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Review Article

Physiology Section

Physiological Role of Leptin: A Bird's Eye View

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ABSTRACT

Since its discovery over fifteen years ago, Leptin remains the cornerstone for researchers because of its important role in central control of energy metabolism. Apart from role in energy metabolism, researchers have identified some newer but important roles of leptin in various areas like neuroendocrine function and regulation of metabolism-immune system interplay. Recently, recombinant human leptin emerged as a therapeutic intervention in various disorders. In this review, we highlighted important biology and physiology of leptin, its association with several disorders, and therapeutic interventions involving leptin.

Keywords: Energy metabolism, Neuroendocrine function, Therapeutic intervention

INTRODUCTION

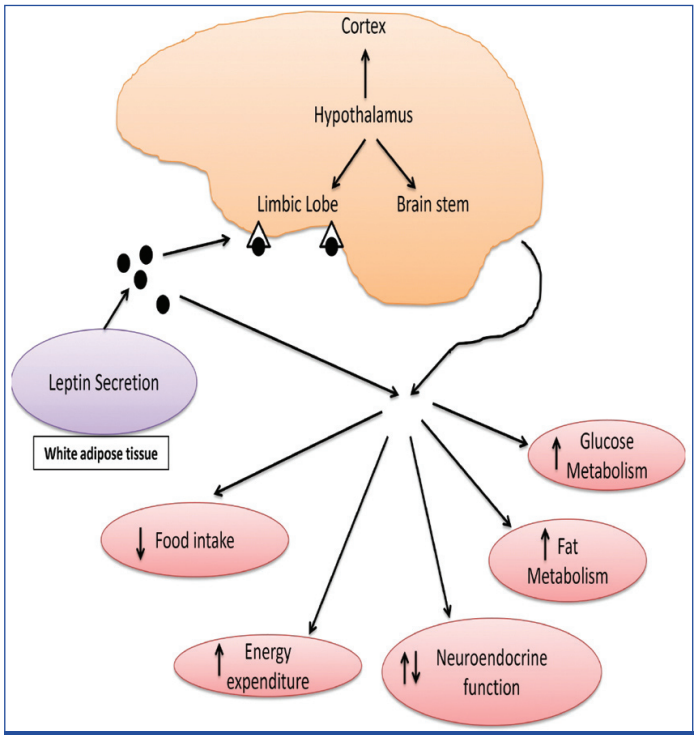
Leptin (Greek 'leptos' meaning thin) a hormone secreted by adipocytes has received so much of interest after its discovery fifteen years ago. It is also named as '*Ob gene*' located on 7q31.31. and also pioneered the concept of adipose tissue which acts as an active endocrine organ apart from an inert energy storage organ [1,2]. Leptin is comprised of 167 amino acids and is produced predominantly by the white adipose tissue of our body. It is said that total concentration of leptin circulating in the body is equal to the total amount of fat of a person. Initial researches showed that leptin might have a role to control excess fat gain in our body but afterwards it was known that greater leptin release leads to greater food intake and fat storage. Leptin is produced by placenta and stomach in fewer amounts [3,4]. Leptin, having 16-kD molecular weight, acts in brain via neuronal hypothalamic pathways and thus regulates energy homeostasis [2]. Studies have shown that leptin deficiency leads to obesity which explains its role in food consumption, energy utilisation, reproduction, thyroid functions and immunity [5]. several studies also suggested that leptin causes oxidation of fats in obese individuals [6]. Owing to its wide variety in functions, researchers put forward their efforts to demonstrate and elucidate leptin's role in physiological point of view. In this review, we summarised about leptin, its genetics, biology and various physiological roles in the human body.

LEPTIN: GENETICS AND BIOLOGY

Leptin was originally discovered through a technique of finding disease-associated gene of *ob/ob* mice, and thus also called '*ob gene*'. This gene is expressed in white adipose tissue, the stomach, the placenta, and, possibly, the mammary gland. It belongs to cytokine family as it showed crystalline structure [7-10]. Leptin being a hormone has a day-time variation with increased levels found in the evening and pulse-wise secretion in early morning hours. As produced by adipocytes, its main role is to regulate energy homeostasis which encompasses food intake, energy utilisation and body weight regulation. It also plays other important functions like regulating immune and inflammatory responses, causing angiogenesis and wound healing. Because of its role in energy homeostasis and regulating body weight, it is also called as anti-obesity hormone. Research suggested that it has role in development of high blood pressure in obese individuals [11-15].

LEPTIN: SIGNALING PATHWAY AND ACTION

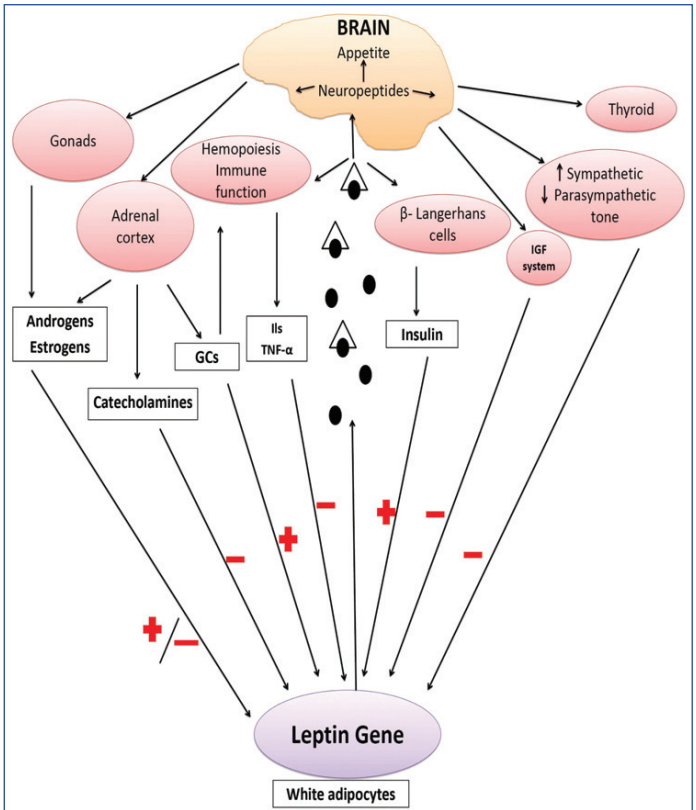
Leptin exerts its effect by binding with leptin receptors (LEPR). LEPR are found in many areas of the brain and brain capillary endothelium. LEPR is a part of glycoprotein 130 family of cytokine receptor. After somatic recombination of LEPR, various isoforms were generated and out of which LEPEb is the most important and the longest isoform that elicits strong signaling pathway. Studies reported mutations in LEPR which cause obesity. After binding with LEPR, leptin exerts signal cascade through Janus Kinase (JAK), Signal Transducer and Activator of Transcription Protein (STAT) pathway. It has been shown in some studies that leptin activates STAT3 pathway in brain hypothalamic region [Table/Fig-1] and [Table/Fig-2] [16-25].



[Table/Fig-1]: The actions of leptin. Leptin acts either directly or by activating specific centers in the central nervous system to decrease food intake, increase energy expenditure, influence glucose and fat metabolism, or alter neuroendocrine function. (Adopted from Mantzoros CS et al., 1999) [25].

LEPTIN: REGULATION [TABLE/FIG-2]

Regulations of leptin occur by many hormones in the body in the form of increase or decrease its synthesis at cellular level. Insulin increases leptin synthesis while epinephrine, norepinephrine and dopamine decrease leptin synthesis. Apart from these factors, tumor necrosis factor-α also increases the secretion of leptin. Glucose and fatty acids also affect the leptin expression and in turn its secretion [26].



[Table/Fig-2]: Feedback loops involving leptin. Leptin after release from adipocytes, binds with LERP in the hypothalamus, and alters expression of several neuropeptides; these in turn decrease appetite, increase energy expenditure by altering sympathetic and parasympathetic tone, and alter neuroendocrine function. Increasing leptin levels activate the thyroid, growth hormone, and gonadal axes and suppress the pituitary–adrenal axis. Leptin, acting directly or indirectly (by altering the levels of other hormones and neuropeptides), also influences hemopoiesis and immune function and improves glucose and fat metabolism. Finally, altered production and circulating levels of hormones and cytokines feeds back to alter leptin production by the adipocytes. GC=glucocorticoids; IGF =insulin-like growth factor; IL =interleukin; TNF-α=tumor necrosis factor-α, +/- represents regulation. (Adopted from Mantzoros CS et al 1999)25.

LEPTIN: PHYSIOLOGICAL ROLE

Energy Homeostasis [Table/Fig-2]

Leptin plays a major role in energy homeostasis by regulating appetite. Leptin activates a composite neuronal loop which comprises of its anorexigenic neurons only (i.e., appetite-diminishing) which releases Proopiomelanocortin (POMC) and orexigenic neurons (i.e., appetite-stimulating) which releases Neuropeptide Y (NPY) that regulates food intake. Recent meta-analysis reported that fasting state and energy-restricted diet to half of the total requirements can significantly lower the leptin levels. Clinically, mutation in leptin gene or its receptor leads to obesity due to hyperphagia. Studies demonstrated that leptin administration in such patients reduces food intake by increased satiety [27-29].

Regulating Neuroendocrine Function

Leptin levels fall during fasting and this is independent on fat mass. Fasting leads to neuroendocrine responses both in human and mice which includes decreasing hormone levels important for reproduction. This in turn decreases the changes of pregnancy (an energy-requiring process), decreasing hormone levels released from thyroid that slows rate of metabolism, increasing growth hormone level that may involve in movement of energy stores in body and may slow growth related activities. But study depicted that patient who has leptin deficiency since birth may have normal growth and development as well as adrenal function, unlike what was seen in mice [30-31].

Insulin Resistance and Metabolic Syndrome

Leptin gene mutation seen in ob/ob mice and db/db mice, and genetic leptin deficiency seen in human showed insulin resistance and some features of metabolic syndrome. Leptin treatment corrected hyperinsulinemia, hyperglycemia before weight loss both in mice and in human. But in human, it also decreased triglycerides, LDL-cholesterol and improved HDL-cholesterol [32]. Leptin has also been implicated for inflammation found in obese females which can lead to Gestational Diabetes Mellitus (GDM). Leptin not only controls balance between satiety and energy in mother but also generated by the placenta which in turn maintains fetal viability. The major source of circulating leptin in mother is its placental production which mobilises fat in mother aggravating chances of onset of GDM. In GDM, Leptin has significant effect on placenta in an autocrine/paracrine fashion. This leads to increased size of placenta, facilitates placental nutrient transport through glycerol transporter aquaporin-9 and increased fetal size (macrosomia). Centrally, insulin resistance may aggravate higher plasma leptin levels in GDM and further obesity-associated inflammation has its own role in developing insulin resistance. Therefore, nutrients which have anti-inflammatory effects are considered for the treatment in GDM. Obesity with insulin resistance is involved in aggravating Polycystic Ovary Syndrome (PCOS) in which researches found higher level of leptin. Recent study demonstrated inducer effect of leptin in immune imbalance seen in PCOS due to induction of interferon-γ (INF-γ) which may be involved in apoptosis in granulose cells [33,34].

Role in Cardiovascular Diseases (CVD) and Non-Cardiovascular Diseases (NCVD)

The role of leptin in CVD is not well understood. Several animal models like diabetic *(db/db)* and obese *(ob/ob)* models clearly depicted the beneficial role of leptin on cardiac metabolism. Under normal physiological conditions, heart uses glucose and fat as a fuel but preferably glucose. In leptin or LEPR deficient animal models, cardiac metabolic regulation is disturbed in terms of metabolic switch from glucose to fat utilisation by heart. This leads to increased oxidation of fat, increased oxygen consumption by myocardium and decreased cardiac efficiency which ultimately leads to systemic metabolic disorders like insulin resistance, leptin resistance, and metabolic dysfunction. Further, elevated triglycerides and fat accumulation in myocardium in such animal models showed lipotoxicity which in turn affects cardiac contractility. The studies done on animal models thus suggest that leptin can protect heart from lipid accumulation by acting as an anti-lipotoxic agent. There were controversial findings observed in various studies regarding association of leptin with Coronary Heart Disease (CHD) and Congestive Heart Failure (CHF). Increased leptin levels have been linked to risk of developing CHD and CHF. However, therapies which reduce leptin levels may contribute to lower cardiovascular risk in such patients. Higher leptin levels have been reported to predict risk of development of stroke, carotid artery disease and Peripheral Artery Disease (PAD). Hyperleptinemia has been reported to accelerate the growth of Abdominal Aortic Aneurysm (AAA) but still further studies will be required to establish clear relation [35,36].

Role in Neonate

Placenta and fetal tissue provide leptin to cord blood which is positively associated with the body weight and fat mass of the neonate. Apart from energy homeostasis, leptin regulates growth, promotes hematopoiesis and lymphopoiesis. Leptin secretion in milk suggests that maternal leptin level may affect growth of infants [37-39].

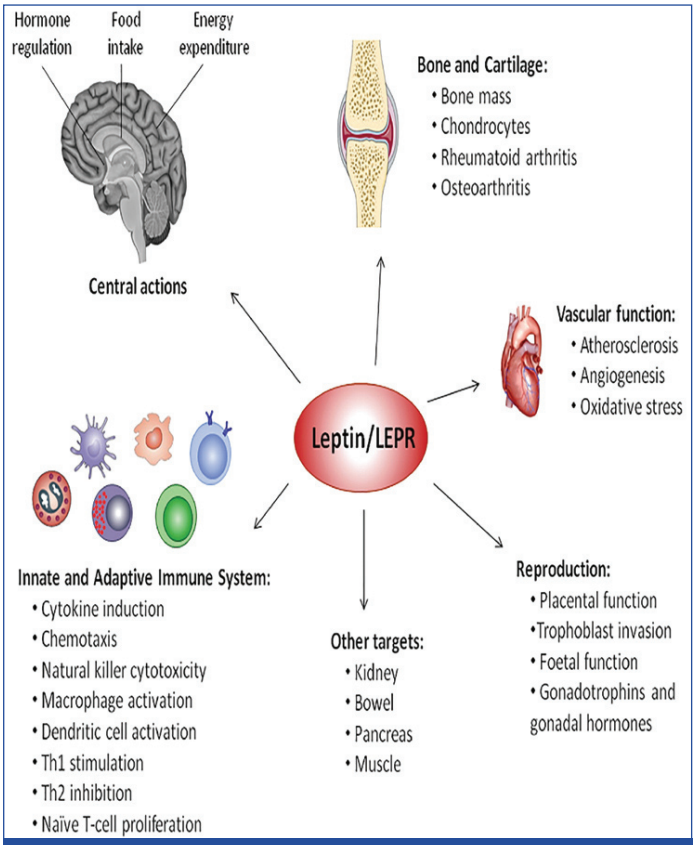
Role in Childhood and Puberty

Leptin sends signal to brain for fat stores that ultimately regulates the pubertal changes, menstrual cycle, and reproduction. At the onset of puberty, increase in body fat mass is due to increased level of leptin in normal children which in turn suggest that it causes puberty in humans. In contrast, persons with mutations of the LEPR are

morbidly obese, remain prepubertal, and have hypogonadotrophic hypogonadism [3,40].

Role in Bone Metabolism and Inflammation [Table/Fig-3]

Leptin was known to play a role in rheumatic disease and osteoarthritis (OA). Leptin level is increased in patients of OA. Most of the studies revealed catabolic role of leptin in cartilages. Leptin's role in these diseases also suggests that it acts as a pro-inflammatory factor on cartilage metabolism. Leptin not only considered as a mediator of inflammation in auto-immune diseases but also in other inflammatory disorders. In reverse to this, chronic inflammatory conditions secondary to metabolic, autoimmune or infectious diseases can lead to leptin resistance centrally followed by obesity which in turn potentiates inflammation [41-44].



[Table/Fig-3]: Pleiotropic nature of leptin. (Adopted from Francisco V et al., 2018) [38].

Role in Immune Responses

Leptin regulates both natural and acquired immune responses. As far as the innate immunity is concerned, leptin increases the power of Natural Killer (NK) cells and facilitates the activation of granulocytes, macrophages and Dendritic Cells (DCs). As far as the adaptive immunity is concerned, leptin increases the multiplication of newly formed T cells and B cells while it reduces that of regulatory T cells. Thus, leptin turns on B lymphocytes to secrete cytokines and controlling B lymphocytes production and maturation [45].

CONCLUSION(S)

Leptin, *an ob gene*, is produced by white adipocytes and reacts with LEPR which in turn initiates signal cascade through JAK-STAT pathway. Leptin signaling produces various neuropeptides like POMC and NPY which leads to decrease and increase appetite respectively. Leptin levels in circulation reflects total amount of energy stores in adipose tissue and this in turn directs CNS to regulate energy homeostasis, neuroendocrine functions, metabolic regulation, growth in neonates, childhood and puberty changes. Deficiency of leptin can be due to either mutation in leptin gene or inherited lipoatrophy. Anorexia nervosa, exercise-induced hypothalamic amenorrhea, and HIV lipoatrophy are some of the common causes of acquired leptin deficiency. This deficiency leads to disturbances in these functions causes, reproductive failure, obesity, insulin resistance, diabetes mellitus, metabolic metabolic syndrome and autoimmune diseases. Researches also showed the benefit of leptin therapy in such diseases. Now more interest is generated towards leptin therapy in various diseases.

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