Obesity Hypertension: Pathophysiological Role of Leptin in Neuroendocrine Dysregulation

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Abstract: 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, 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. Although 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.

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The prevalence of obesity in the adult population of the United States has risen markedly in the past 3 decades, contributing to the increased incidence of diabetes, hypertension and heart disease.[1–3] Indeed, epidemiological evidence indicates that 65% to 75% of the risk for hypertension is attributed to excess weight.[3] In the past decade, an area of research in obesity and hypertension that links these 2 pathological conditions is the endocrinology of adipose tissue. It is now recognized that adipose tissue is a prolific organ that secretes several immunomodulators and bioactive molecules.[3,4] Of these various factors, leptin has emerged as an important hormone with significant pleiotropic actions on several organ systems.[3,5]

The first described major action of leptin was on the hypothalamus to control body weight and fat deposition through its effects on appetite inhibition and stimulation of the metabolic rate and thermogenesis.[3,5] However, current evidence suggests that the biology of leptin extends to other organs including the kidney, heart, sympathetic nervous system and systemic vasculature.[5–8]

BIOLOGY OF LEPTIN RECEPTORS

The leptin receptor (LR), a product of the *LEPR* gene, is a member of the extended class I cytokine receptor family having at least 6 splice variants LR (a–f).[5,8] Significant expression of the *LEPR* gene occurs in the lung and adipocytes, whereas only moderate levels appear in the kidney, with relatively lower levels demonstrated in other tissues like the heart, brain, spleen, liver and muscle.[9] Though the extracellular domain of the LR 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.[9] This long splice variant leads to activation of the Janus kinases (a family of tyrosine kinases) to promote transcription through activation of the signal transduction and activator of transcription-3, phosphatidylinositol-3 kinase and inhibition of adenosine monophosphate-activated protein kinase.[5,9] LRa and LRb can also stimulate mitogen-activated protein kinase, which may be involved in the induction of hypertrophy.[10] Finally, suppressor of cytokine signaling protein-3 and protein tyrosine phosphatase-1b have been identified as negative regulators of leptin signaling.[5–9]

LEPTIN AND VASCULAR SYMPATHETIC TONE

It is well established that leptin can activate the sympathetic nervous system both by local peripheral actions and through centrally mediated effects on the hypothalamus.[11] 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%.[5] Importantly, a similar hypertensive response has been recently demonstrated with the central administration of leptin in the diet-induced obese rat model,[12] which exhibits resistance to the actions of the hormone in other peripheral organs, such as the kidney.[8] To this end, it is pertinent to point out that leptin signaling in the nucleus tractus solitarii increased renal sympathetic flow in normal rats but not in obese Zucker rats, indicating that intact LRs are essential for this vasoactive response.[11]

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In other investigations conducted both in normotensive and hypertensive rats,[7,8,13] 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 counterregulatory vasodilatory mechanisms.[8,14] *In vitro* studies have demonstrated a dose-dependent leptin-induced vasorelaxation in the aortic rings of Wistar-Kyoto rats,[14] which is mediated by nitric oxide (NO). An elevation in plasma NO with intravenous administration of synthetic leptin in normal rats has also been demonstrated.[15] In these studies, blockade of NO synthesis led to a leptin-induced enhancement of arterial blood pressure, whereas blockade of the sympathetic nervous system led to leptin-mediated reduction in blood pressure.[15] 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.[15] This concept requires further validation because the vasodilatory actions of leptin in other vascular beds have been found to be inconsistent.[16] However, in high-calorie-fed obese rats, it has been shown that acutely infused leptin was associated with a hypertensive effect, related, at least in part, to impaired vascular NO synthesis characteristic of obesity.[17]

CHRONIC HYPERLEPTINEMIA, LEPTIN RESISTANCE AND ARTERIAL BLOOD PRESSURE

Chronic hyperleptinemia conditions are characterized by sustained elevations in plasma levels of leptin above the normal range for a given species (ie, 5–10 ng/mL in humans).[3,5] Under these pathophysiological situations, such as obesity, the potential neutral effect of leptin on peripheral vascular resistance described previously may no longer prevail. 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,[18] although this stimulation may be attenuated with the progression of obesity.[19] From these findings, the concept of "selective leptin resistance" as a mechanism for the development of hypertension in obesity has emerged.[18] The precise factors behind this selectivity are yet to be fully defined but may involve alterations in the suppressor of cytokine signaling protein-3 signaling pathway or insulin receptor substrate-1 serine residue phosphorylation.[17,20]

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.[21] Similar increases in systolic blood pressure have been demonstrated in transgenic mice overexpressing leptin where the endogenous level of the hormone was elevated 20-fold.[22] In this regard, it is relevant to point out that hyperleptinemia may increase vascular smooth muscle cell proliferation,[23] an effect that could contribute to the development and/or perpetuation of hypertension. Moreover, mice with leptin deficiency (ob/ob) or with an LR 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.[18] In humans, evidence suggests a direct relationship between hyperleptinemia and hypertension in both men and women,[24] and this effect may be independent of body mass index and insulin resistance.

LEPTIN AND THE RENAL REGULATION OF SODIUM-VOLUME BALANCE

Previous studies have indicated that the LRb LR is localized in the renal medulla,[9] which suggests a functional role of this hormone in renal biology. Indeed, numerous investigations have demonstrated that acute administration of synthetic leptin in the rat produces a significant elevation in urinary sodium and water excretion.[8,25,26]

Villarreal et al[8] demonstrated that in normotensive rats, an intravenous bolus of leptin produced a robust 6- to 7-fold 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 also attenuated in obese Zucker rats.[8] 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.[3,5,27] Moreover, in a rat model of diet-induced obesity, studies by Patel et al[27] have shown markedly attenuated natriuretic and diuretic effects of synthetic leptin and reduced urinary excretion of NO These findings suggest that in obesity, alterations in leptin-induced renal NO synthesis 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 and with the renal generation of NO.[27] In the aggregate, these studies are consistent with the concept that obesity is associated with renal leptin resistance,[8,13,27] 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 treated long term with L-nitro-arginine methyl ester to inhibit NO synthesis.[28] L-nitro-arginine methyl ester-treated rats failed to produce significant natriuresis. However, there was a 2- to 3-fold elevation in sodium excretion induced by leptin with the restoration of NO by sodium nitroprusside,[28] 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 and Wojcicka,[29] 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.[28,29] Beltowski and Wojcicka[29] 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 altered.

The mechanisms for renal resistance to leptin in obesity and hypertension are thought to include receptor downregulation,[7,27] postreceptor signaling alterations,[7,27] excessive degradation of NO produced by oxidative stress[7,27] or increased activation of the efferent renal sympathetic nervous system leading to antinatriuresis.[26,30] Indeed, studies in hypertensive rats[26] that have examined this latter hypothesis using renal denervation indicate that ablation of the renal nerves restored the natriuretic actions of leptin. These findings suggest that the renal efferent sympathetic nervous system is an important counterregulatory mechanism impeding leptin-induced sodium excretion in hypertension, and perhaps also during obesity, which is similarly characterized by a heightened sympathetic nervous tone.[3,5,30] This information is germane to recent clinical trials indicating that renal denervation may be a useful therapeutic alternative in the management of resistant hypertension.[31]

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