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Review

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Leptin: a description of its intriguing biology. A review. Part I

Leptina: descripción de su intrigante biología. Una revisión. Parte I

Yara Irene López-Dionicio,* Miguel Ángel Ortiz-Flores,* Isabel Hidalgo,‡ Pilar Ortiz-Vilchis,§ Gustavo Guevara,§ Nayelli Nájera,* Guillermo Ceballos,* Eduardo Meaney*

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* Laboratorio de Investigación Integral Cardiometabólica. Sección de Estudios de Postgrado e Investigación. Escuela Superior de Medicina. Instituto Politécnico Nacional. Mexico City, Mexico.
‡ Unidad de Investigación Multidisciplinaria, Laboratorio de Investigación en Inmunología y Salud Pública, Facultad de Estudios Superiores Cuautitlán, Universidad Nacional Autónoma de México, Estado de México, Mexico.
§ Sección de Estudios de Postgrado e Investigación, Escuela Superior de Medicina, Instituto Politécnico Nacional. Mexico City, Mexico.

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Abbreviations:
BMI = Body Mass Index
CRH = Cytokine Receptor Homology
CRP = C Reactive Protein
CVD = CardioVascular Diseases
DM2= Type 2 Diabetes Mellitus
FNIII = FibroNectin III-like domains
IGD = ImmunoGlobulin-like Domain
IL-6 = Interleukin-6
JAK2= Janus tyrosine Kinase 2
LepR or ObR = Leptin Receptor
MAFLD = Metabolic Dysfunction-Associated Fatty Liver Disease
MS = Metabolic Syndrome
O/O = Obesity and overweight
PPRγ = Peroxisome Proliferator-Activated Receptor Gamma Agonists
STAT3= Signal Transducer and Activator of Transcription 3
TNF-α = Tumor Necrosis Factor-α

INTRODUCTION

Obesity and overweight (O/O) are significant public health problems worldwide. Recent estimates from the World Health Organization indicate that around two and a half billion adults are overweight, and 850 million are obese (one in eight adults in the world suffers from O/O).[1] These pathologies are defined as chronic, heterogeneous, and recurrent diseases due to an imbalance between caloric intake and energy expenditure, in which an expansion of white adipose tissue occurs, often associated with abnormal adipocyte function, insulin resistance, and secondary hyperinsulinism, low-intensity systemic inflammation, nitroxidative stress, and endothelial dysfunction, affecting various organs and systems of the economy.[2]

The expanding and deepening knowledge of energy metabolism, adipocyte function, and humoral and endocrine control of weight has modified many paradigms supporting their diagnostic and therapeutic management. However, until this time, more attention is paid to the cardiometabolic consequences of O/O (systemic arterial hypertension, dysglycemia, and dyslipidemia) than to the anthropometric, structural, and pathophysiological disorder milieu that generates them, as the increase and dysfunction of adipocyte mass and one of the more overlooked aspects in its genesis, the abnormalities of the appetite/satiety cycle that motivates animals to search for food. The interoceptive sensation of appetite or hunger is present in numerous species.[3] In animals with a more developed brain, appetite is regulated by a complex system of signals and responses involving the hypothalamus' nuclei, the cerebral cortex, digestive hormones, the pancreas, and fatty tissue, among other structures.[3] In animals with a more developed brain, appetite is regulated by a complex system of signals and responses involving the hypothalamus' nuclei, the cerebral cortex, digestive hormones, the pancreas, and fatty tissue, among other structures. The mechanism of the gastrointestinal system-adipose tissue-pancreas-hypothalamus axis, controlling the appetite/satiety cycle, is disturbed in

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O/O. In this context, among the elements of this physiological axis, leptin plays a fundamental role.[4]

This review is focused on describing leptin, an adipocyte-derived hormone (adipohormone), and its receptors, discussing its varied and complex functions, and reviewing the epidemiological data linking it to disorders, such as O/O, the so-called metabolic syndrome (MS), type 2 diabetes mellitus (DM2), metabolic dysfunction-associated fatty liver disease (MAFLD) and cardiovascular diseases (CVD), among others, as well as the pathophysiological mechanisms that trigger its deregulation. This review is based on a question that still has no clear answer: whether a deeper understanding of leptin and other adipohormones levels can improve the prevention, diagnosis, and preventive and therapeutic management of O/O syndrome.

LEPTIN

This adipohormone is a protein composed of 167 amino acid residues, encoded by the LEP gene located on the long arm of chromosome 7.[5] It is a member of the family of long-chain helical cytokines (such as interleukin 6) found not only in terrestrial and marine mammals but also in non-mammalian vertebrates, such as fish and reptiles.[6] Likewise, crustaceans and insects produce the hormone or analogs that form complex loops intestine-brain that regulate appetite.[6] For example, the fruit fly's brain (genus *Drosophila*) produces a series of satiety peptides, one of them an analog of leptin from the family of unpaired proteins (Upd1).[7] Interestingly, leptin analogs have not been found in worms.[8]

Leptin is produced in humans mainly in the white adipocyte, the principal energy reserve and source and target of numerous substances.[9] To a lesser extent, the hormone is secreted in other tissues and organs such as the mammary gland, placenta, ovary, skeletal muscle, stomach, epithelia, pituitary gland, hepatocytes, and lymphoid tissue.[10]

There is sexual dimorphism in the concentration of leptin. The values in thin women and men are 12-13 and 4-5 mg/L, respectively. The different values relate to a more significant amount of fatty tissue in women, estrogens' stimulating effect, and the androgens' inhibitory role.[11-13] Women have a 50% greater leptin production than men, even before puberty and after menopause. Age also influences the concentration of the hormone. *Table 1* shows leptin concentrations at different ages in both genders.

There are also considerable interethnic differences. Europeans have lower circulating levels than Asians and Latin Americans. Afro-American women have the highest levels of this adipohormone.[14,15] Leptin concentrations are also influenced by glucocorticoids, insulin, peroxisome proliferator-activated receptor gamma agonists (PPRγ), estradiol, follicle-stimulating hormone, various proinflammatory cytokines such as interleukin-6 and tumor necrosis factor-α (IL-6 and TNF-α), glucose, fructose, and L-glutamate.[16] Conversely, catecholamines, free fatty acids, exposure to cold, testosterone, and thyroid hormones exert an inhibitory action on its secretion.[17,18] Serum concentrations of this adipohormone present a higher concentration in the early morning[17] and decrease rapidly after fasting or with caloric restriction.[19]

Leptin links the individual's nutritional status with other physiological functions, such as reproduction and immune response. In general, the increase in body mass index (BMI) is associated with a proportional increase in leptin concentration in both genders, correlating better with the percentage of body fat than with BMI, which is known to be a marker of corpulence, which is not only associated with obesity but also with skeletal muscle mass.[18,60] Although most obese persons have hyperleptinemia, a small percentage do not, which is one of the paradoxes of this intriguing molecule.[61] One of the possible explanations for this fact is that the use of BMI can be misleading in muscular subjects and does not reflect the accumulation of visceral fat.[62] Another is that the metabolic disorders of obesity, such as insulin resistance/hyperinsulinism syndrome, dysglycemia, dyslipidemia, the increased production of proinflammatory cytokines, and hyperleptinemia, among others, do not occur in all obese people but only in those with ischemic, dysfunctional and inflamed adipose

Table 1: Leptin concentration values according to age and gender.

Age groups	Number of studies	Gender		Differences Δ (%*)
		Men Mean [range], µg/L	Women Mean [range], µg/L	
Umbilical cord[20-28]	9	6.26 [1.2-11.5][20,21]	9.78 [1.5-19.6][20,21]	3.52 (56)
Newborns[29,30]	2	1.36 [0.93-1.8][29,31]	1.84 [1.38-2.3][29,31]	0.48 (35)
< 6 months[31-33]	3	2.85 [1.5-4.5][31,32]	3.29 [1.73-4.8][31,32]	0.44 (15)
6-12 months[31-33]	3	2.26 [0.43-5.0][31,32]	2.64 [0.53-5.7][31,32]	0.38 (16)
1-4.9 years old[33,34]	2	1.36 [1.3-1.42][33,34]	2.05 [1.9-2.2][33,34]	0.69 (47)
5-10 years old[34-36]	3	3.08 [1.7-4.38][34,35]	4.34 [2.0-5.57][34,36]	1.26 (40)
10-15 years old[12,35-37]	4	3.88 [1.6-7.61][12,37]	9.66 [5.8-15.4][12,37]	5.78 (149)
15-20 years old[12,36-38]	4	3.27 [1.1-6.7][12,37]	13.9 [7.6-16.7][12,37]	10.63 (325)
20-50 years old[39-51]	13	6.7 [1.37-14.9][39,40]	17.28 [5.91-46.3][39,40]	10.58 (157)
50-65 years old[39,41,42,45,47,51-55]	4 (men) 10 (women)	6.31 [2.12-10.0][39,42]	14.47 [5.21-31.4][39,41]	8.16 (129)
> 65 years old[40,42,47,48,50,51,56-59]	5 (men) 10 (women)	5.8 [2.11-10.0][42,56]	15.69 [6.4-25.1][56,57]	9.89 (170)

* Women compared to men.
Average 3.92 ± 2.01 µg/L in men, and 8.73 ± 6.01 µg/L in women (difference of 4.71 µg/L, p = 0.023).

tissue, which is observed when the growth of fat mass exceeds the possibilities of tissue nutrition that depends on appropriate angiogenesis.[63,64] In this respect, our research group has found that 17.4% of subjects with O/O had normal metabolism (5.4% of obese subjects and 12% of those with overweight).[64] Other studies have shown that a higher leptin concentration is associated with dysmetabolism.[65,66] The inflammatory state favors the production of leptin because proinflammatory cytokines induce the synthesis of the hormone.[67] However, other studies did not show significant differences in leptin concentration between «metabolically healthy» obese subjects and those with dysmetabolism.[68] The causes of this apparent paradox remain to be elucidated.

LEPTIN PHYSIOLOGY

Leptin is a classic multifunctional substance with almost 100 known functions in different tissues, organs, and systems. *Table 2* describes some of these actions in the cardiovascular and nervous systems and energy, lipid, and carbohydrate metabolism. However, the hormone has numerous other effects not considered in this review, for example, milk production, various reproductive and placental processes, the systemic immunoinflammatory reaction, bronchial muscle tone, bone density, carcinogenesis, certain mental states such as depression, absorption, and digestion of nutrients in the intestine, and the production of mucus in the colon, among many others.

THE LEPTIN RECEPTOR

The leptin receptor (LepR or ObR) belongs to the class I cytokine receptors family. Six isoforms of this receptor exist, caused by alternative splicing. They share the binding sites and the same N-terminal region while differing in the C-terminal cytoplasmic region. There is a long-form (LepRb), four short forms: LepRa, LepRc, LepRd, LepRf, and a soluble form (LepRe) *(Figure 1)*.[125,126] Only 10 to 20% of LepRb is expressed in the cell membrane; the rest is found

Table 2: Actions of leptin in various functions and systems.

Cardiovascular system	
Vasodilation	Increases eNOS activity, NO availability, EDHF, and endothelin-1 expression[69-71]
Angiogenesis	Stimulates the production of VEGF and the expression of the VEGF-R2 receptor. It raises COX-2 enzymes and promotes endothelial and smooth muscle cell proliferation[72]
Heart rate and blood pressure	Both increase as a consequence of sympathetic nervous system stimulation[73]
Contractility of cardiac and vascular muscle	Increments in the activity of voltage-gated Ca^{++} channels and GPCRs promote the functioning of proteins such as calreticulin, cAMP-dependent protein kinase type II, and tropomyosin. Furthermore, it stimulates cell growth and proliferation through myotrophin, myoferlin, and fibrin-1 synthesis[74]
Coagulation	Increases factor VIII and IX concentrations[75]
Atherosclerosis	Promotes platelet aggregation, ROS formation, and the expression of endothelin-1, MCP-1, and thrombospondin 1. Increases local and systemic inflammation by increasing the production of TNF-α, IL-6, and IL-1β in mononuclear leukocytes[76-81]
Natriuresis	Activates the Na^{+}-K^{+}-ATPase pump in the renal tubule, promoting the excretion of Na^{+} and water[82]
Vascular fibrosis	Causes increased production of metalloproteinases MMP-2 and MMP-9, collagen types I and IV, fibronectin, TGF-β and CTGF[83-85]
Cardiac hypertrophy	It causes cardiac hypertrophy due to increased actin production.[86,87] Furthermore, hypertrophy is stimulated by an increase in heart rate and blood pressure, secondary to overactivation of the sympathetic nervous system[88]
Heart failure	Leptin concentration is a prognostic factor for heart failure in dilated cardiomyopathy, probably due to the induction of inflammation, fibrosis, and alterations in Ca^{++} homeostasis, and also for the induction of hypertrophy and endothelial dysfunction, among several other factors[89,90]
Cardiac protection	Leptin limits the extension of myocardial infarction by stimulating the enzyme RISK, inhibiting cardiomyocyte apoptosis,[91] reducing cardiac lipotoxicity, preventing the opening of the mPTP pore, and inhibiting death cell caspase 3 induced by TNF- α[86]
Central nervous system	
Effect on appetite	It reduces appetite by inhibiting the orexigenic NPY/AgRP neurons and activating the anorexigenic cells of the proopiomelanocortin/CART system.[92,93] It modulates the solitary tract's function, which includes the transmission of food flavor and the regulation of portion sizes.[94] It intervenes in the reward circuit by inhibiting dopaminergic neurons in the ventral tegmental area,[95.96] decreasing the sensitivity of the olfactory bulb[94,97]
Sympathetic nervous system	It activates the sympathetic system through the MTC4 receptor in the paraventricular nucleus that stimulates the sympathetic preganglionic neurons[98,99]
Cognitive functions	It regulates memory and learning functions in the hippocampus through NMDA receptors,[100] stimulates neuroplasticity in some areas of the cortex and hippocampus. It exerts a neuroprotective effect in neurodegenerative diseases such as Parkinson's and Alzheimer's, mediated by the increase of the BDNF factor[101, 102]
Hypothalamic hormones	Releases the hormones GnRH, ACTH, and TRH[102-105]
Metabolic functions	
Lipolysis	This is due to increased sympathetic activation and activation of ATG and HSL lipases[106,107]
Free fatty acid oxidation	Due to the greater activity of PPARα, PGC1α, CPT1, AMPK, and acyl-CoA oxidase[107-111]
Citric acid cycle	Enhanced by stimulating citrate synthase[112]
Lipogenesis	It is inhibited by reducing the SREBP1, FASN, and ACC1 activity in white adipose tissue[93]
Hepatic gluconeogenesis	Decreases hepatic gluconeogenesis by inhibiting phosphoenolpyruvate carboxykinase, glucose 6-phosphate phosphatase, CREB, and PGC1[113,114]
Glycolysis	Incremented by stimulating PFK and hexokinase[115,116]
Cholesterol metabolism	It raises the concentration of LDL by decreasing the density of the hepatic LDL receptor[117] and increasing cholesterol synthesis by stimulating the activity of HMG CoA reductase[118]

Contiuous Table 2: Actions of leptin in various functions and systems.

Relation with insulin	It decreases insulin synthesis by increasing the conductance of K^+ channels in pancreatic cells.[119] Also, it improves insulin sensitivity by sharing the IRS-PI3k signaling pathway with insulin.[120] Finally, it enhances insulin inhibition of gluconeogenesis and hepatic glycogenolysis[121,122]
Glycogen genesis	It is stimulated by increasing insulin sensitivity[120]
Adipose tissue	It induces the expression of the heat-producing protein UCP-1, characteristic of brown and beige adipocytes.[123] It reduces fat mass by activating lipolysis and inhibiting lipogenesis[124]

ACC1 = Acetyl-CoA carboxylase. ACOX1 = Acyl-CoA oxidase 1. ACTH = Adrenocorticotropic hormone. AgRP = Agouti-related peptide. AMPK = AMP-activated protein kinase. ATG = Adipose triglyceride lipase. CART = Cocaine- and amphetamine-regulated transcript. COX-2 = Cyclooxygenase-2. CREB = Cyclic AMP-response element binding protein. CTGF = Connective tissue growth. EDHF = Endothelium-derived hyperpolarizing factor. eNOS = Endothelial nitric oxide synthase- NO, nitric oxide. FASN = Fatty acid synthase. G6PD = Glucose-6-phosphate dehydrogenase. GnRH = Gonadotropin-releasing hormone. GPCRs = G protein-coupled receptors. HD = High-density lipoprotein. HK2 = Hexokinase 2. HMG CoA = β-hidroxi-β-metilglutaril-CoA. HS = Hormone-sensitive lipase. IRS = Insulin receptor substrate. LDL = Low-density lipoprotein. MMP-2 and 9 = Matrix metalloproteinase-2 and -9. NFAT = nuclear factor of activated T cells. NMDA = N-metil-D-aspartate. NPY = neuropeptide Y. PAI-1 = plasminogen activator inhibitor-1. PEPCK = phosphoenolpyruvate carboxykinase. PFK = phosphofructokinase. PGC 1γ = peroxisome proliferator-activated receptor gamma coactivator-1. PGC1α = peroxisome proliferator-activated receptor-gamma coactivator 1-alpha. PI3k = phosphoinositide 3-kinase. POMC = proopiomelanocortin. PPARα = peroxisome proliferator-activated receptor alpha. PT1 = carnitine palmitoyltransferase. ROS = reactive oxygen species. SREBP1 = sterol regulatory element binding protein. TGF-β = transforming growth factor-β. TRH = thyrotropin-releasing hormone. UCP-1 = uncoupling protein-1. VEGF = vascular endothelial growth factor. VEGF-R2 = vascular endothelial growth factor receptor 2.

in the endoplasmic reticulum, the endosomes, and especially in the Golgi apparatus and trans-Golgi system. When internalized, leptin receptors can be transported back to the cell membrane or ubiquitinated (attached to the small protein ubiquitin, which marks them for degradation).[125] The presence of leptin is the primary determinant of modulating the density of LepR in the membrane. It has been shown that when the hormone increases, its receptor is endocytosed by clathrin (a protein that coats some membrane vesicles) dependent pathways. The nutritional status also contributes to the density of the leptin receptor in the membrane; for example, a high-fat diet increases it, while caloric restriction and fasting decrease its density in the membrane.[127]

The primary function of the short receptor isoforms is to transport the hormone into the central nervous system and for renal elimination.[128] The transmembrane isoforms are cleaved by cathepsin L and the metalloproteases ADAM 10 and ADAM 17, forming the soluble receptor LepRe, the central plasma leptin binding protein, thus regulating its availability.[129,130] The long isoform is found mainly in the hypothalamus and other tissues such as the heart, placenta, muscle, liver, pancreas, spleen, prostate, testis, ovary, small intestine, and colon.[131] LepRb has the most extended intracellular portion capable of activating different cell signaling pathways leading to the expression of various proteins, enzymes, and neurotransmitters, in addition to regulating other receptors, hormones, and cytokines, which explain all the complex physiological effects of leptin.[132]

The extracellular region comprises six domains: an N-terminal domain, two cytokine receptor homology (CRH) domains, CRH1 and CRH2, separated by an immunoglobulin-like domain (IGD), and two fibronectin III-like domains (FNIII) *(Figure 1)*. The primary binding sites of the adipohormone to the receptor are CHR2 and FNIII.[132,133]

The Leptin binding to its receptor activates several signaling systems, as shown in *Figure 2*. The Janus tyrosine kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3) is a signaling cascade comprising a receptor, a phosphorylating kinase, and a transcription element. Leptin binding to its receptor induces the transphosphorylation of the kinase, which phosphorylates some tyrosine residues that attach to the STAT3 factor. After it is phosphorylated, it is released from the kinase

and translocated through the nuclear pore, inserting itself into several genes' regulatory, non-coding regions and activating them. As a counter-regulatory loop, STAT3 induces, in turn, the expression of the suppressor of cytokine signaling 3 (SOCS3), which inhibits the phosphorylation and activation of STAT and JAK components. Also, the tyrosine-protein phosphatase non-receptor type 1(PTP1B), expressed during endoplasmic reticulum stress, inhibits the JAK phosphorylation. This negative feedback mechanism prevents the overactivity of the leptin receptor activation. Other signaling pathways are the insulin receptor substrates (IRS)/phosphoinositol 3-kinase (PI3K), the protein tyrosine phosphatase Src homology 2 (SHP-2)/mitogen-activated protein kinases (MAPK), and the 5-AMP-activated kinase (AMPK)/acetyl coA carboxylase (ACC).

In humans, the LepRa is the most abundant isoform, expressed mainly in the choroid plexus, regulating the leptin transport to the central nervous system. Being a receptor-mediated transport, it is a saturable system in which there is no further increase in leptin amount in cerebrospinal fluid when the leptin concentration exceeds 25-30 ng/mL.[133,134]

The LepRe generated by the fragmentation of transmembrane receptors is the main protein regulating the availability of adipohormone. The serum concentration of LepR is lower in obese than in lean persons, contrary to what is expected in hyperleptinemia, and the density of the transmembrane receptors decreases due to ligand-induced receptor sensitization. The Free Leptin Index (FLI), the ratio between the hormone and LepRe serum concentrations, reflects the tissue sensitivity to the hormone, which decreases after weight loss.[135,136]

In this regard, hyperleptinemia in patients with O/O is related and probably caused by tissue resistance to the hormone. Patients with O/O have, in general, higher FLI values than lean subjects. Remarkably, in patients with O/O and hyperleptinemia, a paradoxical fact is observed: the hormone does not suppress appetite and does not activate energetic metabolism.[129] This leptin resistance must be interpreted as an adaptive response in some situations. For example, in grazing animals during winter months or in women during the last trimester of pregnancy, it is a mechanism for storing energy.

Some leptin mutations or its receptors commonly cause tissue resistance in humans. On the other hand, even if there is a genetic predisposition, only 3 to 5% of obesity cases are of genetic origin, either by mutation of leptin, the LepRb receptor, or some substances related to its actions (POMC, proconvertase 1,

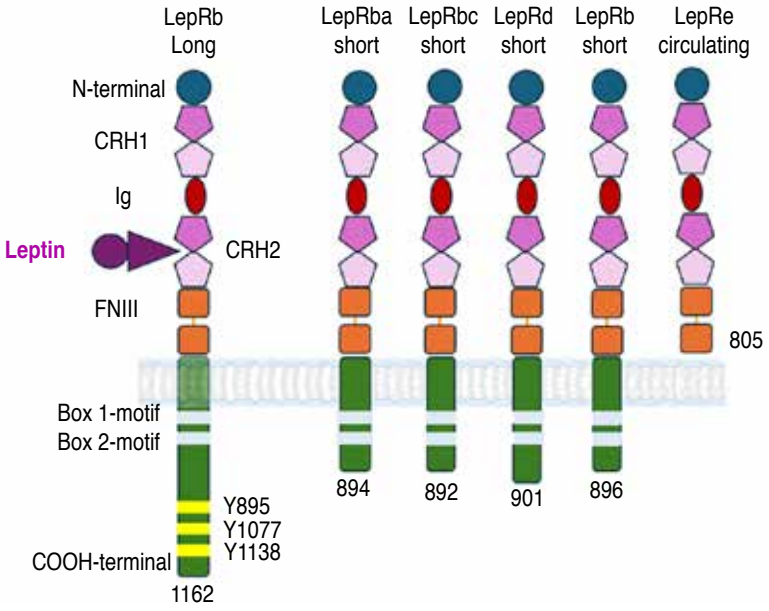

Figure 1:

The leptin receptor isoforms. LepRb (Leptin Receptor b), LepRa (Leptin Receptor a), LepRc (Leptin Receptor c), LepRd (Leptin Receptor d), LepRf ((Leptin Receptor f), LepRe (Leptin Receptor e), CRH1 (cytokine receptor homology 1), CRH2 (cytokine receptor homology 2), IGD (immunoglobulin-like domain), FNIII (fibronectin III-like domain).

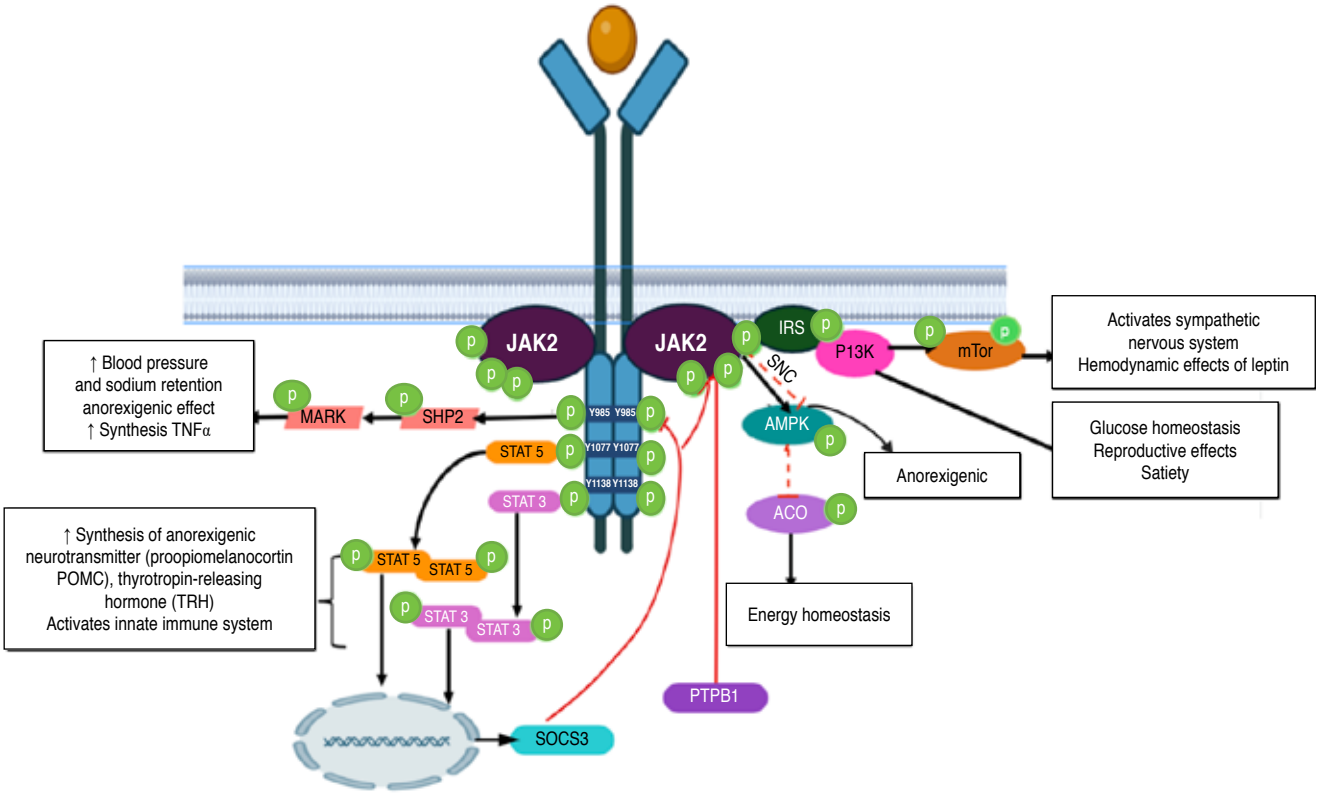

Figure 2: Leptin receptor signaling: Jak2 (Janus tyrosine kinase 2), MAPK, SHP2, STAT 3 (signal transducer and activator of transcription 3), STAT 5 (signal transducer and activator of transcription 5), ACC (acetyl CoA carboxylase), AMPK (5-AMP-activated kinase), IRS (insulin receptor substrates), PI3K (phosphoinositol 3-kinase), mTor (mammalian target of rapamycin), SOCS3 (suppressor of cytokine signaling 3), PTPB1 (protein tyrosine phosphatase 1B).

prohormone convertase 1 (PC1), Sh2b1[137] and MC4R.[138] Congenital leptin deficiency is a rare condition causing hyperphagia and early-onset obesity, accompanied by decreased thyroid-stimulating hormone and hypogonadism.[139] The arrival of leptin to the hypothalamic nuclei is crucial to exert its anorexigenic and metabolic effects. In subjects with hyperleptinemia, there is a decrease in its transport.[140] Despite the exogenous administration of leptin, there is no adequate decrease in appetite and weight.[141] In murine models of obesity, peripheral administration of leptin is not associated with a reduction in appetite and weight.[142] Leptin does not decrease food intake, whereas intrathecal administration does do so. This is because the leptin transport system is receptor-mediated and saturable. A diet high in fat, fructose, and salt decreases the transport to the central nervous system.[143,144]

O/O patients have a condition of chronic low-degree inflammation and substantially higher production of proinflammatory cytokines and markers of inflammation, affecting leptin sensitivity. For example, the concentration of C reactive protein (CRP) is directly proportional to leptinemia.[145] CRP attaches to the hormone, interfering with the leptin-receptor interaction. Also, when incorporated into the receptor's structure (transmembrane and soluble), it is rendered functionally unable. On the other hand, the proinflammatory cytokines causing endoplasmic reticulum stress also activate the NF-κB, a multiple transcription factor, leading to the expression of SOCS3 and PTB1B. These molecules inhibit the functioning of the leptin receptor, as was described before.[146]

The physiology of leptin, a classical multifunctional hormone, exceeds its essential role as a key appetite and energy regulator.

From a biological point of view, nutritional status, depending at large on the sufficient ingestion of food, is a *sine qua non* condition for correct organic performance, immunological competence, and reproductive capacities. The knowledge of this complex, intriguing, and sometimes paradoxical hormone can change the prejudices and false concepts around obesity.

In a forthcoming publication, we will discuss the implications of leptin abnormalities in the clinical settings of obesity, high blood pressure, and diabetes.

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Correspondence:
Eduardo Meaney MD, PhD
E-mail: lalitomini1@gmail.com