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Biological Role of Leptin in Management of Obesity

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ABSTRACT

Nowadays **o**besity is a major health problem all over the worlds especially in developed and developing countries. A person with a BMI equal to or more than 25 is considered overweight. Excess body weight is a result of an imbalance between energy intake and energy expenditure. Obesity is responsible for a number of health complications like diabetic and cardiovascular. Drugs available in market posses a number of adverse effects. Leptin is adipose derived cytokine which is essential for regulation of body weight and energy balance. Leptin regulate lipid profile and glucose metabolism, neuroendocrine functions. Leptin exerts immediate effects by acting on the brain to regulate appetite. Leptin is the first identified adipose-tissue-derived cytokine, which exerts profound functions in the regulation of food intake, energy expenditure, glucose metabolism, reproduction and immune response.

Keywords: Obesity, leptin, appetite cytokine, glucose metabolism, neuro-endocrine.

1. INTRODUCTION

Body mass index (BMI) is a simple index of weight-for-height that is commonly used to classify overweight and obesity in adults. It is defined as a person's weight in kilograms divided by the square of his height in meters (kg/m^2). A person with a BMI of 30 or more is generally considered obese. A person with a BMI equal to or more than 25 is considered overweight (WHO).[1] Hippocrates wrote “Corpulence is not only a disease itself, but the harbinger of others,” recognising that obesity is a medical disorder that also leads to many co-morbidities.[2]

Obesity is one of the most prevalent health problems in the Western world. Obesity increases the risk of medical illness and premature death and thus imposes an enormous economic burden on the health care system.[3] Inadequate of adipocyte hormone leptin, ob/ob mice develop severe obesity as a result of a combination of increased food intake and diminished energy expenditure.[4] Leptin is one of the most abundant and important adipokines. The most well-known effect of leptin is to regulate body weight and energy balance.[5]

The obese gene (ob) protein product leptin is a hormone that is secreted from adipocytes and functions to suppress appetite and increase energy expenditure.[6] but it also has fundamental roles in glucose and lipid homeostasis, reproduction, immunity, inflammation, bone physiology, and tissue remodeling. In its absence, severe and potentially lethal changes in body homeostasis occur.[7] Leptin deficiency is observed in specific conditions, such as lipodystrophy syndromes, hypothalamic amenorrhea, anorexia nervosa and congenital leptin deficiency (CLD) due to mutations in the leptin gene.

The clinical manifestations in these conditions may include increased insulin resistance, hyperglycemia, dyslipidemia, endocrine disruptions, and fatty liver disease. In addition, morbid obesity, impaired cognitive development, and potentially lethal T-cell hyporesponsiveness have been reported in patients with CLD.[8] Leptin is one of the most abundant and important adipokines. The most well-known effect of leptin is to regulate body weight and energy balance.[9]

In this review we discussed the biology and biological role of leptin, we also summarize about different actions of leptin.

2. OBESITY AND LEPTIN

Leptin levels correlate with adiposity, decrease acutely with caloric restriction, and increase with refeeding.[10] Leptin is produced in the adipocytes and acts on the neurons of the arcuate nucleus. The anorectic action of leptin is mediated by the activation of the proopiomelanocortin (POMC) neurons, which increase α-melanocyte-stimulating hormone (α -MSH), a CNS peptide that inhibits feeding.[11] simultaneously leptin suppresses neuropeptide Y and agouti related protein (AgRP), which may also contribute to decreased feeding. In addition to reducing food intake leptin increases the activity of the thermogenetical components of the sympathetic nervous system. Several mutations can result in disturbance of leptin pathway and set the stage for hyperphagia due to an inability to experience satiety. However, most obese humans do not have genetic deviations causing lack of leptin but have high leptin levels, correlating with total body adiposity.[12]

3. BIOLOGY OF LEPTIN

Leptin is an attractive candidate for the treatment of obesity as it is an endogenous protein and has been demonstrated to have potent effects on bodyweight and adiposity in rodents.[13] Leptin, a 167-amino-acid product of the human leptin gene, was originally discovered through positional cloning of ob/ob mice, a mouse model of obesity found serendipitously at Jackson Laboratories. These mice were found to have a homozygous mutation of the leptin gene resulting in complete leptin deficiency, which manifested with hyperphagia, extreme obesity, diabetes, neuroendocrine abnormalities, and infertility. Leptin is secreted mainly by white adipose tissue, and levels are positively correlated with the amount of body fat.[14] Like many other hormones, leptin is secreted in a pulsatile fashion and has a significant diurnal variation with higher levels in the evening and early morning hours.[15, 16]

4. BIOLOGICAL ROLE OF LEPTIN

4.1 Effect on lipids and glucose metabolism in diabetes

leptin plays an important role in the regulation of energy homeostasis, growing evidence suggests that leptin is also critical for glycaemic control.[17] It was found that in the Turkish cohort, leptin replacement normalized blood lipids (reducing triglycerides and increasing HDL), and reduced insulin levels and glucose. Also, glucose levels in the oldest patient, who had the diagnosis of type 2 diabetes before leptin therapy, decreased to normal levels, from 7.3 mmol/L before treatment, to 4.8 mmol/L after 18 months of leptin therapy.[18] Similar effects on triglycerides, HDL and insulin have been observed in the other patients as well.[19,20] Leptin regulates pancreatic β-cells function, by reducing the transcription of insulin, stimulating β-cell proliferation, inhibiting insulin secretion, and suppressing β-cell apoptosis.[21] In glucose, insulin and C-peptide during meal tolerance tests and oral glucose tolerance tests, metreleptin increased insulin sensitivity by at least 5.7 fold, increased insulin hepatic extraction, and decreased insulin secretion.[22]It was also observed that withdrawal of leptin can cause substantial weight gain, up to 10.0 kg after 6 weeks off-leptin, which determined an acute and transient increase in insulin sensitivity while off leptin, as the newly acquired adipose tissue absorbed glucose in excess.[23]

4.2 Energy homeostasis

The most significant roles of leptin include regulation of energy homeostasis, neuro-endocrine function, and metabolism. Other effects of leptin involving regulation of immune function.[24,25] leptin exerts immediate effects by acting on the brain to regulate appetite via ObRb-receptor binding in the hypothalamus, leptin activates a complex neural circuit comprising of anorexigenic (i.e. appetite-diminishing) and orexigenic (i.e. appetite-stimulating) neuropeptides to control food intake. Outside of the hypothalamus, leptin interacts with the mesolimbic dopamine system, which is involved in motivation for and reward of feeding, and the nucleus of the solitary tract of the brainstem to contribute to satiety.[26] Not only does leptin signal the central nervous system to decrease food intake, it may also increase energy expenditure. In mice, leptin can increases sympathetic nerve activity[27] and activates brown adipose tissue thermogenesis[28,29] but these effects have not been confirmed in humans.[30]

4.3 Neuroendocrine function regulation

During fasting, leptin levels fall rapidly before and out of proportion to any changes in fat mass triggering the neuroendocrine response to acute energy deprivation.[31,32,33,34]

4.4 In insulin resistance and the metabolic syndrome

In the *ob/ob* mouse strain, leptin treatment improves hyperglycemia and hyperinsulinemia before weight loss is achieved.[35]Leptin treatment in humans with congenital leptin deficiency has also been shown to improve not only hyperinsulinemia but also levels of low-density lipoprotein cholesterol, high-density liproprotein cholesterol, and triglycerides.[36]

Similarly, mouse models of lipoatrophy, which lack subcutaneous adipose tissue, are hypoleptinemic due to lack of fat available to produce leptin and have metabolic abnormalities, including hyperglycemia, insulin resistance, and hyperlipidemia.[37] Given the improvements in metabolic parameters in *ob/ob* mice after leptin administration, it was hypothesized that lipoatrophic mice may also be responsive to exogenous leptin.[38] Indeed, transplantation of adipose tissue[37,39] which produces leptin, and administration of exogenous leptin[38] in lipoatrophic mice improve hyperglycemia, insulin resistance, hypertriglyceridemia, and hepatic steatosis. This has led to trials in humans with various types of lipoatrophy and associated metabolic abnormalities and found better results.[40-47]

5. CONCLUSION

Now a day's obesity is a major health problem. Despite of large number a drugs available in market for management of obesity synthetic anti-obesity drugs posses more side effects. Drug related side effects are major problem for treatment of obesity. Leptin deficiency occurs in different conditions like lipodystrophy syndromes, hypothalamic amenorrhea, anorexia nervosa and congenital leptin deficiency (CLD). It occurs due to mutations in the leptin gene. The clinically it manifest as insulin resistance, hyperglycemia, dyslipidemia, endocrine disruptions, and fatty liver disease. In addition, morbid obesity, impaired cognitive development, and potentially lethal T-cell hyporesponsiveness have been reported in patients with CLD. Leptin can be use as an alternative for treatment of obese persons. Leptin is synthesized in our body by adipose tissue; it plays a major role in regulating satiety signal to hypothalamus. It reduces dietary intake and lipogenesis and modulates carbohydrate metabolism and energy expenditure. Leptin treatment also improves hyperglycemia and hyperinsulinemia before weight loss is achieved in diabetes so it is useful for treatment of obesity.

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