ISSN: 2754-5008

Journal of Pharmaceutical Research and Reports

SCIENTIFIC Research and Community

Review Article

Open Access

Leptin: Mechanisms Involved In Signaling and Resistance

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ABSTRACT

Leptin is secreted mainly by white adipocyte tissue, and it circulates at levels positively correlated with fat mass, thus reflecting primarily the amount of energy stored in adipose tissue. Leptin levels also change with acute changes in energy intake and thus, secondarily reflect acute energy availability. Several potential mechanisms behind leptin resistance have been identified including: Inflammatory signaling, elevated free fatty acids, high leptin and genetic mutation in *OB* and *DBU* genes. This review summaries all the physiological, biological aspects of leptin hormone including increases energy expenditure, thermogenesis, heart rate, blood pressure but decreases glycaemia. This review summarizes the pharmacological and non-pharmacological treatment of leptin hormone imbalances.

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Received: December 01, 2021; **Accepted:** December 07, 2021; **Published:** December 18, 2021

Keywords: Leptin Receptor Obrb, Leptin Resistance, Genetic Mutations, Signaling Mechanism

Introduction

Leptin is an adipocyte-secreted hormone that regulates the appetite and represents a key factor in the development of obesity, a serious medical, social, and economic problem in modern society. More than 20 years ago, leptin and its receptors were identified as key regulators of body weight and energy homeostasis. A minor increase in leptin concentration reduces the appetite and leads to a decrease in body weight; however, in obesity, despite increased leptin concentration, the efficacy of the anorexic effect of leptin is decreased, with leptin resistance developing due to a defect in intracellular signaling associated with the leptin receptor or decreases in leptin transport across the blood–brain barrier (BBB) [1].

Leptin, also known as a satiety hormone, is a master mediator of food intake and body energy balance. Leptin is produced by adipose tissue and plays multiple regulatory roles in metabolism, immunity, and inflammation. Also, it was shown that leptin is a potent ventilation stimulant acting on central respiratory control nuclei. Leptin exerts its intracellular effects through a long isoform of leptin receptor ObRb. ObRb is found in almost all tissues, and it is expressed at high levels in the brain. Leptin levels in plasma are highly associated with BMI and a degree of adiposity. Therefore, circulating leptin levels are markedly elevated in obese subjects. However, the central satiety effects of leptin are abrogated in obesity. Leptin resistance is defined as a failure of high-circulating levels of leptin to decrease hunger and promote energy expenditure. OSA and IH, powerful triggers of oxidative stress, increase peripheral leptin levels and also induce leptin resistance. Of note, leptin resistance may be implicated in the pathogenesis of OSA through impaired regulation of upper airway patency and diaphragmatic control [2,3].

What causes leptin resistance?

Several potential mechanisms behind leptin resistance have been identified.

These include:

- **Inflammation:** Inflammatory signaling in your hypothalamus is likely an important cause of leptin resistance in both animals and humans.
- **Free fatty acids:** Having elevated free fatty acids in your bloodstream may increase fat metabolites in your brain and interfere with leptin signaling.
- **Having high leptin:** Having elevated levels of leptin in the first place seems to cause leptin resistance.

Most of these factors are amplified by obesity, meaning that you could get trapped in a vicious cycle of gaining weight and becoming increasingly leptin resistant over time [3].

Genetic mutations

Mutations in the *OB* and *DBU* genes in humans are extremely rare and cause hyperphagia, obesity soon after birth, and hypothalamic hypogonadism in homozygotes. Such mutations have only been described in three sisters and resulted in the replacement of guanine by an adenine at the splice-donor site of exon 16 and generation of a truncated leptin receptor lacking transmembrane and intracellular

domains. Mutant receptors at high concentrations circulate and bind leptin. In addition to these consequences, dysfunctional secretion of thyrotropin and growth hormones can also occur. These findings indicate that mutations in the leptin gene and that of its receptor are not the main factors that induce the development of leptin resistance in the general population [1].

Obesity has a substantial genetic component

The identification of mutant genes that cause obesity in mice provided a molecular framework for identifying mutant genes that cause obesity in humans. Thus, mutations in leptin, the LepR, the MC4R, as well as PCSK1, and enzymes required for the processing of POMC cause human obesity, as do other components of the neural circuit that regulates food intake including BDNF and Sim1. Indeed, it now appears that more than 10% of morbid human obesity is a result of Mendelian defects in these (and other) genes, which, in the majority of cases, are in the MC4R and the LepR [1].

Altered leptin transport across the BBB

Leptin resistance can also be developed at the BBB, thereby allowing unregulated transport of leptin from the blood to the brain. Brain blood vessels express short forms of OBR, which bind leptin and transport it from blood to the interstitial tissue of the brain and into the cerebrospinal fluid. At serum leptin levels above the range of 25–30 ng/mL, the concentration of leptin in brain tissues and cerebrospinal fluid does not increase. This phenomenon likely plays a role in the development of leptin resistance and obesity, where excessive levels of leptin in the blood result in decreased BBB permeability [1].

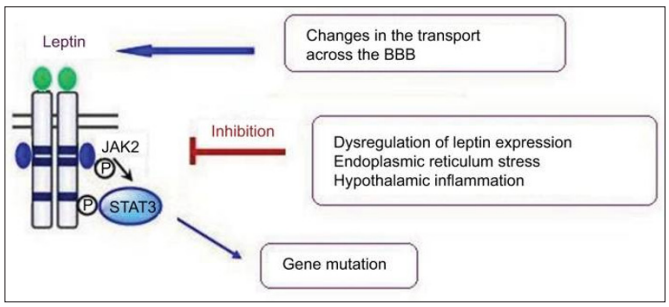

Figure 1

Resistance:

To date, several mechanisms have been identified as potentially underlying leptin resistance. These include a number of molecular and functional alterations characterized by structural changes to the molecule, its transport across the BBB, and the deterioration of leptin-receptor function and signaling.

People who are obese have a lot of body fat in their fat cells.

Because fat cells produce leptin in proportion to their size, people who are obese also have very high levels of leptin.

Given the way leptin is supposed to work, many obese people should naturally limit their food intake. In other words, their brains should know that they have plenty of energy stored.

However, their leptin signaling may not work. While copious leptin may be present, the brain doesn't see it.

This condition — known as leptin resistance — is now believed to be one of the main biological contributors to obesity.

When your brain doesn't receive the leptin signal, it erroneously thinks that your body is starving — even though it has more than enough energy stored.

This makes your brain change its behavior in order to regain body fat. Your brain then encourages:

Eating more: Your brain thinks that you must eat in order to prevent starvation.

Reduced energy expenditure: In an effort to conserve energy, your brain decreases your energy levels and makes you burn fewer calories at rest.

Thus, eating more and exercising less is not the underlying cause of weight gain but rather a possible consequence of leptin resistance, a hormonal defect.

For most people who struggle with leptin resistance, willing yourself to overcome the leptin-driven starvation signal is next to impossible [3].

Leptin resistance may relate either to a defect in the transport of leptin across the blood brain barrier or to deficits in intracellular signaling mechanisms downstream of leptin. Several mechanisms and pathways related to the development of leptin resistance have been described in the past and new ones are continuously discovered. The phosphodiesterase-3B (PDE3B)-cAMP- and Akt-pathways of leptin signaling in the hypothalamus, the fat mass and obesity-related (FTO) gene, transient receptor potential vanilloid type (TRPV)-1 channel, 15-deoxy-Δ(12,14) -prostaglandin J2 (15d-PGJ2), estradiol (E2) and peroxisome proliferator-activated receptor γ (PPARγ) are some of the recently identified molecules/pathways to be involved in leptin's resistance development in animal studies. Although this new knowledge creates new pathways for understanding leptin resistance, these still need to be confirmed in humans [4].

Several studies demonstrated that leptin responsiveness decreases with obesity, aging and neurodegenerative diseases, a phenomenon called leptin resistance. Leptin resistance affects a range of processes such as food intake, insulin sensitivity, inflammation and cognition. In obesity, leptin resistance leads to increased production of leptin by adipocytes and hyperleptinemia, in an attempt of the organism to compensate for low leptin responsiveness. Decreased leptin signaling in the CNS may be related to defective leptin transport across BBB, LepR downregulation and/or deficient leptin signaling downstream LepRs. Triglycerides can impair BBB leptin transport causing central leptin deficiency. Furthermore, it was recently demonstrated that triglycerides can cross the BBB to directly induce hypothalamic leptin and insulin receptor resistance, leading to decreased satiety and cognitive impairment in mice. Interestingly, triglycerides increased leptin binding in different brain regions, suggesting an allosteric or post-receptor rather than a competitive mechanism of inhibition of LepR signaling by triglycerides. In light of longitudinal studies linking increased mid-life triglyceride levels to the risk for AD, the above results suggest that triglycerides may contribute to AD pathogenesis and progression by suppressing leptin signaling in the brain. Deficient leptin transport across BBB by megalin leading to reduced leptin entry into the brain has also been described in aged mice and in mouse models of AD. At the intracellular level, leptin signaling is negatively regulated by the suppressor of SOCS3 and by the PTP1B. SOCS3 binds to LepR and JAK2 to inhibit their activities, whereas PTP1B dephosphorylates tyrosine residues deactivating LepR and JAK2. PTP1B have been linked to central leptin resistance in humans as well as in a variety of animal models of obesity and aging. SOCS3 and PTP1B were also found upregulated in the brains of AD mouse models and AD patients. Therefore, targeting PTP1B and SOCS3 may prove valuable to overcome central leptin resistance in obesity, aging, and AD [5].

Leptin resistance refers to the states in which leptin fails to promote its anticipated effects, frequently coexisting with marked hyperleptinaemia. The assessment of leptin resistance

encompasses diverse aspects. The standard biochemical marker for cellular LepRb action is leptin-induced STAT3 phosphorylation, and impairment of this induction is usually interpreted as an indication of leptin resistance. The measurement of the acute or chronic ability of exogenously-administered leptin to reduce body weight, adiposity and/or food intake is also used to estimate the sensitivity to leptin. Practically speaking, 'leptin resistance' is a broadly applied and context-dependent term with no universal, quantifiable and clinically useful definition. Since a major physiological function of leptin is to signal energy deficiency, the implications of hyperleptinaemia and the concomitant notion of 'leptin resistance' become controversial. Besides, much of the evidence for leptin resistance relies on pharmacological studies that use non-physiological doses or routes of leptin administration. A variety of arguments suggest that a 'leptin resistance' underlies the development of obesity; however, it has been also considered that leptin action naturally faces a ceiling effect, beyond which it promotes little additional effect. The concept of leptin resistance is also dependent on which of the biological effects of leptin are affected. The fact that in some forms of obesity there may be resistance to the anorectic and weight-reducing actions of leptin but preservation of hypertension led to the concept of selective leptin resistance [6].

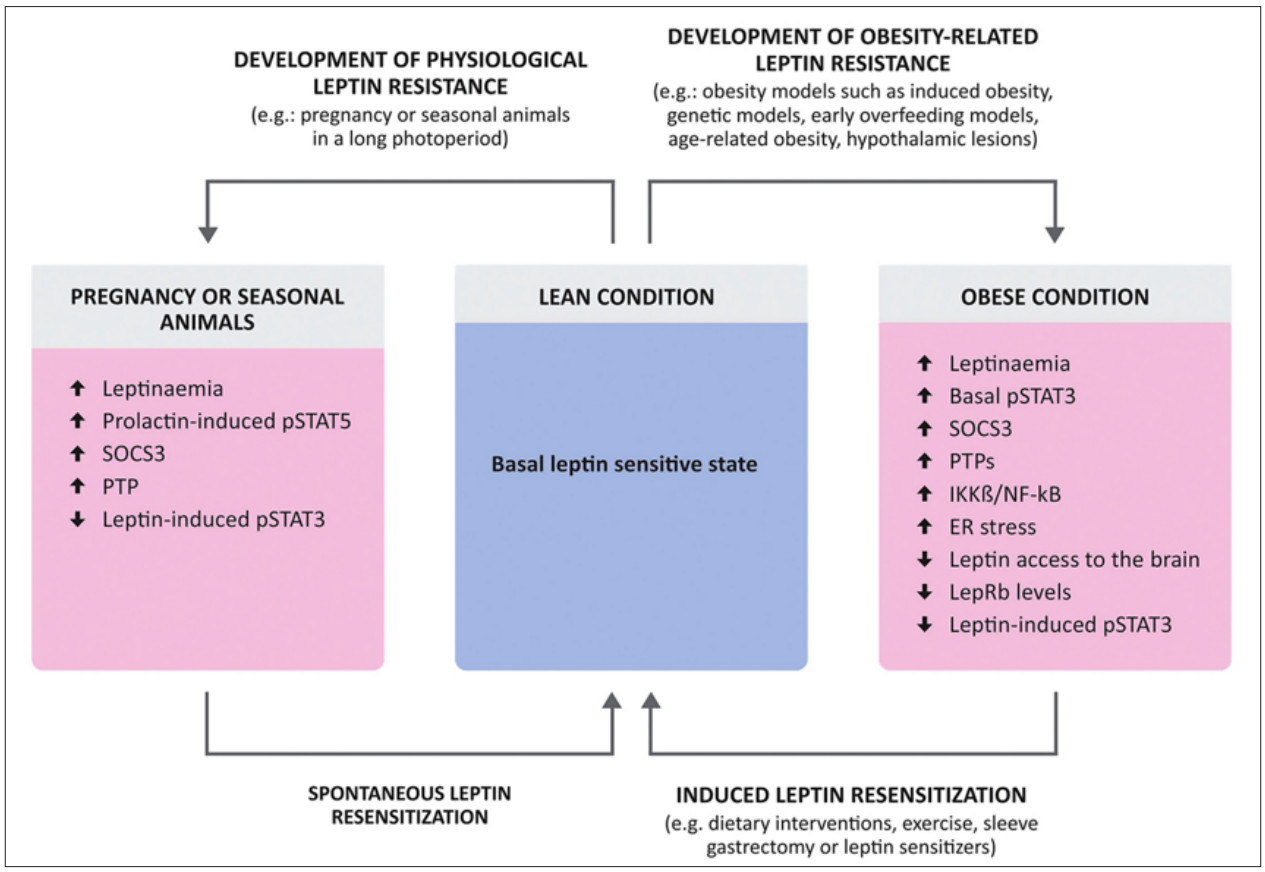

Figure 2

Physiology of leptin:

Leptin is transported to various regions of the brain across the blood--brain barrier (BBB), and most of the actions of this adipokine on body weight are attributable to effects in the hypothalamus. However, leptin has additional pleiotropic functions in peripheral tissues. Leptin effects are mediated by binding to its receptor (ObR). Leptin receptors are expressed not only throughout the hypothalamus, the cortex and several other brain areas but also in peripheral tissues such as adipose tissue, heart, muscle, lung, intestine, liver and breast. Alternative splicing of the ObR mRNA and/or post-translational processing generates at least six isoforms of ObR: four short isoforms (ObRa, ObRc, ObRd and ObRf) with shortened intracellular tails, the secreted isoform (ObRe) that does not carry a transmembrane domain and the long isoform (ObRb). This isoform is considered the main functional receptor of leptin, since it is the isoform with the greater signaling capacity. Leptin binding to ObRb induces a series of intracellular signaling cascades, such as Janus tyrosine kinase family (JAK)/ signal transducer and activator of transcription (STAT), Ras/Raf/ MAPK, phosphatidylinositol 3-kinase (PI3K)/IRS and 5¢-AMP-activated protein kinase (AMPK)/ acetyl-CoA carboxylase (ACC). Furthermore, ObRb is abundant in the hypothalamus and is also present at lower levels elsewhere. The most known function of leptin, the inhibition of food intake, occurs through the activation of any of these signaling pathways in the hypothalamus. However, leptin is able to signal through other ObR isoforms. In particular, leptin activates the JAK2, IRS1 and extracellular signal-regulated kinase (ERK) through the ObRa isoform, ubiquitously expressed and known as the short isoform before the discovery of the ObRc-f isoforms. The JAK/STAT signaling cascade is triggered by the phosphorylation of a JAK2 and subsequent phosphorylation and recruitment of STAT3 binding, although STAT1, STAT5 and STAT6 may be activated by leptin as well. STAT3 forms dimers that translocate into the nucleus to induce the expression of genes involved in the regulation of food intake. Suppressor of cytokine signaling 3 (SOCS3) is a negative regulator of leptin-induced JAK/STAT pathway that inhibits tyrosine phosphorylation of ObR. Other negative molecules of this cascade have been described, such as protein inhibitor of activated STAT 3, which physically interacts with STAT proteins to block their binding to the response elements in the DNA, and the cytosolic protein tyrosine phosphatase non-receptor type 1 (PTP-1B), which negatively

regulates leptin pathway by dephosphorylating JAK2 and STAT3 proteins. Leptin also activates the Ras/Raf/MAPK signaling cascade by ObRb. The binding of leptin to its receptor leads to the phosphorylation of Src homology-2 tyrosine phosphatase (SHP2) that along with the growth factor receptor-bound protein 2 (Grb2) activates ERK. Independently of the phosphorylation of ObRb, JAK2 is also associated with Grb2 and SHP2 and this complex activates further signaling steps. The PI3Ks are heterodimeric complexes composed of regulatory and catalytic subunits. The leptin receptor activation promotes the interaction and formation of the complex SH2B/JAK2/IRS1, causing subsequent activation of downstream targets such as protein kinase B (Akt). Furthermore, AMPK is also activated by leptin. AMPK is the downstream component of a protein kinase cascade that plays a major role in maintaining energy homeostasis. AMPK is a heterotrimeric enzyme that functions as an energy sensor, which is activated by a rise in the AMP:ATP ratio that occurs following a fall in ATP levels. Activation of AMPK requires phosphorylation of the catalytic subunit by either serine/threonine kinase 1 or calcium/calmodulin-dependent protein kinase b. Then phospho-AMPK inhibits the activity of ACC in lipid utilization. Thus, leptin activates different intracellular signaling pathways through which multiple functions are exerted at central and peripheral levels. Leptin negatively regulates feeding in the hypothalamus and enhances the oxidation of fatty acids in peripheral tissues by signaling through the JAK/STAT, MAPK, PI3K and AMPK pathways. Leptin also stimulates glucose uptake and sympathetic activity through the phosphorylation of the MAPK, PI3K and AMPK proteins. Furthermore, leptin evidences a role in the control of the immune function by activating the JAK/STAT, MAPK and PI3K signaling pathways. Importantly, obesity is a risk factor for different types of cancers, and leptin and ObR are expressed in tumor cells such as breast cancer cells. It has been suggested that leptin induced proliferation of breast cancer cell lines, by activating JAK2--STAT3, PI3K--Akt--glycogen synthase kinase 3, ERK1/2 and AP-1 pathways [7].

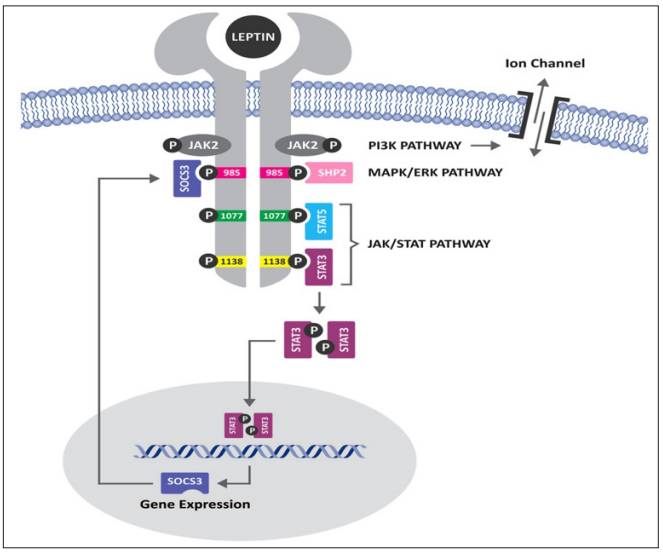

Figure 3

Biological effects of leptin

Leptin is a pleiotropic hormone that displays a variety of effects that seem to depend on its circulating level. Leptinaemia decreases under fasting, playing a critical role initiating the neuroendocrine response to starvation, including limiting procreation, decreasing thyroid thermogenesis and increasing secretion of stress steroids, which together are likely to have survival value during prolonged nutritional deprivation. Leptin replacement blunts some of these fasting-induced adaptations, mainly concerning the gonadal, adrenal and thyroid axes. Thus, studying the effects of systemic administration of leptin to fasted animals, in doses that increase leptinaemia to levels similar to those found in fed animals, has helped to clarify some of the biologically relevant effects of leptin and supported the notion that leptinaemia in the lower concentration range is a key coordinator of the adaptation to negative energy balance conditions. In contrast, the extent to which leptinaemia in the higher concentration range affects some physiological functions is still a matter of debate. Some groups suggest that hyperleptinaemia displays some actions in obesity that prevent further body weight gain, while others argue that the anti-obesity effect of hyperleptinaemia has not been clearly demonstrated. In addition, some effects of leptin have been unmasked by administering pharmacological doses of leptin or by using non-physiological strategies of administration (e.g. chronic infusion, central infusions, and infusions in specific brain areas); thus, the physiological implications of these observations are uncertain. Bearing these considerations in mind, some of the described biological effects of leptin are the following:

Leptin reduces food intake

Exogenous leptin, independently of the route of administration, reduces food intake in lean animals. Importantly, leptin infusion at doses that increase leptinaemia within physiological ranges leads to a transient reduction of food intake and weight loss.

The anorectic effect of leptin is mainly mediated by the hypothalamic arcuate nucleus (ARH). In the ARH, leptin activates anorexigenic neurons that express proopiomelanocortin (POMC), which is cleaved into different neuropeptides, including α-melanocyte-stimulating hormone (α-MSH). α-MSH inhibits food intake via the melanocortin receptor 3 and 4 (MC3R/MC4R). In the ARH, leptin also inhibits orexigenic neurons that produce neuropeptide Y (NPY), agouti-related protein (AgRP) and gamma-aminobutyric acid (GABA). Leptin-responsive neurons outside the ARH could also mediate the anorectic effects of the hormone. Particularly, the ventromedial nucleus (VMH), the dorsomedial nucleus (DMH) and the paraventricular nucleus (PVH) of the hypothalamus are responsive to leptin and work as an interconnected circuit. Other proposed targets of the anorexigenic effects of leptin include glutamatergic neurons of the median preoptic area (MPO), dopamine neurons of the ventral tegmental area (VTA) and neurons of the nucleus of the solitary tract, which is an important relay of gastrointestinal sensory inputs. In spite of these studies, the relative physiological relevance of these non-ARH areas mediating anorexigenic effects of leptin is still unclear. Regulation of food intake by leptin largely depends on pSTAT3, as point mutation of Y1138 or deletion of brain STAT3 lead to hyperphagic obesity. LepRb-induced PI3K signalling appears to be rather important for acute suppression of food intake [6].

Leptin increases energy expenditure and thermogenesis

A single intracerebroventricular (icv) injection or peripheral infusion of leptin slightly increase or have no effect on energy expenditure. Chronic administration of leptin to mimic the leptinaemia kinetics observed in obesity slightly decreases energy expenditure, and higher doses of leptin induce long-lasting effects that can completely deplete body fat stores in animals. In addition, leptin deficiency causes a reduction in metabolic rate in ob/ob mice. Thus, endogenous leptinaemia seems to be able to affect energy expenditure and thermogenesis under normal circumstances [6].

The effects of leptin on energy expenditure are mediated by both the autonomic nervous system and neuroendocrine hypothalamic–pituitary–thyroid (HPT) axis. Leptin up regulates the activity of the sympathetic nervous system presumably via its action on multiple neuronal targets that include not only ARH POMC and NPY/AgRP/GABA neurons but also MPO, VMH and DMH. Leptin activates the HPT axis via its direct action on thyrotropin-releasing hormone (TRH) neurons of the PVH and also via an indirect action through ARH POMC and NPY/AgRP/GABA neurons that provide potent stimulatory and inhibitory inputs, respectively, to PVH TRH neurons [6].

Leptin increases heart rate and blood pressure

LepRb is expressed in brain regions and peripheral organs (e.g. heart, kidneys and adrenals) that are important in cardiovascular control and blood pressure regulation. Central administration of leptin or direct injections in the DMH or the VMH increase both mean arterial pressure and/or heart rate in rodents. However, the physiological significance of these observations is uncertain. In humans, chronic administration of leptin does not elevate blood pressure [6].

Leptin decreases glycaemia

Leptin administration at a dose that does not affect body weight and food intake normalises blood glucose and insulin levels in otherwise hyperglycemic *ob*/*ob* mice. Leptin decreases glycaemia by sensitising metabolically relevant tissues to insulin but also in an insulin-independent manner. Leptin improves the glycaemic control via its effects at both the central and peripheral level, where leptin suppresses the production of glucagon and corticosterone, increases glucose uptake and inhibits hepatic glucose output. The central effects of leptin on glucose homeostasis strongly depend on the ARH [6].

Leptin is a permissive factor for puberty and fertility

The administration of physiological amounts of leptin prevents the fasting-induced delay in ovulation. Leptin signalling is required to enter puberty. LepRb is not expressed in gonadotropin-releasing hormone neurons. Therefore, leptin indirectly controls the reproductive function via interneurons located at the ventral premammillary nucleus or through ARH POMC and NPY/AgRP/GABA neurons [6].

Pharmacological Treatment:

The form of leptin that is currently available for human therapy is known as recombinant methionyl human leptin (metreleptin, Myalept®, Amylin Pharmaceuticals; recently acquired by Bristol-Myers Squibb, and subsequently by AstraZeneca plc), initially available as Leptin A-100 (when its patent was owned by Amgen). Metreleptin is the only pharmaceutical form of leptin, and is composed by the 146 amino acids of mature human leptin, with an additional methionyl residue at the N-terminal end of the recombinant protein. It is a nonglycosylated polypeptide with one disulfide bond between Cys-97 and Cys-147, and a molecular weight of approximately 16.15 kDa. Myalept® has been recently approved by the FDA for the treatment of congenital or acquired generalized lipodystrophy (non-HIV-related), but not for the partial forms of the disease, for which safety and effectiveness have not been established yet. The recommended starting dose varies according to gender and body weight, to a maximum daily dose of 0.13 mg/kg if body weight ≤ 40 kg, and 10 mg/day if body weight > 40 kg (Table 1). Metreleptin is administered once daily at the same time every day, subcutaneously. Due to its short half-life, some researchers prefer to divide the dose into two subcutaneous injections, when treating patients with CLD. Patients need to be evaluated regularly, and doses, recalculated to avoid excessively rapid weight loss [8].

Non-Pharmacological Treatment:

If you have a lot of body fat, especially in the belly area, then you are almost certainly leptin resistant.

It is not entirely clear how leptin resistance can be reversed, though theories abound.

Some researchers believe that reducing diet-induced inflammation may help reverse leptin resistance. Focusing on an overall healthy lifestyle is also likely to be an effective strategy.

There are several things you can do:

•Avoid processed food: Highly processed foods may compromise the integrity of your gut and drive inflammation.

•Eat soluble fiber: Eating soluble fiber can help improve your gut health and may protect against obesity.

•Exercise: Physical activity may help reverse leptin resistance.

•Sleep: Poor sleep is implicated in problems with leptin.

•Lower your triglycerides: Having high triglycerides can prevent the transport of leptin from your blood to your brain. The best way to lower triglycerides is to reduce your carb intake.

•Eat protein: Eating plenty of protein can cause automatic weight loss, which may result from an improvement in leptin sensitivity.

Though there is no simple way to eliminate leptin resistance, you can make long-term lifestyle changes that may improve your quality of life [3].

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