Mechanisms of Abnormal Renal Sodium Handling in Obesity Hypertension

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Obesity-induced hypertension, like all forms of experimental and human hypertension studied thus far, is associated with renal dysfunction characterized by the resetting of pressure natriuresis. In obese subjects, this resetting is primarily a result of increased renal tubular reabsorption as glomerular filtration rate and renal blood flow are markedly elevated. Obesity activates the sympathetic nervous and renin-angiotensin systems, and causes insulin resistance and hyperinsulinemia, all of which have been postulated to increase tubular reabsorption and raise blood pressure. In humans and dogs, chronic hyperinsulinemia, comparable to that found in obesity, does not cause hypertension even in the presence of insulin resistance. Activation of the sympathetic nervous system appears to be important in obesity, as chronic adrenergic blockade or renal denervation greatly ameliorates the hypertension associated with weight gain. Resetting of pressure natriuresis in obesity may also be attributable to altered intrarenal forces caused by histologic changes in the renal medulla that may compress the loops of Henle and vasa recta, increase tubular sodium reabsorption, and activate the renin-angiotensin system. The quantitative importance of these intrarenal changes and their interrelationship with neurohumoral activation in obesity is an important area for further investigation. Am J Hypertens 1997;10:49S–55S © 1997 American Journal of Hypertension, Ltd.

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Excess weight appears to contribute to increased blood pressure in a large proportion of essential hypertensive patients, and may be responsible for much of the increase in blood pressure that occurs in aging in industrialized countries; in populations in which weight gain does not occur with aging, there appears to be little or no increase in blood pressure. Currently, more than 30% of the adult population in the United States is markedly overweight, with a body mass index (BMI) >27 kg/m². In some segments of the population, such as elderly African-American women, the prevalence of obesity may be as high as 70% to 80%.3 One of the most important effects of excess weight gain is increased blood pressure. Population studies show that blood pressure is highly correlated to BMI in normotensive and hypertensive subjects.4–6 The importance of weight gain in causing hypertension is reinforced by experimental studies in animals and humans showing that weight gain raises blood pressure7,8 and weight loss reduces blood pressure in normotensive and hypertensive subjects, even when sodium intake is maintained relatively constant.9

OBESITY CAUSES ABNORMAL RENAL PRESSURE NATRIURESIS

Theoretical and experimental studies have shown that in all forms of hypertension, including obesity hyper-
tension, there is an abnormality of kidney function characterized by a hypertensive shift of renal pressure natriuresis.\textsuperscript{10,11} When obesity is induced by feeding a high fat diet, there is marked sodium retention and expansion of extracellular fluid volume; moreover, the sodium retention and volume expansion exceed that required for the additional adipose tissue associated with weight gain.\textsuperscript{8}

Rocchini et al\textsuperscript{12} found that there was a reduced slope of pressure natriuresis in obese adolescents and that this change was reversible with weight loss (Figure 1). The decreased slope of pressure natriuresis caused blood pressure to be very salt sensitive, with low salt intake greatly ameliorating the hypertension in obese subjects. Other studies in abdominally obese adults less than 45 years old, however, indicate that blood pressure may not be sensitive to salt intake.\textsuperscript{13} Granger and Nakamura\textsuperscript{14} also reported that obesity hypertension in dogs was not salt sensitive and was characterized by a parallel shift, rather than a decreased slope, of pressure natriuresis. The reasons for these differences among obese adolescents and obese adults and dogs is unclear. It seems likely that when obesity is maintained over a lifetime and there is loss of functional kidney mass and decreased slope of pressure natriuresis associated with intrarenal injury that blood pressure may become increasingly salt sensitive. Regardless of the precise characteristics of pressure natriuresis, it is clear that obesity hypertension is invariably associated with abnormal pressure natriuresis, which is shifted toward higher blood pressures.

The impaired pressure natriuresis in obesity could be caused theoretically either by reduced glomerular filtration rate (GFR) or increased renal tubular reabsorption. Studies in dogs and humans, however, indicate that obesity is usually associated with renal vasoconstriction, rather than vasodilation, because there are increases in renal plasma flow, GFR, and filtered sodium load in obese compared to lean subjects.\textsuperscript{8,15} Therefore, sodium retention and altered pressure natriuresis appears to be caused mainly by increased tubular sodium reabsorption (Figure 2).\textsuperscript{8} Moreover, the increased tubular reabsorption occurs at a site distal to the proximal tubules.\textsuperscript{16}

The causes of increased renal tubular reabsorption in obesity have not been fully elucidated, although a role has been suggested for hyperinsulinemia and insulin resistance, activation of the renin-angiotensin system (RAS), and increased sympathetic nervous system activity.\textsuperscript{8,17–20} Recent studies in our laboratory suggest that altered intrarenal physical forces may also be important in causing sodium retention and hypertension in obesity.\textsuperscript{8,16}

**OBESITY CAUSES INSULIN RESISTANCE AND HYPERINSULINEMIA**

Obesity is associated with fasting hyperinsulinemia as well as an exaggerated insulin response to a glucose load or a carbohydrate meal.\textsuperscript{17,20} The increased circulating insulin concentrations are believed to occur as a compensation for an impairment of the metabolic actions of insulin, a condition often referred to as insulin resistance. Hyperinsulinemia, in turn, serves to maintain plasma glucose concentration relatively constant in the face of impaired insulin action.

The concept that insulin resistance and compensatory hyperinsulinemia might mediate obesity-induced hypertension was suggested on the basis of two main lines of evidence: 1) there is a correlation between the blood pressure and plasma insulin concentration in obese hypertensive subjects\textsuperscript{17,20,21} and 2) insulin has been shown in acute studies to have multiple effects on the kidneys and sympathetic nervous system that, if sustained, could lead to altered renal function and increased blood pressure.\textsuperscript{17,18,22} However, there is increasing evidence that insulin also has effects on the cardiovascular system that could tend to reduce blood pressure.\textsuperscript{23,24}

Previously, we have discussed in detail the insulin hypothesis of hypertension.\textsuperscript{24–26} Therefore, only a brief discussion of the key evidence concerning this hypothesis will be presented. Currently there is little direct support for a key role of insulin resistance or hyperinsulinemia in causing obesity hypertension. Short-term studies in humans have found little or no change in blood pressure with marked hyperinsulinemia, although insulin has been shown to cause mild sodium retention and increased sympathetic activity.\textsuperscript{23,27} Although the effects of chronic hyperinsulin-
in rats. The increased blood pressure, however, was not associated with sodium retention or activation of the RAS, in contrast to obesity hypertension in which there is marked sodium retention and increased plasma renin activity. Thus, insulin raises blood pressure in rats through mechanisms that may be very different from those that cause obesity hypertension in humans. Moreover, it is not clear whether the findings in rats are relevant to human hypertension or whether there are pathophysiologic conditions in humans in which the hypertensive effect of insulin may be uncovered. Currently most of the available evidence indicates that hyperinsulinemia cannot explain the altered pressure natriuresis and hypertension associated with obesity.

**OBESITY ACTIVATES THE RENIN-ANGIOTENSIN SYSTEM**

In most obese subjects, plasma renin activity is elevated. Tuck et al. found increased plasma renin activity and increased aldosterone concentration in obese compared with lean subjects, and we have also recently reported that plasma renin activity increased more than twofold as dogs become obese, despite marked sodium retention and increased extracellular fluid volume. Therefore, one potential cause of increased tubular reabsorption, altered pressure natriuresis, and hypertension in obesity is activation of the RAS.

Robles et al. recently reported that blockade of angiotensin II (Ang II) formation markedly attenuated the hypertension associated with a high fat diet in dogs. In these studies, dogs were kept on a high fat diet for 12 weeks either with or without converting enzyme inhibition. The converting enzyme inhibitor-treated group had significantly lower blood pressures after the third week on the high fat diet, and also had lower levels of plasma norepinephrine and fasting blood glucose than the nontreated group. These observations suggest that increased Ang II formation may contribute, in part, to obesity-induced hypertension.

**OBESITY ACTIVATES THE SYMPATHETIC NERVOUS SYSTEM**

Increased caloric intake stimulates the sympathetic nervous system in both experimental animals and humans, whereas caloric restriction suppresses sympathetic activity as assessed by various indirect methods such as norepinephrine turnover in peripheral tissues. Basal plasma norepinephrine levels and the norepinephrine responses to stimuli such as upright posture and isometric hand grip are also elevated in obese compared with lean subjects.

We reported that acute ganglionic blockade caused a greater decrease in blood pressure in obese compared with lean dogs, suggesting increased dependence of blood pressure on sympathetic control in

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**FIGURE 2.** Effects of 5 weeks of a high fat diet on cumulative sodium balance, sodium reabsorption, and glomerular filtration rate. Redrawn from data in Hall et al.
obesity. In addition, the increased heart rate associated with obesity appeared to be related mainly to inhibition of parasympathetic activity. Thus, obesity may increase sympathetic activity as well as decrease parasympathetic activity.

In further studies, we found that combined α- and β-adrenergic blockade greatly ameliorated the development of obesity hypertension. Moreover, renal denervation markedly attenuated sodium retention and hypertension associated with obesity. Using a split-bladder preparation combined with unilateral renal denervation, we found that innervated kidneys retained almost twice as much sodium as denervated kidneys during 5 weeks on a high fat diet. Bilateral renal denervation also markedly blunted the development of hypertension associated with obesity in dogs (Figure 3). These observations suggest that sodium retention and impaired renal pressure natriuresis in obesity is dependent, in part, on increased renal sympathetic activity.

The mechanisms by which obesity activates the sympathetic nervous system are still unknown. Our previous observations suggest that obesity is associated with marked increases in intrarenal pressures that could, theoretically, stimulate renal sympathetic afferents and activate central pressor mechanisms. Recently we tested this possibility by determining whether selective removal of renal effferent nerves, while leaving renal afferent fibers intact, would attenuate obesity hypertension in dogs. This was accomplished by dorsal root rhizotomy between T-10 and L-2 segments, which convey the renal afferent nerves. Our results indicated that renal afferent denervation did not blunt the sodium retention or hypertension associated with feeding a high fat diet for 5 weeks. Thus, although activation of renal efferent sympathetic fibers contributes to sodium retention and hypertension, these changes do not appear to be initiated through afferent pathways originating in the kidneys.

Although insulin has been suggested to stimulate sympathetic activity, even in the absence of hypoglycemia, we have shown that chronic insulin infusion into the cerebral circulation of dogs did not elevate arterial pressure. This is consistent with our previous finding that hyperinsulinemia may not be the primary cause of increased sympathetic activity or hypertension associated with obesity.

Another peptide that has been suggested to contribute to sympathetic activation in obesity is leptin, the product of the “obese gene” that is defective in genetically obese (ob/ob) mice, causing decreased production of leptin. In contrast, other genetic models of obesity, such as the db/db mouse, which has a defect in the leptin receptor expressed in the hypothalamus, have increased production of leptin. Likewise, obese humans have increased plasma levels of leptin.

The finding that animals deficient in leptin production or leptin receptors also have decreased metabolic activity and hypothermia is consistent with the possibility that leptin may interact with its hypothalamic receptors to reduce food consumption and activate the sympathetic nervous system. Further studies are necessary to determine whether increased circulating leptin, at levels comparable to those found in obesity, can cause chronic activation of the sympathetic nervous system and hypertension. However, the fact that leptin has recently been shown to decrease renal tubular reabsorption suggests that the direct effects on the kidney may increase, rather than decrease, sodium and water excretion.

Another potential pathway by which obesity may activate the sympathetic nervous system is through increased levels of fatty acids, which could act directly on the vasomotor centers of the brain or indirectly through afferent pathways originating in the liver. Infusion of the free fatty acid oleate into the portal vein...
resulted in increases in arterial pressure, heart rate, and plasma levels of norepinephrine and epinephrine. However, oleate infusion into the portal vein also raised corticosterone levels, suggesting a stress response that could be attributable to a toxic effect of sodium oleate, rather than a physiologic effect. Further studies are needed to determine the importance of increased fatty acid levels, acting directly on the brain or through other reflex mechanisms, in contributing to increased sympathetic activity and to the development of obesity hypertension. Regardless of the causes of increased sympathetic activity, it is clear that this mechanism plays a major role in contributing to the sodium and water retention, altered pressure natriuresis, and hemodynamic changes associated with obesity.

**OBESITY ALTERS INTRARENAL PHYSICAL FORCES**

Besides activation of neurohumoral systems, obesity also causes changes in intrarenal physical forces that may contribute to increased tubular reabsorption and sodium retention. Observations of kidneys from obese dogs reveal striking histologic changes in the inner renal medulla, including large increases in the number of interstitial cells and extracellular matrix between the tubules that could act as a compressive force on the tubules and vasa recta. The matrix between the tubules appears to be a proteoglycan, because it stains with Alcian blue and periodic acid-Schiff, but not with oil-red O. Also, total glycosaminoglycan content was elevated in the inner renal medulla of obese compared with lean dogs. One glycosaminoglycan that is markedly increased in the inner medulla is hyaluronate, but there may also be other matrix components that are overexpressed in the kidneys of obese subjects.

The possibility that these changes observed in obese dogs are relevant to the pathophysiology of human obesity is supported by preliminary observations indicating that obese humans exhibit similar histologic changes in their renal medulla.

How are these changes in renal medullary histology and biochemistry linked with hypertension? Because the kidney is surrounded by a tight capsule with a low compliance, increased matrix deposition or increased cellularity between the tubules would tend to increase renal interstitial tissue fluid hydrostatic pressure and cause compression of the renal medullary structures, including the tubules and vasa recta. In kidneys of obese dogs, renal interstitial fluid hydrostatic pressure was elevated to approximately 19 mm Hg, compared to only 9 to 10 mm Hg in normal dogs. Although small increases in renal interstitial fluid pressure tend to inhibit tubular reabsorption, large increases in fluid and solid tissue pressures would tend to reduce medullary blood flow and cause tubular compression, slowing the tubular flow rate and increasing fractional tubular reabsorption. It seems likely that tubular compression would be especially important in the loop of Henle, which is very distensible and normally has a luminal hydrostatic pressure of only about 10 to 12 mm Hg. Thus, a compensatory rise in tubular hydrostatic pressure would be necessary to maintain tubular patency and normal urine flow.

One mechanism by which restoration of tubular flow could occur is through increased proximal delivery of fluid, due to increased GFR or decreased proximal tubular reabsorption secondary to increased arterial pressure and intrarenal compensations. A possible explanation for the renal vasodilation and GFR observed in obesity that would also explain the increase in plasma renin activity is that altered renal medullary histology, mainly by increasing tubular reabsorption in the loop of Henle, could activate a macula densa feedback mechanism that would cause renal vasodilation and stimulation of renin secretion. However, this hypothesis must be considered speculative until renal tubular pressures and macula densa feedback function have been evaluated in obesity hypertension.

To summarize, weight gain causes parallel increases in blood pressure in experimental animals and in humans, and weight loss produces corresponding decreases in arterial pressure. Recent studies indicate that the initiation of obesity hypertension may be due to abnormal renal sodium and water handling, char-

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**FIGURE 4.** Postulated mechanisms by which altered renal medullary histology and activation of the sympathetic and renin-angiotensin systems may mediate obesity hypertension. Although insulin resistance and hyperinsulinemia occur in obesity, these changes do not appear to contribute to increased blood pressure.
characterized by a shift of pressure natriuresis toward higher blood pressures. The shift of pressure natriuresis is probably not due to hyperinsulinemia or insulin resistance, but may be due to activation of the RAS and sympathetic nervous system, as well as altered intrarenal physical forces that compress the renal medulla (Figure 4). Further studies are needed to more fully elucidate the quantitative importance of these mechanisms and the factors that stimulate these changes as obesity develops. Because the prevalence of obesity is increasing in most industrialized countries, unraveling the mechanisms by which weight gain raises blood pressure will likely provide a better understanding of human essential hypertension.

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