REVIEW ARTICLE

Medicina Sportiva, Vol. 6 (EE2): E133–E146, 2002

LEPTIN – AN ADIPOSE TISSUE HORMONE AND ITS ROLE IN METABOLISM*

Grażyna Lutosławska

Department of Biochemistry, Faculty of Physiology and Biochemistry, Józef Piłsudski Academy of Physical Education, Warsaw

ABSTRACT

Leptin is a protein produced mainly by peripheral adipose tissue. The leptin gene was identified in 1994, leptin receptors were found in the hypothalamus, liver, skeletal muscles, ovary, testes, kidney and adipose tissue. The role of leptin in metabolism is far from being elucidated. However, it was postulated that leptin contributed to appetite regulation, puberty and fat metabolism. Blood leptin concentration is significantly correlated with body fat content, but also related to body response to insulin. In obese insulin-resistant subjects the blood leptin level was markedly higher than in their lean, insulin-sensitive counterparts. Furthermore, blood leptin was found to be positively correlated with estradiol concentration, but negatively with testosterone levels. In consequence, in females the blood leptin level, irrespective of the age and body fat, was higher than in males. A significant positive correlation was demonstrated between blood leptin concentration and fat consumption. On the contrary, blood leptin was negatively correlated with physical activity. Regular, moderate physical activity was shown to decrease blood leptin concentration, regardless of the decrease in body fat. In sportsmen blood leptin concentration was much lower than in sedentary individuals. Moreover, low blood leptin level in female athletes was recognized as a reason for delayed menarche and menstrual disturbances.

Key words: leptin, body fat, puberty, metabolism, physical activity

Introduction

Leptin discovered in 1994 is a protein built of 167 amino acids with a molecular weight of 16 kDa and synthesized mainly in adipocytes but also in the placenta, stomach and skeletal muscle (3, 86, 99, 105).

Studies on genetically obese mice were fundamental in explaining leptin's biological role. These mice had an excessive appetite, lowered basal metabolic rate and also multiple metabolic disturbances (hyperglycemia, hyperlipidemia, decreased insulin sensitivity, glucose intolerance and diabetes) (11, 76). Two groups of obese animals were distinguished – one had a low blood leptin concentrations (*ob/ob* mice) and the second one a high blood leptin concentrations (*db/db* mice) in comparison with animals with a normal body weight (16, 55). Leptin administration to obese animal with low leptin blood concentrations (*ob/ob* mice) and also to animals with a normal body weight depressed an appetite, increased energy expenditure and brought about a decrease in body weight (30, 76). On the other hand, leptin administration to obese animals with a high leptin blood concentration (*db/db* mice) did not

* The Polish version of the article was published in Medicina Sportiva 6 (3):129-142, 2002

decrease appetite nor cause a decrease in body weight indicating leptin resistance (20, 29). In animals with a normal body weight fed a high fat diet an elevation in leptin concentration in the blood was proportional to the increase in body fat stores (56).

Further studies indicated that leptin crossed the blood-brain barrier and its concentration in cerebrospinal fluid was proportional to the concentration of the hormone in the blood. Leptin receptors were identified in the hypothalamus where it inhibited the secretion of appetite-stimulating neuropeptide Y (NPY) (5, 6, 83, 84). Moreover, in obese animals with a high leptin concentration in the blood *(db/db*) but insensitive to leptin a mutation of the gene encoding the leptin receptor in the hypothalamus was found (16).

The above data allowed a hypothesis to be made concerning the role of leptin as a signal sent by adipose tissue to the central nervous system informing about fat stores in the body. Additionally, it was demonstrated that leptin decreased the release of appetite-stimulating neuropeptide Y (NPY), but increased the release of appetite-inhibiting corticoliberin (CRH) form the hypothalamus and depressed the energy expenditure (84, 91). Furthermore, leptin was found to affect the pro-opiomelanocortin system (POMC) and the release of appetite-inhibiting cocaine- and amphetamine-regulated transcript (CART) peptide and appetite-stimulating *agouti* peptide (48, 49). Therefore, the relationship between appetite regulation in CNS and leptin was recognized as feed-back mechanism of the control of energetic processes (Fig. 1.). The disturbances in leptin secretion and subsequent low hormone blood concentration or leptin receptor mutation in the hypothalamus were postulated to play an important role in the development of obesity at least in animals (28, 79).

It is worth stressing that the gene responsible for leptin synthesis was identified at the same time in experimental animals and in man (105). Moreover, the leptin receptor was identified not only in the hypothalamus but also in adipose tissue, muscle, liver, testes, kidney and ovaries suggesting its direct influence on the metabolic processes in these tissues and organs (92). Leptin receptors were identified as homologues of class I cytokine receptors, distributed in the body in many tissue-specific isoforms (28).

The role of leptin in the regulations of metabolism and in obesity in humans has not been fully explained in spite of many studies. However, the data obtained so far have indicated that also in humans it is a very important and long sought link between the body fat stores and metabolic processes such as reproduction or metabolic disturbances accompanying obesity (e.g. hyperlipidemia or insulin resistance) (65).

Blood leptin concentration and body fat stores

Numerous studies demonstrated that both in women and men leptin synthesis in adipose tissue and its blood concentration were markedly and positively correlated with total body fat stores expressed in kilograms, in percent of body weight and as the body mass index (BMI) (4, 12, 44). A very low leptin blood concentration was found in anorexic females and in children with congenital generalized lipoatrophy (40, 60). In obese subjects leptin blood concentration was markedly higher in comparison to lean ones (57). However, Ortiz-Gonzales et al. (72) and Segal et al. (85) suggested that leptin concentration in insulin-resistant subjects was higher in comparison with insulin-sensitive counterparts regardless of body fat stores which was similar in the two groups. At the same time, however, in obese insulin-resistant subjects it was significantly higher compared to lean insulin-resistant ones. These data indica-

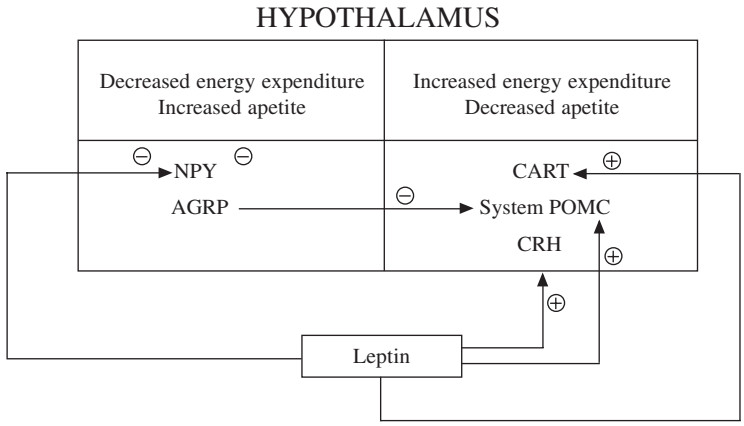

Fig. 1. *Leptin effect on food intake and energy balance (data from human and animal studies)*
NPY - neuropepide Y; AGRP - *agouti* peptide; CART –cocaine and amphetamine regulated transcript; POMC - pro- opiomelanocortin system; CRH -corticoliberin; (+) simulation; (-)-inhibition

ted that besides the percentage of body fat insulin sensitivity was an important factor affecting blood leptin concentration.

Regardless of age and body fat leptin concentration in the blood in girls and women was higher than in boys and men (43, 50, 88, 102). Demerath et al. (24) analyzed leptin concentration in blood in girls and boys aged 8-18 years and found that in both sexes the leptin concentration increased with age but it was already higher in 8-year old girls than in boys of the same age. Additionally, a positive correlation was found in girls between blood leptin and estradiol concentrations. In boys, however, a negative correlation was shown between leptin and testosterone concentrations in the blood. Recent research suggested that in both women and men leptin concentration in the blood was inversely related to testosterone plasma concentrations (82). As testosterone plasma concentrations in girls and women is lower than in boys and men leptin concentration will always be sex-dependent and higher in females than in males.

It is, however, worth noting that in adult women leptin plasma concentration was genetically determined in 34% and in men in 45% (41).

The role of leptin in sexual maturation and reproduction

In longitudinal study in boys Mantzoros et al. (62) evaluated the changes in blood leptin and testosterone concentrations and revealed that significant increases in leptin level (by about 50%) occurred just before the elevation in blood testosterone concentration. Thereafter blood leptin concentration slightly dropped and remained constant for 2 years despite constant increase in body mass.

In regularly menstruating women leptin concentration in the blood was higher in the luteal phase of the menstrual cycle in comparison to the follicular phase (58). However, the sensitivity of the ova cells to gonadotropin in obese women with a high leptin plasma concentration was significantly lower in comparison to lean counterparts with a lower leptin plasma concentration (2). A higher leptin concentration in blood was also found in pregnant as compared to non-pregnant women probably indicating transient leptin resistance in or-

der to increase energy stores essential for pregnancy and subsequent lactation (94). On the other hand, no differences in leptin concentration in blood in young as compared to menopausal women were indicated (15).

In experimental animals (rats and hamsters) high blood leptin concentration (inherited or due to intraperitoneal administration) was found to accelerate sexual maturity both in males and females (98, 103). In isolated pituitary cells from female rats the presence of leptin in the incubation medium in concentrations characteristic for the period of sexual maturation stimulated synthesis and secretion of luteotropic hormone (LH) and of follicle stimulating hormone (FSH) (71).

It has been known for a long time that both an excess of body fat (e.g. in obese women) or its very low content (in anorexic or malnourished women) depresses reproductive function though the mechanism of this phenomenon is not fully understood (21, 53). The presence of leptin receptors in ovaries suggested that a metabolic signal for the reproductive system and the link between body fat stores and reproduction may be played by leptin (7, 42, 95). It was postulated that both central leptin action on hypothalamus and pituitary gland and peripheral effect on gonads was of special importance in reproduction. In females with extremely low body fat and blood leptin concentration the disturbances in reproductory system were probably due to insufficient amount of leptin transported into the CNS. In consequence, regulatory function of hypothalamus and pituitary was depressed. On the contrary, in obese females high blood leptin concentration had no effect on the amount of leptin crossing blood-brain barrier due to saturation of the transport system. However, the excess of leptin was available for peripheral tissues including ovaries and testes depressing gonadal hormone synthesis. The above data indicated that blood leptin concentration essential for normal reproductive function had to be maintain in a relatively narrow range (13) (Fig. 2.).

Direct effects of leptin on fat and carbohydrate contribution to energy metabolism

The above-mentioned presence of leptin receptors in adipose tissue, skeletal muscle and liver suggested that leptin di-

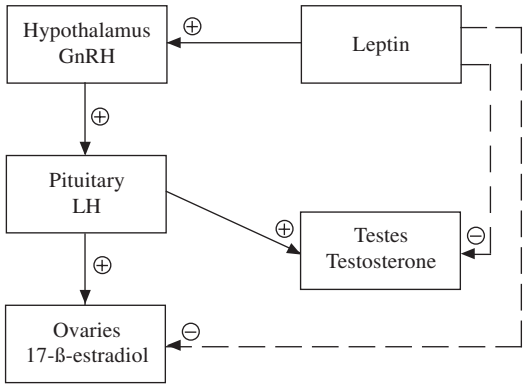

Fig. 2. *The influence of leptin on the hypothamalus-pituitary-gonadal axis*
Both low and excessive blood leptin concentration depresses reproductive system. Low blood leptin level brings about decreased GnRH release from hypothalamus, subsequent depressed pituitary LH, 17-β–estradiol and testosterone secretion (continuous line). In contrast, excessive blood leptin concentration (e.g. in obesity inhibits reproductive hormone synthesis in ovaries and testes (discontinuous line), despite unchanged leptin action on GnRH and LH release.

rectly affected the metabolism of these tissues.

In obese mice with a low blood leptin concentration (*ob/ob* mice) a single intraperitoneal administration of leptin increased energy expenditure and lower the respiratory quotient indicating an increased whole-body fat but depressed carbohydrates utilization. (39). Administration of leptin to rats and an increase in its blood concentration hindered liver glycogen breakdown during 18 h starvation without an effect on glycogen phosphorylase activity. However, administration of leptin did not affect the muscle glycogen stores (70). These data suggested that during the starvation leptin caused a sparing of liver glycogen, probably by increasing gluconeogenesis from fat.

In more detailed studies in obese *(ob/ob)* and normal mice it was noted that an acute administration of leptin inhibited lipogenesis in liver, adipose tissue and muscles and decreased the activity of pyruvate dehydrogenase (PDH) in these tissues – a key enzyme in aerobic carbohydrate metabolism (10). The inhibition of lipogenesis in the above mentioned tissues caused a simultaneous increase of the availability of free fatty acids for energetic processes. Such a "transition" of metabolism in the direction of fat utilization in skeletal muscle under the influence of leptin was also demonstrated by others (66, 67). It is worth noting that the effect of leptin on lipid metabolism is antagonistic to insulin, which increases lipogenesis and at the same time decreases fat contribution in energy production (Fig. 3.).

Recent study indicated that leptin augmented fat utilization exclusively in resting muscle, with no effect on energy metabolism during contraction (52).

Plasma leptin concentration and energy balance

Diurnal rhythm of blood leptin concentration

Numerous studies revealed diurnal rhythm in leptin concentration in the blood. with highest level between midnight and early morning and lowest between early

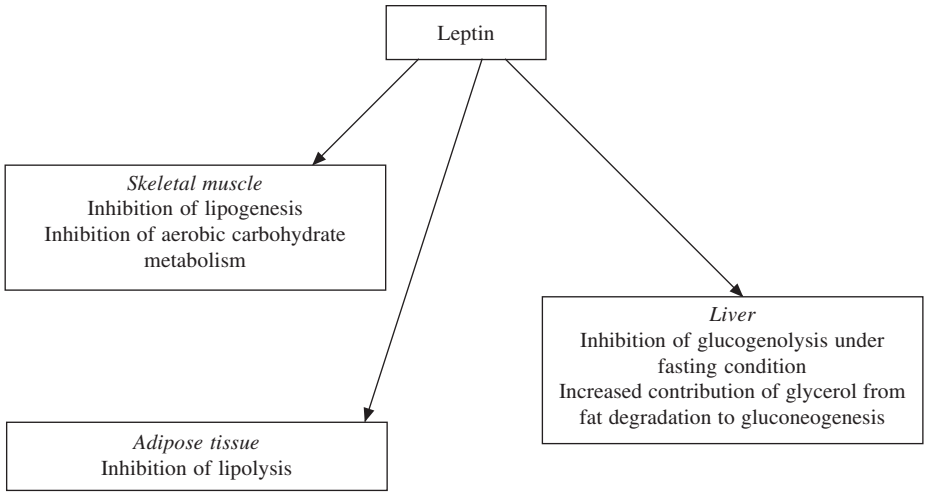

Fig. 3. *Leptin effect on carbohydrate and fat metabolism in selected tissues*
Leptin-induced inhibition of lipogenesis results in elevated lipolysis and increased fat contribution to energy metabolism in the muscle and elevated synthesis in the liver. In addition, the inhibition of aerobic carbohydrate metabolism in the muscle further shifts energetic processes in the muscle to fat utilization.

afternoon and midnight (17, 34). It should be stressed that diurnal rhythmicity in blood leptin concentration disappeared in female amenorrheic athletes characterized by low blood leptin concentration (53). In addition, leptin diurnal rhythm was not observed either in women consuming low- caloric diet (4 days, 10 kcal/kg FFM) or consuming high-caloric diet (4 days, 45kcal/ kg FFM) but with high energy expenditure due to physical activity (35 kcal/ kg FFM day) (37). On the basis of the above data it was postulated that leptin secretion was related to energy (or carbohydrate) availability expressed as the difference between energy supply and expenditure.

Nutritional habits and blood leptin concentration

The above-mentioned relationship between blood leptin concentration and body fat stores reflected the long-term effect of both nutritional habits and energy expenditure on leptin production. However, many studies demonstrated that leptin concentration in blood fluctuated during the day in response to food intake.

Consumption of high-fat meal (65% energy from fat, 1 g fat/kg body weight) in lean subjects caused a successive increase of leptin concentration in the blood statistically significant 6 hours after a meal (23). On the other hand, high-carbohydrate meal (81% of energy from carbohydrates) brought about a greater increase of leptin concentration 4-5 hours after the meal than an isocaloric high-fat meal (79% of energy from fat) (80).

Not only meal consumption, thus the supply of energy itself affected leptin concentration in blood but also the way it was provided. The consumption of 4 meals daily supplying respectively 20%, 30%, 10% and 40% of the daily energy requirements caused a successive increase in leptin concentration during the day. If, however, the same amount of calories was consumed as a single meal, in the evening (binge eating) a successive decrease of leptin concentration in the blood was noted. The average concentration of the hormone in subjects consuming one large meal daily was about 45% lower than in those eating regularly (93). Taking into account leptin contribution to appetite regulation it could not be excluded that lower blood hormone concentration in binge-eating subjects might stimulate food consumption leading to excessive fat accumulation, overweight and obesity.

It is worth stressing that the effect of the energy supply on blood leptin concentration differed significantly with respect to sex. After 7 days of a low-caloric diet (630 kcal for women and 840 cal for men) a significant decrease of leptin concentration was shown in both sexes even, though in women (16.2 to 6.0 ng/ml) it was significantly higher in comparison to men (3.7 mg to 2.2 ng/ml) (26). Moreover, in women an elevation in leptin concentration in blood was found both after a high-carbohydrate and high- fat meal, whereas in men only after a high-carbohydrate meal (81).

Another factor affecting plasma leptin concentration in response to the energy supply was body fat stores. A decrease in the energy supply in lean subjects brought about significant decrease of leptin concentration in the blood already after 6 hours of starvation or consumption of a meal covering only 20% of the energy requirements (23). In addition, in lean women (27% fat in total body mass) leptin synthesis in adipose tissue decreased after 22 h of starvation, but did not change in obese ones (52% fat in total body mass) (45). Moreover, in response to the administration of 75 g glucose solution after overnight fasting leptin concentration in blood in obese women significantly increased,

but did not change in their lean counterparts (8).

Thus obesity and increased body fat stores substantially affected plasma leptin response to the diet composition and energy supply, though the mechanism of this phenomenon was not fully elucidated.

Plasma leptin concentration and the energy expenditure

Data concerning the relationship between leptin concentration in plasma and energy expenditure are not equivocal. Nicklas et al. (69) stated that energy expenditure under resting conditions is significantly correlated with plasma leptin concentration in obese Afro-American women but not in obese Caucasian women. In contrast, Compostano et al. (11) did not find a relationship between basal metabolism rate and leptin concentration in blood in women and men aged 21-50 years. Similarly Soares et al. (89) did not observe such a relation in female and male inhabitants of Australia aged 18-35 years and over 50 years.

However, a significant correlation between total energy expenditure (including both resting energy expenditure and everyday habitual activity) was noted in 8 year old girls and boys (68). The above data indicated that blood leptin concentration was related to total energy expenditure and not only to basal metabolic rate.

Leptin – an important link in hormonal regulation of metabolism

Discussed above relationship between leptin concentration in the blood and the body fat stores, fat utilization, sexual maturation and reproduction clearly indicate that leptin is an important component of hormonal regulation of metabolism. Hence the numerous studies searching for the link between leptin concentration and/or secretion and other hormones of fundamental importance in metabolic processes.

Insulin

In studies concerning relationship between leptin secretion and its blood concentration and other hormones the greatest attention has been paid to the link between leptin and insulin. This aspect of the studies has a special significance in the context of a search for mechanisms responsible for obesity and accompanying metabolic disturbances, especially insulin resistance.

In children with ketoacidosis due to type 1 diabetes and impaired insulin secretion plasma leptin concentration was lower than in healthy children and rose after insulin therapy (32, 33).

Recent studies showed that leptin concentration in blood after overnight fast was positively and significantly correlated with changes in insulin concentration after glucose loading thus with body insulin sensitivity (1). It should be stressed that Thong et al. (96) searching the reason for positive correlation between blood insulin and leptin concentrations hypothesized that insulin is a component of mechanism by which body fat stores might respond to energy balance. Therefore, the above-mentioned leptin effect on lipid metabolism was probably regulated by insulin – an important component of glucostatic mechanism.

Catecholamines

Blood leptin concentration was also affected by blood catecholamines level. An elevation in blood adrenaline concentration brought about by an intravenous administration of the hormone inhibited leptin synthesis in adipose tissue and a decreased its concentration in the blood (14). Moreover, an elevated sympathetic activity and resultant elevation in blood noradrenaline concentration caused by low environmental temperature (6.6^{o}C) also decreased leptin concentration in blood (78). It is postulated that this relationship may be important in the regulation of metabolism during

stress period increasing appetite and at the same time decreasing energy expenditure.

The mechanism of catecholamines action on blood leptin concentration is not fully elucidated. However, Bramlett et al (9) indicated that catecholamines inhibited leptin m-RNA synthesis in the adipose tissue leading to depressed leptin synthesis.

Glucocorticoids, growth hormone, thyroid hormones

A chronic increase in glucocorticoid levels in the plasma in Cushing's syndrome was linked to increased concentration of plasma leptin. (101). It was suggested that glucocorticoids affected leptin concentrations indirectly as in the patients an increased insulin concentration and an increased body fat stores was also observed. On the other hand in adrenalectomized rats glucocorticoid treatment was found to inhibit leptin synthesis and to stimulate an appetite (87, 104).

In short children due to deficient growth hormone secretion plasma leptin concentration was elevated in comparison to a control group and decreased after 12 months of growth hormone administration (64). Similarly, in adults with deficient growth hormone secretion due to pituitary gland dysfunction leptin concentration in blood was higher than in healthy subjects (65).

Data concerning the relationship between blood thyroid hormone and leptin concentrations are not conclusive. Thongh et al. (96) noted positive correlation between blood thyroxine and triiodothyronine and leptin concentrations in females, but others did not confirm these relationships (22, 61). On the other hand, in rats the effect of leptin on energetic metabolism was independent on the effect of thyroid hormones. In thyreoctomized animals both leptin and triiodothyroxine increased oxygen consumption, however the effects were additive suggesting different mechanism of action (100).

Effect of exercise on blood leptin concentration

A close relationship between blood leptin concentration and insulin sensitivity, and as well as high blood leptin concentration in obese individuals and association between blood leptin concentration and energy intake allow to presume that the elevation in energy expenditure could also be a factor significantly affecting blood hormone concentration. This hypothesis was confirmed in rats in which after a single bout of exercise a decrease in leptin mRNA was observed in adipose tissue indicating depressed hormone synthesis in response to physical stress (106).

Leptin concentration in athletes

In all studies concerning blood leptin concentration in subjects participating in various sports a low leptin concentration was found in comparison to their sedentary counterparts. In women cyclists leptin concentration in blood was significantly lower than in the control group but at the same time the two groups differed significantly in percent of body fat. Thus a low plasma leptin concentration in competitors could have both been a consequence of training and of low body fat stores (53).

However, blood leptin concentration of female gymnasts (1.2 ng/ml) was markedly lower than in anorexic women (2.9 ng/ml) in spite of the similar body fat percent in both groups (11.7% and 12.5% in gymnasts and anorexic patients, respectively) (63). Similarly, in male rugby players plasma leptin concentration (3.7 mg/ml) was significantly lower than in sedentary men (6.0 ng/ml) even though both groups did not differ in percent of body fat (31).

The above data suggested that physical activity characterized by high work loads decreased blood leptin concentration and this effect was probably independent on the body fat stores, even though the mecha-

nism of this phenomenon was not explained.

It is also worth noting that taking into consideration the relationship between blood leptin and the process of sexual maturation it could not be excluded that a low leptin concentration in 14 year old female gymnasts (63) might be the cause of the lower biological than chronological age and delayed menarche.

Regular, moderate physical activity and leptin blood concentration

In order to achieve a decrease of blood leptin concentration in response to a regular physical activity a significant role is played by the time of duration of this activity. After 7 days of cycloergometer training (75% $\dot{V}O_2$max, 60 min/day) no changes in blood leptin concentration were found and the percent of body fat also did not change (38). However, Perusse et al. (74) analyzing the effect of regular physical activity on plasma leptin in men and women observed that a 20-week training (cycling, intensity increasing from 55% $\dot{V}O_2$ max 30 min daily to 75% $\dot{V}O_2$ max, 50 min daily) caused a decrease in leptin concentration only in men (from 4.6 to 3.9 ng/ml) in whom a simultaneous decrease in the percent of body fat was observed (from 71.1% to 16.2%). On the contrary, Hickey et al. (36) demonstrated that after 12 weeks of training (cycling, 85% $\dot{V}O_2$ max, 50 min/ day) a decrease in blood leptin concentration (from 17.1 to 16.2 ng/ml) occurred only in women, as only in women did training cause a decrease in the percent of body fat. The relationship between the decreases in plasma leptin concentration and body fat due to regular physical activity was also confirmed by others (18, 25, 47).

However, Pasman et al. (75) found that changes in blood leptin concentration due to an increased physical activity were strictly correlated with the time of duration of activity but independent of the changes in percent of body fat. The effect of regular physical activity independent of body fat on leptin concentration in the blood was also demonstrated by Chu et al. (19). In this study performed with the participation of 268 men aged 47-83, lean and obese it was demonstrated that blood leptin was significantly and positively correlated with a total dietary fat intake, and after elimination of the effect of differences in body weight, significantly and negatively correlated with physical activity.

These results suggested that physical activity regardless of body fat stores decreased blood leptin concentration and this effect was probably due to increased sensitivity of peripheral tissues to leptin. This assumption was indirectly confirmed in rats. The muscle of animals fed a high-fat diet (60% of calories from fat) became resistant to leptin and the stimulation of intramuscular lipolysis by leptin disappeared. This in turn increased intramuscular fat stores (90). The authors postulated that the leptin resistance caused by a fat-rich diet and as a consequence increased intramuscular fat stores might lead to insulin resistance - a phenomenon common in obesity both in humans and in animal. This hypothesis is likely since it is well known that sensitivity of muscle tissue to insulin is inversely related to intramuscular fat stores (59, 77).

A few studies indicated that rather duration of the physical activity than its mode affected leptin concentration in the blood. A decrease in leptin concentration was found in young women after 16 weeks of strength training and also in older women after 9 months of regular running and stair climbing (46, 81).

Response to a single bout of exercise

A single 32-km foot race (70% $\dot{V}O_2$ max) did not affect blood leptin concen-

tration directly after the effort both in lean and obese subjects (35). Similarly, plasma leptin concentration did not change in response to exercise until exhaustion or to 60 min cycling at 50% $\dot{V}O_2$max either directly after the exercise or after 4 hours of recovery (97). On the other hand, a significant decrease (by 32%) of plasma leptin concentration was observed after a 162-km foot race and after a marathon run (by 11%), thus after low-intensity, prolonged exercise (51, 54). However, a laboratory exercise with an intensity of 70% $\dot{V}O_2$ max and energy expenditure of 1500 kcal significantly decreased blood leptin concentration 48 hours after the exercise. If, however, during an exercise of the same intensity energy expenditure equaled 800 kcal no change in plasma leptin was observed (27). The above data suggested that the effect of a single exercise on plasma leptin is delayed and depended mostly on the total energy expenditure during the muscular work and not on its intensity.

Conclusions

In conclusions, it may be stated that leptin – a hormone discovered in 1994 secreted mainly by the subcutaneous adipose tissue is of fundamental importance in the regulation of sexual maturation, reproduction and energy balance, mainly fat metabolism.

Many aspects of leptin's biological role have not been explained but certainly it is an important part of the regulation of metabolism both in the central nervous system and in peripheral tissues.

This work was supported by grant DS-50 from the Academy of Physical Education

References

1. Abbasi F., Carantoni M., McLaughlin T. et al. Plasma insulin concentration is more tightly linked to plasma leptin concentration than is body mass index. Metabolism 49: 544-547, 2000.
2. Bützow T.L., Moilanen J.M., Lehtovirta M. et al. Serum and follicular fluid leptin during in vitro fertilization: relationship among leptin increase, body fat mass, and reduced ovarian response. J. Clin. Metab. Endocrinol. 84: 3135-3139, 1999.
3. Bado A., Lavasseur S., Attoub S. et al. The stomach is a source of leptin. Nature 394: 790-792, 1998.
4. Banerji M.A., Faridi N., Atluri R. et al. Body composition, visceral fat, leptin, and insulin resistance in Asian Indian men. J. Clin. Endocrinol. Metab.84: 137-144, 1999.
5. Banks W.A., Clever C.M., Farell C.L. Partial saturation and regional variation in the blood-to-brain transport of leptin in normal weight mice. Am. J. Physiol. 278: E1158-E1165, 2000.
6. Banks W.A., Kastin A.J., Huang W. et al. Leptin enters the brain by a saturable system independent of insulin. Peptides 17: 305-311, 1996.
7. Barash I.A., Cheung C.C., Weigle D.S. et al. Leptin is a metabolic signal to the reproductive system. Endocrinology 137: 3144-3147, 1996.
8. Bougoulia M., Tzotzas T., Efthymiou H. et al. Leptin concentrations during oral glucose tolerance test (OGTT) in obese and normal weight women. Int. J. Obes. 23: 625-628, 1999.
9. Bramlett S., Zhou J., Harris R.B.S. et al. Does b_3 - adrenoreceptor blockade attenuate acute exercise-induced reduction in leptin mRNA? J. Appl. Physiol. 87: 1678-1683, 1999.
10. Bryson J.M., Phuyal J.L. Swan V. et al. Leptin has acute effects on glucose and lipid metabolism in both lean and gold thioglucose-obese mice. Am. J. Physiol. 277: E417-E422, 1999.
11. Campfield L.A., Smith F.J., Devos R. et al. Recombinant mouse ob protein: evidence for peripheral signal linking adiposity and central neural network. Science 269: 546-549, 1995.
12. Campostano A., Grillo G., Bessarione D. et al. Relationship of serum leptin to body composition and resting energy expenditure. Horm. Metab. Res. 30: 646-647, 1998.
13. Caprio M., Fabbrini E., Isidori A.M. et al. Leptin in reproduction. Trends Endocrinol. Metab. 12: 65-72, 2001.
14. Carulli L., Ferrari S., Bertolini M. et al. Regulation of *ob* gene expression: evidence for epinephrine-induced supression in human obesity. J. Clin. Endocrinol. Metab. 84: 3309-3312, 1999.
15. Castracane V.D., Kraemer R.R., Franken M.A. et al. Serum leptin concentration in women: effect of age, obesity, and estrogen administration. Fertil. Steril. 70: 472-477, 1998.
16. Chen H., Charlat O., Tartaglia L.A et al. Evi-

dence that the diabetic gene encodes the leptin receptor: identification of a mutation in the leptin receptor gene in *db/db* mice. Cell 84: 491-495, 1996.
17. Chen M.-D., Song Y.-M., Lin P.-Y. Zinc may be a mediator of leptin production in humans. Life Sci. 22: 2143-2149, 2000.
18. Christensen J.O., Svendsen O.L., Hassager C. et al. Leptin in overweigth post-menopausal women: no relationship with metabolic syndrome X or effect of exercise in addition to diet. Int. J. Obes. 22: 195-199, 1998.
19. Chu N.F., Stampfer M.J., Spiegelman D. et al. Dietary and lifestyle factors in relation to plasma leptin concentrations among normal weight and overweight men. Int. J. Obes. 25: 106-114, 2001.
20. Chua S.C., Chung W.K., Wu-Peng X.S. et al. Phenotypes of mouse diabetes and rat fatty due to mutations in the OB (leptin) receptor. Science 271: 994-996, 1996.
21. Clark A.M., Ledger W., Gallethy C. et al. Weight loss results in significant improvement in pregnancy and ovulation rates in anovulatory obese women. Human. Reprod. 10: 2705-2712, 1995.
22. Corbetta S., Englaro P., Giambona S. et al. Lack of effects of circulating thyroid hormone levels in serum leptin concentrations. Eur. J. Endocrinol. 137: 659-663, 1997.
23. Dallongeville J., Hecquet B., Lebel P. et al. Short term response of circulating leptin to feeding and fasting in man: influence of circadian cycle. Int. J. Obes. 22: 728-733, 1998.
24. Demerath E.W., Towne B., Wiesemandle W. et al. Serum leptin concentration, body composition, and gonadal hormones during puberty. Int. J. Obes.23: 678-685, 1999.
25. Dirlewanger M., Di Vetta V., Giusti V. et al. Effect of moderate physical activity on plasma leptin concentration in humans. Eur. J. Appl. Physiol. 79: 331-335, 1999.
26. Dubuc G.R., Phinney S.D., Stern J.S. et al. Changes in serum leptin and endocrine and metabolic parameters after 7 days of energy restriction in men and women. Metabolism 47: 429-434, 1998.
27. Essig D.A., Alderson N.L., Ferguson M.A. et al. Delayed effects of exercise on the plasma leptin concentration. Metabolism 49: 395-399, 2000.
28. Friedman J.M., J.L. Halaas. Leptin and the regulation of body weight in mammals. Nature 395: 763-770, 1998.
29. Ghilardi N., Ziegler S., Wiestner A. et al. Defective STAT signaling by the leptin receptor in diabetic mice. Proc. Natl. Acad. Sci. 93: 6231-6235, 1996.
30. Halaas J.L., K.S. Gajiwala, Maffei M. et al. Weight-reducing effects of the plasma protein encoded by the obese gene. Science 269: 543-546, 1995.
31. Haluzik M., Boudová L., Nedvidková J. et al. Lower serum leptin concentrations in rugby players in comparison with healthy non-sporting subjects - relationship to anthropometric and biochemical parameters. Eur. J. Appl. Physiol. 79: 58-61, 1998.
32. Hanaki K., Becker D, Arslanian S.A. Leptin before and after insulin therapy in children with new-onset of type 1 diabetes. J. Clin. Endocrinol. Metab. 84: 1524-1526, 1999.
33. Hathout E.H., Sjarkey J., Racine M. et al. Changes in plasma leptin during the treatment of diabetic ketacidiosis. J. Clin Endocrinol.Metab. 84: 4545-4548, 1999.
34. Heptulla R., Smitten A., Teague B. et al. Temporal patterns of circulationg leptin levels in lean and obese adolescents; relationship to insulin, growth hormone, and free fatty acids rhythmicity. J. Cli. Endocrinol. Metab. 86: 90-96, 2001.
35. Hickey M., Considine R.V., Israel R.G. et al. Leptin is related to body fat content in male distance runners. Am. J. Physiol. 271: E938-E940, 1996.
36. Hickey M.S., Houmard J.A., Considine R.V. et al. Gender-dependent effects of exercise training on serum leptin levels in humans. Am. J. Physiol. 272: E562-E566, 1997.
37. Hilton L.K., Loucks A.B. Low energy availability, not exercise stress, suppresses the diurnal rhythm of leptin in healthy young women. Am. J. Physiol. 278: E43-E49, 2000.
38. Houmard J.A., Cox J.H., Maclean P.S. et al. Effect of short-term exercise training on leptin and insulin action. Metabolism 49: 858-861, 2000.
39. Hwa J.J., Eawzi A.B., Graziano M.P. et al. Leptin increases energy expenditure and selectively promotes fat metabolism in *ob/ob* mice. Am. J. Physiol. 272: R1204-R1209, 1997.
40. Jaquet D., Khallouf E., Lévy-Marchal C. et al. Extremely low values of serum leptin in children with congenital generalized lipoatrophy. Eur. J. Endocrinol. 140: 107-109, 1999.
41. Kaprio J., Eriksson J. Lehtovirta M. et al. Heritability of leptin levels and the shared genetic effects on body mass index and leptin in adult Finnish twins. Int. J. Obes. 26: 132-137, 2001.
42. Karlsson C., Lindell K., Svenson E. et al. Expression of functional leptin receptors in the

human ovary. J. Clin. Endocrinol. Metab.82: 4144-4148, 1997.
43. Kennedy A., Gettys T.W., Watson P. et al. The metabolic significance of leptin in humans: gender-based differences in relationship to adiposity,insulin sensitivity, and energy expenditure. J. Clin. Endocrinol. Metab. 82: 1293-1300, 1997.
44. Klein S., Coppack S.W., Mohamed-Ali V. et al. Adipose tissue leptin production and plasma leptin kinetics in humans. Diabetes 45: 984-987, 1996.
45. Klein S., Horowitz J.F., Landt M. et al. Leptin production during early starvation in lean and obese women. Am. J. Physiol. 278: E280-E284, 2000.
46. Kohrt W.M., Landt M., Birge S.J. Jr. Serum leptin levels are reduced in response to exercise training, but not hormone replacement therapy in older women. J. Clin. Endocrinol. Metab.81: 3980-3985, 1996.
47. Kraemer R.R., Kraemer G.R., Acevedo E.O. et al. Effects of aerobic exercise on serum leptin levels in obese women. Eur. J. Appl. Physiol. 80: 154-158, 1999.
48. Kristiensen P., Judge M.E. Thim J.L. Hypothalamic CART is a new anorectic peptide regulated by leptin. Nature 393: 72-76,1998.
49. Krude H., Grüters A. Implications of pro-opiomelanocortin (POMC) mutations in humans: the POMC deficiency syndrome. Trends Endocrinol. Metab. 11: 15-22, 2000.
50. Lönnerdal B., Havel P.J. Serum leptin concentration in infants: effect of diet, sex, and adiposity. Am. J. Clin. Nutr. 72: 484-489, 2000.
51. Landt M., Lawson G.M., Hegelson J.M. et al. Prolonged exercise decreases serum leptin concentrations. Metabolism 46: 1109-112, 1997.
52. Lau R., Blinn W.D., Bonen A. Stimulatory effects of leptin and muscle contraction on fatty acid metabolism are not additive. Am. J. Physiol. 281: E122 - E 129, 2001.
53. Laughlin G.A., Yen S.S.C. Hypoleptinemia in women athletes: absence of a diurnal rhythm with amenorrhea. J. Clin. Endocrionl. Metab. 82: 318-321, 1997.
54. Leal-Cerro A., Garcia-Luna P.P., Astorga R. et al. Serum leptin levels in male marathon athletes before and after the marathon run. J. Clin. Endocrinol. Metab. 83: 2376-2379, 1998.
55. Lee G.-H., Proenca R., Montez J.M. et al. Abnormal splicing of the leptin receptor in diabetic mice. Nature 379: 632-635, 1996.
56. Lin S., Thomas T.C., Storieln L.H. et al. Development of high fat diet-induced obesity and leptin resistance in C57BI/6J mice. Int. J. Obes. 24: 639-646, 2000.
57. Luizzi A., Savia G., Tagliaferri M. et al. Serum leptin concentration in moderate and severe obesity: relationship with clinical, anthropometric and metabolic factors. Int. J. Obes. 23: 1066-1073, 1999.
58. Łukaszuk K., Liss J., Kusiak E. et al. Serum leptin concentration increase during luteal phase in healthy pre-menopausal women. Horm. Metab. Res. 30: 172-174, 1998.
59. Manco M., Mingrone G., Greco A.V. et al. Insulin resistance directly correlates with increased saturated fatty acids in skeletal muscle triglycerides. Metabolism 49: 220-224, 2000.
60. Mantzoros C., Flier J.S., Lesem M.D. et al. Cerebrospinal fluid leptin in anorexia nervosa: correlation with nutritional status and potential role in resistance to weight gain. J. Clin. Endocrinol. Metab. 82: 1845-1851, 1997.
61. Mantzoros C.S., Rosen H.N., Greenspan S.L. et al. Short-term hyperthyroidoism has no effect on leptin levels in man. J. Clin. Endocrinol. Metab. 82: 497-499, 1997.
62. Mantzoros C.S., Flier J.S., Rogol A.D. A longitudinal assessment of hormonal and physical alterations during normal puberty in boys. V. Rising leptin levels may signal the onset of puberty. J. Clin. Endocrinol. Metab. 82: 1066-1070, 1997.
63. Matejek N., Weiman E., Witzel C. et al. Hypoleptinemia in patients with anorexia nervosa and in elite gymnasts with anorexia athletica. Int. J. Sport, Med. 20: 451-456, 1999.
64. Matsuoka H., Fors H., Boseaus I. et al. Changes in body composition and leptin levels during growth hormon (GH) treatment in short children with various GH secretory capacities. Eur. J. Endocrinol. 140: 35-42, 1999.
65. Mohamed-Ali V., Pinkey J.H., Coppack S.W. Adipose tissue as an endocrine and paracrine organ. Int. J. Obes. 22: 1145-1158, 1998.
66. Muoio D.M., Dohm G.L., Fiedorek F.T. et al. Leptin directly alters lipid partitioning in skeletal muscle. Diabetes 46: 1360-1363, 1997.
67. Muoio D.M., Dohm G.L., Tapscott E.B. et al. Leptin opposes insulin effects on fatty acid partitioning in muscle isolated from obese *ob/ob* mice. Am. J. Physiol. 276: E913-E921, 1998.
68. Nagy T.R., Gower B.A., Shewchuk R.M. et al. Serum leptin and energy expenditure in children. J. Clin. Endocrinol. Metab. 82: 4149-4153, 1997.
69. Nicklas B.J., Toth M.J., Goldberg A.P. et al. Racial differences in plasma leptin concentration in obese postmenopausal women. J. Clin. Endocrinol. Metab. 82: 315-317, 1997.

70. O'Doherty R.M., Anderson P.R., Zhao A.Z. et al. Sparing effect of leptin on liver glycogen stores in rats during the fed-to-fasted transition. Am. J. Physiol. 277: E544-E550, 1999.
71. Ogura K., Irahara M., Kikyokawa M. et al. Effects of leptin on secretion of LH and FSH from primary cultured female rat pituitary cells. Eur. J. Endocrinol.144: 653-658, 2001.
72. Ortiz-Gonzales M., Abundis-Martinez E., Munoz-Balcázar B.R. Serum leptin concentrations in young insulin-sensitive and insulin-resistant volunteers. Horm. Metab. Res. 32: 273-276, 2000.
73. Ozbey N., Algun E., Turgut Sait A. et al. Serum leptin concentrations in hypopituitary patients with growth hormone deficiency. Int. J. Obes. 24: 619-626, 2000.
74. Pérusse L., Collier G., Gagnon J. et al. Acute and chronic effects of exercise on leptin levels in humans. J. Appl. Physiol. 83: 5-10, 1997.
75. Pasman W.J., Westerterp-Plantenga M.S., Saris W.H.M. The effect of exercise training in leptin levels in obese males. Am. J. Physiol. 274: E280-E286, 1998
76. Pelleymounter M.A., Cullen M.J., Baker M.B. et al. Effect of the obese gene product on body weight regulation in *ob/ob* mice. Science 269: 540-543, 1995.
77. Phillips D.I.W., Caddy S., Illic V. et al. Intramuscular triglyceride and muscle insulin sensitivity: evidence for a relationship in non-diabetic subjects. Metabolism 45: 947-950, 1996.
78. Ricci M.R., Fried S., Mittelman K.D. Acute cold exposure decreases plasma leptin in women. Metabolism 49: 421-423, 2000.
79. Rohner-Jeanrenaud F., Jeanrenaud B. Obesity, leptin and the brain. N. Eng. J. Med. 334: 324-325, 1996.
80. Romon M., Lebel P., Velly C. et al. Leptin response to carbohydrate or fat meal and association with subsequent satiety and energy intake. Am. J. Physiol. 277: E855-E861, 1999.
81. Ryan A.S., Pratley R.E., Goldberg A.P. Changes in plasma leptin and insulin action with resistive training in postmenopausal women. Int. J. Obes. 24: 27-32, 2000.
82. Söderberg S., Olsson T., Johnson M. et al. A strong association between biologically active testosterone and leptin in non-obese men and women is lost with increasing (central) obesity. Int. J. Obes. 25:98-105,2001.
83. Schwartz M.W., Baskin D.G., Bukowski T.R. et al. Specificity of leptin action on elevated blood glucose levels and hypothalamic neuropeptide Y gene expression in *ob/ob* mice. Diabetes 45: 531-535, 1996.
84. Schwartz M.W., Seeley R.J., Campfield L.A. et al. Identification of targets of leptin action in rat hypothalamus. J. Clin. Invest. 98: 1101-1106, 1996.
85. Segal K.R., Landt M., Klein S. Relationship between insulin sensitivity and plasma leptin concentration in lean and obese men. Diabetes 45: 988-991, 1996
86. Senaris R., Garcia-Caballero T., Casabiel X. et al. Synthesis of leptin in human placenta. Endocrinology 138: 4501-4504, 1997.
87. Sheu W.H.-H., Lee W.J., Chen Y-T. Gender differences in relation to leptin concentration and insulin sensitivity in non-diabetic Chinese subjects. Int. J. Obes.23: 745-759, 1999.
88. Soares M.J., Piers L.S., O'dea K. et al. Plasma leptin concentrations, basal metabolic rates and respiratory quotients in young and older adults. Int. J. Obes. 24: 1592-1599, 2000.
89. Solano J.M., Jacobson L. Glucocorticoids reverse leptin effects on food intake and body fat in mice without increasing NPY mRNA. Am. J. Physiol. 277: E708-E716, 1999.
90. Steinberg G.R., Dyck D.J. Development of leptin resistance in rat soleus muscle in response to high-fat diets. Am. J. Physiol. 279: E1374-E1382, 2000.
91. Stephens T.W., Basinski M., Bristow P.K. The role of neuropeptide Y in the antiobesity action of the *obese* gene product. Nature 377: 530-532, 1995.
92. Tartaglia L.A., Dembski M., Weng X. Identification and expression of a leptin receptor OB-R. Cell 83: 223-228, 1995.
93. Taylor A.E., Hubbard J., Anderson E.J. Impact of binge eating on metabolic and leptin dynamics in normal weight women. J. Clin. Endocrinol. Metab. 84: 428-434, 1999.
94. Teppa R.J., Ness R.B., Cromblehomle W. et al. Free leptin is increased in normal pregnancy and further increased in pre-eclampsia. Metabolism 49: 1043-1048, 2000.
95. Thong F.S.L., Graham T.E. Leptin and reproduction: is it a critical link between adipose tissue, nutrition, and reproduction? Can. J.Appl. Physiol. 24: 317-336, 1999.
96. Thong F.S.L., McLean C., Graham T.E. Plasma leptin in female athletes: relationship with body fat, reproductive, nutritional and endocrine factors. J. Appl. Physiol. 88: 2037-2044, 2000.
97. Torjman M.C., Zafeiridis A., Paolone A.M. et al. Serum leptin during recovery following maximal incremental and prolonged exercise. Int. J. Sport Med. 20: 444-450, 1999.
98. Wade G.N., Lempicki R.L., Panicker A.K. et al. Leptin falicitates and inhibits sexual beha-

vior in female hamsters. Am. J. Physiol. 272: R1354-R1358, 1997.
99. Wang J., Lin R., Hawkins M. et al. A nutrient-sensing pathway regulates leptin gene expression in muscle and fat. Nature 393: 684-688, 1998.
100. Wang J.-L., Chinookoswong N., Yin S. et al. Calorigenic actions of leptin are additive to, but dependent on, those of thyroid hormones. Am. J. Physiol. 279: E1278-E1285, 2000.
101. Weise M., Abad V., Considine R.V. Leptin secretion in Cushing syndrome preservation of diurnal rhytm and absent response to corticotropin-releasing hormone. J. Clin. Endocrinol. Metab. 84: 2075-2079, 1999.
102. Wiedenhöft A., Müller C., Stenger R. et al. Lack of sex difference in cerebrospinal fluid (CSF) leptin levels and contribution of CSF/plasma rations to variations in body mass index in children. J. Clin. Endocrinol. Metab. 84: 3021-3024, 1999.
103. Yura S., Ogawa Y., Sagawa N. et al. Accelerated puberty and late-onset hypothalamic hypogonadism in female transgenic skinny mice overexpressing leptin. J. Clin. Invest. 105: 749-755, 2000.
104. Zakrzewska K.E., Cusin I., Sainsbury A. et al. Glucocorticoids as counterregulatory hormones of leptin. Diabetes 46: 717-719, 1997.
105. Zhang Y., Proenca R., Maffei M. et al. Positional cloning of the mouse obese gene and its human analog. Nature 372: 425-432, 1994.
106. Zheng D., Wooter M.H., Zhong Q. et al. The effect of exercise on *ob* gene expression. Biochem. Biophys. Res. Commun. 225: 747-750, 1996.

Received: August 16, 2001
Accepted: March 15, 2002

Address for correspondence:
Grażyna Lutosławska, Ph.D.
Department of Biochemistry, Faculty of Physiology and Biochemistry
Academy of Physical Education
01-968 Warsaw
Box 55
Poland
email: grazyna.lutoslawska@awf.edu.pl