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Review Article

Obesity Hypertension: The Regulatory Role of Leptin

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Leptin is a 16-kDa-peptide hormone that is primarily synthesized and secreted by adipose tissue. One of the major actions of this hormone is the control of energy balance by binding to receptors in the hypothalamus, leading to reduction in food intake and elevation in temperature and energy expenditure. In addition, increasing evidence suggests that leptin, through both direct and indirect mechanisms, may play an important role in cardiovascular and renal regulation. While the relevance of endogenous leptin needs further clarification, it appears to function as a pressure and volume-regulating factor under conditions of health. However, in abnormal situations characterized by chronic hyperleptinemia such as obesity, it may function pathophysiologically for the development of hypertension and possibly also for direct renal, vascular, and cardiac damage.

1. Introduction

The prevalence of obesity in the adult population of the United States has risen markedly in the last three decades, contributing to the increased incidence of diabetes, hypertension, and heart disease [1–3]. Indeed, epidemiological studies suggest that 65–75% of the risk for hypertension is attributed to excess weight [4, 5]. Recently, a novel and most promising area of research in obesity and hypertension that links these two pathologic conditions is the endocrinology of adipose tissue. It is now apparent that adipose tissue is a prolific organ which secretes several immunomodulators and bioactive molecules [3, 6]. Of these various factors, leptin has emerged as an important hormone with significant pleiotropic actions on several organ systems [7, 8].

The first described major action of leptin was on the hypothalamus to control body weight and fat deposition through its effects on appetite inhibition, as well as stimulation of the metabolic rate and thermogenesis [9, 10]. However, increasing evidence suggests that the biology of leptin extends to other organs including the kidney, the heart, the sympathetic nervous system, and the systemic vasculature, areas in which it may have prominent effects [7, 8, 11–14].

2. Leptin Receptors: Localization and Function

The leptin receptor (LR), a product of the lepr gene, is a member of the extended class I cytokine receptor family having at least six splice variants LR (a-f) [15–19]. Significant expression of the lepr gene occurs in the lung and adipocytes, while only moderate levels appear in the kidney, with relatively lower levels demonstrated in other tissues like the heart, brain, spleen, liver, and muscle [20]. Though the extracellular domain of the leptin receptor and the short splice variant (LRa) have been detected in many peripheral tissues, the long splice variant (LRb) is expressed in fewer organ systems including the adrenal gland, kidney, and heart [20]. This long splice variant leads to activation of the Janus Kinases (a family of tyrosine kinases)

to promote transcription through activation of the STAT-3 (signal transduction and activator of transcription) and PI3K (phosphoinositol-3 kinase), and inhibition of AMPK (AMP-activated protein kinase) [15–20]. LRa and LRb can also stimulate MAPK (mitogen activated protein kinase) which may be involved in the induction of hypertrophy [21]. Finally, SOCS-3 (suppression of cytokine signaling protein) and PTB1b (protein tyrosine phosphatase 1b) have been identified as negative regulators of leptin signaling [15–19].

3. Leptin, Sympathetic Nervous System, and the Regulation of Arterial Blood Pressure

It is now well established that leptin can activate the sympathetic nervous system both by local peripheral actions as well as through centrally mediated effects on the hypothalamus [22]. Studies with direct infusion of leptin into the cerebral ventricles of normal rats have demonstrated a slow increase of mean arterial pressure (MAP) of approximately 10% [13]. Moreover, recent investigations have suggested that leptin signaling in the nucleus tracti solitarii increased renal sympathetic flow in normal rats but not in obese Zucker rats, indicating that intact leptin receptors are essential for this vasoactive response [22]. In agreement with these concepts, human studies have suggested that genetically mediated leptin deficiency is associated not only with morbid obesity, but also impairment in the sympathetic nervous system activity and postural hypotension in homozygous children and adults [23].

However, it is important to point out that in other investigations conducted both in normotensive as well as hypertensive rats [12, 14, 24], the acute systemic administration of leptin was associated with the peripheral activation of the sympathetic nervous system without elevation in MAP. This raises the possibility of the simultaneous local activation of counter-regulatory vasodilatory mechanisms [14, 25, 26]. *In vitro* studies have demonstrated a dose-dependent leptin-induced vasorelaxation in the aortic rings of Wistar-Kyoto rats [25] which is mediated by nitric oxide (NO) and possibly by endothelial-derived hyperpolarizing factor (EDHF). An elevation in plasma NO with intravenous administration of synthetic leptin in normal rats has also been demonstrated [26]. In these studies blockade of NO led to a leptin-induced enhancement of arterial blood pressure while blockade of the sympathetic nervous system led to leptin-mediated reduction in blood pressure [26]. Thus, leptin's lack of effect on arterial blood pressure in normal subjects may represent a balanced action of vasodilatation primarily mediated by NO and vasoconstriction primarily mediated by the sympathetic nervous system, with a resultant neutral hemodynamic effect [26, 27]. This concept requires further validation because the vasodilatory actions of leptin in other vascular beds have been found to be inconsistent [28, 29]. In high-calorie fed obese rats, however, recent studies by Beltowski et al have indicated that acutely infused leptin was associated with a hypertensive effect related, at least in part, to impaired vascular NO and EDHF production characteristic of obesity [30].

4. Chronic Hyperleptinemia, Leptin Resistance, and Hypertension

In chronic hyperleptinemic conditions such as obesity, the potential neutral effect of leptin on peripheral vascular resistance may no longer be present. It has been previously demonstrated that the agouti yellow obese mouse model is resistant to the satiety actions of leptin but not to the effects of leptin on the sympathetic nervous system [31, 32], although this stimulation may be attenuated with the progression of obesity [33]. From these findings, the concept of "*selective leptin resistance*" as a mechanism for the development of hypertension in obesity has emerged [31, 32]. The precise factors behind this selectivity are yet to be fully defined [32, 34], but may involve alterations in the SOCS3 signaling pathway or IRS-1 (insulin receptor substrate-1) serine residue phosphorylation [30, 35, 36].

Independent of the possibility of selective leptin resistance in obesity, studies in normal rats have demonstrated that chronic hyperleptinemia leads to a persistent elevation in MAP and this hypertensive effect is rapidly reversed upon cessation of the hormone administration [37]. Similar increases in systolic blood pressure have been demonstrated in transgenic mice overexpressing leptin where the endogenous level of the hormone was elevated twenty-fold [38]. In this regard, it is pertinent to point out that hyperleptinemia may increase vascular smooth muscle cell proliferation [38], an effect that could contribute to the development and/or perpetuation of hypertension. Moreover, mice with leptin deficiency (ob/ob) or with a leptin receptor defect (db/db) exhibit significant obesity but do not develop hypertension, suggesting that at least in animal models, leptin may play a role in the regulation of systemic hemodynamics [32]. In humans, emerging evidence suggests a direct relationship between hyperleptinemia and hypertension in both men and women [39, 40], and this effect may be independent of BMI and insulin resistance. In a recent study by Shankar and Xiao of 5,599 Americans, higher plasma leptin levels were positively associated with hypertension after adjusting for multiple covariates including age, sex, race/ethnicity, education, smoking, body mass index, diabetes mellitus, and serum cholesterol [41]. In this regard, recent studies indicating a reduction in serum leptin levels with the use of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers suggest a potential interaction between leptin and the renin-angiotensin-aldosterone system for hemodynamic regulation in obesity [42, 43].

Finally, an additional potential mechanism involved in leptin's regulation of blood pressure implicates the melanocortin system [44]. Recent investigations have suggested that the acute actions of leptin to raise renal sympathetic activity are abolished in Melanocortin 4 receptor-(MC4R-) deficient (−/−) mice, suggesting that the MC4R may mediate the sympathoexcitatory actions of leptin [45]. To this end, Greenfield et al. demonstrated a lower prevalence of hypertension in obese subjects with a loss-of-function mutation in MC4R gene compared to obese controls with the intact gene again implicating melanocortinergic signaling in the control of systemic hemodynamics [46].

5. Leptin and the Regulation of Sodium-Volume Balance

Previous studies have indicated that the LRb leptin receptor is localized in the renal medulla [20, 47] which suggests a functional role of this hormone in renal biology. In the last 5–10 years, numerous studies have demonstrated that acute administration of synthetic leptin in the rat produces a significant elevation in urinary sodium and water excretion [14, 47–49].

Villarreal et al. [14] demonstrated that in normotensive rats, an intravenous bolus of leptin produced a robust six to sevenfold elevation in urinary sodium excretion and fractional excretion of sodium; in contrast, hypertensive rats were refractory to the renal effects of leptin. Interestingly, the natriuretic effect was attenuated in obese Zucker rats [14]. MAP and creatinine clearance remained unchanged in all of the rat strains with the acute infusion of the hormone. Collectively, these findings were interpreted to suggest that leptin might be a natriuretic hormone primarily acting at the tubular level for promotion of sodium and water excretion in normal rats, and that leptin may function pathophysiologically in obesity and hypertension, where chronic hyperleptinemia may contribute to a preferential stimulation of the sympathetic nervous system with further elevation in blood pressure and reduced sodium and water excretion [2, 7, 50]. Moreover, in a rat model of diet-induced obesity, initial studies by Patel et al. have shown markedly attenuated natriuretic and diuretic effects of synthetic leptin as well as reduced urinary excretion of NO [51]. These findings suggest that in obesity, alterations in leptin-induced renal NO production and/or metabolism may account, at least in part, for the blunted natriuretic effects. However, additional observations in diet-induced obese rats indicate that caloric restriction was associated with the restoration of the natriuretic actions of leptin as well as with the renal generation of NO [51]. In the aggregate, these studies are consistent with the concept that obesity is associated with renal leptin resistance [14, 52], and this resistance, at least in part, is reversible with caloric restriction and weight loss.

The significance of NO in the direct modulation of leptin-induced sodium excretion has been investigated in rats chronically treated with L-NAME to inhibit NO production [53]. L-NAME-treated rats failed to produce significant natriuresis. However, there was a two to threefold elevation in sodium excretion induced by leptin with the restoration of NO by sodium nitroprusside [53], indicating that NO may play an important role in mediating or modulating the tubular natriuretic effects of leptin. These observations are supported by the studies of Beltowski et al., [52] which demonstrated that leptin produces a time- and dose-dependent reduction of renal medullary Na-K-ATPase, which may in part be regulated by NO [53, 54]. Beltowski et al., [52] also reported that in diet-induced obese rats, leptin-induced stimulation of plasma NO, reduction of renal Na-K-ATPase, and natriuresis are all significantly impaired.

The mechanisms for renal resistance to leptin in obesity and hypertension are not completely defined but may include receptor down regulation [12, 51], postreceptor signaling alterations [12, 16, 17], excessive degradation of NO produced by oxidative stress [55], or increased activation of the efferent renal sympathetic nervous system leading to antinatriuresis [49]. Indeed, studies which [49] have examined this latter hypothesis using an animal model of renal denervation indicate that the renal efferent sympathetic nervous system is an important counter-regulatory mechanism impeding leptin-induced sodium excretion in hypertension, and perhaps also during obesity, which is similarly characterized by a heightened sympathetic nervous tone [2, 7].

The relevance of endogenous leptin as a distinct sodium-volume regulatory hormone has been examined in normal Sprague Dawley rats that were in a state of mild sodium/volume expansion [56]. Urinary sodium and volume excretion were significantly reduced by approximately 20–25% after blockade of leptin with a polyclonal antibody, indicating an important physiologic role for this hormone in the daily renal control of salt and water balance. The importance of leptin as a regulator of sodium and volume is further supported by recent investigations [56, 57] which have demonstrated that leptin expression in adipose tissue is directly proportional to dietary sodium, a response that would be expected for mechanisms regulating sodium balance.

Thus, the available information to date suggests that leptin's net effect on renal sodium metabolism and ultimately systemic hemodynamics may reflect both direct natriuretic and indirect antinatriuretic actions. The responsiveness to leptin at neural, renal, and other sites which regulate natriuresis and vascular resistance may differ under diverse physiological and pathophysiological conditions, and this in turn, will be a determinant for the overall magnitude of leptin-induced sodium, water, and hemodynamic balance.

6. Leptin and Chronic Renal Insufficiency

Leptin's role in renal physiology and pathophysiology is complex. As previously discussed, leptin may play a significant role in the regulation of sodium and water balance in normal situations. However, in conditions of chronic hyperleptinemia, the hormone has been linked to renal structural changes that specifically have been associated with obesity [58]. Elegant studies by Wolf et al. [59] have determined that in glomerular endothelial cells, leptin can stimulate cellular proliferation, expression of TGF-β1 and type IV collagen synthesis leading to fibrosis. Indeed, chronic infusion of leptin in normal rats promoted the development of glomerulosclerosis and proteinuria [59]. It is of interest that similar renal abnormalities have been found in mice with chronic high fat diet and the metabolic syndrome [60], which is characterized by sustained elevations of circulating leptin [61].

Inappropriate elevation in serum leptin levels has been demonstrated in patients with chronic kidney disease [62–64]. The origin and significance of hyperleptinemia in these patients are not completely defined, but it is important to emphasize that the marked elevation of leptin is out of

proportion to obesity and persists after correction for body mass index [65]. Since the kidney is involved in clearance of leptin, its elevated levels in renal insufficiency are primarily due to reduced renal filtration and metabolism [62, 66]. It remains to be determined whether an increased rate of leptin production also contributes to the high serum leptin levels in renal insufficiency.

Leptin levels appear to be higher in patients receiving peritoneal dialysis (PD) compared to hemodialysis (HD) [67]. The reasons for this phenomenon are multifactorial. It is likely that the elevated body fat mass in patients with PD contributes to the increase in serum leptin [67]. However, other factors are probably involved. For instance, the continuous glucose load in PD results in chronic hyperinsulinemia, an important finding considering that insulin upregulates lepr gene expression [63]. In this regard, it is of interest that even higher leptin levels are observed in patients with renal insufficiency with elevated insulin levels compared to patients with low insulin levels [63, 68].

The pathophysiological significance of hyperleptinemia in renal insufficiency is not completely understood. High levels of leptin have been associated with weight loss in dialysis patients [65, 69–71], and therefore it has been suggested that hyperleptinemia may be a contributing factor in uremic-induced cachexia [64, 69–74]. Other suggested actions in patients with end-stage renal disease which include leptin-induced reduction in erythropoiesis [75, 76], promotion of renal osteodystrophy [77, 78], and chronic inflammation [63, 78, 79].

7. Leptin and the Heart

It is now well recognized that the role of leptin in energy homeostasis extends into cardiac metabolism. The effects of leptin mediated by the LRb receptor include a reduction of insulin signaling with enhanced lipid oxidation and therefore inhibition of anabolic pathways [80]. Similar to the kidney, chronic hyperleptinemia may be indirectly important in the development of cardiac disease via sympathetic activation, pressor effects, enhancement of platelet aggregation, impairment of fibrinolysis as well as proangiogenic actions [12, 35, 81, 82] and systemic inflammation via leptin-induced expression of C-reactive protein [83, 84].

In addition, and although still controversial, leptin may be involved in the pathogenesis of myocyte hypertrophy and cardiac dysfunction [85–87] through direct effects. Indeed, leptin can proliferate, differentiate, and functionally activate hemopoietic and embryonic cells to promote myocyte growth [88–90]. Moreover, in rats with myocardial infarction, cardiac hypertrophy has been shown to be attenuated with the blockade of leptin receptors [91]. Among the suggested mechanisms of leptin-induced hypertrophy are the stimulation of endothelin-1, angiotensin II [92], and reactive oxygen species [93]. Additional studies in rats with myocardial infarction have also indicated that long-term continuous administration of leptin promoted the development of eccentric cardiac hypertrophy [94].

In contrast to these investigations, studies in leptin-deficient mice (ob/ob) with [94, 95] or without myocardial infarction [96] have suggested that leptin can exert protective cardiac effects with reversal of baseline myocyte hypertrophy during leptin supplementation [96]. Also, Tajmir et al. [97] have indicated that leptin can activate ERK 1/2 (extracellular signal-regulated kinase) and phosphoinositol-3 kinase-dependent signaling pathways in cardiomyocytes to promote physiological repair of myocardium. Presently, the reasons for the apparent discrepant effects of leptin on myocyte growth are unclear, but may be related to different experimental conditions, including the variable response of leptin in neonatal compared to adult cells [82–97].

In addition to its potential actions on myocardial cell growth, leptin has been shown to exert direct negative inotropic effects on adult rat ventricular myocytes [98]. The suggested mechanisms involve activation of fatty acid oxidation leading to decreased triglyceride content or an altered adenylate cyclase function [96, 99]. Alternatively, Nickola et al. [98] reported that leptin may abnormally increase expression of Nitric Oxide Synthases in cardiac myocytes promoting oxidative stress and depressed cardiac function. However, similar to the controversy related to cardiac hypertrophy, more recent studies in ob/ob mice [95] or rats [94] with myocardial infarction have suggested that leptin may attenuate adverse cardiac remodeling by reducing apoptosis [95], which may improve left ventricular contractile function, and at least in part, increase survival [94–96].

The relevance of these studies in humans is unclear. Although there is evidence to suggest a direct relationship between the hyperleptinemia of obesity with cardiac hypertrophy [96, 100], and possibly heart failure [101], these are not consistent findings [8, 11]. Additional *in vitro* and *in vivo* studies are needed to define and characterize the potential beneficial or deleterious effects of leptin in cardiac physiology and pathophysiology.

8. Summary and Conclusions

It is well established that cardiovascular and renal functions require the activation of multiple neuro hormonal mechanisms designed to maintain homeostasis. The hormone leptin has multiple actions that may be important not only for energy metabolism, but also in physiological and pathophysiological cardiovascular and renal regulation (Figure 1). Potentially prominent are its effects on renal sodium excretion, NO, sympathetic nervous system activation, and vascular tone. The interaction among the vasoconstricting, vasodilatory, and natriuretic effects of leptin to help achieve volume and pressure homeostasis in normal conditions may be disrupted during chronic hyperleptinemia, and this effect could likely contribute to hypertension and possible cardiac and renal dysfunction. Further research awaits the additional characterization of both direct and indirect mechanisms of action of leptin, including its interface with other important hormonal sodium-volume-pressure regulatory systems, in both health and disease states, particularly obesity and related comorbidities.

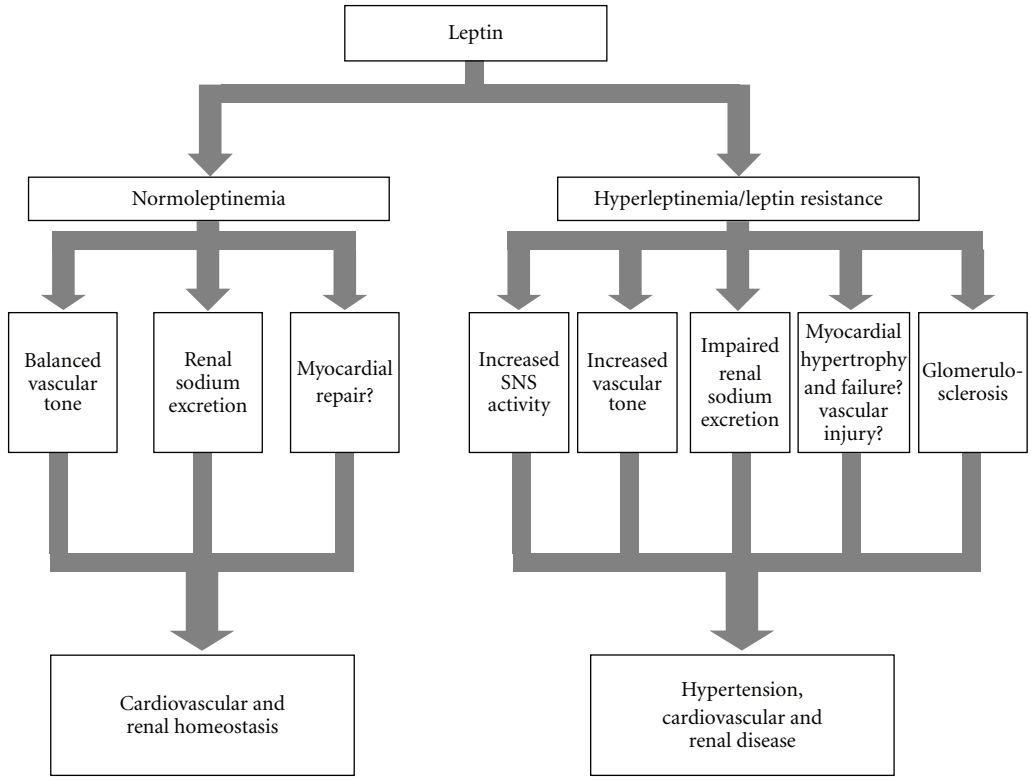

Figure 1: Cardiovascular and Renal Actions of Leptin. SNS: sympathetic nervous system. Adapted from Kshatriya S, Reams GP, Spear RM, Freeman RH, Dietz JR, Villarreal D. Current Opinion in Nephrology and Hypertension, 2010 Jan; 19 (1): 72−8. With Permission from Wolters Kluwer/Lippincott, Williams & Wilkins.

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