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REVIEW ARTICLE

A Review: "Leptin Structure and Mechanism Actions"

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ABSTRACT
Leptin is a cytokine hormone that is derived from the adipose tissue and expressed in the hypothalamus. Leptin or Obesity protein seems to play a role in regulating energy intake and expenditure. Leptin is a 16Kda protein coded by the obesity gene. It is 167 amino acid protein that has a amino terminal signal that is around 41 amino acids long. This terminal signal is cleaved during secretion and is found circulating in the body as a 146 amino acid peptide. The structure of Leptin is a proteins found in the helical cytokine family. It consists of four alpha helices that exhibit an up-up-down-down folding pattern arranged in a left-hand twisted bundle.
KEY WORDS: *Leptin, Obesity protein, Structure, mechanism actions*

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INTERODUCTION

Leptin was discovered in 1994 by Jeffrey M. Friedman at the Rockefeller University and Douglas L. Coleman through the study of such mice [1].Furthermore, administration of recombinant leptin has shown a decrease in food intake and body weight. The Wild-type human leptin aggregates so it cann't be crystallized, however, it has been discovered that a mutant form of the gene has an affinity to be crystallized. This mutant form of Leptin seems to be comparable to the wild-type human form and exhibits a single amino-acid substitution. Instead of a Trp in position 100 on the CD loop, they find a Glu, seen in pink in the figure (1). This Glutamic acid lies on the surface with its side chain pointing towards the solvent, thus increasing its solubility and reducing the hydrophobic interactions of the protein [2].

The effects of leptin were observed by studying mutantobese mice that arose at random within a mouse colony at the Jackson Laboratoryin 1950 [3].These mice were massively obese and excessively voracious. Ultimately, several strains of laboratory mice have been found to be homozygous for single-gene mutations that cause them to become grossly obese, and they fall into two classes: "ob/ob", those having mutations in the gene for the protein hormone leptin, and "db/db", those having mutations in the gene that encodes the receptor for leptin. When ob/ob mice are treated with injections of leptin, they lose their excess fat and return to normal body weights[1].

.Leptin reduces body weight in *ob/ob* mice by decreasing food intake and increasing energy expenditure; however, the mechanisms by which it does the latter are not known. 30% of the weight loss induced by leptin treatment of *ob/ob* mice is due to changes in energy expenditure. In assessing leptin's effects on specific tissues, the study found that hepatic basal metabolic rate was paradoxically decreased 1.7-fold with leptin treatment, which was the result of a 1.6-fold reduction in mitochondrial volume density and altered substrate oxidation kinetics. The altered kinetics were associated with a decrease in protein levels of 2 mitochondrial respiratory chain components cytochrome *c* oxidase subunit VIa and cytochrome *c* oxidase subunit IV. In addition to reduced hepatic metabolism, there was reduced long chain fatty acid production and a 2.5-fold increase in hepatic lipid export, both of which explain the reduced steatosis in leptin-treated animals. These data help clarify the role of the liver in leptin-mediated weight loss and define the mechanisms by which leptin alters hepatic metabolism and corrects steatosis[4].Leptin, the protein product of the *obese (ob*or *Lep)* gene, is a hormone synthesized by adipocytes that signals available energy reserves to the brain, and thereby influences development, growth, metabolism and reproduction. In mammals,leptin functions as an adiposity signal: circulating leptin fluctuates in proportion to fat mass, and it acts on the hypothalamus to suppress food intake. Orthologs of mammalian

*Lep*genes were recently isolated from several fish and two amphibian species. While vertebrate leptins show large divergence intheir primary amino acid sequence, they form similar tertiarystructures, and may have similar potencies when tested *in vitro* on heterologous leptin receptors (LepRs)[5].

Leptin, or OB protein, is a unique protein in that it has no strong sequence similarity with any other protein, so it is difficult to make a model structure as other known structures cannot be used as references. Luckily, through the use of a mutagenic form of leptin which has a substitution of Glu for Trp at position 100, an accurate model of the crystalline structure could be derived. It contains four anti-parallel α-helices that connected by two crossover links, along with one short loop [6]. These are arranged in a left-hand twisted helical bundle, in which, a large hydrophobic core is parallel to the helical bundle that is formed from the conserved residues of the four α-helices that face each other. Specifically, the four α-helices (A, B, C, D) are composed from the following residues in the 146 sequence: A, Pro 2-His 2; B, Leu51-Ser67; C, Arg71-Lys94; D, Ser 120-Ser 143. The last residues in the sequence make a kinked helix off of helix D. Figure (1) shows the helices in red and the loops in green. These helices are very super-imposable, which allow them to join to their receptor in a signal transduction pathway. OB protein, or leptin, also has a disulphide bond between the Cys 96 and Cys 146 residue and connects the last turn of the D α-helix to a loop that extends from the C to D helix. The only β-strand identified is in residues 47–50, though no connections are able to be identified to connect it to any other strand, so it is unlikely that any β-sheets exists in the OB protein [7].

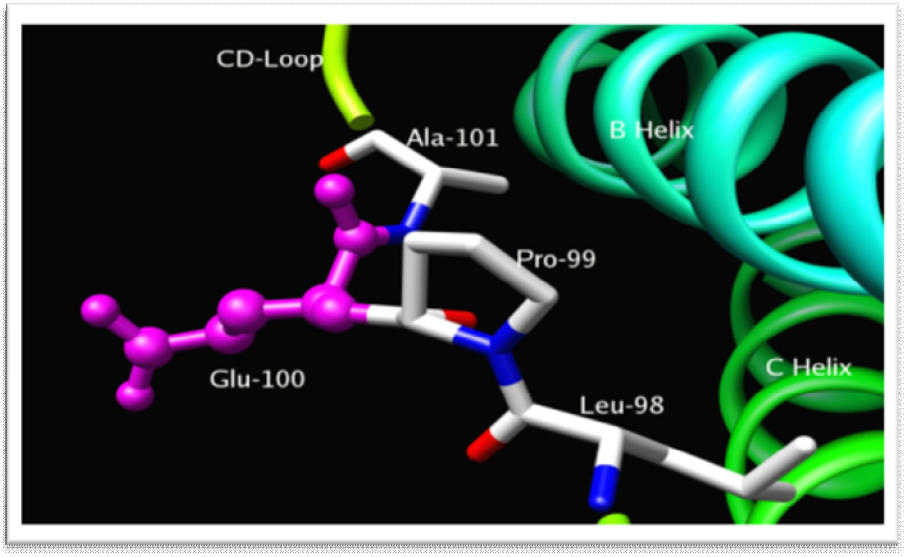


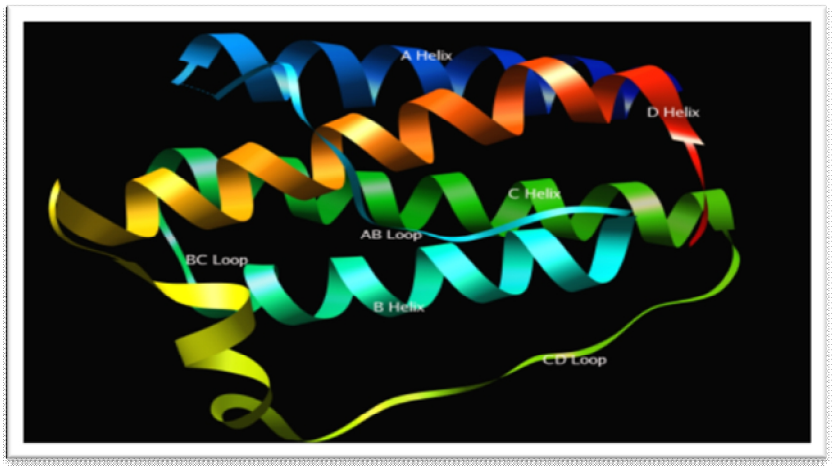
Figure (1): Glutamic Acid found on the CD Loop.[2]

This mutant form of Leptin seems to be comparable to the wild-type human form and exhibits a single amino-acid substitution. Instead of a Trp in position 100 on the CD loop, they found a Glu, seen in pink in the figure above. This Glutamic acid lies on the surface with its side chain pointing towards the solvent, thus increasing its solubility and reducing the hydrophobic interactions of the protein [2].

All the helices seem to be structurally and sequentially similar and run anti parallel to each other. The protein also exhibits a short strand segment and two long random-coil loops [8].

Table(1). Positioning of alpha helices in leptin. [2]

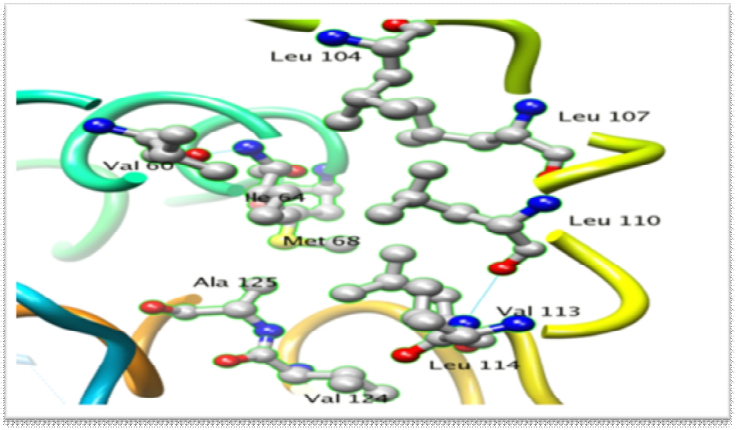
Helix	Position
A	3-26
B	51-67
C	71-94
D	120-143



Figure(2): Leptin (Obesity Protein) Molecule.[7]

Leptin is made up of helices that are connected by loops. The AB Loop connects the A and B helices, BC loop connects the B and C helices and the CD loop connects the C and D helices. The AB loop is an extended loop, which passes in front of the D helix, that allows the B helix to run in the same direction as the A helix. The BC loop is short and allows for the BC stack of helices to be anti parallel. The CD loop is another extended loop that allows the C and D helices to extend in the downward direction. The CD loop also contains helix E, a short and distorted helix. Furthermore, the AB and CD loops wrap around the BD face of the protein [2]. This secondary structure is a common trait seen in all four-helix long bundle cytokines. Yet, leptin displays certain characteristics that are unique. The B helix is about two turns shorter than the B helices of other cytokine proteins and Leptin lacks extra helices in the AB loop. It does, however, exhibit a E helix in the CD loop. The E helix, in this case, makes Leptin similar to the interferon-like cytokines in terms of primary sequence [2]. In general, the lengths of the helices and position of the disulfide bond seem to suggest that leptin is a member of the short-helix cytokine fold [8].

Not much is known of the structure of Leptin. Scientists can only predict the function of the structures that they seen in the crystallography. In figure (2), it is seen that part of the A helix is missing. The inability to crystallize the segment from Thr 27 to Gly 38, predicts that this region is disordered. A disordered region signifies that there is great flexibility within that region. Furthermore, as seen in other cytokines, this region will most likely assume an ordered conformation once the protein is bound to its receptor. Leptin's structure is also characterized by its hydrophobic interactions, which make up for its lack of the usual number of hydrogen bonds formed, and allows for the structural integrity of the protein. Like in other cytokines, Leptin exhibits a rigid hydrophobic core, yet it is unique in the fact that the core is capped by a hydrophobic cap (figure 3). This cap is made up of Leu 104, Leu 107, Leu 110, Leu 114 and Val 113, amino acids located on helix E. The cap serves to bury the lipophlic residues on the surface of the BD helical bundle (Val 60, Ile 64, Met 68, Val 124 and Ala 125), thus maintaining the twisted helix structure of Leptin [8].

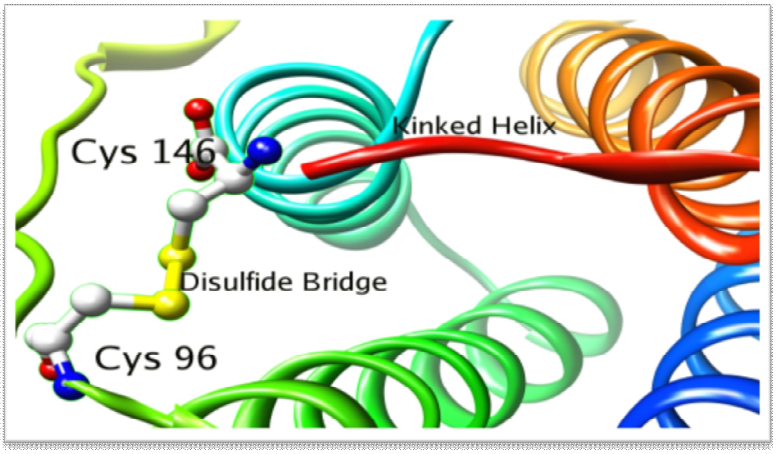


Figure(3): The hydrophobic core found on the BD surface and its cap found on helix E[2].

BINDING AND FUNCTION

The structure of the Leptin Receptor is unknown. Yet, scientists know that the binding of Leptin to its receptor plays a key role in its activity in the human body. If Leptin can not bind to its respective receptor,

the body is not able to regulate its energy expenditure. Furthermore, mutations of the gene have resulted in obesity, weakening of the immune system and hypogonadism [9]. Scientists are looking at the protein to see where the possible binding sites are located. Two suggestions are that the sites are located on the N-terminal or the C-terminal of the protein [10]. The C-terminal, a 50 amino acid long chain, exhibits unique structure which might allow leptin to specifically bond with its receptor. The last five residues in the D helix form a kinked helix. This kink is caused by the two cysteines that form a disulfide bond that is partially exposed to the solvent. In the figure (4), one can see the disulfide bonds between the two cysteines on the CD loop and the C terminal. The kink in helix D is also shown [2].



Figure(4): The Disulfide Bonds and kink in the D helix [2].

The mutation of Leptin to cause the deletion of the two cysteines causes the disappearance of the disulfide bond and twisted helix. This deletion sometimes renders the protein biologically inactive [2].

Studies have shown, however, that Leptin is able to bind with its receptor and maintain energy homeostasis without the disulfide bond and kinked D helix. Instead it seems as if the N terminal is essential for its biological and receptor binding activities. The N terminal, around 94 amino acids long, is folded within three turns and is interwoven with the C terminal loop structure. The deletion of the N terminal showed no effect on food intake and weight gain while the deletion of the C terminal did, suggesting that the N terminal is responsible for the binding of the Leptin to its receptor. The envelopment of the N terminal by the C terminal seems suggests that the C terminal supports the correct folding of the N terminal, allowing it to maintain the correct conformation needed for binding. This idea is further supported by studies that show that the deletion of the C terminal yields a less stable protein. Discovery of humans with a frame shift mutation yielding in the deletion of the C terminal seems to indicate that it is important for secretion, stability and solubility of the protein [10].

Interesting Facts

Leptin has been shown to do more than regulate energy intake and expenditure. It also plays a role in the immune system and reproduction. Furthermore, Leptin has been found to be produced by the placenta, stomach, skeletal muscles, ovaries, mammary epithelial cells, bone marrow, pituitary and liver. The adipose tissue–derived hormone leptin is produced in proportion to fat stores. Circulating leptin serves to communicate the state of body energy repletion to the central nervous system (CNS) in order to suppress food intake and permit energy expenditure [11,12]. Many of the physiological adaptations triggered by prolonged fasting can be attenuated by exogenously administered leptin, which falsely signals to the brain that energy stores are replete[12,13]. Adequate leptin levels permit energy expenditure on the processes of reproduction, tissue remodeling, and growth and similarly regulate the autonomic nervous system, other elements of the endocrine system, and the immune system [13]. Conversely, lack of leptin signaling due to mutation of leptin (e.g., *ob/ob*mice) or the leptin receptor (LR) (e.g., *db/db*mice) in rodents and humans results in increased food intake in combination with reduced energy expenditure and a phenotype reminiscent of the neuroendocrine starvation response (including hypothyroidism, decreased growth and decreased immune function) in spite of obesity [14].

MECHANISM OF ACTION

Leptin is an adipocyte-secreted hormone that acts on hypothalamic centers in the brain to control the energy balance of the body (figure 5) [15]. Leptin deficiency of humans or rodents results in hyperphagia and morbid obesity. In patients with genetic leptin deficiency, therapy with exogenous leptin effectively suppresses hyperphagia and corrects metabolic and other abnormalities [16]. However, in most cases of

obesity levels of circulating leptin are high, implying a state of resistance to the weight-reducing effect of leptin. Consequently, clinical trials using recombinant leptin for the pharmacological treatment of obesity yielded disappointing results [17, 18]. Leptin resistance in rodents can be induced by short-term voluntary overfeeding [19]. by feeding high-fat diet [20]. and by chronically elevated leptin levels [21,22]. Reduced leptin sensitivity is also a physiological mechanism to allow anticipatory energy intake and storage of nutrients, *e.g*. during pregnancy or in hibernators. Mechanisms of leptin resistance include failure of circulating leptin to reach its targets in the brain, inhibition of the intracellular leptin signaling cascade, endoplasmic reticulum stress, and antagonism of the physiological actions of leptin downstream from the primary target cell of leptin[23, 24]. Regardless of the relative contributions of these mechanisms, it is clear that the ability of leptin to activate intracellular signaling pathways is decreased by high chronic blood levels of leptin[25]. However, the mechanisms underlying the leptin-induced state of reduced leptin sensitivity are not yet understood at the molecular level.

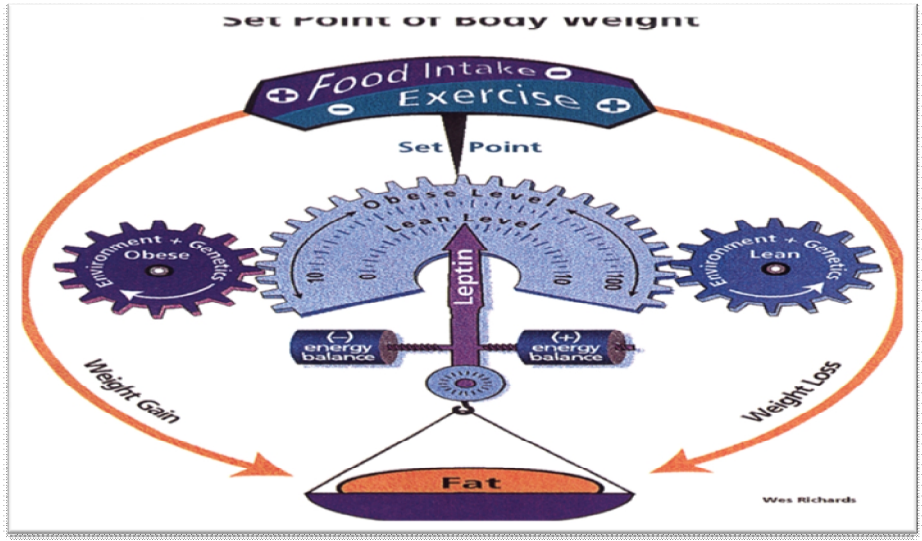


Figure (5): Role of leptin in the regulation of body weight [26].

Role of leptin in the regulation of body weight. A scale measures the amount of fat. The units of the scale are not in kilograms but in leptin units. The horizontalweighted bars on the leptin indicator sense energy balance and can tilt the leptin indicator independently of the amount of fat. The large cogged wheel reads leptinunits,i.e., the lipostat or leptinstat. If leptin value deviates from the set point, food intake,thermogenesis, and exercise are modified to restore leptin to these point values. The large wheel can be moved with the two little cogged gears by the influence of the environment and genetic [26].

The central actions of the hormone leptin in regulating energy homeostasis via the hypothalamus are well documented. However, evidence is growing that this hormone can also modify the structure and function of synapses throughout the CNS. The hippocampus is a region of the forebrain that plays a crucial role in associative learning and memory and is an area also highly vulnerable to neurodegenerative processes[28].

The leptin receptor belongs to the cytokine receptor superfamily and exists in several splicing variants. Leptin binding to the long leptin receptor isoform (LEPRb) activates cytokine-like signal transduction *via* the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway. Leptin stimulation leads to the activation of JAKs that are constitutively associated with LEPRb and in turn phosphorylate tyrosine residues in the intracellular domain of the receptor [28]. The phosphorylated tyrosines (pTyr) provide docking sites for proteins with Src homology 2 (SH2) domains. pTyr985 (numbering refers to the sequence of murine LEPRb) recruits the tyrosine phosphatase SHP2, which mediates the activation of the RAS/RAF/ERK pathway, whereas the STAT proteins bind to pTyr1077 (STAT5) and pTyr1138 (STAT1, STAT3 and STAT5 [29]. The bound STAT factors are phosphorylated by the receptor-associated JAK kinases, dimerize and translocate to the nucleus to control transcription of specific target genes. LEPRb-induced STAT3 activation is essential for leptin regulation of energy balance [30,31]. Although SHP2 has tyrosine phosphatase activity, its overexpression or knockdown only marginally alters the levels of leptin-induced STAT3 phosphorylation [32,33]. Multiple studies support roles for two inhibitory proteins, suppressor of cytokine signaling 3 (SOCS3) and protein tyrosine phosphatase 1B (PTP1B), as negative regulators of leptin signaling. The level of PTP1B expression modulates LEPRb signaling in cell lines and *in vivo* [34]. Numerous studies have demonstrated that the

upregulation of SOCS3 by leptin contributes to the attenuation of LEPRb signaling *in vivo* and in cultured cells [35, 36, 37]. SOCS3 suppresses cytokine signaling by inhibiting the receptor-associated JAK kinase [38] or by targeting bound signaling proteins for proteasomal degradation [36, 39]. Optimal inhibition of JAKs occurs when SOCS3 is recruited to cytokine receptor complexes *via* binding to specific phosphotyrosine motifs (pTyr759 in gp130, pTyr985 in LEPRb, pTyr401 in the erythropoietin receptor, pTyr800 in the IL-12Rβ2) [40]. SOCS1 is structurally similar to SOCS3 and is generally thought to inhibit JAKs by direct binding to the activation loop of the kinase, independent of receptor-tyrosine motifs [41,42].

Numerous studies have implicated the intracellular tyrosine residues of LEPRb in the negative regulation of leptin signaling. Tyr1138 is essential for the STAT3-dependent upregulation of the feedback inhibitor SOCS3 in response to leptin stimulation [43,44], and the mutation of Tyr1138 prevented the attenuation of ERK activation during prolonged leptin stimulation [33]. Moreover, the phenotype of knock-in mice expressing a LEPRb mutant for Tyr1138 provides evidence of increased effects of leptin that are independent of STAT3 [33]. No clear picture has yet emerged concerning the roles of Tyr985 and Tyr1077 in the attenuation of LEPRb signaling. [45] demonstrated that SOCS3 inhibits leptin signaling *via* binding to pTyr985, but the attenuation of LEPRb-induced ERK activation was later shown to occur independently of Tyr985 [33]. Tyr1077 was only recently established as an *in vivo*-phosphorylation site of LEPRb[46]. In addition to the unresolved contribution of Tyr985 and Tyr1077 in the negative regulation of leptin signaling, the molecular mechanisms by which SOCS3 inhibits LEPRb under chronic stimulation remain poorly characterized. The molecular mechanisms of attenuation of leptin signaling under conditions of continuous stimulation. In particular, they focused on the contribution of the intracellular tyrosine residues in LEPRb and their interaction with SOCS1 and SOCS3. The presence of one of the two proximal intracellular tyrosine residues (Tyr985 or Tyr1077) was sufficient for the attenuation of STAT3 activation, and that either tyrosine residue can support the suppression of LEPRb signaling by SOCS3. Finally, the receptor-associated JAK kinase has reduced STAT-phosphorylating activity after two hours of continuous receptor stimulation. However, the kinase is not dephosphorylated or degraded, and the inhibition of activity depends on the presence of Tyr985 and Tyr1077 in LEPRb[47]. In figure (6), Chronichyperleptinemia impairs the centrally mediated metabolic actions of the hormone, although its activation of sympathetic outflow is preserved. Selective central leptin resistance results in obesity and adverse effects on the cardiovascular system including hypertension, atherosclerosis, and LVH. Although leptin can protect against ectopic lipid deposition in nonadipose tissue, whether this effect is abolished because of (selective) peripheral leptin resistance requires further examination [48].

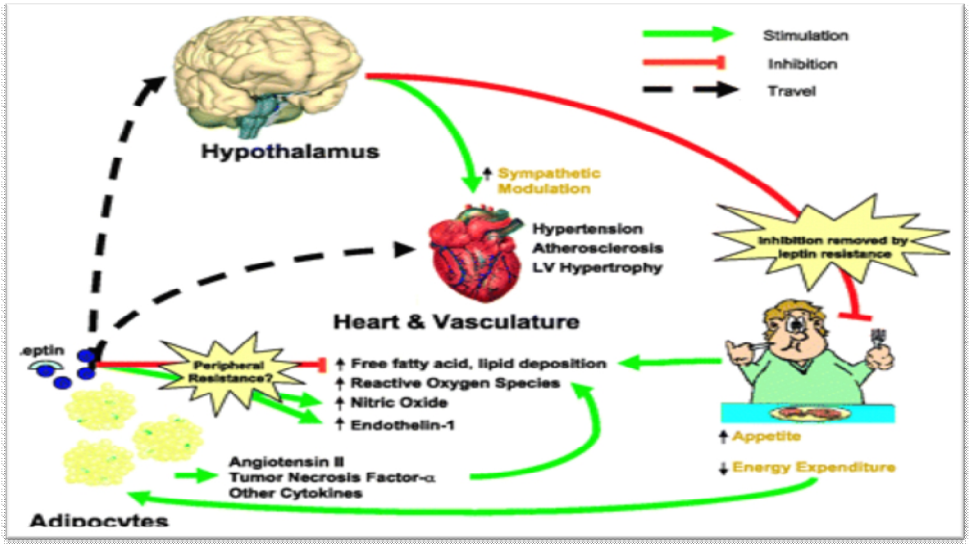


Figure (6):Systemic leptin function. [48]

Intracellular leptin transduction mechanisms

The leptin receptor is a single transmembrane protein from the cytokine-receptor superfamily. After binding to the leptin receptor, the signal is conducted via the janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway. This pathway is essential for transduction of the leptin signal, because interruption of the JAK/STAT pathway in mice results in increased food intake and accumulation of adipose tissue [12]. Another important signalling pathway for the control of food intake by leptin is phosphoinositol-3 kinase, because the effect of leptin on appetite is reversed by blockade of this enzyme

[44]. In addition, AMP-activated protein kinase (AMPK) is another important intracellular enzyme in leptin transduction mechanisms. Leptin decreases the activity of hypothalamic AMPK, and activation of this pathway attenuates the feeding and weight-reducing actions of leptin [49].Thus, the intracellular signaling mechanisms triggered by leptin appear more complicated than originally thought, with several downstream cascades involved in the actions of leptin [50].

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