Does selective leptin resistance cause obesity-related hypertension?

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ABSTRACT
Obesity is a major risk factor for hypertension, diabetes and cardiovascular disease. Leptin is a hormone produced by adipocytes, which has effects on the central nervous system. Leptinemia is increased in obesity and is associated with increased sympathetic nerve activity. Therefore, it is possible that obesity-related hypertension is caused in part by leptin-dependent sympathoactivation. However, obese subjects exhibit resistance to the anorexic and metabolic effects of leptin. One potential explanation for this paradox is selective leptin resistance. Animal models of obesity demonstrate preserved sympathetic actions of leptin despite resistance to its anorexic and metabolic actions. Abnormalities of intracellular signaling at certain central neural pathways may provide the molecular and anatomical bases of selective leptin resistance. Characterization of these pathways could lead to new approaches to the management of obesity-related hypertension.

KEYWORDS
Keywords leptin, obesity, hypertension, selective leptin resistance, sympathetic nervous system.

INTRODUCTION
Obesity is escalating worldwide and has been estimated to contribute to elevated blood pressure in over 70% of hypertensive patients in the United States. The pathogenic mechanisms of obesity-related hypertension are poorly understood, although sympathetic nervous system activation appears to play a prominent role. Several peptides secreted by the adipose tissue, such as angiotensin II, resistin, adiponectin and leptin, may participate in the regulation of blood pressure and the pathogenesis of obesity-related hypertension. To date, the preponderance of evidence supports a particularly important role for leptin. Leptin is a 167 amino acid hormone, predominantly secreted by the adipose tissue, that binds to its long isoform receptor (LRb) on hypothalamic neurons to inhibit feeding behavior and to increase sympathetically-mediated thermogenesis. Thus, leptin functions as an adipostat hormone that should maintain stable adipose tissue mass through a classical negative feedback mechanism (Figure 1). Leptin has multiple actions in addition to anorexia and thermogenesis. In particular, it can increase sympathetic nerve activity to non-thermogenic tissues, and thereby increase blood pressure in rodents¹². Leptin also has direct peripheral and CNS-mediated effects on the endocrine, vascular, hematopoietic, immune, musculoskeletal systems (Figure 1).

Obese subjects exhibit hyperleptinemia from increased adipocyte mass, but remain obese, suggesting some degree of leptin resistance. Indeed, both experimental murine and human polygenic obesity are associated with resistance to the anorexic and weight-lowering effects of leptin. Here, we review the concept of selective leptin resistance as plausible explanation for the maintenance of leptin-dependent sympathoactivation despite resistance to the metabolic effects of leptin. Selective leptin resistance and hyperleptinemia may be important pathogenic mechanisms that lead to hypertension in obesity. Potential molecular mechanisms of selective leptin resistance are also reviewed.
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LEPTIN-DEPENDENT SYMPATHOACTIVATION IS ASSOCIATED WITH HYPERTENSION IN RODENTS

Given the major role of leptin in modulating energy homeostasis, the finding that leptin increases catecholamine turnover in thermogenic brown adipose tissue in rodents was not surprising. Leptin-dependent increases in brown adipose tissue sympathetic nerve activity promote thermogenic metabolism and energy dissipation as heat and may contribute to leptin-induced weight loss. However, leptin has also been shown to increase sympathetic nerve activity to the kidneys, adrenal glands and hindlimbs in rats. These results raised the hypothesis that leptin could contribute to blood pressure modulation. Indeed, demonstrated that transgenic mice with hepatic leptin over-expression develop hypertension despite substantial weight loss that usually would decrease blood pressure. Increases in blood pressure were associated with increased urinary norepinephrine in these transgenic mice. Furthermore, sympathetic blockade with α, and β-adrenergic inhibitors and ganglionic blockers reversed hypertension. Corroborating these results, it has been shown that chronic systemic or intracerebral administration of leptin increases blood pressure in rats, which is preventable by adrenergic blockade.

LEPTIN SIGNALING AND RESISTANCE

Normally, leptin binds to and changes the conformation of its long splice variant form receptor (LRb). This process promotes intracellular activation of Janus kinase 2 (JAK2) and phosphorylation of SH-2 domains of the signal transducer and activator of transcription protein type 3 (STAT3). Phosphorylated STAT3 dimerizes and binds to nuclear promoter regions. In addition to triggering the JAK-STAT pathway, binding of leptin to the LRb also activates phosphatidylinositol-3-kinase (PI3K), mitogen-activated protein kinase (MAPK), and the ATP-sensitive K-channel (Figure 2). Activation of each of these pathways contributes to the anorexic effects of leptin. Physiologically, leptin suppresses appetite, increases thermogenesis, and induces weight loss. Impairment of these actions, as commonly found in obesity, characterizes leptin resistance. Compensatory hyperleptinemia is found in obesity and has been used as a surrogate index of leptin resistance and adipose tissue mass.

The precise mechanisms of leptin resistance have not been elucidated but likely depend on impaired post-receptor signaling. Increased expression of suppressor of cytokine signaling 3 (SOCS 3) may underlie an important mechanism of leptin resistance. SOCS 3 binds to JAK 2 and blocks the docking domain of STAT 3, preventing its phosphorylation, as experimentally seen in Chinese hamster ovary cells in vitro. Normally, SOCS 3 may function as a physiological negative regulator of leptin signaling.
Peripheral or central nervous system administration of physiologic doses of leptin fails to inhibit feeding behavior and to induce weight loss in Ay mice, suggesting resistance to these metabolic effects of leptin. The Ay mouse also exhibits compensatory hyperleptinemia and, notably, higher blood pressure than lean controls. Moreover, in an outstanding manuscript, have demonstrated that high concentrations of plasma leptin contribute to regulation of blood pressure through sympathetic mechanisms in Ay mice despite substantial leptin resistance.

By direct measurement of sympathetic outflow to the kidney, we have demonstrated that, despite partial resistance to leptin’s metabolic effects (i.e. satiety and weight loss), renal sympathetic activation to IV or CNS administration of leptin is preserved in Ay mice. These results indicate that leptin resistance in the Ay mouse is confined to certain metabolic actions of leptin while sparing the hormone’s sympathetic actions.

Selective leptin resistance has also been observed in mice with polygenic, diet-induced obesity. C57BL/6J mice were fed a normal or high fat diet (i.e. 13% vs. 45% of total calories as fat) for 10 weeks. By the end of this period, the high fat group had developed moderate obesity and were ~10% heavier than the normal chow group. In line with previous results with Ay mice, the renal sympathetic response to either systemic or CNS administration of leptin was similar in obese and control mice, despite loss of the anorexic and lipopenic actions of leptin in the obese group (i.e. metabolic leptin resistance). Interestingly, sympathetic activation to brown adipose tissue and lumbar nerves induced by leptin was also blunted in obese mice. These two results have a very interesting and mechanistically appealing interpretation: the preservation of leptin-induced sympathetic activation to the kidneys might underlie pathophysiologic mechanisms that predispose obese animals to hypertension whereas the inhibition of leptin-dependent sympathoactivation to the hindlimbs and, notably, to the brown adipose tissue, could theoretically impair thermogenic metabolism and aggravate obesity (Figure 3).

Most importantly, it was demonstrated that the pressor effect of leptin is preserved in diet-induced obese mice despite metabolic leptin resistance. First, obesity induced by 10 weeks of high fat diet increased mean blood pressure by about 10 mmHg in conscious mice implanted with radiotelemetry probes, confirming the expected hypertensive effect of increased adiposity. Second, long-term (i.e. 12 days) systemic leptin treatment increased mean blood pressure by about 10 mmHg both in lean and obese animals as compared with vehicle-treated animals. Also, mice with diet-induced obesity were poorly responsive to the satiety and lipopenic effects of chronic administration of leptin. These observations indicate that the hypertensive response of chronic systemic administration of leptin is preserved.

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CARDIORENA SYMPATHETIC ACTIVATION TO LEPTIN IS PRESERVED IN LEPTIN-RESISTANT MODELS OF OBESITY: EVIDENCE FOR SELECTIVE LEPTIN RESISTANCE

It has been demonstrated that sympathetic activation by leptin is preserved in leptin-resistant mice with monogenic or diet-induced obesity. This indicates that selective resistance to leptin can occur, affecting only leptin’s anorexic, thermogenic, and lipopenic actions.

The concept of selective leptin resistance originated from experiments with the profoundly leptin resistant obese yellow agouti mouse (Ay mouse). Obesity in Ay mice is genetically determined by ectopic overexpression of agouti peptide. The agouti peptide competitively antagonizes the binding of endogenous α-melanocortin stimulating hormone (α-MSH) to a variety of melanocortin receptors (MC receptors). Physiologically, α-MSH activates MC1 receptors to produce black fur in mice. In addition, hypothalamic MC4 receptors are activated by α-MSH to inhibit feeding behavior and to increase thermogenic metabolism. Thereby, agouti protein inhibition of MC1 and MC4 receptors determine the typical phenotype of Ay mouse: blond fur and obesity, respectively.

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in obese mice despite significant leptin metabolic resistance. Taken together, these results raise the attractive hypothesis that unimpeached sympathoeoxicatory effects of leptin on the kidneys could be associated with leptin-induced hypertension in obese mice with metabolic leptin resistance (Figure 3).

**MOLECULAR MECHANISMS OF LEPTIN RESISTANCE OPERATE IN DISTINCT CENTRAL NERVOUS SYSTEM NETWORKS – IMPLICATIONS FOR THE PATHOGENESIS OF SELECTIVE LEPTIN RESISTANCE**

Leptin receptors have been identified in several hypothalamic and extra-hypothalamic nuclei. The activation of these receptors at different anatomical sites may elicit distinct and perhaps unrelated responses. Indeed, experimental evidence indicates that leptin-dependent sympathetic outflow acting on metabolism and the cardiovascular system do not share common neuronal mechanisms.

Several lines of evidence corroborate this concept. First, while intracerebral administration of leptin increases brown adipose tissue and renal sympathetic nerve activity simultaneously, co-treatment with an a-MSH antagonist (SHU-9119, an MC 4 receptor antagonist) inhibits only the sympathoactivation to brown adipose tissue, preserving leptin sympathetic response to the kidneys. In addition, mice with the gene for the melanocortin-4 receptor knocked out exhibit a gene dose dependent decrease in leptin induced renal sympathoactivation. On the other hand, leptin-dependent sympathetic activation of thermogenic brown adipose tissue is inhibited by the corticotrophin release factor (CRF) receptor antagonist a-helical CRF102. Thus, these results suggest that the sympathetic output to thermogenic brown adipose tissue could be conveyed through neuronal pathways distinct from those that mediate sympathetic modulation of cardiorenal functions.

Second27, have shown that baroreflex activation suppresses leptin-dependent sympathetic stimulation of the kidneys but increased leptin-induced sympathetic output to the brown adipose tissue is not inhibited by the baroreflex. As expected, these results indicate that cardiorenal sympathetic regulation, but not thermogenesis, is influenced by baroreflex signals, suggesting independence of the cardiorenal and thermogenic sympathetic effects of leptin.

Third, it has been shown that the anorexic and lipopenic effects of leptin are mediated by neural networks relayed through the arcuate nucleus, whereas the sympathetic and cardiovascular actions of leptin appear to be associated with neuronal activation of the ventromedial and dorsomedial hypothalamus (Figure 3).

Theoretically, the arcuate nucleus could be the site where selective leptin resistance develops because it is the major hypothalamic nucleus for the leptin-dependent effects on satiety and thermogenesis regulation, both of which are impaired in obesity. Indeed, at the molecular level, arcuate nucleus STAT3-dependent signaling pathways are specifically depressed in mice with diet induced obesity, presumably by increased expression of inhibitory SOCS3, whereas other hypothalamic and extra-hypothalamic nuclei maintain leptin sensitiveness.

Anatomical evidence also singles out the arcuate nucleus as an attractive target for the development of selective leptin resistance. Martin Myers and collaborators at the University of Michigan30 have proposed that the arcuate nucleus, being less insulated from the systemic circulation by the blood-brain barrier, would be particularly influenced by serum leptin and other circulating factors. Normally, leptin binds to its receptor and mainly activates the STAT3 pathway that is opposed by SOCS3 signal in a typical negative feedback loop. In lean animals with normal blood leptin concentration, baseline activation of the STAT3 pathway is modest and SOCS3 expression is low. Therefore, under these circumstances, any additional increase in leptinemia would produce commensurate increases in STAT3 signaling that is not fully suppressed by SOCS3. Sustained increased concentrations of leptin in the blood of obese animals could chronically increase

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**Figure 3.** Mechanisms of selective leptin resistance. Leptin acts in the hypothalamus to decrease food intake and increase thermogenesis, as well as increase sympathetic nerve activity (SNA) to non-thermogenic organs. Increasing evidence suggests that these actions can be dissociated in obesity, with resistance to the anorexic and thermogenic effects of leptin (mediated through the arcuate nucleus) but preservation of cardiorenal sympathoactivation (mediated through medial hypothalamic nuclei: VMH and DMH). This phenomenon might explain in part how hyperleptinemia could be accompanied by obesity (partial loss of appetite and metabolic actions of leptin) but still contribute to sympathetic overactivity and hypertension because of preservation of the sympathetic actions of leptin to some organs involved in blood pressure regulation.
CLINICAL CORRELATIONS BETWEEN LEPTIN AND OBESITY-RELATED HYPERTENSION AND SYMPATHETIC ACTIVATION

Most obese human subjects are leptin resistant and exhibit compensatory hyperleptinemia that also reflects increased adiposity. Human obesity is also characterized by increased sympathetic activity as indicated by increased serum catecholamines and augmented outflow to peripheral skeletal muscle sympathetic nerve fibers. If the concept of selective leptin resistance holds in obese humans, it is plausible that hyperleptinemia could contribute to obesity-related sympathoactivation and perhaps hypertension, despite leptin resistance. Nevertheless the evidence to support this hypothesis is scarce and mostly restricted to observational studies in subsets of specific populations that clearly lack generalizability. Brief descriptions of few illustrative epidemiologic studies showing positive correlations between leptin and blood pressure are provided in his text. However other epidemiologic surveys with mixed results can be found in the literature.

In Japan, cross-sectional studies have shown that blood pressure and leptinemia are modestly correlated in normotensive and hypertensive adults after adjustment for fat mass. In addition, hyperinsulinemia and hyperleptinemia correlate with systolic blood pressure in obese Japanese children regardless of a family history of hypertension. As part of the Olivetti Prospective Heart Study, pressure in obese Japanese children regardless of a family history of hypertension. As part of the Olivetti Prospective Heart Study, hyperinsulinemia and hyperleptinemia correlate with systolic blood pressure and 244 normotensives were compared and, through univariate and multivariate analysis, obesity, dyslipidemia, hyperleptinemia and hyperinsulinemia were shown to be independent risk factors for hypertension.

Clinical studies demonstrating unequivocal effects of leptin on the sympathetic nervous system have not been conducted and correlation studies have led to inconclusive results. Of notice, have shown that leptin levels are 5 to 6 times higher in men with body mass index ≥ 28 kg/m² as compared to lean controls and that renal norepinephrine spillover is significantly correlated with leptinemia in overweight/obese men with wide ranges of leptin levels and adiposity (r = 0.63, p < 0.01). Thus, it is plausible that increased renal norepinephrine spillover could contribute to hypertension in obese subjects with hyperleptinemia.

In apparent contradiction with this study, have administered exogenous leptin to healthy normal weight subjects and did not observe any changes in plasma or urinary catecholamines though these are per se poor indicators of systemic sympathetic activity. However, in a study of leptin reconstitution in formerly obese subjects aiming weight stabilization, the endocrine and sympathetic abnormalities caused by weight loss were reversed by leptin treatment. Importantly, heart rate analysis and increased urinary catecholamines suggest that leptin reconstitution reverses the sympathetic suppression due to weight loss. Larger studies where exogenous leptin was administered to obese subjects have been conducted but no systematic evaluation of sympathetic activity or blood pressure responses was reported.

CONCLUSIONS

Experimental and human obesity are associated with significant metabolic leptin resistance. Nevertheless there is clear evidence that leptin contributes to the regulation of blood pressure. It has also been demonstrated that leptin resistance is selective in A/ and diet-induced obese mice, and is restricted to its metabolic effects. Indeed, the preservation of leptin’s sympatoexcitatory and pressor effects could contribute to the development of obesity-related hypertension. Furthermore, neuroanatomic factors and molecular mechanisms have been described that could support the concept of selective leptin resistance. It may be possible to develop specific treatments targeting CNS molecular mechanisms responsible for cardiorenal sympathetic activation in obesity (i.e. melanocortins), or reverse mechanisms responsible for loss of metabolic leptin actions (i.e. MAPK, SOCS3).

The effects of leptin in the regulation of sympathetic function and blood pressure in humans have been sparsely investigated, mostly through epidemiologic studies. Even though exogenous leptin has been administered to humans in clinical trials, the sympathetic and blood pressure actions of the hormone have not been rigorously assessed. Thus, the occurrence of selective leptin resistance in human obesity awaits experimental and clinical proof.
REFERENCES


