Leptin and its role in neuroendocrinology of obesity

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Abstract
Leptin, a multifunctional hormone, exerts its effects through hypothalamic signaling, regulating satiety, energy expenditure, and body weight. In recent years, an increase in obesity-related mortality has been reported in the Mexican population, positioning this disease as one of the leading causes due to the development of comorbidities associated with its pathology. Extensive research has focused on the involvement of leptin as a pleiotropic hormone with crucial properties in the development of overweight and obesity. Alterations in its receptor have been observed to predispose individuals to leptin resistance, leading to a poor response to satiety stimulation and an increase in food intake. Other studies suggest that diets high in calories result in hyperactivation of the brain cortex associated with the sense of taste, generating a reward stimulus that induces greater food consumption and gradually increases adipose tissue in the body. Investigations using exogenous leptin administration in mice have shown a transient decrease in body weight accompanied by reduced food intake. Therefore, a comprehensive description and analysis of leptin’s involvement in the neuroendocrine signaling of obesity are necessary to enhance our understanding of this complex disease. This manuscript provides an educational overview of this topic.

Keywords: cardiovascular, hormone, leptin, obesity

1. Introduction
Obesity has a significant impact on the increasing mortality rates in the Mexican population, as it is considered a chronic and progressive disease. It is characterized by excessive adipose tissue production, resulting from an imbalance between energy consumption and expenditure, and is associated with the development of cardiovascular, metabolic, neurodegenerative, and neoplastic diseases.

In 2016, the National Health and Nutrition Survey (ENSANUT, for its acronym in Spanish) reported a higher prevalence of obesity in women than in men.1 A year later, reports from the Organization for Economic Cooperation and Development (OECD) ranked Mexico as the second highest in obesity prevalence and the first in obesity and overweight, projecting a 5% increase from 2020 to 2030 based on observed growth patterns.2 In recent years, research has focused on identifying the most probable etiology and risk factors for the development of obesity. It is considered to have a multifactorial nature, but genetic predisposition has been observed to play a significant role, particularly in alterations in genes involved in hunger-satiety regulation.

The most extensively studied alterations within the pathophysiology of obesity are the mutations of the MC4R, BDNF, POMC, and LEPR genes, which are closely related in the central nervous system.

Leptin is considered a pleiotropic cytokine with activities in various peripheral tissues, exerting its action upon interaction with its receptor (LR). In the brain, it is mainly expressed in...
the arcuate, dorsomedial, ventromedial, and lateral nuclei of the hypothalamus, where neurons are activated or inhibited in response to LR activation (Figure 1). This stimulation leads to the synthesis of anorexigenic neuropeptides CART and POMC, inhibiting orexigenic NPY and AgRP. Structurally, the leptin receptor has six isoforms, all of which activate a signaling cascade through Janus kinases (JAKs) for intracellular signaling. Subsequently, they activate STAT3, with the JAK-STAT3 complex (Figure 2) being a critical component in leptin signaling in the hypothalamus.

Due to being a polypeptide hormone produced by adipocytes, its production depends on changes in adipose tissue content and adaptive responses in energy balance control, with normal levels ranging from 5-15 ng/ml in blood. Obesity is influenced by an increase in leptin levels, as well as resistance to its effects since its functions include reducing food intake by generating a sensation of satiety.

However, obesity itself promotes leptin resistance, which can result from factors such as impaired receptor function, and alterations in neuronal pathways, or peripheral tissues. Due to this resistance, serum levels may be above normal ranges as the disease progresses, leading to hyperphagia in obese individuals.

Based on the aforementioned, studies conducted in animals through exogenous leptin administration achieve the goal of reducing body mass in normal animals, being an important determinant in energy expenditure, which suggests that leptin administration as a treatment for obesity is a promising proposal. On the other hand, measuring serum levels could be an important predictor for the development of potential comorbidities to which it predisposes.

2. Obesity

Obesity is a complex multifactorial disease that develops through the interaction between genotype and the environment. Our understanding of how and why it occurs remains incomplete. Like other diseases, obesity has been attributed to a significant genetic component, such as the FTO gene polymorphism in the Mexican population. However, isolated mutations fail to explain the rapid increase and epidemiological characteristics of this disease, indicating a broad integration of social, cultural, physiological, metabolic, and genetic factors.

Studies have provided evidence of increased mortality associated with obesity, particularly in severe cases, compared to normal body weight. Obesity potentially increases the risk of developing metabolic diseases (primarily type 2 diabetes mellitus), cardiovascular diseases (hypertension, acute myocardial infarction, stroke, etc.), neurodegenerative diseases (Alzheimer's disease), as well as certain types of cancer (ovarian, breast, prostate, liver, etc.). Obesity has also been associated with mental health conditions (major depression) and an increased risk of complications in the mother-child relationship (gestational diabetes, pre-eclampsia, miscarriages, and stillbirths).

In the field of public health, type 2 diabetes mellitus is closely related to obesity, which greatly affects the population. In addition to representing a significant direct expense for the economy of a country, it causes indirect costs due to the loss of productivity of affected individuals and premature mortality. The expenses of a person with diabetes are 2 to 3 times higher than those of a person without the disease. In Latin America and the Caribbean, many people with
diabetes have limited access to healthcare. The consequences also result in higher healthcare costs for individuals, as it is estimated that the healthcare expenditure for an obese patient is 42% higher than that of non-obese individuals.  

2.1 Epidemiology of obesity
According to the World Health Organization (WHO), the global prevalence of obesity tripled from 1975 to February 2018. By 2016, over 1.9 billion adults were overweight or obese, with 34% classified as having obesity of any severity. According to the OECD report in 2017, Mexico ranked second in obesity and first in overweight/obesity, surpassing the United States. Furthermore, it is estimated that by 2030, the prevalence of obesity in Mexico will reach 39%.  

In 2008, 35% of adults aged 20 and over were overweight (body mass index (BMI) greater than 25). In the same year, 10% of men and 14% of women worldwide were obese (BMI greater than 30), compared to 5% of men and 8% of women in 1980. An estimated 205 million men and 297 million women aged 20 and over are obese, totaling over half a billion adults worldwide. However, according to the National Health and Nutrition Examination Survey (NHANES), between 2015 and 2016, 18.5% of children and 39.6% of adults had obesity. These are the highest recorded figures by NHANES to date. The prevalence of overweight and obesity is higher in the Americas (62% overweight in both sexes and 26% obesity) and lower in the Southeast Asia region (14% overweight in both sexes and 3% obesity). In all continents, greater severity was found in women than in men. The presence of a high BMI increases with income level, with the difference in overweight prevalence between high-income and low-income countries nearly doubling.  

In 2012, the prevalence of obesity in the Mexican adult population was around 33%, ranking the country in the highest quintile of obesity in Latin America and the Caribbean. A recent meta-analysis of over 100 studies found that individuals with or without overweight share similar risks of mortality, and the highest risk of this outcome is concentrated among those clinically classified as obese.  

2.2 Pathophysiology of obesity
The pathophysiology of obesity can be approached based on four points: genetic, adipose, neurological, and inflammatory factors. While the multifactorial nature of obesity was mentioned earlier, it has been observed that up to 70% of the development of this disease has a hereditary pattern.  

With the advancement of whole-genome sequencing studies (WGSS), some genes highly involved in the development of obesity have been identified, many of which are genes expressed in neurons and are widely linked to the regulation of hunger-satiety sensation. The first gene associated with the genesis of obesity was the Fat Mass and Obesity-associated gene (FTO). This gene is closely related to the development of obesity in individuals with a specific single nucleotide polymorphism (SNP). Initially, alterations attributable to FTO gene SNPs were not confined to the central nervous system (CNS), but later an association with pathologies not directly linked to obesity, such as Alzheimer’s disease, has been observed.  

In the pathogenesis of obesity, mutations in genes such as MC4R, BDNF, POMC, and LEPR play a significant role in the hunger-satiety relationship in the CNS. On the other hand, meals with high caloric content immediately generate signals that stimulate overconsumption of food. Imaging studies have shown hyperactivation in the cerebral cortex related to the sense of taste (insula/rolandic and parietal operculum) and oral somatosensory regions in obese individuals compared to those with normal weight, in response to anticipation of food intake and consumption of various types of palatable food. Additionally, there is hypoactivation in the dorsal striatum and a reduction in the density of striatal D2 dopamine receptors after consuming such food. These findings indicate the relationship between abnormalities in food reward and weight gain, suggesting greater weight gain in those exposed to an unhealthy food environment. All of this leads to an excess of adipocytes that secrete a large number of cytokines contributing to vascular dysfunction in hypertension and dyslipidemia, as manifested in hypercholesterolemia and hypertriglyceridemia. These conditions eventually contribute to the development of atherosclerosis and, when associated with obesity, diabetes, or insulin resistance, constitute metabolic syndrome.  

Stored fat is necessary for survival during periods of nutritional deprivation; during prolonged periods of abundant food, excessive fat consumption leads to an excess of fat storage, eventually resulting in obesity. There are hypotheses suggesting that the storage of fatty acids as triglycerides within adipocytes protects against their toxicity. On the other hand, circulating free fatty acids produce oxidative stress throughout the body.
However, the excessive storage created by obesity eventually leads to the release of these fatty acids through lipolysis, which is stimulated by the sympathetic nervous system.

The release of excessive amounts of fatty acids triggers lipotoxicity, while lipids and their metabolites cause stress to the endoplasmic reticulum and mitochondria. Fatty acids released from triglyceride deposits also inhibit lipogenesis, preventing proper clearance of serum triglyceride levels and contributing to hypertriglyceridemia.

The release of free fatty acids by endothelial lipoprotein lipase due to increased serum triglycerides with elevated lipoproteins causes lipotoxicity, resulting in insulin receptor dysfunction. The subsequent state of insulin resistance leads to hyperglycemia with compensatory hepatic gluconeogenesis, increasing hepatic glucose production and insulin resistance-induced hyperglycemia.

2.3 Adipocytes and adipokines

The main function of adipose tissue is to store and provide energy reserves in the form of triacylglycerol (triglycerides). Fat is stored in specialized cells called adipocytes, which have specific functions. An adipocyte has a diameter of approximately 10-12 μm. After fat accumulation, its diameter increases by 10 times, meaning that its volume increases up to 1,000 times. Adipose tissue has enormous plasticity and capacity for energy storage.

Adipocytes have two main functions: to accumulate and metabolize triacylglycerol. The storage of deposited fat in adipocytes is accomplished by the uptake of triacylglycerol by a capillary network of glycosaminoglycans. The triacylglycerols are subsequently hydrolyzed by lipoprotein lipase. The fatty acids are taken up by adjacent adipocytes. Lipoprotein lipase is synthesized in the adipocyte under the influence of a large number of hormones, with insulin and cortisol being the main ones.

Adipocytes, which represent over a trillion cells, not only store triglycerides in fat deposits in various body sites to provide energy but also constitute the largest endocrine tissue, constantly communicating with other tissues through various substances, such as the adipokines leptin, adiponectin, and visfatin. Together with insulin, these adipokines help regulate body fat. Other groups of genes contributing to adipocyte adipokines include cytokines, growth factors, and complement proteins.

Dyslipidemia, hypertension, and atherogenesis are conditions that, along with insulin resistance, are associated with obesity. They are also influenced by the secretion of various inflammatory adipokines, particularly by white adipose tissues in visceral deposits.

Specific adipokines increase vasomotor tone through the secretion of renin, angiotensinogen, and angiotensin II, which are similar to those in the renin-angiotensin system. However, when secreted by adipocytes, they contribute to hypertension in obese individuals. The secretion of tumor necrosis factor stimulates inflammation.

3. Leptin and its relationship with obesity

A large number of peripheral hormones participate in the control of appetite, food intake, food reward, or addiction by the central nervous system. Both palatable food and drugs activate the mesolimbic dopaminergic pathway involved in the reward system, which is essential for the regulation of addiction in humans and animals.

Hunger and signals from adipose tissue (leptin), the pancreas (insulin), and the gastrointestinal system (cholecystokinin, glucagon-like peptide-1, peptide YY3-36, and ghrelin) contribute to the information that regulates energy status through the gut-brain neuroendocrine axis, primarily targeting the hypothalamus and brainstem, and can interact directly or indirectly with the mesencephalic dopaminergic pathways to impact feeding.

3.1 Leptin

Leptin plays a central role in the control of body weight and homeostasis, but it is a pleiotropic cytokine with activities in various peripheral tissues. This hormone is known to participate in a wide range of biological functions, including innate and adaptive immunity, reproduction, and bone formation.

Leptin crosses the blood-brain barrier via a saturable transport system and communicates the metabolic state of the periphery to the regulatory centers of the hypothalamus. Once it binds to its receptor, leptin inhibits the appetite-stimulating neuropeptides (NPY, AgRP) while stimulating the alpha-melanocyte-stimulating hormone and corticotropin-releasing hormone. The leptin gene is located on the long arm of chromosome 7 (7q31.3) and contains 3 exons and 2 introns.

Leptin is a 16 kDa non-glycosylated protein consisting of 146 amino acids. Human leptin has two exposed tryptophan residues. It adopts the typical structure of a four-helix cytokine, with an up-up-down-down arrangement. The C-terminal residues of the D helix adopt a 3-10 structure. Two long turns, AB and CD, connect the parallel helices, while the antiparallel B and C helices are connected by a short BC loop. Leptin contains 2 cysteine residues (C96 in the CD loop.
and C146 in the C-terminal residue), and this disulfide bridge is essential for its structural stability and biological activity.\(^{19}\)

Leptin is a member of a family of long-chain cytokines; however, its helices are on average one or two turns shorter, resulting in the shorter branch of the family.

### 3.2 Leptin receptor

Structurally, the leptin receptor (LR) can be classified as a class I cytokine receptor. This family consists of a single transmembrane receptor that encompasses receptors marked by the presence of one or more cytokine receptor homologous domains. The extracellular domains may include immunoglobulin-like domains and fibronectin type III domains.

All isoforms of the LR utilize JAK kinases for intracellular signaling (Figure 2). So far, six isoforms of the leptin receptor have been identified: LRa, LRb, LRC, LRD, LRE, and LRf. All of these isoforms, except LRF, have an identical extracellular transmembrane domain but differ in the length of the intracellular tail. LRb, also referred to as the long form of the LR, has 1162 residues, with a 302 residue intracellular domain, and is believed to be the only isoform that employs signaling through the JAK/STAT complex. This isoform is highly expressed in specific nuclei of the hypothalamus, where it carries out its function in the regulation of body weight.

LRa, LRC, LRD, and LRF have only a short intracellular tail (30-40 residues) and a single C-terminal domain. Their precise physiological role remains unclear, but high levels of LRa and LRC expression in the choroid plexus and cerebral microvasculature suggest an important role in leptin transport across the blood-brain barrier.\(^{20}\)

Initially discovered as a defective mutant,\(^{21}\) LRF is a soluble variant in mice that is directly secreted into the bloodstream. In humans, a similar LR fragment is generated by proteolytic cleavage of the ectodomain (by metalloproteases 10 and 17)\(^{22}\) and modulates leptin bioavailability.

There are different isoforms of the LR, known as short and long isoforms. The LR gene is located on the short arm of chromosome 1 (1p31) and contains 20 exons.\(^{23}\)

The LR contains six extracellular domains: a functionally and structurally undefined N-terminal domain (NTD), a first cytokine receptor homology domain (CRH1), an immunoglobulin-like domain (IGD), a second cytokine receptor homology domain (CRH2), and two proximal fibronectin type III domains (FNIII).

The function of the NTD is unknown. CRH1 is not required for LR signaling,\(^{24}\) whereas signaling is completely abolished by the removal of any of the other four domains. The CRH2 domain is the only high-affinity domain for leptin, unlike the other domains that do not show a specific leptin binding site.

### 4. Leptin and obesity

Leptin is a polypeptide hormone produced by adipocytes in proportion to their triglyceride content. It links changes in the body’s energy store (fat) with adaptive responses in the central control of energy balance. By binding to and activating the long form of its receptor (LR-B) in the brain, leptin decreases hunger while increasing energy expenditure.\(^{25}\)

Leptin circulates at levels of 5 to 15 ng/ml, and its expression is increased by food intake, insulin, glucocorticoids, endotoxins, and cytokines, while it is decreased by testosterone, thyroid hormone, and exposure to low temperatures. Increased leptin expression has been observed in the heart during reperfusion after ischemia.\(^{26}\) Its primary role is to prevent and respond to reductions in body fat.\(^{27}\)

Recent studies have shown that the lack of leptin in mice can cause severe obesity due to increased food intake and reduced energy expenditure;\(^{28}\) similar effects have been observed in humans,\(^{29}\) and these effects can be reversed with leptin administration.\(^{30}\)

Obesity is influenced not only by a deficiency of leptin but also by leptin resistance. Since the presence of leptin reduces food intake and body weight, elevated leptin levels can be observed in obese individuals with leptin resistance. The effects of leptin resistance are reversible. For example, if the fat content of obese mice is reduced, they regain leptin sensitivity and glycemic control. Increased leptin sensitivity in melanocortin circuits is believed to influence leptin resistance.

Some animal studies have found that diet-induced leptin resistance occurs in different stages. In the first stage, mice on a high-fat diet exhibited sensitivity to exogenous leptin. In the second stage, as food intake decreased, there was an increase in leptin production and sensitivity. In the final stage, food intake increased, and central leptin sensitivity decreased (Figure 3).

Leptin resistance caused by high-fat intake results in a defect in access to different sites of action in the hypothalamus, significantly reducing the ability of peripheral leptin to activate hypothalamic signaling.
Resistance is also caused by a defect in intracellular signaling in leptin-responsive hypothalamic neurons.

Acute administration of exogenous leptin reduces hunger and body mass in animals and is a major determinant of energy expenditure. These observations establish that leptin deficiency is a key regulator of metabolic and neuroendocrine responses to states characterized by negative energy balance and weight loss, which is why maintaining weight loss is often unsuccessful.6

Leptin resistance also occurs as an adaptive physiological response to allow plastic changes in homeostatic mechanisms, allowing repeated and reversible alterations in body weight in certain situations.31 In recent years, there has been a dramatic increase in the number of genetic mouse models of obesity, making leptin sensitivity measurement a routine process in efforts to investigate the mechanisms of obesity.

Most obese individuals (Figure 4) exhibit elevated circulating leptin levels, associated with their adipose tissue mass.32

Obesity promotes several pathways of leptin resistance, so leptin action may be compromised in obese animals. Certain types of genetic obesity are also related to leptin:4
- Alterations in LR-B or its signaling.5
- Alterations in neural pathways involved in leptin action.
- Alterations in peripheral tissues operating independently of food intake.
- Alterations in central nervous system pathways without a clear link to leptin action.

Leptin has also been associated with atherosclerosis, intima and media thickening; it is believed to be a marker of early stages of atherosclerosis before symptoms start. Researchers have shown that serum leptin concentration is independently and positively related to the intima-media thickness of the common carotid artery.33 Similarly, due to its role in promoting a persistent proinflammatory state associated with obesity, stimulation of type B leptin receptors, oxidation of fatty acids at the cardiac level, increased oxygen consumption by the myocardium, and increased reactive oxygen species occur. This promotes myocardial dysfunction, lipotoxicity, improper calcium handling within myocytes, and long-term fibrosis, which are linked to the pathophysiology of diabetic cardiomyopathy and fibrosis dysfunction.34

5. Dopaminergic regulation of feeding behavior

Neurochemical mechanisms governing body weight and mood exhibit similarities.35 Food intake is a behavior driven by survival motivation, thus involving the dopaminergic neurotransmission system, which is also directly implicated in addiction pathophysiology, reinforcement, and reward mechanisms.36 These systems can be altered in individuals with eating disorders such as anorexia nervosa and bulimia nervosa.37

Several studies have demonstrated the potential of leptin to modulate the reward associated with the consumption of high-fat food.38 These effects may be influenced by the presence of single nucleotide polymorphisms in the gene encoding leptin.39
Such convergence of signaling mechanisms suggests that leptin may be involved in the pathogenesis of neuropsychiatric disorders in individuals with obesity.39

Neurons within the ventral tegmental area (VTA), the origin of the mesolimbic dopaminergic pathway, express leptin receptors.40 Activation of these receptors increases the expression of tyrosine hydroxylase and dopamine content in these neurons while reducing dopamine release in the nucleus accumbens.41 These neurons respond to stimuli that predict food availability (conditioning). Projections from the lateral hypothalamic nucleus to the VTA stimulate food intake through the VTA projections to the nucleus accumbens.40

Feeding behavior is also regulated by other signaling pathways, such as the gut-brain axis,42 partially mediated by the vagus nerve.43 The gastrointestinal tract can secrete various peptides that contribute to the regulation of appetite by acting at the level of the VTA and nucleus accumbens.42 Additionally, the gut microbiome may play a role in the pathophysiology of obesity.44

6. Conclusions

Leptin plays a crucial role in the etiology of obesity, given its involvement in various physiological and pathophysiological processes within the body. As a hormone associated with satiety, alterations in leptin have neuroendocrine implications arising from defects in its production or impaired uptake, leading to insatiable appetite and hyperphagia.

In recent years, the importance of genetic predisposition in the development of overweight and obesity has been emphasized. Moreover, the production of leptin has been linked to the percentage of adipose tissue in the body, with higher adipose tissue levels correlating with increased resistance to leptin uptake. Consequently, measuring leptin levels has been proposed as a marker of predisposition to the development of atherosclerosis, vascular structural alterations, and comorbidities. Exogenous administration of leptin appears to be an innovative solution for addressing obesity in individuals with leptin deficiency, as it promotes appetite reduction and regulation of body weight.

Given the significance of leptin in the development of obesity, it is crucial to highlight that research in this field is key to understanding the neuroendocrine mechanisms and signaling pathways governing the adipose tissue-leptin-hypothalamus relationship. We are progressively advancing toward a better understanding of the genomic relationship with predisposing factors for overweight and obesity. The absence of certain genes results in leptin deficiency or receptor resistance.

There is still much to be analyzed regarding this pathology, making it of utmost importance to invest in research and experimental models for a better understanding of these pathophysiological processes and the search for a solution to the condition.

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