

Versatile Role of Leptin- A Review

Vanaja R¹, Shanmuga Priya R¹ and Balaji Rajagopalan¹

¹Department of Biochemistry, Shri Sathya Sai Medical College and Research Institute, Ammapettai, Kancheepuram District, India.

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Corresponding Author

Vanaja R. E-mail: drvanajaa@gmail.com

ABSTRACT

Leptin, a multifaceted hormone has a pivotal role in many of the body metabolisms. It controls obesity by means of regulating the satiety center in the hypothalamus. When leptin levels were correlated with BMI, the development of Diabetes Mellitus can occur. Studies have shown that CNS may also be affected by obesity, which in turn depends on the leptin levels. Thyroid hormones have an important regulatory effect on the levels of leptin. It plays a significant role in the activation of the immune system. Leptin influences PCOS and fertility and is involved in bone metabolism also.

Key Words: Leptin, obesity, CNS, immunity, PCOS, bone

INTRODUCTION

Leptin is a glycosylated polypeptide hormone secreted by adipocytes and aids in the regulation of dietary intake (1). It is encoded by the obese (ob) gene. Since its involvement in neuroendocrine function and energy expenditure (2), it is corroborated with obesity. Leptin plays a role in providing a signal to the satiety centre in the hypothalamus through its receptors which are of six types, encoded by a single gene, OB-R which is a member of cytokine family (3,4). Leptin is implicated in immunologic responses and inflammatory reactions (5). Experiments were performed using epithelial, endothelial cells, platelets, T cells, skin, and pancreatic cells showed that leptin plays a vital role in normal metabolism. (6-11). Leptin also modulates fertility, bone formation, and density. It is also essential to maintain body weight along with other functions (12).



Leptin and Obesity

Obesity is due to an imbalance in energy metabolism. A complex correlation exists between hormone axis and body fat in maintaining homeostasis. This leads to the integration of various neurotransmitter signals.

The brain receptors are stimulated, when the leptin level is low, which in turn regulates the endocrine secretion. The leptin-receptor complex reduces the craving for food. The mutation of the (ob) gene causes obesity. The mutated gene produces inactive leptin or no leptin (13,14). Even though the mutated leptin increases adiposity, the rate varies in relation to different BMI (15). It was proved that leptin resistance also promotes obesity (16). There are two important reasons for leptin resistance which are mediated through peripheral (due to defective transport across the blood-brain barrier) and central (aberrant receptor) mechanisms. Studies in rats have shown that increased dietary intake of fructose reduces leptin Levels.

Role of Leptin in Diabetes Mellitus

Studies have shown that there is no direct relation of leptin with Diabetes Mellitus. Leptin levels were found to be elevated when correlated with BMI in Diabetes Mellitus (17). The fact that obesity can be the result of leptin resistance, it may be assumed that leptin resistance, in turn, involves in the development of Diabetes Mellitus. It was reported that leptin levels were augmented in conditions of Polycystic ovarian disease (PCOD), which is positively associated with BMI (18). Leptin therapy combined with a diet that stimulates leptin signaling may be the underlying mechanism in controlling Diabetes and Obesity.

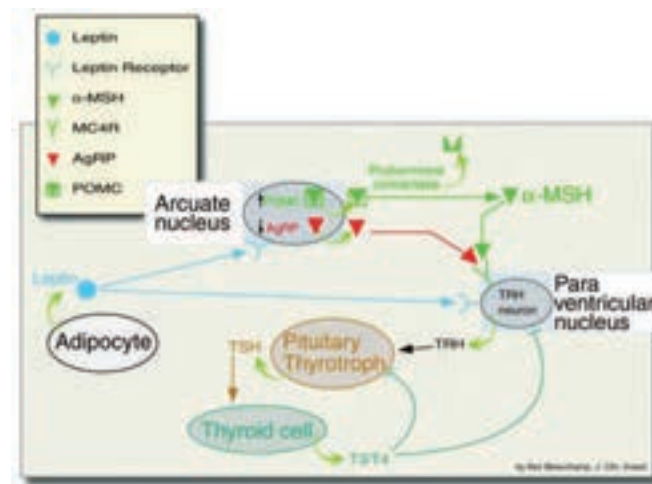
Involvement of Leptin in CNS

Literature shows that CNS may also be affected by obesity and related metabolic changes. Obesity is associated with a decline in cognitive functions like anorexia and depression. The mechanism by which obesity affects the cognitive function has to be elucidated. Obesity regulates brain function may accentuate neurodegeneration. Studies showed that there are diet-induced metabolic disturbances in the development of dementia. Leptin may also be important in the CNS response to obesity. It functions as an afferent adiposity signal to the brain, suppresses appetite, and increases energy expenditure (19). Leptin influences neuronal excitability via the activation of the K^+ channel in the brain, which may be important in the regulation of food intake and cognition (20). Increased melatonin, a hormone that controls biological rhythm inhibits MSH, a hunger suppressant hormone and hence leptin levels are declined. Abnormal sleep-wake cycle pattern reduces leptin levels and leads to obesity (21). Animal studies

have shown that alteration of brain proteins and impaired neuronal function due to the deficiency of leptin can be alleviated by leptin injection (22).

Impact of Leptin on Thyroid Function

Thyroid hormones were found to have an important regulatory effect on the levels of leptin. Studies have shown that the leptin levels were elevated in subclinical hyperthyroid status, especially in women. Starvation rapidly suppresses T4 and T3 levels (23,24). The mechanism behind this might be the decline of TRH, which reduces both TSH levels and leptin secretion, which in turn increases appetite and decreases energy expenditure. TRH neurons are targets of leptin and enhance its actions (25).



Influence of Leptin on Immune System

The adipokine leptin has a pivotal role in the activation of the immune system. It is also involved in the pathogenesis of chronic inflammation (26). T-Lymphocyte functions are affected by varying levels of leptin. Elevated levels of leptin are seen in chronic inflammatory diseases like hypertension, metabolic syndrome, and cardiovascular diseases (27). White blood cell counts are found to be highly increased in correlation with leptin levels. Increased leptin act as a pro-inflammatory response for cellular stress due to high-calorie intake to prevent overeating (28). It has been established that leptin acts as an inflammatory marker for cytokines. Leptin plays a significant role in the activation of innate immunity by various actions. Some of the actions of leptin are enhancing the proliferation of the monocytes and macrophages and phagocytosis. Leptin also induces the secretion of IL-1R α in monocytes. It also triggers the secretion of growth hormone-mediated by protein kinase C and nitric oxide-dependent pathways. Proliferation,

differentiation, and activation of Natural killer cells are stimulated by leptin and thereby improves the innate immunity. Role of Leptin in autoimmune diseases such as Rheumatoid arthritis has been studied (29). Leptin is cleared by kidneys. Leptin plays a role in the development of glomerulosclerosis, which eventually leads to proteinuria (30).

The Relevance of Leptin on PCOS and Fertility

The polycystic ovarian syndrome is generally an endocrine disorder in women of reproductive age. Obesity is observed in most of the females with PCOS. Leptin has a role in augmenting the reproductive function. The leptin levels were found to be elevated in PCOS (31). A correlation was found between leptin and fertility by means of irregular menstrual cycles. Leptin plays a vital role in the gametogenesis and steroidogenesis process of ovary (32). Leptin exerts direct regulatory action in ovarian folliculogenesis, and it is involved in estradiol production in the ovary. Absence of ovulation and increased androgen levels are related to the leptin levels, which in turn affects fertility. Leptin shows a negative correlation with the neuroendocrine regulation of reproduction because obese people develop leptin resistance and hence, satiety is not reached.

Effect of Leptin on Bone Mass

Leptin receptors are found in osteoblast and chondrocytes, which shows that leptin has a direct effect or it may be through activation of fibroblast factor 23 (FBF-23) on bone metabolism. Experimental studies on animals have shown that the effect of leptin may be through the brain stem and serotonergic action. It takes part actively in the development of bone mass through activating the sympathetic nervous system and triggering the secretion of neuropeptides. Further, the anabolic effect of leptin leads to the differentiation of bone marrow cells into osteoblasts (33). Regulatory pathways of leptin enhance the osteoblastic activity, and it can be utilized for the treatment of osteoporosis. The control of bone mass formation mainly depends on the signaling by leptin and not on body weight. The anti-osteogenic activity of leptin was also experimented on vertebrates and observed that increased bone resorption was the underlying mechanism (34). It is involved in regulating the osteocalcin levels, which is responsible for bone growth.

CONCLUSION

Evaluation of leptin levels in various metabolic alterations is of immense importance in modulating different disease states. Leptin deficiency or resistance may promote obesity, which in turn cause Diabetes mellitus and also leads to alterations in CNS. TRH neurons are regulated by leptin, and it also enhances the immune system. Leptin levels were elevated in PCOS, and its deficiency affects fertility. Studies show that leptin may alleviate the complications of bone diseases, especially osteoporosis.

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