Obesity-Induced Hypertension
New Concepts From the Emerging Biology of Obesity

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Abstract—Obesity is associated with an increased risk of hypertension. In the past 5 years there have been dramatic advances into the genetic and neurobiological mechanisms of obesity with the discovery of leptin and novel neuropeptide pathways regulating appetite and metabolism. In this brief review, we argue that these mounting advances into the neurobiology of obesity have and will continue to provide new insights into the regulation of arterial pressure in obesity. We focus our comments on the sympathetic, vascular, and renal mechanisms of leptin and melanocortin receptor agonists and on the regulation of arterial pressure in rodent models of genetic obesity. We suggest 3 concepts. First, the effect of obesity on blood pressure may depend critically on the genetic-neurobiological mechanisms underlying the obesity. Second, obesity is not consistently associated with increased blood pressure, at least in rodent models. Third, the blood pressure response to obesity may be critically influenced by modifying alleles in the genetic background. (Hypertension. 1999;33[part II]:537-541.)

Key Words: leptin ■ melanocortins ■ sympathetic nervous system ■ agouti ■ rats, experimental ■ obesity

Obesity is a leading risk factor for chronic arterial hypertension.1,2 A prevailing concept has been that obesity-induced hypertension is secondary to insulin resistance and hyperinsulinemia3 despite the fact that experimental studies in humans4 and dogs5 have challenged this concept. Recently, interest has focused on the role of the kidney and renal sympathetic nerves in obesity-induced hypertension.5,6

Since the discovery of leptin about 5 years ago, knowledge regarding the genetic and neurobiological mechanisms of obesity has mushroomed. We review here the sympathetic and cardiovascular actions of leptin and melanocortin receptor agonists and the regulation of arterial pressure in murine genetic models of obesity associated with leptin deficiency or resistance and melanocortin-4 receptor antagonism. We argue that the escalating advances regarding the genetic and neurobiological mechanisms of obesity will provide new insights and concepts regarding the regulation of blood pressure in obesity. Two converging lines of evidence prompt this view: first, recent studies implicating renal sympathetic nerves in obesity-induced hypertension5 and, second, knowledge that the neurobiological mechanisms of obesity involve alterations in sympathetic regulation.7,8

Sympathetic and Cardiovascular Actions of Leptin
Leptin increases thermogenic metabolism in addition to inhibiting appetite.9,10 Sympathetic nerves have been implicated in the regulation of thermogenesis in brown adipose tissue in rodents. This prompted consideration of the influence of leptin on sympathetic nerves. Collins et al demonstrated that leptin increases norepinephrine turnover in brown adipose tissue, suggesting increased sympathetic activity.11 We subsequently studied effects of intravenous infusion of leptin on regional sympathetic nerve activity recorded directly with microelectrodes in Sprague-Dawley rats.12 Leptin increased sympathetic nerve activity to brown adipose activity, confirming the results of studies measuring norepinephrine turnover (Figure 1, which is from Reference 12).

Surprisingly, leptin also produced increases in sympathetic nerve activity to the kidney (Figure 1), adrenals, and hindlimb.12 The sympathetic effects of leptin occurred in the absence of changes in plasma glucose or insulin and had a different regional pattern than responses to insulin, suggesting that the sympathoexcitatory actions of leptin were independent of insulin. Surprisingly, despite the increase in overall sympathetic nerve activity, leptin did not increase arterial pressure.

Obese Zucker rats that have a mutation in the leptin receptor gene were resistant to the sympathoexcitatory actions of leptin, indicating that these actions of leptin were receptor mediated.12 The fact that leptin did not acutely increase arterial pressure despite sympathetic activation suggested that it may activate counterregulatory mechanisms that oppose a prohypertensive influence of sympathetic activation.

There are several potential depressor actions of leptin (Figure 2). First, Jackson and Li reported that acute infusion...
of human leptin into a renal artery in anesthetized rats produced an ipsilateral increase in sodium excretion and urine volume without significant effects on renal blood flow or glomerular filtration rate. An increase in renal sodium and water excretion has also been observed in normotensive rats during intravenous infusion of leptin. Thus, leptin may act on the renal tubules to promote natriuresis and diuresis, but, as discussed later, this effect may not occur with physiological or pathophysiological levels of leptin. Second, Sivitz et al have reported that leptin acutely increases insulin sensitivity before the opportunity for weight loss. This may have importance in the regulation of metabolism, but it seems doubtful that it would produce an acute depressor action. Third, Lembo and colleagues recently reported that leptin increases the production of endothelial nitric oxide in isolated blood vessels. It is tempting to speculate that an endothelial vasorelaxant effect of leptin may constitute a counterregulatory mechanism opposing a vasoconstrictor and pressor effect of leptin mediated via sympathoexcitation. With opposing increases in sympathetic activity and endothelial nitric oxide, leptin parallels the autonomic cardiovascular actions of insulin.

Leptin has very recently been found to promote angiogenesis. The mechanism and physiological significance of this action are unknown, but their study demonstrated that endothelial cells contain long forms of leptin receptors that are coupled to the JAX-STATS signaling pathway.

Although leptin possesses both depressor and pressor actions, the chronic effects of leptin appear to be predominantly pressor. Shek et al demonstrated that intravenous infusion of leptin at a dose that increased plasma leptin from 1 to 94 ng/mL for 12 days increased arterial pressure from 87 ± 1 to 93 ± 1 mm Hg (P < 0.05) in Sprague-Dawley rats (Figure 3). This increase occurred despite a decrease in food intake that would be expected to decrease pressure (adapted from Reference 18).

Ogawa et al recently reported that transgenic mice overexpressing mouse leptin developed elevations of arterial pressure. Parenthetically, leptin was overexpressed in the liver in this study, in contrast to the physiological state in which leptin is expressed in white adipose tissue. Plasma leptin levels in the transgenic mice were approximately 20-fold higher than in nontransgenic littermates. At 17 weeks of age, systolic blood pressure was 119 ± 2 mm Hg in transgenic mice versus 102 ± 3 mm Hg in nontransgenic mice (P < 0.05). There was no significant difference in heart rate between the 2 groups in this study. Interestingly, the elevation in systolic blood pressure in transgenic mice was abolished by intraperitoneal injection of an alpha receptor blocker that did not affect blood pressure in the nontransgenic littermates.

What is the significance of these observations with these experimental models (ie, chronic infusion of leptin and transgenic mice overexpressing leptin) to regulation of arterial pressure in models of spontaneous obesity with leptin?
deficiency or resistance? Does the absence of a pressor influence of leptin lower arterial pressure even in the presence of obesity? Alternatively, as conventional concepts would hold, does a pressor influence of obesity override the loss of a pressor influence of leptin? We have recently addressed these questions by measuring arterial pressure directly in ob (obese) mice with severe genetic leptin-deficiency–modulated obesity. Our observations indicate that when fed a low salt diet, mean arterial pressure is significantly lower in the obese leptin-deficient mice than in their lean controls (Shaffer et al, unpublished observations, 1998). Moreover, several groups including ours have demonstrated that when fed a low salt diet Koletsky obese leptin-resistant spontaneously hypertensive rats surprisingly have lower arterial pressure than their lean spontaneously hypertensive controls. Thus, evidence from several genetic models suggests that severe leptin deficiency or resistance lowers arterial pressure despite the presence of morbid obesity.

These findings from recent advances in the genetics and neuroendocrinology of obesity introduce 2 new concepts regarding the regulation of blood pressure in obesity. First, leptin produces physiologically significant sympathetic and cardiovascular effects. Second, obesity is not universally associated with an increase in arterial pressure in rodents. Indeed, rodent models of severe leptin-deficient or -resistant obesity surprisingly have lower arterial pressures than their lean controls when fed a low salt diet, presumably because of a loss of pressor actions of leptin.

The relevance of these concepts to arterial pressure in human obesity is uncertain. Unquestionably, most human obesity is not monogenetic and is not caused by mutations in the leptin or leptin receptor gene. These rare monogenetic forms of obesity are associated with dominantly inherited human obesity. Blood pressure response to obesity. For example, the hypertensive effects of obesity are less in Pima Indians, Hispanic Americans, and African Americans than it is in whites. Even among whites, not all obese individuals are hypertensive. For example, Alexander et al, from a study in which intra-arterial measurements of pressure were used, reported that of individuals with severe obesity, 5% to 10% had severe hypertension; about 50% had mild to moderate hypertension; and remarkably about 40% had normal arterial pressures. Rapp et al have emphasized that the influence of genes on blood pressure is greatly dependent on modifying alleles in the human forms of obesity caused by mutations in the leptin or leptin receptor gene. Two articles have just appeared reporting frame-shift mutations in the melanocortin-4 receptor gene. Agouti syndrome, although it seems likely that these will be identified, but 2 articles have just appeared reporting frame-shift mutations in the melanocortin-4 receptor gene associated with dominantly inherited human obesity.

We have recently observed that the stimulation of hypothalamic melanocortin-4 receptors by intracerebroventricular injection of MTII increases sympathetic nerve activity to brown adipose tissue and to the kidney in Sprague-Dawley rats. These responses were blocked by SHU9119. Interestingly, as with leptin these sympathetic responses to the activation of melanocortin-4 receptors were not accompanied by any appreciable increases in arterial pressure.

We also have recent evidence that agouti yellow obese mice have significantly higher arterial pressures than their lean controls when fed a low salt diet (Shaffer et al, unpublished observations, 1998). Agouti obese mice develop obesity that is milder than ob mice. Thus, whereas ob mice with severe obesity have lower arterial pressures than their lean controls, agouti obese mice with milder obesity have higher arterial pressures than their lean controls. The lean control mice in the ob and agouti experiments had the same genetic background. The mechanisms of the increased arterial pressure in the agouti obese mice are not known. Nevertheless, the findings of contrasting blood pressure effects of obesity in the ob and agouti mice suggest an important new concept, namely that the blood pressure effects of obesity may be critically (indeed qualitatively) influenced by the genetic/neurobiological mechanisms producing the obesity.

Role of Genetic Background in Blood Pressure Effects of Obesity

We have suggested above that the genetic-neurobiological mechanisms of obesity may critically influence the effect of obesity on blood pressure. In addition, there are clues that genetic factors may modify the influence of the blood pressure response to obesity. For example, the hypertensive effect of obesity is less in Pima Indians, Hispanic Americans, and African Americans than it is in whites. Even among whites, not all obese individuals are hypertensive. For example, Alexander et al, from a study in which intra-arterial measurements of pressure were used, reported that of individuals with severe obesity, 5% to 10% had severe hypertension; about 50% had mild to moderate hypertension; and remarkably about 40% had normal arterial pressures. Rapp et al have emphasized that the influence of genes on blood pressure is greatly dependent on modifying alleles in the human forms of obesity caused by mutations in the leptin or leptin receptor gene. Two articles have just appeared reporting frame-shift mutations in the melanocortin-4 receptor gene associated with dominantly inherited human obesity.

We are not aware of reports of human counterparts of the agouti syndrome, although it seems likely that these will be identified, but 2 articles have just appeared reporting frame-shift mutations in the melanocortin-4 receptor gene associated with dominantly inherited human obesity.

Blood pressures in the affected individuals were not reported.

Melanocortin-4 Receptors and Arterial Pressure in the Agouti Obesity Syndrome

The agouti yellow obesity syndrome in mice has recently been linked to a mutation in the agouti gene that leads to ubiquitous overexpression of agouti protein. The agouti protein binds to melanocortin-1 receptors and prevents alpha melanocyte-stimulating hormone (alpha MSH) from stimulating melanin synthesis and terminal pigmentation of the hair follicles, hence the yellow hair. The mechanism of agouti-related obesity was obscure until melanocortin-4 receptors were cloned and delineated in the hypothalamus and demonstrated to participate in the regulation of feeding. Subsequently, it was demonstrated that blockade of alpha MSH effects on melanocortin-4 receptors in the hypothalamus causes obesity in the agouti syndrome. Intracerebroventricular administration of the melanocortin-4 receptor antagonist MTII inhibits feeding; administration of the melanocortin antagonist SHU9119 enhances feeding. Furthermore, targeted disruption of the melanocortin-4 receptor recapitulates the critical features of the agouti obesity syndrome in mice. Boston et al have proposed that the proopiomelanocortin pathway (which is the primary source of the ligand for the melanocortin-4 receptor) and the leptin pathway are independent and additive, although other investigators have suggested that melanocortins may be part of the leptin signaling pathway.

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the genetic background. Coleman and Hummel demonstrated that modifying genes have a substantial effect on the phenotypic expression of the ob gene in the mouse. Thus, there is a strong rationale for the concept that modifying genes could importantly influence the blood pressure effects of obesity. We have recently obtained evidence that supports this concept. We measured arterial pressure directly and continuously using radiotelemetry in 2 strains of obese rats with mutations in the leptin receptor gene—the Zucker obese rat with the fa/fa mutation and the Koletsky obese spontaneously hypertensive rat with the fak/fak mutation. Both mutations result in a loss of function of the leptin receptor and the obese Zucker rats (like ob mice) had slightly lower pressures than their lean controls. During high salt diet, the Koletsky obese rats developed striking salt-sensitive increases in arterial pressure. The obese Zucker rats did not. These findings suggested that the effects of leptin-resistant obesity on blood pressure were quite different in these 2 strains. During low salt diet, obese Zucker rats had slightly higher pressures than their lean controls, whereas obese Koletsky rats (like ob mice) had slightly lower pressures than their lean controls. During high salt diet, the Koletsky obese rats developed striking salt-sensitive increases in arterial pressure. The obese Zucker rats did not. These findings suggested that the effects of leptin-resistant obesity on blood pressure in the 2 strains are influenced by differences in genetic background in the 2 strains. This concept merits further study.

Summary
Recent advances in the genetics and neurobiology of obesity have begun to contribute to our understanding of the mechanisms of obesity-induced hypertension. Our review has focused on 4 new concepts that have emanated from these advances. First, in addition to its effects on appetite and metabolism, leptin has sympathetic, vascular, and renal actions that can influence blood pressure. Second, the effect of obesity on blood pressure may depend critically on the genetic-neurobiological mechanisms underlying the obesity. Third, obesity is not always associated with increased blood pressure, at least in rodent models. Fourth, modifying alleles in the genetic background may critically influence the blood pressure response to obesity.

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