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Review: The Role of Hyperleptinemia in Chronic Degenerative Diseases

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Abstract: **Leptin is a protein that belongs to the family of cytokines, it's mainly produced by adipose tissue and its main function is to inform the nervous system about the amount of such tissue present in the organism, it also participates in the regulation of the neuroendocrine function and in the control of food intake; however, this molecule can also act in other tissues because their receptors are present in them. It has been identified that abnormal values of this protein can lead to have or aggravate some pathologies, such as cardiovascular, inflammatory, cancer, etc; since leptin is considered as a hormone that has proliferative, mitogenic, antiapoptotic and proinflammatory activity.**

Hyperleptinemia is a condition presented when leptin levels are above the normal level in the bloodstream (1-15 ng/ml) usually caused by physiological disorders such as obesity. Hyperleptinemia has been associated with several chronic degenerative diseases, where it has a strong relationship with the molecular basis of these diseases, either by direct action on the tissue or by its chemotactic ability to attract other molecules involved in the development of the disease. Because of these, abnormal levels of leptin in the body can be considered as a marker of disease, as described in this review.

Keywords: **leptin, hyperleptinemia, cancer, obesity, immune system, cardiovascular system, neuroendocrine control.**

I. INTRODUCTION

Leptin is a hormone secreted by adipose tissue that acts at different levels in the organs that make up the human body, including the stomach, placenta, liver, hypothalamus, mammary gland, heart, pancreas, hematopoietic cells, etc. Structurally, it is a protein formed by 167 amino acids, of a molecular weight of 16 kD, with a three-dimensional arrangement of four α-helices and a disulfide bridge. The normal blood leptin concentration ranges from 1-15 ng / mL [14]. This hormone has the ability to cross the blood-brain barrier and thereby interact with other neuropeptides and modify the neuroendocrine function, the intake and the energy expenditure in the body [15].

It acts through the interaction with its receptor, which belongs to the family of cytokines I, and presents six different isoforms, including long, short and soluble forms. Such receptors lack enzymatic activity, but are associated with kinase Jak tyrosine residues. The binding of leptin to its receptor activates the Jak-2 kinase, causing the phosphorylation of white proteins contained in the cellular cytoplasm [1].

Leptin also acts in peripheral tissues, where the soluble isoform of the leptin receptor plays an important role. The interaction of leptin with the nervous system and the peripheral tissue contributes to the control of glucose levels in the organism [20]. Leptin plays a determinant role in different systems and may favor the presence of some diseases that affect the population, such as: obesity, breast cancer, arthritis, etc.

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II. LEPTIN AND OBESITY

Obesity is considered as a disease in which there is an excessive increase in the amount of adipose tissue in a person; this disease may also have physical, psychological and social impacts. It is one of the diseases that has exponentially increased its incidence rate, with a prevalence in one third of adults [2]. Obesity can be presented by an imbalance of a set of environmental, nutritional, cultural and genetic interactions. The genetic contribution for obesity has an influence between 40-70% of the phenotype. Leptin is a hormone produced by adipose tissue, its concentration in blood plasma depends on the amount of fat in the body. [3] Obesity is related to resistance to leptin, a condition that causes elevated levels of leptin in the bloodstream. High levels of leptin lead to a poor energy balance in the body, causing a greater intake of food and less energy, which aggravates the problem of obesity [19].

III. LEPTIN AND CARDIOVASCULAR SYSTEM

It has been determined that leptin has adverse effects at a cardiovascular level, since people with hyperleptinemia have been associated with the presence of atherosclerosis, hypertension and metabolic syndrome. The effects of leptin at the cardiovascular level are closely related to blood pressure, insulin resistance, pro-inflammatory effects, and parasympathetic nervous system activity. Elevated levels of leptin in the bloodstream increase heart rate and blood pressure by triggering the parasympathetic nervous system and increasing the release of catecholamines. There are other mechanisms by which leptin is considered to have an influence on blood pressure control and is related to the direct action of leptin on renal sodium reuptake and a decrease in diuresis. [4]

Other cardiovascular conditions related to elevated levels of leptin are an increased risk of myocardial infarction, stroke, endothelial dysfunction and coronary artery calcification. [4]

It is known that leptin acts as a promoter of atherogenesis and vascular plaque vulnerability, which leads to an increase in lipid deposition in the vascular lumen and this in turn causes healing of the arterial wall, which results in atherosclerosis [5]. In the study by Ortiz-Segura et al, they identified a positive correlation between elevated levels of leptin and a significant risk of presenting endothelial dysfunction damage in adolescent patients who also had obesity linked to insulin resistance. Endothelial dysfunction is considered as an early marker for the development of cardiovascular diseases, such as myocardial infarction, previously referred. The mechanism by which a relationship between acute myocardial infarction and leptin levels is presented, is due to elevated levels of leptin in the blood favoring the secretion of different molecules such as ICAM-1. It has been clearly established that the increase of this adhesin is associated with myocardial infarction [17]

Another possible mechanism by which leptin is associated with cardiac damage is that leptin is considered to be a profibrotic factor of the heart, which contributes significantly to the development of cardiac fibrosis. [18]

Elevated levels of leptin are also positively correlated with decreased cardiopulmonary capacity, as demonstrated by Bjornstad et. al, who did a study in adolescents that presented type one diabetes with obesity and found that these patients had elevated levels of leptin that led to a reduction in their cardiopulmonary capacity through a mechanism independent of insulin sensitivity and obesity alone. [2. 3]

Therefore, it is possible determine that elevated levels of leptin increase the development of cardiovascular diseases as indicated in figure 1, where can be observed some of the causes of the increase of leptin levels in the organism and its effects in the cardiovascular system.

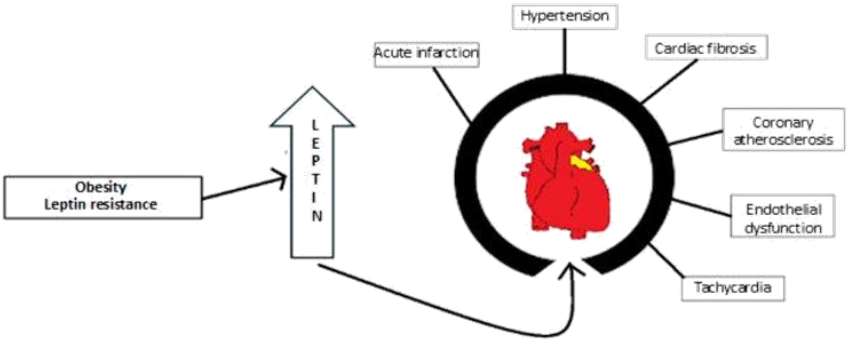

Figure 1. Causes and effects of hyperleptinemia in the cardiovascular system

IV. LEPTIN AND CANCER

Leptin is considered as a pleiotropic hormone, since it exerts its function on different tissues, in recent years it has been established that it plays an important role in the pathogenesis of different types of cancer such as lung, colon, pancreas, breast, etc. [25]. Leptin regarding oncological processes can influence different levels among them in cell growth, apoptosis processes, migration and invasion of some types of cancer, this is because the interaction of leptin with its receptor in cancerous tissues triggers a series of intracellular mechanisms that activate signaling pathways such as JAK / STAT, PI3K / PTEN / Akt / mTOR, Raf / MER / ERK. [27]

Leptin is considered to be a very important angiogenic agent in the development of some types of cancer. This is due to the fact that leptin positively influences the production of vascular endothelial growth factor, which is considered as the factor with the highest angiogenic activity [36].

Leptin is therefore recognized as an adipokine with proliferative, mitogenic, antiapoptotic and proinflammatory activity that contributes to the development of certain types of cancer. There are studies in different types of cancer that contribute to establish the above, for example:

Hepatocellular cancer:

It has been identified that in patients with hepatocellular carcinoma and prostate cancer there are elevated levels of leptin compared to healthy individuals, added with this it has been observed that these increased leptin levels favor an increased expression of leptin receptors in the tumors, which correlates with increased tumor growth and progression. [25]

Lung cancer:

In lung cancer it has been observed that there is a greater expression of leptin in people who present the disease, especially in patients with lymph node metastases. [25]

Some studies have found that some polymorphisms present in the leptin gene or its receptor increase the susceptibility to develop non-small cell lung cancer. [26]

Gastrointestinal cancer:

In one study Yunbao et. al found that patients with gastrointestinal cancer had high levels of leptin and its receptor in cancerous tissues and blood circulation, but found an additional factor since the most significant difference was found in those patients who, in addition to presenting gastrointestinal cancer, presented a picture of concomitant depression. [27]

Breast cancer:

Breast cancer is currently the leading cancer and the leading cause of death worldwide. Hyperleptinemia is a factor that represents a greater risk to suffer or worsen the state of said disease. Leptin is able to regulate and activate several signaling pathways and oncogenes that are highly related to breast cancer. [39]

One study found that leptin induces the proliferation of breast cancer cells but does not do so with normal breast cells, which is indicative that leptin is directly involved in the development of breast cancer. [30]

Leptin levels are positively correlated with an increase in breast cancer mortality. It is considered that there is a relationship between leptin levels and tumor necrosis factor alpha that play an important role in breast cancer mortality [6]. These levels of tumor necrosis factor alpha and proinflammatory molecules are due to the presence of macrophages, which also favor the production of proangiogenic factors, providing an ideal microenvironment for the adipose tissue to increase its expansion and thus a tumor progression. [28] Recent studies have found that the presence of elevated levels of leptin in the blood leads to increased incidence of metastatic tumors of breast cancer, triggering a worse prognosis, higher rate of recurrence and mortality. [6]

Leptin favors the proliferation of breast cancer by activating different cellular functions such as the cyclin D1 and Cdk2 pathway, avoiding apoptosis and favoring the angiogenic processes that are responsible for supplying nutrients to the tumor and thus its maintenance. [28]

The obASC gene is closely related to the level of leptin in breast cancer patients because it generates an overexpression of their plasma levels, the expression of this gene also increases the proliferation, migration and invasion of the estrogen

receptor positive. It is suggested that inhibition of leptin secreted by the obASCs gene may result in reduced tumor volume and distant organ metastasis, reducing the burden of obesity associated with breast cancers. [2]

This was confirmed in a study where the MCF-7 breast cancer cell line found that leptin promotes aromatase activity in cells, which enhances the ability of estradiol production in situ and leads to increased tumor proliferation estrogen-dependent. [28]

In a recent study by Shouman et. al. found that leptin is capable of inducing cells to produce carcinogenic adducts of DNA-N3-adenine and N7-guanine, this formation of adducts is mainly due to the fact that leptin acts by increasing levels of CYP1B1, which is related to the processes of estrogen metabolism.

It was also found that leptin influences an overexpression of leptin and estrogen receptor levels, so hyperleptinemia is considered a major risk factor for the development of breast cancer. [28]

Leptin has been shown to act as a mitogen in neoplastic cells of breast cancer and other sources. In the neoplastic cells leptin activates the JAK2 / STAT3 signaling pathway, which ends up with the activation of genes such as C-MYC, CYCLIN D1, P21 WAF1, C-JUN, JUNB, ERG-1 and BCL-2 , which are strongly involved in cell growth and proliferation. [7]

An additional mechanism by which leptin influences breast cancer is by the production of interleukin-18 through the action of the PI3K-AKT / ATF-2 pathway, which leads to increased metastasis and tumor invasion.

In this study Kuangfa Li, et. al. found that the release of interleukin-18 and the action of leptin-stimulated tumor-associated macrophages are indispensable for the invasion and migration of breast cancer cells. [32]

There are also some genetic conditions that may influence the action of leptin on breast cancer, which may lead to the development of breast cancer or, in the opposite case, decrease the risk factor, since, for example, the polymorphism in the PNS Rs1045895 present in the leptin receptor gene is associated with a decreased risk of breast cancer, while the SNP rs7799039 present in the leptin gene, leads to an increased risk of breast cancer and once presented promotes a larger tumor size. [38]

Ovarian cancer:

Leptin receptors OB-Rb and OB-Ra have been identified in ovarian cancer cells. The interaction of leptin with these receptors results in an increase in tumor growth, in addition to inhibiting cellular apoptosis.

This is because leptin acts by increasing the expression of cyclin D1 and Mcl-1 proteins. Cyclin D1 acts as an agent that favors cell proliferation, whereas Mcl-1 protein is related to the inhibition of cellular apoptosis. [29]

Gallbladder cancer:

Hao Zou, et. al. identified in a study that in patients with gallbladder cancer there is an overexpression of leptin levels and its Ob-Rb receptor, compared to those patients who did not present the disease. These elevated levels of both leptin and its receptor are considered as a factor that aggravates the prognosis of the disease.

In this study it was also determined that leptin plays an important role in the control of the migration of gallbladder cancer cells to other organs, favoring tumor metastasis. The pathway mediating the mechanism by which the above occurs is the JAK2 / STAT3 / SOCS3 pathway.

An additional factor that presents in this disease is the presence of the enzyme collagenase, which has been related to aggressive tumors, in this case it was verified that leptin is able to activate collagenases 3 and 9, which increases the severity of the illness. [31]

Colorectal cancer:

In patients with colorectal cancer, elevated levels of leptin have been found in the bloodstream, especially in those in the advanced stages of colon cancer. In addition, an overexpression of leptin receptors has been found in these patients, which contributes to a greater activity of the protein and decreases its elimination from the organism, which maintains its high concentration in the plasma. [3. 4]

Overexpression of leptin receptors has been found in colorectal cancer biopsies and colon cancer cell lines such as HT-29 [35]. These high concentrations of leptin are associated with increased proliferation of cancer cells, increased inflammation and promotion of angiogenesis, which supports the tumor and favors its metastasis. [34] It has also been observed that an increase in the expression of leptin receptors in colorectal cancer can generate histochemical abnormalities in the mucin promoting an increase in the secretion of low acid sialomucins, which has been positively related to an increase in the aggressiveness of cancer. [40]

Melanoma:

Melanoma or skin cancer, is one of the most common cancers at present, one of the main complications of this type of cancer is metastasis to the lymph nodes immediately to the area of the tumor. Junna Oba, et. al. identified that in patients who presented melanomas with metastases to lymph nodes presented higher levels of leptin than the patients who did not present said disease. This suggests that leptin may influence as a marker of tumor progression in this type of cancer. [33]

Osteosarcoma:

Osteosarcoma is a type of cancer that originates in the mesenchymal tissue, is an aggressive and localized cancer that affects the bones. Helin et. al. showed that elevated levels of leptin and sirtuin-1 were found in patients with osteosarcoma. It was determined that leptin positively influences the expression of sirtuin-1 and that together these two molecules are capable of promoting tumor metastasis. Therefore, elevated levels of leptin and sirtuin-1 are associated with unfavorable clinical manifestations and can be considered as poor prognosis for the disease. [37]

V. LEPTIN AND NEUROENDOCRINE CONTROL

The main neurological interaction of leptin is to inform the central nervous system about the amount of energy in the body, food intake and regulate neuroendocrine function. The main site of action of leptin in the nervous system is the hypothalamus, where it acts through the interaction and activation of the long isoform of the leptin receptor (ObRb) [8].

The interaction of leptin on the sympathetic nervous system triggers a series of responses among which is an activation of adrenergic receptors, which is of vital importance for leptin to exert its lipostatic activity. [22]

However, it has now been found that obesity causes an increase of inflammation in the hypothalamus which leads to generate hypothalamic resistance to leptin, which is considered as a negative mechanism of energy control of the organism, which is related to an increased hyperleptinemia present in obese patients and is considered as a negative factor that increases the pathogenesis of obesity. [12]

The control of bone mass in the body has a strong base in the sympathetic nervous system and with the different levels of sleep that people present, Kuriyama et. al. in a recent study identified that people with chronic short sleep periods present a hyperactive sympathetic nervous system, which triggers an increase in the level of leptin in the blood circulation and leads to a loss of bone mass, especially at the level of cortical bone mass. [21]

VI. LEPTIN AND THE IMMUNE SYSTEM

The neuroendocrine system has important interactions with the immune system through hormones of the hypothalamic-pituitary-adrenal complex, which correspond to the hormones corticotropin, adrenocorticotropin and glucocorticoids.

These hormones act in situations of stress, inflammation and control of immune system response [12]. Leptin is a hormone that can interfere with the release of hormones from the hypothalamic-pituitary-adrenal complex and thereby affect the mediation of innate and adaptive immune response. [8]

There is also another mechanism by which leptin can act on the immune response and is the presence of leptin receptors (LepR) in cells mediating the immunological action. [9]

Leptin and regulation of innate immunity

In innate immunity, leptin controls the activation of macrophages, neutrophils, monocytes, dendritic cells and Natural Killer cells, in addition to promoting the production of proinflammatory cytokines. [1]

Low levels of leptin in blood have been found to be related to a decrease in the phagocytosis capacity of macrophages. An increase in the levels of leptin acts favoring the synthesis of leukotrienes, both factors are determinants in the antibacterial action exerted by these immune cells. [8]

Leptin has been shown to promote the proliferation and activation of human monocytes in vitro, in addition to expression of activation markers such as CD69, CD25, CD38, CD71, etc. [8]

In neutrophils the short isoform of leptin receptors is expressed, where their interaction prevents cellular apoptosis, stimulates the production of hydrogen peroxide. Leptin also acts to promote the release of pro-inflammatory cytokines, such as interleukin-8, which is an important kyomotractic factor of neutrophils. [10]

In dendritic cells, which are the most important antigen presenting cells for T lymphocyte response, leptin can intervene at different levels. A decrease in the leptin concentration leads to an alteration in the maturation of dendritic cells, decreases the production of interleukin-12, interleukin-6 and tumor necrosis factor alpha and maintains the production of transforming growth factor beta, which favors the differentiation of regulatory T cells. [11]

Recent studies show that the action of leptin on Natural Killer cells is related to the activation of the signal transducer and transcription activator3 (STAT3) phosphorylation and the increase of interleukin-2, which leads to a maintenance of The cytotoxic activity of these cells. [8]

Leptin in adaptive immunity:

Leptin plays an important role in the adaptive immune response by promoting the proliferation of T-lymphocytes through the release of interleukin-12, favoring the excretion of chemotactic factors such as gamma interferon and tumor necrosis factor alpha and thus the migration of immune cells. It promotes the expression of adhesion molecules such as ICAM1 and VLA2 by the action of CD4 + T lymphocytes stimulated by an increase of gamma interferon. [8]

Leptin also affects B lymphocytes, where deficiencies in leptin levels have been found to lead to decreased lymphocyte production, while normal levels favor homeostasis, prevent apoptosis, and stimulate release of cytokines such as interleukin-6, Interleukin-10, and tumor necrosis factor alpha. [8]

Table 1: Effects caused by leptin on immune cells [14]

Immune cells	Effect caused by leptin
Neutrophils	Increases their survival. Stimulates the release of IL-6, IL-8, IL-10,TNF alpha
Eosinophils	It increases their survival, migratory capacity. Stimulates the release of IL-6, IL-8, MCP-1
Macrophages	It increases its proliferation and phagocytosis capacity. Stimulates release leukotrienes and H2O2
Natural Killer	It increases their differentiation, proliferation and cytotoxic activity. Stimulates IL-2 and IL-12 release
Dendritic cells	Increases their survival, migratory ability and antigen presentation. Stimulates the release of IL-6, IL-8, IL-12, TNF-alpha
T lymphocytes	Increases their survival, proliferation and response of Th1 lymphocytes
B lymphocytes	Increases their survival, maturation and release of IL-6, IL-10 and TNF alpha

Leptin is considered as a pro-inflammatory agent because it acts on immune cells, as can be seen in Table 1. This activation of immune cells measures inflammatory processes. [24] Which may lead to the development of some autoimmune diseases such as lupus.

Systemic lupus erythematosus is a serious autoimmune disease, where the immune system of a person, recognizes the same as strange, which triggers a response affecting different tissues and organs. [16] Recent studies have shown that in people suffering from lupus leptin levels are higher in the normal range, these levels also influence the pathogenesis of leptin since leptin acts as a pro-inflammatory cytokine, which favors the production of interleukin -1, interleukin-6 and tumor necrosis factor alpha, molecules that occur in inflammatory processes. [16]

VII. CONCLUSIONS

Leptin is a protein that is normally found in the body because of its production in adipose tissue. This protein has the particularity of acting at different levels in different tissues, which provides a great amount of physiological actions, being the main one the control of the food intake as a function of the amount of adipose tissue present, through its interaction with the neuroendocrine system. A number of studies have found a positive correlation between elevated levels of leptin and various chronic diseases. The main reason for the high levels of leptin in the body is obesity, since in this pathology is observed an excessive increase in body fat, which leads to a greater release of leptin into the bloodstream.

Among the different diseases in which leptin has been identified as positively influencing increased progression or development are different types of cancer, such as melanoma, lung, colorectal, breast cancer, in which different molecular mechanisms have been identified that explain the mitogenic, antiapoptotic and proliferating activity that leptin presents in these pathologies. It has also been identified that leptin plays an important role in the development of cardiovascular, neuroendocrine, inflammatory and immunological diseases, because the leptin receptor (OBR) is found in all these tissues and favors the action of leptin on them, for example in immune cells has direct action on the release of different chemotactic and inflammatory factors.

For all of the above it can be concluded that although leptin is a protein normally found in the body, its elevated levels can be used as a risk marker to suffer or develop with greater severity different diseases mentioned before.

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