Leptin and endurance exercise: implications of adiposity and insulin*

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ABSTRACT

Obesity currently is qualified as a worldwide health epidemic and its consequences include diabetes mellitus as far as cardiac disease. Genetic and environmental factors contribute to obesity, although the genetic component is still poorly understood in humans. With the cloning of mouse ob gene and its receptor, leptin was discovered, the "satiety hormone". Leptin is expressed and secreted primarily by adipose tissue and is highly correlated to body fat mass. Nevertheless, many factors can regulate leptin synthesis and expression, such as fasting, sympathetic activity, insulin, exercise and changes in energy balance. Aerobic physical activity effects on leptin are still not very clear, seeing that there are contradictory studies about its effects on leptin regulation. Transversal studies suggest that leptin concentrations are not acutely affected after an exercise bout. However, reductions in leptin concentrations are observed following extreme bouts of exercise such as ultramarathons, where the extenuating physical activity induces a deficit in energy balance. Also, long-term (≥ 60 min) exercise seems to be associated with a delayed reduction in leptin concentrations 48 hr after the exercise bout, possibly due to an energy imbalance. Some longitudinal studies show that aerobic exercise training does not affect leptin levels, others that any changes in leptin levels are due to possible changes in body fat, and, lastly, some studies show a reduction in leptin levels and/or expression independently of any changes in adiposity. That suggests there may be other factors besides adiposity that regulate the reduction in leptin levels after exercise training, being insulin the main candidate for such role. Therefore, this review analyses the main aspects of leptin, its action, function and regulation, its association with insulin, and also the effects of acute and chronic endurance exercise on leptin synthesis and secretion and possible implications of insulin and adiposity.

Keywords: Acute aerobic exercise. Endurance training. Metabolism.

INTRODUCTION

Nowadays obesity is a pandemia[1]. The World Health Organization (WHO) estimates that there are over 1 billion of adults worldwide with surplus fat [body mass index – BMI (kg/m^2) > 27], out of which 300 million are obese (BMI > 30)[2]. Obesity is not a disease present only in developed countries. Some low income countries present levels similar or higher than those found in the United States and other developed countries[3]. In Brazil, demographic, socioeconomic and epidemiological changes over the time allowed a transition from nutritional standards, with progressive decrease of malnutrition as well as increase of number of overweight individuals[4].

Obesity is associated with countless co-morbidities such as diabetes mellitus, dyslipidemias, cardiovascular diseases and some kinds of cancer, representing hence a huge health problem[5]. Several studies have been conducted in order to identify the main factors which contribute to the development of this disease, once it is not a singular disorder, but a heterogeneous group of conditions with multiple causes. The main environmental factors related with the increase in the number of obese individuals in the western world has been the modern supply of food as well as availability of highly fatty food for consumption inside and outside home[6], joined with changes in work as well as leisure physical activity patterns[7]. Genetic factors are not very well-defined yet. However, although excessive energetic intake and/or reduction of the energy expenditure derived from physical activity are responsible for the increase in the prevalence of this disease, genetic factors seem to be crucial to its susceptibility. Therefore, some authors emphasize that the prevalence of obesity may be attributed to environmental factors which, interacting with the genetic factors, would be able to explain the accumulation of the excessive body fat in great proportions in the world population[8].

For many years, scientists have been trying to find a possible messenger that would signal to the brain as well as to the other tissues the state of the body energy reserves. Kennedy[9] was the first one to propose the lipostat theory of body weight regulation. According to this theory, when the adipose mass expands, the circulating concentration of the signal molecule may increase and act in the neural circuits of the brain, controlling the energy consumption and balance. The identification of the *ob* gene by the Friedman group in 1994[10] for that reason, was extremely innovative and highly significant since it provided evidence that the 'lipostatic' factor postulated by Kennedy[9] had been identified, provoking great spread on research over the energy balance.

LEPTIN

One of the products of the *ob* gene is leptin, known as the 'satiety hormone'. Leptin is one peptide constituted for 146 amino acids, coded by the *ob* gene[11], which circulates as a monomer of 16 kilodaltons. It is expressed and secreted in a pulsate way by the white adipose tissue and the placenta[10]. It circulates either freely or linked to a protein[11], until it ligates to its cellular surface receptor or it is expelled by the kidneys.

Leptin acts either through express central receptors or peripherically. Its receptors are found in many tissues, including the hypothalamus, choroid plexus, spleen β cells, adipose tissue, liver, kidneys, jejunum, lung, adrenal marrow, ovaries, testicles, placenta, heart and skeletal muscle[12-13]. There are at least six isoforms of receptors (OBRa, OBRb, OBRc, OBRd and OBRe and OBRf)[14],

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which can be divided in three classes: long, short and soluble[15]. The OBRa, OBRb, OBRc and OBRd and OBRf receptors contain a single transmembrane region, while the OBRe is stuck close to this region. This receptor acts as a circulating soluble protein ligated to leptin, being the main leptin linking component in plasma[16]. Potentially the OBRe modulates the stable concentrations (*steady-state*) of leptin, when linking to it and avoids its degradation and clearance[15]. Therefore, the OBRe increases the available leptin in the circulation, regulating the active leptin concentrations in the plasma[14].

Only the OBRb receptor (long form) contains intracellular domain which is able to perform the total transduction of the leptin ligation signal to the cell[14,17]. The long form of the receptor (OBRb) is prevalent in the hypothalamus. It is probably hence the responsible for the leptin central actions[18,19]. Moreover, in the hypothalamus, OBRb concentration peaks are observed in areas concerned with the control of food intake and energy expenditure[20], such as the arched, paraventricular, dorsomedial and ventromedial nucleus[14], playing a crucial role in the energetic homeostasis. Thus, the brain seems to be the primary target for the leptin anorexigenic action[21-23]. On the other hand, the short forms (OBRa, OBRc and OBRd) are found in the majority of the other tissues. Differently from the long receptors, it is not clear yet how efficient and how the short ones signal[19]. Its function is not well outlined yet; however, it has bee suggested that the short receptors act in the leptin clearance, in facilitating its transportation for the central compartments[14] and allowing the passage of leptin from the plasma through the blood-brain barrier[14,24-25].

One of the most evident leptin functions is to be an afferent signal for the central nervous system (CNS), acting within a negative feeback when inhibiting the leptin gene expression[13], consequently regulating the adipose tissue mass[17], body weight and appetite[15].

Many effects of leptin in the control of food intake and energy expenditure are mediated in the central nervous system, more precisely in the hypothalamic regions, in areas associated with the body weight regulation. Leptin has its action in the neurons which produce neuropeptides and orexigenic and anorexigenic neurotransmissors[17]. Such mechanisms will be described later on.

Since leptin receptors are also found in several organs and tissues, there is evidence that leptin acts in peripheral tissues. Such evidence suggests that leptin may regulate the energetic homeostasis through direct peripheral actions in lipidic metabolism[14]. According to Minokoshi *et al.*[26], leptin increases the oxidation of fatty acids in the skeletal muscle through the activation of the AMPK (activated AMP kinase protein). AMPK is an intracellular indicator of energy and plays an important role in the regulation of fatty acids oxidation (FA). The AMPK is activated when the AMP:ATP cellular ratio increases after the decrease of the ATP levels. Once it is removed, the AMPK begins ATP production processes (e.g. FA oxidation) and inhibits processes of ATP expenditure (e.g. FA synthesis)[14]. Such fact facilitates the ability of the cells to reestablish the energetic homeostasis. The AMPK phosphorylyzation and activation stimulated by the leptin in the skeletal muscle may occur daily, but also indirectly, through the sympathetic nervous system[26]. Leptin, again through the AMPK activation, seems to promote the increase of the depletion of triacylglycerols (TAG)[27] and stimulate the lipolysis in the skeletal muscle[28] and white adipose tissue[29]. Therefore, the AMPK seems to be the mediator of the leptin effects in the metabolism of fatty acids in the muscle. These data suggest that leptin stimulates the oxidation of substrates, promoting their usage instead of storing them[27].

There is high correlation between the leptin expression and plasma concentrations and the adipose tissue mass[15,17,21-22,30-34] and the percentage of body fat[35-36]. Thus, the higher the amount of adipose tissue, the slower leptin is produced and released in the blood stream[21]. Nevertheless, several physiological mechanisms influence the expression and synthesis of leptin, changing this correlation. Fasting, glucocorticoids, sympathetic activity, insulin, physical exercise and alterations in body weight and in the energetic balance may dramatically alter the amounts of leptin intrinsically associated with the fatty mass[17].

Rosenbaum *et al.*[32], Considine *et al.*[21] and Ostlund *et al.*[36] reported that the loss or gain of body weight seem to provoke, respectively, decrease and increase of leptin concentrations. The reduction of 10% of the body weight in obese humans resulted in reduction of 53% of plasma leptin[21], and 10% of increase of body weight caused increase of 300%[37].

When the energetic balance is steady, the expression and secretion of leptin reflect the mass of the adipose tissue in humans and rats[13,38]. Food deprivation (12 to 48 h) results in expressive decrease of leptin expression[34,39]. More subtle alterations in the energetic balance also produce deep effects in this expression. Thus, leptin does not act only as an 'adipostate', signaling to the brain about the situation of the body energy storage, but also as a sensor of the energetic balance[13,17].

The regional fat depot also seems to contribute for the leptin regulation mechanism. Differences in leptin expression by the different depot were observed in adipocytes of humans and rats[40-45]. In rats, the leptin expression seems to be bigger in the visceral adipose tissue (VAT) than in the subcutaneous adipose tissue (SAT)[41-42,44-45]. In humans, the leptin expression and excretion are higher in the SAT than in the VAT[40,43]. Possibly this fact occurs due to the smaller size of the VAT adipocytes in humans[40,46]. However, fasting causes reduction in the mRNA expression of the leptin with no alteration of the size of the adipocytes in rats and humans, suggesting that the energetic balance also influences leptin expression[44].

According to Rayner and Trayhurn[47], the SNS is an important regulator of the leptin production and leptin, in return, mediated some of its actions through the SNS. The sympathetic activation inhibits the leptin expression and its secretion in the adipose tissue. Rayner[48] suggests that the SNS has tonic inhibiting action in the leptin synthesis, which may be pulsatile. Therefore, once the leptin increases the SNS activity and the SNS inhibits its expression and secretion, it is suggested that there is a negative feedback mechanism between the SNS and the leptin synthesis and secretion by the adipose tissue[49].

As other hormones, plasma leptin exhibits a circadian cycle, varying its concentrations during the cycle, and having concentrations peaks close to midnight in humans and rats[10]. The pulsatile secretion and dynamics of insulin and leptin show high synchronicity. Moreover, correlation analyses show a temporal relationship, in which alterations in leptin concentrations follow alterations in insulin concentrations, suggesting that there is insulin influence in the control of the leptin secretion dynamics[27].

Leptin and insulin

Although leptin is the prototype of the 'body adiposity signaling', insulin may be considered as the second adiposity signaling, which was relatively taken for granted in the literature[1].

Insulin is synthesized in the langerhans islets, which are cells of the endocrine pancreas. Its anabolic peripheral effects are already very well established in the literature. According to Pereira and Lancha JR[50], the most important physiological effect of insulin is the stimulation of the glucose transportation in many tissues. Besides that, insulin promotes synthesis of glycogen, triglycerides, increase of amino acids consumption by the cells, while it inhibits lipolysis[51].

Nevertheless, strong evidence suggests that insulin is also a catabolic hormone extremely important in the central regulation of energetic intake and body adiposity. Plasma insulin concentrations are directly correlated with body weight and, especially, with body adiposity[46]. Differently from leptin, plasma insulin concentrations

reflect more acute alterations of the energetic metabolism as well as body fat than leptin. The insulin concentrations increase right after meals and other positive energetic balance conditions, and decrease during fasting as well as periods of negative energetic balance, being its half-life in blood from 2 to 3 minutes. Therefore, insulin secretion strictly follows the alterations of energetic balance from minutes to hours, and these alterations are always directly proportional to the size of the adipose depots[46]. Obese animals and humans have higher basal concentrations of plasma insulin and secrete more insulin in response to a given meal in relation to non-obese individuals and animals[52]. Leptin is secreted by the adipocytes in direct proportion to the metabolism of the adipocytes. Leptin concentrations are then steady and reliable indicators of body fat. Therefore, insulin concentrations reflect the interaction of the metabolic processes and body adiposity while the leptin concentrations reflect the adipocytes activity more directly[46].

Regardless the differences, leptin and insulin provide important information afferent to the brain. The neurons found in the arched nucleus of the hypothalamus also express insulin receptors, being then target of this hormone's action[52].

In the hypothalamic regions, more precisely in the arched nucleus, leptin and insulin have their actions in the neurons which produce neuropeptides and primary neurotransmissors[53] which increase (orexigenic) or decrease (anorexigenic) food intake[17]. The orexigenic neuropeptides not only stimulate food intake, but also decrease energy expenditure. The anorexigenic neuropeptides act in the opposite way, decreasing food intake and increasing energy expenditure[46]. The primary orexigenic neuropeptides are the neuropeptide Y (NPY) and the peptide agouti (AgRP); once the anorexigenic neuropeptides belong to the melanocortin family: the POMC precursor (pro-opiomelanocortin), with its cleavage product α-MSH (alfa-melanocite-stimulant hormone) and the transcript related to cocaine and amfetamine (CART)[54]. The Os α-MSH neuropeptides and CART of the arched nucleus have short inhibiting connections with the NPY and AgRP neuropeptides and long inhibiting connections with neurons located in the lateral hypothalamus nucleus (LH), besides having long exciting connections with neurons of the paraventricular nucleus (PVN). The neuropeptides NPY and AgRP seem to have only long inhibiting connections with the PVN and long exciting with the LH[55]. The connections of both types of neuropeptides are made with two distinct subpopulations of secondary neurons, both from PVN and in LH[53]. In the PVN, there are neurons which express CRH neurotransmissors (corticotrophin releaser hormone) and the TRH (thyreotropin releaser hormone), which have anorexigenic and pro-thermogenic functions, increasing the energetic cost[55]. In the LH, there are also two distinct subpopulations which express the orexin and the MCH (melanin concentrator hormone), which play orexigenic and anti-thermogenic functions[55].

When there is a situation of low concentrations of leptin and insulin, for example, during prolonged fasting, the NPY and AGRP expression is activated, resulting in increase of the orexin and MCH expression in the LH, besides reduction of TRH and CRH expression in the PVN. On the other hand, after a meal when the insulin concentrations increase, or when there is a discreet gain in adipose mass, promoting increase in the leptin and insulin concentrations, the activation of the POMC, α-MSH and CART neuropeptides in the arched nucleus occurs, generating reduction of the orexin and orexin expression and MCH in the LH and increase of TRH and CRH expression in the PVN[53]. The balance between these two systems, orexigenic and anorexigenic, is what determines the nutritional eating behavior as well as the amount of body fat[46].

Thus, leptin and insulin seem to act stimulating the synthesis of anorexigenic neurons (POMC, CART) and inhibiting the orexigenic neurons synthesis (NPY and AgRP)[18,24,39], found in the ARC, which seem to work as primary neurons in a neural set of circuits which inhibits the food intake and increases the energetic cost and the activity of the sympathetic nervous system[1,48,56], a better established mechanism in rats.

Insulin and leptin act hence as antagonists in the reduction of food intake and in the increase of energy expenditure via action in the hypothalamic neurons and can be called as 'body adiposity signals'[57]. The similar central effects of these two hormones suggest that there may be a modulation between them.

The interaction between leptin and insulin is very complex. The basal concentrations of leptin and insulin are positively correlated in individuals sensitive to insulin, and both decrease in response to weight loss[27]. Doucet *et al.*[58] divided individuals with the same total body fat amount into 'high insulemia' individuals and 'low insulemia' individuals. The group with 'high insulemia' presented leptin concentrations of 32% and 22% higher than the 'low insulemia' individuals, in men and women, respectively, emphasizing the positive correlation between insulin and leptin concentrations. The decrease in the leptin expression and concentration is observed after decrease of fasting insulin concentrations[38,59]. Nevertheless, while acute and chronic exposition to insulin result in increased leptin expression and secretion[18,38,45,60], only sustained hyperinsulemia (24 to 72 hours) can increase the plasma concentrations of leptin in humans and rats[37,39,61].

Leptin, on the other hand, increases peripheral sensibility to insulin, while it inhibits its secretion by the B cells of the pancreas[27]. As previously described, leptin peripheral effects in the skeletal muscle include the increase of glucose incorporation and oxidation as well as fatty acids oxidation increase (FA), besides depletion of triacylglycerols (TAG), which promotes improvement in insulin sensitivity[27].

Leptin and physical exercise

The benefits of physical exercise are well established and investigations continue to confirm the important role of regular exercising in the maintenance of global health as well as wellness[62]. Evidence of epidemiological and experimental studies has shown that regular physical exercise offers protection against the development and progress of countless chronic diseases (such as coronary diseases, hypertension, obesity, type 2 diabetes, among others), being hence a relevant component of a healthy life style.

Studies have been conducted in order to verify the effects of moderate prolonged acute and chronic aerobic exercise in the concentrations of leptin, also determining the influence or not of other variables. The results are mostly conflicting.

Acute physical exercise

When the effect of moderate prolonged acute exercise was observed, according to some studies, no significant difference was identified between pre and post exercise leptin concentrations[31,35,63-64]. Plasma leptin was measured before, 10-12 minutes after the beginning of 50 W of cycle ergometer and immediately after maximal exertion. No difference was found when the basal concentrations were compared. Racette *et al.*[31] measured arteriovenous leptin concentrations in the adipose tissue during 60 min of cycle ergometer and did not find alterations. According to Torjman *et al.*[63], after 60 min of treadmill exercise, at 50% of $\dot{V}O_{2max}$, there were no alterations in the plasma leptin concentrations in up 4 hours after the session end. Other studies also concluded that leptin does not answer for increase in the energy expenditure immediately after exercise[31-32,63-64].

On the other hand, Essig *et al.*[65] found reduction in 30% of leptin 48 h after two separated exercise bouts, which generated burn of approximately 800 and 1500 Kcal. However, immediately after and 24 h after the bouts, there were no differences in these concentrations. Landt *et al.*[66] found reduced leptin concentrations after a marathon. Tuoeminen *et al.*[67] also found 34% of reduction in the plasma leptin concentrations 44 hours after 2 hours of exer-

cise at 75% of $\dot{V}O_{2max}$. Olive and Miller[68] analyzed the plasma leptin concentrations 24 and 48 h after 1 hour of moderate exercise (~900 Kcal burnt) and after intense exercise of short duration (~200 Kcal burnt). There was decrease of 18% (24 h) and 40% (48 h) after moderate and prolonged activity and there was not alteration after short and intense activity. These data suggest that the decrease of leptin concentrations after an acute exercise bout only occurs if the physical exertion is extreme, such as in an ultramarathon, during which there is a negative balance, induced by the extenuating physical activity. Moreover, long duration exercises (≥ 60 min) seem to be associated with late decrease of the leptin concentrations after, approximately 48 hs after the activity. The mechanisms for this delayed effect are not established yet; however, it has been suggested that such effect occurs due to a possible energetic imbalance[69].

Chronic physical exercise

Longitudinal studies also presented contradictory results. Kraemer *et al.*[70] did not find alterations in the plasma leptin of obese women after nine weeks of aerobic training (approximately 1256 Kcal burnt per bout). There was no difference either of adipose mass and the subjects maintained their diets normal during the study. Houmard *et al.*[23] did not find alterations in the leptin concentrations after 7 consecutive days of aerobic training (1 h/day at 75% $\dot{V}O_{2max}$). There was no alteration of the body fat percentage; however, improvement in insulin sensitivity was observed. Such studies suggest that aerobic training does not independently modulate the fasting plasma leptin concentrations and that insulin sensitivity improvement induced by training may not be associated with alterations in fasting plasma leptin.

Other studies show reduction of plasma leptin concentrations and/or expression in response to aerobic training as a chronic effect[12,35,71-75].

In obese men, after 12 months of aerobic training (3 to 4 weekly bouts; 1 h per bout at moderate intensity), lower plasma leptin concentration in relation to the control group was observed. After analysis of the independent effect of training, corrected by the alterations of insulin and percentage of body fat, the number of weekly training hours was still significantly correlated with the alterations of leptin concentrations. Such fact led the authors to conclude that physical training, regardless the adipose mass alterations and insulin concentration, decreases the circulating leptin concentrations[74].

Zachwieja *et al.*[75] observed lower concentrations of plasma leptin and expression of leptin mRNA in the white adipose tissue of sensitive Osborne-Mendel rats (OM) and OM rats resistant to diet-induced obesity, after 7 weeks of voluntary exercise training. Moreover, the animals of the two trained groups presented amount of adipose tissue even lower in relation to their respective control group. There is correlation between leptin concentration and the sum of the amount of fat of the different fat depots. In addition to that, only the obese OM presented higher sensitivity to insulin, suggesting that the effects of the physical training in the leptin expression and secretion could occur independently of the insulin sensitivity.

Perusse *et al.*[35] observed the reduction of leptin concentrations after an aerobic training program of 20 weeks (3 weekly sessions, 30-50 minutes per session at 55-75% of $\dot{V}O_{2max}$). However, this reduction was attributed to the fat mass loss, not occurring improvement in insulin sensitivity either. Thong *et al.*[76] analyzed the effects regardless exercise and weight loss in leptin concentrations. The subjects trained on treadmill (daily sessions at 75% of $\dot{V}O_{2max}$; 700 Kcal spent per session), for 12 weeks. The alterations found were correlated with the alterations of the total and subcutaneous adipose tissue. The authors observed that, regardless the effect in the energetic balance and weight loss, the exercise did not promote alterations in leptin concentrations. Friedman *et al.*[30] observed that after 8-12 weeks of aerobic training (5 days a week; 1.5 h per day at 70% of $\dot{V}O_{2max}$) the leptin mRNA expression in the subcutaneous adipose tissue was 85% lower in trained rats. The trained group also presented lower percentage of body fat, showing association between leptin expression and amount of body fat. There was no difference in fasting insulinemia between groups. Levin and Dunn-Meynell[77] observed leptin concentrations 35% lower in trained rats on treadmill for 6 weeks than in sedentary ones. Nevertheless, the trained rats presented lower body fat in 36% comparing with the sedentary ones. Besides that, no difference in fasting insulinemia was found. Since training causes changes in the body composition, especially fat mass loss, when this variable is controlled, some studies did not observe significant variations of the leptin concentrations.

After a 12-week aerobic training program (4 weekly sessions; 30-45 min per session[78], the plasma leptin concentrations significantly decreased 17.5% in women; however, no significant reduction was observed in men. There was not alteration of fat mass in neither of the groups; however, significant improvement in the insulin sensitivity was observed (35% in men and 82% in women). Hayase *et al.*[79] found significant decrease in the plasma leptin concentrations in women, but not in the insulinemia, after 10 weeks of swimming (2 weekly sessions, 60 min/session at 60% of $\dot{V}O_{2max}$). There was extremely high correlation between leptin decrease and body fat reduction, suggesting hence that the decrease of leptin concentrations after training strongly depended on body fat loss, especially of subcutaneous adipose tissue. Nonetheless, when correcting the leptin concentrations by the amount of fat, the authors also observed significant decrease of leptinemia. Therefore, it was suggested that there was another factor besides the adipose tissue which modulates the leptin concentrations after training. Miyatake *et al.*[72] observed decrease of plasma leptin concentrations in overweighed men, after 1 year of aerobic training (3 weekly sessions, 50 minutes per session at 65% of $\dot{V}O_{2max}$), regardless body fat percentage decreases, weight loss and BMI decrease. The authors have suggested that insulin could be responsible for these effects, once there was improvement in the insulin sensitivity. After one year of aerobic training (3 weekly sessions, 60 minutes per session), men with metabolic syndrome (high lipids concentrations in the blood, high pressure, and so on) presented plasma leptin concentrations significantly reduced, even after adjustment of these concentrations by the fat mass loss and weight loss[31]. The authors have also suggested that the improvement of insulin sensitivity may have promoted the alterations in leptin concentrations found. Moreover, Perusse *et al.*[35] suggested that once there was not improvement of insulin sensitivity after training, this would be responsible for the lack of alterations in leptin concentrations after correction by the fat mass loss.

Thus, one can say that the studies which approach the chronic effects of aerobic physical activity in leptin are still very contradictory. Some authors did not observe alterations in the plasma leptin[23,70]; others found alterations only concerning adiposity alterations[30,35,74-77] and, finally, some studies observed decrease of plasma leptin concentration and/or expression regardless alterations of fat mass[31,72,78-79], suggesting that there is one or more factors besides body fat content, which modulates the decrease of plasma leptin concentrations after aerobic training. Many authors suggest that insulin is the main candidate for such modulation, once it seems to modulate the leptin synthesis and secretion[18,38,45,60]. The mechanisms for such modulation, though, have not been well-established yet[80].

FINAL CONSIDERATIONS

Obesity is a huge health risk factor. Many individuals who lose weight usually regain part of it, or even it all. In experimental models, leptin acts in the nutritional behavior and energy expenditure.

It is known that exercise represents a big fraction of the energy expenditure in humans, stimulates fat mass loss and aids in the maintenance of lean mass[35], besides promoting alterations in hormones such as insulin and its physiological action[74]. Therefore, considering the leptin role in the energy expenditure, the leptin response to alterations in the body composition, energy expenditure and insulin[30,63] and aerobic exercise seems to be an important factor of the leptin concentrations, implying in possible chronic effects of physical training. However, the studies seem to be very contradictory about the possible modulators of the plasma leptin expression and concentration concerning acute and chronic aerobic physical activity.

The plasma leptin expression and regulation concentrations in relation to the aerobic physical activity are complex. Acutely, the energetic imbalance induced by physical effort seems to be essential for possible alterations in the leptin concentrations. Chronically, aerobic physical training not only has effects in the body composition, but also in the hormonal regulation, more specifically in insulin sensibility, which are factors which directly influence the expression and concentration of this hormone. Thus, due to the importance to know about leptin and its response to physical exercise, further studies are needed in order to discover about the mechanisms which are involved in the leptin regulation concerning this stimulus and especially, its physiological and metabolic implications.

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REFERENCES

1. Niswender KD, Baskin DG, Schwartz MW. Insulin and its evolving partnership with leptin in the hypothalamic control of energy homeostasis. Trends Endocrinol Metab. 2004;15(8):362-9.
2. WHO (World Health Organization). Diet, nutrition and the prevention of chronic diseases. WHO Technical Report Series 916. Geneva; 2003.
3. OPAS. (Organização Pan-Americana de Saúde). Doenças crônico-degenerativas e obesidade: estratégia mundial sobre alimentação saudável, atividade física e saúde. Organização Pan-Americana de Saúde: Brasília; 2003.
4. Monteiro CA, Mondini L, Souza ALM, Popkin BM. The nutrition transition in Brazil. Eur J Clin Nutr. 1995;49:105-13.
5. Allison DB, Saunders SE. Obesity in North America, an overview. Med Clin North Am. 2000;84:305-32.
6. WHO (World Health Organization). Obesity: preventing and managing the global epidemic. Report of a WHO Consultation on Obesity. Geneva; 1998.
7. Popkin BM, Doak CM. The obesity epidemic Is a worldwide phenomenon. Nutr Rev. 1998;56:106-14.
8. Hill JO, Melanson EL, Wyatt HT. Dietary fat intake and regulation of energy balance: implications for obesity. J Nutr. 2000;120:284S-8S.
9. Kennedy GC. The role of depot fat in hypothalamic control of food intake in the rat. Proc R Soc Lond B Biol Sci. 1953;140:578-92.
10. Friedman JM, Hallas JL. Leptin and the regulation of body weight in mammals. Nature. 1998;395:763-70.
11. Zhang Y, Proença R, Maffel M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Science. 1994; 372:425-32.
12. Hickey MS, Calsbeek DJ. Plasma leptin and exercise: recent findings. Sports Med. 2001;31(8):583-9.
13. Houseknecht KL, Baile CA, Matteri RL, Spurlock ME. The biology of leptin: a review. J Anim Sci. 1998;76:1405-20.
14. Zhang F, Chen Y, Heiman M, Dimarchi R. Leptin: structure, function and biology. Vitam Horm. 2005;71:345-72.
15. Koerner A, Kratzsch J, Kiess W. Adipocytokines: leptin – the classical, resistin – the controversial, adiponectin – the promising, and more to come. Best Pract Res Clin Endocrinol Metab. 2005;19(4):525-46.
16. Lammert A, Kiess W, Bottner A, Glasgow A, Kratzsch J. Soluble leptin receptor represents the main leptin binding activity in human blood. Biochem Biophys Res Commun. 2001;283:982-8.
17. Negrão AB, Licínio J. Leptina: diálogo entre adipócitos e neurônios. Arquivos Brasileiros de Endocrinologia e Metabologia. 2000;44(3):205-14.
18. Meier U, Gressner AM. Endocrine regulation of energy metabolism: review of pathobiochemical and clinical chemical aspects of leptin, ghrelin, adiponectin, and resistin. Clin Chem. 2004;50(9):1511-25.
19. Tartaglia LA, Dembski M, Weng X, Deng N, Culpepper J, Devos R, et al. Identification and expression cloning of a leptin receptor, OB-R. Cell. 1995;83:1263-71.
20. Funahashi H, Yada T, Suzuki R, Shioda S. Distribution, function, and properties of leptin receptors in the brain. Int Rev Cytol. 2003;224:1-27.
21. Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, et al. Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med. 1996;334:292-5.
22. Hallas JL, Gajiwala KS, Maffei M, Cohen SL, Chait BT, Rabinowitz D, et al. Weight-reducing effects of the plasma protein encoded by the obese gene. Science. 1995;269:543-6.
23. Houmard JA, Cox JH, MacLean PS, Barakat HA. Effect of short-term exercise training on leptin and insulin action. Metabolism. 2000;49(7):858-61.
24. Munzberg H, Bjornhol M, Bates SH, Myers Jr MG. Leptin receptor action and mechanisms of leptin resistance. Cell Mol Life Sci. 2005;62:642-52.
25. Hossner KL. Cellular, molecular and physiological aspects of leptin: potential application in animal production. Can J Anim Sci. 1995;78:463-72.
26. Minokoshi Y, Kim YB, Peroni OD, Fryer LG, Muller C, Carling, et al. Leptin stimulates fatty-acid oxidation by activating AMP-activated protein kinase. Nature. 2002; 415:339-43.
27. Yildiz BO, Haznedaroglu IC. Rethinking leptin and insulin action: therapeutic opportunities for diabetes. Int J Biochem Cell Biol. 2006;38:820-30.
28. Dyck DJ, Heigenhauser GJF, Bruce CR. The role of adipokines as regulators of skeletal muscle fatty acid metabolism and insulin sensitivity. Acta Physiol. 2006; 186(1):5-16.
29. Jequier E, Tappy L. Regulation of body weight in humans. Physiol Rev. 1999; 79(2):451-80.
30. Friedman JE, Ferrara CM, Aulak KS, Hatzoglou M, Melune SA, Park S, et al. Exercise training down-regulates *ob* gene expression in the genetically obese SHHF/Mcc-fa^{cp} rat. Horm Metab Res. 1997;29:214-9.
31. Racette SB, Coppack SW, Landt M, Klein S. Leptin production during moderate-intensity aerobic exercise. J Clin Endocrinol Metab. 1997;82(7):2275-7.
32. Rosenbaum M, Nicolson M, Hirsch J, Murphy E, Chu F, Leibel RL. Effects of weight change on plasma leptin concentrations and energy expenditure. J Clin Endocrinol Metab. 1997;82(11):3647-54.
33. Speakman JR, Stubbs RJ, Mercer JG. Does body fat mass play a role in the regulation of food intake? Proc Nutr Soc. 2002;61:473-87.
34. Wadden TA, Considine RV, Foster GD, Anderson DA, Sarwer DB, Caro JS. Short- and long-term changes in serum leptin in dieting obese women: effects of caloric restriction and weight loss. J Clin Endocrinol Metab. 1998;83(1):214-8.
35. Perusse L, Collier G, Gagnon J, Leon AS, Rao DC, Skinner JS, et al. Acute and chronic effects of exercise on leptin levels in humans. J Appl Physiol. 1997; 83(1):5-10.
36. Ostlund RE, Yang JW, Klein S, Gingerich R. Relation between plasma leptin concentration and body fat, gender, diet, age, and metabolic covariates. J Clin Endocrinol Metab. 1996;81(11):3909-13.
37. Kolaczynski JW, Ohannesian JP, Considine RV, Marco CC, Caro JF. Response of leptin to short-term and prolonged overfeeding in humans. J Clin Endocrinol Metab. 1996;81:4162-5.
38. Ahima RS, Flier JS. Leptin. Annu Rev Physiol. 2000;62:413-37.
39. Cusin I, Rohner-Jeanrenaud F, Stricker-Krongrad A, Jeanreanud B. The weight-reducing effect of an intracerebro-ventricular bolus injection of leptin in genetically obese rats. Diabetes. 1996;45:1446-50.
40. Hube F, Lietz U, Igel M, Jensen PB, Tornqvist H, Joost HG, et al. Difference in leptin mRNA levels between omental and subcutaneous adipose tissue from obese humans. Horm Metab Res. 1996;28(12):690-3.
41. Li H, Matheny M, Nicolson M, Tumer N, Scarpace PJ. Leptin gene expression increases with age independent of increasing adiposity in rats. Diabetes. 1997; 46:2035-9.
42. Ogawa Y, Masuzaki H, Isse N, Okazaki T, Mori K, Shigemoto M, et al. Molecular cloning of rat obese cDNA augmented gene expression in genetically obese Zucker fatty (fa/fa) rats. J Clin Invest. 1995;96:1647-52.
43. Russel CD, Petersen RN, Rao SP, Ricci RM, Prasad A, Zhang Y, et al. Leptin expression in adipose tissue from obese humans: depot-specific regulation by insulin and dexamethasone. Am J Physiol Endocrinol Metab. 1998;275:E507-15.

44. Zhang Y, Guo K, Diaz PA, Heo M, Leibel RL. Determinants of leptin gene expression in fat depots of lean mice. Am J Physiol Regul Integr Comp Physiol. 2002; 282:R226-34.
45. Zheng D, Jones JP, Stephen JU, Dohm GL. Differential expression of ob mRNA in rat adipose tissues in response to insulin. Biochem Biophys Res Commun. 1996;218:434-7.
46. Benoit SC, Clegg DJ, Seeley RJ, Woods SC. Insulin and leptin as adiposity signals. Recent Prog Horm Res. 2004;59:267-85.
47. Rayner DV, Trayhurn P. Regulation of leptin production: sympathetic nervous system interactions. J Mol Med. 2001;79:8-20.
48. Rayner DV. The sympathetic nervous system in white adipose tissue regulation. Proc Nutr Soc. 2001;60:357-64.
49. Mark AL, Rahmouni K, Correia M, Haynes WG. A leptin-sympathetic-leptin feednack loop: potential implications for regulation of arterial pressure and body fat. Acta Physiol Scand. 2003;177:345-9.
50. Pereira LO, Lancha Jr AH. Effect of insulin and contraction up on glucose transport in skeletal muscle. Prog Biophys Mol Biol. 2004;84(1):1-27.
51. McArdle WD, Katch FI, Katch VL. Fisiologia do exercício: energia, nutrição e desempenho humano. Rio de Janeiro: Guanabara Koogan; 1996.
52. Woods SC, Seeley RJ, Baskin DG, Schwartz MW. Insulin and the blood-brain barrier. Curr Pharm Des. 2003;9:795-800.
53. Schwartz MW, Woods SC, Porte Jr D, Seeley RJ, Baskin DG. Central nervous system control of food intake. Nature. 2000;404:661-71.
54. Halpern ZSC, Rodrigues MDB, Da Costa RF. Determinantes fisiológicos do controle do peso e apetite. Rev Psiquiatr Clin. 2004;31(4):150-3.
55. Velloso LA. O controle hipotalâmico da fome e da termogênese: implicações no desenvolvimento da obesidade. Arq Bras Endocrinol Metabol. 2006;50(2):165-76.
56. Seals DD, Bell C. Chronic sympathetic activation: consequence and cause of age-associated obesity? Diabetes. 2004;53:276-84.
57. Stockhorst U, De Fries D, Steingrueber HJ, Scherbaum WA. Insulin and the CNS: effects on food intake, memory, and endocrine parameters and the role of intranasal insulin administration in humans. Physiol Behav. 2004;83:47-54.
58. Doucet E, St-Pierre S, Alméras N, Mauriège P, Després JP, Richard D, et al. Fasting insulin levels influence plasma leptin levels independently from the contribution of adiposity: evidence from both a cross-sectional and intervention study. J Clin Endocrinol Metab. 2000;85:4231-7.
59. Cammisotto PG, Gélinas Y, Deshaies Y, Bukowiecki LJ. Regulation of leptin secretion from white adipocytes by insulin, gycolytic substrates, and amino acids. Am J Physiol Endocrinol Metab. 2005;289:E166-71.
60. Walker CG, Bryson JM, Bell-Anderson KS, Hancock DP, Denver GS, Caterson ID. Insulin determines leptin responses during a glucose challenge in fed and fasted rats. Int J Obes. 2005;29(4):398-405.
61. Bryson JM, Phuyal JL, Proctor DR, Blair SC, Caterson ID, Cooney GJ. Plasma insulin rise precedes rise in *ob* mRNA expression and plasma leptin in gold thioglucose-obese mice. Am J Physiol Endocrinol Metab. 1999;276:E358-64.
62. ACSM (American College of Sports Medicine). Benefícios e riscos associados aos exercícios. In: _____. Teste de esforço e prescrição de exercício. Rio de Janeiro: Revinter; 2000.
63. Torjman MC, Zafeiridis A, Paolone AM, Wilkerson C, Considine RV. Serum leptin during recovery following maximal incremental and prolonged exercise. Int J Sports Med. 1999;20:444-50.
64. Weltman A, Pritzlaff CJ, Wideman L, Considine RV, Fryburg DA, Gutgesell ME, et al. Intensity of acute exercise does not affect serum leptin concentrations in young men. Med Sci Sports Exerc. 2000;32(9):1556-61.
65. Essig DA, Alderson NL, Ferguson MA, Bartoli WP, Durstine JL. Delayed effects of exercise on plasma leptin concentration. Metabolism. 2000;49:395-9.
66. Landt M, Lawson GM, Helgeson JM, Davila-Roman VG, Ladenson JH, Jaffe AS, et al. Prolonged exercise decreases serum leptin concentrations. Metabolism. 1997;46(10):1109-12.
67. Tuoeminen JA, Ebeling P, Laquier FW, Heiman ML, Stephens T, Koivisto VA. Serum leptin concentration and fuel homeostasis in healthy man. Eur J Clin Invest. 1997;27:206-11.
68. Olive JL, Miller GD. Differential effects of maximal-and moderate-intensity runs on plasma leptin in healthy trained subjects. Nutrition. 2001;5:420-2.
69. Kraemer RR, Chu H, Castracane VD. Leptin and exercise. Exp Biol Med. 2002; 227:701-8.
70. Kraemer RR, Kraemer GR, Acevedo EO, Hebert EP, Temple E, Bates M, et al. Effects of aerobic exercise on serum leptin levels in obese women. Eur J Appl Physiol. 1999;80:154-8.
71. Kohrt M, Landt M, Birge SJ. Serum leptin levels are reduced in response to exercise training, but not hormone replacement therapy, in older woman. J Clin Endocrinol Metab. 1996;81(11):3980-5.
72. Miyatake N, Takahashi K, Wada J, Nishikawa H, Morishita A, Suzuki H, et al. Changes in serum leptin concentrations in overweight Japanese men after exercise. Diabetes Obes Metab. 2004;6(5):332-7.
73. 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. 1999;26:415-20.
74. Pasman WJ, Westerterp-Plantenga MS, Saris WH. The effect of exercise training on leptin levels in obese males. Am J Physiol Endocrinol Metab. 1995;274: E280-6.
75. Zachwieja JJ, Hendry SL, Smith SR, Harris RBS. Voluntary wheel running decreases adipose tissue mass and expression of leptin mRNA in Osborne-Mendel rats. Diabetes. 1997;46:1159-66.
76. Thong FS, Hudson R, Ross R, Janssen I, Graham TE. Plasma leptin in moderately obese men: independent effects of weight loss and aerobic exercise. Am J Physiol Endocrinol Metab. 2000;279:E307-13.
77. Levin BE, Dunn-Meynell AA. Chronic exercise lowers the defended body weight gain and adiposity in diet-induced obese rats. Am J Physiol Regul Integr Comp Physiol. 2004;286:R771-8.
78. Hickey MS, Houmard JA, Considine RV, Tyndall GL, Midgette JB, Gavigan KE, et al. Gender-dependent effects of exercise training on serum leptin levels in humans. Am J Physiol Endocrinol Metab. 1997;272:E562-6.
79. Hayase H, Nomura S, Abe T, Izawa T. Relation between fat distributions and several plasma adipocytokines alter exercise training in premenopausal and postmenopausal women. J Physiol Anthropol. 2002;21(2):105-13.
80. Considine RV. Invited editorial on "Acute and chronic effects of exercise on leptin levels in humans". J Appl Physiol. 1997;83:3-4.