MINIREVIEW

Leptin and Exercise

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Short-term exercise (<60 min) studies suggest that leptin concentrations are not acutely affected in healthy males and females. Most reports of reductions in serum leptin may be attributed to circadian rhythms or hemoconcentration. For long-term (≥60 min) exercise, a reduction in leptin concentrations reported from 1 to 3 hr of running or cycling has been attributed to diurnal reduction in circulating leptin, independent of exercise. Exercise that produces a sufficient energy imbalance (kilocalorie intake versus kilocalorie expenditure) suppresses 24-hr mean and amplitude of the diurnal rhythm of leptin in women. Suppression of leptin concentrations may be counterbalanced by feeding and may explain consistent reports of reductions in leptin concentrations following extreme bouts of exercise such as marathons or ultramarathons. In addition, leptin concentrations are reduced 48 hr after long-term aerobic exercise and long-term resistance exercise is associated with delayed leptin reduction 9 hr postexercise. Training studies have documented that short-term exercise training (≤12 weeks) does not affect leptin levels, with the exception of patients with type 2 diabetes. Exercise training protocols that result in reduced fat mass will lower leptin concentrations, thus, most investigators have reported leptin concentrations after accounting for fat loss. There are disparate findings concerning long-term (>12 weeks) training studies, with a number of studies finding no effect of training on leptin concentrations other than effects induced by fat loss, and other studies finding reductions in leptin concentrations after accounting for fat loss. Exercise training-induced reductions in leptin levels have been attributed to alterations in energy balance, improvements in insulin sensitivity, alterations in lipid metabolism, and unknown factors. Hormone replacement does not seem to affect leptin adaptations to training. Patients with type 2 diabetes show delayed effects of short-term resistance exercise on leptin concentrations, reduced leptin levels with long-term training, and appear to be more sensitive to training-induced leptin adaptations than other populations. Exp Biol Med 227:701–708, 2002

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Leptin was discovered in 1994 following the isolation of the *ob* gene (1). Leptin, a protein with a helical structure similar to cytokines and a relative mass of 16 kDa (2), assists in the regulation of body weight and energy homeostasis (3, 4). Adipose tissue is the major source of leptin expression, however, other sites have been identified, including skeletal muscle, mammary epithelium, the placenta, and the brain (2). It is thought that a major role of leptin is to relay information to signal transducing receptors in the hypothalamus concerning the status of energy stores (5, 6) and thus aid in reduced feeding (3, 4). The discovery of leptin has led to numerous experiments to better understand its function, and a portion of those studies have focused on leptin and exercise. In this minireview, we will summarize the role of leptin in energy balance and reproduction and we then discuss the existing prospective research concerning the effects of exercise on leptin in humans.

Leptin as a Regulator of Energy Balance

The leptin receptor (with long and short isoforms) is a member of the cytokine family of receptors and is expressed in a variety of tissues including the hypothalamic nuclei (7). Neurons in the arcuate, ventromedial, and dorsomedial hypothalamic nuclei that are sensitive to leptin express neuropeptides/neurotransmitters that are associated with central regulation of energy balance (2). Leptin receptor mutations cause early onset obesity in rodents and occur in humans, but are very rare (2, 8).

Leptin is regulated by the status of fat storage, with

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larger adipocytes containing more leptin than smaller ones in the same individual (9). Nutrition-related control of leptin has been suggested to be partially regulated by insulin. It has been demonstrated that leptin expression occurs after elevation of insulin in response to feeding (10), and a decline in leptin levels follows reduction in insulin during fasting (11). Some early studies reported no acute effect of eating on leptin concentrations, but later studies that controlled for fasting demonstrated that meals and insulin acutely affect leptin concentrations (12). Other hormones associated with the regulation of leptin that are altered by exercise include glucocorticoids, growth hormone, and catecholamines (13, 14). Growth hormone and cortisol have been shown to promote leptin production (15, 16), whereas catecholamines inhibit leptin production (17, 18).

Leptin as a Regulator of Reproductive Function

Gender influences leptin levels and may affect the status of reproduction. Leptin levels are higher in females than in males (19, 20). Higher leptin levels in females have been attributed to a number of factors, including stimulation by estrogens, inhibition by androgens, and fat-depot differences in leptin expression (2, 21). Interestingly, Maccario *et al.* (22) have reported that gender differences in growth hormone and leptin are abolished after a 36 hr fast. Increases in circulating levels of leptin are associated with the onset of menarche in girls (23). Leptin levels in normally cycling females are greater than in young males, even after accounting for differences in adiposity (19), and this holds true for males and females of older ages (24–26). Elevated leptin levels in hypogonadal males are reduced when testosterone is administered (27). Moreover, *in vitro* experiments using newly developed human adipocytes have demonstrated that testosterone and dihydrotestosterone, its biologically active metabolite, both suppress leptin secretion into the culture medium by as much as 62% (16). Finally, leptin expression is greater in subcutaneous than in visceral adipose tissue, and females have a greater amount of subcutaneous fat than males (2).

Effects of Exercise on Leptin

There are many investigations that have examined the effects of exercise on leptin. There are several reasons why leptin responses and adaptations to exercise may have important ramifications: exercise is known to effectively reduce obesity (fat mass), thus, if leptin levels are affected, this may provide some explanation of how exercise affects obesity; exercise (specifically, caloric expenditure leading to energy imbalance) may lead to reproductive dysfunction (28), and because leptin is associated with reproductive function, exercise-induced alterations in leptin may elucidate the mechanisms explaining effects of exercise on reproduction, such as the condition of exercise-induced amenorrhea; and exercise alters concentrations of certain hormones that may alter leptin concentrations, including insulin, cortisol, catecholamines, estrogen, testosterone, DHEA, and growth hormone (29–36). The ensuing sections will include a review of leptin responses to short-term exercise, followed by a discussion of responses to long-term exercise and training studies.

Acute Exercise and Leptin

Short-Term (<60 min) Exercise. Most studies that have investigated effects of short-term exercise on leptin have shown reductions or no change in leptin concentrations. Elias *et al.* (37) reported a decline in leptin concentrations in males (age 18–55) after a graded treadmill exercise test to exhaustion. The authors suggested that the decline may be associated with elevated production of nonesterfied fatty acids during exercise, which have previously been shown (38) to be inversely correlated with leptin levels. A control trial was not conducted in this study to determine whether diurnal changes accounted for observed reductions.

Fisher *et al.* (12) administered a standardized meal to subjects and observed increases in leptin during 41 min of cycling at 50% of the cycling intensity of VO_{2max}.This was followed by a reduction in leptin concentrations during recovery that increased to control values after 2 hr. Cortisol and epinephrine concentrations rose sharply during exercise, and epinephrine declined quickly after the exercise. Cortisol stimulates leptin expression, whereas epinephrine and norepinephrine inhibit leptin expression. It was hypothesized that large increases in cortisol concentrations would stimulate increases in leptin levels, but only a weak relationship between leptin and cortisol was found. However, the nutrient factors, glucose, insulin, and glucose × insulin, explained 86% of the variance in final leptin levels. The authors reported normalized leptin concentrations (using serum protein content) for plasma volume shifts and concluded that the short-term exercise-related changes are due to alterations in hemoconcentration rather than to leptin mass.

We have demonstrated that 30 min of exercise at 80% of VO_{2max} is associated with reduced leptin concentrations in postmenopausal females regardless of whether they are on or off hormone replacement therapy (HRT), but the reductions were due to the circadian rhythms of leptin as determined from control trial samples from the same subjects (14). Cortisol and growth hormone, both hormones that affect leptin concentrations, increased in these females in response to exercise (29, 34). It is possible that under certain exercise conditions, hormones that stimulate leptin expression (e.g., cortisol) are countered by hormones that inhibit leptin secretion (e.g., epinephrine), such that no alteration from these regulators is evident.

Weltman *et al.* (39) reported that 30 min of exercise at, above, and below lactate threshold, an index of accelerated metabolism and exercise intensity, did not alter leptin concentrations in young males during exercise or recovery (3.5 hr postexercise) compared with control values. In this study,

exercise intensity was not a factor in affecting leptin responses in young men.

We recently reported significant increases in leptin responses to a graded exercise test to exhaustion in young adolescent (14–16 years) runners over the course of a short track season (32). The increases in the study may have been due to hemoconcentration, which would have presented higher concentrations of leptin to the leptin receptors.

Thus, short-term (<60 min) exercise studies suggest that leptin production is not acutely effected by short-term exercise, regardless of exercise intensity, in healthy males and females. Reported reductions or increases can be attributed to circadian rhythms or hemoconcentration. It remains to be determined how hormones and metabolites that appear to stimulate (e.g., cortisol, insulin, and glucose) or inhibit (e.g., epinephrine and norepinephrine) leptin work together to prevent decline under some conditions but not in other conditions (12). Further work is also required to determine whether acute increases produced by hemoconcentration produce any effect on tissues. The absence of any reduction in leptin reported in short-term exercise study may be due to the limited energy expenditure of these exercise bouts or the protocol of these studies that excluded prolonged post exercise blood sampling (≤4 hr postexercise). As will be shown in the next section, when blood samples are collected 48 hr following long-term exercise, reductions in leptin are found.

Long-Term (≥60 min) Exercise. As for short-term exercise, long-term exercise studies have typically revealed no change or a decline in leptin following exercise. Racette *et al.* (40) measured arteriovenous differences in leptin concentrations from abdominal adipose tissue during 60 min of cycle ergometry exercise, and reported no change in leptin. Samples were not collected during recovery. Torjman *et al.* (41) measured leptin concentrations following 60 min of treadmill exercise at 50% of VO_{2max}. After leptin concentrations were corrected for hemoconcentration, they found no effect on leptin concentrations during a 4-hr recovery period. Trained males completing 60 min of running at approximately 70% of VO_{2max} showed leptin concentrations that were significantly lower 48 hr after the exercise compared with before, immediately after, and 24 hr after the exercise (42). The leptin responses did not appear to be related to changes in insulin or glucose concentrations. Blood samples were also collected from the same subjects after a short-term maximal exercise test, and leptin levels did not decline immediately after, or 24 or 48 hr postexercise. Essig *et al.* (43) reported lower leptin concentrations in trained males 48 hr after but not 0 and 24 hr after two separate exercise tests, an 800- and 1500-kcal treadmill run. The authors speculated that alterations in the leptin stimulators, growth hormone, cortisol, and insulin, as well as the leptin inhibitors testosterone, epinephrine, and norepinephrine, may have affected leptin concentrations. The above studies demonstrate that long-term exercise induces lower leptin concentrations, which is not seen at shorter intervals of recovery. Moreover, it suggests a need for determining the exact point at which delayed leptin reduction occurs. This would require greater sampling frequency than 24 and 48 hr.

Leptin responses to much longer durations of exercise have been examined. One of the first such studies investigated leptin responses of well-trained male runners to a 20-mile treadmill run at an intensity of 70% of VO_{2max} (44). No change in leptin concentrations were found after this extreme bout of exercise. One of the limitations of the study (and other studies to follow) was an infrequent blood sampling protocol. Duclos *et al.* (38) compared a 4-hr resting trial to a 2-hr run/2-hr resting trial in subjects that consumed a standardized meal 2-hr before exercise to control for fasting. There was a 30% reduction in postexercise resting leptin concentrations. The investigators reported significant inverse correlations between leptin and glycerol as well as free fatty acid levels, but no correlation with cortisol. Tuominen *et al.* (45) used a 4-hr euglycemic insulin clamp and muscle biopsies to study the effects of 2 hr of treadmill exercise at 75% of VO_{2max}. Exercise reduced leg muscle glycogen by 32% compared with the control clamp trial, and there was a 34% reduction in leptin concentrations. Serum leptin concentrations were reduced by glycogen-depleting exercise and were increased during a hyperinsulinemic clamp. Leptin concentrations correlated directly with serum insulin, cortisol, and triglycerides, and inversely with growth hormone concentrations. The authors concluded that leptin is associated with factors that govern fuel homeostasis.

Leal-Cerro *et al.* (46) controlled for circadian variations and reported a small reduction in leptin levels in males following a marathon (~26 miles, ~2800 kcals) and suggested the actual reduction was greater than measured reduction because hemoconcentration occurred during the marathon. The authors concluded that large changes in energy expenditure may regulate serum leptin concentrations. Karamouzis *et al.* (47) studied leptin responses following a 25 km sea swim and reported that lower leptin concentrations were associated with an 81% increase in plasma neuropeptide Y which is associated with energy regulation.

Landt *et al.* (48) reported an 8% reduction in fasting serum leptin concentrations following 2 hr of exercise that included cycling at ~75% of VO_{2max} and culminated with five 1-min cycle sprints. The reduction was similar to that of a control group that fasted an identical time period, attributing the exercise related decline to diurnal reduction. The same authors studied pre- and postleptin concentrations that were obtained from runners who completed an ultramarathon, a 101-mile race (average exercise time ~35 hr), and demonstrated a 32% decline in leptin. The authors suggested that the large reduction in leptin in the ultramarathoners was due to energy imbalance and that leptin may serve as an important signal of energy imbalance, but only at imbalance extremes.

In a well-controlled study by Hilton and Loucks (49),

effects of energy imbalance on leptin, energy intake and expenditure were carefully controlled in sedentary and exercising females, and blood sampling was completed over a 24-hr period to determine whether leptin circadian rhythm was altered. The authors found that low energy availability suppresses the 24-hr mean and amplitude of the diurnal rhythm of leptin; however, exercise had no impact on the diurnal rhythm of leptin in young females except for its effect on energy balance. The authors concluded that the diurnal rhythm of leptin depended on energy or carbohydrate availability. Previous studies have shown that secretion of leptin was inversely proportional to carbohydrate in the diet (50). The authors suggested that there is a reduction threshold of energy availability to change the dynamics of the diurnal rhythm of leptin. These observations suggest that leptin levels may be effected by the total exercise energy expenditure from increased metabolism during exercise as well as during recovery from exercise.

In an energy balance study of young males, van Agel-Leijssen *et al.* (51) showed that exercise decreased peak and average 24-hr leptin concentrations and that high physical activity in a positive energy-balanced state increases the amplitude of the 24-hr leptin concentrations. However, the negative energy-balance condition did not affect 24-hr leptin concentrations, initially suggesting a gender difference in effects of energy balance when examined with regard to the study of females by Hilton and Loucks (49). However, it should be noted that the there was a 28% negative energy condition in this study of males compared with a 78% reduction in energy intake in the study of females (49), which likely explains the different results.

Koistinen *et al.* (52) examined the effect of feeding before 3 hr of cycling exercise on leptin concentrations in healthy and type I diabetic males. The authors concluded that exercise may lower circulating leptin concentrations, however, the small reduction may be counterbalanced by feeding or an elevation in cortisol concentrations.

To summarize long-term (≥60 min) exercise effects on leptin, a reduction in leptin concentrations reported from 1 to 2 hr of running or cycling has been attributed to diurnal reduction in circulating leptin, independent of exercise. Very long bouts of exercise are more likely to reduce leptin levels, which is probably due to disruption of energy balance. The seminal work by Hilton and Loucks (49) and van Agel-Leijssen *et al.* (51), which represent the best well-controlled studies for energy balance to date, provide clear evidence of the importance of careful control for energy balance in leptin and exercise studies, and thus impinge on all work in this area. Exercise that produces a sufficient energy imbalance (kilocalorie intake versus kilocalorie expenditure) suppresses 24-hr mean and amplitude of the diurnal rhythm of leptin. Suppression of leptin concentrations may be counterbalanced by feeding. This appears to explain consistent reductions reported in leptin concentration after extreme bouts of exercise such as marathons or ultramarathons. In addition, long-term exercise (≥60 min) appears to be associated with reduced leptin concentrations 48 hr after exercise. The mechanism explaining these observations remains to be elucidated.

Leptin Levels Following Exercise Training

Short-Term (<12 weeks) Training. A number of studies have investigated the effects of training on leptin concentrations. These studies have tended to report either no effect of training on leptin concentrations with short-term training, unless the training was associated with fat loss, or a reduction in leptin levels beyond that accounted for by reduction in fat mass in long-term training studies. Houmard *et al.* (53) studied the effects of short-term (7 consecutive days) aerobic training (1 hr/day at 75% VO_{2max}) on leptin concentrations and insulin action in healthy young and older males. Although the training improved insulin sensitivity (determined by an i.v. glucose tolerance test), leptin concentrations were not effected.

Dirlewanger *et al.* (54) measured leptin concentrations after 3 days of no exercise and an isoenergetic diet; exercise (cycling for 30 min at 60% of VO_{2max}) twice daily with the same caloric intake as trial 1; and exercise with dietary intake to cover exercise energy expenditure. There were no changes in leptin concentrations in any of the trials. The authors reported that plasma leptin is unaltered by exercise or small changes in energy balance over short periods of time.

We have studied the effects of a 9-week training program on leptin concentrations of middle-age obese females (55). Training consisted of 3–4 days of exercise including 20–30 min of step aerobics 2 days per week and treadmill running or stationary cycling on additional days. Although cardiorespiratory fitness levels (VO_{2max}) increased after training, there were no changes in fat mass or leptin concentrations.

In a study of adolescent female runners, we measured resting and postmaximal exercise leptin concentrations over the course of a short track season (32). Resting leptin levels were not altered over the 7 weeks, nor were the acute responses to intense exercise.

Halle *et al.* (56) studied obese males with type 2 diabetes and reported that 1 month of cycling exercise combined with a low-caloric diet resulted in reduced body weight and leptin concentrations. The lower leptin concentrations were associated with reduced cholesterol and triglyceride levels, which was independent of improvements in glucose control. The authors suggested that the relationship between leptin and insulin might be indirectly due to elevated serum triglycerides or fatty acid concentrations. In a 6-week study of 50 sedentary subjects with type 2 diabetes, exercise training (low-intensity walking and cycling) coupled with diet therapy led to lower leptin concentrations independent of changes in body composition, insulin, or glucocorticoids (57). A group on diet therapy without exercise did not show reductions in leptin concentrations.

Long-Term (≥12 weeks) Training. Hickey *et al.* (20) reported significant reductions in fasting leptin levels in young females (mean age 29 y), but not young males (mean age 27 y) after aerobic exercise training, 4 days/wk, 30–45 min/day, for 12 weeks. These leptin reductions in females occurred in the absence of significant alterations in fat mass and results suggest that training has a greater effect on circulating leptin levels in females than in males. A study of obese children (24 girls and 10 boys) reported that after correction for loss of fat mass, leptin concentrations were lowered after 4 months of exercise training (exercise on machines and playing games), but that levels increased in a subsequent 4-month period without physical training (58). The authors speculated that the reduction in leptin concentrations were caused by changes in energy balance.

Middle-age obese males were trained (low to moderate exercise intensity, three to four times per week) and maintained a very low-energy diet for 4 months (59). The authors concluded that leptin concentrations were reduced from aerobic exercise training independent of changes in body fat and plasma insulin concentrations.

Okazaki *et al.* (60) examined the effects of mild aerobic exercise (50% VO_{2max}) and personal diet counseling for 12 weeks on fat loss and leptin concentrations in obese and nonobese middle-aged sedentary females. The ratio of leptin concentrations to fat mass and to body mass index (BMI) was reduced after the training. The authors suggested that reduced leptin concentrations were probably due to weight reduction and some unknown factor(s).

A large cohort of males with metabolic syndrome (elevated blood lipids, blood pressure, body composition, etc.) were divided into four treatment groups: diet, diet and exercise, exercise, and control (61). Exercise consisted of 60 min of fast walking, jogging, and circuit training three times per week for 1 year. The authors found that both diet and exercise were associated with reduced leptin concentrations beyond the reduction expected from changes in body fat. It was speculated that an improvement in insulin sensitivity could alter leptin concentrations.

Thong *et al.* (62) examined the independent effects of exercise and weight loss on sedentary males with upper body obesity. Subjects trained for 12 weeks with brisk walking or jogging. Alterations in leptin correlated with changes in both total and subcutaneous adipose tissue. The authors reported that independent of its effect on energy balance, exercise has little effect on leptin secretion.

Males and females with normal body composition were studied in a progressive training protocol of cycling three times per week for 20 weeks (63). Subjects were administered a mild exercise test before and after training in which they cycled for 10–12 min at a low intensity (50 W) and progressed to exhaustion. After adjusting for fat mass loss, resting leptin levels were not altered from training, nor were acute leptin responses to the exercise.

Noland *et al.* (64) measured leptin concentrations in young male and female intercollegiate swimmers across a competitive season. There were no changes in body fat for the males, but there was a reduction for the females with increased training volume. There were no changes in leptin in either group despite the fat loss in females. The authors speculated that no change in leptin with fat loss might be due to training-induced increases in cortisol with intense training.

Kohrt *et al.* (65) trained postmenopausal females on and off (HRT) first for 2 months with flexibility exercises, then 9 months with walking, jogging, and stair climbing. Regardless of HRT treatment, there were no independent effects of exercise on leptin levels other than the indirect effect of fat loss. In a related nonexercise study, we reported that when body composition is taken into account, estrogen treatment, either in young females receiving estrogen-progestin oral contraceptives or in postmenopausal females who are receiving HRT, does not affect serum leptin concentrations (19).

Thus, short-term exercise training (≤12 weeks) does not affect leptin levels, with the exception of patients with type 2 diabetes. Exercise training protocols that result in reduced fat mass will lower leptin concentrations, hence, most investigators have reported leptin concentrations after accounting for fat loss. There are disparate findings concerning long-term (>12 weeks) training studies, with a number of studies finding no effect of training on leptin concentrations other than effects induced by fat loss, and other studies finding reductions in leptin concentrations after accounting for fat loss. Exercise training-induced reductions in leptin levels have been attributed to alterations in energy balance, and glucoregulatory factors including improvements in insulin sensitivity, lipid metabolism, and unknown factors. Despite numerous studies and different protocols, mechanisms responsible for leptin regulation remain to be determined. Hormone replacement does not seem to affect leptin adaptations to training. Patients with type 2 diabetes show a reduction in leptin with long-term training and seem to be more sensitive to training-induced leptin adaptations than other populations.

Effects of Resistance Exercise on Leptin

There are three prospective studies that have examined the effects of resistance exercise (weight training) on leptin. Kanaley *et al.* (66) demonstrated a reduction in plasma leptin levels in type 2 diabetic patients ~24 hr following lower and upper body resistance exercises, whereas normal subjects did not show the same decline. The authors speculated that a reduction in glucose availability to adipocytes in the diabetic patients may have produced the different response. They also found no effect of chronic resistance training on leptin levels.

In a recent, carefully controlled study, Nindl *et al.* (67) measured leptin concentrations overnight following 50 total sets of resistance exercise including squats, bench press, leg press, and lat pull-down exercise. Leptin concentrations were lower compared to the control trial at 3 hourly time

points, 9, 12, and 13 hr following exercise. Estimated energy expenditure was considerable, averaging 856 kcal. These data, coupled with previous studies (e.g., 42, 43) suggest that exercise with energy cost ≥800 kcal produces delayed leptin reduction, however it was documented much earlier in this study compared with previous studies. The authors demonstrated the importance of determining leptin concentrations well after completion of the exercise.

Ryan *et al.* (68) studied effects of 16 weeks of resistance training in obese postmenopausal females with and without weight loss, on plasma leptin and insulin action. The resistance training increased fat-free mass and resting metabolic rate in combined data from both groups. Leptin concentrations declined by 36% in the group that lost weight. Changes in leptin levels were not related to alterations in resting metabolic rate or plasma catecholamines. However, the authors speculated that weight loss in the resistance training/weight loss subjects may have mediated increases in insulin action reported in the study.

Suggestions for Future Research

Although many studies have been published on the effects of exercise on leptin, numerous questions remain to be answered. There is a need to better define the relation of adiposity in both genders to leptin responses and adaptations to exercise. Future studies should also compare the effects of negative energy balance on leptin levels in males and females, and should better describe the effects of different degrees of fasting on leptin response to exercise. The work by Hilton and Loucks (49) and van Agel-Leijssen *et al.* (51), provide clear evidence of the importance of careful control for energy balance in future leptin and exercise studies. The evidence that leptin levels decline 9 hr after resistance exercise of substantial kcal expenditure (long-term) and 48 hr after long-term aerobic exercise suggests that there is a delayed reduction in leptin that may be due to energy imbalance. Thus, in order to determine the true dynamics of exercise-induced leptin responses, future studies should examine leptin concentrations for much longer periods after exercise. These studies should involve stringent controls for energy balance and more frequent sampling. Improved studies are also needed to examine other endocrine factors that may impinge on leptin regulation during exercise. Many studies have examined insulin and cortisol, but they leave other important regulatory factors unstudied. The use of hormone antagonists might be helpful in determining individual roles for specific hormones that regulate leptin. It would also be useful for future studies to examine the independent effect of alterations in lipid metabolism and glucose control on leptin concentrations to elucidate the mechanisms that explain the observed reductions in leptin from acute and chronic exercise. Finally, there is a need for more investigations to compare the effects of aerobic versus resistance exercise on leptin.

1. Zhang Y, Proenca R, Maffei M, Barone M, Lepold M, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature **373:**425–432, 1994.
2. Ahima RS, Flier JS. Adipose tissue as an endocrine organ. Trends Endocrinol Metab **11:**327–331, 2000.
3. Campfield LA, Smith FJ, Guisez Y, Devos R, Burn P. Recombinant mouse OB protein: evidence for a peripheral signal linking adiposity and central neural networks. Science **269:**546–549, 1995.
4. Pellymounter MA, Cullen MJ, Baker MB, Hecht R, Winters D, Boone T, Collins F. Effects of the obese gene product on body weight regulation in *ob/ob* mice. Science **269:**540–543, 1995.
5. Jequier E, Tappy L. Regulation of body weight in humans. Physiol Rev **79:**451–480, 1999.
6. Sihna MK, Caro JF. Clinical aspects of leptin. Vitam Horm **54:**1–30, 1998.
7. Friedman JM, Hallas JL. Leptin and the regulation of body weight in mammals. Nature **395:**763–773, 1998.
8. Clement K, Viasse C, Lahlou N, Cabrol S, Pelloux V, Cassuto D, Gourmelen M, Dina C, Chambaz J, Lacorte JM, Basdevant A, Bougneres P, Lebouc Y, Froguel P, Guy-Grand B. A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. Nature **392**(6674):330–331, 1998.
9. Hamilton BS, Paglia D, Lwan AYM, Dietel M. Increased obese mRNA expression in omental fat cells from massively obese humans. Nat Med **1:**953–956, 1995.
10. Saladin R, De Vos P, Guerre-Millo M, Leturque A, Girard J, Staels B, Auwerx J. Transient increase in obese gene expression after food intake or insulin administration. Nature **377:**527–529, 1995.
11. Boden G, Chen Z, Mozzoli M, Ryan I. Effect of fasting on serum leptin in normal human subjects. J Clin Endocrinol Metab **81:**3419–3423, 1996.
12. Fisher JS, Van Pelt RE, Zinder O, Landt M, Kohrt WM. Acute exercise effect on postabsorptive serum leptin. J Appl Physiol **91:**680–686, 2001.
13. Ahima RS, Flier JS. Leptin. Annu Rev Physiol **62:**413–437, 2000.
14. Kraemer RR, Johnson LG, Haltom RW, Hebert EP, Gimpel T, Castracane VD. Serum leptin concentrations in response to acute exercise in postmenopausal females with and without hormone replacement therapy. Proc Soc Exp Biol Med **221:**171–177, 1999.
15. Berneis K, Vosmeer S, Keller U. Effects of glucocorticoids and of growth hormone on serum concentrations in man. Eur J Endocrinol **135:**663–665, 1996.
16. Wabitsh M, Blum WF, Muche R, Braun M, Hube F, Rasher W, Eberhard H, Teller W, Hauner H. Contribution of androgens to the gender difference in leptin production in obese children and adolescents. J Clin Invest **100:**808–813, 1997.
17. Gettys TW, Harkness PJ, Watson PM. The β3-adrenergenic receptor inhibits insulin-stimulated leptin secretion from isolated rat adipocytes. Endocrinology **137:**4054–4057, 1996.
18. Carulli L, Ferrari S, Bertilini M, Tagliafico E, Del Rio G. Regulation of *ob* gene expression: evidence for epinephrine-induced suppression in human obesity. J Clin Endocrinol Metab **84:**3309–3312, 1999.
19. Castracane VD, Kraemer RR, Franken MA, Kraemer GR, Gimpel T. Serum leptin concentration in females: effect of age, obesity, and estrogen administration. Fertil Steril **70:**472–477, 1998.
20. Hickey MS, Houmard JA, Considine RV, Tyndall GL, Midgette JB, Gavigan KE, Weidner ML, McCammon MR, Israel RG, Caro JF. Gender-dependent effects of exercise training on serum leptin levels in humans. Am J Physiol Endocrinol Metab **272:**E562–566, 1997.
21. Rosenbaum M, Leibel RL. Clinical review 107: role of gonadal steroids in the sexual dimorphisms in body composition and circulating concentrations of leptin. J Clin Endocrinol Metab **84:**1784–1789, 1999.
22. Maccario M, Aimaretti G, Corneli G, Gauna C, Grottoli S, Bidlingmaier M, Strasburger CJ. Short-term fasting abolishes the sex-related

difference in GH and leptin secretion in humans. Am J Physiol Endocrinol Metab **279:**E411–E416, 2000.
23. Garcia-Mayor RV, Andrade MA, Rios M, Lage M, Dieguez C, Casanueva FF. Serum leptin levels in normal children: relationship to age, gender, body mass index, pituitary-gonadal hormones, and pubertal stage. J Clin Endocrinol Metab **82:**2849–2855, 1997.
24. Mantzoros CS. The role of leptin in human obesity and disease: a review of current evidence. Ann Intern Med **130:**671–680, 1999.
25. Karlsson C, Lindell K, Svensson E, Bergh C, Lind P, Billig H, Carlsson LMS, Carlsson B. Expression of functional leptin receptors in the human ovary. J Clin Endocrinol Metab **82:**4144–4148, 1997.
26. Agarwal SK, Vogel K, Weitsman SR, Magoffin DA. Leptin antagonizes the insulin-like growth factor-i augmentation of steroidogenesis in granulosa and theca cells of the human ovary. J Clin Endocrinol Metab **84:**1072–1076, 1999.
27. Jockenhovel F, Blum WF, Vogel E, Engalro P, Muller-Weiland D, Reinwein D, Rascher W, Krone W. Testosterone substitution normalizes elevated serum leptin levels in hypogonadal males. J Clin Endocrinol Metab **82:**2510–2513, 1997.
28. Loucks AB, Verdun M, Heath EM. Low energy availability, not stress of exercise, alters LH pulsatility in exercising women. J Appl Physiol **84:**37–46, 1998.
29. Johnson LG, Kraemer RR, Haltom RW, Kraemer GR, Gaines HE, Castracane VD. Effects of estrogen replacement therapy on dehydroepiandrosterone, dehydroepiandrostereone sulfate, and cortisol responses to exercise in postmenopausal females. Fertil Steril **68:**836–843, 1997.
30. Kjaer M, Farrell PA, Christensen NJ, Galbo H. Increased epinephrine response and inaccurate glucoregulation in exercising athletes. J Appl Physiol **61:**1693–1700, 1986.
31. Kraemer RR, Acevedo EO, Synovitz LB, Durand RJ, Johnson LG, Petrella E, Fineman MS, Castracane VD. Glucoregulatory endocrine responses to exercise and the role of a pancreatic β-cell peptide, amylin. Metabolism **51:**657–663, 2002.
32. Kraemer RR, Acevedo AO, Synovitz LB, Hebert EP, Gimpel T, Castracane VD. Leptin and steroid hormone responses to exercise in adolescent females runners over a 7-week season. Eur J Appl Physiol **86:**85–91, 2001.
33. Kraemer RR, Heleniak R, Tryniecki J, Kraemer G, Okazaki N, Castracane VD. Follicular and luteal phase hormonal responses to low-volume resistive exercise in women. Med Sci Sports Exerc **27:**809–817, 1995.
34. Kraemer RR, Johnson LG, Haltom R, Kraemer GR, Gaines HE, Drapcho M, Castracane VD. Effects of hormone replacement on growth hormone and prolactin exercise responses in postmenopausal women. J Appl Physiol **84:**703–708, 1998.
35. Kraemer RR, Kilgore JL, Kraemer GR, Castracane VD. Growth hormone, IGF-1, and testosterone responses to resistive exercise. Med Sci Sports Exerc **24:**1346–1352, 1992.
36. Callies F, Fassnacht M, van Vlijmen JC, Huebler D, Seibel MJ, Arlt W, Allolio B. Dehydroepiandrosterone replacement in females with adrenal insufficiency: effects of body composition, serum leptin, bone turnover, and exercise capacity. Med Sci Sports Exerc **86:**1968–1972, 2001.
37. Elias AN, Pandian MR, Wang L, Suarez E, James N, Wilson AF. Leptin and IGF-I levels in unconditioned male volunteers after short-term exercise. Psychoneuroendocrinology **25:**453–461, 2000.
38. Duclos M, Corcuff JB, Ruffie A, Roger P, Manier G. Rapid leptin decrease in immediate post-exercise recovery. Clin Endocrinol (Oxf) **50:**337–342, 1999.
39. Weltman A, Pritzlaff J, Wideman L, Considine V, Fryburg A, Gutgesell ME, Hartman ML, Veldhuis JD. Intensity of acute exercise does not affect serum leptin concentrations in young males. Med Sci Sports Exerc **32:**1556–1561, 2000.
40. Racette SB, Coppack SW, Landt M, Klein S. Leptin production during moderate-intensity aerobic exercise. J Clin Endocrinol Metab **82:**2275–2277, 1997.
41. Torjman MC, Zafeiridis A, Paolone AM, Wilkerson C, Considine RV. Serum leptin during recovery following maximal incremental and prolonged exercise. Int J Sports Med **20:**444–450, 1999.
42. Olive JL, Miller GD. Differential effects of maximal- and moderate-intensity runs on plasma leptin in healthy trained subjects. Nutrition **17:**365–369, 2001.
43. Essig DA, Alderson NL, Ferguson MA, Bartoli WP, Durstine JL. Delayed effects of exercise on the plasma leptin concentration. Metabolism **49:**395–399, 2000.
44. Hickey MS, Considine RV, Israel RG, Mahar TL, McCammon MR, Tyndall GL, Houmard JA, Carro JF. Leptin is related to body fat content in male distance runners. Am J Physiol **271:**E938–E940, 1996.
45. Tuominen JA, Ebeling P, Laquier FW, Heiman ML, Stephens T, Koivisto VA. Serum leptin concentration and fuel homeostasis in healthy man. Eur J Clin Invest **27:**206–211, 1997.
46. Leal-Cerro A, Garcia-Luna PP, Astorga R, Parejo J, Peino R, Dieguez C, Casanueva FF. Serum leptin levels in male marathon athletes before and after the marathon run. J. Clin Endocrinol Metab **83:**2376–2379, 1998.
47. Karamouzis I, Karamouzis M, Vrabas IS, Christoulas K, Kyriazis N, Giannoulis E, Mandroukas K. The effes of marathon swimming on serum leptin and plasma neuropeptide Y levels. Clin Chem Lab Med **40:**132–136, 2002.
48. Landt M, Lawson GM, Helgeson JM, Davila-Roman VG, Ladenson JH, Jaffe AS, Hickner RC. Prolonged exercise decreases serum leptin concentrations. Metabolism **46:**1109–1112, 1997.
49. Hilton LK, Loucks AB. Low energy availability, not exercise stress, suppresses the diurnal rhythm of leptin in healthy young females. Am J Physiol Endocrinol Metab **278:**E43–49, 2000.
50. Jenkins AB, Markovic TP, Fleury A, Campbell LV. Carbohydrate intake and short-term regulation of leptin in humans. Diabetologia **40:**348–351, 1997.
51. van Aggel-Leijssen DPC, vanBaak MA, Tenenbaum R, Campfield LA, Saris WHM. Regulation of average 24 h human plasma leptin level: the influence of exercise and physiological changes in energy balance. Int J Obesity **23:**151–158, 1999.
52. Koistinen HA, Tuominen JA, Ebeling P, Heiman ML, Stephens TW, Koivisto VA. The effect of exercise on leptin concentration in healthy males and in type 1 diabetic patients. Med Sci Sports Exerc **30:**805–810, 1998.
53. Houmard JA, Cox JH, Maclean PS, Barakat HA. Effect of short-term exercise training on leptin and insulin action. Metabolism **49:**858–861, 2000.
54. Dirlewanger M, Di Vetta V, Giusti V, Schneiter P, Jequier E, Tappy L. Effect of moderate physical activity on plasma leptin concentrations in humans. Eur J Appl Physiol **79:**331–335, 1999.
55. Kraemer RR, Kraemer GR, Acevedo EO, Hebert EP, Temple E, Bates M, Etie A, Haltom R, Quinn S, Castracane VD. Effects of aerobic exercise on serum leptin levels in obese females. Eur J Appl Physiol **80:**154–158, 1999.
56. Halle M, Berg A, Garwers U, Grathwohl D, Knisel W, Kuel J. Concurrent reductions of serum leptin and lipids during weight loss in obese males with type II diabetes. Am J Physiol Endocrinol Metab **277:**E277–E282, 1999.
57. Ishii T, Yamakita T, Yamagami K, Yamamoto T, Miyamoto M, Kawasaki K, Hosoi M, Yoshioka K, Sata T, Tanaka S, Fujii S. Effect of exercise training on serum leptin levels in type 2 diabetic patients. Metabolism **50:**1136–1140, 2001.
58. Gutin B, Ramsey L, Barbeau P, Cannady W, Ferguson M, Litaker M, Owens S. Plasma leptin concentrations in obese children: changes during 4-mo periods with and without physical training. Am J Clin Nutr **69:**388–394, 1999.
59. Pasman WJ, Westerterp-Plantenga MS, Saris WHM. The effect of exercise training on leptin levels in obese males. Am J Physiol Endocrinol Metab **274:**E280–E286, 1998.
60. Okazaki T, Himeno E, Manri H, Ogata H, Ikeda M. Effects of mild

aerobic exercise and mild hypocaloric diet on plasma leptin in sedentary females. Clin Exp Pharmacol Physiol **26:**415–420, 1999.

61. Reseland JE, Anderssen SA, Solvoll K, Hjermann I, Urdal P, Holme I, Drevon C. Effect of long-term changes in diet and exercise on plasma leptin concentrations. Am J Clin Nutr **73:**240–245, 2001.
62. Thong FSL, Hudson R, Ross R, Janssen I, Graham TE. Plasma leptin in moderately obese males: independent effects of weight loss and aerobic exercise. Am J Physiol Endocrinol Metab **279:**E307–E313, 2000.
63. Peruse L, Gollier G, Gagnon J, Leon AS, Rao DC, Skinner JS, Wilmore JH, Nadeau A, Zimmet PZ, Bouchard C. Acute and chronic effects of exercise on leptin levels in humans. J Appl Physiol **83:**5–10, 1997.
64. Noland RC, Baker JT, Boudreau SR, Kobe RW, Tanner CJ, Hickner RC, McCammon MR, Houmard JA. Effect of intense training on plasma leptin in male and female swimmers. Med Sci Sports Exerc **33:**227–231, 2001.
65. Kohrt WM, Landt M, Birge SJ. Serum leptin levels are reduced in response to exercise training, but not hormone replacement therapy, in older females. J Clin Endocrinol Metab **81:**3980–3985, 1996.
66. Kanaley JA, Fenicchia LM, Miller CS, Ploutz-Synder LL, Weinstock RS, Carhart R, Azevedo JL. Resting leptin responses to acute and chronic resistance training in type 2 diabetic males and females. Int J Obesity **25:**1474–1480, 2001.
67. Nindl BC, Kraemer WJ, Arciero PJ, Samatalee N, Leone CD, Mayo M, Hafeman DL. Leptin concentrations experience a delayed reduction after resistance exercise in males. Med Sci Sports Exerc **34:**608–613, 2002.
68. Ryan AS, Pratley RE, Goldberg AP. Changes in plasma leptin and insulin action with resistive training in postmenopausal females. Int J Obes Relat Metab Disord **24:**27–32, 2000.