Hypertension Highlights

Obesity-Associated Hypertension
New Insights Into Mechanisms

Kamal Rahmouni, Marcelo L.G. Correia, William G. Haynes, Allyn L. Mark

Abstract—Obesity is strongly associated with hypertension and cardiovascular disease. Several central and peripheral abnormalities that can explain the development or maintenance of high arterial pressure in obesity have been identified. These include activation of the sympathetic nervous system and the renin-angiotensin–aldosterone system. Obesity is also associated with endothelial dysfunction and renal functional abnormalities that may play a role in the development of hypertension. The continuing discovery of mechanisms regulating appetite and metabolism is likely to lead to new therapies for obesity-induced hypertension. Better understanding of leptin signaling in the hypothalamus and the mechanisms of leptin resistance should facilitate therapeutic approaches to reverse the phenomenon of selective leptin resistance. Other hunger and satiety signals such as ghrelin and peptide YY are potentially attractive therapeutic strategies for treatment of obesity and its complications. These recent discoveries should lead to novel strategies for treatment of obesity and hypertension. (Hypertension. 2005;45:9-14.)

Key Words: hypertension, obesity ■ nervous system, sympathetic renal ■ vasculature ■ kidney

The increasing prevalence of obesity worldwide is a serious health hazard. This is particularly true for the United States, where ∼300 000 deaths each year are associated with being overweight and obese. Obese individuals are at increased risk for diabetes, hypertension, renal failure, and other cardiovascular diseases. Clinical and animal studies have confirmed a strong relationship between obesity and hypertension.1 Accumulating evidence points to visceral obesity as the most important risk factor for hypertension and cardiovascular disease.2 Recent work has identified several mechanisms that have therapeutic implications as potential causes of obesity-hypertension. In addition, to these advances, there has also been a revolution in our understanding of neuroendocrine mechanisms regulating appetite, metabolism, and adiposity since the discovery of leptin just >10 years ago. If, as we predict, these advances soon translate into safe and effective pharmacological treatment of obesity, this would also greatly impact the management of obesity-hypertension. Consequently, we briefly review some highlights on advances in understanding the pathophysiology of obesity in addition to highlights on obesity-induced hypertension.

New Developments in Neurobiology of Obesity

The identification of leptin represents the most significant breakthrough in obesity research because it helped unravel the architecture of neuroendocrine circuitry that controls appetite and energy homeostasis. Leptin is an adipocyte-derived hormone that acts in the hypothalamus to regulate appetite and energy expenditure. Recently, increasing attention has been dedicated to leptin transduction mechanisms (Figure 1). The leptin receptor is a single transmembrane protein belonging to the cytokine-receptor superfamily known to signal via the janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway. This pathway is essential for regulation of energy homeostasis by leptin but not for the control of reproductive function, growth, or glucose homeostasis by leptin. Specific disruption of the JAK/STAT pathway in mice results in obesity and hyperphagia attributable to the impaired effect of leptin on the melanocortin system.3 However, these mice remain fertile and less diabetic than the db/db mice lacking the long form of the leptin receptor, perhaps because of the preserved activity of hypothalamic AMPK, and activation of this pathway attenuates the feeding and weight-reducing actions of leptin.6 Thus, the intracellular signaling mechanisms triggered by leptin appear more complicated than originally thought, with several downstream cascades involved in the actions of leptin.

The excitement that followed leptin discovery was soon modulated by the realization that obesity is associated with hyperleptinemia, defining a state of leptin resistance. Suppressor of cytokine signaling (SOCS) proteins have emerged recently as 1 potential mechanism of leptin resistance. In the...
hypothalamus, SOCS-3 negatively regulates leptin receptor signaling by inhibiting JAK tyrosine kinase activity. Also, obesity is associated with preserved ability of leptin to activate hypothalamic SOCS-3.\(^7\) In addition, SOCS-3 haploinsufficiency or brain SOCS-3 deficiency increases leptin sensitivity and protects mice against development of obesity induced by high-fat diet.\(^8,9\) Thus, SOCS-3 appears an important mechanism of leptin resistance, suggesting that targeting this system may offer a novel therapeutic approach for treatment of obesity and associated diseases. Protein tyrosine phosphatase 1b (PTP1b) is another negative regulator of leptin signaling that might contribute to leptin resistance. Mice lacking PTP1b exhibit enhanced leptin sensitivity and are protected from diet-induced obesity.\(^10,11\) Inhibition of this pathway is considered a potential target for antiobesity drug and represents an active front of research.\(^12\)

Several other peripheral signals that regulate appetite and energy homeostasis have been identified in recent years. Ghrelin is a circulating hormone produced principally by the stomach but also by the hypothalamic neurons.\(^13\) This hormone is a potent stimulant of appetite and increases adiposity in rodents, but surprisingly, knockout of ghrelin does not affect food intake in mice.\(^14\) Plasma levels of ghrelin increase before meals and during fasting and fall shortly after meals. Although the effect of ghrelin on appetite appears mediated by vagal afferents originating in the gastrointestinal tract, this hormone may also directly modulate the neuroendocrine network in the hypothalamic arcuate nucleus.\(^13\) Although obesity is generally associated with decreased circulating ghrelin, elevated plasma levels of ghrelin in some forms of obesity, such as in individuals with Prader Willi syndrome,\(^15\) suggest a role for this hormone in the etiology of at least some forms of human obesity and the possibility of using a ghrelin receptor antagonist for treatment of some forms of the disease.

Peptide YY (PYY) is a gut hormone released into the circulation after a meal that seems to influence the central mechanisms that control metabolism. This peptide suppresses appetite presumably through its action in the arcuate nucleus. Circulating levels of PYY3-36, which is considered the main form of PYY, have been found lower in obese than in lean individuals.\(^16\) More importantly, infusion of PYY3-36 reduces food consumption of obese subjects.\(^16\) These data suggest that PYY is involved in the pathophysiology of obesity and that administration of PYY may be a valuable therapeutic strategy for treatment of obesity.

Adiponectin is an abundant protein produced by adipose tissue that modulates insulin sensitivity by its action in liver and muscle. The recent demonstration that adiponectin enters the cerebrospinal fluid to act centrally to regulate body weight extends the role of this hormone beyond its peripheral action on glucose metabolism.\(^17\) Interestingly, adiponectin appears to induce weight loss through an increase in energy expenditure because food intake is not affected by either central or systemic adiponectin.\(^17\) Thus, reduced plasma adiponectin in obese subjects may be an important pathophysiological mechanism.

Clearly, in recent years, real progress has been made in understanding the molecular and physiological process that regulates energy homeostasis. However, how the different signaling systems are integrated in the centers of command remains unknown. Additionally, the role and significance of peripheral action of hormones such as leptin in health and diseases deserve more attention. According to Unger, the primary role of leptin is to protect the accumulation of lipids in nonadipose tissues such as the heart, liver, and skeletal muscle.\(^18\) The loss of leptin action associated with obesity and hyperleptinemia may lead to lipotoxicity of nonadipose tissues with adverse cardiovascular consequences.
Sympathetic Nervous System Activation in Obesity

Overactivity of the sympathetic nervous system is a common feature of obesity in humans and in animal models. Recent work has highlighted the key role of increased sympathetic activity in obesity-hypertension. Long-term sympathoactivation could raise arterial pressure by causing peripheral vasoconstriction and by increasing renal tubular sodium reabsorption. Study of regional sympathetic nerve activity in obese humans using norepinephrine spillover has demonstrated that obesity is associated with increased sympathetic activity to the kidney, a key organ of the cardiovascular homeostasis. Elevated renal sympathetic nerve activity was also reported in animal models of dietary obesity. Several factors may account for the increased sympathetic outflow associated with obesity (Figure 2).

Role of Leptin

Recent evidence indicates that leptin may represent a link between excess adiposity and increased cardiovascular sympathetic activity. Besides its effect on appetite and metabolism, leptin acts in the hypothalamus to increase blood pressure through activation of the sympathetic nervous system. Elevated renal sympathetic nerve activity was also reported in animal models of dietary obesity. Several factors may account for the increased sympathetic outflow associated with obesity (Figure 2).

Figure 2. Summary of mechanisms and hormonal systems involved in obesity-associated hypertension. FFA indicates free fatty acids; SNA, sympathetic nerve activity.

leptin resistance. Interestingly, high circulating levels of leptin are reported to explain much of the increase in renal sympathetic tone observed in obese human subjects. Collectively, these data suggest that leptin may be an important cause of cardiovascular sympathoactivation associated with obesity in humans. The mechanisms of selective leptin resistance are just beginning to be unraveled. In obese mice, the inability of leptin to activate leptin-signaling pathways such as STAT3 proteins appears to be restricted to the arcuate nucleus of the hypothalamus. Leptin-induced increases in renal sympathetic activity and blood pressure are mediated by the ventromedial and dorsomedial hypothalamus. Therefore, selectivity in leptin resistance may be attributable to the inability of leptin to activate downstream signaling pathways in the arcuate nucleus but preservation of leptin action in other cardiovascular-related hypothalamic areas.

The selectivity in leptin resistance may also relate to the divergent signaling pathways downstream from the leptin receptor. Phosphoinositol-3 kinase is an important intracellular signaling pathway in the control of renal sympathetic outflow by leptin because renal sympathoactivation to leptin is prevented by inhibition of this enzyme (Figure 1). The melanocortin system is also an essential downstream mediator of leptin action on renal sympathetic outflow and blood pressure. In contrast, we have preliminary evidence that mitogen-activated protein kinase regulates sympathetic activity to thermogenic brown adipose tissue but not to the kidney (K. Rahmouni, CD Sigmund, WG Haynes, AL Mark, unpublished data, 2004). This may represent a molecular substrate for selective leptin resistance. These data indicate that different pathways are selectively engaged in leptin regulation of different physiological processes.
Other Mechanisms
Hyperinsulinemia may also play a role in overactivity of the sympathetic nervous system associated with obesity. In rats, insulin, like leptin, causes sympathoactivation to different tissues, including the kidney. The ability of insulin to stimulate renal sympathetic outflow is preserved in obese animals such as the db/db mice, despite the severe insulin resistance that characterizes this condition. Despite these findings, a role for hyperinsulinemia and insulin resistance in obesity-associated hypertension remains controversial. For instance, treatments such as furosemide combined with low salt or prazosin prevent hypertension in high-fat-fed dogs without preventing development of insulin resistance. On the other hand, improvement of insulin resistance with aspirin therapy did not prevent development of hypertension in these dogs. These data suggest that neither insulin resistance nor hyperinsulinemia is responsible for obesity-associated hypertension in dogs.

High circulating levels of free fatty acids in obese subjects appear to participate in activation of the sympathetic nervous system. The increased release of free fatty acids into the portal vein from lipolysis in visceral fat depots with increasing amounts of fat could therefore explain the strong association between visceral obesity and increased sympathetic nerve outflow and blood pressure.

Longitudinal and cross-sectional studies indicate a possible role of some of newly discovered peptides in cardiovascular risks associated with obesity. Low plasma ghrelin is associated with hypertension. Similarly, plasma adiponectin concentration is significantly lower in men with hypertension than in normotensive men and is negatively correlated with blood pressure in subjects without hypertension. These data suggest that low ghrelin and adiponectin may be independent risk factors for hypertension. Ghrelin and adiponectin may participate in regulation of blood pressure and cardiovascular function through different mechanisms, including a modulation of sympathetic nervous system. For instance, ghrelin has been shown to act in the nucleus of the solitary tract to suppress renal sympathetic activity and to decrease arterial pressure. The potential role of ghrelin and adiponectin in obesity-associated hypertension remains controversial because of the limited available data on the interaction between these peptides and arterial pressure.

Activation of the Renin-Angiotensin System in Obesity
There is much evidence in support of an activation of the renin-angiotensin system (RAS) in obesity. This has led to the notion that blockade of RAS might be a beneficial strategy for management of hypertension associated with obesity.

Adipose RAS has received much attention recently because accumulated experimental evidence has shown its involvement in the pathophysiology of obesity-hypertension. In mice, adipocyte-derived angiotensinogen can act locally to affect adipocyte growth and differentiation and can also be secreted into the bloodstream, contributing to the circulating pool of angiotensinogen. This demonstration that angiotensinogen produced by the adipose tissue may be released in the bloodstream suggests that the high circulating levels of angiotensinogen associated with obesity may be attributable in part to increased fat mass. We found recently that mice with obesity induced by high-fat diet exhibited greater angiotensinogen gene expression in intra-abdominal fat but not in other fat depots or nonadipose tissues. Interestingly, increased production of angiotensinogen by intra-abdominal fat appears to explain the high circulating levels of this peptide observed in dietary obesity.

Activation of adipose RAS is also involved in development of high blood pressure in a model of visceral obesity. This model consists of transgenic mice overexpressing an enzyme, 11β-hydroxysteroid dehydrogenase type 1, in fat tissue. These transgenic mice show an increase in enzyme activity similar to that seen in obese humans and replicate visceral fat accumulation and high blood pressure. The hypertension observed in this model was abolished by selective angiotensin II receptor blockade. These data establish adipose RAS as an important pathophysiological mechanism for obesity-hypertension. This activation of adipose RAS may also explain the link between excessive visceral fat and cardiovascular diseases.

Benefits of Aldosterone Antagonism in Obesity-Hypertension
Aldosterone has been implicated in development of hypertension associated with obesity. Plasma aldosterone levels are elevated in some obese hypertensives, especially patients with visceral obesity. The mechanisms by which excess fat could increase aldosterone are unknown, but it may relate to the production by adipocytes of potent mineralocorticoid-releasing factors or to the ability of oxidized derivatives of linoleic acid to induce aldosterone synthesis. The involvement of aldosterone in obesity-associated hypertension was demonstrated by blockade of mineralocorticoid receptors with the specific antagonist eplerenone, which inhibited development of high blood pressure in the high-fat-fed dogs without affecting the weight gain of these animals. These results indicate that aldosterone may play a significant role in development of obesity-hypertension. Aldosterone can raise blood pressure in obesity through an action on mineralocorticoid receptors located in different tissues, including the kidney, vasculature, and brain.

The above evidence that blocking the sympathetic nervous system, the RAS, or the aldosterone receptors prevents or greatly attenuates obesity-induced hypertension raises a question or caveat. To wit, if each of these systems is critically involved in the causation of obesity-induced hypertension, how is it that blocking only 1 of these systems reverses or attenuates the hypertension? What is the significance of this? Does it imply that the 3 systems are interactive in their causation of obesity-induced hypertension? Or does it imply that 1 of the 3 systems plays an essential facilitative role but not necessarily a causative role?

Our current reading of the literature is that despite the above insight into mechanisms and treatment of experimental obesity-induced hypertension, there is yet no evidence that 1 specific therapy has been proven superior to others in the treatment of obesity-induced hypertension in humans.
Vascular Alterations

Endothelial dysfunction such as decreased NO responsiveness is a common abnormality in obesity. Damage to the endothelium is an important risk factor for cardiovascular diseases because it leads to structural changes, such as thickening of the intima and media of the vessel wall. Although mechanisms linking obesity with endothelial dysfunction have not yet been fully clarified, several factors may contribute to this abnormality.

Increased vascular production of endothelin-1 in hypertensive patients with increased body mass has been suggested as a potential mechanism for endothelial dysfunction. Blockade of the endothelin A (ETₐ) receptors induces significant vasodilatation in overweight and obese humans but not in lean hypertensive subjects. This indicates a selective enhancement of ETₐ receptor–dependent vasoconstrictor tone in obese hypertensive patients. In contrast, da Silva et al found that long-term blockade of ETₐ receptors reduced arterial pressure similarly in a rat model of visceral obesity and in control normotensive animals, suggesting that endothelin-1 does not contribute to the elevation of arterial pressure in this model of central obesity. These data may also indicate that endothelin antagonism alone is not sufficient to restore the impaired NO bioavailability in obesity. In contrast, treatment with pioglitazone (an agonist of peroxisome proliferator–activated receptor-γ) prevented development of high arterial pressure in diet-induced obese rats by reducing free-radical production and by increasing NO production/availability.

A potential role for perivascular fat in the vascular alterations associated with obesity has been proposed. Accumulating evidence suggests that adipose tissue surrounding blood vessels modulates vascular tone and reactivity. Verhoren et al have shown recently that periadventitial fat attenuates the contractile response of rat mesenteric arteries to several agents, including serotonin, phenylephrine, and endothelin-1. The vasodilatory effect of adipose tissue is purportedly mediated by an adipocyte-derived relaxing factor (ADRF), analogous to endothelium-derived relaxing factor. Future studies are required to determine the identity of ADRF and also to examine whether the periadventitial adipose tissue has a pathophysiological role in the vascular dysfunction associated with obesity.

Abnormalities of Renal Function

Several alterations in renal structure and function have been associated with obesity. Activation of the sympathetic nervous system and the RAS as well as increases in plasma aldosterone levels can cause abnormal sodium retention and raise arterial pressure (Figure 2). Compression of the kidney by the surrounding fat and the renal structural changes associated with obesity may also play a role in the renal damage associated with obesity. Other intrarenal changes that accompany obesity could also promote hypertension. For instance, high-fat–fed rats exhibit reduced activity of arachidonic acid pathways in renal tubular sites. Given the importance of arachidonic acid metabolites in inhibition of ion transport along the nephron, Wang et al speculate that downregulation of arachidonic acid pathways in obesity may be involved in the increased sodium reabsorption thereby promoting blood pressure elevation.

In addition to its effect on sympathetic nervous system to the kidney, leptin may act directly on the kidney to increase oxidative stress, as evidenced by increased plasma concentration and urinary excretion of isoprostanes, increased level of lipid peroxidation products in renal homogenates, and reduced renal aconitase activity in rats treated with leptin.

References


Acknowledgments

The authors’ research is supported by grants HL44546 and HL14388 from the National Heart, Lung, and Blood Institute, and RR00059 from the National Center for Research Resources General Clinical Research Centers program.
Hypertension


5. Howard JK, Cave BJ, Oksanen LJ, Tzameli I, Bjorbaek C, Flier JS. Intracellular mechs with overlapping physiological and intracellular signaling capa-


8. Vaz M, Jennings G, Turner A, Cox H, Lambert G, Esler M. Regional sympathetic nerve activity with overlapping physiological and intracellular signaling capa-


24. Alvarez GE, Beske SD, Ballard TP, Davy KP. Sympathetic neural activ-


30. Alvarez GE, Beske SD, Ballard TP, Davy KP. Sympathetic neural activ-