

Leptin and its cardiovascular effects: Focus on angiogenesis

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Abstract

Leptin is an endocrine hormone synthesized by adipocytes. It plays a key role in the energy homeostasis in central and peripheral tissues and has additional roles attributed to it, such as the regulation of reproduction, immune function, bone homeostasis, and angiogenesis. The plasma concentration of leptin significantly increases in obese individuals. In the present review, we give an introduction concerning leptin, its receptors, signaling pathways, and its effect on cardiovascular system, especially on angiogenesis.

Key Words: Angiogenesis, cardiovascular disease, leptin, leptin resistance

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INTRODUCTION

Leptin is an adipocyte-derived hormone discovered in 1994 which created dramatic interest in the field of white adipose tissue (WAT) research and related diseases such as hypertension, coronary atherosclerosis, myocardial hypertrophy, diabetes, and dyslipidemia.^[1,2] Leptin mirrors the body's fat stores and acts for maintenance of energy homeostasis in central and peripheral tissues.^[3] Also, it is involved in the regulation of other physiological processes such as reproduction, bone homeostasis, and immune function.^[4]

Leptin acts on target cells by binding to plasma membrane receptors. Six isoforms of ob-R (a–f) have been identified based on different lengths of

the intracellular domains.^[5] These isoforms are classified into three groups: long form (ob-Rb), short form (ob-Ra, c, d, f) (these forms represent the dominant isoforms in the heart and most of the biological effects of leptin are mediated by ob-Rb isoform), and the third isoform is secretory form (ob-Re).^[6,7] The actions of leptin are mediated via ob-R modulation of the janus-activated kinase/signal transducers and activators of transcription (Jak/STAT) as the main signaling pathway in addition to phosphatidylinositol 3-kinase (PI-3K) and mitogen-activated protein kinase (MAPK) signaling pathways.^[8]

Endothelium plays a crucial role in modulating both vascular health and tone by producing both vasodilating and vasoconstricting substances.^[9] Leptin increases vasodilation and blood perfusion in the adipose tissue through induction of endothelial nitric oxide synthase (eNOS) activity in the endothelial cells and smooth muscle cells. This may be essential to supply of growing adipose tissue in obesity that is associated with high leptin levels.^[10,11]

Interactions of leptin with some hormones and neuropeptides in some studies have been demonstrated.

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Leptin interacts with neuropeptides present in central nervous system (CNS) in different ways. It suppresses neuropeptide Y (NPY) neurons in arcuate nucleus of hypothalamus and inhibits orexigenic peptide, the Agouti regulated peptide (AgRP); it also stimulates the neurons of alpha-melanocyte stimulating hormone (α -MSH) and cocaine-amphetamine regulated transcripts.^[12] In addition, leptin interacts with hormone regulators of energy metabolism, including insulin.^[13] Current studies show that basal plasma leptin and insulin concentrations parallel each other as leptin resistance (a state of decreased sensitivity to leptin action or, in other words, despite increased leptin level, there is inadequate response) can lead to insulin resistance and diabetes.^[14,15] In one study, leptin treatment could reduce plasma insulin concentration in children with congenital leptin deficiency.^[16] Also, several studies have demonstrated the inhibitory effect of leptin at supraphysiological concentration on glucose-stimulated insulin secretion *in vitro* both in rodent and human isolated pancreatic islets.^[17-19] Meanwhile, at a gene expression level, leptin reduces preproinsulin mRNA in pancreatic beta cells.^[20]

Leptin concentration is important for puberty spurt initiation and normal reproductive life through stimulation of gonadotropin releasing hormone (GnRH) and, consequently, follicle stimulating hormone (FSH) and luteinizing hormone (LH).^[21] Study on leptin (ob/ob) or leptin receptor (db/db) with knock-out mice reveals low gonadotropin concentration and incomplete development of reproductive organs.^[22] Both ovaries and testes express leptin receptors. Thus, in obesity with high leptin levels, sex hormone steroidogenesis is reduced.^[23]

ROLE OF LEPTIN IN CARDIOVASCULAR DISEASES

Extensive investigation in the general population and animal studies focusing on beneficial or detrimental effects of leptin on cardiovascular function including hypertension, diabetes, atherosclerosis, and coronary heart disease have shown paradoxical evidences. For example, leptin can lead to obesity associated with hypertension through central sympathetic activation,^[24] whereas several *in vitro* studies demonstrated an activation of endothelial nitric oxide in human aortic endothelial cells,^[25] besides the endothelium-independent vasodilator effects of leptin in saphenous vein and internal mammary artery vascular ring of coronary artery disease (CAD) patients.^[26]

Also, acute hyperleptinemia through an increased expression of peroxisome proliferator activated receptor alpha (PPAR- α) following fatty acid oxidation

and down-regulation of lipogenesis is protective in the heart and other tissues.^[27] On the contrary, long-term exposure to hyperleptinemia decreases the fatty acid oxidation and increases its cellular uptake, and therefore can lead to fatty acid loading in cardiomyocytes and programmed cell death or lipoapoptosis.^[28,29]

On the other hand, a community-based Framingham Heart Study showed cardioprotective influence of leptin on left ventricular (LV) remodeling; also, leptin concentrations were inversely associated with LV mass, LV wall thickness, and left atrial size.^[30] In a murine model, leptin at levels of 10 nM in obese humans reduced the infarct size via p38 MAPK pathway.^[31] In addition, leptin may protect the heart in an autocrine manner against ischemia/reperfusion (I/R) injury by delaying mitochondrial permeability transition pore (MPTP) opening.^[32]

This apparent discrepancy between the protective actions and impaired cardiovascular outcome of leptin in many studies results in a broad spectrum of cardiovascular effects of leptin and dose-dependent and time-course effects of leptin.

Several studies have shown that hyperleptinemia is associated with cardiovascular diseases such as hypertension, diabetes, atherosclerosis, and coronary heart disease.^[33]

Clinical and animal studies have shown a strong relationship between obesity and hypertension. Obesity is associated with chronic low-grade inflammatory condition, and serum leptin levels increase in obesity and correlate with the body mass index (BMI).^[3,34,35] Leptin can be involved in hypertension [Table 1] through an increase in the production of pro-inflammatory cytokines such as tumor necrosis factor (TNF)- α , interleukin (IL)-6, and reactive oxygen species (ROS) in the endothelial cells and induction of endothelial dysfunction by reducing the bioavailability of NO in the endothelial cells.^[37,38]

Leptin facilitates thrombosis formation and atherosclerosis in obesity through mechanisms including stimulation of hypertrophy, and proliferation, migration, and calcification of vascular smooth muscle cells (VSMCs). Also, its angiogenic effects on endothelial cell proliferation and remodeling and endothelial dysfunction^[39] can result in increased oxidative stress and decrease in NO bioavailability.^[40,41] In an *in vivo* study, leptin-deficient ob/ob mice were resistant to atherosclerosis. Also, in human studies, plasma leptin concentrations were associated with atherosclerosis in different

Table 1: Effect of leptin on cardiovascular diseases

	<i>In vitro</i> studies	<i>In vivo</i> studies	Human studies
Leptin and cardiovascular effect	Activation of eNOS in human aortic endothelial cells ^[25] Endothelium-independent vasodilator effect in saphenous vein and internal mammary artery ^[26] <i>In vitro</i> studies have shown that leptin induced hypertrophy in cultured neonatal rat ventricular myocytes in a concentration-dependent manner	In a murine model, leptin at a level of 10 nM reduced the infarct size ^[31] Hyperleptinemia is obligatory for the development of obesity-associated hypertension Leptin-deficient ob/ob mice in the study were resistant to atherosclerosis The ob/ob mice showed lower level of thrombus formation that was reversed by leptin supplementation	Cardioprotective Influence of leptin on left ventricular remodeling and is inversely associated with LV mass, LV wall thickness in a community-based framingham heart Study ^[30] Clinical studies showed that plasma leptin concentrations were associated with atherosclerosis in different patients ^[36]

eNOS: endothelial nitric oxide synthase

patients.^[36,42] Another *in vivo* study in ob/ob mice showed lower level of thrombus formation that was reversed by leptin supplementation.^[43]

Also, via endothelin-1 (ET-1) and ROS generation, leptin can participate in cardiomyocyte hypertrophy, as in a study, the hypertrophic effect of ET-1 was found to be inhibited by antibodies to either leptin or leptin receptors.^[44] In addition, *In vitro* studies have shown that leptin induced hypertrophy in cultured neonatal rat ventricular myocytes in a concentration-dependent manner.^[45,46]

LEPTIN AND ANGIOGENESIS

Angiogenesis is defined as a biological mechanism of new blood vessel formation from preexisting ones and plays important roles in many physiological and pathological conditions such as wound healing, menstrual cycles, placenta and mammary gland growth during pregnancy, tumor development, cardiovascular diseases, arthritis, retinopathies, and atherosclerosis.^[47,48] Angiogenesis includes coordinated events such as extracellular matrix degradation, migration and proliferation of the endothelial cells and mural cells to assemble the new vessel, and lumen formation and construction of the vessel wall via the mural cell layer which is associated with pericytes and/or smooth muscle cells.^[49]

Several studies have shown that leptin can be a potent angiogenic factor or angiogenesis inducer. Leptin was found to induce angiogenesis in two *in vivo* angiogenesis assays of cornea pocket and chick chorioallantoic membrane (CAM).^[50] Also, another study using two different *in vitro* models of angiogenesis (endothelial cell-coated microcarrier-induced and monolayer-induced formation of capillary-like tubes in fibrin gels) has demonstrated that leptin-induced proliferation and/or survival and 3D matrix formation of capillary-like tubes was similar with that elicited by vascular endothelial growth factor (VEGF) 165. Whereas VEGF165 is considered as a major proangiogenic

factor thus support from leptin as an endothelial growth factor.^[51]

Leptin and VEGF induce similar increase in vascular permeability in mice and vascular fenestrations in cornea pocket vessels, as leptin may potentiate VEGF-mediated angiogenesis dose-dependently because of increased endothelial cell VEGF secretion.^[52,53] In CAM assay, leptin neovascularization in developing embryo was impaired by inhibition of fibroblast growth factor 2) FGF2 (function, suggesting that FGF2 signaling pathways in endothelial cells are necessary for leptin angiogenesis.^[54] Meanwhile, leptin indirectly augments angiogenesis through induction of matrix metalloproteinase-2 (MMP-2) and MMP-9 activity.^[53]

In a study, tissue burn wound was created in male rats by electrocautery and then, the burn wounds were treated with leptin recombinant. In those animals that received leptin, there was greater number of total blood vessels in the subcutaneous tissue of the wound and leptin could mitigate cellular response of burn injury by augmenting the production of nutrient blood vessels; this supports the role of leptin in wound healing via angiogenesis process.^[55]

On the other hand, through induction of eNOS activity, leptin regulates vasodilatation and vascular permeability in the adipose tissue. Garonna *et al.* showed that leptin promotes proliferation, directional migration, and differentiation of endothelial cells through increase in cyclooxygenase-2 (COX-2) activity and causes rapid VEGFR2 phosphorylation upstream P38 MAPK/AKT/COX-2 which is needed for leptin-stimulated neoangiogenesis *in vivo*, and MAPK including P38 MAPK regulates COX-2 expression in endothelial cells treated with physiological and pathological stimuli.^[56]

It is demonstrated that both short and long isoform receptors of leptin which exist in endometrial cancer cells can potently enhance endometrial cancer growth and invasiveness through JAK/STAT and AKT pathways. Also, in the same study it was

demonstrated that leptin potently induced the invasion of endometrial cancer cells in a matrigel invasion assay.^[57] In addition, leptin is a mammary tumor growth promoting factor causing increase in cell number and the expression of VEGF/VEGFR2.^[58]

Although there is growing evidence for the angiogenic effects of leptin, on the contrary, some studies have indicated the antiangiogenic properties of leptin. It was found in a study that leptin, as an inflammatory cytokine and antiangiogenic protein, increased 2 months earlier than the appearance of symptoms of preeclampsia in amniotic fluid, and could possibly be considered as a predictive biomarker for preeclampsia.^[59] Also, there was inverse correlation between plasma levels of leptin and prostate cancer weight, and leptin appeared as a cellular proliferation and angiogenesis repressor in androgen-insensitive cells RM1 *in vivo*.^[60]

A recent study has reported that despite several strong evidences regarding the angiogenic effects of leptin *in vitro* and in animal studies, metreleptin administration in pharmacological (0.3 mg/kg) or physiological (0.1 mg/kg) dose *in vivo* to 15 healthy normoleptinemic volunteers and (50 and 100 ng/ml) *in vitro* in a three-dimensional human umbilical vein endothelial cell (HUVEC) angiogenesis model did not regulate circulating angiogenic factors in humans^[61] [Table 2]. It seems further studies are required to evaluate the mechanisms underlying the broad-spectrum effects of leptin as an angiogenic and/or antiangiogenic factor. The underlying mechanisms by which leptin induces angiogenesis in physiological and pathological conditions have been illustrated in Figure 1.

LEPTIN RESISTANCE

Leptin resistance means reduced ability of leptin to suppress appetite and control weight gain, which can be considered as an important risk factor for the development of obesity.^[63] Although the exact mechanisms of leptin resistance are still unclear,

however, there are many factors underlying the molecular mechanism leading to this phenomenon.

Leptin resistance can be inherited. In other words, ob gene mutation produces leptin whose ineffective signaling leads to hyperleptinemia and leptin resistance. Also, leptin receptor mutation can be created in diabetic db/db mice and Zucker fatty (fa/fa) rats. Of course, genetic mutation in humans is uncommon in typical obese population.^[64,65]

Leptin, like other biological signaling pathways, regulates its own receptor and signaling. Receptor down-regulation can be involved in leptin resistance^[66] that is observed in rodent models of diet-induced obesity (DIO).^[67] Saturation in transport mechanism of entry into CNS by limited tissue access can lead to leptin resistance.^[68]

Intracellular suppressor of cytokine signaling 3 (SOCS3) by inhibiting leptin JAK/STAT signaling, together with protein tyrosine phosphatase 1B (PTP1B) and cytokine-inducible SH2 protein can be candidate components of the intracellular leptin negative feedback loop.^[69-71] It is indicated that PTP1B, via dephosphorylation of jak2, results in diminished LRb (leptin receptor) signaling, which is involved in endoplasmic reticulum (ER) stress that induces leptin resistance.^[63] Stress signals lead to accumulation of unfolded proteins, consequently impairing ER function and causing ER stress. Homocysteine, a product of demethylation of methionine, is increased in obese patients and is positively associated with the serum leptin levels. High levels of plasma homocysteine may cause leptin resistance through ER stress.^[72,73]

Several studies have demonstrated that DIO animals are leptin resistant through neural mechanisms such as decreased anorectic response or diminished amplitude of maximal LRb signaling in the hypothalamus in response to leptin treatment by reduction in STAT3 phosphorylation.^[74,75] Cellular leptin resistance

Table 2: Effect of leptin on angiogenesis including *in vivo*, *in vivo*, and human studies

	<i>In vitro</i> studies	<i>In vivo</i> studies	Human studies
Leptin	In two <i>in vitro</i> models of angiogenesis, endothelial cell-coated microcarrier-and monolayer-induced formation of capillary-like tubes in fibrin gel, leptin induced proliferation and/or survival and 3D matrix formation of capillary-like tubes similar to that elicited by VEGF ^[51]	Leptin in <i>in vivo</i> angiogenesis assay of cornea pocket induced angiogenesis and in <i>in vivo</i> angiogenesis assay of chick chorioallantoic membrane induced increased vascular fenestration and permeability in mice ^[52,53] Tissue burn was created in male rats by electrocautery and one group was treated with leptin recombinant which showed greater number of total blood vessels in subcutaneous tissue of the wound ^[55] In a matrigel assay, leptin induced invasion of endometrial cancer cells ^[57]	Metreleptin administration in pharmacological (0.3 mg/kg) or physiological (0.1 mg/kg) dose <i>in vivo</i> in 15 healthy normoleptinemic volunteers and (50 and 100 ng/ml) and <i>in vitro</i> in three-dimensional human umbilical vein endothelial cell (HUVEC) angiogenesis model does not regulate circulating angiogenic factors (PDGF-AA, MMP, EGF, angiogenin in humans) ^[61]

VEGF: Vascular endothelial growth factor, MMP: Matrix metalloproteinase, PDGF-AA: Platelet-derived growth factor-AA, MMP: Matrix Metalloproteinase, EGF: Epidermal growth factor

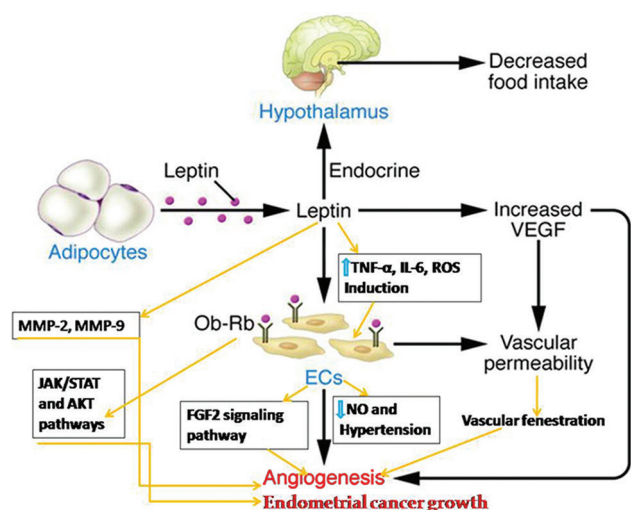


Figure 1: Underlying mechanisms by which leptin induces angiogenesis in physiological and pathological conditions^[62]

was prominently detected in the arcuate nucleus of hypothalamus of DIO animals because of increased access of leptin from the circulation to the arcuate nucleus.^[76,77] Obesogenic effects of tasty foods, due to their nutrient content besides the rewarding properties of these foods in DIO animals, can be involved in cellular leptin resistance, which is reversed by replacing them with the standard chow.^[74,78] Leptin may control food reward in consequence of its interaction with the mesolimbic dopamine system and the core of this system lies in a set of dopamine neurons in the ventral tegmental area (VTA).^[79]

Extracellular circulating factors including five serum leptin interacting proteins (SLIPs) in human blood were introduced by Chen *et al.*, which alter leptin bioavailability and bioactivity.^[75] SLIP-1 is identified as C-reactive protein (CRP) and SLIP-2 as APOJ or clusterin.^[80,81] SLIPs 3–5 have not been characterized. In a study in ob/ob mice, increased human CRP in continuous infusion mitigated the physiological actions of leptin administration on food intake, body weight, blood glucose and leptin metabolism.^[80]

CONCLUSIONS

Leptin as an adipocyte-derived hormone primarily acts in the hypothalamus and plays a crucial role in the regulation of food intake, body weight, and energy expenditure. Changes in leptin concentration are involved in several pathological conditions including cardiovascular diseases, obesity, immune and reproductive disorders, and recently, it has been identified as a potent angiogenic factor. With regard to the paradoxical and complex

effects of leptin on angiogenesis, understanding these results requires further investigations.

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