Obesity-Hypertension: Emerging Concepts in Pathophysiology and Treatment

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ABSTRACT: The incidence and prevalence of obesity has risen markedly in the last decade, and this epidemic represents a serious health hazard with significant morbidity and mortality. Although hypertension is recognized as one of the most serious consequences of obesity, its pathophysiology remains incompletely understood. Contemporary research suggests that the recently discovered hormone leptin may represent a common link between these 2 pathologic conditions. Leptin is primarily synthesized and secreted by adipocytes. One of the major functions of this hormone is the control of energy balance. By binding to receptors in the hypothalamus, it reduces food intake and promotes elevation in temperature and energy expenditure. In addition, increasing evidence suggests that leptin, through both direct and indirect actions, may play an important role in cardiovascular and renal functions. Although the relevance of endogenous leptin needs further clarification for the control of renal sodium excretion and vascular tone, it appears to be a potential pressure and volume-regulating factor in normal situations. However, in conditions of chronic hyperleptinemia, such as obesity, leptin may function pathophysiologically for the development of hypertension as well as cardiac and renal disease. Thus, in addition to weight control, reduction of circulating leptin may confer cardiovascular and renal protective effects in patients with obesity-hypertension. **KEY INDEXING TERMS:** Leptin; Natriuresis; Endocannabinoid-1 receptor; Cardiac hypertrophy. **[Am J Med Sci 2007; 334(1):23–30.]**

The prevalence of obesity in the adult population of the United States has risen markedly from approximately 23% in the 1980s to greater than 30% in 2004, contributing in turn to the increased incidence of diabetes, hypertension, heart disease, and the metabolic syndrome.[1,2] This epidemic of obesity represents a serious health hazard with significant morbidity and mortality. Indeed, the data from the Framingham Heart Study suggests that 65% to 75% of the risk for hypertension is attributed to excess weight.[3] Historically, elevations in cardiac output, activation of the renin-angiotensin and sympathetic nervous systems, and changes in glomerular filtration rate have been considered important mechanisms relating obesity to vascular disease.[2,3] More recently, a novel and most promising area of research in obesity and hypertension that link these two pathologic conditions is the endocrinology of adipose tissue. In the last decade, it has become apparent that adipose tissue is a prolific organ that secretes several immunomodulators and bioactive molecules, including leptin, adiponectin, TNF-α, resistin, angiotensinogen, interleukin-6, plasminogen activator inhibitor–1, and C-reactive protein.[4] Of these various factors, leptin has emerged as an important hormone with potentially broad actions on several organ systems.[5–8]

Leptin is synthesized and secreted into the circulation primarily by adipocytes.[5–8] The first described major action of this hormone was on the hypothalamus to control body weight and fat deposition through its effects on appetite inhibition as well as stimulation of metabolic rate and thermogenesis.[5–8] However, over the last 5 to 10 years, 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.[5–10]

This review is focused on the potential role of leptin as a regulatory mechanism to produce significant cardiovascular and renal modifications in physiological and pathophysiological conditions, including obesity, hypertension, and the cardiometabolic syndrome. A number of excellent reviews related to other functions of leptin are available for the interested reader.[6,7,11]

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Leptin, Sympathetic Nervous System and Arterial Blood Pressure

It is now well established that leptin can activate the sympathetic nervous system both by local peripheral actions as well as centrally mediated effects on the hypothalamus.[11] Studies with direct intracerebral infusion of leptin have demonstrated a rise in lumbar and adipose tissue sympathetic nerve activity.[9] Also, intravenous administration of leptin has been shown to produce a slow, dose-dependent increase in sympathetic discharge from the renal nerves and the brown adipose tissue in the Sprague Dawley rat.[8] In this investigation, sympathoactivation was maintained even after transection of the renal nerve distal to the recording site indicating efferent rather than afferent nerve activation.[8,9] In a different study,[5] urinary norepinephrine excretion as an index of efferent renal sympathetic nerve activity was examined in groups of intact Sprague-Dawley rats and spontaneously hypertensive rats. In both strains of rats, acute administration of leptin was associated with significant elevations in urinary norepinephrine excretion, confirming the concept of leptin-induced activation of the renal efferent sympathetic nervous system.[8] In studies with direct local infusion of leptin into the cerebral ventricles of normal rats, Dunbar et al[9] reported that the intracerebral infusion of leptin leads to a slow increase of mean arterial pressure by approximately 10%. Consistent with this effect, the lumbar sympathetic nerve activity also increased progressively to a maximum of 10% during the infusion. Interestingly, renal flow remained unaltered despite the rise in the renal sympathetic nerve activity, and this may have been related to concurrent renal vasodilatation. Thus, in the context of available information, it is evident that intracerebral administration of the leptin acutely increases the sympathetic outflow similar to that observed with systemic administration of the hormone. However, the reported absence of arterial blood pressure elevation in the latter case raises the possibility of the simultaneous local activation of counter-regulatory vasodilatory mechanisms to help maintain systemic hemodynamics. In support of this concept, *in vitro* studies performed by Lembo et al,[12] in the aortic rings of Wistar-Kyoto rats, have demonstrated a dose dependent leptin-induced vasorelaxation, which could be largely abolished by either N^{*}-nitro-L-arginine methyl ester (L-NAME) administration or endothelial denudation, suggesting that nitric oxide (NO), and possibly endothelium-derived hyperpolarizing factor (EDHF), mediated the vasodilatory response.[12] Consistent with these findings, it has been previously demonstrated that leptin can promote NO production through stimulation of endothelial nitric oxide synthase.[13] Moreover, Fruhbeck[14] demonstrated a dose-dependent elevation in plasma NO produced by intravenous administration of synthetic leptin in normal rats. The effect required an intact leptin receptor, as it could not be elicited in the fa/fa rat model, a strain that lacks a functional leptin receptor.[14] Of major interest in this study, blockade of NO led to a leptin-induced enhancement of arterial blood pressure. Conversely, blockade of the sympathetic nervous system led to leptin mediated reduction in blood pressure.[14] Thus, it is possible to suggest that during acute systemic administration, the lack of effect on arterial blood pressure by leptin may represent a balanced action of vasodilatation primarily mediated by NO as well as vasoconstriction mediated primarily by the sympathetic nervous system, with a resultant neutral or minimal hemodynamic effect.[14] This postulate requires validation because the vasodilatory actions of leptin in different vascular beds have been found to be inconsistent[15,16] and because under certain conditions, leptin may promote other potent vasoconstrictive agents, including endothelin-1[17] and perhaps reactive oxygen species,[18] which may ultimately affect systemic hemodynamics.

Chronic Hyperleptinemia, Leptin Resistance, and Hypertension

In chronic hyperleptinemia conditions such as obesity, the potential neutral effect of leptin on the peripheral vascular resistance may not remain. Relevant to this concept, it is pertinent to point out that obesity is characterized by abnormal NO production and metabolism,[7] and this NO deficiency, in turn, could lead to the preponderance of leptin-induced vasoconstriction via the continuous and unopposed stimulation of the sympathetic nervous system. To this end, previous studies have indicated that the Agouti yellow obese mouse model is resistant to the satiety actions of leptin but not on the effects of leptin on enhancing the sympathetic nervous system.[11] From these latter findings, the concept of “selective leptin resistance” as a mechanism for the development of hypertension in obesity has emerged.[19] Accordingly, it has been suggested that in some obese states with hyperleptinemia, there is resistance to the satiety action of leptin, but the sympathetic overactivity leading to elevated blood pressure is preserved. The precise mechanism behind this selectivity remains yet to be fully defined.[11,19]

Independent of the possibility of selective leptin resistance in obesity, studies by Shek et al[20] in lean normal rats have demonstrated that chronic hyperleptinemia produced by continuous leptin administration for several days leads to a persistent elevation in mean arterial blood pressure of 10 to 15 mm Hg, and this hypertensive effect is rapidly reversed on the cessation of the hormone administration. In subsequent studies from the same laboratory in normal rats with chronic exogenous hyperleptinemia,