IJBPAS, June, 2022, 11(6): 2605-2621

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

LEPTIN- THE METABOLIC HORMONE BEHIND OBESITY

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Received 18th June 2021; Revised 19th Aug. 2021; Accepted 17th Sept. 2021; Available online 1st June 2022

https://doi.org/10.31032/IJBPAS/2022/11.6.6140

ABSTRACT

Leptin is a metabolic hormone secreted by adipose tissue. This hormone acts in the central nervous system and produces a negative feedback signal for regulation of appetite, metabolism and sexual maturation. The major hormone behind the management of weight is not given attention widely. There are adipocytokines which are secreted by the adipose cells. This adipocytokines namely, leptin, which is an adiponectin and one more adipocytokine- the tumor necrosis factor (TNF)-α, in recent days have gained a lot of attention in the medical field, and are known to be involved in weight change through roles in food intake, energy consumption, and glycolipid metabolism. Our main intention in writing this review is to highlight the role of leptin the metabolic cycle. In our detailed review, we have focused on the role of leptin, the mode of action of leptin, factors that regulate leptin, leptin resistance in obesity.

Keywords: Metabolism, Obesity, Role of leptin, Leptin Resistance, Pharmacological Therapy

INTRODUCTION

Excess consumption of foods rich in energy (i.e. unhealthy food habits), sedentary life style, lack of health care services and financial support, the developing countries are facing high risk of obesity and their adverse consequences (i. e diabetes, ischemic heart disease) **[1]**. Many studies reported that there are 1.9 billion adults who are in overweight category and almost 650 million people are obese globally. The risk is not only excessive weight and other associated disorders but there is a high chance in fatality

rate. There were around 2-8 million deaths reported because of being overweight or obese. Leptin-signaling pathway helps in recognizing the imbalance between excess energy intake and expenditure of energy. The excess storage of this surplus energy leads to obesity. So there is a high need in understanding the role of leptin in the metabolic processes for new drug discovery **[2]**.

Adipose tissue secretes a hormone called Leptin, which acts in the central nervous system as a negative feedback signal to regulate appetite, metabolism and sexual maturation **[3]**. Adipocytokines secreted by adipose cells, namely, leptin, adiponectin, and tumor necrosis factor (TNF)-α, have gained attention in the medical field, and are known to be involved in weight change through roles in food intake, energy consumption, and glycolipid metabolism **[4]**. The level of leptin increases with respect to the amount of fat present in the body **[5]**. Increased amounts of energy are associated with hyperleptinemia, but the hypothalamus is resistant or tolerant to the effects of increased leptin. The problem with hypoleptinemia results in insufficiency in energy levels. As a result, a complex neural circuit comprising orexigenic and anorexigenic signals is activated to increase food intake. The level of leptin varies according to the gender. In Women, there are higher leptin concentrations than men, as a result of this there are differences in the sex hormones **[6]**.

Functions of Leptin

Leptin hormone regulates the adipose tissue mass by controlling the effects of hunger, use of energy produced by food, physical exercise and energy balance the central hypothalamus mediated. Peripherally, leptin plays secondary functions like modulating the energy expenditure, helps in modulation between the fetal and maternal metabolism, and that of a permissive factor in puberty, also acts as an activator of immune cells, beta islet cells, and growth factor **[7]**. In **Figure 1**, few functions were highlighted.

Mechanism of Leptin (Figure 2)

Leptin is secreted in a pulsatile fashion and has a significant diurnal variation with higher levels in the evening and early morning hours **[8, 9]**. The levels of leptin in circulation reflect the amount of energy which is stored in the form of fat and also indicates the calorie intake (10). Obesity receptors (ObRs) expressed in the brain as well as in peripheral tissues. Alternative splicing generates several isoforms of ObRs. The short leptin receptor isoform of ObRa, plays an important role in transporting leptin across the blood–brain

barrier **[11]**. The long leptin receptor isoform of ObRb which mediates signal transduction and is strongly expressed in the hypothalamus, an important site for the regulation of energy homeostasis and neuroendocrine function **[12]**. The binding of leptin to the ObRb receptor activates several signal transduction pathways, including Janus Kinase-Signal Transducer and Activator of Transcription-3 (JAK-STAT3), which is important for regulation of energy homeostasis **[13]**, and Phosphatidylinositol 3-Kinase (PI3K), which is important for regulation of both food intake and glucose homeostasis **[14]**.

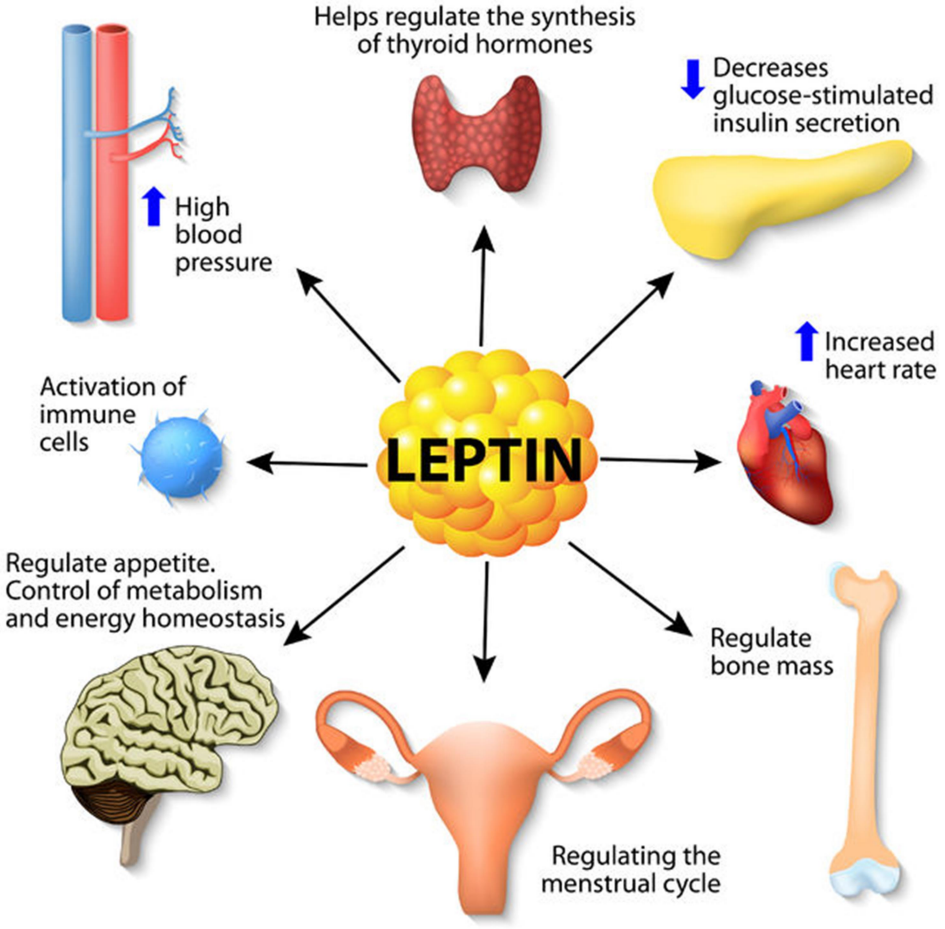

Figure 1: Functions of Leptin

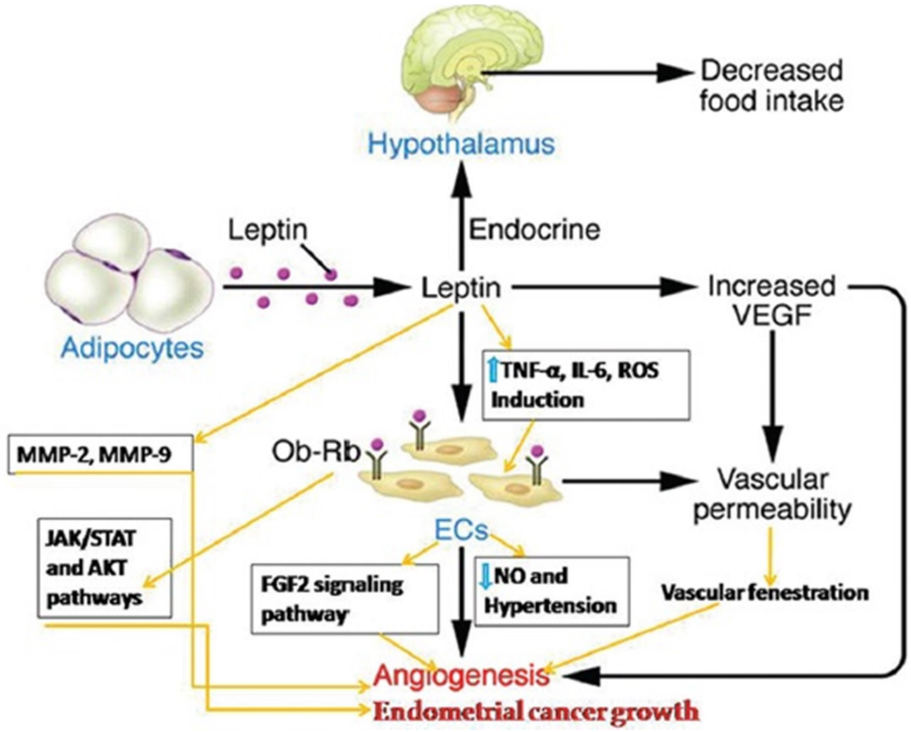

Figure 2: Underlying mechanisms by which leptin induces angiogenesis in physiological and pathological conditions

Factors that regulate circulating Leptin levels

- Unlike animals, in humans PPARγ agonists decrease leptin gene expression but increase subcutaneous fat mass. Thus, the net effect is null.
- Women have higher levels than men, even after adjusting the body mass index and the effects of sex steroids, mainly due to different body-fat distribution **[15, 16]**.

Leptin Resistance in Obesity

The leptin deficiency is not always the reason in persons who suffer from obesity. Most of these obese individual's exhibits increased levels of circulating leptin in proportion with their adipose mass **[17]**. High levels of leptin don't directly link to the suppression of feeding by reducing hunger or decrease body weight. These effects suggest that there is a relative resistance to the catabolic effects of leptin action in obesity **[18]**. The concept of leptin resistance is well established and patients with obesity are characterized by hyperleptinaemia **[19]**.

Many mechanisms have been proposed to explain leptin resistance; which include alterations in the transport of leptin across the BBB, alterations in cellular LRb signaling, perturbations in developmental programming, and others such as genetic mutation, inflammation **[20, 21]**. Indeed each of these

mechanisms may contribute to the totality of leptin resistance. Obesity can also be occurred with intake of over nutrition which leads to excess deposition of fats in turn stimulating release of leptin and pro-inflammatory cytokines **(Figure 3)**.

Mechanism of Leptin Resistance

Numerous mechanisms have been identified as potent underlying reasons for leptin resistance. **(Figure 4)**. These include a number of molecular and functional alterations characterized by structural changes to the molecule, its transport across the BBB, and the deterioration of leptin-receptor function and signaling **[22, 23]**.

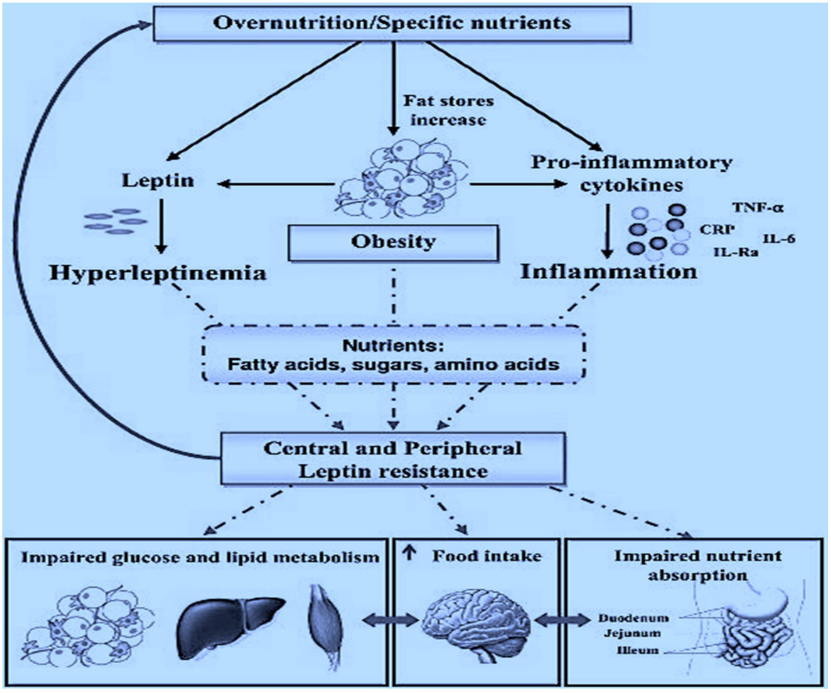

Figure 3: Leptin Resistance in Obesity

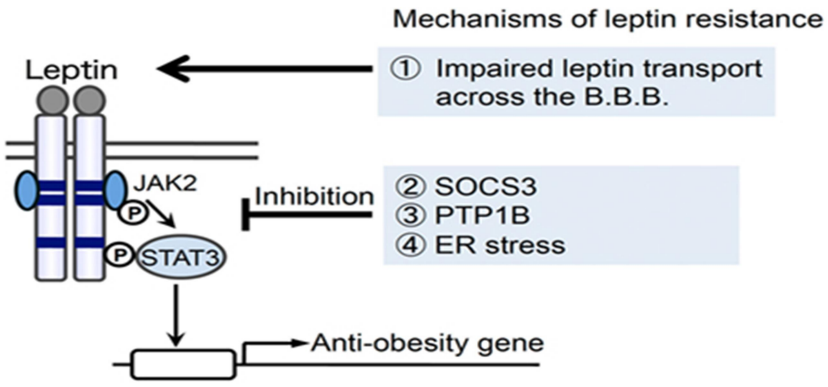

Figure 4: Mechanism of Leptin resistance

Genetic Mutation

In the Obesity gene (Ob) and DBU genes are extremely rare in humans and cause hyperphagia, obesity soon after birth, and hypothalamic hypogonadism in homozygotes. Such mutations have only been described in three sisters and resulted in the replacement of guanine by an adenine at the splice-donor site of exon 16 and generation of a truncated leptin receptor lacking transmembrane and intracellular domains. Mutant receptors at high concentrations circulate and bind to leptin. In addition to these consequences, dysfunctional secretion of thyrotropin and growth hormones can also occur. These findings indicate that mutations in the leptin gene and that of its receptor are not the main factors that induce the development of leptin resistance in the general population **[24-26]**.

Altered Leptin Transport Across BBB

Leptin resistance can also be developed at the BBB, thereby allowing unregulated transport of leptin from the blood to the brain. Brain blood vessels express short forms of OBR, which bind leptin and transport it from blood to the interstitial tissue of the brain and into the cerebrospinal fluid **[27, 28]**. At serum leptin levels above the range of 25–30 g/mL, the concentration of leptin in brain tissues and cerebrospinal fluid does not increase **[29]**. This phenomenon likely plays an importantrole in the development of leptin resistance and obesity, where excessive levels of leptin in the blood result in decreased BBB permeability.

Leptin itself plays an important role in the development of its resistance, with this phenomenon termed “leptin-induced leptin resistance”. Developing resistance to leptin increases the predisposition of patients to diet-induced obesity, which in turn contributes to a further increase in leptin levels and aggravation of existing leptin resistance in a vicious cycle. Additionally, hypothalamic inflammation, endoplasmic reticulum stress, and autophagy disorders are involved in the development of obesity-associated leptin resistance **[30]**.

Inflammation Induced Leptin Resistance

Given the functional and anatomical relationship between adipocytes and lymphoid cells, it is likely that leptin affects the neuroendocrine and immune systems. Morphologically, the accumulation of lymphoid tissue, including lymph nodes, omentum, thymus, and bone marrow, is associated with adipose tissue.

Fat deposits not only exhibit structural, metabolic, and heat-insulating functions but also provide a microenvironment conducive to supporting immune responses **[31]**. In particular, lymphoid and adipose tissues

interact through common mediators known as adipokines, molecules derived from adipocytes that connect metabolism and immune homeostasis (these molecules include leptin, adiponectin, chemokines, and other proinflammatory cytokines). Mattace Raso *et al* demonstrated that a high-fat diet induces low-grade inflammation in peripheral tissues (especially in adipose tissue and the liver), leading to an increase in inflammatory cytokines, such as IL-6 and tumor necrosis factor (TNF)-α **[32]**.

Menopause induced Leptin Resistance

Hot flashes have been postulated to be linked to the development of metabolic disorders. In one of the studies, the aim was to evaluate the co-relation between hot flashes, adipocyte-derived hormones, and insulin resistance in healthy, non-obese postmenopausal women. This cross-sectional study was performed on a total of 151 women aged 45–60 years who were stratified into one of three groups according to hot-flash status over the past three months: never experienced hot flashes (Group N), mild-to-moderate hot flashes (Group M), and severe hot flashes (Group S). Variables measured in this study included clinical parameters, hot flash experience, fasting levels of circulating glucose, lipid profiles, plasma insulin, and adipocyte-derived hormones. They have used multiple linear regression analysis to evaluate the associations of hot flashes with adipocyte-derived hormones, and with insulin resistance. (The result of the study provides evidence that hot flashes are associated with insulin resistance in postmenopausal women. It further suggests that hot flash association with insulin resistance is dependent on the combination of leptin and adiponectin variables **[33]**.

Leptin Resistance in Obstructive Sleep Apnea (OSA)

Obesity-related sleep breathing disorders such as obstructive sleep apnea (OSA) and obesity hypoventilation syndrome (OHS) cause intermittent hypoxia (IH) during sleep, a powerful trigger of oxidative stress. Obesity leads to a steep increase in the leptin levels. The reason behind is leptin resistance. IH is a potent stimulator of leptin expression and release from adipose tissue. Hyperleptinemia and leptin resistance may upregulate generation of reactive oxygen species, increasing oxidative stress and promoting inflammation **[34]**.

Diagnosis

Leptin Serum Test

Leptin serum test is performed to test the amount of leptin in your blood. It is a blood test by withdrawing blood from a vein in your arm or hand. The test results are

dependent on age, gender, health history, the method used for the test, and other things. Generally, the level of leptin is higher in women than in men and usually fall with ageing **[35]**. Serum leptin was significantly higher in the obese than normal weight women, with p value 0.002 **[36]**.

Treatment Strategies to overcome Leptin Resistance

Pharmacological Therapy

The strategies employed in most of the weight loss treatments usually target the dietary modifications in order to decrease the intake number of calories that a person consumes. As this is a temporary process and is of a short duration plan, it aids only in a short term weight loss. But this is followed by about 97-99% of people and they eventually gain it back **[37-39]**. So, instead of focusing on appetite, they must focus on balancing and maintaining the leptin levels (which may mean increasing or decreasing leptin depending on the situation). There are some lists of medications which can be target and reverse the leptin resistance.

Glucagon-like peptide-1 agonist (GLP-1 Agonist):

Drug Repurposing is a major area of research and one such example is seen with GLP-1 agonists previously, they came into existence to treat diabetes but it was later found that they also have a profound effect on weight. The main reason for weight loss is they act by suppressing the appetite. GLP-1 agonists seem to help prevent that drop in leptin seen in the post-weight loss timeframe. They also help promote leptin sensitivity **[40, 41]**.

Metformin

Metformin is the first-line medication for early insulin resistance **[42]**. It helps in decreasing the leptin levels which helps in persons who are suffering with leptin resistance and needs to lower your leptin level temporarily to help promote sensitivity **[43]**. It is not effective in people with moderate to heavy leptin resistance.

SGLT-2 Inhibitors:

SGLT-2 inhibitors, stand for sodium-glucose cotransporter-2 inhibitors.SGLT-2 inhibitors work by reducing leptin expression in white adipose tissues. SGLT-2 inhibitors are not as effective as GLP-1 agonists but are more effective than metformin **[44]**.

Non-Pharmacological Therapy

Avoid processed food: By avoiding highly processed foods, helps in improving in the gut health and inflammatory responses

Eat soluble fiber: Improves gut health and may protect against obesity.

Exercise: A mild to moderate physical activity might help in reversing leptin resistance.

Sleep: Adequate sleep is solves the problems with leptin.

Lower your triglycerides: Having high triglycerides can prevent the transport of leptin from your blood to your brain. The best way to lower triglycerides is to reduce your carbohydrates intake **[45-52]**.

Eat protein: Eating plenty of protein can cause automatic weight loss, which may result from an improvement in leptin sensitivity. Though there is no simple way to eliminate leptin resistance, you can make long-term lifestyle changes that may improve your quality of life **[52, 53]**.

Pre-clinical studies of Leptin

There were many studies on preclinical studies of Leptin. In one study on leptin-resistantDIO rats, the scientists at Amylin Pharmaceuticals showed that combination treatment with amylin and leptin leads to marked, synergistic reductions in food intake (up to 45%) and body weight (up to 15%) **[54, 55]**. In this study, the scientists considered leptin as an orphan drug and studied the use of it in a randomized clinical trial for obesity treatment, the concept of leptin replacement, preclinical studies on leptin/amylin combination and recent clinical studies on this combination. Due to safety concerns, these drug therapies were stopped.

In 2005, Pramlintide and Metreleptin were approved by the FDA. Pramlintide acetate which is a synthetic analog of amylin, can be administered through subcutaneous injection before major meals to lower postprandial glucose excursions in type 1 and 2 diabetics. Amylin is a 37-amino-acid peptide hormone that is co-secreted with insulin by pancreatic β- cells. The most common side effects in pramlintide are gastrointestinal problems which includes vomiting, nausea and abdominal pain. Metreleptin is an analog of human hormone leptin. It is also known as recombinant methionyl human leptin and is administered to patients with congenital leptin deficiency, lipodystrophy and hypothalamic amenorrhea.

Leptin replacement therapy

Replacement therapy is a safe and effective therapy which helps in the treatment of hypothalamic amenorrhea (HA), a disorder characterized by the cessation of menstrual cycles usually caused by chronic energy deficiency secondary to strenuous exercise and/or reduced food intake such as in patients with anorexia nervosa **[56, 57]**. In a study, Estrogen levels, thyroid hormone levels were normalized and more importantly, restored ovulatory menstruation **[58]**. A subsequent randomized, double-blinded placebo-controlled trial of 36 weeks of human recombinant leptin (metreleptin) replacement

therapy in women with HA also was found show similar improvements **[59]**. Women with this disorder tend to be more hypoleptinemic **[60, 61]** and the results of improvement could be seen in 3 months of leptin replacement therapy.

Leptin replacement strategy for obesity therapy

The metabolic response which aims to weight loss is a major factor to reduce obesity. The characteristics of this response is by a drop in energy expenditure beyond that predicted by changes in body composition **[62-64]**, blunted neuroendocrine functions (the thyroid and reproductive axes are suppressed, there is decreased sympathetic activity and increased parasympathetic activity) and circulating leptin levels are increased. This metabolic adaptation to caloric restriction explains the regain of lost body weight over time and appears to be related to the drop in leptin which occurs with weight loss **[65-67]**. It was proposed that rather than being a satiety signal, leptin's primary physiological role is to defend body fat stores in the face of prolonged energy deficit **[68-70]**.

CONCLUSION

The problem in management of weight is mainly due to failing to cut on high carbohydrate diet, lack of change in the sedentary life style and exercise. These factors ultimately results in weight gain. But in few cases, even when these factors were taken care of, still there is a chance of increase in weight. Leptin is a metabolic hormone which can be a reason behind this weight gain. In our review, we have highlighted the role of leptin, functions of leptin, the pharmacological & non-pharmacological therapies, clinical studies of leptin in obesity and amenorrhea. This could help in understanding the significance of leptin metabolism and the management of leptin levels to maintain ideal weight which could have future prospects in the development of new drug molecules.

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