Delayed Effects of Exercise on the Plasma Leptin Concentration

David A. Essig, Nathan L. Alderson, Michael A. Ferguson, William P. Bartoli, and J. Larry Durstine

Recent studies have concluded that a single exercise session has no immediate effect on the plasma concentration of leptin, a putative satiety factor. We tested the hypothesis that an increase in energy expenditure would decrease the leptin concentration but the effects would be manifest in a 48-hour period following exercise. Eleven active males completed two treadmill exercise sessions with different energy expenditure (800 or 1,500 kcal) at 70% maximal O_2 consumption ($\dot{V}O_{2max}$). Subjects maintained constant energy intake on the day before, the day of, and 2 days after exercise, as verified by dietary recall. Compared with preexercise in either exercise session, there were no differences in plasma leptin concentrations following exercise (0 and 24 hours postexercise) except at 48 hours postexercise, where an approximately 30% decrease ($P < .05$) was observed. With either duration of exercise, plasma glucose increased about 10% ($P < .05$), insulin decreased 35% to 46% ($P < .05$), and cortisol increased 41% to 50% ($P < .05$, 1,500 kcal only) immediately following exercise, but returned to preexercise values at 24 and 48 hours postexercise. A statistically significant correlation was observed between the changes in leptin and insulin ($r = .49$, $P < .0001$). Single exercise sessions of varying energy expenditure decreased the plasma leptin concentration after 48 hours in association with a preceding decrease in insulin.

LEPTIN is an adipocyte-specific hormone that is hypothesized to communicate with the brain regarding the amount of adipose tissue in the body. There is a positive relationship in humans between the adipose tissue mass and plasma leptin concentration. This relationship holds across a wide range of body fat percentage, from massively obese to extremely lean individuals.[1,2] Leptin production is also influenced acutely by wide fluctuations in energy intake. In both humans and rodents, serum leptin levels decrease dramatically with short-term fasting and increase with prolonged overfeeding.[3-6] The observation that energy intake regulates the plasma leptin concentration suggested that acute or chronic changes in energy expenditure may also influence leptin levels.

In the past 2 years, several groups have tested the hypothesis that increasing the energy expenditure via exercise will lead to a decrease in plasma leptin, but the results have been equivocal. In the majority of these investigations, plasma leptin was unchanged immediately following either a single exercise session consisting of a 10-minute maximal exercise test,[7] 2- to 2.5-hour treadmill run at 70% maximal O_2 consumption ($\dot{V}O_{2max}$),[2] 1-hour cycling test at 50% $\dot{V}O_{2max}$,[8] 2-hour cycling test at 75% $\dot{V}O_{2max}$,[9] or a 3-hour run.[2] In a 1997 editorial, Considine[10] suggested that energy expenditure via exercise may not alter serum leptin levels except perhaps at the very extremes of energy expenditure. This was later confirmed in a report by Landt et al[9] in which subjects who participated in a 101-mile ultramarathon (36 hours) showed a 32% decrease in plasma leptin immediately following the event. On the other hand, two recent studies have reported small but significant decreases in leptin immediately following either a 3.5-hour marathon run[10] or a 2-hour treadmill running session.[11]

One explanation for the lack of change in the leptin concentration noted in many studies was provided by Hickey et al.[2] They suggested that the lack of change in circulating leptin immediately following shorter-term exercise does not preclude the possibility of a delayed effect that may be manifested following exercise. The delay may correspond to the time required to observe a decrease in plasma leptin after a decrease in leptin gene expression in the adipocyte or the energy balance of the subjects prior to exercise. Consistent with this hypothesis, Tuominen et al[12] measured plasma leptin at a single time point 44 hours following a 2-hour treadmill exercise session at 70% $\dot{V}O_{2max}$ and observed a 34% decrease. These findings indicate that the leptin concentration may change in concert with alterations in fuel homeostasis during recovery from increased energy expenditure.

The purpose of the present study was to make repeated measurements of the leptin concentration during a 48-hour period following a period of increased energy expenditure. We determined the effects of two submaximal treadmill-running exercise sessions (800 or 1,500 kcal) on the plasma leptin concentration measured 0, 24, and 48 hours after the conclusion of each session. Subjects maintained a constant energy intake on the day before, the day of, and 2 days after exercise, as verified by dietary recall. To uncover possible mechanisms to account for the changes in leptin levels following exercise, we also determined the time course of changes in insulin, cortisol, and glucose.

SUBJECTS AND METHODS

Subjects

Eleven moderately trained men aged 21 to 44 years were recruited. Moderate training was defined as participation in regular structured exercise 3 to 5 times per week (>90 minutes weekly). All potential subjects were informed about the experimental procedures and provided written consent in accordance with the Human Subjects Review Committee, School of Public Health, University of South Carolina. The present study was a component of another experiment and used the same design and subjects. A detailed description of these subjects including age, height, weight, percent body fat, and $\dot{V}O_{2max}$ has already been presented.[13]

Experimental Design

Each subject completed 4 randomized and counterbalanced treadmill-running exercise sessions at 70% $\dot{V}O_{2max}$ with caloric expenditures of

From the Department of Exercise Science, School of Public Health, University of South Carolina, Columbia, SC; and Department of Biology, Geneva College, Beaver Falls, PA.

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Address reprint requests to J. Larry Durstine, PhD, Department of Exercise Science, University of South Carolina, 1300 Wheat St, Columbia, SC 29208.

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800, 1,100, 1,300, and 1,500 kcal as previously described.[13] For this experiment, data were obtained from the 800- and 1,500-kcal sessions. Each exercise protocol was completed at least 2 weeks apart. Venous blood samples were collected in EDTA vacutainers following a 12-hour fast at time points corresponding to 24 hours before exercise (24 hours preexercise), immediately before (0 hours preexercise) and immediately after (0 hours postexercise) exercise, and 24 (24 hours postexercise) and 48 hours after exercise (48 hours postexercise). All subjects refrained from exercise for 24 hours before blood collection. To minimize diurnal variation in plasma leptin concentrations, all blood samples were collected at the same time of day.

Dietary Analysis

Subjects were asked to consume the same diet over each of the experimental periods. They completed diet diaries for a total of 4 days, including 1 day prior to exercise, the day of exercise, and the 2 days following exercise. To reinforce dietary compliance and to ensure that energy intake remained constant during the experimental protocol, feedback from the first dietary analysis was given to the subjects before the subsequent experimental exercise protocol. A commercially available software program (Nutritionist III; N-Squared Computing, Silverton, OR) was used to analyze total caloric intake, cholesterol, and dietary carbohydrate, fat, and protein content.

Blood Analysis

Leptin levels were measured by a human leptin radioimmunoassay (RIA) kit (HL-81K; Linco Research, St. Charles, MO). The assay limits of detection and linearity were 0.5 and 100 ng · mL^{-1}. The interassay and intraassay coefficient of variation was 4.3% and 2.9%, respectively. The plasma insulin concentration was measured by a human plasma insulin RIA kit (Diagnostic Products, Los Angeles, CA). Plasma glucocorticoid was determined by RIA (Diagnostic Products). The plasma glucose concentration was measured using the glucose oxidase procedure (Sigma, St Louis, MO). All samples for a particular variable were analyzed on the same day in the same assay to minimize interassay variation. Hormone concentrations were adjusted[14] for plasma volume changes following the exercise sessions as described in Ferguson et al.[13]

Statistical Analysis

Differences in plasma leptin and dietary variables within treatments were analyzed with a 1-way ANOVA with repeated measures. Tukey's post hoc analysis was used when appropriate. Correlation analyses were performed using the Pearson product moment. Statistical significance was set at a P level less than .05. All analyses were made with PC-SAS software (SAS Institute, Cary, NC).

RESULTS

There were no significant changes in any dietary variables examined over the 4-day exercise period for either the 800- or 1,500-kcal trial (Table 1). In particular, the mean value for energy intake remained the same on the 2 days (day 3 and day 4) following exercise as on the day prior to exercise (day 1) and the day of exercise (day 2). This was an important finding because it permitted us to dissect the effects of increased energy expenditure independently of energy intake.

The effects of 800- or 1500-kcal exercise on circulating levels of leptin, glucose, and insulin are presented in Table 2. For each variable measured 24 h or 0 hours prior to a given exercise session (800 or 1,500 kcal), the mean values were not significantly different and were combined into a single "preexercise" group. The overall pattern of change in plasma leptin was a gradual decline that appeared approximately 24 hours postexercise. Immediately following either 800 or 1,500 kcal of energy expenditure, plasma leptin levels were unchanged ($P > .05$) compared with preexercise values. At the 24-hour postexercise time point, leptin concentrations were 8% and 15% lower in the 800- and 1,500-kcal groups, respectively, compared with preexercise values. However, only in the 1,500-kcal group did the difference begin to approach significance ($P = .097$). On the other hand, after 48 hours of recovery, plasma leptin concentrations were about 30% less than preexercise values ($P < .05$) following either 800 or 1,500 kcal energy expenditure. In general, the largest decreases in leptin during recovery were found in subjects with the highest preexercise leptin value (data not shown).

Plasma indices of glucose metabolism were measured in parallel with the assay of plasma leptin. Exercise at either 800 or 1,500 kcal energy expenditure had a mild hyperglycemic effect as observed previously.[15,16] For example, immediately following the 800-kcal exercise session, plasma glucose increased 9% from 77.6 ± 1.3 to 85 ± 1.7 mg/dL ($P < .05$). Plasma glucose decreased thereafter at 24 and 48 hours postexercise to concentrations that were not different from the preexercise value. Immediately following the 800- and 1,500-kcal exercise sessions, plasma insulin significantly ($P < .05$) decreased 39% and 50%, respectively, compared with the preexercise concentration. Between 0 and 24 hours postexercise, plasma insulin increased to values that were not different from the preexercise concentration and then remained at these levels through 48 hours of recovery. Plasma cortisol increased following the 800- and 1,500-kcal sessions by about 50%, but only reached statistical significance in the 1,500-kcal session. Thereafter, cortisol decreased to the preexercise value at the 24- and 48-hour postexercise time points.

Table 1. Dietary Intake and Composition

Session (kcal expended)	Day	Energy (kcal)	Carbohydrate (%)	Fat (%)	Protein (%)	Cholesterol (mg)
800	1	2,205 ± 230	55 ± 3	26 ± 2	19 ± 2	226 ± 45
	2	2,402 ± 191	60 ± 4	23 ± 4	17 ± 1	248 ± 60
	3	2,355 ± 319	59 ± 4	25 ± 3	17 ± 2	181 ± 25
	4	2,325 ± 160	56 ± 3	25 ± 3	19 ± 1	289 ± 92
1,500	1	2,463 ± 194	55 ± 3	28 ± 3	17 ± 1	355 ± 72
	2	2,592 ± 451	60 ± 3	23 ± 3	18 ± 1	272 ± 85
	3	2,312 ± 351	62 ± 2	23 ± 2	15 ± 2	177 ± 31
	4	2,366 ± 330	56 ± 4	25 ± 3	18 ± 2	216 ± 31

NOTE. Values are the mean ± SE (n = 11 subjects). There were no significant differences within or between sessions. Data are from Ferguson et al.[13]

Table 2. Plasma Leptin, Glucose, Insulin, and Cortisol Concentrations Before and During Recovery From Exercise Sessions of Varying Energy Expenditure

Variable	Preexercise	Postexercise		
		0 h	24 h	48 h
Leptin (ng/mL)				
800	2.6 ± 0.5	2.5 ± 0.4	2.4 ± 0.3	2.0 ± 0.3*
1,500	2.7 ± 0.5	2.9 ± 0.6	2.3 ± 0.4	2.1 ± 0.3*
Glucose (mg/dL)				
800	77.6 ± 2.3	85.0 ± 1.7*	79.5 ± 1.9	79.1 ± 2.1
1,500	80.2 ± 1.4	88.5 ± 1.4*	80.6 ± 2.5	79.8 ± 1.7
Insulin (μU/mL)				
800	28.0 ± 7.3	17.7 ± 4.1*	24.2 ± 4.6	22.1 ± 4.6
1,500	28.3 ± 5.9	15.4 ± 5.3*	29.2 ± 7.0	22.4 ± 5.6
Cortisol (μg/dL)				
800	16.8 ± 2.6	24.7 ± 6.0	14.7 ± 1.8	16.5 ± 2.3
1,500	19.4 ± 3.0	29.7 ± 3.8*	16.3 ± 2.5	16.0 ± 2.0

NOTE. Values are the mean ± SE. Values for leptin, insulin, and cortisol are corrected for plasma volume shifts.

*$P < .05$ *v* preexercise.

The observed variation in plasma leptin at rest (preexercise) was tested for possible correlations with variables measured in this study and previously in the same subjects in another study.[13] In resting subjects (preexercise values: 24 hours preexercise and 0 hours preexercise), plasma insulin ($r = .34$, $P < .05$) and plasma triglyceride ($r = .42$, $P < .005$) showed statistically significant correlations with the plasma leptin concentration. The percent body fat was also positively correlated with the plasma leptin concentration ($r = .45$, $P < .01$). Relative $\dot{V}O_{2max}$ (mL/kg/min) was negatively correlated with plasma leptin ($r = -.50$, $P < .05$), while $\dot{V}O_{2max}$ expressed per liter or relative to lean body mass showed no relationship to plasma leptin at rest. There were no significant correlations for the resting plasma leptin concentration and age, waist to hip ratio, body mass index, plasma glucose, plasma cortisol, or any of the dietary intake variables measured.

Changes in the leptin concentration following increased energy expenditure (0, 24, and 48 hours postexercise) were tested for correlations with a number of variables. For these correlations, data from both exercise sessions were combined, since there were no intergroup differences for any variable measured at any time point. There was a modest but highly significant correlation between the change in the leptin concentration and the circulating level of insulin ($r = .49$, $P < .0001$). On the other hand, no significant correlations were observed between changes in the leptin concentration and plasma glucose, plasma cortisol, or triglyceride concentrations or any of the dietary variables previously measured in the same subjects.[13]

DISCUSSION

Acute Energy Expenditure and Plasma Leptin

Energy expenditures of either 800 or 1,500 kcal did not change plasma leptin immediately postexercise, but had a delayed depressive effect on plasma leptin in the period between 24 and 48 hours postexercise. Our findings confirm other studies with regard to the lack of change in the leptin concentration immediately after exercise[2,7,9] and the small but significant decline in leptin about 48 hours postexercise.[12] The data represent the first time-course analysis of the leptin concentration following an increase in energy expenditure. The results highlight a potentially important time delay in the response of leptin following energy expenditure. The results of a dietary recall analysis performed during the course of this study suggest that the changes in leptin during recovery were not due to a change in energy intake. Energy intake in the subjects as measured by dietary recall was not different over the entire 4-day experimental period (24 hours preexercise, 0 hours preexercise, 24 hours postexercise, and 48 hours postexercise) for either exercise session (Table 2). Another variable that may have affected a decrease in leptin unrelated to energy expenditure is a decrease in fat cell mass. Although the percent body fat in our subjects appeared to be a factor in determining basal levels of leptin, it is difficult to envision that sufficient changes in body fat mass could occur over a 2-day period to cause the decrease in leptin concentration. Hence, in the absence of changes in energy intake and apparent changes in body fat mass, we maintain that increased energy expenditure caused by exercise was the major reason for the decrease in the leptin concentration observed during recovery.

The relative decreases in the leptin concentration during recovery were apparently independent of the total energy expenditure during the exercise sessions. While it is tempting to speculate that there should be a difference, the variability in resting leptin levels may complicate the measurement of the effect. A major factor determining basal leptin levels is the total fat mass, as shown by the correlation in this study and others.[1] In addition, the fitness level measured by $\dot{V}O_{2max}$ expressed per body mass was inversely related to resting leptin levels.[12] Hence, it may be easier to detect a decline in subjects with relatively high leptin levels than in subjects with low leptin levels that approach the sensitivity limits of the assay. Future studies may need to use wider variations in energy expenditure and a larger number of subjects with similar body composition and fitness to test whether the decline in leptin may be dependent on energy expenditure.

The reasons for the delayed decrease in plasma leptin were not immediately apparent from the results of this study. Given the function of leptin as a satiety factor, the timing for a decline in leptin must be related to the onset of the deficit in energy supply relative to demand. In the present study, we instructed the subjects to maintain their normal eating habits over the 4-day period. This was verified by the dietary recall records after each exercise session (Table 1). It is entirely possible that our subjects refrained from eating the extra food during the recovery period that would be necessary to completely offset the energy expended during exercise. Hence, the energy deficit may have occurred after the cessation of exercise. A second reason may relate to the nature of the exercise session and/or the degree to which subjects were fasted prior to exercise. A recent study by Koistinen et al[17] observed a decrease in leptin levels immediately after 3 hours of cycling. This finding is in contrast to the present study and others.[2,7,9] However, it is noteworthy that subjects in the study by Koistinen et al[17] showed a hypoglycemic response to exercise, whereas our subjects had a hyperglycemic response. A previous investigation has shown that when glucose is infused during fasting, the decline in leptin

is inhibited.[5] Hence, the hyperglycemic effect observed in our subjects may have provided a counterbalancing effect to an impending decline in leptin. In short, the timing for the decline in leptin may be related to the integration of factors regulating both energy intake and the amount of fuel used during energy expenditure.

Mediators of Plasma Leptin Concentration Following Exercise

Immediately following exercise, plasma insulin was depressed and then increased to the control value during the first 24 hours of recovery. This transient decline in the insulin level preceded any significant decline in the plasma leptin concentration. Since elevated insulin levels have been shown to stimulate the plasma leptin concentration,[2,5,18,19] a reduction in insulin levels during exercise or recovery from exercise might signal a temporary reduction in the synthesis/release of leptin from the adipocyte, resulting in lower plasma levels. However, it should be noted that the acute stimulatory effects of insulin on leptin are somewhat controversial.[19] Other studies indicate that the effects of insulin on leptin are observed only after 6 to 24 hours of hyperinsulinema and may be concomitant with changes in fat mass.[20,21] Hence, establishing the significance of the association between insulin and leptin levels following exercise must await future investigation.

Other circulating hormones singly or in combination could also regulate the leptin level following energy expenditure. Adipocyte leptin synthesis may have been suppressed through increases in adrenal or sympathetic nerve–derived norepinephrine. Sympathetic stimulation via injection of adrenoceptor agonists with a dramatic reduction of leptin expression in white adipose tissue in mice[22,23] and humans[24] has been shown. Endurance exercise results in an increase of norepinephrine and epinephrine release,[25] and residual hormone/neurotransmitter may slowly decrease during recovery. Leptin synthesis has also been shown to be diminished by increased levels of testosterone.[26] During prolonged submaximal exercise, circulating levels of testosterone have been shown to increase.[27] Hence, it is also possible that exercise-induced increases in testosterone may have suppressed the leptin concentration following exercise. The degree to which leptin levels were depressed by adrenergic or androgenic hormones may have been tempered by the increases in growth hormone and cortisol that accompany exercise of this duration.[28] Both of these hormones stimulate plasma leptin levels when infused in intact humans.[29]

A Role for Leptin During Exercise Recovery?

Given the apparent effects of exercise on leptin levels in plasma, the question arises as to what might be the potential function of leptin during recovery. A decrease in leptin may facilitate the restoration of body fuel homeostasis during recovery from periods of increased energy expenditure.[12] Low leptin levels after exercise may stimulate food intake, as well as repletion of energy stores in muscle fibers recruited during exercise. Leptin receptors have been found to be expressed in muscle tissue,[30] and elevated leptin levels shift muscle metabolism away from free fatty acid esterification toward oxidation.[31,32] Hence, lower leptin concentrations may permit a greater level of free fatty acid storage as triglyceride. The effects of leptin on glucose metabolism are less clear. Leptin inhibited glycogen resynthesis in isolated soleus muscle from obese (ob/ob) mice,[30] but had no effect on soleus muscle from wild-type mice.[30,31]

Summary

Our results indicate that 800 or 1,500 kcal energy expenditure had a depressive effect on the concentration of plasma leptin that was not evident until 48 hours postexercise. The percentage decline in leptin was similar at both energy expenditures. A decline in insulin, a known inducer of leptin expression in adipocytes, occurred prior to the observed decrease in leptin and may have mediated the decline in leptin concentration. Lower circulating levels of leptin may facilitate the restoration of energy homeostasis following periods of increased energy expenditure.

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