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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 rodents[1,2]. 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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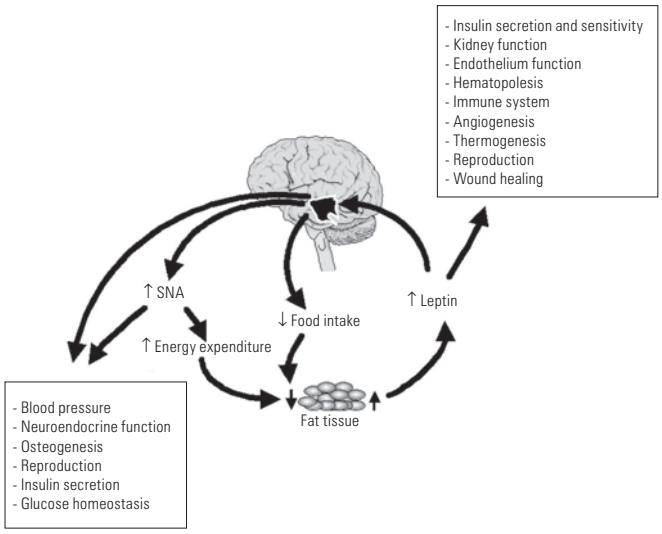


Figure 1. Biological roles of leptin: leptin is secreted by adipocytes and circulates in the blood in a concentration proportional to fat mass content. In addition to regulation of appetite, thermogenesis and body weight, leptin has multiple other biological actions. Binding of leptin to the LRb receptor in the hypothalamus inhibits food intake and increases energy expenditure through stimulation of sympathetic nerve activity (SNA). Leptin also modulates different other functions by direct peripheral action in various tissues or through activation of thermogenic and cardiorenal SNA.

LEPTIN-DEPENDENT SYMPATHOACTIVATION IS ASSOCIATED WITH HYPERTENSION IN RODENTS

Given the major role of leptin in modulating energy homeostasis, the finding that leptin increases cathecholamine turnover in thermogenic brown adipose tissue in rodents was not surprising[3]. 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[4]. However, leptin has also been shown to increase sympathetic nerve activity to the kidneys, adrenal glands and hindlimbs in rats[1]. These results raised the hypothesis that leptin could contribute to blood pressure modulation. Indeed,[5] 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_1 and β-adrenergic inhibitors and ganglionic blockers reversed hypertension[5]. Corroborating these results, it has been shown that chronic systemic or intracerebral administration of leptin increases blood pressure in rats[6,7], which is preventable by adrenergic blockade[8].

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[9]. In addition to triggering the JAK-STAT pathway, binding of leptin to the LRb also activates phosphatidylinositol-3-kinase (PI3K)[10], mitogen-activated protein kinase (MAPK)[11], and the ATP-sensitive K-channel (Figure 2). Activation of each of these pathways contributes to the anorexic effects of leptin[10-12]. 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[13].

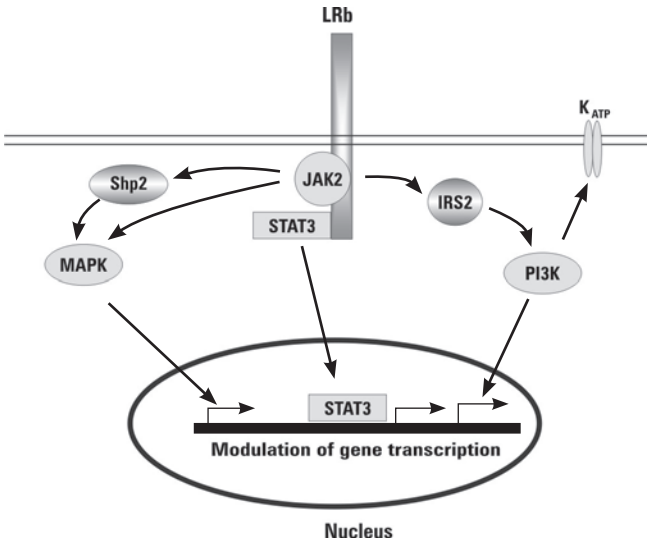


Figure 2. Molecular mechanisms involved in leptin receptor (LRb) signaling in the hypothalamus. Leptin modulates gene transcription via the activation of signal transducer and activator of transcription 3 (STAT3) proteins, phosphoinositol 3 kinase (PI3K) and mitogen activated protein kinase (MAPK). The PI3 kinase pathway is also involved in modulation of neuronal firing rate via activation of membrane potassium-ATP channels (K_{ATP}).

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[14]. Normally, SOCS 3 may function as a physiological negative

feedback to leptin intracellular signaling, given that leptin induces SOCS 3 expression[14]. However, excessive expression of SOCS 3 might contribute to leptin resistance, such as in the hypothalamic nuclei of profoundly leptin-resistant agouti obese mice[15]. Also, leptin resistance could be explained by reduced phosphorylation of STAT 3 as demonstrated in mice with fat diet-induced obesity[16].

Another molecular candidate mechanism for leptin resistance is protein tyrosine phosphatase 1B (PTP1B). Recent in vitro evidence indicates that PTP1B regulates leptin-dependent signaling by direct and specific dephosphorylation of JAK 2 and STAT 3[17]. These results corroborate experiments showing that PTP1B attenuates phosphorylation of JAK2-STAT3 induced by leptin in hypothalamic cell lines. Additionally, PTP1B appears to regulate leptin-dependent gene expression given that overexpression of PTP1B in these cell lines reduced mRNA expression of STAT3[18]. Microarray analysis showing PTP1B-dependent suppression of STAT3 gene expression further supports this experimental observation[18]. In vivo studies in PTP1B-deficient mice support a pathophysiological role for PTP1B. These mice exhibit increased sensitivity to leptin reflected by increased leptin-mediated weight loss and augmented feeding suppression. Also, hypothalamic tissue from PTP1B-deficient show increased STAT3 phosphorylation induced by leptin[19]. Nevertheless, unlike SOCS 3, dysregulation of hypothalamic PTP1B has not been demonstrated in experimental models of obesity[20].

CARDIORENAL 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[21,22]. This indicates that selective resistance to leptin can occur, affecting only leptin's anorexic, thermogenic, and lipopenic actions.

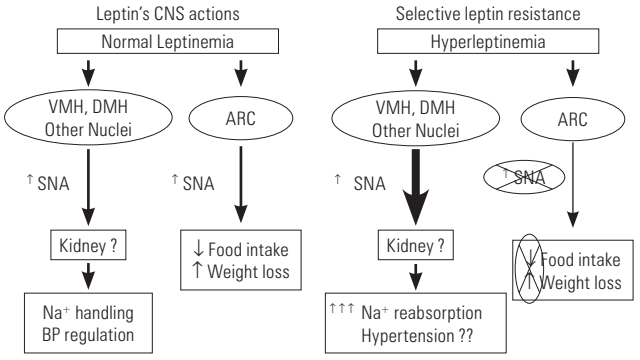
The concept of selective leptin resistance originated from experiments with the profoundly leptin resistant obese yellow agouti mouse (A^y mouse). Obesity in A^y mice is genetically determined by ectopic overexpression of agouti peptide. The agouti peptide competitively antagonizes the binding of endogenous 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 A^y mouse: blond fur and obesity, respectively.

Peripheral or central nervous system administration of physiologic doses of leptin fails to inhibit feeding behavior and to induce weight loss in A^y mice, suggesting resistance to these metabolic effects of leptin[23]. The A^y mouse also exhibits compensatory hyperleptinemia and, notably, higher blood pressure than lean controls[5,24]. Moreover, in an outstanding manuscript[5], have demonstrated that high concentrations of plasma leptin contribute to regulation of blood pressure through sympathetic mechanisms in A^y 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 A^y mice[21,25]. These results indicate that leptin resistance in the A^y 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[22]. 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 A^y 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[22]. 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



CNS: central nervous system; ARC: arcuate nucleus;
VMH: ventromedial hypothalamus; DMH: dorsomedial hypothalamus.

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.

in obese mice despite significant leptin metabolic resistance. Taken together, these results raise the attractive hypothesis that unimpeded sympathoexitatory 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[26]. In addition, mice with the gene for the melanocortin-4 receptor knocked out exhibit a gene dose dependent decrease in leptin induced renal sympathoactivation[10]. 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 CRF_{9-41}[2]. 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.

Second[27], 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[28] (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[29].

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 Michigan[30] 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

baseline STAT3 resulting in higher basal expression of SOCS. Thereby, in obesity, whenever circulating leptin further increases, there would be no significant increment of leptin-dependent responses due to SOCS3 inhibitory actions. The easy access of circulating leptin to the arcuate nucleus, likely by-passing the receptor-dependent leptin transport system across the blood-brain barrier, would make the arcuate particularly susceptible to this potential SCOS3 mechanism. Conversely, other central nervous system nuclei would be relatively protected from the overflow of leptin from the systemic circulation and would remain sensitive to the site-specific actions of leptin. Interestingly, activation of MAPK may be the specific arcuate neuron signal that is altered in obesity, because pharmacological inhibition of MAPK recapitulates the pattern of selective leptin resistance, namely loss of the anorexic and thermogenic effects of leptin with preservation of renal sympathoactivation[11].

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[30]. If the concept of selective leptin resistance holds in obese humans, it is plausible that hyperletinemia 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[31,32]. 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[33], demonstrated that the log-transformation of serum leptin was positively, independently but modestly associated with systolic and diastolic blood pressure in a cohort of factory male workers from Naples, Italy. The same study also shows that the prevalence of untreated hypertension is almost twice as high in subjects with elevated plasma concentrations of leptin after adjustment for age and waist circumference. In Mexico, 255 subjects with high 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[34].

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[35], have shown that leptin levels are 5 to 6 times higher in men with body mass index ≥ 28 kg/m^2 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[36], 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 cathecolamines suggest that leptin reconstitution reverses the sympathetic suppression due to weight loss[37]. 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^y and diet-induced obese mice, and is restricted to its metabolic effects. Indeed, the preservation of leptin's sympathoexcitatory 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

1. Haynes WG, Morgan DA, Walsh SA, *et al*. Receptor-mediated regional sympathetic nerve activation by leptin. *J Clin Invest.* 1997;100:270-8.
2. Correia ML, Morgan DA, Mitchell JL, *et al*. Role of corticotrophin-releasing factor in effects of leptin on sympathetic nerve activity and arterial pressure. *Hypertension.* 2001;38:384-8.
3. Collins S, Kuhn CM, Petro AE, *et al*. Role of leptin in fat regulation. *Nature.* 1996;380:677.
4. Halaas JL, Gajiwala KS, Maffei M, Cohen SL, Chait BT, Rabinowitz D, *et al*. Weight-reducing effects of the plasma protein encoded by the obese gene. *Science.* 1995;269(5223):543-6.
5. Aizawa-Abe M, Ogawa Y, Masuzaki H, *et al*. Pathophysiological role of leptin in obesity-related hypertension. *J Clin Invest.* 2000;105:1243-52.
6. Shek EW, Brands MW, Hall JE. Chronic leptin infusion increases arterial pressure. *Hypertension.* 1998;31:409-14.
7. Correia ML, Haynes WG, Rahmouni K, *et al*. The concept of selective leptin resistance: evidence from agouti yellow obese mice. *Diabetes.* 2002;51:439-42.
8. Carlyle M, Jones OB, Kuo JJ, Hall JE. Chronic cardiovascular and renal actions of leptin: role of adrenergic activity. *Hypertension.* 2002;39:496-501.
9. Akira S. Functional roles of STAT family proteins: lessons from knockout mice. *Stem Cells.* 1999;17(3):138-46.
10. Rahmouni K*, Haynes WG, Morgan DA, Mark AL: Intracellular mechanisms involved in leptin regulation of sympathetic outflow. *Hypertension.* 2003;41:763-7.
11. Rahmouni K, Sigmund CD, Haynes WG, Mark AL. Mitogen activated protein kinase: a newly discovered mediator of selective leptin actions. *Hypertension.* 2005;46: 867.
12. Bates SH, Stearns WH, Dundon TA, Schubert M, Tso AW, Wang Y, *et al*. STAT3 signalling is required for leptin regulation of energy balance but not reproduction. *Nature.* 2003;421:856-9.
13. Frederich RC, Hamann A, Anderson S, Lollmann B, Lowell BB, Flier JS. Leptin levels reflect body lipid content in mice: evidence for diet-induced resistance to leptin action. *Nat Med.* 1995;1(12):1311-4.
14. Bjorbaek C, El-Haschimi K, Frantz JD, Flier JS. The role of SOCS-3 in leptin signaling and leptin resistance. *J Biol Chem.* 1999;274(42):30059-65.
15. Bjorbaek C, Elmquist JK, Frantz JD, Shoelson SE, Flier JS. Identification of SOCS-3 as a potential mediator of central leptin resistance. *Mol Cells.* 1998;1(4):619-25.
16. El-Haschimi K, Pierroz DD, Hileman SM, Bjorbaek C, Flier JS. Two defects contribute to hypothalamic leptin resistance in mice with diet-induced obesity. *J Clin Invest.* 2000;105(12):1827-32.
17. Lund IK, Hansen JA, Andersen HS, Moller NP, Billestrup N. Mechanism of protein tyrosine phosphatase 1B-mediated inhibition of leptin signalling. *J Mol Endocrinol.* 2005;34(2):339-51.
18. Kaszubska W, Falls HD, Schaefer VG, Haasch D, Frost L, Hessler P, *et al*. Protein tyrosine phosphatase 1B negatively regulates leptin signaling in a hypothalamic cell line. *Mol Cell Endocrinol.* 2002;195(1-2):109-18.
19. Cheng A, Uetani N, Simoncic PD, Chaubey VP, Lee-Loy A, McGlade CJ, *et al*. Attenuation of leptin action and regulation of obesity by protein tyrosine phosphatase 1B. *Dev Cell.* 2002;2(4):497-503.
20. Munzberg H, Myers MG Jr. Molecular and anatomical determinants of central leptin resistance. *Nat Neurosci.* 2005;8(5):566-70.
21. Correia ML, Haynes WG, Rahmouni K, *et al*. The concept of selective leptin resistance: evidence from agouti yellow obese mice. *Diabetes.* 2002;51:439-42.
22. Rahmouni K, Morgan DA, Morgan GM, Mark AL, Haynes WG. Role of selective leptin resistance in diet-induced obesity hypertension. *Diabetes.* 2005; 54:2012-8.
23. Halaas JL, Boozer C, Blair-West J, Fidahusein N, Denton DA, Friedman JM. Physiological response to long-term peripheral and central leptin infusion in lean and obese mice. *Proc Natl Acad Sci U S A.* 1997;94(16):8878-83.
24. Mark AL, Shaffer RA, Correia ML, Morgan DA, Sigmund CD, Haynes WG. Contrasting blood pressure effects of obesity in leptin-deficient ob/ob mice and agouti yellow obese mice. *J Hypertens.* 1999;17(12 Pt 2):1949-53.
25. Rahmouni K, Haynes WG, Morgan DA, Mark AL. Selective resistance to central neural administration of leptin in agouti obese mice. *Hypertension.* 2002; 39:486-90.
26. Haynes WG, Morgan DA, Djalali A, *et al*. Interactions between the melanocortin system and leptin in control of sympathetic nerve traffic. *Hypertension.* 1999;33:542-7.
27. Hausberg M, Morgan DA, Chapleau MA, *et al*. Differential modulation of leptin-induced sympathoexcitation by baroreflex activation. *J Hypertens.* 2002;20:1633-41.
28. Marsh AJ, Fontes MA, Killinger S, Pawlak DB, Polson JW, Dampney RA. Cardiovascular responses evoked by leptin acting on neurons in the ventromedial and dorsomedial hypothalamus. *Hypertension.* 2003;42(4):488-93.
29. Munzberg H, Flier JS, Bjorbaek C. Region-specific leptin resistance within the hypothalamus of diet-induced obese mice. *Endocrinology.* 2004;145(11):4880-9.
30. Grassi G, Seravalle G, Cattaneo BM, Bolla GB, Lanfranchi A, Colombo M, *et al*. Sympathetic activation in obese normotensive subjects. *Hypertension.* 1995;25 (4 Pt 1):560-3.
31. Agata J, Masuda A, Takada M, *et al*. High plasma immunoreactive leptin level in essential hypertension. *Am J Hypertens.* 1997;10:1171-4.
32. Matsubara M, Chiba H, Maruoka S, Katayose S. Elevated serum leptin concentrations in women with components of multiple risk factor clustering syndrome. *J Atheroscler Thromb.* 2000;7:231-7.
33. Barba G, Russo O, Siani A, *et al*. Plasma leptin and blood pressure in men: graded association independent of body mass and fat pattern. *Obes Res.* 2003;11:160-6.
34. Alvarez-Aguilar C, Mondragon-Jimenez LI, Ramirez-Enriquez J, Gomez-Garcia A, Paniagua-Sierra R, Amato D. Hyperleptinemia as a risk factor in obesity-related hypertension. *Med Clin (Barc).* 2004;123(20):766-9.
35. Eikelis N, Schlaich M, Aggarwal A, *et al*. Interactions between leptin and the human sympathetic nervous system. *Hypertension.* 2003;41:1072-9.
36. Mackintosh RM, Hirsch J. The effects of leptin administration in non-obese human subjects. *Obes Res.* 2001;9(8):462-9.
37. Rosenbaum M, Goldsmith R, Bloomfield D, Magnano A, Weimer L, Heymsfield S, *et al*. Low-dose leptin reverses skeletal muscle, autonomic, and neuroendocrine adaptations to maintenance of reduced weight. *J Clin Invest.* 2005;115(12): 3579-86.