Review Article

The Impact of Leptin on Nutrition and Dietetics

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Abstract

Leptin, a hormone secreted by adipose tissue, is integral to the regulation of energy balance, influencing both appetite and metabolic functions. It exerts its effects primarily on the hypothalamus, where it influences the expression of neuropeptides and communicates the body's energy status, thereby affecting food consumption and energy expenditure. Nonetheless, the regulation of energy is multifaceted, involving various factors in addition to leptin, which positions it as a crucial, albeit not exclusive, player in metabolic regulation. Current research emphasizes leptin's significant involvement in obesity, revealing that its signaling pathways are modulated by insulin and thermogenic responses, which may provide insights for nutrigenomics and tailored nutritional strategies. This review explores the physiological roles of leptin, particularly its function in appetite suppression, fat accumulation, and its interactions with other neuroendocrine signals, including insulin, ghrelin, and neuropeptide Y. Clinical investigations highlight the potential of leptin as a therapeutic agent, particularly in the management of obesity and associated metabolic disorders. Despite its promise in regulating body weight through fat mass control, the phenomenon of leptin resistance observed in obese individuals poses a significant barrier to its therapeutic application. Ongoing research into leptin-targeted therapies, especially when integrated with lifestyle modifications and personalized medicine, shows potential for effectively addressing obesity and chronic metabolic conditions. In summary, while leptin represents a valuable target for therapeutic strategies aimed at weight management and metabolic health, further investigation is essential to enhance its effectiveness and tackle the challenges posed by leptin resistance. Understanding the intricate mechanisms underlying leptin's action and its interactions with other metabolic pathways will be crucial for developing effective interventions in the fight against obesity and related metabolic disorders.

Keywords: Leptin, Obesity, Nutrition, Adipose, Dietetics.

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1. Introduction to Leptin

Leptin is an adipose-derived hormone that plays a crucial role in energy homeostasis. It is estimated that approximately 50% of the variability of a person's body fat can be explained by blood leptin levels, which thus appears to be tightly controlled at a certain level of body fat or energy reserves. Originally discovered as an obesity gene, the product leptin was shown to be regulated by plasma insulin levels and could regulate body fat mass by crossing the blood-brain barrier and affecting the expression of hypothalamic neuropeptides, such as alpha-melanocyte stimulating hormone and agouti-related protein. However, leptin is no longer seen as the sole regulator of appetite and energy metabolism but rather one influence on the complex hypothalamic control of metabolism. The leptin control system is now generally considered to be one of the major humoral signalers of the body's energy status to the brain (absence of leptin indicates lack of body fat and the need to take in more calories)[1,2,3].

Leptin is considered the most critical hormone combating obesity in humans. Therefore, a number of research studies have been conducted on the potential of leptin in the regulation of insulin, thermogenesis, and the barrier function of the intestine in the presence of obesity. The discovery of this obesity gene and its gene product signaled "absence of obesity" if leptin was present. This discovery was initiated by phenotype-driven genetic studies in rodents and reversed by the generation of leptin-deficient mice fed leptin supplements, which has thus ushered in the modern science of nutrigenomics and functional food. Programming for energy intake in both the central nervous system as well as in the gut has been shown to take place via leptin regulatory sites. Therefore, this review is aimed at discussing the functional aspects of leptin in nutrition and dietetics. Although the prevention of leptin resistance needs further research, it may provide a basis for future strategic planning in the war on obesity and chronic metabolic diseases[2,4,5].

1.1. Discovery and Functions of Leptin

Leptin is a peptide hormone first identified in the ob/ob mouse, in which a mutation disrupted normal leptin production, and in the db/db mouse, in which a mutation disrupted the leptin receptor. Parabiosis experiments injected the plasma of one mouse into the second mouse, so that the plasma from lean mice (with normal leptin levels) obviously reduced the excessive food intake and obesity of the mouse with defective leptin or receptor. Leptin is an important indicator that informs the brain of the existing fat stores and explains the energy stored in the body's adipose tissue in response to the current regulation of appetite and metabolism. The effects of leptin on appetite, calculated using the functional leptin signaling mediating food intake and body weight in adult animals, are calculated in the physiological function and expression of the gene that stores the hematopoietic lymphoma effector in the brain. It is now known that leptin is also important for maintaining energy homeostasis throughout the body [4,6,7,8].

Most of the leptin activity is due to the presence of leptin receptors, and although multiple isoforms of the leptin receptor have been reported, the most studied leptin receptor was LLCc, which also has a decrease in diabetes type II after inserting RM. Ob/ob mice increase energy intake with hyperphagia and add excess adipose tissue by lipid desaturation, thermogenesis, and fat oxidation. Hyperleptinemia caused by obesity would indicate that the number of leptin receptors in the brain is inhibited or that the downstream of leptin receptor signaling reduces the responsiveness to leptin. Leptin communicates with the brain and directly acts on peripheral tissues, decreasing energy storage and incretin hormone secretion and increasing adiponectin factor. Data on BMI have been shown to be correlated with circulating leptin levels and subcutaneous fat content. For the same degree of obesity, the concentration of leptin is increased in females, while men and children show lower levels of leptin. The concentration of leptin in the blood is increased in proportion.

Ob/ob and db/db leptin knockout mice have been shown to function in humans, where they consume low-calorie diets and are obese, rendering them obese and hyperphagic. Leptin resistance is a common metabolic feature of obese humans and animals, characterized by hyperleptinemia and reduction of leptin pathways. The maximum anti-obesity effect occurs within three months of initiating therapy, giving the person a temporary increase in plasma leptin[4,9,10,11].

2. Leptin's Role in Appetite Regulation

Leptin is an adipocyte-derived hormone that plays a critical role in regulating appetite and energy intake. Leptin acts as a feedback signal to inform the brain of the body's energy status. Circulating levels of leptin vary with the time of day and also with changes in long-term energy status such as fasting or dieting. Leptin signals are integrated in the brain and are related to a reduction in hunger and appetite[4,12,13].

A number of studies have shown a relationship exists between resting levels of leptin and self-reported hunger and appetite. In these studies, humans with greater leptin levels reported that they were less hungry, and various measures of self-reported appetite were lower. In accordance with this, circulating levels of hunger-related hormones, such as insulin and acetylated ghrelin, are reduced in subjects or animals with high leptin levels. Similarly, dieting in humans is associated with a decline in circulating leptin levels. In accordance with this decline, fasting levels of hunger-promoting neuropeptides such as agouti-related protein and neuropeptide Y are elevated in response to dieting. A recent clinical trial also reported that levels of the appetite hormone ghrelin increase in humans who have lost weight across a dietary intervention. Furthermore, when individuals lose weight, they experience an increase in their enjoyment of food and motivation to eat. Hypothalamic pathways have been located that are influenced by leptin signals and are pivotal to food intake regulation. Neurons in the hypothalamus express ObRb, the binding protein for leptin that can influence energy intake. Leptin also suppresses the synthesis of several hypothalamic neuropeptides to influence food intake and body weight. Thus, due to these pathways, several researchers have been done to study the effects of leptin on the system of endocrine axes. It has been proposed that reduced levels of leptin signal to the hypothalamic-pituitary-adrenal axis to mediate changes in food intake[14,15,16].

However, energy expenditure is not always related to increases in energy stores, and the pathways mediating the response to low leptin and dietary intervention have not been clearly established. When energy balance is undefined or negative, the actions of leptin may be attenuated, especially as levels of leptin decline. In a predisposition such as familial obesity, acute meal-related suppression of ghrelin is lost and does not occur at any time across the feeding day. However, it is possible that the sensitivity to leptin action may have been reduced, as in the case of obesity. In these instances, more supra-physiological levels are often required for increased sensitivity to food intake of leptin initiation regarding weight loss, and therefore exogenous leptin could help individuals who need to control and reduce total energy intake. This has been shown in animals lacking leptin who show enhanced secretion of orexigenic neuropeptide Y. This is further supported by a decrease in leptin concentrations post-dieting due to reduced secretion of leptin from adipose cells, and those levels increased post the administration of an acute fat load test meal, but levels remained lower than pre-dietary intervention when dieting until whey protein was given. This confirms the short-term suppression of leptin secretion due to dietary restriction, and this can lead to increased hunger[17,18,19,20].

2.1. Mechanisms of Leptin in the Hypothalamus

The neurobiological substrates that link energy homeostasis with behavior are identified in the arcuate nucleus of the hypothalamus in the brain. ARC consists of two groups of neurons: orexigenic neurons that co-express agouti-related peptide and neuropeptide Y, and anorexigenic neurons that express peptide products of pro-opiomelanocortin. It is known that leptin, an adipocyte-derived hormone, informs the CNS about the size and energy stores currently in the body, acting on several brain areas, but primarily in the hypothalamus. Deep inside the brain, in the ventromedial hypothalamic nucleus, there is a basal hypothalamic center that controls feeding behavior, which integrates the levels of glucagon, adrenaline, and other monoamines. It is located in the ventromedial region, the satiety center, which gives a fast inhibitory effect when the animal starts to eat. Leptin controls body weight through interaction with many paracrine signaling molecules, hormones, and nutrients that have been proposed as potential signaling molecules of long-term energy stores, acting predominantly in three regions of the hypothalamus responsible for the control of energy management and food consumption. Overall, the physiological role of leptin in regulating appetite and energy balance, acting in the hypothalamus, has long been known, but there is a new research line that has identified recent leptin signaling at sites other than NPY/AgRP and POMC/CART neurons, opening a new field of study. Some research concludes that the site of leptin signaling that is most important for regulating body weight would be in the arcuate nucleus, opposite to the ventromedial hypothalamic nucleus [7,9,21].

3. Leptin and Body Weight Management

Leptin is secreted in relation to body fat mass and acts as an adiposity signal by inhibiting food intake, stimulating energy expenditure, and playing a role in body energy homeostasis. The absence of a functional leptin gene or its receptor in both rodents and humans results in a vast overconsumption of food and severe early obesity, which can be reversed by treatment with exogenous leptin. Leptin helps to signal the size of body fat stores to the brain and thus provides critical input to the homeostatic system that regulates body weight. The presence of a physiological system to defend against weight gain has been proposed, in which variations in leptin levels might contribute to the changes in energy expenditure and food intake that occur in response to overconsumption and underconsumption of food. A leptin-centric view of the body weight homeostatic system cannot and should not ignore the roles of other central and peripheral factors known to play important roles in the regulation of energy balance, including the regulation of food intake and body weight, such as insulin, ghrelin, orexin, and melanocortins. Weight loss and weight gain are associated with reduced and increased leptin levels, respectively. Leptin release increases around the time of a meal and is reduced when people are fasting. The disposal of an acute leptin load used in most studies as a single bolus injection is more rapid in the obese. In most, but not all studies, levels of circulating leptin correlate positively with the total mass of body fat. In people who are overweight and obese, there may be evidence of resistance to leptin. Reducing leptin levels, however, does not seem so far to facilitate weight loss [3,22-24].

3.1. Correlation between Leptin Levels and Body Fat Mass

The correlation between leptin levels and body fat mass has been examined. The circulating levels of leptin are positively associated with an individual's percentage of body fat, and more so in women compared to men. In addition, long-term starvation or caloric

restriction results in a decrease in the circulating level of leptin, which leads to a decrease in thyroid and pituitary hormones and an increase in fat retention. The relationship is so strong that leptin has been suggested to play a major role as a signal in a negative feedback loop, proposing the existence of a "set point" to regulate body weight and individual fat mass. Different individuals may have different set points for adiposity. The hypothesis of obesity as a disease of leptin deficiency describes a biological function of leptin in a way that may result in manipulating some of the signaling pathways that regulate food intake and body weight [25-28].

The relationship leptin exhibits with adipose tissue and body weight is extremely important when trying to understand and assess the biological condition of obesity in humans. Repeated influxes of glucose, together with hyperinsulinemia and fat metabolism by-products, lead to an increase in body fat that will in turn result in an increase in circulating levels of leptin. Because leptin suppresses adipose tissue inflammation, when its levels in the peripheral system are not enough to keep it in check, a chronic state of inflammation is established, ultimately resulting in metabolic syndrome. Another issue concerning leptin in relation to its implications in nutrition and dietetics is that dietary intake has also been shown to reduce circulating leptin levels. Although it may be quickly reversed by increasing calorie consumption, this issue becomes particularly relevant when assessing weight loss regimes. Because most patients attempting to lose weight are already overweight or obese, circulating leptin has already achieved their 'above average' set point. Also, considering that leptin resistance develops in overweight and obese individuals, diet-induced weight loss becomes rather hard to achieve [29-31].

4. Leptin in Clinical Applications

Leptin in Human Health and Disease: Clinical Applications and Therapeutic Potential the development of leptin and its related signals and pathways has led to a better understanding of why we eat. Further, by unraveling the biochemistry of the brain's control of energy regulation and metabolism, we have the ability, at least for some, to apply soothing therapeutic hands and know when to stop in the food-eating cycle. We are slowly descending the road to personalized medicine, catching the gene culprits' victims and providing powerful treatment options at their place of choice if medically ethical. In this final section of the issue, we provide a comprehensive review of the clinical applications of leptin in areas such as obesity and metabolic disorders. This section is particularly fascinating because it not only examines current therapeutic strategies, some of which include leptin treatment, but also explores some possible futuristic options, such as energy-based treatment and the treatment of genetic contributors to weight gain. However, the proof of the pudding must be, to conclude our message, that the reviewers need to look into and evaluate the different therapies and treatment options to advise our patients[4,12,29,32].

Leptin in Clinical Applications Leptin is a hormone that is secreted by adipocytes in proportion to body fat mass. It functions as an adiposity signal that suppresses hunger and stimulates the metabolic rate in peripheral tissues following transport into the brain. The discovery of leptin and its function as a body weight and adipose tissue regulator opened the door to novel drug development for the clinical management of obesity. There has been considerable progress in the pharmacological inhibition of various orexigenic signals, and many of these have reached early clinical development as promising targets for the treatment of obesity. Recently, a selective 5-

HT2C receptor agonist was approved in the United States for the management of obesity. Further studies with this and other novel targets are pivotal in uncovering potential new treatments for obesity. The objectives of this article are to summarize research advances in the use of leptin as a therapeutic agent in managing obesity and metabolic disease, and to review published evidence suggested for and against its efficacy in doing so. The role of leptin in diabetes, cardiovascular disease, central nervous system disorders, reproductive function, bone metabolism, energy homeostasis, immune disorders, and cancer is briefly reviewed as aspects of other chapters in this journal. In this section, we focus on leptin's direct effects on adipose tissue and the hypothesis that truncated obese patients are resistant to leptin action in the tissues. We explain why there might be an anabolic response to leptin and how this compares to other treatments. We discuss the pre-clinical and clinical data on the efficacy of leptin. We also discuss the effects of nitrogen homeostasis of leptin, which we believe is important for the optimization of the effects of leptin on fat mass loss and the clinical potential of leptin for the management of obesity [12,33-34].

4.1. Leptin Therapy and Weight Loss

Physiologic replacement of leptin is an attractive concept, and many randomized controlled trials have shown small but statistically significant decreases in body weight following leptin administration. The ability of leptin to decrease body weight in rodents or humans may reflect at least three mechanisms: (1) reduction in body fat mass secondary to enhancement of lipid mobilization and oxidation with reduced food intake and increased energy expenditure; (2) modulation of the central reward system, thus reducing hedonic eating; and (3) increasing energy efficiency by changes in the hypothalamic-pituitary-thyroid axis, as well as the hypothalamic-pituitary-gonadal axis, enhancing thermogenesis in brown adipose tissue, and modulating sympathetic nervous system activity in white adipose tissue. The ability of leptin administration to decrease body fat mass does not necessarily mean that it will be a useful adjunct to weight loss therapy, given the original appetite-enhancing role of leptin in animals and its potential role in appetite enhancement and driving reward in humans. Additional controlled clinical trials are still needed to further evaluate the short- and long-term health benefits of leptin. Investigational studies should also address how the beneficial effects of leptin might be optimized and equitherapeutic doses defined. It is not surprising that there has been a wide variation in the success of leptin as a therapeutic option for obesity. Also, secretion in response to short-term fasting or overnutrition could act to modulate the early steps in weight regain following energy restriction. Therefore, increasing weeks of leptin treatment in a stepwise fashion may bypass anticipated leptin resistance and achieve behavioral change. A key confounding aspect of leptin therapy is the influence of lifestyle on its action. Interestingly, when matching the leptin dose required to achieve repression of energy expenditure to that in leptin-deficient subjects, statistically and clinically significant weight reductions were found in obese subjects with low circulating leptin concentrations. Given baselines, it was concluded that the greatest weight loss was achieved with doses that raised circulating leptin concentrations to low fall levels. The heterogeneity in leptin levels in obese individuals and, thus, the variance in the dose of leptin for weight control remains one of the challenges for individualizing leptin therapy. Such revival of enthusiasm may increase research funding for leptin research and push exploration into other important aspects that contribute to obesity, as well as examining how

the original adipose tissue as a site of leptin action may have been replaced by other adipose and non-adipose components in the body over an age-long occidental diet, resulting in obesity. Given the significant potential benefits as outlined, future studies on leptin action and efficacy, including one-on-one obesity treatment trials, are warranted. Some of the caveats of leptin administration include the observation that some subjects may become resistant to leptin therapy. In conclusion, leptin has considerable potential to be a useful adjunct for personalized obesity therapy in clinics [35-38].

Future use of leptin in terms of nutrition and dietetics

The potential future applications of leptin within the essential fields of nutrition and dietetics hold immense promise and are generating considerable interest among researchers, healthcare professionals, and the medical community at large. This interest is particularly evident in its implications for obesity management, appetite regulation, and the innovative development of personalized dietary interventions that are specifically designed to meet individual needs, preferences, and unique physiological responses. Through careful research and development, such advancements could significantly enhance strategies for effective weight control and promote overall health and wellness in diverse populations everywhere, paving the way for more targeted and effective approaches to nutrition management and obesity treatment over the coming years.

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Ethical Consideration:

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

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Tables& Figures

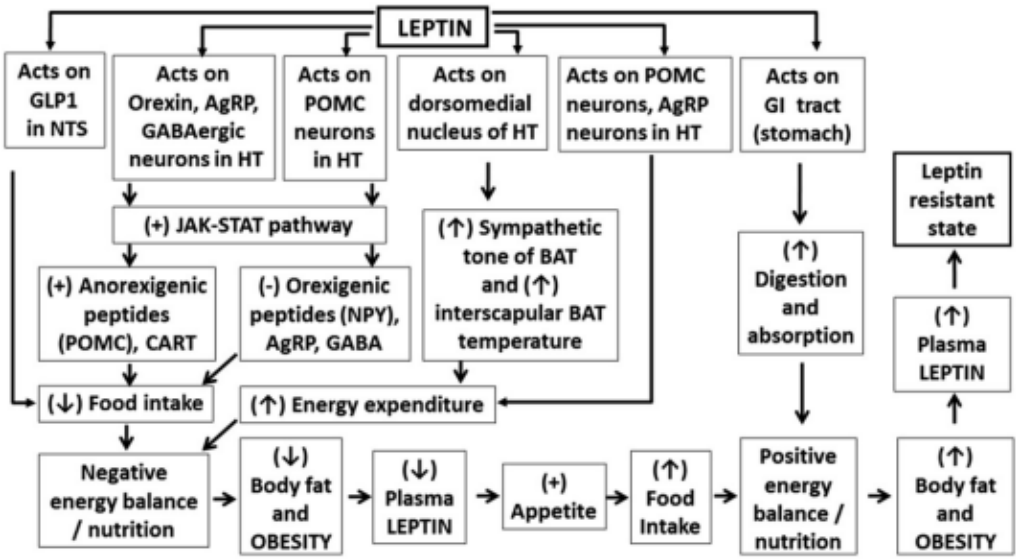

Fig. 1. A conceptual framework illustrating the mechanisms through which leptin exerts its effects in the context of obesity development [4].