International Journal of Health Sciences and Research
www.ijhsr.org ISSN: 2249-9571

Review Article

Leptin Dysfunction: A Cause for Obesity

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Received: 13/11/2015 *Revised: 03/12/2015* *Accepted: 08/12/2015*

ABSTRACT

High prevalence of obesity and the numerous negative health effects that are associated with this phenotype, it is relevant to examine the pathway of leptin in order to determine effective treatment options. The Ob gene, which is known to encode the 16 kDa protein hormone leptin, is one of the main genes that have been linked to the obesity phenotype in humans. Leptin is primarily synthesized and secreted by white adipose tissue and acts through a complex mechanism involving receptors in the brain and several peripheral tissues. Its plasma concentration varies in proportion to fat mass. Mutations of the leptin or leptin receptor gene are associated with obesity and insulin resistance. Leptin deficiency is a very rare in humans. In contrast, many obese humans have a high circulating leptin concentration, which apparently does not prevent the growth of their adipose tissue, suggesting that leptin resistance. Thus high prevalence of obesity and the numerous negative health effects that are associated with this phenotype, it is relevant to examine the pathway of leptin in order to determine effective treatment options. Binding of leptin to its receptors in the hypothalamus and brain stem coordinates the activity of neuroendocrine unit that inhibit food intake and increase energy expenditure, metabolism, neuroendocrine axis, and immune function. Loss of function mutations of the leptin or leptin receptor gene is associated with obesity and insulin resistance. Current treatment options, including both gene therapy and direct leptin injections have proven to be modestly successful.

Keywords: Leptin; Obesity (ob) gene; LEPR (Leptin Receptor); Obesity; Arcuate nucleus (ARC).

INTRODUCTION

Obesity is now a pandemic health problem in both developed and developing countries throughout the world. Obesity is defined as increased in mass of adipose tissue. Although not a direct measure of adiposity, the most widely used method to gauge obesity is the body mass index (BMI), which is equal to weight/height^2 (kg/m^2). [1] The World Health Organization has precisely defined obesity as BMI of 30 and above for west and 27.5 and above for the Asian. [2] The BMI describes the body weight relative to height; it correlates strongly in adults with the total body fat content. [3] Obesity is therefore more effectively defined by assessing its linkage to morbidity or mortality. Along with the social stigma of being obese; number of other medical conditions can result, such as coronary heart disease, hypertension, [4] type 2 diabetes, cancer (including endometrial, breast, and colon), dyslipidemia, stroke, liver disease, gallbladder disease, sleep apnea, respiratory problems (asthma,

obstructive sleep apnea), osteoarthritis, and reproductive problems in women. [5,6] The mechanism underlying this association is unknown but may relate to the fact that intraabdominal adipocytes are more lipolytically active than those from other depots. Adipokines and cytokines that are secreted by visceral adipocytes may play a role in systemic complications of obesity. [1] Release of free fatty acids into the portal circulation has adverse metabolic actions, especially on the liver.

Worldwide, prevalence of overweight and obesity combined rose by 27·5% for adults and 47·1% for children between 1980 and 2013. The number of overweight and obese individuals increased from 857 million in 1980, to 2·1 billion in 2013. The USA accounted for 13% of obese people worldwide in 2013, with China and India jointly accounting for 15%. Although age-standardised rates were lower in developing than in developed countries overall, 62% of the world's obese individuals live in developing countries. [7] In U.S. alone, the consequences of obesity account for an estimated 300,000 deaths per year. [8]

Maintenance of body weight is achieved by the interaction of very complex hormonal and neurological factors, with the goal of increasing appetite and preserving body fat when energy stores are low. [9] Sensory receptors located within the stomach get stimulated due to stretching of stomach which than directly send signal to the brain through nerve impulses for satiety. Also glucose, fatty acids, and amino acids in the blood levels indirectly stimulate the perception of satiety in brain centers and suppress eating behavior. [10]

Obesity is multi-factorial as it is based on genetic, behavioral and environmental factors. [5] Various genetic disorders can cause obesity in isolation or mostly in syndromic form. Environment plays a key role in shaping an individual's habits and lifestyle. There are many environmental influences that can impact your health decisions, which contribute to the development of a high degree of body fat. Present society has developed a more sedentary lifestyle such as television watching, internet, video games etc. Walking has been replaced by driving cars, basic physical activity has been replaced by technology and nutrition has been overcome by fast foods. Based on food choices, many people now select diets that are calorie-rich, but nutrient-poor. This behavioral problem also relates to the increase in meal quantity at home and when dining out. Fast foods have high fat and energy content. Extensive evidence support that the maladaptation of the biological system for weight maintenance makes it extremely difficult for people to maintain weight loss. [11] Obesity results from an imbalance between food intake and energy expenditure, resulting in excessive accumulation of fat in adipose tissue, liver, muscle and other organs involved in metabolism. [12] Obesity is also associated with low-grade chronic inflammation within the adipose tissue. Excessive fat storage leads to stress reactions within fat cells, which in turn lead to the release of pro-inflammatory factors from the fat cells themselves and immune cells within the adipose tissue. [13] Before the discovery of association on the role of leptin in obesity, three main theories existed regarding the way in which the body can regulate body weight: a) a thermoregulation theory, where maintenance of a basal body temperature through energy expenditure influences weight: b) a glucostatic theory, where plasma glucose regulates all energy stores and c) a lipostatic theory, where the metabolic product of fat circulates in the blood and interacts with various receptors to maintain fat stores. Leptin functions as a peripheral signal in a negative feedback loop system to control body weight. [14]

LEPTIN: Leptin (from the Greek *leptos*, meaning thin) was originally identified in 1994 as the gene defect responsible for the obesity syndrome in mice. [15] It is a 167-amino acid protein hormone with important effects in regulating body weight, metabolism and reproductive function. [16] Leptin is described as 16-kDa hormonal product of obesity (ob) gene located on chromosome 7 in humans. [17] Leptin action is opposed by the hunger hormone called ghrelin. Both hormones act on receptors in the arcuate nucleus of the hypothalamus. [18] Its primarily produced by adipocytes. [19] Number of hormones modulate ob gene expression, including glucocorticoids and insulin. [20] The fat cells produce leptin and this is secreted into our bloodstream. It is secreted as a hormone mainly from white adipose tissue. Smaller amounts of leptin are also secreted by the epithelium cells of the stomach and in the placenta. Leptin is secreted in ratio to adipose mass, thus its levels increase with weight gain and decrease with weight loss. [21] Subcutaneous fat depot seems to be a stronger predictor of leptin levels than intrabdominal fat. [22] Women have higher leptin levels than men because of an increase in leptin expression in subcutaneous adipose tissue, and stimulation of leptin synthesis by estrogen, and inhibition of leptin synthesis by testosterone. [23] Leptin levels are increased by insulin, glucocorticoids, and pro-inflammatory cytokines and decreased by catecholamines. [24]

Physiologic Effects of LEPTIN: High leptin levels signal the presence of sufficient energy stores to sites in the central nervous system, which responds by reducing appetite and increasing energy expenditure, preventing severe obesity. [25] Therefore, leptin signals the nutritional status from the periphery to the area of the brain involved in the homeostasis of energy balance. [26] Leptin upgrades the general sympathetic nerve activity and this leads to a significant increase in energy expenditure. [27] This complex system of appetite control can become disturbed in obesity as excess fat stores contribute to chronically elevated leptin levels. [28] Leptin's functions are quite pleiotropic, and it is implicated in a variety of cellular processes, including the modulation of immune cell function. [29] Leptin is secreted in humans in a circadian and pulsatile pattern (maximal secretion from midnight to 7 AM, and a pulse frequency of 32 pulses/24 hours, each lasting 33 min). The half-life in blood is approximately 25 minutes, which is not modified by body condition (normal or obese). [30] Serum leptin levels decrease during starvation, and leptin has been proposed to be a major regulator of the central nervous system-mediated adaptation to starvation. Absence of leptin is responsible for the obese phenotype of ob/ob mice, and administration of this hormone to these animals reverses many of the endocrine defects. [31] Furthermore, studies in rodents support a possible role of leptin in regulating adiponectin, showing that fasting acutely decreases leptin expression and its serum concentration, also decreases adiponectin gene expression in adipose tissue, whereas refeeding normalizes the expression of both hormones. [32]

LEPTIN Receptors (Lepr): Leptin receptors, which have sequence homology to members of the cytokine receptor super family, which includes interleukin and growth hormone [33] and are widely distributed throughout the body. [34] In 1995 db gene that encodes the leptin receptor was confirmed. [35,36] Leptin receptors are highly expressed in areas of the hypothalamus, as well as in T lymphocytes and vascular endothelial cells. The leptin receptor exists in at least six isoforms, one of which (Ob Rb), the so-called 'long form', is thought to be the most important for transmitting the leptin

signal in cells. Ob Rb is located predominantly in the hypothalamus. [37]

Regulation of Energy Expenditure, Food Intake and Body Weight by LEPTIN: It appears that as adipocytes increase in size due to accumulation of triglyceride, they synthesize more and more leptin. Leptin's effects on body weight are mediated through effects on hypothalamic centers that control feeding behavior and hunger, body temperature and energy expenditure. [38] Leptin directly targets two neuronal populations in the arcuate nucleus (ARC) co-expressing proopiomelanocortin (POMC)/cocaine- and amphetamineregulated transcript (CART), and agouti-related peptide (AgRP) and neuropeptide Y (NPY). [39] Leptin stimulates POMC/CART expression and inhibits AgRP/NPY expression, thereby reducing food intake, increasing energy expenditure, and decreasing body weight. In addition, leptin inhibits feeding by reducing the expression of melanin-concentrating hormone (MCH) and orexins in the lateral hypothalamic area (LHA). Leptin has also been shown to stimulate the expression of brain-derived neurotrophic factor and steroidogenic factor-1 (SF-1) neurons in the ventral medial hypothalamus (VMH), leading to inhibition of feeding. [40,41]

Leptin's activation of Janus kinase 2 (JAK2)/ signal transducer and activator of transcription 3(STAT3) signaling appears to play a major role in energy homeostasis and neuroendocrine function. Deletion of STAT3 in neurons decreases POMC and increases AgRP and NPY levels, culminating in hyperphagia, obesity, infertility, and thermal dysregulation. [42] Leptin exerts an inhibitory effect on AMPK (5' adenosine monophosphate-activated protein kinase) in the hypothalamus, thereby stimulating ACC (acetyl-CoA carboxylase) and subsequently suppressing food intake. Constitutive activation of hypothalamic AMPK blocks leptin's anorexigenic effect.

Leptin directly regulates adipose tissue metabolism through inhibition of lipogenesis and stimulation of lipolysis. DNA microarrays have shown that leptin has novel (indirect) effects on gene expression in adipose tissue. [43] Leptin also improves the insulin resistance and hyperglycemia evident in a diabetic lipodystrophic transgenic mouse line. [44] The anti-diabetic effects of leptin in these animals appear to come from leptin's ability to stimulate lipolysis and fatty acid oxidation in liver, skeletal muscle, and other peripheral tissues.

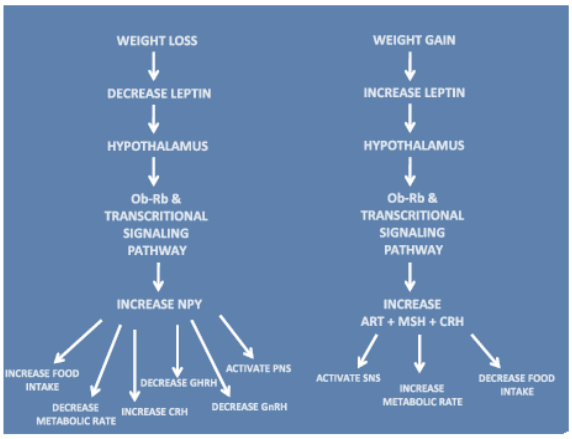

Figure 1 : Body response to change in leptin level

LEPTIN in Obesity: Deficiency of the adipocyte-derived hormone leptin leads to increased appetite and hyperphagia that result in obesity, infertility, and impaired T-cell–mediated immunity in humans. [45] Proopiomelanocortin is regulated by leptin and is cleaved by prohormone convertases to yield a melanocyte stimulating hormone. [46] In 1997 the two children first cousins of Pakistani origin, who were homozygous for a frameshift mutation in the ob gene that resulted in undetectable circulating leptin and a syndrome of hyperphagia and severe obesity were reported. [47] Subsequently six additional mutations were described. The most recently described eighth mutation reported in January 2015, in a child with Turkish parents, is unique in that leptin levels were elevated; but the leptin does not turn on the leptin receptor, so the

patient has functional leptin deficiency. [48] All these represent monogenic form of obesity. Leptin levels in obese humans are proportionate to fat mass and, thus, obese humans have higher leptin levels than do non-obese humans [38,49,50] and these high leptin levels fail to reduce excess adiposity, indicating a state of leptin resistance. A number of mechanisms have been proposed to explain leptin resistance. At least 3 mechanisms have been found responsible for leptin resistance: these include 1. Impaired transit of leptin across the BBB; 2. reduced number of leptin receptors in critical target sites, or 3. Post-receptor signal transduction defects. [51-54] Indeed, each of these mechanisms may contribute to the totality of leptin resistance. Although the absolute lack or genetic alteration of LRb does not underlie most leptin resistance. [49,55] the preponderance of data confirm that alterations in cellular LRb signaling, especially in the ARC, play a crucial role in leptin resistance. [52,54,56]

TREATMENTS FOR OBESITY BY INCREASING LEPTIN LEVELS

Gene Therapy: In individuals that have reduction in leptin levels due to mutations in the Ob gene, the most direct means of increasing leptin is to alter its expression on the genomic level. The most promising approach in correcting this metabolic disorder is through gene therapy using recombinant adenoviruses. Several studies have used these types of vectors to carry cDNA for leptin to induce hyperleptinemia in rats. [57,58] In a study conducted by Chen et al. (1996), hyperleptinemia was induced in an experimental group of rats containing no leptin-related mutations it was found that with an increase in leptin there was a 30-50% reduction in food intake The major disadvantage of this approach is that the duration of expression of adenovirally expressed genes is limited. This is likely caused by an immune response that destroys the genetic material of these vectors due to specific viral-encoded genes that initiate a host immune response. [57,58]

Direct Administration of Leptin Effectively Reverses Obesity Phenotype: Increasing leptin levels through direct injections is another therapeutic method that has been studied in order to correct leptin deficiency as a result of mutations in the Ob gene. [19,59,60] Several studies have demonstrated that peripheral administration of leptin shows modest decreases in food intake, resulting in the reduction of adipose tissue mass. However centrally administered leptin is more effective in producing long-standing effects in the reduction of food intake than peripherally administered.

CONCLUSION

Leptin plays an important role in the control of energy balance and insulin action in humans, as evidenced by the fact that leptin deficiency leads to morbid obesity and insulin resistance. Its plasma concentration varies in proportion to fat mass. Leptin functions through a complex mechanism involves binding to its receptors in the specific hypothalamic regions and brain stem that intricate the activity of neuroendocrine collectively which inhibit food intake and increase energy expenditure. This means that the therapy options must somehow manipulate this pathway in order to be effective. Current treatment options, including both gene therapy and direct leptin injections, although have proven to be modestly successful. However, both approaches present serious drawbacks, which would require further research.

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How to cite this article: Nabi T, Rafiq N, Qayoom O et al. Leptin dysfunction: A cause for obesity. Int J Health Sci Res. 2016; 6(1):498-505.

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