REVIEW

Metabolic regulation of leptin: mini review

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ABSTRACT

Being discovered in 1994, the leptin hormone unites with special receptors in the body, and they together control body weight, food intake, energy expenditure, and generally, it's secreted by adipose tissues. Besides adipose tissues, leptin is also produced in placental trophoblasts, heart, bone, and the like fat tissues and fundus epithelium. Leptin passes to the brain with a special transportation system by blood path. In obese, this transportation system weakens and forms a resistance against leptin. Because of their structural similarities to cytokines, they are also classified as a cytokine. In case of the lack of leptin or resistance, it results in obesity, diabetes, and infertility.

In the search for scientific literature related to this review the US National Library of Medicine (PubMed) used MEDLINE and SportDiscus data and the terms "Leptin", "exercise", "obesity", and "osteogenesis" were used. The relevant literature has also taken its source from the research of relevant articles from reference lists derived from data studies.

The primary effects of leptin exist in lymphoid organ homeostasis, bone volume, blood pressure, growth, anti-obesity, fertility, hematopoiesis, angiogenesis, and many systems like the T lymphocyte system. Growth hormone treatment decreases body weight and also in a roundabout way, leptin

Leptin can be said to it's also effective on growth apart from the fact that many factors play role in the synthesis and secretion of leptin, regular exercising decreases leptin levels and affects inhibiting obesity. On the other hand, there is a close relationship between leptin levels, diabetes, and obesity. So, leptin treatment with an appropriate exercise program is expected to yield positive results in diabetes and metabolic syndrome.

Keywords: leptin, osteogenesis, exercise, obesity

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INTRODUCTION

1. Leptin and Its Metabolic Functions

It's a 167 aminoacid hormonal protein product of the obesity gene, which is after being discovered by Zhang et al., researched extensively [1]. It was claimed that leptin had been defined as leptin regarding saturation and energy balance in the beginning and an anti-obesity factor which was from adipocytes to hypothalamus feedback effective. The reports in

studies emphasize the importance of the leptin hormone which is very essential for regulating body weight and food intake both in animals and humans [2].

After discovering the leptin hormone, many studies were done to learn its effects and it is deduced that it plays an important role in regulating the body weight of living creatures. It's also stated that adipocyte tissue is not only a storage function for only fat but also it's an important endocrine gland with the discovery of leptin. It's an important adipokine that is primarily secreted by placental trophoblasts, stomach fundus epithelium, and choriocarcinoma cells [1].

It's known that leptin receptors are in the category of cytokine receptors which exist in periphery tissue and the central nervous system. There are two types of receptors: (L-RL(Long-form) and L-RS(Short form). L-RL receptor is biologically active and has a capacity for signal transduction. Although they primarily exist in the hypothalamus, they don't transport all required segments for the lungs, kidney, liver, skeleton muscle, heart, testicles, and hematopoietic cells. Therefore they don't have many roles in the production of the signal. The main tissues where L-RS receptors exist are, however, the kidney, lung, and some parts of the brain [3].

When considering the primary functions of leptin in humans and mammals, it is effective in regulating nourishment conducts, activating the sympathetic neural system, and alerting angiogenesis, growth, and evolution. Leptin forms most of the metabolic effects by interacting with specific receptors in the central neural system and peripheric tissues. Apart from the hypothalamus, leptin receptors also exist in the cerebellum, brain cortex, hippocampus, thalamus, choroid plexus, and leptomeninges. These parts play important role in nutritional habits. Receptors also are determined in fat tissue, the brain, and the testicles [4]. It's unknown how leptin affects organs and systems and it takes part in literature as a hormone that actuates neuroendocrine, reproductive, hemopoietic, and metabolic functions to control metabolism apart from body weight.

Leptin has settled receptors in the brain and peripheric tissues and it's stated that it has a role in regulating functions related to thermogenesis, immunity system, fertility, bone density, brain development, hemodynamics, respiration, sympathetic neural activity, and insulin in the liver. It plays two major roles in regulating nutrition and hypothalamic-hypophysis endocrine organ centerline [5].

It's known that leptin is proportional to blood concentration's fat content in the body. Because women have higher fat content and its distribution is different, leptin blood levels are higher. Testosterone's suppressing leptin level is among the factors which play role in this situation [6].

In the situation of the menstrual cycle, leptin levels of women differ. It's at the highest level in ovulation, high in the luteal phase, and before menstruation, it decreases [7,8]. For men, plasma leptin levels are inversely proportional to blood testosterone levels. This is thought to have a testosterone negative effect on leptin expression [9,10]. Depending on aging and the

decrease of testosterone in men, leptin levels increase. However for women after menopause leptin levels decrease. Considine et al. think that this differentiation results from the effects of sex steroids [2]. When comparing normal-weight women and men and obese women and obese men, women have higher serum leptin levels. It's thought that whereas the determiner of leptin level for women is the body mass index, the most important determiner for men is waist circumference [11,12,13,14].

2. The relationship between leptin and obesity

DL Coleman and RBS Harris defined obese animal models in 1969 to explain the genetic mechanism of obesity. These defined animals are ob/ob rats (genetically obese), db/db rats (diabetic obese), and fa/fa rats (hypothalamic obese), and even today these animals have been used for studies [15-17]. While ob/ob rat reacts to leptin by losing weight, dp/dp rat doesn't react [15,17,18].

Obesity is body fat index showing extreme accumulation. Being an important problem in the community, obesity has a relationship with cancer, diabetes, osteoarthritis, hypertension, hyperinsulinemia, and dyslipidemia. Although there are many opposing points of view, basically it results from a chronic unbalance between energy intake and consumption. Obesity has become an epidemic problem related to early death all over the world. A strong relationship between obesity and IR has been shown in obese events for both diabetes and nondiabetes [19].

In obesity treatment, leptin was tried on humans and experimental animals as leptin IV, IP, SC, and ICV, and as a lack of leptin, a decrease in body weight was observed in animals so they increased energy expenditure [20,21].

Resulting of the lack of leptin, obesity is known to be treated by leptin injections [22]. Leptin is used during obesity treatment with many medicine applications in combination [23].

Among the reasons for obesity resulting from leptin in humans, there is a defect of leptin synchronization and synthesis in fat tissue, transportation problem of leptin in blood, leptin receptor and inadequacy of signal transmission in the hypothalamus and leptin's not being able to overcome the barrier of KBB and blood BOS. Obesity in humans may exist as a result of the lack of leptin like in ob/ob rate or db/db's being leptin however leptin receptor mutation. Most human obesity reacts to losing weight by decreasing food intake to leptin and increasing energy expenditure, few groups are refractory to leptin [22].

3. The relationship between leptin and osteogenesis

In leptin-defective fa/fa rats, decreased bone mass, increased bone resorption activity, and hypercalciuria draws attention to the leptin and bone relationship [24]. Reforming of bones and depending on this, skeletal homeostasis is controlled by endocrine and/or humoral factors. Among the anthropometric and

metabolic factors, body weight is the main determiner of bone density.

Under in vitro circumstances, leptin rat bone marrow leads to the increase of many mineralized bone nodules in its cultures. On the other hand, with giving leptin to ob/ob rats (congenital leptin lack), osteoblastic activity as in vivo and the increase of osteogenesis is observed [25,26]. Leptin is secreted with regulation which makes them different from adipose tissue adipocytes, and adipocytes in the bone marrow and it's thought that this event plays a supportive role in hematopoiesis and osteogenesis [27]. In the bone marrow, its inducing osteoblast differentiation and decreasing adipocyte differentiation explains the negative correlation between bone mineral density and body fat ratio [28]. In obese during obesity forming years, osteogenesis is denser. However, in the later phases of life, the bone loss ratio is happening more slowly. Leptin plays a role in the differentiation of bone marrow stromal cells to osteoblasts. It affects inhibiting osteogenesis in a hypothalamic way, as well [29].

It's reported that for humans, leptin level shows a positive correlation with obesity, increased bone density, and the speed of osteogenesis, having a bone-friendly function, leptin inhibits resorption by stimulating osteogenesis [30].

DISCUSSION

It's thought that exercise has an effect on leptin by the symphatoade energic system and it causes a reduction of fat mass by increasing energy expenditure and changing energy balance [31]. Weltman et al. reported in their study that without observing exercise intensity for 30 minutes acute exercise didn't change serum leptin [32]. It's also reported that short-time exercise doesn't lead to changes in serum leptin levels or it makes a little change [33], but short-time exercises for 41 minutes and under can change serum leptin concentration if they are intense [34]. However exercises over an hour lead to a decrease in serum leptin levels [35, 36, 37].

Karamouzis et al. explained that exercise with 12 km increased NPY at the rate of 81% and decreased leptin regarding energy unbalance [38]. Kraemer et al. showed that 30 minutes of exercise with max. VO2's 80% regarding the decrease of leptin concentration. However thanks to control samples taken from the same individuals, it was understood that the decrease of leptin depended on circadian rhythm [39].

Occurred by exercise, growth hormone, cortisone insulin and testosterone, norepinephrine, and epinephrine may show some changes and it's thought that these changes result in delayed leptin decrease 36. The effects of energy expenditure which increases with exercise on leptin concentration are less than the ones that occur with diet [40,41].

However, short-time training for 12 weeks doesn't affect leptin levels as long as they don't decrease fat mass [39].

It's observed that 3-4 days per week and a 20-30-minute exercise program doesn't change body fat and serum leptin levels [42].

Gomez-Merino et al.stated that a 4-week exercise program decreased serum leptin levels without having any change in Body Mass Index. This 4-weeks exercise program was a military education and very hard and daily energy expenditure was over 500 kilocalory [43].

When considering the effects of resistance exercises and leptin concentration, the studies were limited in number. Kanaley et al. attributed the decrease of leptin after 24 hours from type 2 diabetes patients' acute resistance exercises to the less arrival of glucose in fat tissue. When considering the results of the same study, leptin concentrations dropped after 9 hours of chronic resistance exercises [44].

Growth hormone has a more alert effect on leptin in a short time, whereas it has a pressor effect in a long-time. However, it's a question of debate whether leptin has a role in growth factors during hunger and IGF-I levels or not. There is 2 conflicting point of view about whether leptin affects growth factor or not. According to one of these views, it's very likely that leptin stimulates the secretion of growth factors. Because leptin resistance reduces this effect. According to the other view, leptin inhibits the secretion of growth factors. Thus, low growth factor secretion occurs in obese [45,46,47]. Although growth hormone treatment doesn't affect plasma leptin concentration as acutely [48], it reduces body fat ratio and leptin concentration for a long time. The decrease in plasma leptin levels may prove that performed growth hormone treatment is successful [49,50].

Leptin affects developing glucose homeostasis and inhibiting lipide metabolism in fat cells and its effects' mechanism is not known yet [51,52]. Researchers reported that the main production area of leptin is fat tissues [18,22,51]. However, apart from fat tissues, leptin is also secreted [53-55] but studies have been going on to make its functions in these tissues clear.

CONCLUSION

Studies show that there's an important relationship between obesity and obesity-derived diseases. One of the factors that are supposed to reduce leptin levels and regulate obesity is exercising. There are strong opinions about the fact that leptin hormone's forming and secretion is affected by exercise and this event may have a positive effect on diseases regarding obesity. It's explained in the reports that daily using leptin in 0.01—0.30 mg/kg subcutaneously is safe, however as a side effect, there is only local erythema. When using a treatment program for nearly a month with a diet, a kilo is lost. When the length of the treatment program is 6 months, this weight loss is supposed to be between 5 and 6 kg. Leptin inhibits obesity problems by functioning as a coordinator in the central neural system and body fat storage. Besides this, it functions as a multifunctional hormone that plays role in many areas like hematopoiesis fertility, wound healing, thermogenesis immune system, regulation of glucose metabolism, gastrointestinal functions, and osteogenesis. In the beginning, the leptin gene was thought to be effective only on energy balance and body fat distribution, but thanks to the development of technology its unknowns about physical and physiopathological functions from fetal growth to hematopoiesis skin skeletal system

development and pubertal developments will be explained with the results of studies.

On the other hand, leptin and diabetes have a close relationship. Leptin treatment is supposed to show positive results in diabetes cases. For this positive result, the increase of studies concerning leptin treatment being safe and effective has an important role. In the future, leptin treatment is thought to be a solution not only for diabetes patients but also for obesity, fertility diseases, weight control, etc. Recent studies have shown that exercise results in different results on leptin. It can be said that regarding diet and other factors, exercises that may affect energy balance and body fat mass, are effective on leptin secretion.

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