

Hypertension

JOURNAL OF THE AMERICAN HEART ASSOCIATION



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The Kidney, Hypertension, and Obesity

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Hypertension 2003;41:625-633; originally published online Jan 20, 2003;

DOI: 10.1161/01.HYP.0000052314.95497.78

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75214

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The Kidney, Hypertension, and Obesity

John E. Hall

Abstract—This paper provides a personal perspective of the role of abnormal renal-pressure natriuresis in the pathogenesis of hypertension. Direct support for a major role of renal-pressure natriuresis in long-term control of arterial pressure and sodium balance comes from studies demonstrating that (1) pressure natriuresis is impaired in all forms of chronic hypertension and (2) prevention of pressure natriuresis from operating, by servo-control of renal perfusion pressure, also prevents the maintenance of sodium balance hypertension. Although the precise mechanisms of impaired pressure natriuresis in essential hypertension have remained elusive, recent evidence suggests that obesity and overweight may play a major role. Obesity increases renal sodium reabsorption and impairs pressure natriuresis by activation of the renin-angiotensin and sympathetic nervous systems and by altered intrarenal physical forces. Chronic obesity also causes marked structural changes in the kidneys that eventually lead to a loss of nephron function, further increases in arterial pressure, and severe renal injury in some cases. Although there are many unanswered questions about the mechanisms of obesity hypertension and renal disease, this is one of the most promising areas for future research, especially in view of the growing, worldwide “epidemic” of obesity. (*Hypertension*. 2003;41[part 2]:625-633.)

Key Words: blood pressure ■ sodium excretion ■ renin ■ angiotensin ■ sympathetic nervous system ■ renal disease

Historical Perspectives: The Kidney and Hypertension

Early investigators recognized that hypertension is closely related to renal dysfunction, although they did not fully understand the mechanisms involved in this linkage. The *Yellow Emperor's Classic of Internal Medicine*¹ pointed out over 4500 years ago that “When the pulse is abundant but tense and hard and full like a cord, there are dropsical swellings,” and suggested that “the kidneys pass on the diseases to the heart. . . .” Traube² in 1871 suggested that hypertension might be a homeostatic response to impaired renal excretory function, and Richard Bright³ noted that kidney disease and hypertension often occur together. In the early 1900s Starling⁴ further clarified the concept that volume homeostasis and blood pressure regulation are closely linked and emphasized the importance of renal fluid retention in maintaining arterial pressure in circumstances associated with circulatory depression, such as heart failure.

The role of renal sodium excretion in regulating arterial pressure remained rather vague, however, until the 1960s when Guyton⁵ and Borst and Borst-deGeus⁶ working independently clearly articulated the idea that long-term blood pressure regulation is inextricably linked to renal excretory function. This concept was expressed quantitatively by Guyton and Coleman⁷ in a systems analysis that predicted the kidneys acted as an overriding regulator of blood pressure through a “renal-body fluid feedback” (Figure 1). A key

component of this feedback was the effect of arterial pressure on sodium excretion (ie, pressure natriuresis), which had been demonstrated by Goll⁸ in 1854 and by Selkurt et al⁹ in 1949, who showed that pressure natriuresis could occur without major changes in renal blood flow or glomerular filtration rate. These studies, however, involved only acute changes in arterial pressure, whereas the basic assumption of Guyton and Coleman's model was that arterial pressure exerted important long-term effects on sodium and water excretion.

The central role of renal excretory function in the etiology of hypertension remained highly controversial, primarily because no obvious renal defects or disturbances in sodium excretion were found in most hypertensive patients and there was no clear proof that arterial pressure had a long-term effect on sodium excretion. The most readily observable abnormality in hypertension is an increase in total peripheral vascular resistance, leading many investigators to focus on abnormalities of vasoconstriction as a primary cause of hypertension.

The fact that a normal rate of sodium excretion (equal to sodium intake) is maintained despite higher blood pressure indicates that pressure natriuresis is reset in chronic hypertension. The question of whether the resetting of pressure natriuresis plays a primary role in *causing* hypertension or merely occurs secondarily to increased blood pressure, however, was controversial and difficult to test experimentally. In this brief review, I will discuss (1) the basic mechanisms that link renal excretion of sodium and water with blood pressure

Received October 25, 2002; first decision December 3, 2002; revision accepted December 5, 2002.

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This paper was sent to Curt D. Sigmund, associate editor, for review by expert referees, editorial decision, and final disposition.

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Hypertension is available at <http://www.hypertensionaha.org>

DOI: 10.1161/01.HYP.0000052314.95497.78

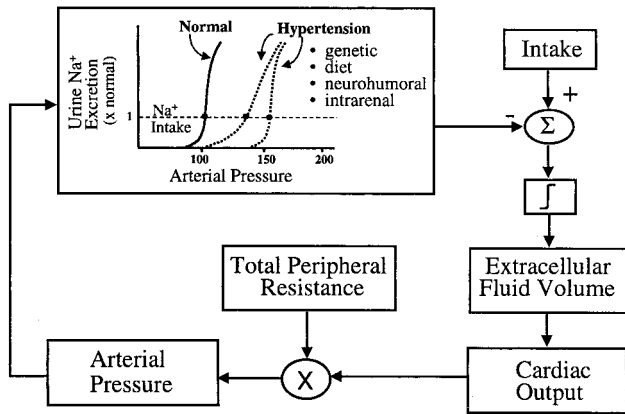


Figure 1. Basic renal-body fluid feedback mechanism for long-term regulation of blood pressure and body fluid volumes.

regulation, (2) experimental evidence that abnormalities of pressure natriuresis plays a causal role in hypertension, and (3) the role of excess weight gain as a cause of impaired renal-pressure natriuresis in essential hypertension, as well as potential mechanisms that may link obesity with altered renal function. I have reviewed mainly the work from our laboratory and apologize in advance for omitting the important work of many researchers who contributed to the concepts discussed.

Renal-Body Fluid Feedback Control of Arterial Pressure

It is obvious that over the long term, there must be a precise balance between the intake and excretion of water and electrolytes and that chronic hypertension cannot develop unless there is a shift of renal-pressure natriuresis to higher blood pressures. In the absence of altered pressure natriuresis, disturbances that tend to increase blood pressure, such as increased peripheral vascular resistance, would cause only a transient increase in blood pressure because they would also provoke increased sodium excretion; as long as sodium excretion exceeded intake, extracellular fluid volume would continue to decrease until arterial pressure returned to normal (Figure 2). For sodium balance to be maintained in the face of increased arterial pressure, there must be a shift of renal-pressure natriuresis to higher blood pressures.

There are 2 potential explanations, however, for abnormal pressure natriuresis in hypertension. The most prevalent view in the 1970s and early 1980s was that hypertension is caused by mechanisms that increase peripheral vascular resistance or cardiac pumping ability and that the kidneys then somehow adapt to the higher blood pressure as a result of either intrarenal or neurohumoral changes that alter kidney function. The implication of this viewpoint is that arterial pressure does not have a long-term effect on sodium excretion and that pressure natriuresis is not a major long-term controller of blood pressure.

The opposing view, articulated in the model of Guyton and Coleman,⁷ is that hypertension occurs secondarily to impaired pressure natriuresis and that arterial pressure is regulated at the level required to maintain sodium balance. The implication of this model is that pressure natriuresis plays a dominant role in long-term regulation of blood pressure. These 2 opposing views hinged on the question of whether changes in renal perfusion pressure have a long-term effect on sodium and water excretion. When we began our studies, there were no experimental data that would allow a definitive choice between these 2 opposing views. Therefore, we began several years of research to test these concepts by (1) determining whether perfusion pressure has a long-term effect on sodium excretion and whether servo-controlling renal perfusion pressure prevents sodium balance from being maintained in various forms of experimental hypertension and (2) determining how various neurohumoral and intrarenal mechanisms alter pressure natriuresis chronically, and therefore blood pressure regulation.

Servo-Control of Renal Perfusion Pressure in Hypertension Caused by Antinatriuretic Hormones

Excessive secretion of antinatriuretic hormones such as aldosterone or angiotensin II (ANG II) typically causes only transient sodium retention. The sodium retention usually lasts only a few days and is followed by an “escape,” where sodium excretion returns to normal as hypertension develops.^{10,11} The mechanisms responsible for this escape have been the subject of considerable research, and various factors have been proposed, including increased formation of various natriuretic factors, such as atrial natriuretic factor, prostaglan-

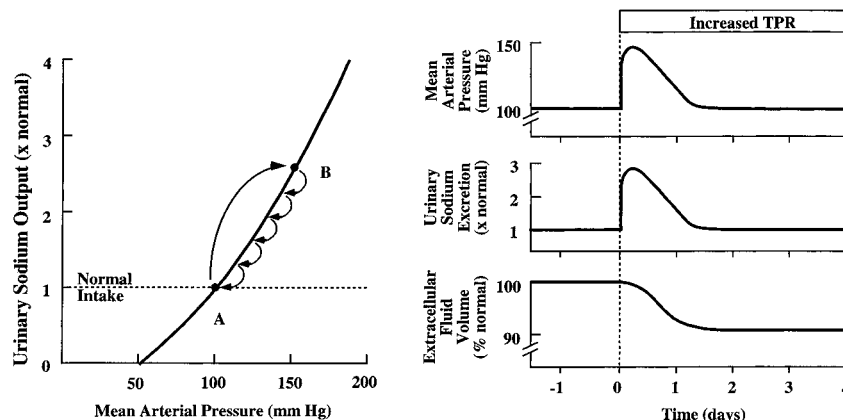


Figure 2. Effects of a hypertensive stimulus, such as increased total peripheral vascular resistance (TPR), with no impairment of pressure natriuresis. Blood pressure initially increases from point A to point B, but hypertension cannot be sustained because sodium excretion exceeds intake; extracellular fluid volume continues to decrease until arterial pressure returns to normal and sodium intake and output are balanced.

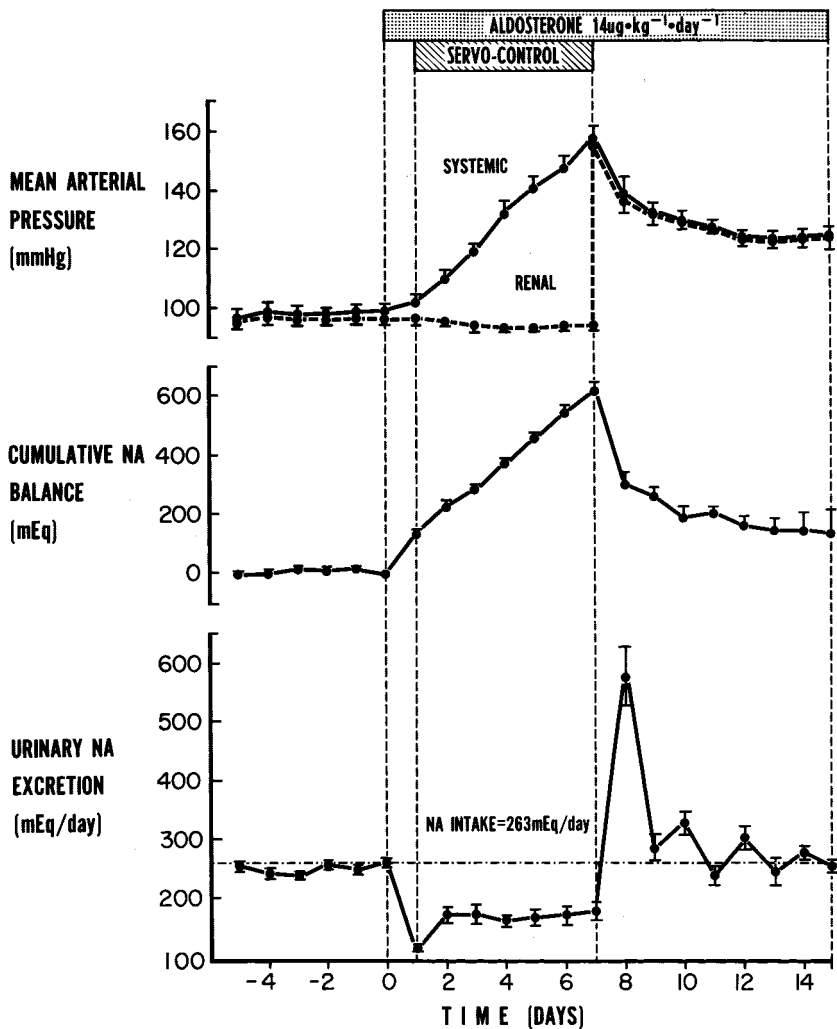


Figure 3. Effects of aldosterone infusion when renal perfusion pressure was servo-controlled at the normal level. After 7 days of continued sodium and water retention, severe systemic arterial hypertension and edema occurred. When the servo-controller was stopped and renal perfusion pressure was permitted to increase, the kidneys escaped from sodium retention and sodium balance was rapidly restored.¹¹

dins, kinins, or other natriuretic hormones.^{12,13} According to the renal-body fluid feedback concept, aldosterone and ANG II reduce renal excretory capability, initiating a sequence of events that elevates blood pressure. The increased arterial pressure then serves to restore sodium excretion to normal via pressure natriuresis. However, total peripheral vascular resistance often increases during hypertension, even when hypertension is initiated by sodium retention and volume expansion, and the elevated blood pressure has also been suggested to be caused by direct or indirect effects of these hormones to constrict the peripheral vasculature.

To directly test these opposing views and to quantify the importance of pressure natriuresis in hypertension, we compared the chronic blood pressure and renal effects of various antinatriuretic hormones in dogs in which renal perfusion pressure was either permitted to increase or servo-controlled at the normal level to prevent pressure natriuresis.^{10,11,13,14} This required us to develop an electronic servo-control system that precisely regulated renal perfusion pressure 24 hours a day for long periods of time,¹⁵ a task that took us almost 2 years to complete before we were able to obtain consistently reliable data in chronically instrumented conscious animals.

Infusion of aldosterone in normal dogs caused relatively mild hypertension and only transient reductions in sodium excretion, which returned toward control after 1 to 2 days of infusion. After several days of aldosterone infusion, cumulative sodium balance and extracellular fluid volume were only slightly increased, and there were no obvious changes in renal function, except that glomerular filtration rate (GFR) was increased significantly. However, when renal perfusion pressure was servo-controlled, aldosterone infusion caused continued sodium retention and progressive increases in cumulative sodium balance and extracellular fluid volume, resulting in severe circulatory congestion and edema (Figure 3). When the servo-controller was stopped and renal perfusion pressure was allowed to increase to hypertensive levels, there was a prompt escape from sodium retention, cumulative sodium balance, and extracellular fluid volumes decreased, and sodium balance was reestablished.¹¹

The same results were obtained during chronic ANG II infusion in which servo-control of renal perfusion pressure prevented escape from sodium retention, resulting in severe increases in cumulative sodium balance and pulmonary edema within a few days (Figure 4).¹⁰ These experiments

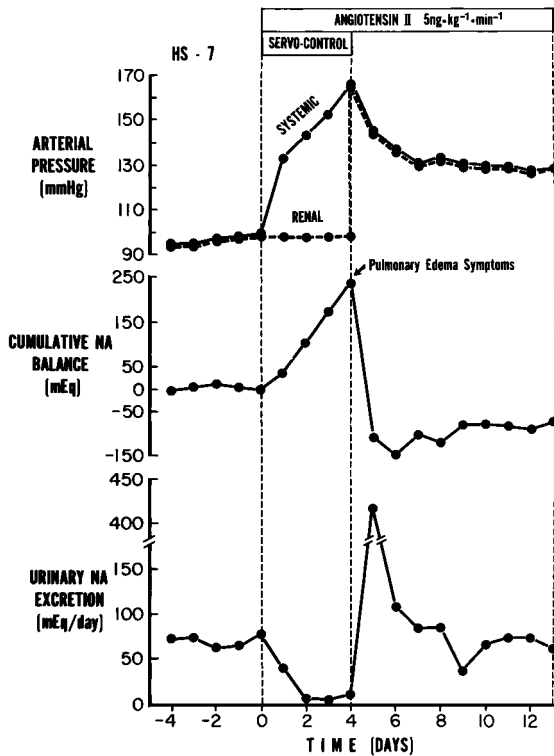


Figure 4. Effects of angiotensin II infusion when renal perfusion pressure was servo-controlled at the normal level. After 4 days, severe systemic arterial hypertension and sodium retention occurred, resulting in pulmonary edema. When the servo-controller was stopped, sodium balance was rapidly restored.

demonstrated for the first time the extreme importance of pressure natriuresis in long-term control of sodium balance and arterial pressure.

Servo-Control of Renal Perfusion Pressure in “Vasoconstrictor” Hypertension

We extended our investigation of pressure natriuresis to other types of hypertension, including experimental models that do not initially involve sodium retention but instead are associated with high levels of vasoconstrictors such as vasopressin and norepinephrine. In fact, these vasoconstrictors often elicit transient natriuresis when they are administered chronically at rates sufficient to cause hypertension.^{16,17}

Although vasopressin and norepinephrine are powerful peripheral vasoconstrictors, they usually cause only small increases in blood pressure when chronically infused, as long as kidney function is not markedly impaired.^{16,17} That these potent vasoconstrictors cause only mild hypertension, even though they initially elicit large increases in vascular resistance and blood pressure during acute infusions, is difficult to explain if one considers that increased peripheral vascular resistance is the primary cause of hypertension. However, the failure of vasopressin or norepinephrine to cause sustained, severe hypertension is understandable if one considers the fact that they also have relatively weak antinatriuretic actions.

How can the chronic hypertensive actions of vasopressin or norepinephrine be attributed to their renal actions if they actually increase sodium excretion and decrease extracellular fluid volume? Figure 5 shows the relationship between blood pressure and sodium excretion after an infusion of a powerful peripheral vasoconstrictor with relatively weak antinatriuretic action, such as norepinephrine. The antinatriuretic effect of the vasoconstrictor shifts the pressure natriuresis to higher blood pressures, thereby necessitating a small increase in blood pressure to maintain sodium balance. However, if the vasoconstrictor has a weak antinatriuretic effect compared with its peripheral vascular actions, arterial pressure would initially rise above the renal set-point for regulation of sodium balance and cause a transient natriuresis. The sodium loss would be transient because extracellular fluid volume would decrease and arterial pressure would eventually stabilize at a point where sodium intake and output are balanced.

This explanation fits with our experimental findings that the chronic natriuretic effects of norepinephrine and vasopressin were completely abolished when renal perfusion pressure was prevented from increasing. When renal perfusion pressure was servo-controlled during vasopressin or norepinephrine hypertension, there was continued sodium retention, marked volume expansion, and an inability to maintain sodium and water balance, indicating that these “vasoconstrictors” actually have significant effects to cause sodium and/or water retention and to impair pressure natriuresis and diuresis.

In all forms of hypertension that we have investigated, there is a shift of renal-pressure natriuresis that initiates and sustains the hypertension.^{13,18–20} In some instances, the

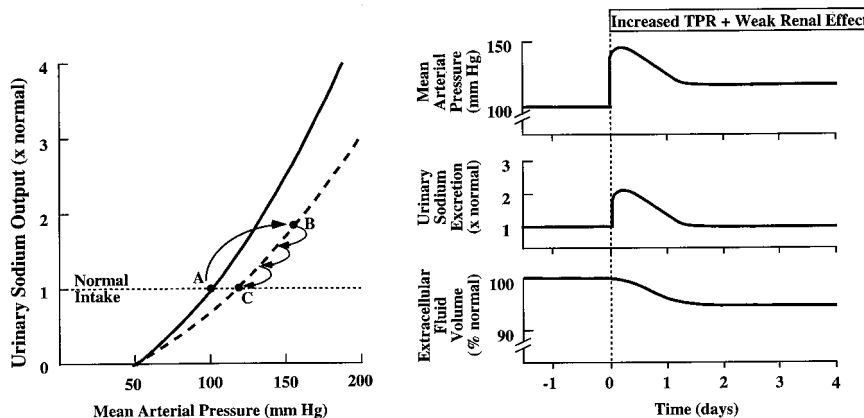


Figure 5. Long-term effects of a powerful vasoconstrictor that has a relatively weak effect in impairing pressure natriuresis. The normal curve (solid line) is compared with the vasoconstrictor curve (dashed line). Initially the vasoconstrictor raises blood pressure (from point A to point B) above the renal set point for sodium balance. Increased arterial pressure, however, causes a transient natriuresis and decreases extracellular fluid volume until arterial pressure eventually stabilizes at a level (point C) at which sodium intake and output are balanced.

sodium-retaining actions of these hypertensive stimuli are obscured by other effects, such as peripheral vasoconstriction, that raise blood pressure above the renal set-point at which sodium balance is maintained. In these cases, sodium excretion may increase and extracellular fluid volume may actually decrease as hypertension develops. However, the maintenance of high blood pressure chronically depends on the changes in renal function that shift pressure natriuresis to higher blood pressures. The increase in arterial pressure then serves to maintain sodium balance, via pressure natriuresis, despite impaired renal excretory function.

Chronic Effects of Renal Perfusion Pressure on Excretion of Sodium

We also directly tested whether pressure natriuresis has a long-term effect on sodium and water excretion by using a split-bladder preparation to collect urine separately from each kidney and servo-controlling renal perfusion pressure in each of the 2 kidneys independently.²¹ Because the 2 kidneys in each animal were exposed to the same neurohumoral influences, these studies were able to quantitate the chronic effects of small changes in renal perfusion pressure per se on electrolyte excretion and renal hemodynamics. These studies demonstrated that relatively small changes in renal artery pressure cause large alterations in sodium and water excretions that persisted as long as renal artery pressure was altered (12 days). Thus, the kidneys did not appear to adapt their excretory function during chronic changes in perfusion pressure. In fact, the long-term effects of renal artery pressure on sodium excretion are considerably greater than those observed during acute changes in pressure.

Neurohumoral Modulation of Renal-Pressure Natriuresis

We examined extensively the intrarenal mechanisms of pressure natriuresis and its modulation by various neural, endocrine, and paracrine systems. One of the most powerful of these proved to be the renin-angiotensin system (RAS). When the RAS is fully functional, the chronic relationship between arterial pressure and sodium excretion is extremely steep, and sodium balance can be maintained over a wide range of intakes with minimal changes in arterial pressure²²⁻²⁴ (Figure 6). A major reason for the usual effectiveness of the pressure natriuresis mechanism is that ANG II levels can be suppressed during high sodium intake and increased when sodium intake is restricted. This modulation therefore helps to adjust renal sodium excretion appropriately without the need to invoke large changes in arterial pressure to maintain sodium balance. When ANG II is prevented from being suppressed by the infusion of small amounts of ANG II, pressure natriuresis is impaired and blood pressure becomes very salt-sensitive, increasing markedly when sodium intake is raised.²²

Blockade of the RAS, with ANG II receptor antagonists or angiotensin converting enzyme (ACE) inhibitors, greatly enhances renal excretory capability, so that sodium balance can be maintained at reduced arterial pressures²² (Figure 6). However, blockade of the RAS also decreases the slope of pressure natriuresis and makes blood pressure salt-sensitive.²²

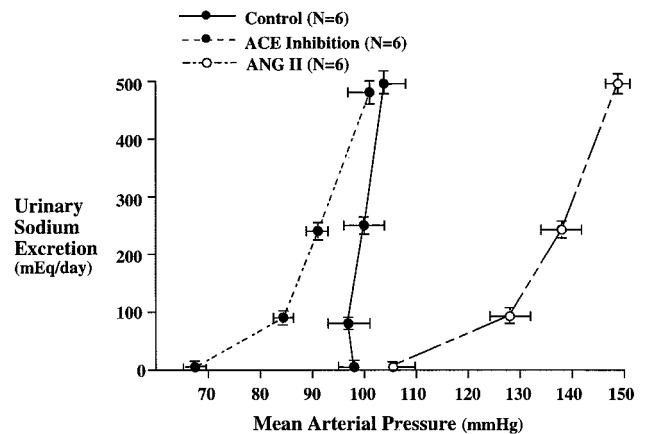


Figure 6. Chronic relationships between arterial pressure and sodium intake and excretion in dogs with a normal renin-angiotensin system, after blockade of ANG II formation with an angiotensin-converting enzyme inhibitor and after continuous infusion of a low dose of ANG II (5 ng/kg per minute) to prevent circulating ANG II levels from being suppressed when sodium intake was increased. Note that the inability to modulate ANG II levels decreases the slope of pressure natriuresis and causes marked salt-sensitivity of blood pressure. Redrawn from data in Hall et al (1980).²²

Thus, either inappropriately high levels of ANG II or the inability to decrease ANG II formation further as sodium intake is raised causes blood pressure to be very salt-sensitive.

Although there are other hormonal systems that influence the effectiveness of pressure natriuresis and, therefore, long-term blood pressure regulation, few have proved to be as powerful as the RAS. This is evidenced by the effectiveness of drugs that block the RAS in improving renal excretory function and permitting sodium balance to be maintained at reduced blood pressures. The sympathetic nervous system, however, also has a powerful influence on pressure natriuresis and long-term blood pressure regulation, especially in hypertension caused by excessive weight gain, as discussed below.

Abnormal Pressure Natriuresis in Essential Hypertension

Although pressure natriuresis is clearly reset in human essential hypertension, the precise causes of impaired pressure natriuresis have remained elusive. Measurements of various indices of kidney function, such as serum creatinine, GFR, or renal blood flow, after hypertension is established, or even during the slow insidious development of hypertension, often do not reveal the pathophysiological processes that initiate hypertension because these measurements represent a summation of compensatory mechanisms and abnormalities that cause hypertension. In some patients with essential hypertension, renal plasma flow and GFR are actually increased, suggesting that the impairment of pressure natriuresis may be due primarily to increased renal tubular reabsorption rather than renal vasoconstriction. It seems likely that multiple aberrations of renal function may contribute to impaired pressure natriuresis in different patients with essential hypertension and that changes in renal function are highly

Cardiovascular, Neurohumoral, and Renal Changes in Experimental Obesity Caused by a High Fat Diet and in Human Obesity

Model	Arterial Pressure	Heart Rate	Cardiac Output	Renal		Renal Tubular Reabsorption	GFR*
				Sympathetic Activity	Na ⁺ Balance		
Obese rabbits (high fat diet)	↑	↑	↑	↑	↑	↑	↑
Obese dogs (high fat diet)	↑	↑	↑	↑	↑	↑	↑
Obese humans	↑	↑	↑	↑	↑	↑	↑

PRA indicates plasma renin activity; GFR, glomerular filtration rate.

*The GFR changes refer to the early phases of obesity before major loss of nephron function has occurred.

time dependent.^{19,20} Although it is probably unwise to ascribe a single cause to all essential hypertension patients, recent studies suggest that excess weight gain may play a key role in impairing pressure natriuresis and raising blood pressure in a majority of hypertensive patients.^{25–27}

Obesity as a Cause of Essential Hypertension

The prevalence of obesity has risen dramatically in the past 2 decades. In 1999–2000, the age-adjusted prevalence of obesity, defined as a body mass index (BMI) >30, was 30.5% compared with 22.9% in the 1980s and early 1990s.²⁸ The prevalence of overweight, defined as a BMI >25.0, has also increased to 64.5% of the population.²⁸

The relationship between obesity and hypertension is now widely recognized, with experimental studies showing that weight gain raises blood pressure, clinical studies showing that weight loss is effective in lowering blood pressure in most hypertensive patients, and population studies showing that excess weight gain is one of the best predictors for development of hypertension.^{25–27,29–31} Evidence that obesity is a major cause of hypertension also comes from multiple studies showing that most hypertensive patients are overweight. Results from the Framingham Heart Study,³¹ for example, suggest that approximately 65% to 75% of the risk for hypertension can be directly attributed to excess weight.

Although the importance of obesity as a cause of essential hypertension is well established, the mechanisms by which excessive weight gain alters renal function and raises blood pressure are only beginning to be elucidated. Experimental studies in animals have permitted a mechanistic approach toward the problem, and dietary models of obesity, especially those produced by feeding a high fat diet, mimic very closely the metabolic, neurohumoral, renal, and cardiovascular changes observed in obese humans.^{25–27,32–34} The Table summarizes some of these changes, including increases in arterial pressure, cardiac output, and heart rate, activation of the renin-angiotensin and sympathetic nervous systems, sodium and water retention and expansion of extracellular fluid volume, and increases in GFR.

Hemodynamic Changes Associated With Excess Weight Gain

Obesity is associated with increases in regional blood flows, cardiac output, and arterial pressure.^{25–27,32–34} Cardiac index (cardiac output/body weight) does not change significantly during weight gain, but absolute cardiac output increases markedly. Although part of the increased cardiac output is

due to the additional blood flow required for the extra adipose tissue, blood flows in nonadipose tissue, including the heart, kidneys, gastrointestinal tract, and skeletal muscle also increase with weight gain.^{25–27,32–34} The vasodilatation in these tissues appears to be due in part to increased metabolic rate and local accumulation of vasodilator metabolites, as well as growth of the organs and tissues in response to their increased metabolic demands.

Impaired Renal-Pressure Natriuresis in Obesity Hypertension

As is true with other forms of hypertension, the increased blood pressure associated with obesity is accompanied by impaired pressure natriuresis.^{33,35} In obese subjects, impaired pressure natriuresis is initially due to increased renal sodium reabsorption because GFR and renal plasma flow are actually increased.^{25,35} With prolonged obesity, increases in arterial pressure, renal vasodilation and glomerular hyperfiltration, neurohumoral activation, and metabolic changes may cause glomerular injury and further impairment of renal-pressure natriuresis, resulting in more severe hypertension and a gradual loss of kidney function.^{25,35}

Three mechanisms appear to be especially important in mediating increased sodium reabsorption associated with weight gain: (1) increased renal sympathetic activity, (2) activation of the renin-angiotensin system, and (3) altered intrarenal physical forces. Another mechanism, hyperinsulinemia, has also been suggested to raise arterial pressure in obese subjects, although most of the available evidence suggests that elevated insulin levels do not raise blood pressure in dogs or humans.³⁶

Sympathetic Activation Alters Renal Function and Increases Blood Pressure in Obesity

Multiple observations in animals and humans indicate that excess weight gain is associated with increased sympathetic activity, especially in the kidney.^{27,37,38} We have shown that combined α - and β -adrenergic blockade markedly attenuates the rise in blood pressure during the development of dietary-induced obesity in dogs²⁷ and that combined α - and β -adrenergic blockade reduced arterial pressure to a greater extent in obese than in lean hypertensive humans.³⁹ Increased sympathetic activity appears to raise blood pressure mainly through the renal sympathetic nerves, because renal denervation blunted the sodium retention and markedly attenuated the rise in blood pressure associated with dietary obesity in dogs.⁴⁰ Because renal sympathetic activity is also increased in

obese humans,³⁸ it is likely that the renal nerves also play a key role in human obesity-related hypertension.

We have studied several potential mechanisms by which obesity may increase sympathetic activity, but one of the most promising of these is hyperleptinemia.²⁷ Leptin is produced by adipocytes, and fasting plasma leptin levels rise in proportion to adiposity. Leptin regulates energy balance by decreasing appetite and also by stimulating thermogenesis via sympathetic activation. Although acute infusions of leptin raise sympathetic activity,⁴¹ the question of whether these effects would cause chronic hypertension was unclear until leptin infusions were demonstrated to cause sustained increases in blood pressure in rats despite marked hypophagia and weight loss.⁴² The hypertensive effect of leptin was completely abolished by combined α - and β -adrenergic blockade.⁴³ Studies in transgenic mice in which leptin is secreted ectopically by the liver also indicate that hyperleptinemia causes mild hypertension.⁴⁴

Another observation that points toward leptin as a potential mediator of obesity-related hypertension is the finding that obese mice that are leptin deficient and obese rats that have leptin receptor mutations usually have little or no hypertension compared with lean control mice.^{27,45} Therefore, increased leptin synthesis and functional leptin receptors appear to be necessary for obesity to cause significant increases in blood pressure in rodents. Whether this is true in other species or in humans, however, is still uncertain.

The mechanisms of leptin-induced sympathoactivation are still unclear, although recent studies suggest important interactions with other neurochemicals in the hypothalamus. For example, leptin stimulates the proopiomelanocortin pathway, and antagonism of the melanocortin 3/4-receptor (MC3/4-R) completely abolished the acute effects of leptin to stimulate renal sympathetic activity.⁴⁶ Moreover, chronic blockade of the MC3/4-R in rats caused rapid and marked weight gain, but little or no increase in arterial pressure and a reduction in heart rate.⁴⁷ Because weight gain usually raises arterial pressure and heart rate, these observations are consistent with the possibility that a functional MC3/4-R is important in linking weight gain with increases in sympathetic activity and arterial pressure, at least in rodents. However, the role of the MC3/4-R and its interactions with leptin in mediating sympathetic activation and increased arterial pressure in obese humans has not been investigated.

Renin-Angiotensin System Alters Renal Function and Increases Blood Pressure in Obesity

Although excess weight gain is associated with marked sodium retention and expansion of extracellular fluid volume, obese subjects usually have increases in plasma renin activity (PRA), plasma angiotensinogen, angiotensin-converting enzyme (ACE) activity, and plasma ANG II levels. A significant role for ANG II in stimulating sodium reabsorption, impairing renal-pressure natriuresis, and causing hypertension in obesity is supported by the finding that treatment of obese dogs with an ANG II antagonist or ACE inhibitor blunts sodium retention and volume expansion, as well as increased arterial pressure.^{48,49} Also, ACE inhibitors are

effective in reducing blood pressure in obese humans, particularly in young patients.⁵⁰

In addition to raising blood pressure, activation of the RAS may also contribute to glomerular injury and nephron loss associated with obesity because increased ANG II formation constricts the efferent arterioles and exacerbates the rise in glomerular hydrostatic pressure caused by systemic arterial hypertension.^{23,24} Studies in patients with type II diabetes, who are usually overweight, clearly indicate that ACE inhibitors and ANG II receptor antagonists slow progression of renal disease.^{24,51} However, additional studies are needed in nondiabetic obese subjects to determine whether RAS blockers are more effective than other antihypertensive agents in reducing the risk of renal injury.

Structural and Functional Changes in the Renal Medulla and Cortex May Contribute to Obesity Hypertension

Adipose tissue almost completely encapsulates the kidneys and penetrates into the medullary sinuses of obese subjects causing compression and increased intrarenal pressures.^{25,35} Intra-abdominal pressure of obese subjects is also increased in proportion to the sagittal abdominal diameter, reaching levels as high as 35 to 40 mm Hg in some subjects with central obesity.⁵² Therefore, increased intrarenal pressures caused by fat surrounding the kidneys and increased abdominal pressure may impair pressure natriuresis and contribute to obesity-associated hypertension.^{25,35}

Obesity also causes marked changes in renal medullary histology that could compress the medulla and impair pressure natriuresis. Total glycosaminoglycan content and hyaluronan, a major component of the renal medullary extracellular matrix, are markedly elevated in the inner medulla of obese dogs and rabbits compared with the controls.^{53,54} Because the kidney is surrounded by a capsule with low compliance, increased extracellular matrix would raise renal interstitial pressure and solid tissue pressure, thereby causing compression of the thin loops of Henle, reducing vasa recta blood flow, and increasing tubular reabsorption. In support of this hypothesis, we have found that renal interstitial fluid pressure is markedly elevated in obese dogs.^{25,35}

Obviously, renal compression cannot explain the initial rise in blood pressure associated with rapid weight gain, but it could contribute to more sustained increases in tubular reabsorption, volume expansion, and hypertension associated with chronic obesity. Renal compression could also explain why there is a much better correlation between abdominal obesity and hypertension than observed with lower body obesity and hypertension.

Obesity Causes Glomerular Injury and Is a Major Risk Factor for End-Stage Renal Disease

The compensatory renal vasodilation, increased GFR, and higher blood pressure associated with obesity are important in overcoming increased sodium reabsorption. In the long term, however, these compensatory responses may cause glomerular injury. We found significant glomerular injury after only 7 to 9 weeks of a high fat diet in dogs, including enlargement of Bowman's space, increased glomerular cell proliferation,

increased mesangial matrix, and thicker basement membranes, as well as increased expression of glomerular transforming growth factor β .⁵⁵

These early glomerular changes in obesity may be the precursors of more severe glomerular injury and progressive impairment of pressure natriuresis. For example, more than 90% of obese Zucker rats die of end-stage renal disease (ESRD), but restricting their food intake by less than 20% markedly decreases renal injury and increases life span.⁵⁶ Although there have been no long-term studies on the effects of food restriction or weight loss on renal function in humans, there is no doubt that obesity is closely associated with the 2 main causes of ESRD, diabetes and hypertension.⁵⁷ Studies in humans have also shown that obesity is associated with proteinuria even before there are major histologic changes in the kidney.⁵⁸ Moreover, obese subjects have glomerulomegaly and focal segmental glomerulosclerosis, even in the absence of diabetes.⁵⁸ A review of almost 7000 renal biopsies indicated that the incidence of obesity-related glomerulopathy, defined as combined focal segmental glomerulosclerosis and glomerulomegaly, rose 10-fold from 1990 to 2000, coincident with rapid increase in the prevalence of obesity during this period.⁵⁹ Given this information, as well as the fact that obesity is closely associated with 2 main causes of ESRD, it seems likely that obesity may greatly increase the risk for ESRD. This would explain why the prevalence of ESRD has risen dramatically in the past 20 to 30 years, in parallel with increasing prevalence of obesity, even though other risk factors for vascular disease such as smoking and hypercholesterolemia have been decreasing.²⁵

Summary and Perspectives

Research during the past 3 decades has clearly demonstrated the central role of renal-pressure natriuresis in long-term blood pressure regulation and its impairment in all forms of hypertension, including human essential hypertension. Although the precise causes of impaired renal-pressure natriuresis in essential hypertension are still unclear, recent evidence suggests that overweight and obesity play a major role. Excessive weight gain increases renal tubular reabsorp-

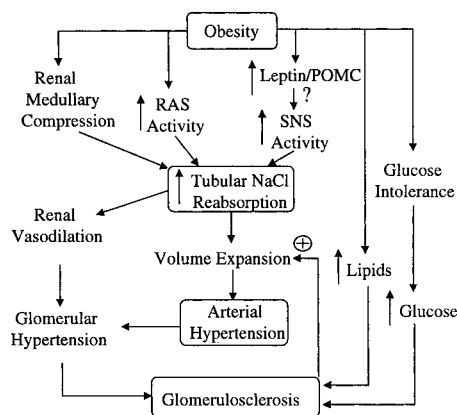


Figure 7. Summary of mechanisms by which obesity increases renal tubular sodium reabsorption, impairs pressure natriuresis, and causes hypertension as well as progressive glomerular injury.

tion and impairs pressure natriuresis, in part, through activation of the sympathetic and renin-angiotensin system as well as physical compression of the kidney (Figure 7). With prolonged obesity, there are also structural changes in the kidney that eventually cause loss of nephron function, further impairment of pressure natriuresis, and further increases in arterial pressure. Although there are still many unanswered questions about how obesity activates the sympathetic nervous system, alters renal function, and causes hypertension and target organ injury, this is one of the most exciting areas for future biomedical research, especially in view of the growing “epidemic” of obesity throughout the world.

Acknowledgments

I am grateful for the important contributions of my colleagues in the Department of Physiology and Biophysics at the University of Mississippi Medical Center. I also thank the National Heart, Lung, and Blood Institute for continuously supporting my research since 1975.

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