Renal and Cardiovascular Mechanisms of Hypertension in Obesity

John E. Hall

Abstract In all forms of hypertension, including human essential hypertension, pressure natriuresis is reset to higher blood pressures. Because human essential hypertension is a heterogeneous disease, it is likely that there are multiple neurohumoral and intrarenal causes of abnormal pressure natriuresis and increased blood pressure. Weight gain is recognized to be an important contributor to essential hypertension, although the mechanisms that link obesity with altered renal function and high blood pressure have not been fully elucidated. In obese dogs and humans, the shift of pressure natriuresis to higher blood pressures appears to be due mainly to increased tubular reabsorption, as glomerular filtration rate and renal plasma flow are increased compared with normal. Multiple causes of increased tubular reabsorption and hypertension in obesity have been postulated, including insulin resistance and hyperinsulinemia, activation of the sympathetic nervous and renin-angiotensin systems, and physical changes within the kidney itself. Support for the insulin resistance–hyperinsulinemia link between obesity and hypertension has been inferred mainly from acute and epidemiologic studies showing a correlation between insulin and blood pressure. Recent studies suggest that chronic hyperinsulinemia, comparable to that found in obesity, cannot account for obesity hypertension in dogs or humans. Activation of the sympathetic nervous system may play a role in obesity-induced hypertension, and there is evidence for a role of altered intrarenal physical forces caused by histological changes within the renal medulla. The quantitative importance of each of these abnormalities in altering renal function and raising blood pressure in obesity remains to be determined but is an important area of research for understanding human essential hypertension. (Hypertension. 1994;23:381-394.)

Key Words • natriuresis • kidney • blood pressure • renin-angiotensin system • sympathetic nervous system • obesity • insulin

Louis K. Dahl was a true pioneer in the field of hypertension research and was widely recognized for his work that linked hypertension to altered sodium homeostasis and other environmental and genetic factors. He recognized that there is considerable heterogeneity of the blood pressure responses to changes in salt intake, depending on genetic as well as acquired factors, such as weight gain. The interplay between genetic and environmental factors in contributing to hypertension was clearly demonstrated by the development of Dahl's salt-sensitive and salt-resistant rat strains.

Dahl also helped to elucidate the critical importance of altered renal function in hypertension by demonstrating with cross-transplantation studies in salt-sensitive and salt-resistant rats that the hypertension followed the kidney; transplantation of kidneys from salt-sensitive rats into salt-resistant rats caused hypertension in resistant rats, whereas transplantation of kidneys from normotensive salt-resistant rats into salt-sensitive rats prevented the usual rise in blood pressure found in salt-sensitive rats.1,2 These pioneering studies of Dahl pointed toward the kidney as a key link between genetic and environmental factors in regulating blood pressure.

Our research has been aimed primarily at understanding the basic physiological mechanisms by which the kidney normally regulates blood pressure and how abnormalities of kidney function may lead to hypertension. In this article, I will briefly review some of the most important mechanisms that link the kidney to hypertension and how they are altered in obesity, which appears to be a very important cause of human essential hypertension.

Abnormalities of Kidney Function

Play a Central Role in Human Essential Hypertension

The fact that abnormal kidney function is associated with hypertension has long been recognized. However, there has been considerable controversy about whether impaired renal function plays a causal role or occurs merely as a consequence of hypertension, particularly in essential hypertensive patients. Strong evidence that altered kidney function can cause hypertension comes from the fact that most forms of experimental hypertension begin with some obvious insult to the kidney that affects either renal hemodynamics or tubular reabsorption. For example, Goldblatt hypertension begins with stenosis of one or both of the renal arteries; perinephritis hypertension is initiated by compression of the kidney; mineralocorticoid hypertension begins with increased tubular reabsorption; and angiotensin II (Ang II) hypertension is associated with increased tubular reabsorption and renal vasoconstriction. As hypertension progresses, some of these initial changes are obscured by compensations that restore kidney function toward normal. Secondary to increased blood pressure, a cascade of cardiac and vascular alterations occurs that may be more striking than the disturbance of renal...
function, even though the initial abnormality was in the kidney. For this reason, the importance of changes in renal function in causing hypertension has often been underestimated.

In most patients with hypertension, no specific renal disease can be identified, at least in the early stages of the hypertension, and there is usually little evidence for neural or humoral causes. Thus, the hypertension of these patients is referred to as "idiopathic" or "essential," indicating a cause of unknown origin. Because essential hypertension is usually associated with increased total peripheral resistance, many investigators have concentrated their efforts on the various factors that can cause peripheral vasoconstriction. For the same reasons as in human essential hypertension, it has also been difficult to demonstrate a specific cause in various animal models of genetic hypertension.

Direct evidence that abnormalities of kidney function play a causal role in animal models of genetic hypertension and human essential hypertension comes from kidney cross-transplantation studies (see References 3 through 6 for reviews). In Okamoto spontaneously hypertensive rats, stroke-prone spontaneously hypertensive rats, Dahl salt-sensitive rats, and Milan hypertensive rats, transplantation of kidneys from hypertensive donors into normotensive controls raised blood pressure in the recipient rat.7-11 In the Dahl rat model of hypertension, there may also be neurohumoral factors that contribute to increased blood pressure during high sodium intake,12,13 but these abnormalities could also influence renal function. A potential criticism of cross-transplantation studies is that the kidneys from hypertensive rats may have been damaged during the transplantation or as a result of increased blood pressure before transplantation. More persuasive is the observation that transplantation of kidneys from normotensive controls into hypertensive rats normalized blood pressure in the recipient animal.9 (see Reference 6 for review). Therefore, in most animal models of genetic hypertension studied thus far, normotension or hypertension follows the kidneys and is not dictated by the various systemic abnormalities that accompany the hypertension.

The possibility that these observations in rats may be relevant to the pathogenesis of human essential hypertension is supported by the findings of Curtis et al,14 who reported that transplantation of kidneys from normotensive donors into patients with essential hypertension and renal failure led to complete normalization of blood pressure. If the high blood pressure were caused by some factor extrinsic to the kidneys, hypertension should have eventually reappeared after transplantation. However, blood pressure remained normal in all patients for an average follow-up period of 4.5 years. These observations lend additional support to the view that essential hypertension is caused by some type of renal defect.

The precise nature of the renal defects responsible for human essential hypertension has been difficult to elucidate, possibly because essential hypertension is a heterogeneous disease, beginning with different abnormalities of renal hemodynamics and/or tubular reabsorption in different patients. Unfortunately, measurements of various indexes of kidney function after hypertension is established, or even during the slow, insidious development of hypertension, may not provide a great deal of insight into the pathophysiological processes that initiate hypertension because these measurements represent a summation of compensatory changes and abnormalities that cause the hypertension. For example, renal vascular resistance is often increased in patients with essential hypertension15-18; yet high renal vascular resistance could be an autoregulatory response to increased blood pressure in some cases, or it could play a causal role in others if it increased sufficiently to reduce glomerular filtration rate (GFR).

The various mechanisms by which the kidneys participate in acute and chronic blood pressure regulation have been reviewed elsewhere19-24 and will be discussed only briefly in this article. The kidney is the source of vasoconstrictor and vasodilator systems that can influence peripheral vascular resistance as well as cardiac function, and the kidney can influence sympathetic activity via renal afferent nerve fibers. Importantly, the kidneys also regulate blood pressure by controlling body fluid volumes. This function of the kidney is especially important in long-term blood pressure control and the development of chronic hypertension. Therefore, the basic mechanisms that link renal excretion of sodium and water with altered blood pressure regulation will be considered briefly before the specific mechanisms by which kidney function may be altered in human essential hypertension, particularly obesity-induced hypertension, are discussed.

Renal-Body Fluid Feedback Links Control of Arterial Pressure and Renal Excretion

Because arterial pressure is the product of cardiac output and total peripheral resistance, it is easy to overlook the importance of renal excretory function in regulating blood pressure and to focus on factors that directly affect vascular and cardiac function. Although this viewpoint is certainly applicable to short-term regulation of blood pressure, long-term pressure control is more complex because it involves the control of body fluid volume, which is determined by a balance between fluid intake and renal excretion. Even temporary imbalances between intake and excretion can alter circulatory volume, which can in turn alter cardiac output and eventually peripheral vascular resistance via autoregulatory mechanisms.21-23,24 Under steady-state conditions, fluid intake and output must be precisely balanced; otherwise, continued expansion or contraction of body fluid volumes would lead to circulatory collapse within a few days.

For overall homeostasis, it is even more critical for precise fluid balance to be maintained than normal blood pressure, and, as discussed below, increased blood pressure can serve as a means of achieving fluid balance in the face of impaired kidney function. Under normal conditions, however, precise fluid balance can be maintained in the absence of large changes in blood pressure. This is possible because of interactions between neurohumoral and intrarenal mechanisms that influence kidney function and because of the powerful effect of blood pressure itself on sodium and water excretion, as discussed below.
Pressure Natriuresis Is a Key Component of Renal-Body Fluid Feedback

When kidney function is not impaired, abnormalities that tend to raise blood pressure also increase sodium and water excretion via pressure natriuresis and diuresis (Fig 1). As long as excretion exceeds intake, extracellular fluid volume would continue to decrease, reducing venous return and cardiac output until blood pressure returned to normal and fluid intake and output were balanced once again. Conversely, when blood pressure decreases, the kidneys retain salt and water until arterial pressure is restored to normal. In this way, pressure natriuresis acts as a key component of the feedback system that normally serves to stabilize blood pressure and body fluid volumes.

An extremely important feature of pressure natriuresis in normal blood pressure regulation is the fact that various neurohumoral systems can greatly amplify or blunt the basic effect of blood pressure on sodium and water excretion.21-23,26 For example, during chronic increases in sodium intake, the effectiveness of pressure natriuresis is greatly enhanced mainly because of suppressed Ang II formation, and sodium balance can be maintained with minimal increases in blood pressure.27

Another important aspect of pressure natriuresis is that it continues to operate until blood pressure is restored to the original set point, which is determined by renal excretory capability.21,28 Thus, as long as pressure natriuresis is unaltered, it theoretically provides an infinite-gain feedback control system; any disturbance that tends to raise blood pressure without altering pressure natriuresis cannot cause chronic hypertension.21,28 For sodium balance to be maintained in the face of a sustained increase in blood pressure, there must be a concomitant shift of pressure natriuresis (Fig 1). Without a shift of pressure natriuresis, increased arterial pressure would cause continued loss of sodium and water until blood pressure returned to normal. Thus, chronic hypertension can occur only if there is an abnormality of kidney function that shifts pressure natriuresis so that sodium balance is maintained at elevated blood pressures.

Although it is obvious that a shift of pressure natriuresis must occur whenever blood pressure is chronically increased, there are two possible explanations for altered pressure natriuresis in hypertension. One explanation, consistent with the renal-body fluid feedback concept discussed above, is that some abnormality of kidney function shifts pressure natriuresis and initiates a compensatory rise in blood pressure that helps to maintain sodium balance. In other words, hypertension is an essential "trade-off" that permits the kidney to excrete normal amounts of sodium in the face of impaired excretory capability. The opposing view is that chronic changes in blood pressure, initiated by nonrenal abnormalities that alter cardiac output or total peripheral resistance, cause adaptive renal changes that maintain sodium balance despite the high blood pressure.

Recently, we addressed this problem by examining the role of pressure natriuresis in various models of experimental hypertension in which the direct effects of renal perfusion pressure were separated from other mechanisms that influence renal excretion during increased blood pressure.29-33 The results from these studies indicated that renal perfusion pressure has a major long-term effect on sodium excretion in every experimental model of hypertension studied thus far. When renal perfusion pressure was servo-controlled to prevent pressure natriuresis from operating in different forms of hypertension, continued sodium retention occurred and often resulted in peripheral edema, pulmonary edema, or both within a few days. These studies strongly support the renal-body fluid feedback concept of blood pressure control.

We also recently measured the direct long-term effects of renal perfusion pressure on sodium excretion using a split-bladder preparation to collect urine from each kidney separately; in these experiments, renal perfusion pressure to each of the two kidneys could be controlled independently.34 Because both kidneys were exposed to the same neurohumoral influences, these studies were able to measure the effects of long-term changes in renal perfusion pressure per se on renal hemodynamics and electrolyte excretion. These studies indicated that relatively small changes in renal perfusion pressure caused large alterations in renal sodium and water excretion that persisted as long as renal artery pressure was altered. Thus, the kidney does not appear to adapt its excretory function during chronic changes in perfusion pressure; instead, blood pressure adapts to the level required for maintenance of sodium and fluid balance. When hypertension occurs, it appears...
to be an essential compensation that permits sodium and water homeostasis despite abnormalities of kidney function that shift pressure natriuresis to higher levels.

**Pressure Natriuresis Is Abnormal in Essential Hypertension**

One common misconception is that renal function is normal in most essential hypertensive patients, at least in the early stages of hypertension. Although GFR, renal plasma flow, sodium excretion, and other indexes of renal function are often in the normal range, it is clear that renal excretory function is not normal in essential hypertension because normal sodium excretion is maintained only at elevated blood pressures. This observation alone indicates that the capability of the kidney to excrete sodium is reduced. Omvik et al. also demonstrated in patients with essential hypertension that when arterial pressure was acutely reduced by infusion of nitroprusside, sodium excretion decreased below normal, indicating that pressure natriuresis was attenuated in these patients. The precise causes of impaired pressure natriuresis in essential hypertension, however, are not clear and remain a fertile area for further investigation. It seems likely that multiple aberrations are involved because in some patients blood pressure is salt sensitive with a decreased slope of pressure natriuresis, whereas in others blood pressure is salt insensitive with a parallel shift of pressure natriuresis.

An analysis of the characteristics of altered pressure natriuresis in different forms of experimental hypertension provides some insight into the potential mechanisms of human essential hypertension (Fig 2). For example, in those forms of hypertension characterized by increased preglomerular resistance, such as the one-kidney, one-clip Goldblatt model, there is a parallel shift of pressure natriuresis, and blood pressure is relatively insensitive to changes in sodium intake. On the other hand, hypertension associated with increased tubular reabsorption in distal parts of the nephron, such as occurs with mineralocorticoid excess, is often characterized by a decreased slope of pressure natriuresis leading to a salt-sensitive form of hypertension. Reductions in the glomerular capillary filtration coefficient ($K_f$), such as occurs with chronic glomerulonephritis or a decrease in the number of functional nephrons, also lead to a reduction in the slope of pressure natriuresis and salt-sensitive hypertension.

Another major factor that conveys salt sensitivity of blood pressure is the inability to adequately suppress Ang II formation when salt intake is raised. Experimental studies indicate that the steepness of the normal long-term relation between arterial pressure and sodium excretion is largely due to the ability to suppress Ang II formation. Blockade of Ang II formation or infusion of constant amounts of Ang II to prevent suppression of Ang II when salt intake is increased causes blood pressure to be very sensitive to changes in salt intake. It is likely that salt sensitivity of blood pressure in low-renin forms of hypertension is due to the inability to further suppress Ang II formation when salt intake is high. Thus, by knowing the causes of altered pressure natriuresis in experimental hypertension, one can gain insight into basic renal abnormalities that may lead to human essential hypertension.

**Weight Gain Is an Important Cause of Essential Hypertension**

One factor recognized as a contributor to increased blood pressure in many essential hypertensive patients is increased body weight. Population studies show a good correlation between body weight and blood pressure in normotensive and hypertensive individuals. In addition, weight gain appears to contribute to much of the increased blood pressure that occurs with aging. In those populations in which weight gain does not occur with aging, there appears to be little or no age-related increase in blood pressure. Studies in experimental animals and humans show that weight gain, even over a period of several weeks, increases blood pressure and that weight loss produces a corresponding decrease in blood pressure. Modest weight losses may lower arterial pressure to normal levels in many hypertensive patients even though they have not returned to ideal body weight. Furthermore, weight loss can reduce blood pressure independently of decreased sodium intake.

The fact that some obese individuals have normal blood pressure and some essential hypertensive patients are not overweight has led to doubt about the importance of obesity as a cause of essential hypertension. Yet if one considers that there is a distribution of blood...
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NORMOTENSION  HYPERTENSION

LEAN » BESE

BLOOD PRESSURE

Fig 3. Plot shows postulated effect of weight gain on frequency distribution of mean arterial pressure.

pressures in obese and lean individuals, this apparent discrepancy is easier to understand (Fig 3). Some lean individuals are hypertensive, but a greater percentage of obese individuals tend to have elevated blood pressures, and the distribution of blood pressures is shifted toward higher blood pressures with increasing body weight. Thus, weight loss should reduce blood pressure even in normotensive obese patients, a prediction supported by clinical experience.40,50

Despite the recognition that obesity and hypertension are closely associated, the mechanisms responsible for weight-related increases in blood pressure are still obscure. Elucidation of the causes of obesity-induced hypertension has been hampered by the lack of experimental studies in which sequential changes in renal, cardiovascular, and endocrine function have been examined during the development of hypertension or after blocking one or more of the abnormal feedback systems that could contribute to elevated blood pressure. Most of our current knowledge of obesity hypertension comes from anecdotal observations or from correlations between one or more variables and increased blood pressure in obese patients. Recently, however, a resurgence of interest in this field has led to renewed investigations of the physiological mechanisms that may contribute to weight-related increases in blood pressure.

Systemic Hemodynamics in Obesity-Induced Hypertension

In 1939 Wood and Cash51 developed an experimental model of obesity-induced hypertension by feeding dogs a high-fat diet. However, the mechanisms of hypertension in this model were not characterized, and there has been little effort in the past 50 years to further develop and characterize a large-animal model of obesity. Recently, studies by Rocchini and his colleagues43,44 and in our laboratory45 have demonstrated that dogs fed a high-fat diet have many of the characteristics of obese humans, including hyperinsulinemia, insulin resistance, sodium retention, and hypertension. Figs 4 and 5 show the changes in systemic hemodynamics during 5 weeks of a high-fat diet in dogs. Note that blood pressure increased in parallel with increased body weight and that the hypertension was associated with tachycardia and increased cardiac output. A study by Rocchini52 also suggested that weight gain increased cardiac output, but when cardiac output was expressed per unit body weight (cardiac index), there were no significant changes associated with obesity. Similar results have been obtained when obese and nonobese humans are compared.53,54 However, normalization for body weight may not be appropriate in obese subjects, because much
of the weight gain may be due to increased adipose tissue, which has relatively low blood flow compared with many other tissues. Thus, obesity may be associated with generalized peripheral vasodilation and increased blood flow in nonadipose tissue. In support of this possibility, we previously reported that renal blood flow was markedly elevated in obese dogs, and others have found that blood flows in the heart, brain, gastrointestinal tract, and skeletal muscle are greater in obese than nonobese subjects. The mechanisms responsible for regional vasodilation in obesity are still unclear and deserve further investigation.

Abnormal Pressure Natriuresis in Obesity-Induced Hypertension

As discussed above, numerous experimental studies and theoretical analyses indicate that renal excretory function is altered in all forms of experimental and human essential hypertension studied thus far, including obesity-induced hypertension. Rocchini et al reported that pressure natriuresis was shifted to higher blood pressures in obese adolescents. Moreover, the shift of pressure natriuresis was characterized by a decreased slope, indicating that blood pressure was sensitive to salt intake (Fig 6). During high sodium intake blood pressure was markedly elevated in obese subjects, whereas during low sodium intake there was little difference in blood pressure between nonobese and obese patients. Furthermore, the decreased slope of pressure natriuresis was reversed by modest weight loss.

Recent studies in abdominally obese adults, however, have suggested that blood pressure is not sensitive to changes in salt intake. Granger and Nakamura also found that obesity-induced hypertension in dogs was not salt sensitive and was characterized by a parallel shift, rather than a decreased slope, of the pressure-natriuresis curve. The reasons why the slope of pressure natriuresis is reduced in obese adolescents, whereas in obese adults and dogs there is a parallel shift of pressure natriuresis, remain unclear. Nevertheless, obesity-induced hypertension is invariably associated with a shift of pressure natriuresis toward higher blood pressures, although the mechanisms that cause this change are not well understood.

In obese dogs, weight gain caused by feeding a high-fat diet caused marked increases in cumulative sodium balance that appeared to exceed the sodium required for the additional tissue associated with weight gain because extracellular fluid volume and plasma volume were markedly elevated with weight loss. In obese women, there is also a relative expansion of extracellular fluid volume compared with total body fluid volume.

The shift of pressure natriuresis and impaired renal excretory capability could theoretically be caused by altered renal hemodynamics, increased tubular reabsorption, or both. Although the mechanisms responsible for sodium retention in obesity have not been fully elucidated, studies in dogs and humans suggest that it is not due to renal vasoconstriction and decreased filtered sodium load. In fact, GFR, filtered sodium load, and renal blood flow are markedly elevated during the development of obesity-induced hypertension. Thus, obesity is associated with an increased absolute and fractional sodium reabsorption that may occur at some site distal to the proximal tubules. Although increased tubular reabsorption appears to play an important role in shifting pressure natriuresis to higher blood pressures during weight gain, the mechanisms

![Graph showing effects of 5 weeks of a high-fat diet on heart rate, cardiac output, and total peripheral vascular resistance. Values represent weekly averages obtained from measurements made 18 hours each day. C indicates average values for 5 control days preceding the high-fat diet. Reproduced with permission from Hall et al.]
Role of Hyperinsulinemia and Insulin Resistance in Obesity-Induced Hypertension

Obesity is associated with fasting hyperinsulinemia as well as an increased insulin secretory response to a glucose load. Elevated circulating levels of insulin are believed to occur as a compensation by the pancreatic beta cells for an impairment of the metabolic effects of insulin, particularly its effects on glucose metabolism; however, hyperinsulinemia may also occur from impairment of receptor-mediated clearance of insulin by resistant peripheral target cells. The hyperinsulinemia in turn serves to maintain plasma glucose concentration relatively constant in the face of impaired insulin action, which is often referred to as “insulin resistance.”

The term insulin resistance has often been used rather loosely, especially in whole-animal and clinical studies, and can refer to decreased sensitivity to the hormone, characterized by a rightward shift of the dose-response curve, or a decreased maximum response to insulin. Possible explanations for impaired insulin action (relative to plasma concentration) include abnormalities at the prereceptor level (eg, decreased delivery of insulin and glucose to the tissues), altered insulin receptors (eg, decreased receptor affinity or a reduction in the number of insulin receptors), and abnormal cell functions that determine the response to a given concentration of insulin-receptor complexes. Further complexity is added to the difficulty of measuring insulin resistance in vivo by the fact that insulin resistance is tissue specific, not only in terms of the mechanisms involved but also because some tissues (eg, kidney) retain their sensitivity to insulin in so-called insulin-resistant states. These few examples illustrate the potential for multiple causes of insulin resistance and the complexity of the syndrome. Although the etiology of insulin resistance in obesity is still the subject of intense investigation, there is evidence that insulin resistance may be due in part to postreceptor abnormalities in obese hypertensive subjects.

Currently, there are three primary in vivo methods for assessment of insulin resistance in whole-animal and clinical studies: (1) fasting plasma insulin concentration, (2) plasma insulin or glucose responses to an oral or intravenous glucose load (eg, glucose tolerance test), and (3) the rate of glucose infusion needed to maintain euglycemia during insulin infusion at various rates (eg, hyperinsulinenic euglycemic clamp method). Each of these methods has limitations and may provide different estimates of insulin resistance under various conditions. In the postabsorptive state, glucose homeostasis is a balance between hepatic glucose production and glucose disposal in various tissues. Under fasting conditions, in which glucose disposal is not a major consideration, plasma insulin more closely reflects the ability of insulin to suppress hepatic glucose output than to stimulate peripheral glucose uptake. Therefore, when insulin resistance is defined by fasting hyperinsulinemia, the most likely cause is a decreased insulin-mediated suppression of hepatic glucose output. On the other hand, when insulin resistance is defined by the response to a glucose load or by the euglycemic clamp method, the most likely cause is an impairment of the ability of insulin to stimulate peripheral glucose uptake, particularly in the skeletal muscle. Currently, the precise causes of insulin resistance in various tissues, including skeletal muscle and liver, are still unclear and remain an important area for further investigation.

In recent years, there has been considerable interest in the possibility that insulin resistance and compensatory hyperinsulinemia might mediate obesity-induced hypertension. This hypothesis is supported by two main lines of evidence: First, obese hypertensive patients tend to be hyperinsulinemic when compared with normotensive control subjects, and several studies have shown a correlation between blood pressure and plasma insulin concentrations. Second, insulin has been shown in acute studies to have multiple effects on the kidney, sympathetic nervous system, and cardiovascular system that, if sustained, could lead to high blood pressure. However, several studies have failed to find a correlation between insulin and blood pressure, and it is now recognized that insulin has multiple effects on the cardiovascular system that could tend to elevate or reduce blood pressure. Equally important, it is difficult to extrapolate results from acute administration of insulin to the problem of chronic obesity-induced hypertension because it is still uncertain whether the acute effects of insulin can be sustained sufficiently to influence long-term blood pressure regulation. Although epidemiologic studies may provide insight into a potential role of insulin in hypertension, the quantitative importance of hyperinsulinemia in the etiology of hypertension cannot be established solely from correlational studies.

The primary mechanisms by which insulin has most frequently been postulated to raise blood pressure are by causing sodium retention, or stimulating vascular smooth muscle growth and hypertrophy. Several studies have shown that insulin causes antinatriuresis in experimental animals and humans. Insulin-mediated decreases in sodium excretion appear to be mainly due to increased sodium reabsorption at a site beyond the proximal tubule, possibly the loop of Henle. If the antinatriuretic effects of insulin were maintained chronically, blood pressure could rise as a result of sodium retention and extracellular fluid volume expansion.

Insulin could also elevate blood pressure by activating the sympathetic nervous system. High caloric intake in rats increases sympathetic nervous system activity and plasma insulin concentration in parallel, whereas caloric restriction lowers plasma insulin and sympathetic activity as assessed by indirect methods such as tissue norepinephrine turnover. However, it is difficult to determine from these overfeeding studies whether insulin is the key factor in elevating blood pressure and adrenergic activity or whether other mechanisms associated with weight gain are more important.
Only a few studies have directly examined the acute effects of insulin on blood pressure and adrenergic activity. Insulin infusion reportedly raised plasma noradrenaline levels even when plasma glucose was held constant, and blockade of adrenergic activity attenuated the rise in blood pressure associated with insulin injections. However, because large pharmacologic doses of insulin were used, it is difficult to ascertain the relevance of these observations to the problem of obesity-induced hypertension.

Recently, several studies have examined the acute effects of pathophysiological levels of insulin on sympathetic nervous system activity, blood pressure, and vascular resistance in humans. Increasing insulin concentration approximately 10–fold or greater stimulated sympathetic activity in skeletal muscle and raised peripheral resistance and cardiac output, possibly as a result of increased metabolic rate in skeletal muscle associated with increased glucose uptake. Whether chronic hyperinsulinemia causes increases in sympathetic activity, however, has apparently not been reported.

Thus, acute studies have confirmed that insulin may have effects on the kidney and sympathetic nervous system that, if sustained, could lead to hypertension. On the other hand, insulin also has acute vasodilator actions that tend to lower blood pressure. The net effect of insulin on these various cardiovascular and renal functions is complex and may lead to an increase, no change, or even a decrease in blood pressure. Most studies suggest that insulin raises blood pressure acutely only with superphysiological concentrations in normotensive humans and animals.

**Chronic Hyperinsulinemia and Blood Pressure Regulation**

Recently, we performed a series of studies to directly test whether chronic hyperinsulinemia could explain obesity-induced hypertension. These experiments were designed to determine whether chronic increases in plasma insulin concentration, comparable to those found in obese hypertensive patients, would cause sustained increases in blood pressure and a shift of pressure natriuresis. In one group of studies, insulin was infused into normal dogs at a rate that raised plasma insulin concentration approximately fivefold to sixfold. Although insulin infusion caused a transient reduction in sodium excretion, sodium balance was reestablished in 2 to 3 days, and there was actually a decrease in blood pressure of about 10 mm Hg rather than an increase. A major part of the sodium retention associated with hyperinsulinemia may have been secondary to the fall in blood pressure caused by peripheral vasodilation; infusion of insulin for 7 days in normal dogs reduced total peripheral resistance and raised cardiac output, possibly as a result of increased metabolic rate in skeletal muscle associated with increased glucose uptake.

Even though insulin did not cause hypertension in normal dogs, we considered the possibility that insulin might raise blood pressure in circumstances associated with preexisting impairment of kidney function. Other antinatriuretic hormones, such as aldosterone, have a much greater effect on blood pressure when kidney mass is reduced or when sodium intake is elevated. Therefore, we also investigated the effects of hyperinsulinemia in dogs after removal of 70% of kidney mass 4 to 5 weeks before the experiment (Fig 7). In addition, these animals were maintained on a high sodium intake, and hyperinsulinemia was sustained for 28 days to be certain that sufficient time was provided for insulin to exert a hypertensive action. However, in these studies insulin also reduced blood pressure by approximately 10 mm Hg during the first few days of infusion. In additional studies, we found that chronic hyperinsulinemia for 4 weeks did not potentiate the blood pressure or renal effects of other pressor substances such as norepinephrine or angiotensin. Thus, several studies in dogs indicate that chronic hyperinsulinemia per se cannot explain obesity-induced hypertension and does not appear to potentiate the hypertensive effects of other pressor systems that may be activated in obesity. On the contrary, hyperinsulinemia appears to exert a hypotensive action.

A potential criticism of these studies is that additional factors associated with obesity might be essential for insulin to cause hypertension. For example, the presence of insulin resistance, and therefore resistance to the vasodilator effects of insulin, could be an important factor in allowing insulin to raise blood pressure. In normal dogs that are sensitive to the metabolic effects of insulin, insulin infusion could stimulate glucose uptake and raise tissue metabolism, leading to decreased peripheral vascular resistance and a tendency to offset any hypertensive action that insulin might have because of its effects on the kidney or the sympathetic nervous system. In fact, it has been hypothesized that an impaired peripheral vasodilator action of insulin, due to the presence of insulin resistance, might permit hyperinsulinemia to cause hypertension.

To test this hypothesis, we designed studies to determine whether chronic hyperinsulinemia would raise blood pressure in obese dogs that were resistant to the metabolic effects of insulin. In these experiments, dogs were made insulin resistant by placing them on a high-fat diet for 5 to 6 weeks. The presence of insulin...
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resistance was confirmed by measurements of fasting hyperinsulinemia, impaired responses to glucose tolerance tests, and by the euglycemia clamp technique. In addition, chronic insulin infusion in these experiments failed to cause significant decreases in peripheral vascular resistance or increases in cardiac output, in contrast to normal dogs, which demonstrated a 30% to 35% increase in cardiac output and a marked decrease in total peripheral vascular resistance during hyperinsulinemia.104,108 These observations indicated that the obese dogs were resistant to the metabolic and vasodilator actions of insulin. However, despite this insulin resistance, chronic insulin infusion did not significantly raise blood pressure in obese dogs. Thus, the presence or absence of insulin resistance does not appear to greatly influence the chronic blood pressure response to hyperinsulinemia in dogs. These observations indicate that other factors besides hyperinsulinemia are much more important in raising blood pressure in obese dogs.

**Possible Species Variations in Blood Pressure Responses to Hyperinsulinemia**

Although studies in dogs have failed to support the concept that hyperinsulinemia is a major cause of obesity-induced hypertension, there are species variations in the blood pressure responses to insulin infusion. Recent studies by Brands et al109,110 in our laboratory have shown that in rats chronic insulin infusion increases blood pressure. The increased blood pressure was not associated with sodium retention or activation of the RAS.109 These observations contrast with obesity-associated hypertension in humans, which is characterized by marked sodium retention and increased plasma renin activity.117-118 Recent studies suggest that hyperinsulinemia in some rat strains, such as the Dahl salt-sensitive rat, causes hypertension by increasing adrenergic activity.111 However, there may be differences in the chronic blood pressure responses to insulin in various rat strains, and further studies are needed to examine the specific mechanisms of insulin-induced hypertension in rats.

In humans, there have been no reported studies on the long-term renal and cardiovascular responses to insulin infusions. Acute studies indicate that insulin infusion causes many of the same changes observed in dogs, including peripheral vasodilation, modest sodium retention, and little or no change in blood pressure.115,116 Long-term increases in hyperinsulinemia and insulin resistance associated with insulinoma do not elevate blood pressure in humans, even when associated with insulin resistance.112-114 Moreover, several population studies have shown either no correlation or a weak relation between blood pressure and plasma insulin concentration in healthy humans.81-83 In one study of more than 2000 subjects, Ferrannini et al115 reported that after adjustment for age, sex, body mass index, and the ratio of waist to hip circumference, the slope of the regression line for blood pressure versus insulin concentration predicted that an increase of 200 μU/mL in insulin concentration could account for a rise in blood pressure of only 1 mm Hg. Because fasting plasma insulin concentration is usually increased by less than 20 μU/mL in obese hypertensive subjects compared with healthy subjects,47,71,78 these findings also question the significance of hyperinsulinemia in contributing to elevated blood pressure in humans. Although the issue of whether hyperinsulinemia accounts for obesity-induced hypertension remains controversial, most of the available evidence suggests that insulin may not be a primary cause of high blood pressure in obese dogs or humans.

**Role of the Renin-Angiotensin System in Obesity**

Another potential cause of increased tubular reabsorption and hypertension in obesity is activation of the RAS. The RAS is one of the body’s most powerful humoral regulators of blood pressure, and the ability to appropriately adjust Ang II levels allows adaptations to large variations in salt intake without major changes in blood pressure or body fluid volumes.15,27 Even small increases in Ang II levels can elevate blood pressure, especially when associated with volume expansion.25,27,36

Previous studies of the RAS in obesity have yielded conflicting results; Rocchini et al43 reported no change in plasma renin activity but increased plasma aldosterone concentration in obese dogs, whereas Tuck et al46 found that plasma renin activity and aldosterone levels were both elevated in obese subjects. Moreover, weight reduction lowered plasma renin activity and aldosterone concentration in obese subjects.34 In our study of obese dogs, plasma renin activity was elevated more than twofold after 5 weeks of a high-fat diet despite marked sodium retention and increased extracellular fluid volume.45

The failure to suppress Ang II levels despite volume expansion and hypertension suggests that there may be a powerful underlying stimulus for renin secretion in the development of obesity. As discussed below, there is evidence for activation of the sympathetic nervous system and altered intrarenal physical forces that could contribute to enhanced renin secretion. However, preliminary observations in our laboratory indicate that chronic α- and β-adrenergic blockade had little effect on plasma renin activity in obese dogs, suggesting that increased sympathetic activity may not be the primary stimulus for activation of the RAS in obesity (unpublished observations). Another potential mechanism for increased renin secretion is a reduction in macula densa sodium chloride delivery. As discussed above, obesity causes marked increases in renal absolute and fractional sodium reabsorption at a site beyond the proximal tubule, as estimated by measurements of fractional lithium reabsorption.86,117 If increased reabsorption occurred at a site prior to the macula densa (eg, the loop of Henle), this could account for several observations in obese dogs, including sodium retention, increased GFR and renal plasma flow, and increased renin secretion (Fig 8). With an increase in loop of Henle sodium chloride reabsorption, a reduction in distal sodium chloride delivery would initiate a compensatory rise in GFR, via tubuloglomerular feedback,118 and stimulation of renin secretion by a macula densa mechanism.17,119 The increased GFR and high blood pressure would tend to return distal tubular sodium chloride delivery toward normal and restore sodium balance.

The exact mechanisms that could stimulate loop of Henle sodium chloride reabsorption are uncertain but may be related to histological changes in the renal medulla that contribute to increases in renal interstitial
fluid and solid tissue pressures, which in turn tend to cause tubular compression. As discussed below, very large increases in renal interstitial fluid hydrostatic pressure, similar to the changes that we have observed in obese dogs, could increase resistance to flow through the loop of Henle, thereby slowing tubular flow rate and increasing fractional sodium reabsorption, particularly in the thin ascending loop of Henle. However, this hypothesis must remain speculative until it can be tested with direct measurements of loop of Henle reabsorption in obese compared with nonobese animals. In addition, the quantitative importance of increased Ang II formation to the altered pressure natriuresis and hypertension associated with obesity has not been directly assessed. Although blockade of Ang II formation reduces blood pressure in obese hypertensive patients, it is not clear whether this treatment is more effective than in other forms of hypertension. In addition, there are no published studies, to my knowledge, that have directly tested whether blockade of Ang II formation prevents the changes in renal function and hypertension associated with weight gain.

Role of the Sympathetic Nervous System in Obesity

Another mechanism that could contribute to elevated tubular reabsorption, altered pressure natriuresis, and hypertension in obesity is increased sympathetic activity. Increased caloric intake appears to activate 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 plasma norepinephrine response to stimuli such as upright posture and isometric handgrip may also be elevated in obese subjects. Moreover, several studies have shown that weight loss with hypocaloric diets reduces sympathetic activity (see References 65 and 88 for review). In contrast to these observations, some investigators have found no evidence of heightened sympathetic activity in obesity.

To test the importance of the sympathetic nervous system in obesity, we recently investigated the effects of acute ganglionic blockade and chronic adrenergic blockade in dogs fed a high-fat diet for 5 to 6 weeks. Ganglionic blockade with hexamethonium caused a much greater reduction in blood pressure in obese compared with nonobese dogs. However, elevated sympathetic activity did not appear to account for increased heart rate in obese dogs; instead, the elevated heart rate appeared to be due to reduced cholinergic inhibition. These observations suggest that obesity may be accompanied by increased sympathetic and decreased parasympathetic activity. In additional studies, we found that combined α- and β-adrenergic blockade for 7 days in obese dogs decreased blood pressure by approximately 25 mm Hg compared with less than 10 mm Hg in nonobese dogs. These preliminary observations are consistent with the hypothesis that the sympathetic nervous system may play an important role in altering pressure natriuresis and contributing to high blood pressure in obesity. However, further studies are needed to more fully assess the importance of the sympathetic nervous system in obesity-induced hypertension and to examine the specific mechanisms that lead to sympathetic activation in obesity.

Abnormal Intrarenal Physical Forces in Obesity-Induced Hypertension

In addition to activation of various neurohumoral systems, obesity also causes changes in intrarenal physical forces that could contribute to increased tubular reabsorption and hypertension. In preliminary studies, we found that obesity-induced hypertension in dogs was associated with increased sodium reabsorption at a nephron site beyond the proximal tubule. The increased reabsorption was accompanied by large increases in GFR and renal plasma flow and activation of the RAS. Hyperinsulinemia, sympathetic activation, and activation of the RAS cannot account for the renal vasodilation and increased GFR associated with obesity. Therefore, it seems likely that there are additional intrarenal changes that may contribute to altered renal hemodynamics and sodium retention.

One factor that could cause increased tubular reabsorption in obesity is altered intrarenal physical forces associated with histological changes. Preliminary studies in kidneys from obese dogs reveal striking histological changes in the renal medulla, including large increases in the number of interstitial cells and especially noncellular matrix material between the tubules. The matrix between the tubules stained with alcin blue and periodic acid–Schiff but not oil-red O, indicating increased proteoglycans rather than lipids in the renal medulla. Interestingly, these changes were observed only in the renal medulla and not in the renal cortex. Because the kidney is surrounded by a tight capsule with a low compliance, increased numbers of interstitial
cells or matrix deposition between the tubules could raise renal interstitial fluid hydrostatic pressure and cause compression of the tubules and blood vessels (vasa recta) of the renal medulla (Fig 9). Preliminary observations indicate that renal interstitial fluid hydrostatic pressure was approximately 10 mm Hg higher in kidneys of obese compared with nonobese dogs.60 Although small increases in renal interstitial hydrostatic pressure might tend to reduce tubular reabsorption, large increases in fluid and solid tissue pressures (especially when originating from extratubular changes) could cause tubular compression, which in turn would increase resistance to flow in the tubule, decrease tubular flow rate, increase tubular transit time, and raise fractional tubular reabsorption.124,125 It is likely that a tendency toward tubular compression would occur especially in the loop of Henle, which is very distensible and normally has a luminal hydrostatic pressure of approximately 10 mm Hg. Because renal interstitial fluid pressure was elevated to more than 19 mm Hg in the kidneys of obese dogs and because the loop of Henle probably behaves like a collapsible tube,125 intraluminal pressures in the loop of Henle must also increase above this level to maintain flow in the tubule. A compensatory rise in loop of Henle hydrostatic pressure and a restoration of tubular flow rate toward normal could occur as a result of enhanced proximal delivery due to increased GFR or decreased proximal tubular reabsorption, secondary to increased arterial pressure or intrarenal adaptations. Preliminary studies suggest that proximal tubular reabsorption was not reduced (based on measurements of fractional lithium reabsorption) in kidneys of obese dogs.40 However, GFR was elevated by approximately 35% to 50%. It seems unlikely that increased GFR was solely due to increased blood pressure, because GFR and renal blood flow autoregulatory capability of kidneys from obese dogs was not markedly impaired (unpublished observations). One possible explanation for the renal vasodilation observed in obesity that would also explain the increased plasma renin activity is that altered renal medullary histology could increase resistance to tubular flow and raise reabsorption in the loop of Henle, which in turn would decrease sodium chloride delivery to the macula densa, as discussed above. Thus, obesity-induced hypertension may be due in part to histological changes in the renal medulla that increase intrarenal pressures, shift pressure natriuresis to higher blood pressures, and necessitate increased blood pressure to maintain sodium balance. The possibility that these changes observed in dogs may also be applicable to humans comes from preliminary observations which indicate that similar histological changes occur in the renal medullas of obese humans (G. Herrera, personal communication).

In summary, weight gain is a major cause of increased blood pressure in many patients with essential hypertension and is probably responsible for much of the age-related increases in blood pressure that occur in many societies. Although the precise mechanisms by which weight gain raises blood pressure have not been fully elucidated, obesity-induced hypertension, like all forms of hypertension studied thus far, is associated with a shift of renal pressure natriuresis. Studies in obese dogs suggest that altered pressure natriuresis is mainly due to increased tubular sodium reabsorption. Hyperinsulinemia and insulin resistance do not appear to account for altered renal function and increased blood pressure associated with obesity in dogs and humans, although pathophysiological levels of insulin can raise blood pressure in rats. Nevertheless, insulin resistance and compensatory hyperinsulinemia may contribute to metabolic abnormalities and an increased risk of cardiovascular disease associated with obesity-induced hypertension. Recent studies suggest that activation of the sympathetic nervous system and altered intrarenal physical forces caused by histological changes within the renal medulla may play an important role in the pathogenesis of obesity-induced hypertension. However, the mechanisms by which obesity initiates these abnormalities are unknown and deserve further study, particularly in view of the importance of weight gain as a cause of human essential hypertension.

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