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**Review article**

# LEPTIN, ITS IMPLICATION IN PHYSICAL EXERCISE AND TRAINING: A SHORT REVIEW

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**ABSTRACT**

Leptin, a hormone synthesized by fat tissue had been noted to regulate energy balance and metabolism and thus to influence body weight. The influence of acute exercise and chronic exercise training on circulating leptin and its relationship with hormonal and metabolic changes that induce energy balance are presented. Research that has examined the influence of exercise under various experimental conditions on leptin and the conflicts in the literature are presented. It appears that a significant caloric perturbation (> 800 kcals) is necessary for acute exercise to result in a significant reduction in leptin. In contrast, exercise training can result in a leptin decline but typically this manifests a reduction in adipose tissue stores. In addition, future directions are presented.

**KEY WORDS:** Leptin, exercise, training, hormones.

## INTRODUCTION

Leptin, the product of the *ob* gene, is a recently discovered single-chain proteohormone with a molecular mass of 16 kDa that is thought to play a key role in the regulation of body weight (Friedman et al., 1998). Leptin acts on the central nervous system, in particular the hypothalamus, suppressing food intake and stimulating energy expenditure (Webber, 2003).

Leptin is produced by differentiated adipocytes, although production has been demonstrated in other tissues, such as the fundus of the stomach, skeletal muscle, liver, placenta (Baratta et al., 2002), heart (Green et al., 1995), in granulose and cumulus oophorus cells in the human ovaries (Cioffi et al., 1997), in human mammary gland (Smith-Kirwin et al., 1998) and in gastric epithelium (Buyse et al., 2004). Additionally, leptin is known to be positively correlated with indices of adiposity such as body fat mass and body mass index (BMI) (Unal et al. 2004). Leptin can also be affected by nutritional supplementation. Baltaci et al., (2003) suggested that zinc-deficiency exerts a negative influence on leptin concentrations and that zinc-supplementation has the opposite effect.

The discovery of leptin has led to numerous experiments to better understand its function, and many of these studies have focused on leptin's response to both acute exercise and exercise training.

In this review, we will summarize the physiological effects of leptin, its role in hormonal secretion, then, we will discuss its implications with acute physical exercise and training.

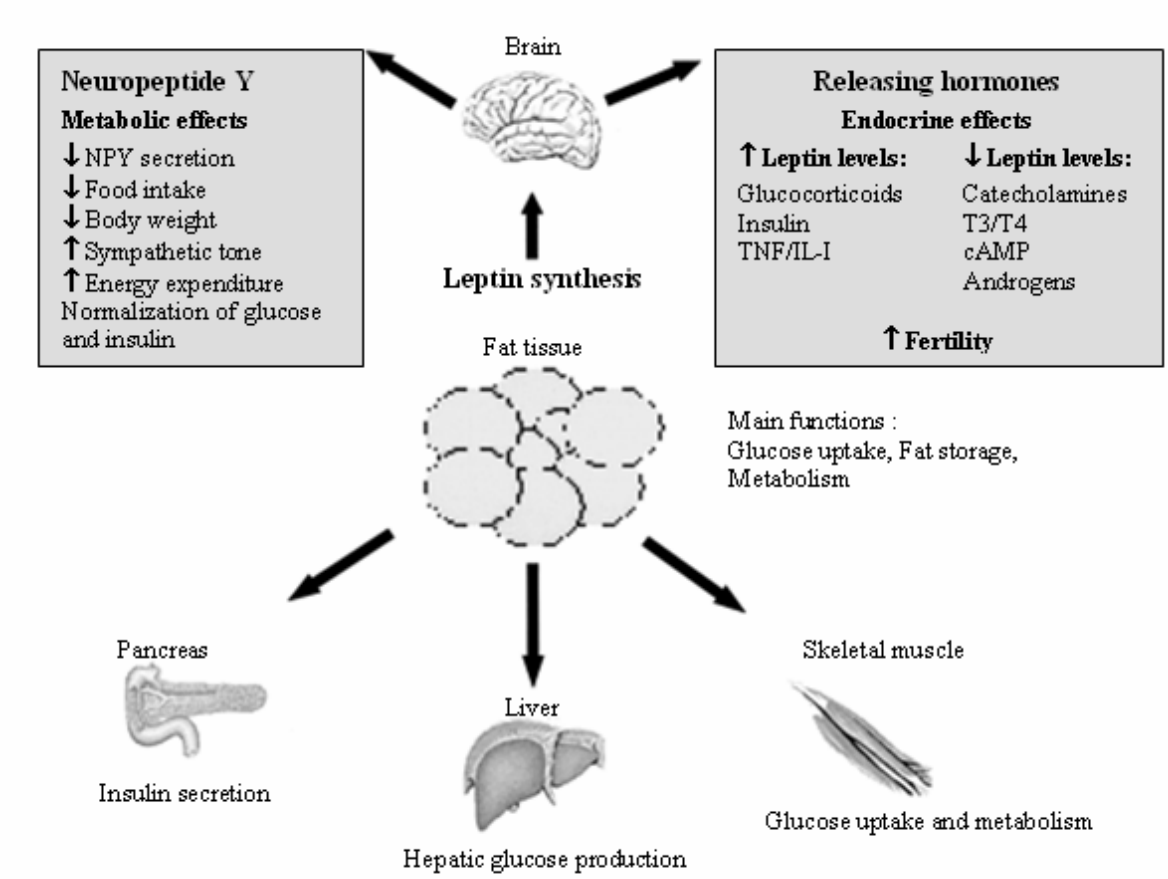


**Figure 1.** Action of leptin on the hypothalamus and peripheral organs (pancreas, liver. and skeletal muscle). IL-1, interleukin-1; T3, triiodothyronine; T4, thyroxin (Meier and Grassner, 2004).

## THE PHYSIOLOGICAL EFFECTS OF LEPTIN

In addition to its central effects on appetite control and energy expenditure, leptin has been shown to have a strong influence on fatty acid (FA) metabolism and on thel endocrine axis (Meier and Gressner, 2004) (Figure 1). Leptin has also been demonstrated to have profound effects on skeletal muscle FA metabolism, resulting in an increase in the capacity to oxidize FA and a lowering of triacylglycerol stores (Dyck, 2005). Muoio et al., (1997) further demonstrated that leptin acutely alters skeletal muscle FA metabolism. Their results indicated that leptin stimulates FA oxidation while simultaneously decreases the incorporation of FA into the intramuscular triacylglycerol pool in incubated murine muscle.

It was recently shown in humans that decreasing leptin concentrations in response to food deprivation was responsible for the starvation-induced suppression of the hypothalamic-pituitary-gonadal axis (Veniant and LeBel, 2003) as well as the malfunction of several other neuroendocrine axes. Thus, it seems that leptin may act as a critical link between adipose tissue, hypothalamic centers regulating energy homeostasis, and the reproductive system, indicating whether adequate energy reserves are present for normal reproductive function (Chehab et al., 2002).

These actions may, at least in part, be explained by the suppressive effect of leptin on neuropeptide Y (NPY) (Friedman et al., 1998) production and secretion by neurons in the accurate nucleus (Magni, 2003). NPY is a strong stimulator of appetite (Sainsbury et al., 2002) and is known to be involved in the regulation of various pituitary hormones: suppression of growth hormone (GH) through stimulation of somatostatin (Chan et al., 1996), suppression of gonadotropins (Pierroz et al., 1999), or stimulation of the pituitary–adrenal axis (Rohner-Jearenaud, 2002).

In addition, recent data indicated that polymorphism of leptin contributes to human variation in resting metabolic rate and in the relative rates of substrate oxidation during low-intensity

steady state exercise but not in a resting state (Loos et al., 2006).

## LEPTIN AND HORMONAL SECRETION

### *Leptin and cortisol*

Glucorticoids appear to play an important role in the physiological regulation of leptin (Dagogo-Jack et al., 2005). Cortisol has been shown to stimulate leptin production *in vitro* and *in vivo*. Isolated adipocytes showed a clear stimulatory effect of glucocorticoids on leptin synthesis and secretion (Wabitsh et al., 1996). Peripheral infusion of glucocorticoids to rats induced ob gene expression in adipose tissue and hyperleptinemia, followed by a decrease in food consumption and a subsequent lower body weight gain than controls (Zakarzewska et al., 1999).

In humans, the administration of glucocorticoids increased leptin secretion, although acute stimulation of the corticotrophic axis did not always significantly alter leptin levels (Kolaczynski et al., 1997). It was suggested that chronic hypersecretion of cortisol could be the cause of inducing not only hyperleptinaemia but also leptin resistance in some groups of obese humans (Ur et al., 1996). Pre-treatment with leptin prevents the stress induced elevation of adrenocorticotropic hormone (ACTH) and corticosterone in mice. Leptin inhibits hypoglycemia-induced surges in corticotropin releasing hormone (CRH) secretion in isolated hypothalamus from rats, while leptin does not affect ACTH secretion in rat cultured pituitary cells. Thus, the inhibition of CRH release is a likely mechanism by which leptin inhibits the activation of the hypothalamus-pituitary-adrenal axis in response to stress (Heiman et al., 1997).

Leptin also directly inhibits the secretion of cortisol in adrenocorticotropic cells (Pralong et al., 1998).

### *Leptin and insulin*

Insulin appears to be involved in the regulation of leptin mRNA expression, although its effects vary depending upon circulatory glucose status (Andersen et al., 1997).

It has been demonstrated that leptin production occurs after increases in insulin in response to feeding, and that a decrease in leptin concentrations follows insulin declines during fasting (French and Castiglione, 2002). Emilsson et al. (1997) demonstrated that supraphysiologic leptin concentrations inhibit basal insulin secretion in the perfused pancreas of ob/ob mice, but had no effect in the pancreas of Zucker fa/fa rats. Pocai et al., (2005) indicated that central administration of leptin rescues the hepatic insulin resistance induced by short-term hyperphagia.

There appears to be a synchronicity between leptin and insulin. The directionality of the cross-correlation suggests a temporal construct in which changes in insulin precede those of leptin by about 275 minutes (Koutkia et al., 2003). On the other hand, the direct effect of insulin on ob mRNA could not be shown on isolated rat adipocytes (Murakami et al., 1995), or entirely differentiated adipocytes (MacDougald et al., 1995) or in freshly isolated human preadipocytes (Wabitsch et al., 1996).

### *Leptin and growth hormone*

Growth hormone appears to have a negative feedback loop with leptin as leptin treatment stimulates the production of growth hormone from the pituitary by inhibiting hypothalamic somatostatin production and stimulating the production of growth hormone releasing hormone (Cocchi et al., 1999). The administration of leptin antiserum decreases spontaneous growth hormone (GH) secretion, and leptin administration reverses the inhibitory effect of fasting on growth hormone secretion in rats (Carro et al., 1997). Intracerebroventricular administrated leptin stimulated growth hormone secretion (Tannenbaum et al., 1998).

Several studies showed that the chronic administration of GH in deficient GH adults was accompanied by decreased leptinemia (Gill et al., 1999). Lisset et al. (2001) studied the effects of a GH bolus (0.67 mg) in healthy subjects and showed a significant increase in the serum leptin after 24 hours of the bolus and a significant reduction after 72 hours. Thus, leptin appears to be a signal of nutritional status that helps to regulate the pulsatile secretion of growth hormone.

### *Leptin and other hormones*

A number of negative feedback loops appears to exist between leptin and other hormones. Leptin was purported to promote the production of T3 (Legradi et al., 1997), whereas high T3 levels have been shown to reduce circulating leptin (Escobar Morreale et al., 1997). Popovic et al. (2005) indicated that prolonged fasting suppresses serum leptin, while suppressing thyroid stimulating hormone (TSH) secretion. Intervention with leptin replacement can prevent fasting-induced changes in TSH, suggesting that leptin regulates TSH.

Catecholamines play a role in the regulation of leptin production. These hormones depress leptin production through their production of intracellular cAMP (Fritsche et al., 1998). Leptin receptors have been found in the adrenal medulla and leptin was shown to strongly stimulate the synthesis and release

of epinephrine and norepinephrine from cultured chromatic cells (Takekoshi et al., 1999).

Strong correlations exist between plasma concentrations of some of the sex hormones and leptin: oestrogen is positively correlated, while testosterone is negatively correlated with leptin (Paolisso et al., 1998). Oestrogen has been shown to stimulate leptin production (Kristensen et al., 1999) and testosterone production appears to be regulated, at least in part, by leptin (Tena-Sempere et al., 1999). Wabitsch et al., (2001) demonstrated that leptin might also play an important role in the regulation of the hypothalamo-pituitary-gonadal axis in underweight males and females.

## THE EFFECT OF PHYSICAL EXERCISE ON LEPTIN SECRETION

The effect of physical exercise on leptin concentrations is currently controversial. Several investigators reported that exercise may result in reductions depending on the duration and calorie expenditure whereas others have reported no change in leptin concentrations.

### *Exercise don't generate decrease in leptin concentrations*

Weltman et al. (2000) found that 30 min of exercise at various intensities and caloric expenditure (from 150 ± 11 to 529 ± 45 kcals) in 7 healthy young men did not cause modifications in leptin levels during the exercise and during the recovery (3.5 hours). In this study, the intensity and the duration of the exercise did not appear to be sufficient enough to affect the leptin concentration in these young subjects. We demonstrated (Bouassida et al., 2004) that 45 seconds of supra-maximal exercise at 120% of peak aerobic power was not associated with a reduction of plasma leptin concentrations in 5 males and 12 females who were physically active. Cortisol, a hormone that can affect leptin concentrations, increased in these males and females in response to exercise. In these conditions, leptin production seemed insensitive to short intense exercise. Torjman et al. (1999) measured leptin concentrations following 60 minutes of treadmill exercise at 50% of $VO_{2max}$ in 6 healthy untrained males. After leptin concentrations were corrected for hemoconcentration, they found no effect of exercise on leptin concentrations during a 4 hour recovery period in spite of a decrease in insulin and free fatty acid levels.

Landt et al. (1997) reported an 8% insignificant reduction in fasting serum leptin concentrations after 2-hours of cycling exercise in 12 men. The exercise was 4 segments of 30 minutes at 75% of $VO_{2max}$ separated by a 4-minute rest interval and cumulated with 5 sprints of 1 min at 100% of $VO_{2max}$ separated by a 3-minute rest period. There was a similar insignificant leptin reduction for the control group that fasted during this identical time period. Therefore, the authors attributed the modest exercise related decline to diurnal reductions.

Zoladz et al. (2005) studied the response of leptin in 8 healthy men following two incremental exercises: the maximal incremental exercise was performed in the fed state however the sub-maximal incremental exercise test up to 150 w was performed in a fasted state. The authors reported no significant changes in leptin concentrations. In this study, the stability of leptin was accompanied by an increased growth hormone and norepinephrine concentrations.

Thus, several studies suggest that generally short-term exercises (<60 minutes) and exercises that generated energy expenditure lower than 800 kcals do not modify the concentrations of leptin (Kraemer et al., 2002). The recorded decreases could be allotted to the circadian rhythm of the leptin.

### *Exercise that generated decrease in leptin concentrations*

Essig et al. (2000) reported lower leptin concentrations in trained males after 2 separate exercise tests, an 800 and 1500 kcals treadmill run. These authors concluded that the decrease in plasma leptin concentrations after 48 was preceded by a decrease in insulin concentrations. Nine trained males completed 60 min of running at 70% of $VO_{2max}$ (energy expenditure 882.7 ± 14.4 kcals) showed leptin concentrations that were significantly lower immediately after exercise, 24 and 48 hours during recovery (Olive and Miller, 2001). The leptin responses did not appear to be related to changes in insulin or glucose concentration. Blood samples were also collected from the same subjects after a short term maximal exercise test (energy expenditure 197.5 ± 11.8 kcals), and leptin levels did not decrease immediately after, or at 24 or 48 hrs post exercise. Other authors (Kraemer et al., 1999a) demonstrated that 30 minutes of exercise at 80% of $VO_{2max}$ was associated with reduced leptin concentrations in postmenopausal women (with and without replacement therapy). The reductions of leptin were due to circadian rhythm of leptin as determined from control trial samples from the same subjects. The two hormones which would affect the leptin concentration (cortisol and growth hormone) increased in these women in response to exercise.

Nindl et al., (2002) measured leptin concentrations following 50 sets of resistance exercise: 15 sets squat, 15 sets bench press, 10 sets

leg press, 10 lat pull down exercise (energy expenditure 855.42 ± 114.38 kcals). Leptin concentrations were lower compared to the control trial after 9, 12 and 13 hours following the exercise. This decline in leptin concentration was likely associated with the disruption in metabolic homeostasis created by high-intensity, long-duration, energy expenditure and subsequent excess post oxygen consumption from the acute exercise and was not due to fat mass loss.

In a recent study, Zafeiridis et al. (2003) controlled the effects of maximum strength, muscular hypertrophy and resistance exercise protocols on serum leptin concentrations. Leptin concentrations significantly decreased 30-minute into recovery after exercise protocols compared with the respective baseline values. These protocols were accompanied by increased glucose and growth hormone concentrations.

Leptin responses after much longer durations of exercise have also been examined. Leal-Cerro et al. (1998) controlled the variations of the circadian rhythm of leptin after a marathon of 42 km and found a small reduction in leptinemia. These authors associated this fall with the energy expenditure generated by the marathon. Karamouzis et al. (2002) studied the response of the concentration of leptin after a 12-km and found that the decrease leptinemia was associated to an increase (81%) in plasmatic neuropeptide Y and an energy imbalance. Zaccaria et al. (2002) studied the effects of three competitive endurance races in 45 males who participated in one of three competitive endurance races: a half-marathon run (estimated energy expenditure 1400 kcals), a ski-alpinism race (estimated energy expenditure 5000 kcals), and an ultramarathon race (estimated energy expenditure 7000) on serum leptin concentrations. The results indicated that only prolonged endurance exercises involving high energy expenditure, like the ski-alpinism and the ultramarathon races, induced a marked reduction in circulating serum leptin levels.

In summary, the decrease in leptin concentration after a long-term exercise (≥ 60 min) has been attributed to diurnal reduction in circulating leptin and hormonal changes induced by exercise. Exercises of very long duration that generated a sufficient energy imbalance (kilocalorie intake versus kilocalorie expenditure) suppress the amplitude of the diurnal rhythm of leptin. This suppression of the secretion of leptin could be counterbalanced by feeding and may explain the reduction in leptin following extreme exercises such as marathon or ultramarathon. These results highlight the close relationship which exists between leptinemia and energy expenditure. The results suggest that the delayed leptin response to exercise can be observed from an energy deficit equal to or higher than 800 kcals.

It still needs to be determined how the hormones and the metabolites affecting the secretion of leptin work together and can lower the concentration of leptin under certain conditions, but not in others (Fisher et al., 2001).

## THE EFFECT OF TRAINING ON LEPTIN SECRETION

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 (< 12 weeks), or a reduction in leptin levels in long-term training (≥ 12 weeks) studies.

### *Training that does not generate decreases in leptin concentration*

Short-term aerobic training (60 minutes at 75% of $VO_{2max}$ during 7 successive days) does not modify leptin concentrations in healthy young and older males (Houmard et al., 2000). Although the training improved insulin sensitivity, leptin concentration was not affected. Gippini et al. (1999) measured leptin concentration in body builders, in sedentary subjects who were mildly overweight and in sedentary subjects with normal weight and concluded that resistance exercise did not influence leptin production independent of the variation in body composition.

In a study of adolescent female runners, Kraemer et al. (2001) measured resting and post maximal exercise leptin concentration over the course of a short track season. Resting leptin levels were not modified over the 7 weeks, nor were the acute responses to intense exercise despite a significant reduction in skin folds.

Kraemer et al. (1999b) also studied the effect of a 9 week training program (3-4 days of exercise including 20-30 min of step aerobics 2 days/week and treadmill running or stationary cycling on additional days) in middle-age obese women. Although $VO_{2max}$ after training increased, there were no significant changes in fat mass or leptin concentration.

### *Training that generated decrease in leptin concentration*

Gomez-Merino et al. (2002) reported a reduction in leptinemia after 3 weeks of a military training. They allotted this decrease to the rise in the catecholamines and hypoinsulinemia induced by this exercise. The fat mass in this study was not

measured, but the body weight remained stable. Unal et al. (2005a) measured leptin concentrations in trained young male athletes (from different sports) and in healthy sedentary subjects. They noted a significant lower leptin after exercise and concluded that regular exercise, by reducing fat percentage, suppresses serum leptin levels. In another study, Unal et al. (2005b) examined leptin responses in 10 professional football players and 17 healthy sedentary males. The results indicated that the BMI in athletes was higher than the sedentary subjects and that the leptin levels of the football players were significantly lower than healthy males. The authors demonstrated that serum leptin levels are in direct proportion with BMI in general and that the major determinant of serum leptin level was body fat. As regular exercising reduces body fat, it also reduces serum leptin levels.

Fatouros et al. (2005) also reported a decrease in plasma leptin concentration after resistance training (6 months, 3 days/week, 10 exercises/three sets) in fifty inactive men. These authors noted that this decrease was accompanied by a reduced skin fold sum and BMI. Ishii et al., (2001) showed a reduction in leptinemia after 6 weeks of an aerobic training in type 2 diabetic subjects. This decrease of leptin concentration was independent of the changes in fat mass, insulin, or glucocorticoids. Hickey et al., (1997) reported a diminution of the concentration of leptin after 12 weeks of an aerobic training among young women. This decrease appeared despite the absence of significant changes in fat mass.

Okazaki et al., (1999) examined the effects of mild aerobic exercise (50% of $VO_{2max}$) and personal diet counselling for 12 weeks on fat loss and leptin concentration in obese and non obese middle aged sedentary females. The ratio of leptin concentration to fat mass and to BMI was reduced after training. The authors suggested reduced leptin concentration was probably due to weight reduction.

Thus, short-term training (< 12 weeks) and long-term training (≥ 12 weeks) have disparate findings concerning leptin concentration. The reduction of leptin has been attributed to alteration in energy balance, improvements in insulin sensitivity, alteration in lipid metabolism and lipid concentration, and unknown factors.

## CONCLUSION

The implication of leptin in physical exercise and during its recovery is still unclear. There are several reasons that can explain the modification of the response of leptin to muscular exercise. Physical exercise and or training can reduce fat mass, play a significant role in energy expenditure and affect hormonal concentrations (insulin, cortisol, growth hormone, catecholamines, testosterone etc.) and metabolites (free fatty acids, lactic acid, triglycerides etc.). For all these reasons we believe that physical exercise and training could modify the leptin response depending on several factors.

The discordance in the literature is probably related to several factors, such as, the intensity and the duration of the exercise, the nutritional status of the subject, the circadian rhythm of leptin, the hour of blood sampling and the caloric imbalance imposed by the exercise.

We feel that many questions remain unanswered such as:

- What are the effects of a decreased or stable leptinemia during and/or after the physical exercise?
- What are the mechanisms which intervene in the regulation of the synthesis and the release of leptin during and after the exercise?

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## KEY POINTS

- Physical exercise and training have both inhibitory and stimulatory effects on leptin.
- Exercise with energy expenditure higher than 800 kcal can decrease leptinemia.
- Acute training may cause a decline in circulating leptin levels.

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