Energy expenditure was four and a half times greater during the END test compared with MAX. Relative exercise intensity during the endurance test was 69% ± 2% of maximum oxygen consumption with a mean respiratory exchange ratio 0.91. Based on this value, calculated energy usage during the END run was 614 kcal from carbohydrates and 257 kcal from fat.

Separate one-way repeated-measures ANOVAs were conducted for plasma leptin, insulin, and glucose concentrations across the blood collection times (preexercise, immediately postexercise, 24 h postexercise, and 48 h postexercise) for MAX and END (Table II). Leptin values were not significantly different across the four times for the MAX run. However, significant differences were found across time for the END run ($F[3,18] = 10.21$, $P \leq 0.05$). Post hoc analyses indicated that the preexercise and postexercise leptin values were significantly greater than 48 h postexercise. There was a trend ($P = 0.10$) for the preexercise leptin values to be greater than those measured at 24 h postexercise. There was no significant difference between leptin measurements taken preexercise and immediately postexercise.

For insulin, significant differences were found across the four time periods for both the MAX and END runs ($F[3,21] = 9.94$, $P < 0.05$, $F[3,24] = 4.76$, $P < 0.05$, respectively). Pairwise comparisons for the MAX test data indicated that there was a delayed decrease in insulin levels from the exercise session, and this difference became significant by 48 h postexercise, as insulin levels were significantly lower after the second day of exercise compared with either the pre- or immediately postexercise measurement. There was a trend for immediately postexercise levels to be greater than those at 24 h postexercise, but this difference failed to reach statistical significance ($P = 0.08$). A similar trend was also apparent for the END test with a delay in response observed. A significant decrease in insulin was observed at 24 h postexercise (but not 48 h postexercise) as compared with preexercise values.

Analyses showed that both the MAX and END exercise tests produced significant changes in blood glucose levels across the experiment ($F[3,24] = 26.53$, $P < 0.00$, $F[3,24] = 3.86$, $P < 0.05$, respectively). Post hoc analyses revealed that for MAX, glucose increased significantly during the exercise bout, but returned to preexercise values by 24 h and 48 h postexercise. Although the omnibus test was significant, post hoc comparisons did not reveal any significant differences between individual means for glucose during the endurance test.

Pearson product moment correlations were conducted between immediate postexercise, 24-h postexercise, and 48-h postexercise leptin values and total energy expenditure for both MAX and END tests, along with carbohydrates and fats used for the endurance test. Total energy expenditure for the END run was negatively correlated to leptin concentration at 24 h ($r = -0.746$, $P = 0.021$) and 48 h postexercise ($r = -0.824$, $P = 0.006$). No other correlations for either MAX or END exercise sessions were significant. In addition, correlational analyses of leptin with insulin and glucose were performed for both MAX and END tests. There were no statistically significant correlations for similar times for either leptin and insulin or leptin and glucose.

Because the paired samples *t* test showed no significant difference between the preexercise leptin values for MAX and END ($t[8] = -0.138$, $P > 0.05$), leptin values were pooled and the mean preexercise leptin concentration, 3.47 ng/mL (SEM = 0.51), was used for correlation analyses of body fat, body mass, BMI, and dietary intake. A significant correlation was observed between preexercise leptin and percent body fat ($r = 0.900$, $P = 0.001$) and weight ($r = 0.68$, $P = 0.044$). There were no significant correlations between preexercise leptin levels and dietary variables, including total energy intake, carbohydrate intake, and fat intake.

DISCUSSION

As hypothesized, this research study provides evidence that a 1-h duration, moderate intensity exercise bout that expends ~900 kcal decreases plasma concentrations of leptin over a 48-h period. In contrast, a short-duration, maximal test that expends ~200 kcal had no apparent effect on plasma leptin. Although changes in plasma levels of insulin and glucose were also apparent from the exercise sessions, there were no correlations between these variables with plasma leptin levels. At 24 and 48 h after the END run, plasma leptin levels were lowered by 18% and 40%, respectively. This study did not examine whether these changes continue past

TABLE II.

PLASMA LEPTIN, INSULIN, AND GLUCOSE LEVELS FOR MAXIMUM AND ENDURANCE TESTS MEASURED AT DIFFERENT TIMES

	Leptin (ng/mL)		Insulin (IU/mL)		Glucose (mg/dL)	
Time period	Maximum	Endurance	Maximum	Endurance	Maximum	Endurance
Preexercise	3.5 (0.6)	3.1 (0.3)^{a}	11.2 (1.1)^{a}	8.9 (0.9)^{a}	72.7 (6.3)^{b}	86.4 (1.8)
Postexercise	3.3 (0.7)	3.0 (0.3)^{a}	18.2 (2.7)^{a}	9.4 (1.8)^{ab}	131.5 (5.7)^{a}	99.6 (7.2)
24 h postexercise	3.1 (0.4)	2.5 (0.4)^{ab}	7.3 (2.1)^{ab}	4.2 (0.3)^{b}	78.0 (5.1)^{b}	79.2 (5.1)
48 h postexercise	3.3 (0.6)	2.2 (0.3)^{b}	5.3 (0.8)^{b}	8.5 (1.0)^{a}	68.8 (5.1)^{b}	80.5 (2.4)

Values are means (SEM). Means with different letter superscripts within a column are significantly different, $P \leq 0.05$.

48 h. Our results are in agreement with Essig et al.[21] and van Aggel Leijssen et al.,[22] who also observed significant decreases in plasma leptin 48 h after an exercise session. Essig and colleagues found a significant decrease in leptin at 48 h postexercise during the 1500- and 800-kcal exercise bouts. In addition, we evaluated a short-term strenuous exercise bout in which subjects expended approximately 200 kcal, to determine if a shorter-duration, high-intensity exercise would affect plasma leptin levels. Our study is unique in that a comparison was done investigating leptin responses to short-duration, high-intensity exercise and moderate intensity exercise for extended periods postexercise. These results suggest that the MAX test was not of sufficient energy expenditure or duration to alter leptin levels.

Our findings are consistent with other studies in which no significant changes in leptin levels were found during either a short-duration exercise (10–12 min)[17,20] or a relative low-intensity exercise period (<50% of VO_2max).[19,20] However, these studies investigated this response only immediately postexercise[17,19] or 4 h after exercise.[20] By extending the follow-up period to 48 h postexercise, we have demonstrated that there is no delayed response in leptin levels with this type of exercise bout as observed with the longer duration exercise. A possible explanation for our findings is that high levels (≥800 kcal) of energy expenditure may be needed to elicit changes in leptin levels. It could be postulated that this level of energy expenditure may be necessary to elicit an, as of yet, unidentified neural or hormonal signal that depresses leptin synthesis. Alternatively, mobilization of non-esterified fatty acids from adipose tissue for use as an energy substrate may be a controlling factor in leptin levels, consistent with results from van Aggel-Leijssen and colleagues.[22] Additional research would help determine the level of energy expenditure or metabolic response from the exercise that alters plasma leptin. This information could be valuable in understanding mechanisms underlying its control and consequential effects on energy balance in the body.

The delayed decrease in plasma leptin observed with the END run has been confirmed by others.[21,22] Furthermore, the observation that plasma leptin levels were not affected immediately after exercise is consistent with many other studies.[16–20] However, an extended exercise bout, consisting of a 36-h, 101-mile run, was shown to decrease plasma leptin values by 33% immediately postexercise.[18] In that study, leptin was still 16% lower from baseline values at 18–24 h after the race. Similarly, in our study leptin values were 18% lower 24 h after the endurance exercise in comparison with preexercise values, although the difference was not statistically significant. No other studies have replicated these rapid responses observed by Landt et al.[18]; nor has any other study had participants exercise at this level.

Wisse et al.[15] provided evidence that leptin may be closely regulated to glucose utilization by the adipocytes. Although it is recognized that exercise more closely reflects glucose use by muscle cells, it could be argued that exercise shifts glucose utilization by the adipose tissue to the muscle cells. Thereby exercise may indirectly affect glucose metabolism in adipocytes. Although we did not look at glucose use by either adipose or muscle tissue in this study, it was of interest to determine if changes in glycemia are related to the decrease in leptin after exercise. We did find that neither plasma glucose nor insulin changes were correlated with plasma leptin levels. It has been documented that acute rises in glucose or insulin in women have no significant correlation with serum leptin levels.[23] Thus, it is not surprising that the acute changes with insulin and glucose during the exercise had no significant relationship with plasma leptin levels, even though the genders differ between our study and that of Ryan and Elahi.[23] The continued decrease in leptin at 48 h postexercise after the 60-min, moderate-intensity run further suggests that factors other than insulin might influence leptin levels, because changes in insulin levels were not apparent at this later time point. These other mechanisms may include total or rate of energy expenditure, other hormones, or energy substrates. Consistent with this hypothesis, van Aggel-Leijssen and colleagues[22] observed that changes in leptin levels 24 h postexercise, fasting, and overfeeding were most highly correlated with non-esterified fatty acid levels and glucose, but not insulin.

Alternatively, it could be argued that the leptin response following the END run may be due to changes in the body's energy balance. Van Aggel-Leijessen and colleagues[22] found a significant decrease in leptin levels with exercise in subjects only when they were maintained in energy balance, with no change in leptin when subjects were in negative energy balance. Based on these findings, it may be suggested that the decrease in leptin is not likely the result of a negative energy balance created by exercise, but may be related to other exercise-induced changes. We did not examine energy balance in this study. However, further studies that control for energy balance may be warranted. Furthermore, it was also found that exercising with a positive energy balance condition over 24 h caused an increase in the amplitude of the 24-h plasma leptin curve, thereby thwarting the decrease in leptin caused by exercise.[22]

Leptin levels at 24 and 48 h postexercise were negatively correlated to exercise energy, with higher energy expenditure associated with lower leptin levels. The lack of correlation between the amount of fat used and plasma leptin level indicates that fat metabolism due to the exercise test is not related to postexercise decreases in leptin. Subjects oxidized an average of 28 g of fat during the endurance test.

These findings are significant because they address how different exercise intensities affect leptin response. Obese individuals have been shown to have high levels of plasma leptin.[6] Although this study did not measure leptin response to exercise in obese individuals, it could be extrapolated that exercise could be an important component in decreasing leptin levels in individuals who are obese. Additionally, many obese individuals are resistant to leptin's actions, which is hypothesized to result from an insensitivity of receptors to leptin because of hyperleptinemia, similar to non–insulin-dependent diabetics who are insensitive to insulin. Exercise could potentially be beneficial in treating this problem. The decrease in leptin concentration that is caused by an exercise bout could increase the effectiveness of these receptors, thus allowing the leptin to function in a typical manner. Thus, with a better understanding of the impact of exercise on leptin concentration, we have a more precise idea about the prevention and treatment of obesity.

Several limitations exist in this study. The small sample size introduces low power into the analyses. All subjects were healthy, active men, thus, the findings cannot be generalized to other populations. This study did not consist of a control group nor did it control for factors such as differences in diet or exercise between individuals. Lastly, it is not clear from this study if the exercise bout in itself caused the changes in plasma leptin levels or if it was a result of changes in energy balance. This area needs to be researched more to define the type of exercise, the intensity, the effect of energy balance, and how long the decrease in leptin occurs.

In summary, the findings from this study indicate that the type of exercise affects the leptin response. A long-duration, moderate-intensity bout of exercise expending 900 kcal causes a decrease in plasma leptin concentration for up to 2 d postexercise, whereas a short-duration, maximal-intensity exercise bout (~200 kcal) shows no effect. The lack of a correlation with plasma insulin suggests that this hormone does not play a role in the leptin changes after exercise. These findings and those of van Aggel-Leijssen and colleagues[22] give some indication that the exercise bout may have a significant effect on plasma leptin levels independent of the effects of exercise on energy balance; however, more research needs to be conducted in this area.

CONCLUSION

Long-duration, moderate-intensity exercise decreases plasma leptin concentration with a delayed response (48 h postexercise), whereas a short-duration, maximal-intensity exercise bout (~200 kcal) had no effect on leptin levels. No correlation was found between leptin and insulin or glucose, indicating that they are not involved in the regulation of leptin at these time points in lean, healthy men.

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(For an additional perspective, see Editorial Opinions)