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Leptine and its Participation in the Development of Obesity

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ABSTRACT

Background: *Obesity is a chronic, multifactorial disease that increases significantly in the world population, affecting both adults and children and adolescents. In addition, it can lead to developing other diseases. Leptin is a hormone that is produced in various tissues of the body, adipose tissue being the protagonist in this pathology; giving it great relevance in terms of its participation as a producer of substances that make it an active tissue.*

Methodology: *A narrative review was carried out, in which different databases were used, in English and Spanish languages, obtaining a total of 21 articles, 15 of which met the inclusion criteria.*

Results: *Obesity is generated due to an energy imbalance, between caloric intake and expenditure. Likewise, leptin varies, according to its intravascular concentration, it modulates food consumption, responding to fasting states and the presence of glucose, so that when a deficit of this occurs, obesity can arise either in isolation or in concomitance with other factors that also induce its development.*

Conclusions: *Leptin is a hormone that is produced in adipose tissue, which has various functions in the body. It is currently known to play an important role in the development of obesity. However, its mechanism of action must be further studied and elucidated so that as a drug many more results can be generated in favor of the treatment of this pathology.*

Keywords: Leptin, obesity, metabolism, adipose

I. INTRODUCTION:

According to the WHO, obesity has tripled worldwide. In 2016, it affected more than 650 million adults and more than 340 million children and adolescents between the ages of 5 and 19, figures that are highly relevant considering that obesity is a preventable disease. Obesity is a chronic disease where there is an accumulation of excessive fat where the Body Mass Index is 25. Which brings with it an increase in morbidity and constitutes a risk factor that predisposes to developing multiple diseases in people who suffer from it. [1]

Leptin is a hormone that regulates appetite, modulating food intake and thus energy expenditure, which is secreted by adipocytes. This hormone acts under mechanisms at the neuroendocrine level; that is to say, its action is detected by the hypothalamus generating information about the nutritional status of the organism. Leptin modulates neuropeptide factors by increasing or decreasing caloric intake. Studies in mice have shown that the absence of leptin causes severe obesity because it produces an increase in food intake reducing energy expenditure [2]. Additionally, leptin-deficient mice can also develop hyperinsulinemia, which often leads to diabetes mellitus. [2]

II. MATERIALS AND METHODS:

A narrative review was carried out, in which different databases were used such as Scielo, PubMed, Sciencedirect, academic google, among others. The selection of articles was made through indexed journals in English and Spanish languages from 2010 to 2021. As key words, the following terms were used according to the terms DeCs and MeSH: Leptin, Obesity, appetite, metabolism. In this review, 21 original and review publications related to the subject under study were identified, of which 15 met the inclusion criteria used. Within the inclusion criteria, it was found that they were full-text articles, that at the time of the search allowed the reading of the abstract, that were related to the subject studied, that were within the established years. Exclusion criteria: That their publication date was less than 2010 and that they did not allow the full text to be read.

III. RESULTS:

Leptin has a structure of 167 amino acids, which is found in different tissues of the body, including adipose. This leptin is secreted in a pulsatile manner, showing a circadian rhythm, presenting lower levels in the mid-afternoon and higher levels at midnight. In addition, this varies according to sex since in women who tend to have more subcutaneous adipose tissue than men, they may present higher levels, however, during menopause they decrease significantly. It has been identified that it acts on the central nervous system, mainly the arcuate nucleus. Generating a stimulation of neuropeptides and suppressing proopiomelanocortin (table 1). [3]

Table 1. Leptine functions

LEPTINE FUNCTIONS	REGULATION OF BONE REMODELING	ACTIVATION OF IMMUNE CELLS
STIMULATES INSULIN SECRETION	**THERMOGENESIS**	**REGULATES APPETITE AND ENERGY EXPENDITURE**

HELPS REGULATE THE SYNTHESIS OF THYROID HORMONES	**ANGIOGENESIS / FIBROGENESIS**	**REGULATES THE MENSTRUAL CYCLE**

Leptin plays a very important role in obesity, in terms of its mechanism, it can affect people either due to a congenital deficiency due to a mutation in the gene that produces it or due to resistance to it. One of the mechanisms that are known about leptin in obesity is the one that occurs when high levels of leptin concentration are generated, which leads to saturation of the blood-brain transport system or the development of an alteration that affects its receptors in the choroid plexus. [4] This leads to obese patients developing excessive obesity and hyperphagia; that is to say, the appetite is increased in an extreme way, increasing the consumption of food. In the resistance to this hormone, the brain cannot capture its action and generate a response as it would be normal. Rather, an insensitivity occurs by not detecting elevated blood levels. [4]

Obesity is generated due to an energy imbalance, between caloric intake and consumption. Likewise, leptin varies its intravascular concentration, according to fasting states and in response to the presence of glucose. There are two types of adipose tissue: white and brown; where this excess calories accumulate is the white type, which releases leptin among other hormones and cytokines, making it an active tissue. People with leptin deficiency not only manifest obesity, they can also develop hyperinsulinemia, an alteration in immunity since it is found in various tissues and participates in processes such as thermogenesis, hematopoiesis, bone physiology, among others (figure 1). [5]

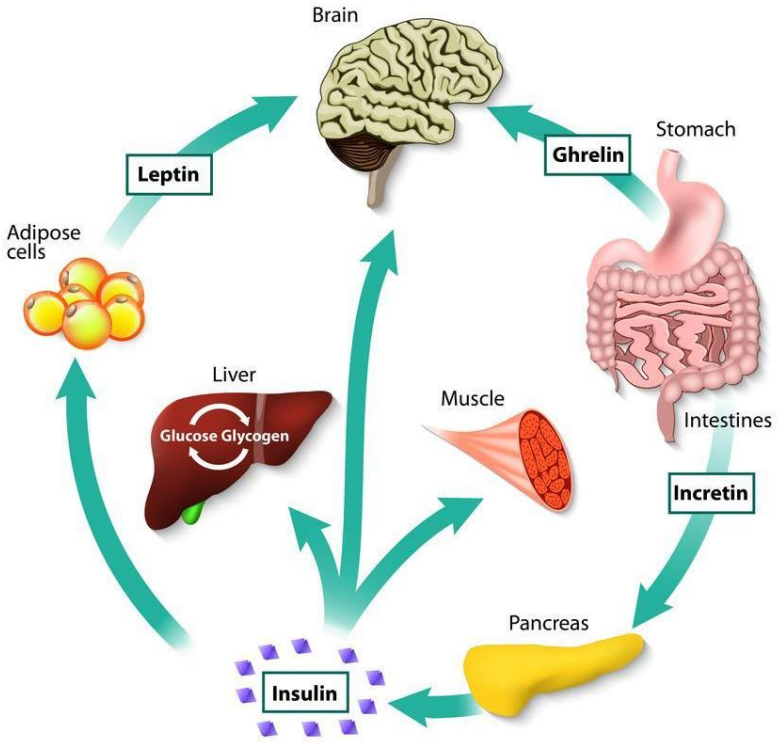

Figure 1. Leptin cycle

Replacement therapy with leptin has been implemented in humans. Leptin deficiency is seen in specific conditions, such as lipodystrophy syndromes, hypothalamic amenorrhea, anorexia nervosa, and congenital leptin deficiency. The clinical manifestations that occur in these conditions can include increased insulin resistance, hyperglycemia, dyslipidemia, endocrine disorders and fatty liver disease, which is why it is important to develop drugs based on this active principle, which may contribute to avoid morbid obesity. Replacement therapy is performed with recombinant human metreleptin or methionyl leptin, which is composed of 146 amino acids and has a short half-life. It is applied subcutaneously and is eliminated. The most common adverse reactions are headache, hypoglycemia, weight loss, and abdominal pain. Leptin replacement therapy results in significant weight loss in patients with mutations in the leptin gene; that is to say, they present a deficit, however, in common obesity it has not shown as much efficacy. [6.7]

A generalized or localized decrease in fat mass is associated with hypoleptinemia. Such conditions can be both congenital and acquired and are known by the term, lipodystrophy. These congenital lipodystrophy syndromes are rare, but leptin replacement therapy has been shown to improve metabolic parameters, such as insulin sensitivity, lipid profile, glucose control, and liver steatosis, as well as reduced fat mass. central. Initially, leptin showed that its deficiency through a mutation of the lep gene resulted in profound obesity and type 2 diabetes mellitus. Patients with inherited total leptin deficiency respond to treatment with leptin, showing a decrease in appetite and the consequent loss of appetite. This condition is not very common, but it must be taken into account in the differential diagnosis of young patients with obesity, since they can be improved with the administration of leptin. Very high doses of leptin do not always induce significant changes in body weight. Currently, the combination of leptin with pramlintide, an amylin analog, has been shown to result in greater weight loss than either drug alone. This could be attributed to the activation of overlapping leptin and amylin signaling pathways. [8.13]

In studies, mice are obese because their brains interpret a low level of leptin as a sign that their adipose tissue mass is highly low. For this reason, while they eat voraciously and show massive weight gain, they manifest a syndrome different from that generally associated with obesity. This observation initially suggested that leptin levels, in addition to inducing a state of positive energy balance to restore lost weight, activates an adaptive 'hunger' response whose net effect is to conserve energy in times of deprivation. Consequently, leptin treatment corrects all abnormalities. [9]

Leptin administration also changes the way these patients respond to visual food cues. During functional magnetic resonance imaging, in a patient with congenital leptin deficiency, 6-month leptin replacement resulted in altered reward-related activity to food cues. In another study of two patients with this same disorder, 1 week of leptin replacement decreased the activation of food images in areas of the striated brain. Furthermore, in three other patients, leptin replacement reduced the activity of food images in areas related to attention, satiety and increased activation in areas related to cognitive control and satiety. These studies suggest that in leptin deficiency, leptin replacement may influence neural circuits related to the perception of food reward and thus facilitate weight loss. [10]

Replacement therapy with leptin can have a very beneficial effect in patients with hypothalamic amenorrhea since both these patients and those with congenital leptin deficiency also have dysregulation of the gonadal, thyroid, growth hormone and adrenal axes. Hypothalamic amenorrhea consists of the lack of menstruation due to a dysfunction of the hypothalamic-pituitary-gonadal axis, this is caused by a chronic energy deficiency related to exercise, stress, the prolonged decrease in food intake, so it can restored to normal levels with the hormone. [10.14]

The binding of leptin to the long form of its receptor LepRb activates a downstream signaling pathway, which regulates food intake and energy expenditure. The central melanocortin system is a target for leptin to regulate glucose and energy homeostasis. [11.15]

IV. CONCLUTION:

The discovery of Leptin and the knowledge of its participation in obesity changed the vision regarding the metabolism and the functionality of adipose tissue. Leptin acts in many important physiological processes in the body, which opens the doors to continue studying its mechanisms in order to take advantage of its benefits for the management of this pathology. The action of leptin in common obesity is not very effective, however, in patients with congenital deficits it can generate a great therapeutic effect, improving most endocrine and metabolic abnormalities in these patients.

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