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Leptin Resistance: A Possible Interface of Inflammation and Metabolism in Obesity-Related Cardiovascular Disease

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Nonstructured Abstract

Leptin is an adipocyte-derived hormone and cytokine that regulates energy balance through a wide range of functions, including several important to cardiovascular health. Increased circulating leptin, a marker of leptin resistance, is common in obesity and independently associated with insulin resistance and cardiovascular disease (CVD) in humans. Mechanisms of leptin resistance include genetic mutation, leptin self regulation, limited tissue access and cellular or circulating molecular regulation. Evidence suggests that central leptin resistance causes obesity and that obesity-induced leptin resistance injures numerous peripheral tissues, including liver, pancreas, platelets, vasculature, and myocardium. This metabolic- and inflammatory-mediated injury may result from either resistance to leptin's action in selective tissues, or excess leptin action from adiposity associated hyperleptinemia. In this sense, the term "leptin resistance" encompasses a complex pathophysiological phenomenon. The leptin axis has functional interactions with elements of metabolism, such as insulin, and inflammation, including mediators of innate immunity such as interleukin-6. Leptin is even purported to physically interact with C-reactive protein (CRP), resulting in leptin resistance, which is particularly intriguing given CRP's well-studied relationship to CVD. Given that plasma levels of leptin and inflammatory markers are correlated and also predict cardiovascular risk, it is conceivable that part of this risk may be mediated through leptin-resistance related insulin resistance, chronic inflammation, type II diabetes, hypertension, atherothrombosis and myocardial injury. Leptin resistance and its interactions with metabolic and inflammatory factors, therefore, represent potential novel diagnostic and therapeutic targets in obesity-related cardiovascular disease.

Keywords

obesity; leptin resistance; inflammation; atherosclerosis; cardiovascular disease

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Introduction

Since its discovery over a decade ago, leptin has been established as a key regulator of energy balance (1,2). Increased circulating leptin, a marker of leptin resistance, is common in obesity and independently associated with insulin resistance (3) and cardiovascular disease (CVD) (4–7) in humans. These associations may reflect the marked metabolic dysregulation that occurs in leptin resistance due to leptin's key homeostatic physiological functions. Inflammation compounds these metabolic disturbances since leptin regulates components of innate and adaptive immunity, including T lymphocytes and monocytes (8). Leptin also has structural and functional resemblance to pro-inflammatory cytokines such as interleukin-6 (IL-6) (8) and may modulate C-reactive protein (CRP) (9). Therefore, it is conceivable that the convergence of increased levels of leptin and inflammatory markers (10) in CVD has a functional basis rather than mere association. The intent of this review is to integrate knowledge on leptin, leptin resistance, metabolism and inflammation to provide a cohesive clinical perspective regarding their interactions in obesity-related CVD. To this end, we discuss fundamentals of leptin, the concept and mechanisms of leptin resistance, as well as potential pathways from leptin resistance to CVD.

Fundamentals of Leptin

Ob/ob Mice and the Discovery of Leptin

In 1950, Ingalls *et al*. (11) described a new mutant strain of obese mice (ob/ob) which are characterized by severe obesity from increased energy intake (hyperphagia) and decreased energy expenditure (reduced metabolic rate, thermogenesis and physical activity). In 1973, Coleman (12) reported weight normalization in ob/ob mice when their circulation was connected to wild-type mice, suggesting ob/ob mice were deficient in a circulating factor involved in energy balance. Employing positional cloning two decades later, Friedman and colleagues (13) at Rockefeller University isolated the ob gene coding for this circulating factor. Shortly thereafter, recombinant ob gene product was administered to ob/ob mice, correcting their obesity (14). The ob gene product was subsequently named leptin, after the Greek, *leptos*, meaning 'thin.' Leptin's discovery stimulated considerable research into the hormone's biology, physiometabolic function and impact in human disease.

Leptin: A Pleiotropic Hormone and Cytokine

Leptin is primarily expressed in adipocytes and numerous human and animal studies (15–18) have shown that leptin levels increase with adiposity, presumably to inform the brain regarding the quantity of stored fat. Leptin also has a structural and functional relation to pro-inflammatory cytokines, such as IL-6 (19), reinforcing its classification as an "adipocytokine" (20). These observations, coupled with the wide expression of leptin and/or its receptor in peripheral tissues, including monocytes and lymphocytes, vascular tissue, pancreas, skeletal muscle and myocardium (21), suggest that leptin is pleiotropic in action and a pivotal link in obesity-related disease. Indeed, leptin is involved in several processes relevant to CVD, including insulin signaling, immunity, vascular function and arterial pressure regulation.

Leptin Receptor and Signaling

Leptin signals by engaging an IL-6 type glycoprotein 130 cytokine receptor, encoded by the diabetes (db) gene (22,23). Six leptin receptor isoforms are known (Ob-Ra–f) (24), varying in length, location and functionality. They share identical extracellular ligand-binding domains (second CK-F_3) , but differ in their intracellular domains (24). Most is known about Ob-Rb (also known in humans as Ob-RL; L=long), which is highly expressed in the hypothalamus and is the only isoform that activates the janus kinase signal transduction and translation (JAK/STAT) system. Ob-Rb and other isoforms may signal via mitogen activated protein kinases (MAPK), phosphatidylinositol 3-kinase, and nitric oxide pathways. Ob-Ra is widely distributed in peripheral tissues, shows signaling capability, and is thought to transport leptin across the blood-brain barrier (25). Some isoforms may function in leptin clearance (Ob-Rc, Rd) (24) or buffering (Ob-Re; also known as soluble leptin receptor) (26).

Leptin Resistance

Concept

In the context of obesity and disease, leptin resistance began as the idea that the body's biomolecular milieu decreases overall sensitivity to leptin action such that normal or, classically, elevated levels produce an inadequate response (relative leptin deficiency). This concept (27) is reinforced by the observation that the majority of obese individuals are not leptin deficient, but actually have elevated serum leptin concentrations (28). The leptin resistance theory gained further credence when a randomized, placebo controlled, dose-escalation trial of recombinant leptin was disappointing in producing weight loss in obese adults (with 20–30 times normal physiologic concentrations of leptin necessary to produce significant weight reduction) (29). It is not clear whether high endogenous leptin levels are appropriately high in the setting of increased adiposity and central resistance to leptin action. However, it is clear that these levels, even with the addition of large amounts of exogenous leptin, are not signaling sufficiently to maintain a healthy weight. Thus, in total, these observations imply that the majority of obese patients operate on a resistant, or flat, leptin dose-response curve, at least for weight regulation. This phenomenon of leptin resistance may have several possible underlying mechanisms (Fig. 1).

Mechanisms

Genetic Mutation—Leptin resistance can be inherited, albeit not commonly. According to the laws of feedback signaling, an ob gene mutation producing leptin that is secreted, but ineffective at signaling, could lead to hyperleptinemia and leptin resistance. Similar results could be obtained through leptin receptor mutation. In fact, diabetic (db/db) mice and Zucker fatty (fa/fa) rats have dysfunctional leptin receptors, causing marked hyperleptinemia and leptin resistance (30). While cases are seen in humans, such mutations are uncommon in the typical obese population (31). Thus, Mendelian inheritance patterns in leptin or its receptor are not major players in leptin resistance in the general population. However, polygenetic inheritance patterns in other gene products exerting influence on the leptin axis may still contribute significantly to generational transmission of genetic predisposition to leptin resistance.

Self Regulation—Like other biological signaling pathways, leptin appears to regulate its own receptor and signaling and receptor downregulation may promote pathological leptin resistance (32). Reduced hypothalamic leptin receptor expression and leptin signaling are seen in rodent models of age-related (33) and diet-induced (34) obesity. The reduction appears to be a direct byproduct of increased central leptin. This is supported by rodent models in which chronically elevated leptin, due to transgene overexpression, decreased hypothalamic leptin receptor expression and protein levels, impairing leptin signaling (35). Consistent with this, increasing central leptin desensitizes its physiological responses over time (36) rendering lean rodents more prone to diet-induced obesity (37). Hence, obesity promotes hyperleptinemia, which in turn self promotes leptin resistance and further obesity, making leptin resistance both a consequence and cause of obesity.

Limited Tissue Access—Resistance to leptin's action may occur via limited tissue access, such as at the blood-brain barrier. While debate over leptin's exact port and route of entry into the central nervous system continues, the current thought is that leptin entry is via Ob-Ra as a saturable, unidirectional system, located in the vascular endothelium and choroid plexus epithelium of the blood-brain barrier (38,39). Saturation in this transport mechanism could lead to leptin resistance. Perhaps this is why obese hyperleptinemic mice (40) and humans (41) have a decreased cerebrospinal fluid to serum leptin ratio. Indeed, leptin administration into the cerebrospinal fluid of hyperleptinemic obese mice resulted in short-term weight loss (40). However, in the long-term, limiting leptin's brain access could be protective in the sense that it could prevent high central leptin levels and thus receptor downregulation and impaired signaling. The blood-brain-barrier appears to be a site for leptin regulation and resistance, though such theories demand further testing.

Molecular—Cellular and circulating molecules can inhibit leptin to cause resistance (Fig. 2).

Cellular: Intracellular suppressor-of cytokine-signaling-3 (SOCS3) is induced by and inhibits leptin JAK/STAT signaling (27,42), a negative feedback mechanism shared with other tyrosine kinase receptors including cytokine and insulin receptors. More recently, protein tyrosine phosphatase 1B was found to similarly regulate leptin signaling in cells (43). Related molecules, such as additional SOCS family members (44), cytokine-inducible SH2 protein (45), JAK binding protein (46), and STAT-induced STAT inhibitor-1 (47) appear to regulate intracellular cytokine signaling and are candidate components of the intracellular leptin negative feedback loop.

Circulating: Extracellular circulating factors may bind leptin, altering its bio-availability and -activity. In 2006, Allan Zhao and coworkers (9) isolated five serum leptin-interacting proteins (SLIPs) in human blood utilizing leptin-affinity chromatography, mass spectrometry and immunochemical analysis. The group identified SLIP-1 as CRP (9) and SLIP-2 as APO-J (also known as clusterin) (48), while SLIPs 3–5 are yet to be further characterized. The concept of circulating leptin binding proteins is not new. In fact, Ob-Re, the soluble leptin receptor, is known to bind leptin in the circulation (49), reducing its free

concentration and activity (50). Recently described SLIPs were distinct from and present in significantly higher concentrations than soluble leptin receptor.

The Zhao report frames a role for human CRP in the induction of leptin resistance via direct physical interaction (9). *In vitro* investigation demonstrated the ability of human CRP to directly inhibit leptin binding to its receptor and related cell signaling in HEK293 cells or hypothalamic neurons. This is in contrast to IL-6, which also appears to bind to CRP, but without a change in cell signaling (51). In ob/ob mice, increased human CRP, from continuous infusion or transgene expression, attenuated the physiological actions of exogenous leptin on food intake, body weight, blood glucose and lipid metabolism (9). Moreover, physiologic leptin concentrations boosted CRP expression *in vitro* in human primary hepatocytes. Correspondingly, studies in healthy humans show a strongly positive independent association between leptin and CRP blood concentrations (52,53). Clinical investigations of whether leptin administration *in vivo* enhances CRP concentration were positive in non-obese individuals (54,55), but negative in obese subjects (56), perhaps attributable to leptin resistance. Therefore, preliminary evidence points to an adipo-hepato axis whereby leptin enhances CRP expression and CRP, in turn, may antagonize leptin action. These findings are provocative for a functional CRP effect, as well as for an interface of metabolism and inflammation in the pathogenesis of cardiometabolic disease.

However, the role of CRP in the induction of leptin resistance and as a mediator in CVD is not yet established. Limiting acceptance is the absence of an explicit mechanism by which CRP causes leptin resistance. For instance, regarding leptin's central action, it is not known whether CRP inhibits leptin inside or outside the central nervous system. Furthermore, Zhao and colleague's proposed leptin-CRP interaction prompted a robust correspondence and data against such an interaction (57–59). A reply from the Zhao group offered explanations for the apparent discrepancies (48). This debate emphasizes the need for validation of leptin-CRP interaction in humans, and careful experimental technique in this pursuit, particularly as species specificity limits the utility of rodent models (60).

Pathways from Leptin Resistance to Cardiovascular Disease

Innate Immunity, Inflammation and Atherosclerosis

Leptin may be directly atherogenic (61). Ob/ob mice are resistant to atherosclerosis (62) and leptin receptors have been detected in human atherosclerotic lesions (63). Considering atherosclerosis is increasingly viewed as an inflammatory disease, driven by lipoproteins, metabolic signals, hemodynamic stress and the integrated activity of immune cells and inflammatory cytokines, it is intriguing that leptin and inflammatory pathways demonstrate reciprocal modulation and shared association with cardiovascular risk. Leptin regulates human immune functions (64) while activation of innate immunity induces leptin in rodents (65) and humans (66–68). T cell hyporesponsiveness is a core manifestation of leptin deficiency in mice (69) and humans (64). In fact, several immune cells implicated in atherosclerosis, including T lymphocytes, monocytes and macrophages bear the leptin receptor and are generally activated by leptin (8). Leptin stimulates central T cell production and a peripheral shift in favor of T helper (Th) 1 adaptive immune responses (pro-inflammatory) as opposed to Th2 responses (anti-inflammatory). Further augmenting the

inflammatory milieu that fosters atherosclerosis, leptin promotes intimal monocyte recruitment (70), elicits macrophage foam cell formation (71) and induces secretion of pro-inflammatory (8), atherogenic cytokines. In this setting, leptin itself can be considered to be a pro-inflammatory cytokine.

Notably, multiple downstream inflammatory biomarkers, including CRP, are independent predictors of CVD (66). Despite correlations with CRP, several macrophage and T-cell cytokines, including IL-18, IL-6 and tumor necrosis factor-α levels have also been associated with coronary artery calcification, incident myocardial infarction (MI) and recurrent CVD in most (72–74) but not all (75) prospective epidemiological studies. Recent evidence suggests that leptin induces CRP expression in human coronary artery endothelial cells (76) where CRP itself may promote atherosclerosis (77). Overall, multiple immune and inflammatory pathways, which may be modulated by leptin, hyperleptinemia and leptin resistance, have been implicated in atherosclerosis in humans as well as in experimental models (10).

A limited pool of data is available on the association of leptin with measures of subclinical atherosclerosis in humans. In a study population of 200 type II diabetics without clinical manifestations of CVD, we found an association between plasma leptin levels and coronary artery calcification even after controlling for established risk factors, adiposity and CRP (7). Recently, we also reported a positive relationship between plasma leptin and coronary calcification in 860 non-diabetic healthy adults independent of established CVD risk factors (78). In 126 normal-weight or obese, but otherwise healthy patients, an association of leptin with intima-media thickness of the common carotid artery was attenuated after adjustment for body mass index (BMI) (79). In addition, several small studies failed to establish an association between leptin and intima-media thickness, including in obese or type I diabetic children (80), healthy elderly men (81), and healthy obese women (82). Thus, the relation of leptin to subclinical atherosclerosis in humans requires further study.

Several clinical studies have correlated leptin levels with cardiovascular events. The first of these reports, from Soderberg *et al*., saw a positive association of plasma leptin with first MI, independent of traditional risk factors, in a small population based case-control study (4). In the largest of these studies to date, a case-control analysis of over 1000 hypercholesterolemic patients, Wallace *et al*. (5) found that plasma leptin positively predicted acute cardiovascular events (MI, need for revascularization, death), after adjusting for BMI, plasma glucose, lipids and CRP. Other investigations have connected hyperleptinemia with stroke (83,84) and major adverse cardiac events (6) including restenosis after percutaneous coronary intervention (85). In contrast, conflicting data comes from two small analyses in which plasma leptin levels were unrelated to (86) or negatively predicted (87) CVD. All told, the majority of data favors positive cardiovascular risk prediction for both inflammatory markers and leptin. Thus, it is important to further dissect the diverse mechanisms that may underlie this convergence in CVD (Fig. 3).

Insulin Resistance and Diabetes

Diabetes and insulin resistance are major cardiovascular risk factors. It is not surprising that leptin interacts with other hormonal regulators of energy metabolism, such as insulin.

Interestingly, leptin deficient mice (11,14) and humans (60,64,88) have diabetic features, which correct with leptin replacement even before weight loss. One can infer that leptin resistance (a state of relative leptin deficiency) would lead to insulin resistance and diabetes. This idea of leptin as an insulin-sensitizing hormone and leptin deficiency, or resistance, as a potential link between obesity and diabetes has been reviewed recently (89). Indeed, leptin-induced SOCS3 results in resistance to insulin receptor signaling. As a cautionary note, the bulk of literature comes from *in vitro* and animal studies and there have been some inconsistencies between reports. However, one cannot overlook the accumulating body of work supporting the direct involvement of leptin in glucose homeostasis.

Human data shows that basal plasma leptin and insulin concentrations parallel each other (90,91). Elevated leptin is associated with hyperinsulinemia and insulin resistance, independent of BMI (3). Consistent with a bidirectional adipoinsular axis, insulin and glucose appear to stimulate leptin secretion in adipocytes (92–94). Indeed, insulinoma elevates leptin levels (95). In response, leptin decreases insulin secretion via direct action on leptin receptors in pancreatic B-cells (96), while enhancing skeletal muscle glucose uptake and oxidation (97,98), and suppressing hepatic glucose production (99). Furthermore, leptin might reduce lipotoxicity (triglyceride accumulation in nonadipose tissue which contributes to insulin resistance) and consequently improve hepatic, muscular and whole body insulin sensitivity (100). Although leptin therapy was disappointing in trials of common obesity (perhaps due to leptin resistance), it has shown success in other patient populations. For instance, leptin therapy improved diabetic measures in children (60,64) and adults (101) with familial leptin deficiency, and in lipoatrophic diabetes (102). Taken together, these data imply that leptin resistance may induce insulin resistance and diabetes. In view of recent evidence that inflammatory cell infiltration promotes adiposity, insulin resistance and type II diabetes (103) and that elevated IL-6 and CRP predict incident type II diabetes (104–106), it is intriguing to consider a leptin-CRP interaction as a possible mechanism linking these disorders.

Hypertension

Hypertension is a major cardiovascular risk factor linked to hyperleptinemia and leptin resistance. Cross-sectional investigations in human subjects show increasing leptin concentrations with increasing blood pressure in subjects in both the normotensive (107) and hypertensive range (108–110). Moreover, hypertensive, overweight women have higher leptin levels than their normotensive counterparts (111). Possible causal pathways for hyperleptinemia in hypertension, based mainly on animal studies, were described in detail in recent reviews (112–115). Briefly, chronic leptin-mediated central sympathetic activation, originating in the hypothalamus, results in a systemic pressor effect that is believed to play a chief role in obesity-related hypertension. In the kidney, sympathoactivation, along with decreased natriuresis leading to volume retention, may contribute to increased blood pressure. Conversely, there is suggestion, but lack of consensus, that leptin decreases arterial tone in the vascular wall through direct actions on the endothelium and smooth muscle although uncertainty surrounds the mechanism of action, acute versus chronic effects and the relevance to human physiology. Regardless, chronic infusion or transgenic

overexpression of leptin induces hypertension pointing to a sympathetic pressor effect as the dominant hemodynamic action of leptin, at least over the longer-term.

The paradoxical notion of a leptin-mediated pressor effect persisting in the setting of an otherwise leptin-resistant state might be reconciled by the concept of selective leptin resistance (116) (Table 1). It posits that certain actions of leptin (e.g., sympathoexcitatory actions) persist despite resistance to others. This concept is supported by data from murine models of genetic (117) and diet-induced obesity (118). Yet, how leptin resistance blocks some actions of leptin, but not others, is not clearly understood, especially outside of rodent models. A leading hypothesis is that post-receptor leptin signaling encounters greater feedback (e.g., higher SOCS-3 concentration) in resistant tissues, compared to non-resistant tissues (119). Other possibilities include differential leptin tissue access and circulating leptin inhibitors. Such hypotheses call for further testing.

Thrombosis

Leptin may be prothrombotic. Ob/ob mice show impaired thrombus formation in response to vascular injury and this is reversed by leptin replacement (120,121), suggesting leptin signaling promotes arterial thrombosis. One target of such signaling may be platelets. Ob-Rb is found on platelets (122) and leptin enhances platelet aggregation in the presence, but not in the absence, of this receptor (121). While high concentrations of leptin corresponding to levels in obese individuals increase platelet aggregation, lower concentrations do not (122). This suggests leptin's prothrombotic effect might be limited to obese hyperleptinemic individuals, thus acting as a unique link between obesity and cardiovascular events. Coagulation-fibrinolysis balance represents a second possible system for leptin mediated thrombosis. Leptin levels have been positively correlated with plasminogen activator inhibitor-1 (123–125), fibrinogen (126), von Willebrand factor (126), and factor VIIa (127), and negatively correlated with tissue plasminogen activator (125,128), tissue factor pathway inhibitor (129), and protein C (129). These findings from various human cohorts imply that increased leptin concentration, either as a marker or through direct effect, favors coagulation over fibrinolysis. The concept of leptin as prothrombotic is of clinical importance because it could directly implicate leptin resistance in acute CVD beyond a relationship with atherosclerosis. It is noteworthy, in fact, that leptin was an independent predictor of acute cardiovascular events in patients with angiographically confirmed coronary disease (6). Overall, whether via platelets or clotting factors, high leptin may confer risk for thrombosis.

Myocardial Injury

Leptin signaling may alter cardiomyocyte structure and function, as thoroughly reviewed recently by Yang and Barouch (130). Evidence implicates the leptin axis in decreased cardiomyocyte contractility and through nitric oxide, B-adrenergic intermediates, reactive oxygen species, ceramide, and pro-inflammatory factors. Contractility may also be impaired by cardiac lipotoxicity secondary to decreased fatty acid oxidation in late stage leptin resistance in contrast to the increased fatty acid oxidation that characterizes early leptin resistance and protects from steatosis. This example draws an important distinction between early and late stage leptin resistance, which may turn out to be conceptually similar to the progression seen in insulin resistance towards type II diabetes. Besides anti-steatosis,

additional benefits of short-term hyperleptinemia may include compensatory cardiac hypertrophy and protection from ischemia/reperfusion injury. Yet chronically, leptin-related cardiomyocyte hypertrophy, proliferation, apoptosis, and extracellular matrix reorganization may all contribute to maladaptive cardiac remodeling in obesity. Hypertrophic and proliferative effects may account for the observation that, independent of blood pressure, fasting plasma leptin levels are positively associated with left ventricular hypertrophy in hypertensive patients (131).

Leptin signaling pathways in the myocyte are complicated by different isoform signaling capabilities, but as detailed (130), significant progress has been made in elucidating pathological disturbances in cardiac disease, including in the JAK/STAT, MAPK, nitric oxide, and B-adrenergic pathways. In myocardium, leptin deficiency and hyperleptinemia generally appear to produce the same result, perhaps because hyperleptinemia reflects a state of leptin resistance, and thus functional leptin deficiency. However, whether leptin resistance occurs in the myocardium itself is not yet firmly established. Faced with these issues, we can expect continued challenge in attempting to isolate the physiological actions of leptin from pathological ones in leptin deficiency, resistance, or excess.

Leptin Resistance and the Obesity Epidemic in Evolutionary Terms

Leptin resistance and the surfacing of the obesity epidemic are logical when viewed in the context of evolution. Rapid environmental changes introduced by industrialization, namely increased food availability and decreased physical exertion, were in sync with the rise in obesity. This environmental change presumably had such an impact because it exerted its influence on a human biological system with a propensity for obesity. Such propensity likely stems from an evolutionary survival advantage, in the face of periodic famine, injury or infection, for those best equipped to store energy at times of nutritional abundance. Inflammation-related induction of CRP or other leptin inhibitors with attenuation of central leptin signaling would promote adiposity, the most efficient energy depot in humans. Evolutionarily preprogrammed to store energy, it is not surprising that entry of humans into the energy dense modern society has resulted in the emergence of obesity as a major public health issue. It appears our biological system regulating energy balance has taken on a maladaptive role, which may lead to a host of negative cardiometabolic consequences.

Conclusions and Outstanding Questions

Following a doubling in obesity over the last quarter century, approximately one-third of American adults were classified as obese and two-thirds overweight (132). These figures highlight the need to better understand the etiology of obesity and find effective treatments. Leptin resistance may be an interface of metabolic dysregulation with inflammation in the pathogenesis of obesity, its co-morbidities, and ultimately CVD. Such an interface provides one possible pathophysiological explanation for the convergence of leptin and inflammatory biomarkers in prediction of CVD in humans.

Several questions need to be addressed. For example, harmful leptin effects arising in an otherwise leptin resistance state raise the question of selective leptin resistance. If this exists, how does it occur? Are cellular and circulating inhibitors of leptin signaling major players in

leptin resistance and capable of tissue selective effects in humans? Such questions underscore that much is yet to be defined, but should help focus basic and translational research. The potential clinical implications of leptin resistance are provocative. First, leptin resistance may represent an integrated marker for the inextricably linked disease states of obesity, metabolic syndrome, insulin resistance, type II diabetes, hypertension, atherothrombosis and myocardial disease (133). More study is needed to determine whether leptin resistance markers would be valuable in future approaches to cardiovascular risk stratification in clinical practice. Second, knowledge of the mechanisms of leptin resistance, particularly tissue selectivity, cellular mechanisms and circulating modulators (e.g., SLIPs) may direct us toward therapeutic interventions aimed at overcoming leptin resistance. For example, molecules that alter the bioavailability of circulating leptin (e.g., interfere with leptin interactions with SLIPs) or modify post-receptor signaling (e.g., block SOCS3 actions) might represent new targets for therapeutic development. These therapeutic possibilities add promise in combating the obesity epidemic and its devastating consequences. This background provides impetus for further investigation of leptin resistance.

Abbreviations

BMI	body mass index
CVD	cardiovascular disease
CRP	C-reactive protein
IL	interleukin
JAK/STAT	janus kinase signal transduction and translation
MAPK	mitogen activated protein kinases
MI	myocardial infarction
SLIPs	serum leptin-interacting proteins
SOCS3	suppressor-of cytokine-signaling-3

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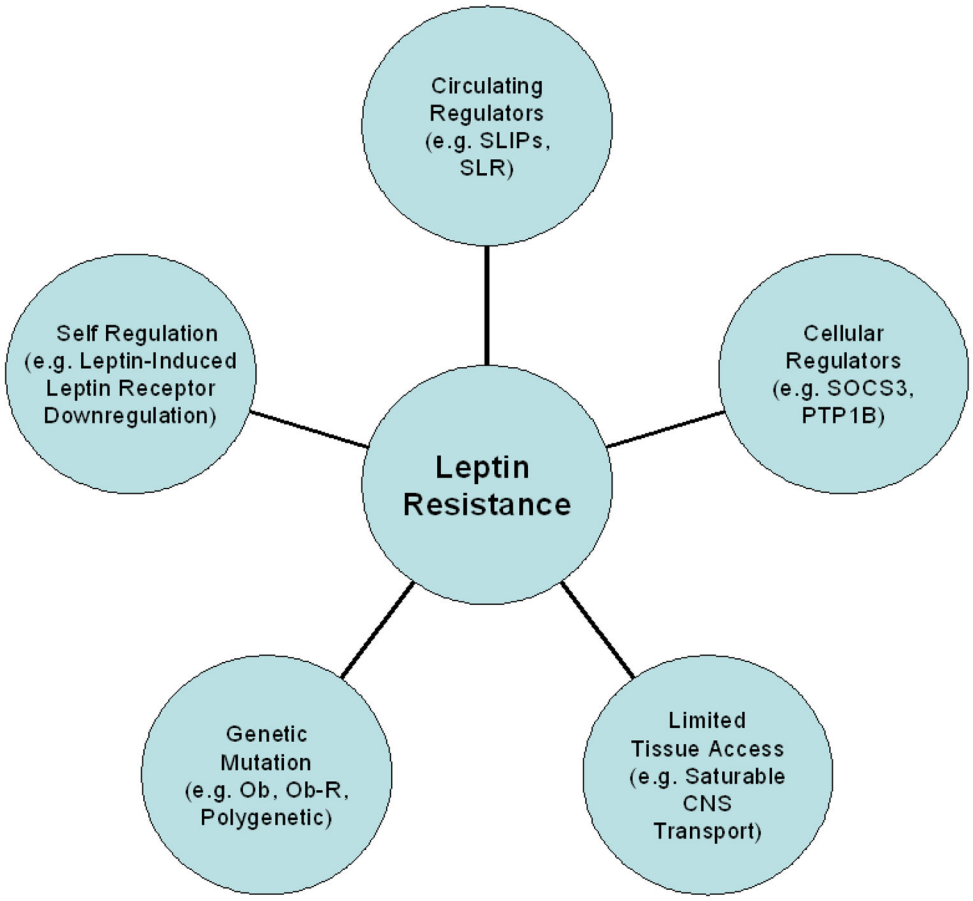

Figure 1. Mechanisms of leptin resistance

CNS = central nervous system; Ob = leptin gene; Ob-R = leptin receptor gene; PTP1B = protein tyrosine phosphatase 1B; SLR = soluble leptin receptor; SLIPs = serum leptin-interacting proteins; SOCS3 = suppressor-of cytokine-signaling-3.

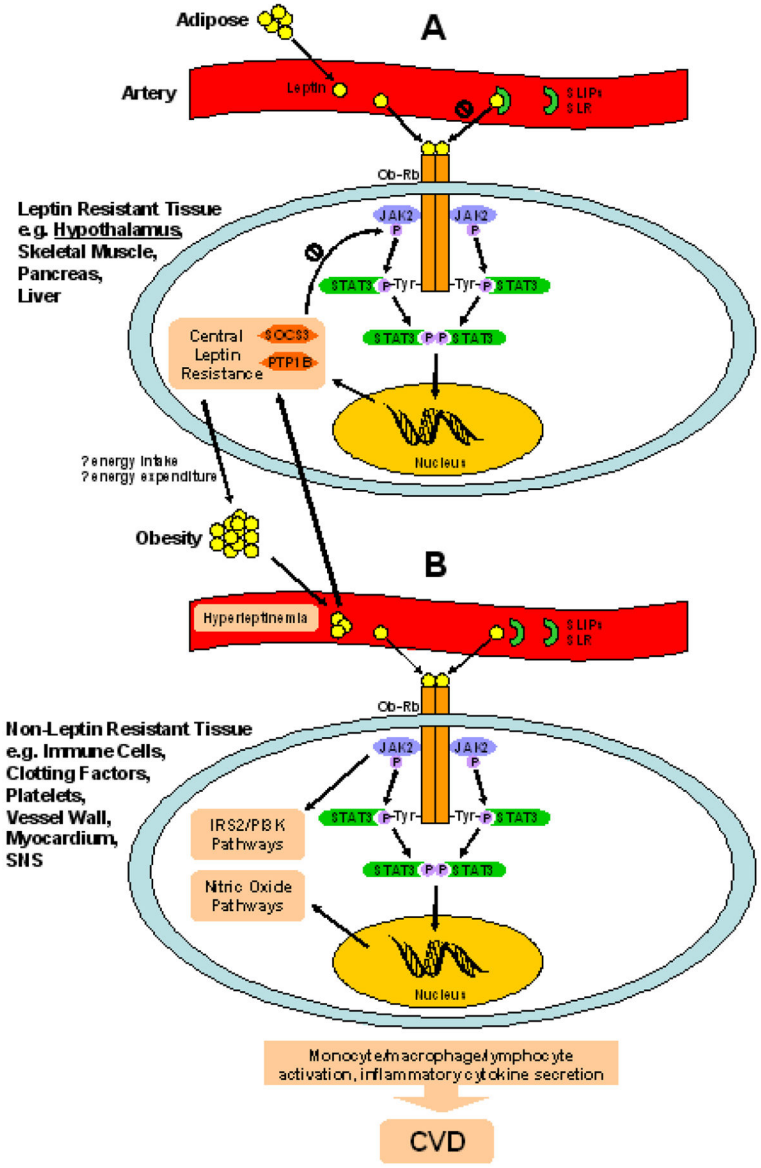

Figure 2. Theoretical cellular and molecular mechanisms of leptin pathophysiology

(A) In leptin resistant tissue (e.g., hypothalamic cell illustrated), serum leptin-interacting proteins (SLIPs) and soluble leptin receptor (SLR) may bind circulating adipose-secreted leptin and inhibit its action. Free leptin engages the long form of its receptor (Ob-Rb), which homodimerizes. Intracellularly, activated janus kinase 2 (JAK2) phosphorylates a specific tyrosine docking site (Tyr1138) on Ob-Rb. Signal transduction and translation protein 3 (STAT3) recognizes and binds to activated Tyr1138 via its src homology 2 (SH2) domain. The Ob-Rb/JAK2 complex activates STAT3, which homodimerizes, then translocates to the nucleus to modulate gene transcription. STAT3 upregulates expression of suppressor-of cytokine-signaling-3 (SOCS3) and protein tyrosine phosphatase 1B (PTP1B), which block JAK2 phosphorylation. It is thought that central leptin resistance promotes obesity, driving greater hyperleptinemia. (B) In non-leptin resistant tissue (e.g., immune cell illustrated) exposed to hyperleptinemia, Ob-Rb may signal excessively through multiple signaling

pathways, including JAK/STAT, insulin receptor substrate-2/phosphatidylinositol 3-kinase (IRS-2/PI3K), and nitric oxide that may ultimately promote cardiovascular disease (CVD) through tissue specific mechanisms.

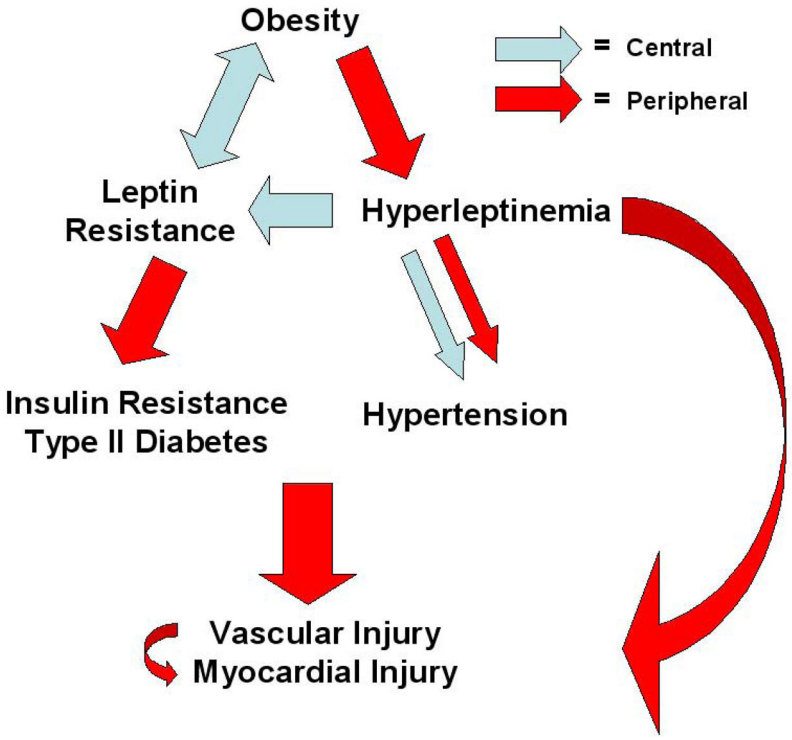

Figure 3. Overview of leptin resistance and hyperleptinemia in obesity-related cardiovascular disease

A leptin resistant/hyperleptinemic state is a putative link between obesity and diverse vascular and myocardial injury via direct effects or intermediary disorders. Site of effect (central versus peripheral) is depicted.

Table 1

Theoretical model of selective leptin resistance and hyperleptinemia in cardiovascular disease pathophysiology.

	Resistant	Non-Resistant
Tissue	Hypothalamus (metabolic centers), skeletal muscle, pancreas, liver	Immune cells, clotting factors, platelets, vessel wall, myocardium, sympathetic nervous system
Leptin concentration	High	High
Pathophysiology	Insensitivity to leptin (relative leptin deficiency) causes disease	Retained sensitivity to leptin in the setting of hyperleptinemia causes disease
Disease manifestations	Obesity, insulin resistance, diabetes	Hypertension, atherothrombosis, myocardial disease
Response to exogenous leptin	Disease improvement	Disease worsening
Potential response to targeted treatment of leptin resistance/ hyperleptinemia	Disease improvement	Disease improvement