CHAPTER 39

Role of the Kidneys in Hypertension

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Over 40 years ago Guyton and Coleman[1–3] proposed that if an increase in arterial pressure could produce sustained elevations in sodium and water excretion through a mechanism of renal pressure natriuresis and diuresis, then this system would have a near infinite gain for the long-term control of arterial pressure by regulating blood volume. Thus, whenever arterial pressure is elevated, renal arterial pressure would enhance the excretion of sodium and water until blood volume is reduced sufficiently to return arterial pressure to control values. According to the renal–body fluid system concept, hypertension can develop only when something impairs the excretory ability of the kidney and shifts the relation between sodium excretion and arterial pressure toward higher levels.[1–4] Although there is strong theoretical and experimental evidence that the kidney is a major determinant of the long-term control of arterial pressure, the initial abnormality of the kidney need not be intrinsic to the development of hypertension.[4–6] A shift of pressure natriuresis can occur as a result of intrarenal abnormalities such as enhanced formation of angiotensin II or genetic defects that enhance renal sodium transport mechanisms. In other instances, the altered kidney function is caused by extrarenal disturbances, such as increased sympathetic nervous system activity or excessive formation of antinatriuretic hormones such as aldosterone.[4–6]

RENAL-BODY FLUID FEEDBACK SYSTEM FOR LONG-TERM BLOOD PRESSURE REGULATION

According to the renal–body fluid feedback mechanism for long-term control of arterial pressure, extracellular fluid volume is determined by the balance between intake and excretion of salt and water by the kidneys (Fig. 39.1). A temporary higher intake than output would lead to an increase in extracellular volume and arterial pressure. If the excretory ability of the kidney is not impaired, the increase in arterial pressure raises sodium excretion and extracellular fluid volume would then decrease, thereby reducing venous return and cardiac output until blood pressure returns to normal and fluid intake and output are reestablished. Conversely, when sodium output exceeds intake and extracellular fluid volume and blood pressure fall below normal, the kidneys retain sodium and water until arterial pressure is restored to the normal set-point. Thus, according to the renal–body fluid feedback mechanism concept, the set-point for long-term blood pressure control is the arterial pressure at which sodium and water intake and output are at equilibrium.[4–7]

A key component of this mechanism for regulating salt and water balance is pressure natriuresis/diuresis, which is the effect of increased arterial pressure to raise sodium and water excretion. An important feature of pressure natriuresis is that various hormonal and neural control systems can amplify or blunt the pressure natriuresis mechanism.[5,7,9–11] For example, in most individuals, chronic increases in sodium intake are associated with only small changes in arterial pressure. The lack of significant increases in arterial pressure in response to elevations in sodium intake results in decreased formation of antinatriuretic hormones and/or increased formation of natriuretic factors, which enhance the effectiveness of pressure natriuresis and allow sodium balance to be maintained with little or no increase in arterial pressure. On the other hand, excessive activation of antinatriuretic systems or abnormalities in natriuretic systems can reduce the effectiveness of pressure natriuresis, thereby necessitating greater increases in arterial pressure to maintain sodium and water balance. Thus, excessive activation of antinatriuretic systems or abnormalities in natriuretic systems impairs the excretory ability of the kidney and shifts the relation between sodium excretion and arterial pressure toward higher levels and resets the set-point for long-term blood pressure control (Fig. 39.2).

Although total peripheral resistance and cardiac output are determinants of arterial pressure, one prediction of the renal–body fluid feedback mechanism is that if the pressure natriuresis mechanism is not impaired, a primary increase in total peripheral resistance or increases in cardiac pumping ability would not result in long-term alterations in arterial pressure.[2–6] For instance, an increase in total peripheral resistance would result in an immediate elevation in arterial

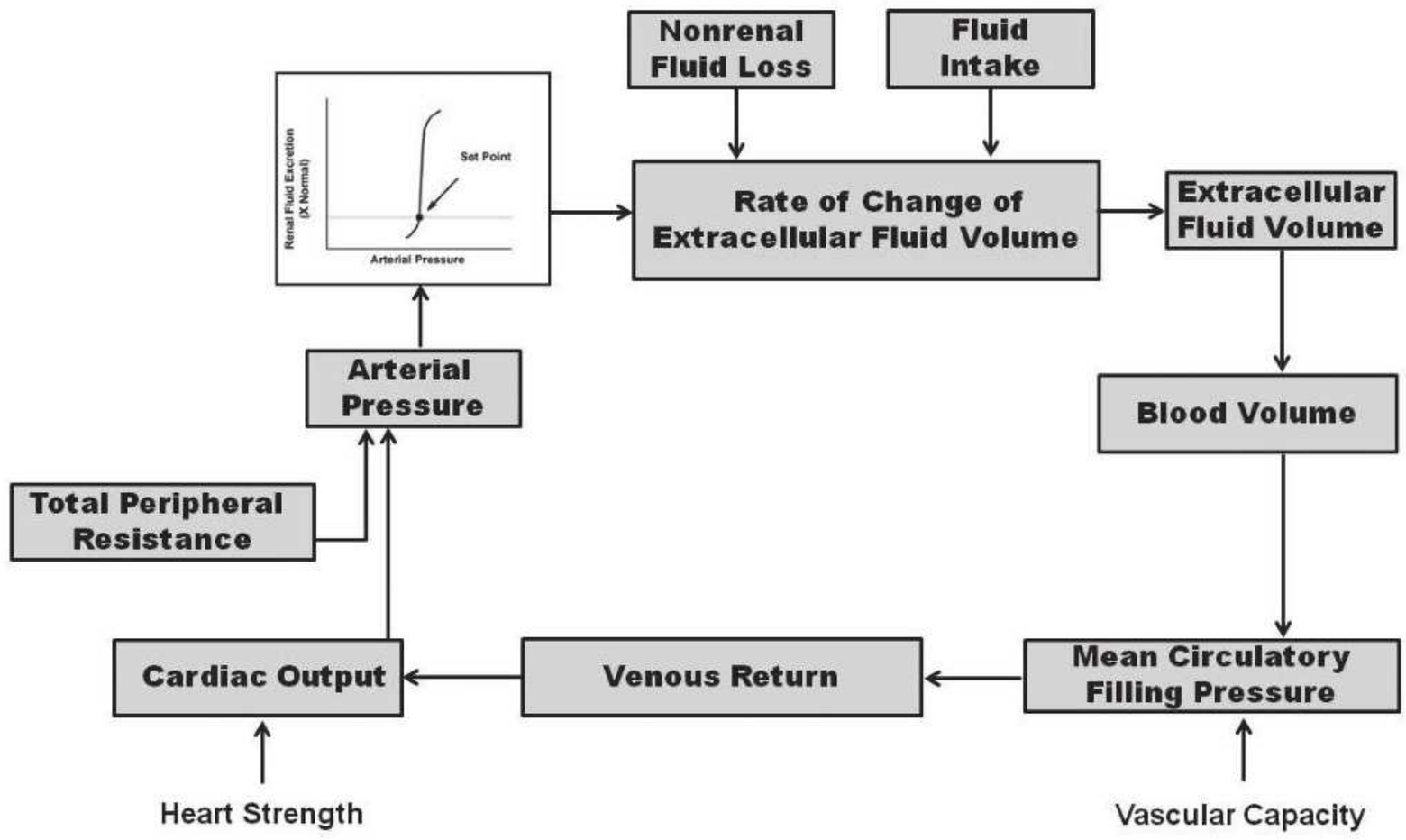

FIGURE 39.1 Basic renal–body fluid feedback mechanism for long-term regulation of blood pressure and body fluid volumes. (Redrawn from Granger JP, Hall JE. Role of the kidney sodium and fluid excretion in hypertension. In: Lip GYP, Hall JE, eds. *Comprehensive Hypertension*. New York: Elsevier; 2007.)

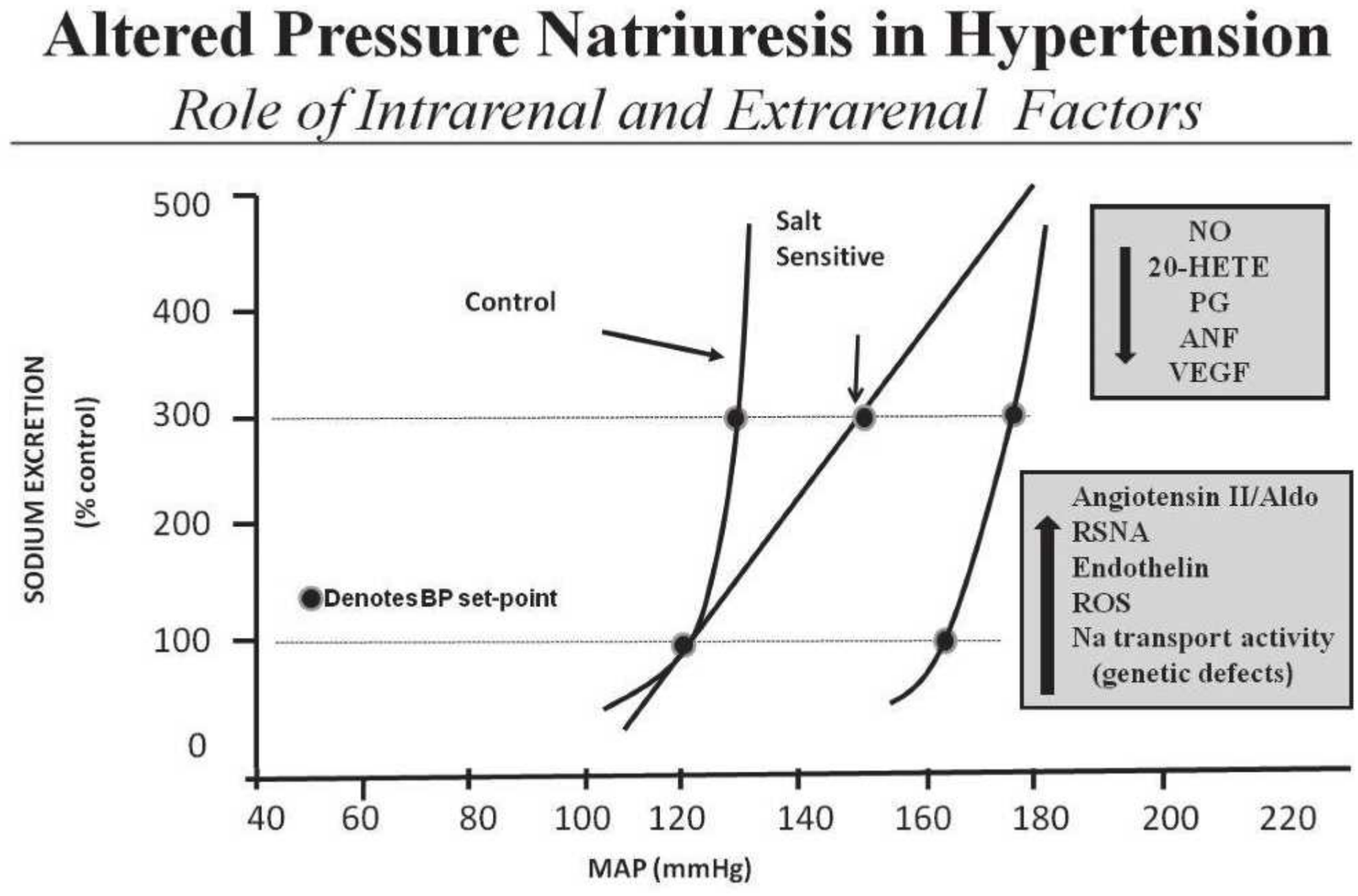

FIGURE 39.2 Steady-state relationships between arterial pressure and urinary sodium excretion and sodium intake for control subjects with normal kidneys and for subjects with a rightward hypertensive shift in the pressure-natriuresis relationship. A shift in the pressure natriuresis relationship can occur as a result of *intrarenal* abnormalities such as enhanced formation of angiotensin II (ANGII), reactive oxygen species (ROS), inflammatory cytokines and endothelin (via ET_A receptor activation), or decreased synthesis of nitric oxide (NO), natriuretic prostanoids (PG), vascular endothelial growth factor (VEGF), or even genetic defects that enhance renal sodium transport mechanisms. In other instances, the altered kidney function is caused by *extrarenal* disturbances, such as increased sympathetic nervous system (SNS) activity or excessive formation of antinatriuretic hormones such as aldosterone (Aldo) or decreased atrial natriuretic peptide (ANP).

pressure. The increase in arterial pressure would increase sodium and water excretion, via pressure natriuresis. As long as fluid excretion exceeds fluid intake, extracellular fluid volume will continue to decrease, reducing venous return and cardiac output, until blood pressure (BP) returns to normal and fluid balance is reestablished. Thus, according to the renal–body fluid volume control system concept, primary increases in total peripheral resistance or increases in cardiac pumping do not result in long-term alterations in arterial pressure and hypertension can develop only when something impairs the excretory ability of the kidney and shifts the relation between sodium excretion and arterial pressure toward higher levels.[2–6]

Although hypertension is a result of a reduction in the kidney's ability to excrete sodium and water (reduced pressure natriuresis), the hypertension may not necessarily be associated with increases in extracellular fluid volume. Indeed, many forms of hypertension are associated with increased total peripheral resistance and reduced rather than increased extracellular fluid volume. This occurs when a vasoconstrictor, such as norepinephrine, has a potent extrarenal vasoconstrictor effect to increase total peripheral resistance but a relatively weak antinatriuretic action. The antinatriuretic effect of norepinephrine shifts pressure natriuresis and the set-point for arterial pressure to a higher level. However, because norepinephrine has a more powerful extrarenal vasoconstrictor effect, arterial pressure initially increases above the renal set-point for sodium balance and causes transient natriuresis and decrease in extracellular fluid volume. Eventually arterial pressure stabilizes at a point where sodium intake and output are balanced. Thus, sodium retaining actions of norepinephrine are masked by peripheral vasoconstriction which raises BP above the renal set-point at which sodium balance is maintained causing increased renal excretion and decreased extracellular fluid volume. It is important to reiterate that the maintenance of high blood pressure chronically depends on norepinephrine's renal actions because norepinephrine's extrarenal effects to increase total peripheral resistance would in itself, as pointed out previously, only result in a transient increase in blood pressure.

PRESSURE NATRIURESIS: A KEY FACTOR IN MAINTAINING SODIUM BALANCE IN HYPERTENSION

Another important prediction of the renal–body fluid feedback control system concept is that an increase in BP in hypertensive states is an essential compensatory mechanism that allows sodium balance to be maintained in the face of an underlying sodium retaining defect.[5–7] The importance of the pressure-natriuresis mechanism in the regulation of sodium excretion can best be illustrated under conditions in which a sodium-retaining abnormality exists within the kidney and an increase in arterial pressure occurs to compensate for this abnormality. Such a condition is illustrated in the hypertension caused by aldosterone excess. To determine the importance of the pressure-natriuresis mechanism in achieving sodium balance during aldosterone-induced hypertension, Hall and colleagues[12] examined the long-term effects of aldosterone on sodium excretion and arterial pressure in normal dogs and in dogs in which renal artery pressure was prevented from increasing with an electronically servocontrolled aortic occluder. In dogs in which renal artery pressure was permitted to increase during chronic aldosterone infusion, sodium excretion decreased markedly on the first day and then returned to control levels on days 2 to 3 of aldosterone infusion as arterial pressure increased (Fig. 39.3). In contrast, in dogs in which renal artery pressure was prevented from increasing, sodium excretion decreased on the first day and remained below sodium intake for the 7 days of aldosterone infusion. The sustained sodium retention resulted in dramatic increases in cumulative sodium balance and systemic arterial pressure. The results from this study clearly demonstrated that an increase in renal arterial pressure is essential in allowing the kidneys to escape from the chronic sodium-retaining actions

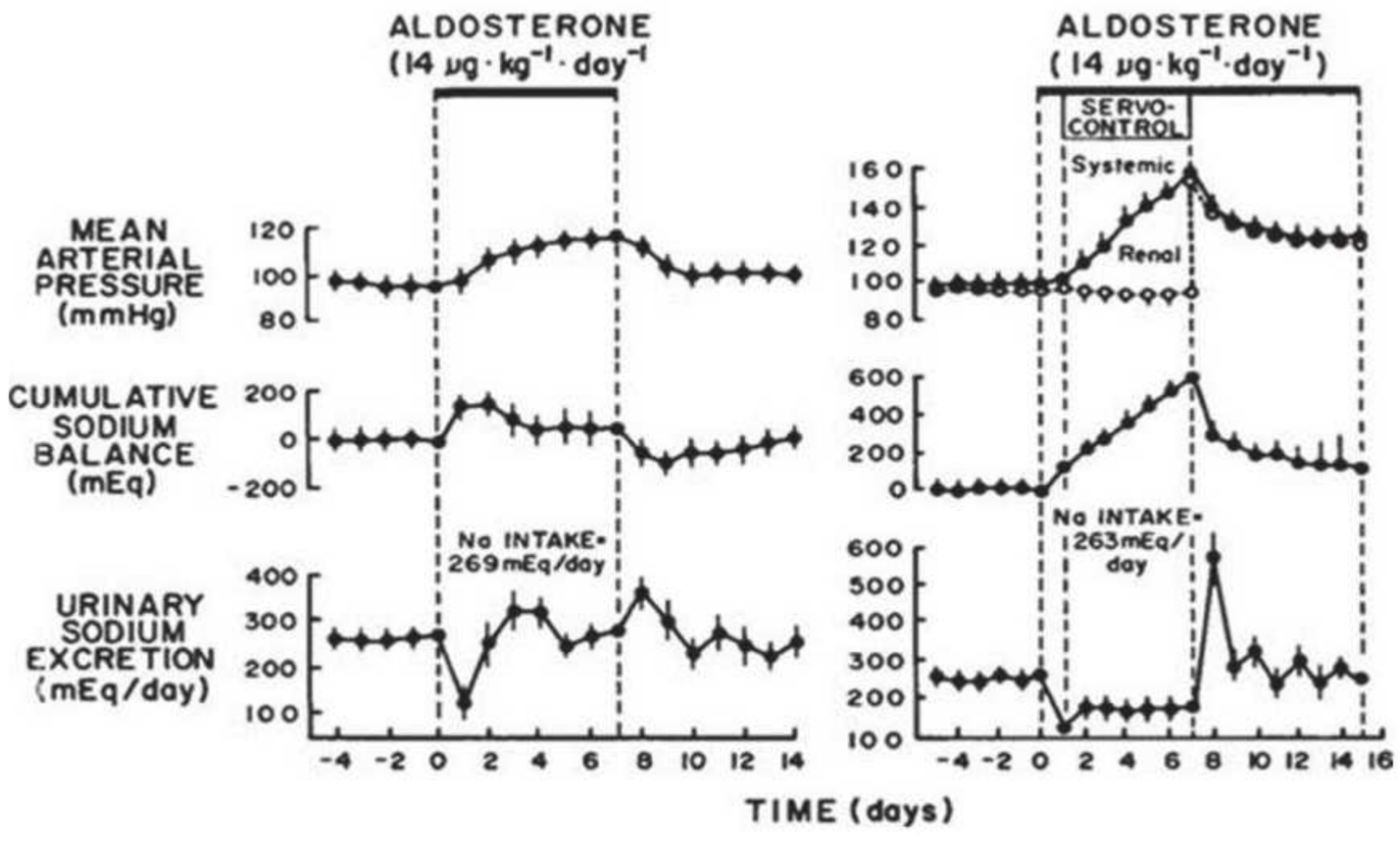

FIGURE 39.3 Effects of chronic aldosterone infusion on sodium excretion when renal perfusion pressure was allowed to increase (*left panel*) and was servo-controlled (*right panel*). Notice that when renal perfusion pressure was prevented from increasing, "escape" from sodium retention did not occur and cumulative sodium balance and systemic arterial pressure continued to increase. (Redrawn from Hall JE, Granger JP, Smith MJ, et al. Role of renal hemodynamics and arterial pressure in aldosterone "escape." *Hypertension*. 1984, 6(suppl I): I-183–I-192.)

of aldosterone and to achieve normal sodium balance. Similar findings were reported from the same group during chronic administration of other sodium-retaining hormones, such as angiotensin II and norepinephrine.[13,14] Thus, it appears that during pathophysiologic conditions associated with excess levels of sodium-retaining hormones, such as aldosterone or angiotensin II, the pressure-natriuresis mechanism is important for the maintenance of sodium balance.[15,16]

MECHANISM UNDERLYING RENAL PRESSURE NATRIURESIS

The ability of the kidney to alter urine flow and sodium excretion in response to acute changes in renal perfusion pressure has been of interest to investigators for many years.[17–19] Changes in sodium excretion in response to changes in renal perfusion pressure are thought to be due to alterations in tubular reabsorption of sodium, because glomerular filtration rate (GFR) and the filtered load of sodium are usually well autoregulated.[20] Thus, a decrease in renal perfusion pressure results in an increase in tubular reabsorption of sodium and a decrease in sodium excretion. In contrast, increases in renal perfusion pressure lead to decreases in tubular reabsorption of sodium and increases in sodium excretion, a phenomenon commonly referred to as pressure natriuresis.

The specific intrarenal mechanism responsible for the decrease in tubular reabsorption in response to increases in renal perfusion pressure appears to be related to increases in hemodynamic factors such as medullary blood flow and renal interstitial hydrostatic pressure (Fig. 39.4).[20–25] The mechanism whereby renal interstitial hydrostatic pressure (RIHP) increases in the absence of discernible changes in whole kidney renal blood flow and peritubular capillary hydrostatic and/or oncotic pressures may be related to increases in renal medullary flow as a result of nitric oxide-induced reductions in renal medullary vascular resistance.[26] Preventing RIHP from increasing in response to increases in renal perfusion pressure markedly attenuates pressure natriuresis.[24] Furthermore, direct increases in RIHP, comparable to increases measured in response to increases in renal perfusion pressure, have been shown to significantly decrease tubular reabsorption of sodium in the proximal tubule and increase sodium excretion.[20–24] The exact mechanism whereby RIHP influences tubular reabsorption is unknown but may be related to alterations in tight junction permeability to sodium in proximal tubules, redistribution of apical sodium transporters, and/or release of renal autacoids such as prostaglandin E2.[27–31]

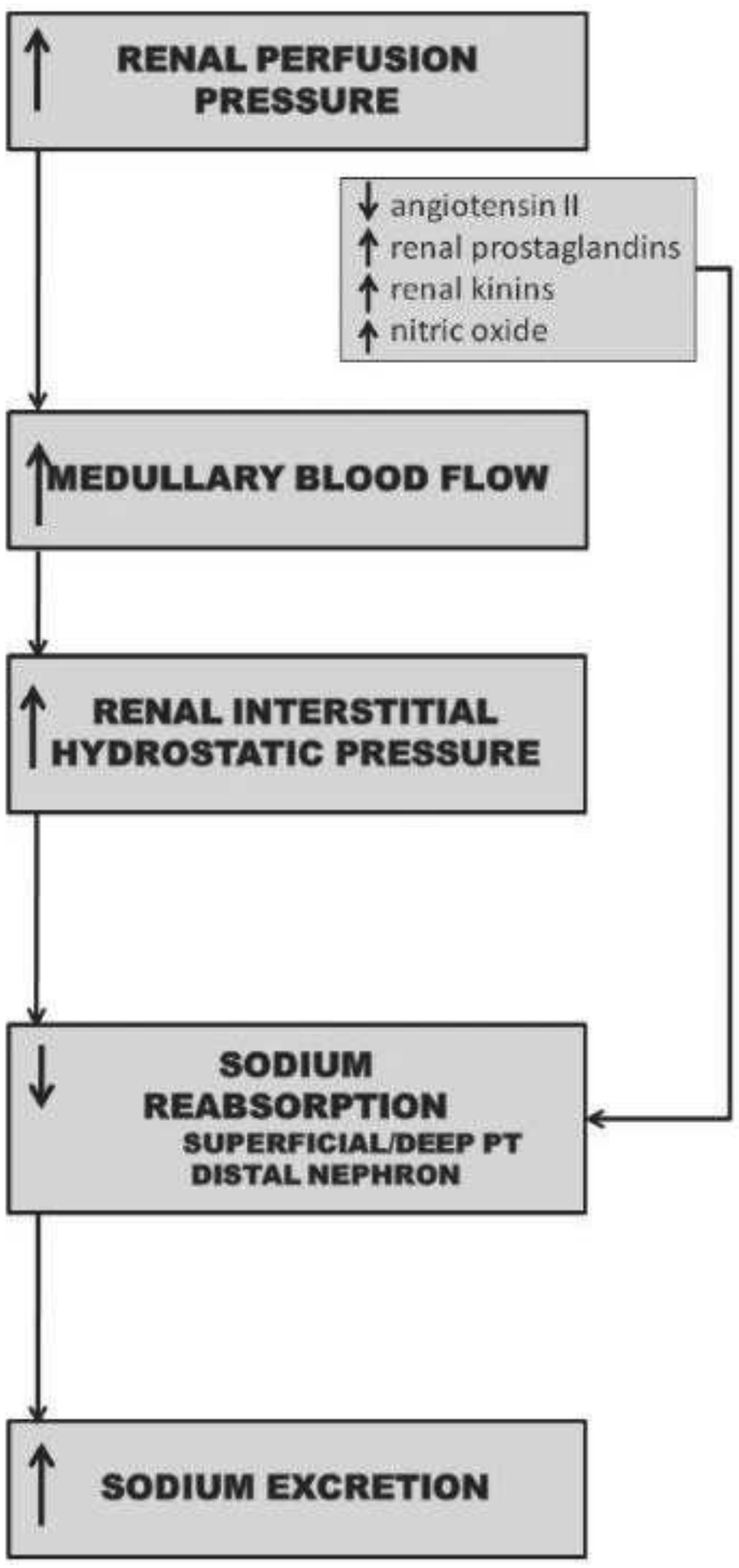

FIGURE 39.4 Mechanisms whereby increases in renal perfusion pressure enhance sodium excretion.

MECHANISMS OF IMPAIRED RENAL-PRESSURE NATRIURESIS IN HYPERTENSION

Several lines of evidence support an important role for the kidneys in the development and maintenance of hypertension. Some of the strongest evidence for a key role of the kidneys in hypertension derives from renal cross-transplantation studies.[4] Transplantation of a kidney from a hypertensive donor into a normotensive recipient has been demonstrated to produce sustained elevations in arterial pressure in numerous genetic models of hypertension (e.g., SHR, Dahl).[32] Of particular relevance to human hypertension is the study of Curtis et al.[33] demonstrating that BP returns to normal levels in hypertensive patients who were recipients of kidneys from normotensive donors. Another observation that points toward abnormal kidney function as a key factor in causing hypertension is that almost all forms of experimental hypertension are caused by perturbations to the kidneys that alter renal hemodynamics or tubular reabsorption and reduce the kidney's ability to excrete sodium and water. For example, constriction of the renal arteries (e.g., Goldblatt hypertension), compression of the kidneys (e.g., perinephritic hypertension), or administration of sodium-retaining hormones (e.g., ANG II) are all associated with either initial reductions in renal blood flow and GFR or increases in renal tubular reabsorption prior to development of hypertension.[7,34] Further evidence

supporting an important role for the kidneys in the development and maintenance of hypertension is that in all known monogenic forms of human hypertension, the common pathway to hypertension appears to be increased renal tubular reabsorption caused by mutations that directly increase renal electrolyte transport (e.g., Liddle or Gordon syndromes) or the synthesis and/or activity of antinatriuretic hormones (e.g., glucocorticoid remediable aldosteronism).[8]

Although specific abnormalities of kidney function are difficult to identify in most patients with primary hypertension, the one aspect of kidney function that is abnormal in all types of experimental and clinical hypertension is renal pressure natriuresis.[4,5,7,15,16,34] A shift in the pressure natriuresis relationship can occur as a result of intrarenal abnormalities such as enhanced formation of angiotensin II, reactive oxygen species (ROS), inflammatory cytokines, and endothelin (via ET_A receptor activation) or decreased synthesis of nitric oxide and natriuretic prostanoids or even genetic defects that enhance renal sodium transport mechanisms (Fig. 39.2). In other instances, the altered kidney function is caused by extrarenal disturbances, such as increased sympathetic nervous system (SNS) activity or excessive formation of antinatriuretic hormones such as aldosterone. The remaining portion of this chapter discusses how these intra- and extrarenal factors impair renal pressure natriuresis and lead to chronic hypertension.

The Renin-Angiotensin System

The renin-angiotensin system (RAS) plays a critical role in the long-term regulation of blood pressure and is involved in the pathogenesis of various forms of hypertension including renovascular hypertension and human essential hypertension.[10,15,34] Although the RAS has many components, its most important effects on renal hemodynamics and sodium reabsorption are exerted by angiotensin II (ANGII) via an ANGII type 1 (AT1) receptor (Fig. 39.5). ANGII also acts on ANGII type 2 receptors to cause renal vasodilation and natriuresis; however, the relative importance of this antihypertensive pathway is equivocal.[35–37] More recently, fragments of ANGII such as ANG 1–7 have also been suggested to have physiologic effects within the kidney, often opposing the actions of ANGII.[35–37] An isoform of angiotensin-converting enzyme (ACE), known as ACE2, appears to be involved in the formation of angiotensin 1–7.[35–37] Although experimental findings on Ang 1–7 are equivocal, ANG 1–7 has been shown to induce renal vasodilation, an effect that is thought to occur independently of binding to AT_1 or AT_2 receptors

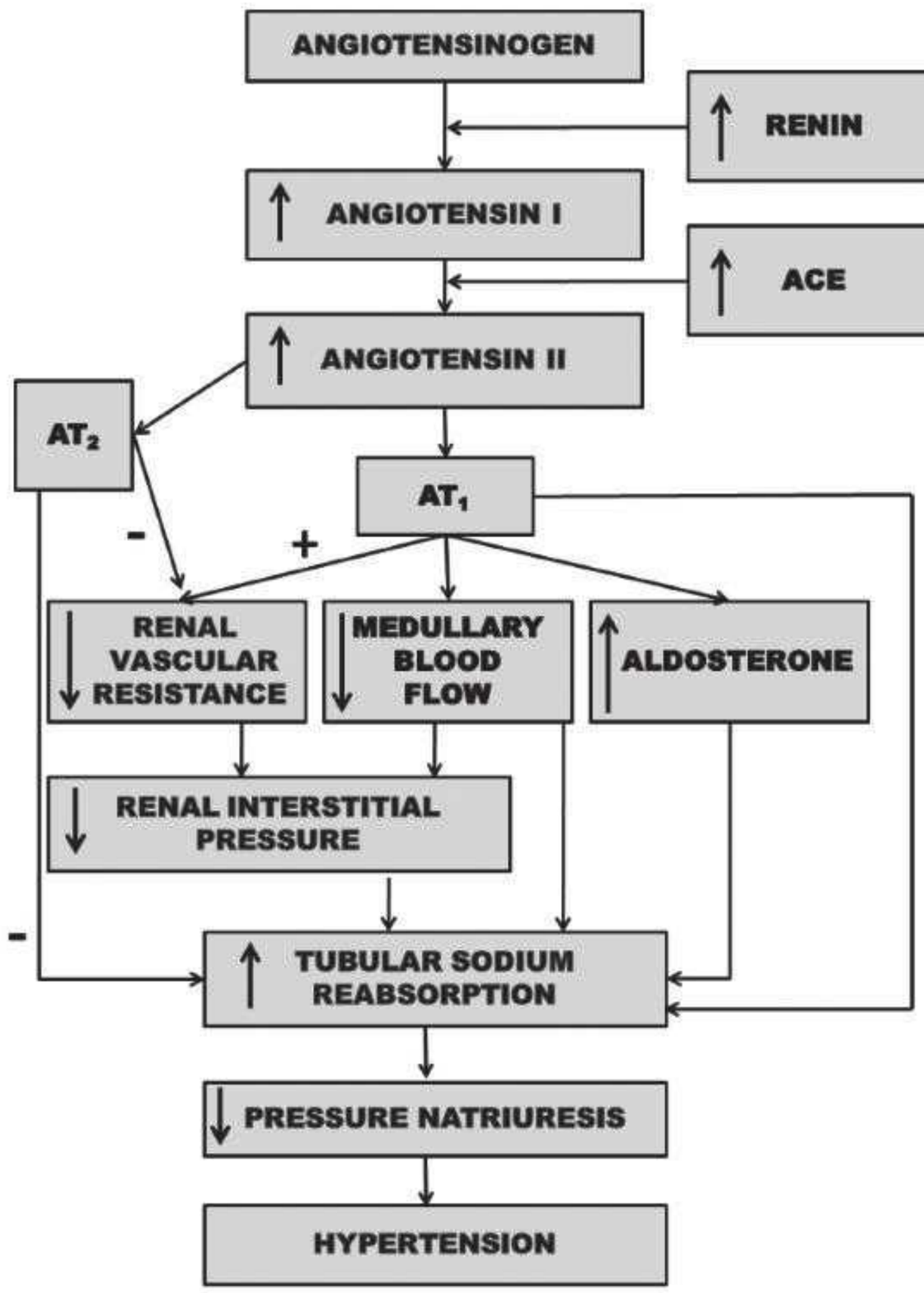

FIGURE 39.5 Renal mechanism whereby activation of the renin-angiotensin system reduces pressure natriuresis relationship and leads to hypertension.

but rather through a G protein–coupled Mas receptor.[35–37] Although ANG 1–7, ACE2, and the Mas receptor have all been detected within the kidney and an imbalance of these peptides, enzymes, or receptors have been reported to occur in various cardiovascular and renal diseases, the physiologic and pathophysiologic importance of ANG 1–7 has yet to be fully elucidated.[35–37]

The RAS, via AT1 receptor, plays an important role in maintaining sodium balance and a relatively normal pressure as sodium intake is altered from low to high levels.[9] As sodium intake is increased to high levels, ANGII levels are suppressed allowing sodium excretion to increase to match sodium intake. Conversely, when sodium intake is restricted ANGII levels increase and sodium excretion is reduced to match the low sodium intake. Thus, with a fully functional RAS, sodium balance is maintained in response to changes in sodium intake without the need to invoke significant changes in blood pressure. An inability to suppress the RAS in response to increases in sodium intake could be one potential mechanism for salt-sensitive hypertension in humans.[7,10]

The importance of the RAS in controlling blood pressure during changes in sodium intake is highlighted by the study of Hall and colleagues[9] where they reported that blockade of the RAS, with ANGII receptor blockers (ARB) or ACE inhibitors, increases renal excretory capability so that sodium balance can be maintained at reduced BPs (Fig. 39.6). However, blockade of the RAS also reduces the slope of pressure natriuresis and makes BP salt-sensitive.[9] Inappropriately high levels of Ang II reduce renal excretory capability and impair pressure natriuresis, thereby reducing the slope and necessitating increased blood pressure to maintain sodium balance.

The effect of ANGII to reduce renal pressure natriuresis and cause hypertension is the result of its effects to directly or indirectly stimulate sodium transport (Fig. 39.5). Infusion of a physiologic dose of ANGII is usually accompanied by an increase in renal vascular resistance and filtration fraction which favors tubular reabsorption.[10,38,39] In addition, acute administration of an ANGII antagonist or converting enzyme inhibitor under conditions where BP is not dramatically reduced results in a natriuresis that is associated with increases in renal blood flow and a reduction in filtration fraction.[10] ANGII has been shown to reduce peritubular capillary pressure, whereas converting enzyme inhibition increases peritubular capillary and renal interstitial hydrostatic pressure.[10] Thus, alterations in Starling forces across the peritubular capillaries provide an important mechanism whereby the RAS affects the tubular reabsorption of sodium.

Alterations in medullary blood flow may be another renal hemodynamic mechanism whereby ANGII could influence tubular reabsorption of sodium.[7,10,40] Ang II-induced constriction of efferent arterioles of the juxtamedullary nephrons or pericytes of descending vasa recta would decrease inner medullary blood flow. This, in turn, would enhance sodium reabsorption by increasing medullary interstitial tonicity. In support of this mechanism are studies demonstrating that ANGII, at a dose that does not alter whole-kidney GFR or renal blood flow, markedly reduces medullary blood flow and sodium excretion.[10] Studies by Cowley and associates have also shown that inner medullary blood flow is reduced in sodium-depleted dogs, a condition associated with enhanced activity of the RAS.[40] Moreover, ANGII blockade has been shown to improve medullary blood flow and enhance pressure natriuresis in various animal models of hypertension.[7,10,40]

Experimental evidence also suggests an important direct tubular action of ANGII.[10,38,39] Various studies suggest that increased proximal tubule transport in response to physiologic concentrations of ANGII is mediated by changes in HCO_{3-} coupled with Na transport.[38] This effect of ANGII has been attributed to activation of Na/H exchange. In addition to a proximal tubule effect on sodium transport, evidence also indicates ANGII may have direct actions on more distal parts of the nephron.[10,38,39]

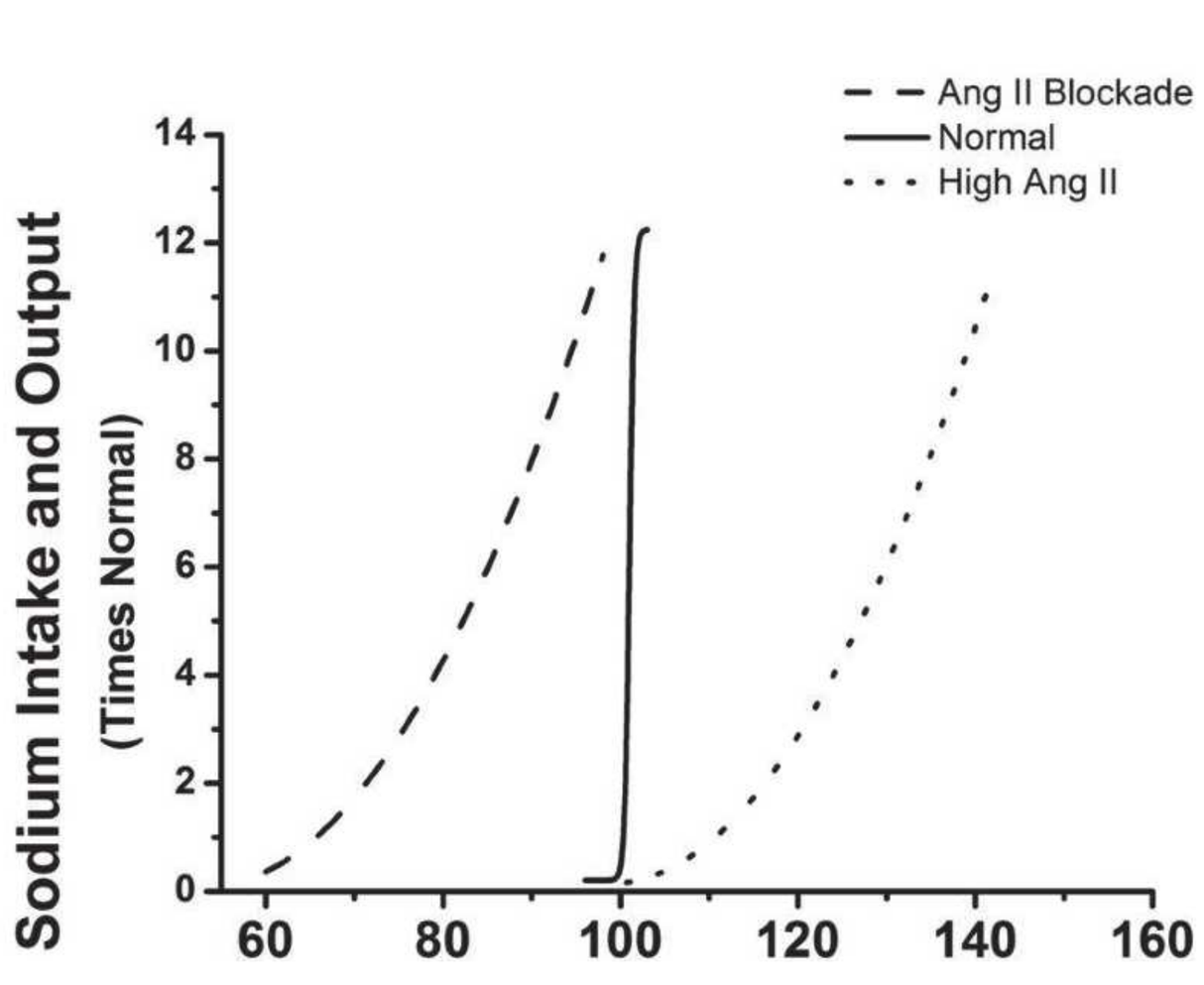

FIGURE 39.6 Effect of changes in mean arterial pressure during chronic changes in sodium intake after angiotensin-converting enzyme (ACE) inhibition, or when angiotensin II was infused at a constant low dose (5 ng/kg/min) to prevent angiotensin II from being suppressed when sodium intake was raised. (Redrawn from data in Hall JE, Guyton AC, Smith MJ Jr, et al. Blood pressure and renal function during chronic changes in sodium intake: Role of angiotensin. *Am J Physiol.* 1980;239:F271–F280.)

Although AT1 receptors are prominently expressed in the kidney, they are also expressed in the heart, blood vessels, adrenal glands, and the brain.[10] Because AT1 receptors are ubiquitously expressed, dissecting the quantitative importance of each individual organ system, including the kidney, in the long-term regulation of blood pressure has been difficult. Utilizing a combined gene targeting with renal cross transplantation approach, Coffman and colleagues examined the role of AT1 receptors in the kidney and their contribution to the development of ANGII-induced hypertension.[41–44] They found that ANG II causes hypertension primarily through effects on AT1 receptors in the kidney associated with reduced urinary sodium excretion, independent of actions of the sympathetic nervous system or aldosterone. When AT1 receptors are eliminated from the kidney, the extrarenal AT1 receptors are not sufficient to induce hypertension (Fig. 39.7). Thus, despite the fact that ANGII activates extrarenal vascular receptors and increases total peripheral resistance, when AT1 receptors are eliminated from the kidney, ANGII does not alter the pressure natriuresis relationship or increase arterial pressure.

More recently Coffman and colleagues reported that abrogation of AT1 receptors in the proximal tubule alone reduces proximal fluid reabsorption, alters expression of key sodium transporters, improves pressure-natriuresis, and significantly attenuates ANGII hypertension.[42] Collectively, the findings of Coffman and colleagues highlight the critical role of the kidney in the pathogenesis of ANGII-dependent hypertension. In addition, they suggest that the major mechanism of action of RAS inhibitors in hypertension is attenuation of ANG II effects in the kidney.

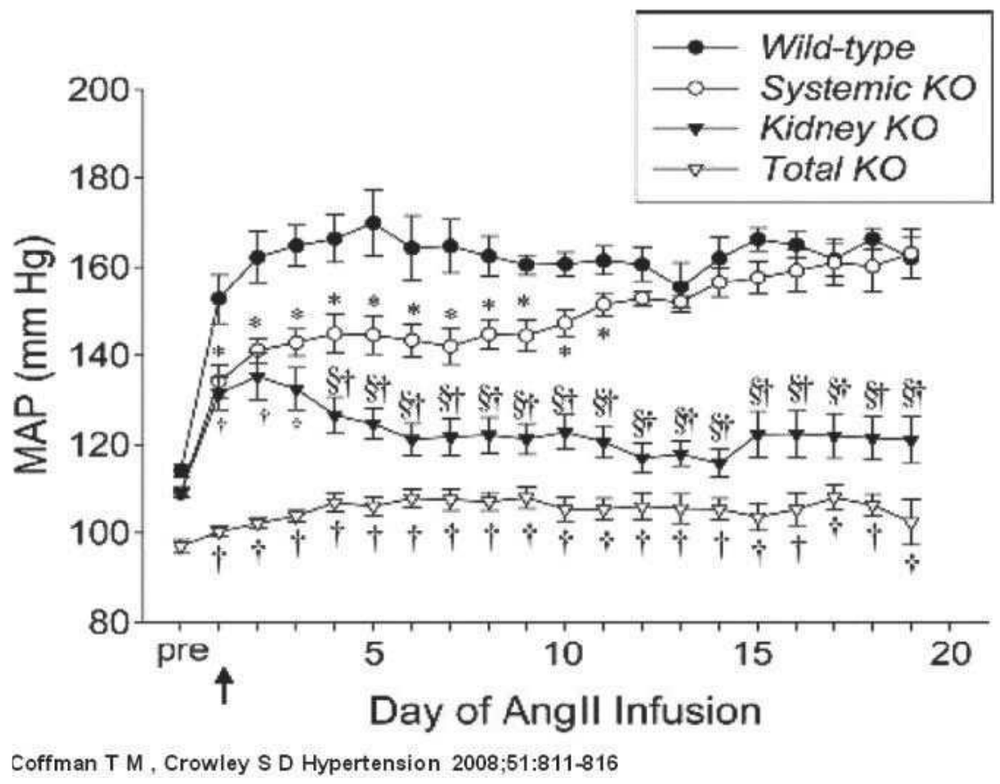

FIGURE 39.7 Blood pressures in cross-transplanted mice during 21 days of AngII infusion. Blood pressure response to AngII in systemic knockout (KO) recapitulates that of the wild-type group by day 12 of AngII infusion. Absence of renal AT_{1A} receptors in kidney KO animals ameliorates AngII–induced hypertension. Total KO blood pressure shows minimal response to AngII infusion. (Coffman TM, Crowley SD. Kidney in hypertension: Guyton redux. *Hypertension*. 2008;51(4):811–816.)

Aldosterone

Aldosterone also plays an important role in the chronic regulation of BP via its sodium-retaining actions on the kidney.[10,45–47] Aldosterone alters the renal pressure natriuresis relationship by enhancing sodium transport in the distal tubules and cortical collecting ducts. The sodium retaining effect of aldosterone is due to binding of aldosterone to the intracellular mineralocorticoid receptor and activation of transcription by target genes. These target genes, in turn, stimulate synthesis or activation of the sodium-potassium ATP-ase pump on the basolateral epithelial membrane and activation of amiloride-sensitive sodium channels on the luminal side of the epithelial membrane.[47,48]

As sodium intake is increased to high levels, aldosterone levels are suppressed allowing sodium excretion to increase to match sodium intake. Conversely, when sodium intake is restricted aldosterone levels increase and sodium excretion is reduced to match the low sodium intake. Thus, a change in aldosterone production in response to changes in sodium intake is another important hormone in the maintenance of sodium balance. An inability to suppress aldosterone production in response to increases in sodium intake therefore is another potential mechanism for salt-sensitive hypertension in humans.[46] In addition to primary hyperaldosteronism, excess activation of the mineralocorticoid receptor by aldosterone has also been implicated in several forms of human hypertension including renovascular hypertension, patients with resistant hypertension, and obesity-related hypertension.[46–51]

The Sympathetic Nervous System

Another antinatriuretic system that can reduce the renal pressure natriuresis relationship and cause chronic hypertension is the renal sympathetic nervous system.[52–56] The kidneys receive extensive sympathetic innervation and increases in renal sympathetic nerve activity reduce sodium excretion by increasing tubular reabsorption or decreasing the filtered load of sodium via alpha adrenergic receptor activation (Fig. 39.8).[52] Renal nerves can act directly on the tubule to increase sodium reabsorption or indirectly by increasing renal vascular resistance and reducing medullary blood flow and renal interstitial pressure. In addition, increased renal sympathetic nerve activity can enhance tubule reabsorption by activating the RAS.

Excessive activation of the renal SNS has been implicated in the pathogenesis of several experimental and genetic forms of hypertension.[52–56] Evidence for a role of the renal nerves in hypertension derives from animal studies showing that renal denervation attenuates or delays the development of hypertension in several forms of experimental hypertension.[56] One particular experimental form of hypertension that is mediated via enhanced renal sympathetic nerve activity is obesity-related hypertension.[56,57] Obesity is often associated with increased sympathetic activity.[56,57] To determine the role of renal nerves in mediating the sodium retention

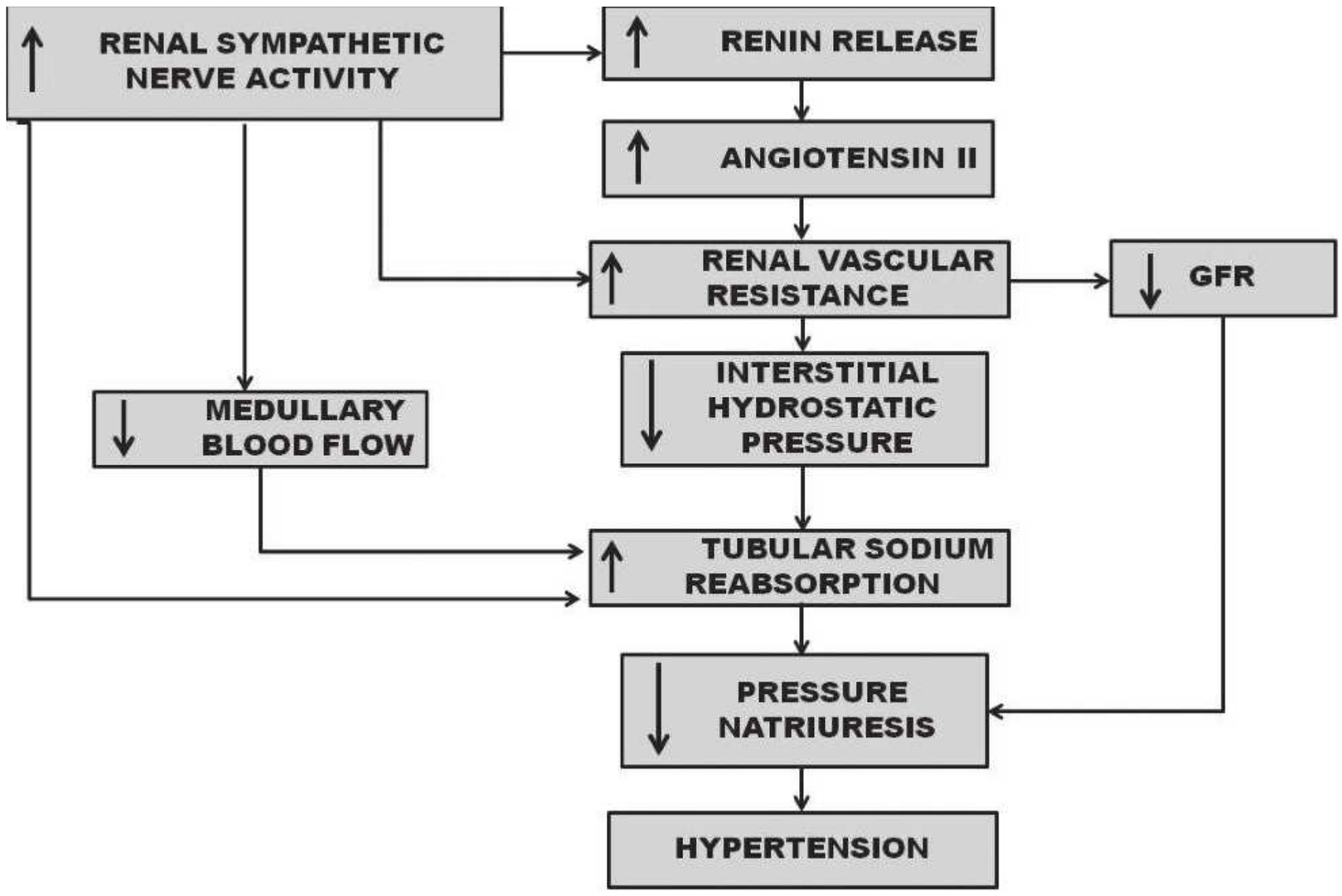

FIGURE 39.8 Renal mechanisms whereby activation of the sympathetic nervous system reduces pressure natriuresis relationship and leads to hypertension.

and hypertension associated with obesity, Kassab and colleagues[58] determined the hemodynamic and renal excretory responses to a high-fat diet in control and bilaterally renal-denervated dogs (Fig. 39.9). In response to a high-fat diet, body weight increased similarly (about 40%) in the control and bilaterally renal-denervated groups. Arterial pressure increased by 15% in the control group but in sharp contrast, 5 weeks of a high-fat diet in the bilaterally renal-denervated group did not significantly increase arterial pressure. Furthermore, after 5 weeks of a high-fat diet, cumulative sodium retention was 455 ± 85 mmol in the control group and only 252 ± 47 mmol in the bilaterally renal-denervated

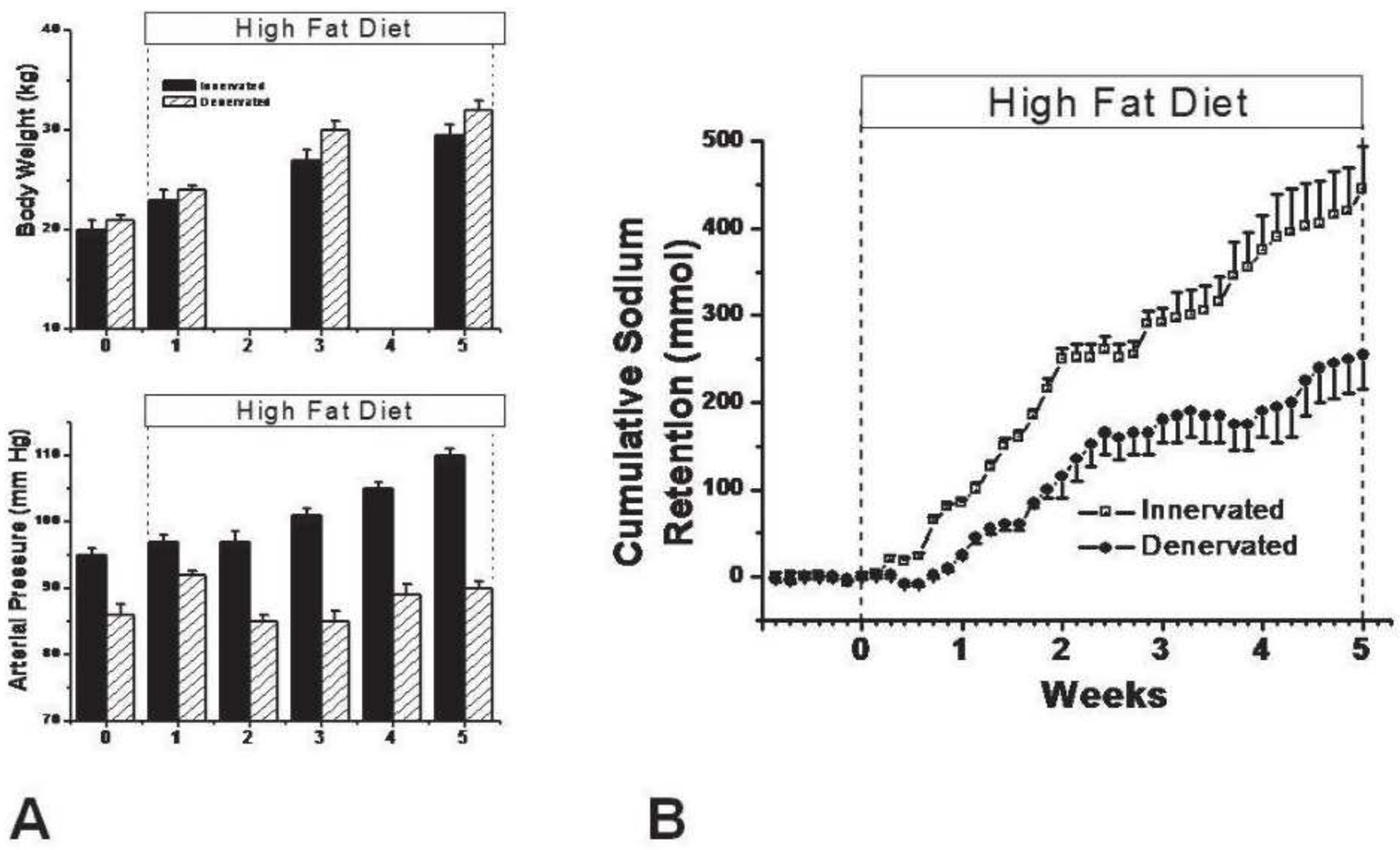

FIGURE 39.9 Changes in body weight and arterial pressure **(A)** and cumulative sodium balance **(B)** in response to a high-fat diet in dogs with innervated and denervated kidneys. (Redrawn from Kassab S, Kato T, Wilkins FC, et al. Renal denervation attenuates the sodium retention and hypertension associated with obesity. *Hypertension*. 1995;25:893–897.)

group. Similar increases in GFR and renal plasma flow occurred in both groups in response to the high-fat diet, indicating that the sodium retention in response to a high-fat diet was due to enhanced sodium reabsorption.[58] The results of this study indicate that the renal nerves play an important role in mediating the sodium retention and hypertension associated with obesity.

Although there is growing evidence for a role of the renal SNS in the development of several animal models of hypertension, the importance of renal nerves in the pathogenesis of human hypertension has yet to be fully elucidated.[56] Application of the norepinephrine spillover methodology in humans has demonstrated activation of the sympathetic nervous outflow to the kidneys in humans with essential hypertension.[56] Renal norepinephrine spillover, on average, is elevated two- to threefold in both normal weight patients with essential hypertension and in obesity-related hypertension.[56] The most compelling evidence for a role of renal nerves in human hypertension are the recent findings that ablation of the renal sympathetic nerves with a radiofrequency-emitting catheter inserted percutaneously significantly reduces BP in patients with resistant hypertension.[59] The level of BP reduction achieved in the resistant hypertensive patients undergoing renal nerve ablation was a mean reduction of 24/10 mm Hg at 3 months and 29/16 mm Hg at 12 months (Fig. 39.10). In a more recent study, the Symplicity HTN-2 trial,106 patients with treatment-resistant hypertension were assessed and renal denervation resulted in impressive reductions in mean office-based measurements of BP (32/12 mm Hg at 6 months), whereas BP remained almost unchanged in the control group.[60] Home and ambulatory measurements of BP followed a similar pattern; the corresponding reductions were 20/12 mm Hg and 11/7 mm Hg with renal denervation, whereas no significant reductions were observed in the control group. It is interesting to note that the average body mass index (BMI) of patients in the study was in the obesity range. Although these data support a potential role for renal nerves in patients with resistant hypertension, it remains unclear as to the relative importance of destruction of renal afferent versus efferent nerves in the antihypertensive effect achieved by the radiofrequency ablation procedure.[56]

The Endothelin System

Endothelin-1 (ET-1) is derived from a 203 amino acid peptide precursor, preproendothelin, which is cleaved after translation to form proendothelin.[61–65] Proendothelin is cleaved in the presence of a converting enzyme to produce the 21 amino acid peptide, ET-1. ET-1 receptor binding sites have been identified throughout the body with the greatest numbers of receptors in the kidneys. ET-1 can either elicit a prohypertensive, antinatriuretic effect by activating endothelin type A (ET_A) receptors and causing renal vasoconstriction or an antihypertensive, natriuretic effect via endothelin

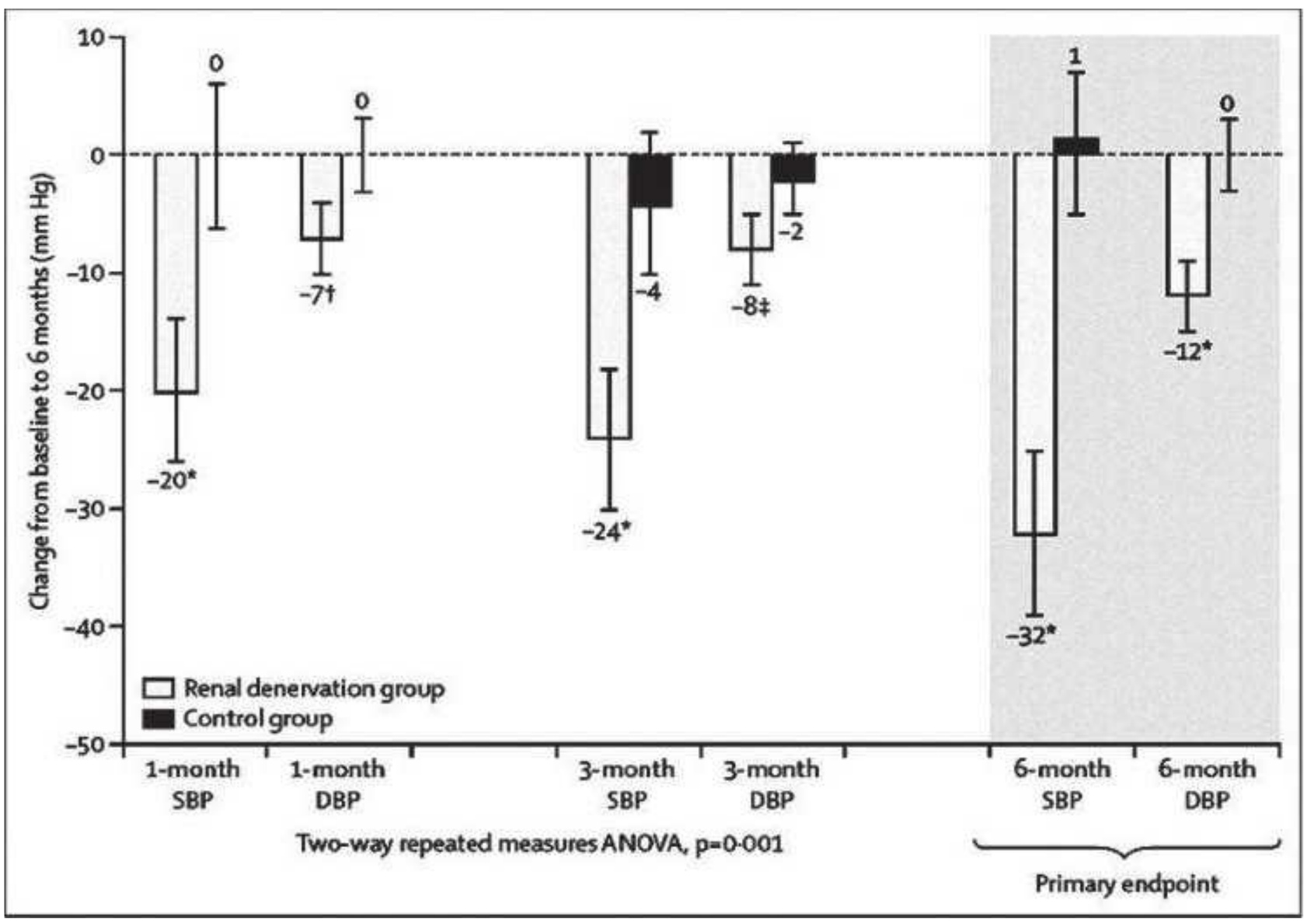

FIGURE 39.10 Blood pressure (BP) lowering effect of radiofrequency ablation of the renal sympathetic nerves for 18 months (M) in patients who were resistant to the usual antihypertensive drugs. *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure. (Krum H, Whitbourn R, Sobotka P, et al. Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof- of-principle cohort study. *Lancet*. 2009;373:1275–1281.)

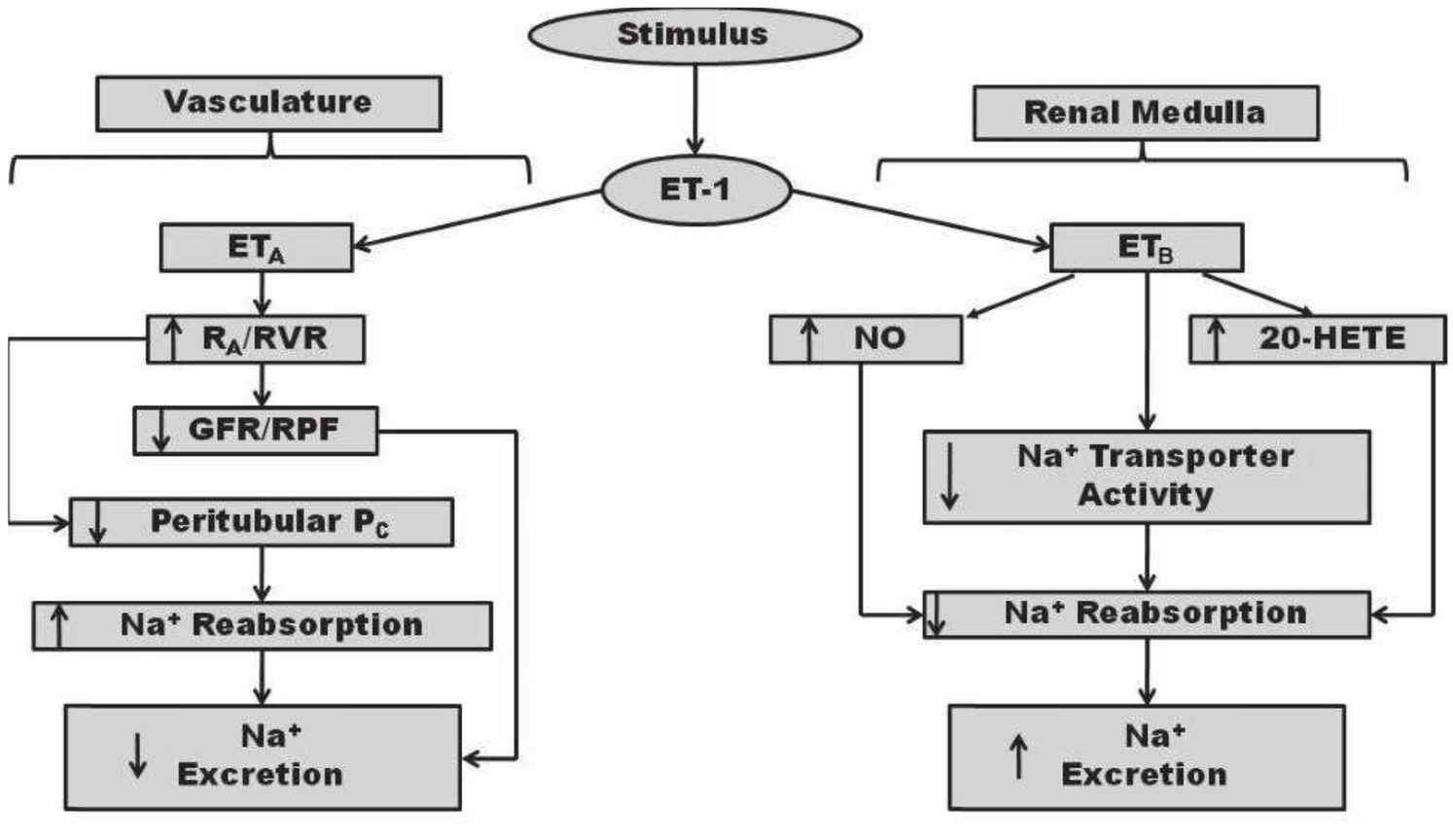

FIGURE 39.11 Summary of the pro- and antihypertensive actions of endothelin-1 (ET-1). The ability of ET-1 to influence blood pressure regulation and renal pressure natriuresis is highly dependent on where ET-1 is produced and which renal ET receptor type is activated. ET-1 can elicit a prohypertensive, antinatriuretic effect by activating ET_A receptors in the kidneys. Activation of renal ET_A receptors increases renal vascular resistance (RVR), which decreases renal plasma flow (RPF) and glomerular filtration rate (GFR), and enhances sodium reabsorption by decreasing peritubular capillary hydrostatic pressure (Pc). The net effect of renal ET_A receptor activation would be increased sodium retention and blood pressure. Conversely, ET-1 can elicit an antihypertensive, natriuretic effect via ET_B receptor activation. Activation of the renal ET_B receptor leads to enhanced synthesis of nitric oxide (NO) and prostaglandin E2 (PG) and suppression of the renin-angiotensin system. The net effect of renal ET_B receptor activation would be decreases in sodium retention and blood pressure.

type B (ET_B) receptor activation (Fig. 39.11). Thus, the ability of ET-1 to influence BP regulation and renal pressure-natriuresis is highly dependent on where ET-1 is produced in the kidney and which renal ET receptor type is activated.[66]

ET-1, via ET_A receptor activation, exerts a variety of actions within the kidney that, if sustained chronically, could contribute to the development of hypertension and progressive renal injury.[66] ET-1 decreases GFR and renal plasma flow.[66,67] Long-term effects of ET-1 on the kidney include stimulation of mesangial cell proliferation and extracellular matrix deposition as well as stimulation of vascular smooth muscle hypertrophy in renal resistance vessels.[68] Previous studies have indicated that expression of ET-1 is greatly enhanced in animal models of severe hypertension with renal vascular hypertrophy and in models of progressive renal injury.[66–68] In addition, treatment with endothelin receptor antagonists attenuated the hypertension and small artery morphologic changes and improved kidney function in these models.[66–68]

Several lines of evidence suggest that ET-1 may play an important role in salt-sensitive forms of hypertension. Dahl salt-sensitive (DS) rats placed on a high-sodium diet are characterized by an attenuated pressure natriuresis; development of hypertension and extensive renal lesions in the form of glomerulosclerosis, renal arteriolar, and tubular injury; and progressive renal failure in late phases of the disease.[69,70] Prepro-ET-1 mRNA and vascular responsiveness to ET-1 are increased in the renal cortex of DS rats compared with Dahl salt-resistant (DR) rats and a positive correlation between ET-1 generation in the renal cortex and the extent of glomerulosclerosis has been reported in DS hypertensive rats.[69,70] Acute infusion of a nonselective ET_A-ET_B receptor antagonist directly into the renal interstitium improves renal hemodynamic and excretory functions in DS rats but not in DR rats.[69,70] Moreover, chronic blockade of ET_A receptors attenuates the hypertension and proteinuria and ameliorates the glomerular and tubular damage associated with high salt intake in DS rats (Fig. 39.12). An interesting unanswered question that emerges is whether the beneficial effect of the ET_A blockade in reducing renal injury is mediated through reducing BP or through direct renal mechanisms.

Although ET-1 clearly plays a significant role in the pathogenesis of some forms of experimental hypertension, especially salt-sensitive models, its role in human hypertension has yet to be fully elucidated. Selective ET_A receptor blockade in hypertensive patients with chronic kidney disease produces a significant reduction in BP, suggesting an upregulation of the ET-1 system in chronic kidney disease–associated hypertension.[71] Krum and colleagues reported that bosentan, a nonselective ET receptor antagonist, reduces BP in patients with essential hypertension as much as did enalapril 20 mg.[72] In another study, 6 weeks of darusentan, a selective ET_A receptor antagonist, lowered both systolic and diastolic BP.[73] Bakris et al.[74] and Weber et al.[75] also showed that darusentan reduced mean 24-hour systolic BP more than placebo in patients with treatment-resistant

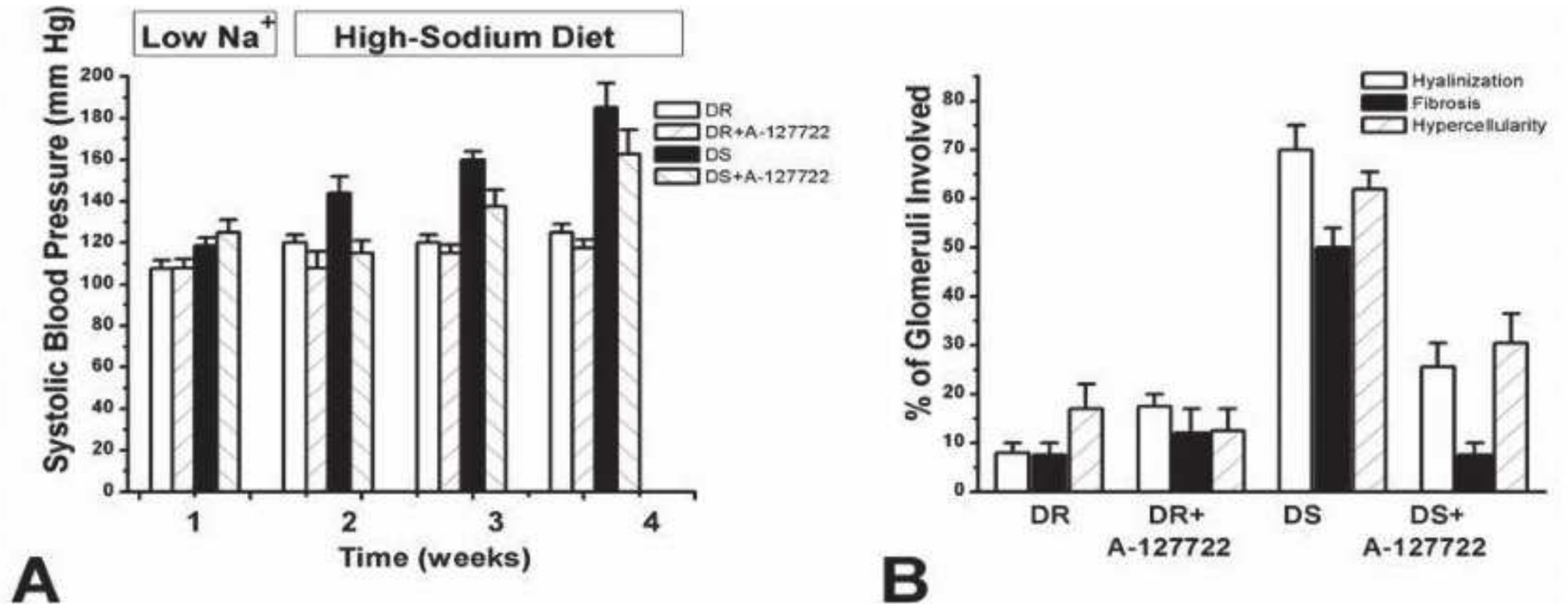

FIGURE 39.12 **A:** Systolic pressures in DS and DR control rats and in those chronically treated with a selective endothelin type A receptor antagonist, A-127722. **B:** Histopathologic changes within the glomeruli of DS and DR rats and in those chronically treated with A-l27722 . Data are expressed as percentage of glomeruli involved with fibrosis, hyalinization, or hypercellularity. (Redrawn from data in Kassab S, Miller M, Novak J, et al. Endothelin-A receptor antagonism attenuates the hypertension and renal injury in Dahl salt-sensitive rats. *Hypertension*. 1998;31:397–402.)

hypertension. Although these clinical studies suggest a potential role for ET-1 in several forms of human hypertension, the importance of ET-1 in human hypertension deserves further investigation.[76–78]

Although much attention has been given to the role of ET-1 in the pathophysiology of cardiovascular and renal disease acting via an ET_A receptor, recent studies indicate an important physiologic role for ET-1 in the regulation of sodium balance and arterial pressure via ET_B receptor activation.[68] The most compelling evidence that the endothelin system may play a significant role in the regulation of sodium balance and arterial pressure are the reports that transgenic animals deficient in ET_B receptors develop a severe form of salt-sensitive hypertension.[79,80] Additional evidence comes from studies indicating that pharmacologic antagonism of ET_B receptors produces significant hypertension in rats.[81]

Although systemic ET_B receptor blockade produces significant hypertension that is salt-sensitive, the physiologic mechanisms involved in mediating the hypertension are still unknown. Because ET_B receptors are located on multiple cell types through the body, including endothelial cells and renal epithelial cells, both intrarenal and extrarenal mechanisms may mediate the hypertension produced by chronic disruption of the ET_B receptor. However, several recent studies suggest that the renal endothelin system plays a major role in controlling BP under high sodium intake conditions. To examine the role of endothelial cell ET_B receptors in salt-sensitive hypertension, Bagnall and colleagues generated an endothelial cell-specific ET_B receptor in knockout mice using a Cre-loxP approach.[82] They reported that ablation of ET_B receptors exclusively from endothelial cells produces endothelial dysfunction in the absence of hypertension. In contrast to models of total ET_B receptor ablation, the BP response to a high-salt diet was unchanged in endothelial cell-specific ET_B receptor knockouts compared to control mice. These important findings suggest that nonendothelial cell ET_B receptors are important for regulation of BP.

There is growing evidence to suggest that ET-1, acting through the renal medullary ET_B receptors, is involved in the regulation of sodium balance and BP under normal physiologic conditions. The kidney is an important site of ET-1 production, and ET_B receptors are expressed at important renal sites of ET-1 synthesis, particularly in the renal medulla.[68] Some of the first studies using synthetic ET-1 demonstrated that nonpressor doses of ET-1 produced significant natriuresis and diuresis.[68] It is now known that ET_B receptors are located in various parts of the nephron, including the proximal tubule, medullary thick ascending limb, collecting tubule, and the inner medullary collecting duct.[68] The highest concentration of ET_B receptors appears to be on the inner medullary collecting duct in the renal medulla.[68] Activation of ET_B receptors has been reported to inhibit sodium and water reabsorption along various parts of the nephron.[68] Taken together, these data indicate that ET-1, via ET_B receptors, may influence the renal handling of sodium and water. The exact mechanism whereby ET_B receptor activation inhibits sodium reabsorption is unclear but could involve other autocoid factors such as nitric oxide, PGE2, and/or 20-HETE.

For the renal ET-1 system to be an important control system for the regulation of sodium balance, the production of renal ET-1 should change in response to variations in sodium intake. Moreover, blockade of ET_B receptors should result in a salt-sensitive form of hypertension. Although there is ample data showing that ET-1 can influence sodium reabsorption, there is a paucity of data in the literature examining the relationship between sodium intake and renal production of ET-1. A recent study by Pollock and Pollock,[81] however, has shown a positive correlation between sodium intake and renal excretion of ET-1. The most convincing

evidence for a role of the renal ET-1 in controlling sodium excretion and arterial pressure during chronic changes in sodium intake is the result of several recent studies. Gariepy and colleagues demonstrated that rats deficient in ET_B receptor expression display salt-sensitive hypertension.[80] Likewise, Pollock and Pollock reported that chronic pharmacologic blockade of the ET_B receptor in rats resulted in hypertension that was sensitive to dietary sodium intake.[80] Moreover, Ohuchi et al. reported elevation in BP by genetic and pharmacologic disruption of the ET_B receptor in mice.[83]

In a recent report by Ge and colleagues,[84] disruption of the ET_B receptor in the collecting duct cells of mice was found to produce significant hypertension that was salt-sensitive. Collecting duct ET_B knockout mice on a normal sodium diet were hypertensive.[84] Collecting duct ET_B knockout mice on a high-sodium diet had worsened hypertension, reduced urinary sodium excretion, and excessive weight gain.[84] Similar findings were found in mice with combined ET_B and ET_A receptor knockout in the collecting duct cells (Fig. 39.13).[85] These findings provide strong evidence that the collecting duct ET_B receptor is an important physiologic regulator of renal sodium excretion and blood pressure.

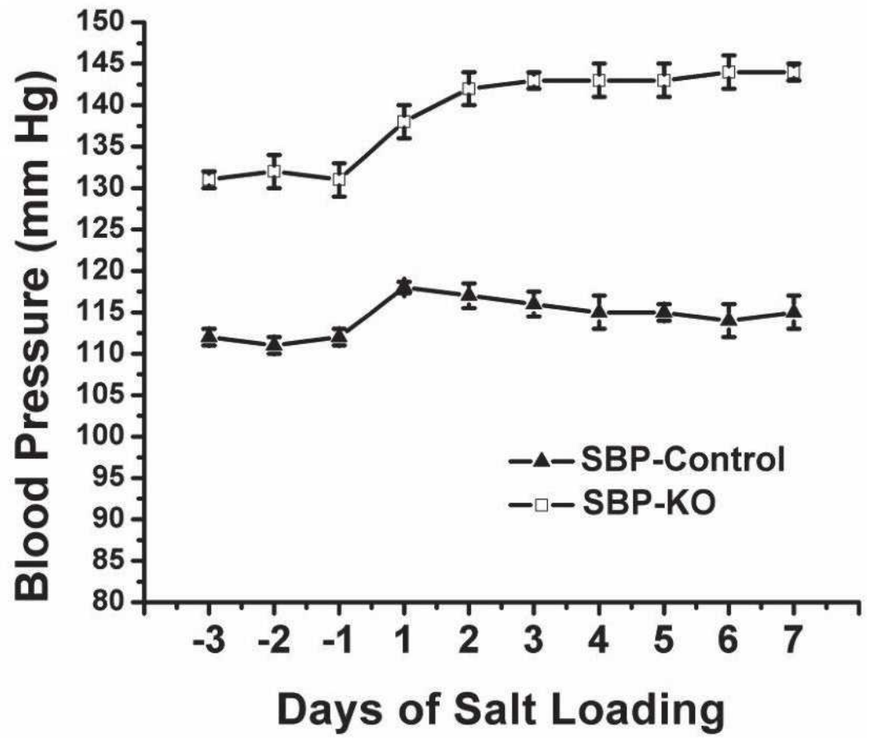

FIGURE 39.13 Collecting duct knockout of the endothelin B and A receptors (CD ETB/ETA KO) causes a hypertensive shift in the pressure natriuresis relationship and salt-sensitive hypertension. (Redrawn from Ge Y, Bagnall A, Stricklett PK, et al. Combined knockout of collecting duct endothelin A and B receptors causes hypertension and sodium retention. *Am J Physiol Renal Physiol.* 2008;295(6):F1635–1640.)

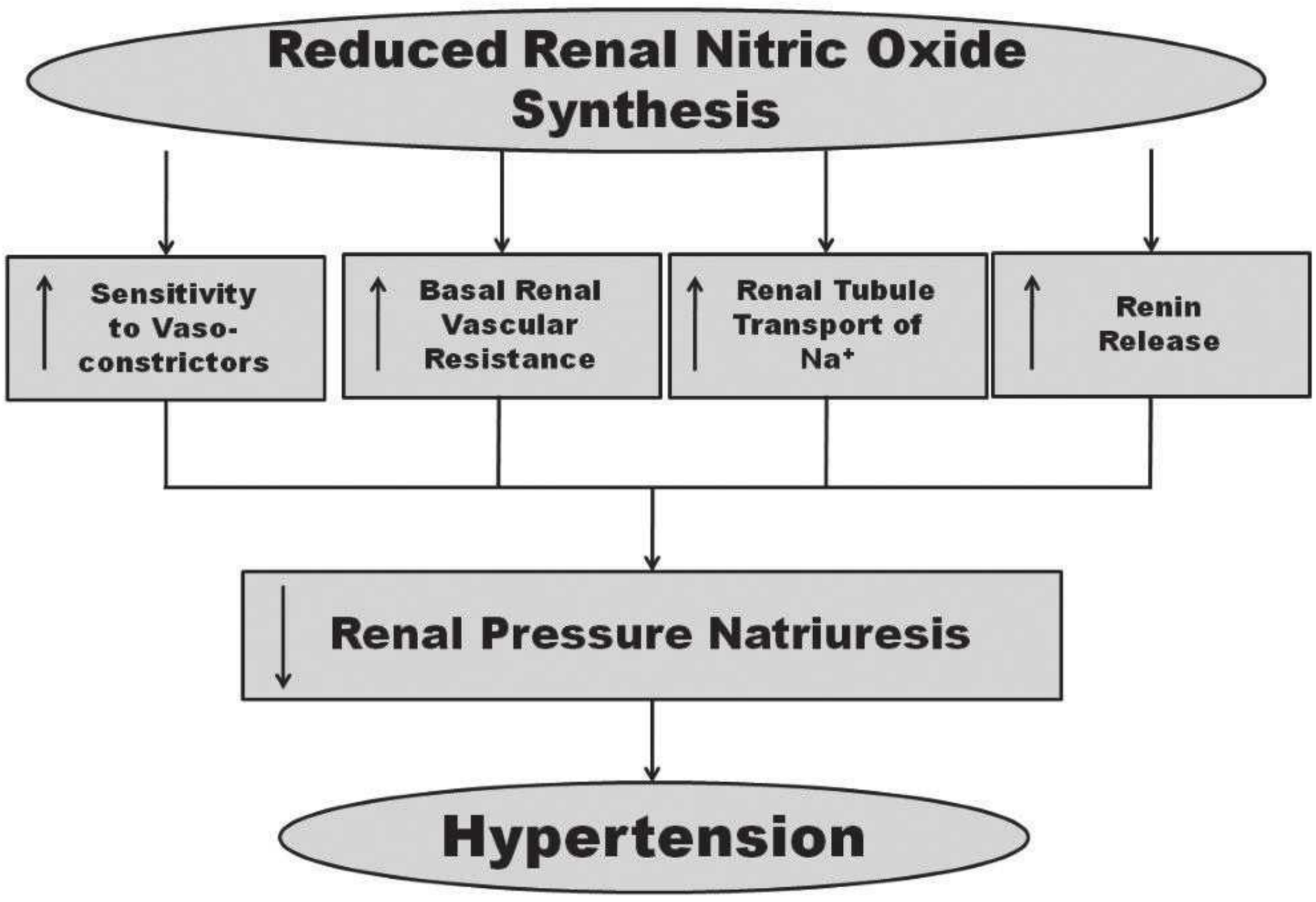

FIGURE 39.14 The renal effector mechanisms whereby reductions in NO synthesis decrease pressure natriuresis and increase blood pressure. A reduction in endothelial derived nitric oxide (EDNO) synthesis leads to a decrease in renal sodium excretory function by directly increasing basal renal vascular resistance, enhancing the renal vascular responsiveness to vasoconstrictors such as ANGII or norepinephrine, or activating the renin-angiotensin system. Reductions in NO synthesis also reduce sodium excretory function either through direct effects on tubular transport or through changes in intrarenal physical factors such as renal interstitial hydrostatic pressure or medullary blood flow.

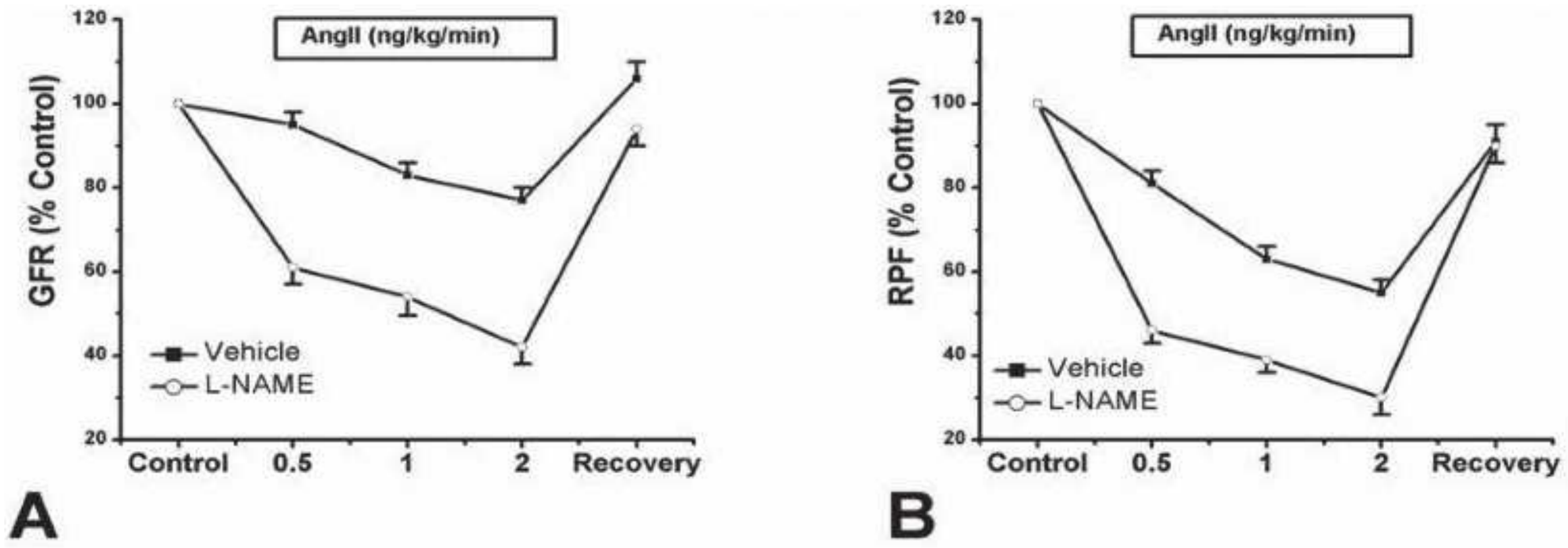

FIGURE 39.15 Glomerular filtration rate (GFR) and renal plasma flow (RPF) in response to intrarenal infusions of ANGII in control dogs (vehicle) and in dogs pretreated intrarenally with a nitric oxide synthesis inhibitor, L-NAME. (Redrawn from Ge Y, Bagnall A, Stricklett PK, et al. Combined knockout of collecting duct endothelin A and B receptors causes hypertension and sodium retention. *Am J Physiol Renal Physiol.* 2008;295(6):F1635–1640.)

Nitric Oxide

All components of the nitric oxide (NO) system are located within the kidney and pharmacologic or genetic disruption of this system results in a sustained hypertension associated with reductions in renal hemodynamics and pressure-natriuresis.[85–87] The magnitude of the increase in BP is also dependent on the dietary sodium intake.[85–87] These findings have led to the concept that NO is not only important in the long-term regulation of sodium balance and BP but also to the notion that abnormalities in NO production result in altered pressure natriuresis and a salt-sensitive form of hypertension.

The renal effector mechanisms whereby reductions in NO synthesis alter pressure natriuresis can be divided into hemodynamic and tubular components each of which may be modulated by processes that are intrinsic and extrinsic to the kidney (Fig. 39.14). For example, reductions in NO synthesis could lead to a decrease in renal sodium excretory function by directly increasing basal renal vascular resistance or by enhancing the renal vascular responsiveness to vasoconstrictors such as AngII or norepinephrine (Fig. 39.15).[87–90] Reductions in NO synthesis also reduce sodium excretory function either through direct effects on tubular transport or through changes in intrarenal physical factors such as renal interstitial hydrostatic pressure or medullary blood flow.[85,86,91,92] Consistent with this hypothesis are observations that the acute infusion of an NO synthase (NOS) inhibitor directly into the renal medulla significantly reduces papillary blood flow, renal interstitial hydrostatic pressure (RIHP), and decreases urinary sodium and water excretion without affecting GFR or systemic pressure.[91–93] Chronic medullary interstitial infusion of NOS inhibitors in conscious rats results in sustained reductions in medullary blood flow, sustained sodium and water retention, and hypertension which are reversed when the infusion is discontinued (Fig. 39.16). These findings demonstrate that

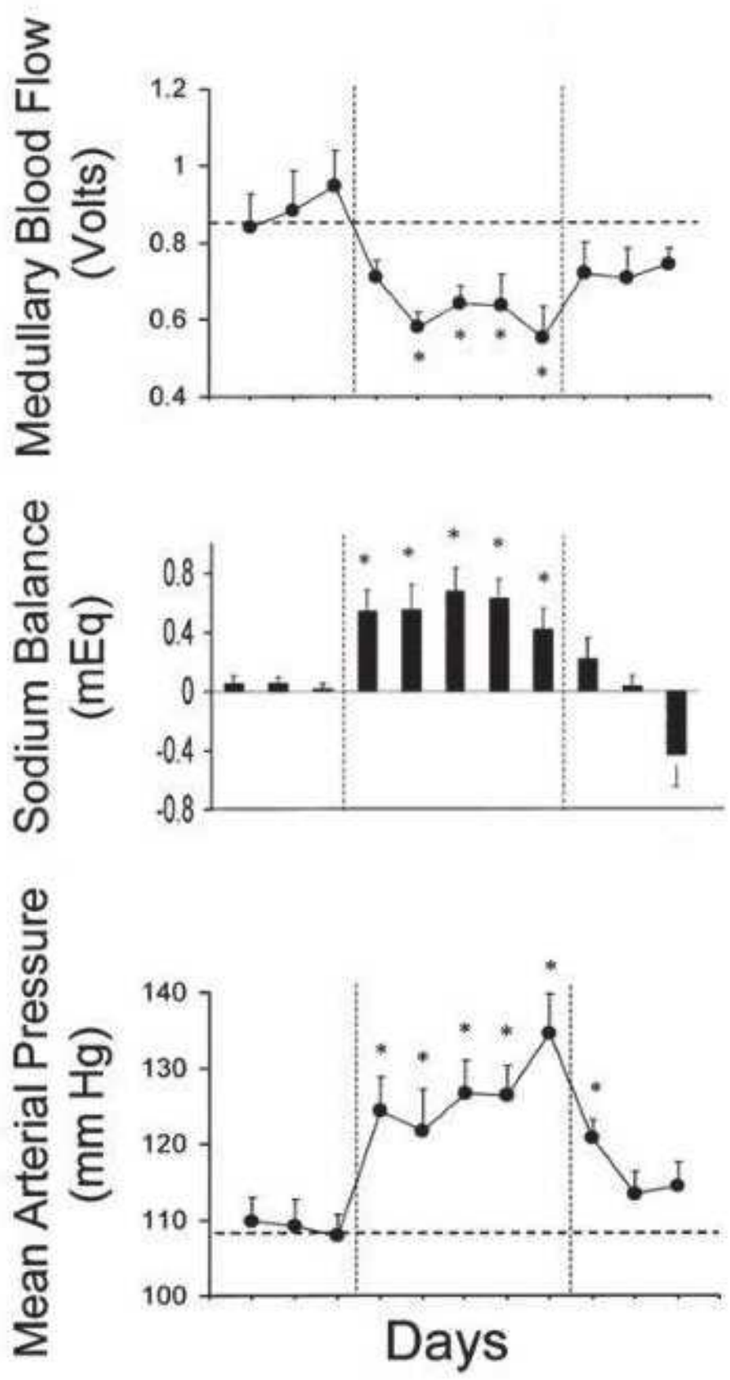

FIGURE 39.16 Chronic effect of renal medullary interstitial infusion of the nitric oxide synthase inhibitor L-NAME (8.6 mg · kg^{-1} · day^{-1}) on renal medullary blood flow (*top*), daily sodium balance (*middle*), and mean arterial blood pressure (*bottom*) in conscious Sprague-Dawley rats. Vertical dashed lines indicate the L-NAME infusion period. *Significant difference from control ($P < 0.05$). (Mattson DL, Lu SH, Nakanishi K, et al. Effect of chronic renal medullary nitric oxide inhibition on blood pressure. *Am J Physiol Heart Circ Physiol.* 1994;266:H1918–H1926.)

reductions in medullary blood flow may be another important mechanism whereby inhibition of NO in the kidney leads to a hypertensive shift in pressure natriuresis.[91]

Inhibition of NO synthesis may have direct effects on renal tubule transport.[86,94] NO has direct effects on sodium uptake in cultured cortical collecting duct cells by altering apical sodium channels.[86] Sodium transport in the cortical collecting duct in vivo is mediated through changes in cyclic GMP. Micropuncture studies have shown NOS inhibitors decrease proximal tubule reabsorption in anesthetized rats.[86] This effect has been attributed to antagonism of Ang II–mediated sodium transport. An effect of NO on proximal reabsorption has also been inferred from changes in lithium clearance induced during inhibition of NO production.[86] Thus, NO can affect sodium reabsorption via direct effects on tubular transport or indirectly via alteration in medullary blood flow or renal interstitial hydrostatic pressure.

Another mechanism whereby NO synthesis inhibition may reduce pressure natriuresis is via activation of the RAS.[85] Inhibition of NO production enhances renin release from rat cortical kidney slices.[85] Inhibitors of NO synthesis also increase plasma renin activity. Intrarenal inhibition of NO increased renin release in dogs, an effect that is dependent on the macula densa mechanism.[95]

Several lines of evidence suggest that NO may play an important role in the regulation of sodium balance and in pathogenesis of salt-sensitive hypertension.[84,94] An increase in renal NO production or release as evidenced by increased urinary excretion of NO metabolites or the NO second messenger, cyclic GMP, has been reported to be essential for the maintenance of normotension during a dietary salt challenge. Prevention of this increase in renal NO production results in salt-sensitive hypertension.[84,85,94]

There is also ample in vitro evidence demonstrating that NO synthesis is impaired in some vascular beds in human essential hypertension. The extent to which these observations reflect effects of the hypertensive process or reflect important mechanisms for the pathogenesis of the hypertensive condition remains unclear.

Atrial Natriuretic Peptide

Atrial natriuretic peptide (ANP) elicits an antihypertensive, natriuretic effect via its receptors (NPR-A). ANP is a 28 amino acid peptide synthesized and released from atrial cardiocytes in response to stretch.[96,97] Once ANP is released from the atria, it enhances sodium excretion through extrarenal and intrarenal mechanisms.[96] ANP increases GFR while having no effect on renal blood flow.[96,98] However, increased GFR is not a prerequisite for ANP to enhance sodium excretion. A deficiency in ANP production or a defect in its receptors may reduce pressure natriuresis and lead to hypertension by enhancing tubular sodium reabsorption either directly by enhancing the active tubular transport of sodium or indirectly via alterations in medullary blood flow, physical factors, and intrarenal hormones (Fig. 39.17).

ANP also has actions at several sites of the RAS cascade.[96,98] Intrarenal or intravenous infusion of ANP reduces the renin secretion rate, presumably by a macula densa mechanism because ANP failed to reduce renin secretion in nonfiltering kidneys. The reduction in renin secretion would decrease intrarenal levels of AngII, which could contribute to ANP-induced natriuresis. When intrarenal levels of AngII were prevented from decreasing the natriuretic effects of ANP were blunted.[96]

ANP also decreases aldosterone release from the adrenal zona glomerulosa cells.[96] Two mechanisms for ANP-induced suppression of aldosterone release have been suggested: (1) a direct action on adrenal glomerulosa cells and (2) reduced circulating levels of AngII due to suppressed renin secretion under in vivo conditions.[96] Although the suppression

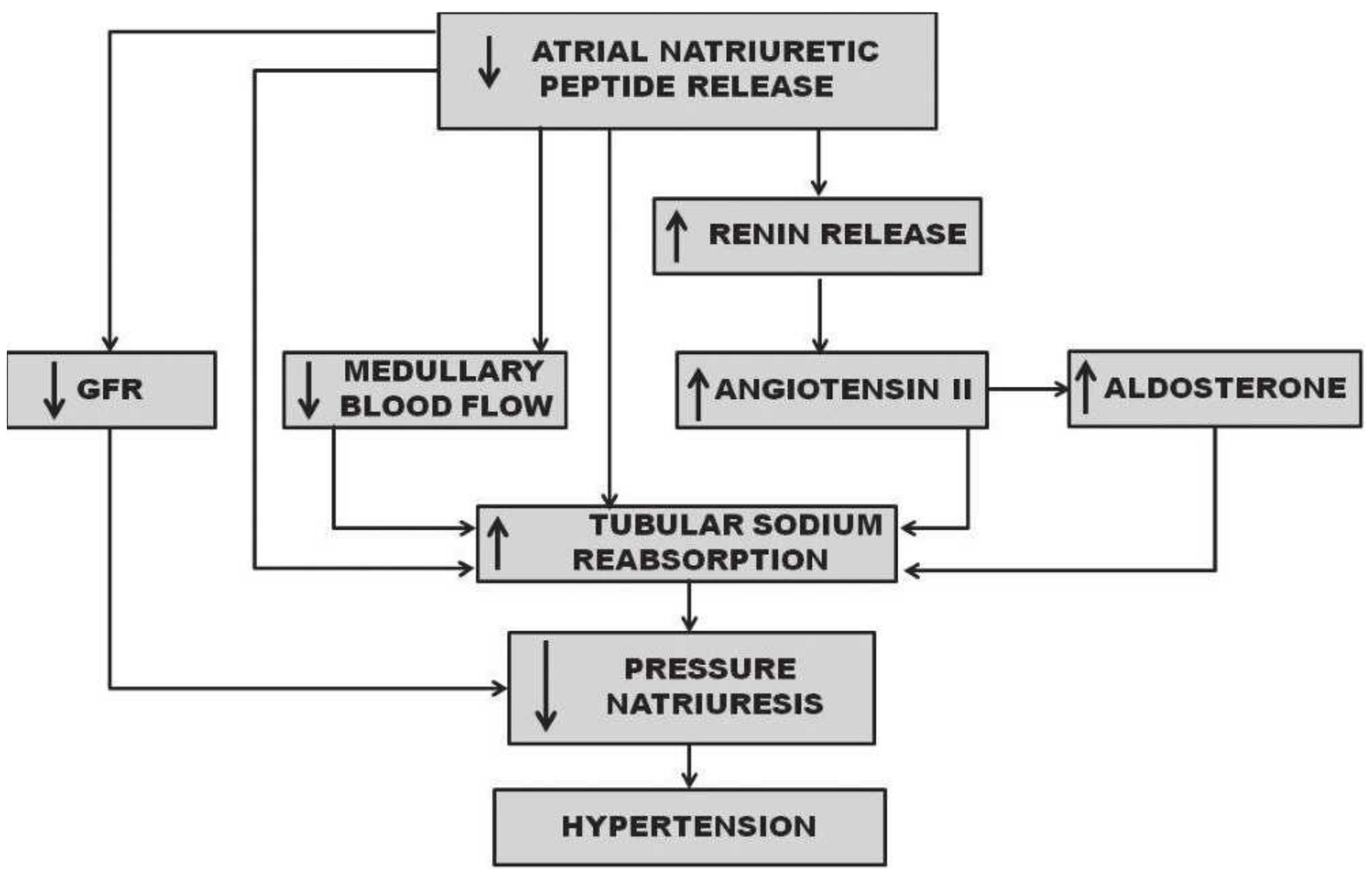

FIGURE 39.17 Renal mechanisms whereby reductions in atrial natriuretic peptide synthesis or atrial natriuretic peptide receptor defects reduce pressure natriuresis relationship and lead to hypertension.

of aldosterone release would not play a role in mediating the acute natriuretic responses to ANP, decreases in circulating levels of aldosterone could contribute to the long-term actions of ANP on sodium balance and arterial pressure regulation.

Plasma levels of ANP are elevated in numerous physiologic conditions associated with enhanced sodium excretion.[96,97] Acute saline of blood volume expansion consistently elevates circulating levels of ANP. Some, but not all, investigators have reported that chronic increases in dietary sodium intake raise circulating levels of ANP. Several studies have reported that infusions of exogenous ANP at rates that result in physiologically relevant plasma concentrations, comparable to those observed during volume expansion, have significant renal and cardiovascular effects.[96,97] Infusion of ANP at a rate that causes a twofold increase in plasma ANP elicits significant natriuresis, especially in the presence of other natriuretic stimuli, such as high renal perfusion pressure.[96] Long-term physiologic elevations in plasma ANP also shift the renal-pressure natriuresis relationship and reduce arterial pressure.[98]

The development of genetic mouse models that exhibit chronic alterations in expression of the genes for ANP or its receptors (NPR-A, NPR-C) have also provided compelling evidence for a role of ANP in chronic regulation of renal pressure natriuresis and BP.[99] Transgenic mice overexpressing ANP gene are hypotensive relative to the nontransgenic littermates, whereas mice harboring functional disruptions of the ANP or NPR-A genes are hypertensive. The ANP gene knockout mice develop a salt-sensitive form of hypertension in association with failure to adequately suppress the RAS (Fig. 39.18). These findings suggest that genetic deficiencies in ANP or natriuretic receptor activity could play a role in the pathogenesis of salt-sensitive hypertension.[100] Indeed, common genetic variants at the NPPA-NPPB locus associated with circulating natriuretic peptide concentrations may contribute to interindividual variation in blood pressure and hypertension.

Arachidonic Acid Metabolites

Cyclooxygenase metabolizes arachidonic acid into prostaglandin (PG) G_2 and subsequently to PGH_2, which is then further metabolized by tissue-specific isomerases to PGs and thromboxane.[101,102] Although the kidney produces many types of PGs with multiple functions, the major renal prostaglandin controlling sodium excretion is probably PGE_2.[101,102] However, production of other arachidonate acid metabolites, such as prostacyclin, thromboxane, and 20-HETE, may also influence renal-pressure natriuresis and BP regulation. The largest production of PGE_2 occurs in the medulla with decreasing synthesis in the cortex. PGE_2 is synthesized and rapidly inactivated and, once synthesized, is released and not stored. Once released, PGE_2 influences sodium transport by several intrarenal mechanisms.

Despite numerous reports that PGs may contribute to the natriuresis of acute physiologic perturbations, the importance of endogenous renal PGs in the long-term

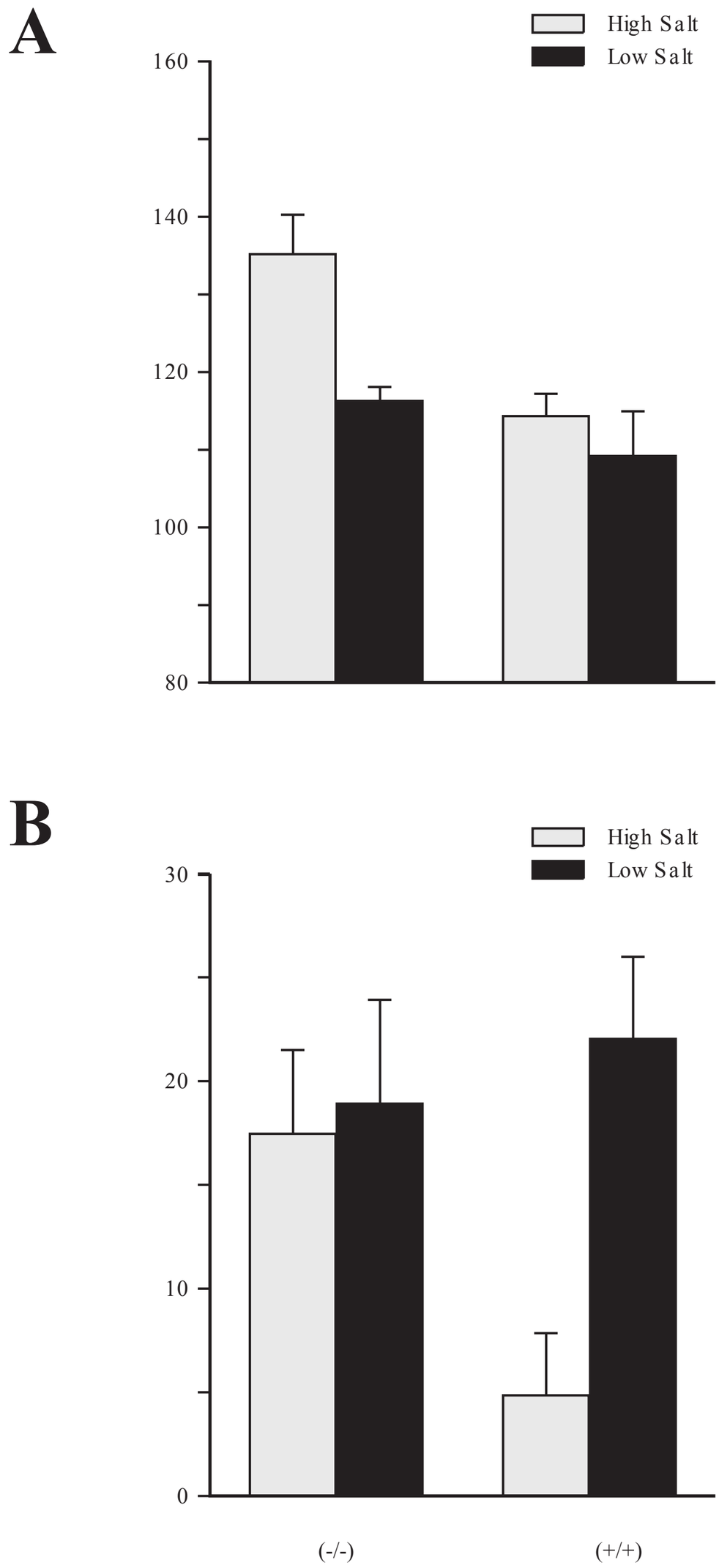

FIGURE 39.18 Mean arterial pressure (MAP) and plasma renin activity (PRA) in atrial natriuretic peptide knockout mice fed on HS or LS diets for 3 to 4 weeks. (Redrawn from Melo LG, Veress AT, Chong CK, et al. Salt-sensitive hypertension in ANP knockout mice: potential role of abnormal plasma renin activity. *Am J Physiol.* 1998; 274: R255–R261.)

regulation of sodium balance remains unclear.[101] Increases in dietary sodium intake have little or no effect on urinary PG excretion. In addition, nonspecific cyclooxygenase inhibitors do not affect the sodium excretory or BP responses to chronic alterations in dietary sodium intake. Thus, it appears that endogenous renal PGs may not play a major role

in regulating sodium excretion during chronic changes in sodium intake.[101]

Although long-term administration of PG synthesis inhibitors has very little effect on volume and/or arterial pressure regulation under normal physiologic conditions, renal PGs may be important in pathophysiologic states associated with enhanced activity of the RAS.[101] In vitro and in vivo studies indicate that renal PGs protect the preglomerular vessels form excessive AngII-induced vasoconstriction.[101] In the absence of this protective mechanism in pathophysiologic states the renal vasculature could be exposed to the potent vasoconstrictor actions of AngII. This could lead to significant impairment of renal hemodynamics, reduced excretory function, and hypertension.

It is now known that there are at least two distinct cyclooxygenases, COX-1 and COX-2.[53] COX-1 is called the constitutive enzyme because of its wide tissue distribution, whereas COX-2 has been termed as inducible because of its more restricted basal expression and its upregulation by inflammatory and/or proliferative stimuli.[101] COX-2 inhibition has been shown to decrease urine sodium excretion and induce mild to moderate increases in arterial pressure. In addition, nonsteroidal anti-inflammatory drugs (NSAIDs) in general and COX-2 inhibitors in particular can aggravate preexisting hypertension. Moreover, blockade of COX-2 activity can have deleterious effects on renal blood flow and GFR.[101] In addition to physiologic regulation of COX-2 expression in the kidney, increased renal cortical COX-2 expression is seen in experimental models associated with altered renal hemodynamics and progressive renal injury. Thus, NSAIDs can cause acute kidney injury in patients with compromised renal hemodynamics.

In addition to renal PGs generated via the COX pathway, other eicosanoids that inhibit tubular sodium transport are produced by cytochrome P450 (CYP) monooxygenase metabolism of arachidonic acid.[102] CYP enzymes metabolize arachidonic acid primarily to 20-HETE and EETs. 20-HETE is a potent constrictor of renal arterioles that may have an important role in autoregulation of renal blood flow and tubuloglomerular feedback (Fig. 39.19).[102] 20-HETE and EETs also inhibit sodium reabsorption in the proximal tubule and thick ascending loop of Henle (TALH). Compelling evidence suggests that the renal production of CYP metabolites of arachidonic acid is altered in genetic and experimental models of hypertension and that this system contributes to the resetting of pressure natriuresis and the development of hypertension. In the SHR, the renal production of 20-HETE is increased and inhibitors of the formation of 20-HETE decrease arterial pressure.[102] Blockade of 20-HETE synthesis also reduces BP or improves renal function in deoxycorticosterone acetate (DOCA)-salt, angiotensin II-infused, and Lyon hypertensive rats.[102] In contrast, 20-HETE formation is reduced in the thick ascending limb

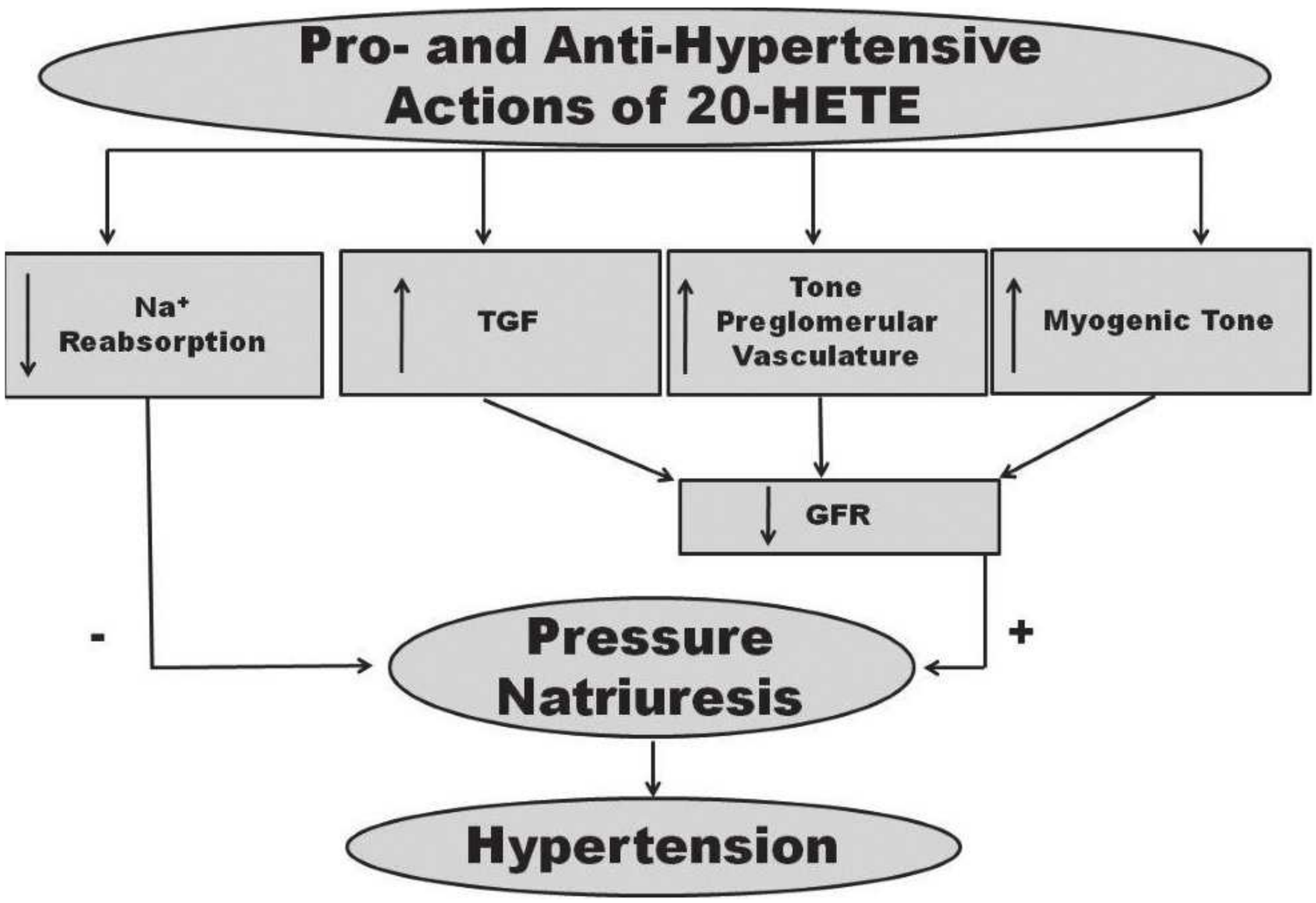

FIGURE 39.19 Summary of the pro- and antihypertensive actions of 20-HETE. 20-HETE produced in the renal tubules inhibits sodium transport and lowers blood pressure. In the renal vasculature and glomerulus, 20-HETE is a constrictor that lowers glomerular filtration rate, promotes sodium retention, and increases arterial pressure. In the peripheral circulation, 20-HETE increases vascular tone and increases blood pressure. *TGF*, tubuloglomerular feedback; *TPR*, total peripheral resistance.

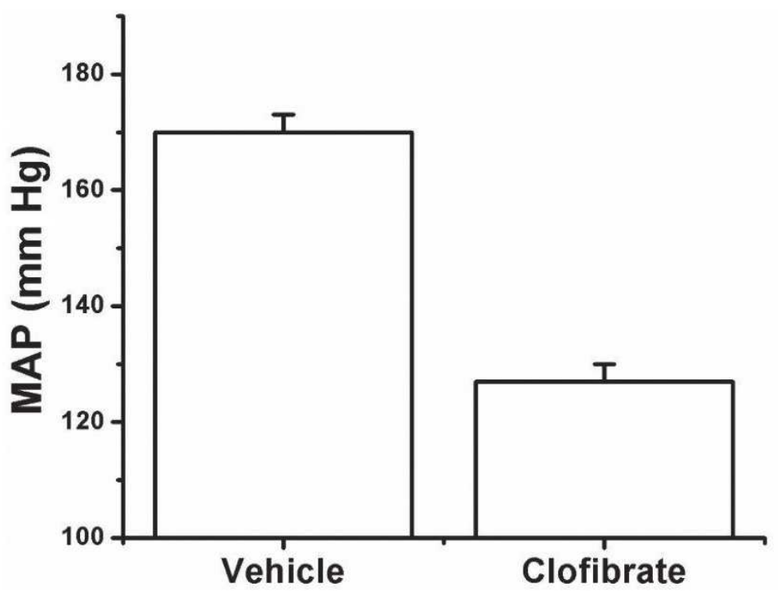

FIGURE 39.20 Left: effect of induction of the renal production of 20-HETE and expression of CYP4A protein with clofibrate on mean arterial pressure (MAP) of Dahl S rats fed a high-salt diet for 4 weeks. (Redrawn from Roman RJ. P-450 metabolites of arachidonic acid in the control of cardiovascular function. *Physiol Rev.* 2002;82:131–185.)

of Dahl S rats and this contributes to elevated sodium reabsorption.[102] Enhanced 20-HETE synthesis improves pressure-natriuresis and lowers BP in Dahl S rats (Fig. 39.20) whereas inhibitors of 20-HETE production promote the development of hypertension in Lewis rats.[102]

Studies in humans also suggest that CYP metabolites may play a role in sodium homeostasis. Urinary 20-HETE excretion is regulated by salt intake and is differentially regulated in salt-sensitive versus salt-resistant subjects.[103,104] Moreover, there appears to be a strong negative relationship between the excretion of 20-HETE and body mass index (BMI), suggesting that some factor related to obesity may be responsible for decreased synthesis or excretion of this eicosanoid in hypertension.[103,104] These observations support the possibility that impaired renal production of 20-HETE could contribute to impaired renal-pressure natriuresis in human hypertension, especially when associated with obesity. However, further mechanistic studies are needed to test the importance of 20-HETE in human hypertension.

Oxidative Stress

Recent studies suggest that ROS may play a role in the initiation and progression of cardiovascular dysfunction associated with diseases such as hyperlipidemia, diabetes mellitus, and hypertension.[105–108] In many forms of hypertension, the increased ROS are derived from NAD(P)H oxidases, which could serve as a triggering mechanism for uncoupling endothelial NOS by oxidants.[105,106]

ROS produced by migrating inflammatory cells and/or vascular cells have distinct functional effects on each cell type.[105] These effects include endothelial dysfunction, renal tubule sodium transport, cell growth, migration, inflammatory gene expression, and matrix regulation. ROS, by renal hemodynamics and renal tubule cell function (Fig. 39.21),

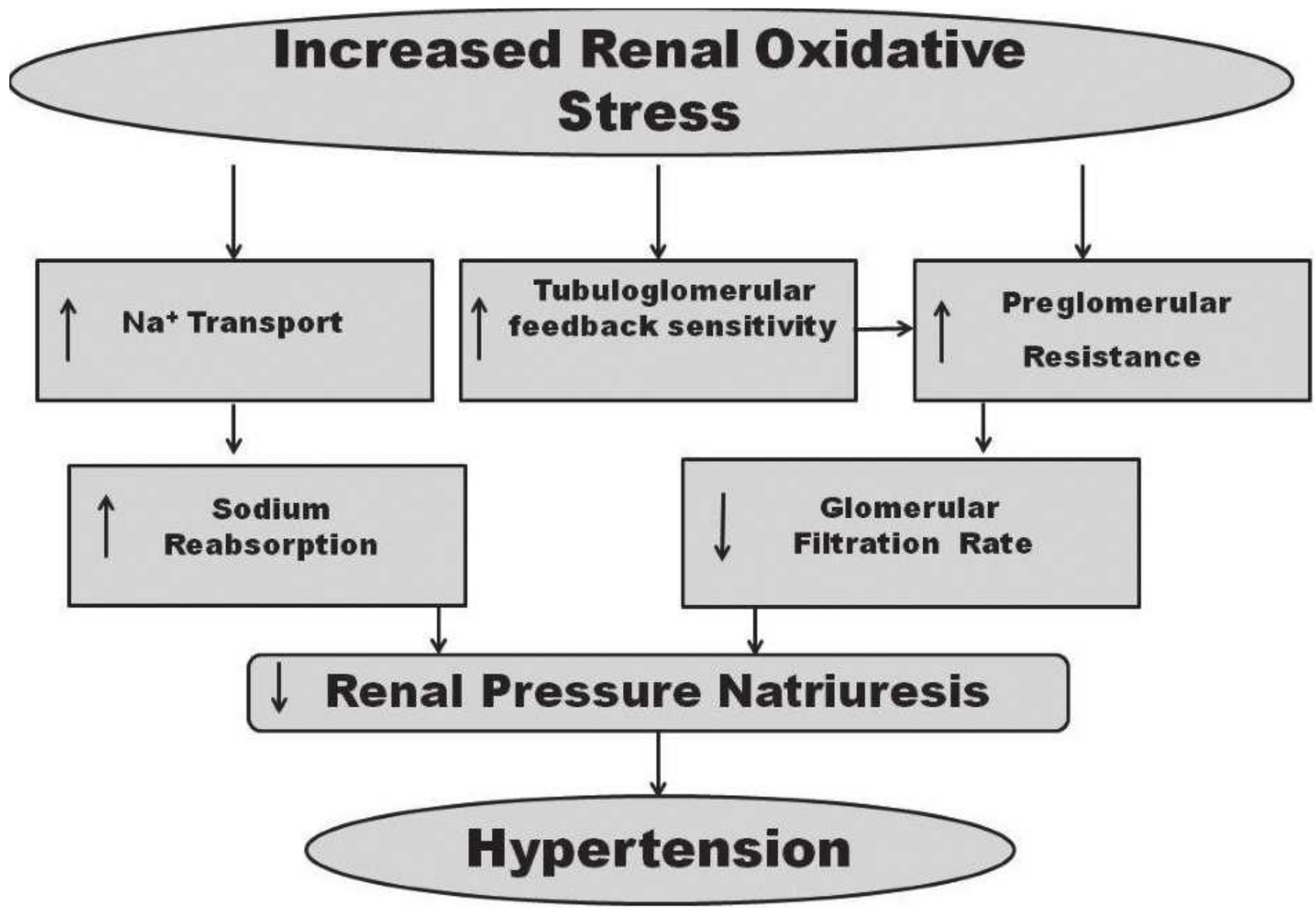

FIGURE 39.21 Renal mechanisms whereby reactive oxygen species impair pressure natriuresis and increase blood pressure. An increase in renal oxidative stress impairs renal pressure natriuresis by increasing renal vascular resistance or enhancing tubuloglomerular feedback, both of which decrease the glomerular filtration rate. Renal oxidative stress also reduces sodium excretion by direct effects to increase renal tubular reabsorption.

can play a role in altering renal pressure natriuresis and BP regulation.[105,108–111]

Growing experimental evidence supports a role for ROS in various animal models of sodium-sensitive hypertension.[105–111] The Dahl salt-sensitive (S) rat has increased vascular and renal superoxide production and increased levels of H_2O_2. The renal protein expression of superoxide dismutase (SOD) is decreased in the kidney of Dahl S rats, and long-term administration of Tempol, a superoxide mimetic, significantly decreases arterial pressure and renal damage. Another salt-sensitive model, the stroke-prone spontaneously hypertensive rat (SP-SHR), has elevated levels of superoxide and decreased total plasma antioxidant capacity. Superoxide production is also increased in the deoxycorticosterone acetate (DOCA)-salt hypertensive rat. Treatment of the DOCA-salt rats with apocynin, an NADPH oxidase inhibitor, decreases aortic superoxide production and arterial pressure.

The importance of oxidative stress in human hypertension is unclear. An imbalance between total oxidant production and the antioxidant capacity in human hypertension has been reported to occur in some but not all studies.[105,106] The equivocal findings in human studies are most likely due to difficulty of assessing oxidative stress in humans. Moreover, most recent human studies have found that vitamin E and C supplementation has little or no effect on BP.[105,106] However, the relatively low doses of vitamin E and C used in many of these studies are weak antioxidants. Thus, further clinical studies are necessary to determine the quantitative role of oxidative stress in human hypertension.

Inflammatory Cytokines and the Immune System

Although inflammation and the immune system were first associated with hypertension over four decades ago, growing evidence over the last 5 years have shown that both innate and adaptive immunity directly contribute to hypertension and renal injury.[112,114–116] Inflammatory cells, including macrophages and T cells, have been reported to accumulate in the kidney of hypertensive animals.[116] Additional support for a role for cytokines in hypertension are findings that plasma levels of proinflammatory cytokines correlate with increased BP in human hypertension and in some experimental animal models of hypertension.[117,118] Moreover, several studies have demonstrated that chronic increases in plasma cytokines, comparable to concentrations observed in the hypertension associated with hypertension preeclampsia, cause significant and sustained increases in BP.[117,118]

Lee and coworkers[119] found that hypertension caused by chronic ANGII excess may depend, at least in part, on

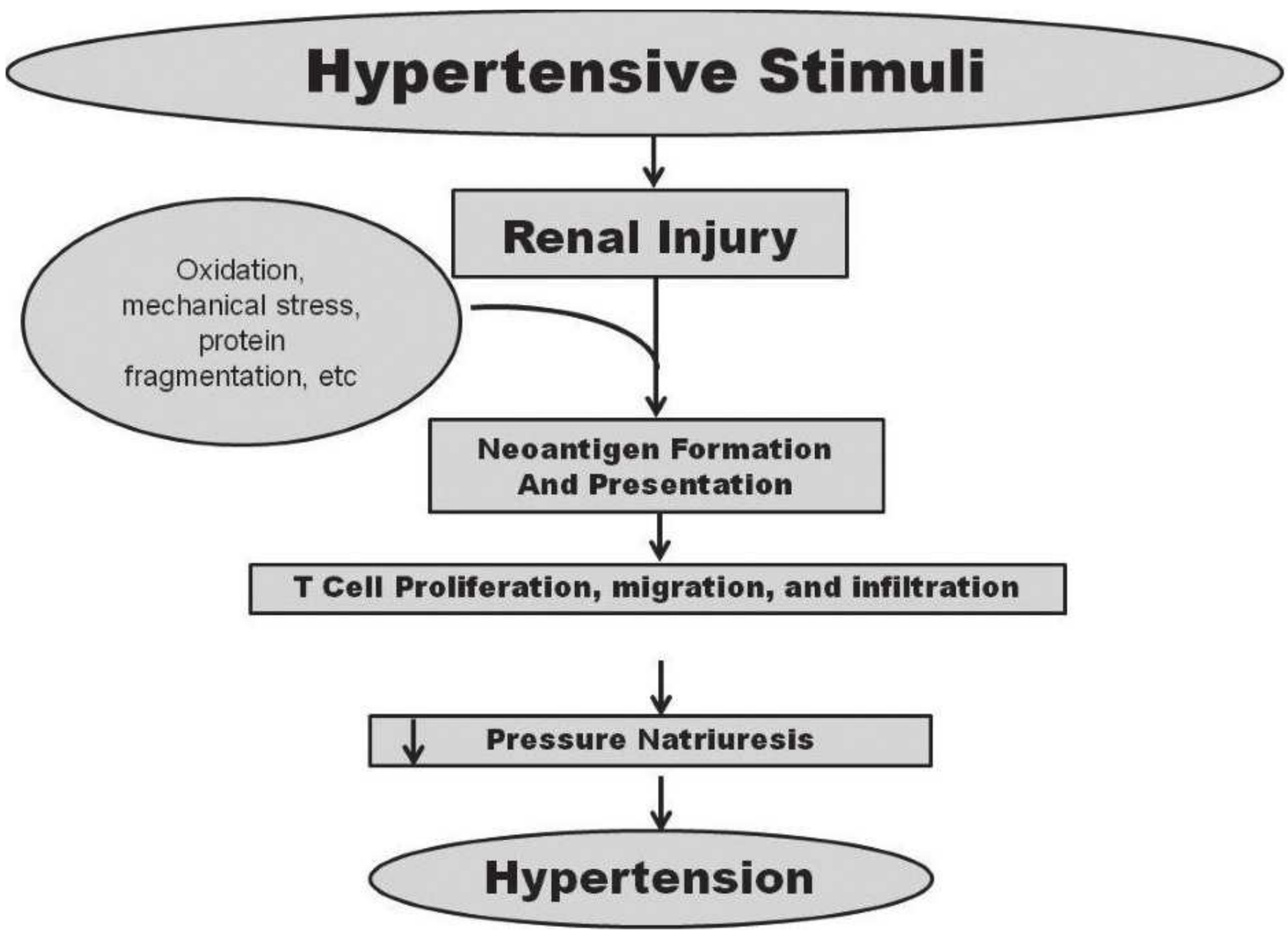

FIGURE 39.22 Proposed role of T cells and inflammation in progression of chronic hypertension. Initial hypertensive stimuli leads to renal injury, neoantigen formation, and eventual T cell activation within the kidney. T cell–derived signals promote entry of other inflammatory cells such as macrophages which result in renal vasoconstriction and sodium reabsorption, thereby increasing the severity of hypertension. (Redrawn from Granger JP, Hall JE. Role of the kidney sodium and fluid excretion in hypertension. In: Lip GYP, Hall JE, eds. *Comprehensive Hypertension*. New York: Elsevier; 2007.)

the presence of interleukin 6 (IL-6). Mice with knockout of IL-6 had significantly lower BP than wild-type mice during 2 weeks of ANGII infusion. Although these findings demonstrate a significant role for IL-6 in mediating the chronic hypertensive response to ANGII in mice, the importance of inflammatory cytokines in the pathogenesis and progression of the various forms of human hypertension is unclear and is currently an area of active investigation.

Several recent studies have demonstrated that T cells play an important role in the progression of hypertension.[115,120] Harrison and colleagues proposed that hypertensive stimuli lead to renal injury, neoantigen formation, and eventual T cell activation within the kidney.[120] T cell–derived signals promote entry of other inflammatory cells such as macrophages which result in renal vasoconstriction and increased sodium reabsorption, thereby increasing the severity of the hypertension (Fig. 39.22). Supporting this concept is a recent report that RAG-1–/– mice, which lack T cells and B cells, do not develop the degree of hypertension in response to ANGII infusion as the wild type mice, an observation that was attributed to lack of T cells (Fig. 39.23).[121] Moreover, chronic ANGII infusion was associated with a greater number of activated T cells as well as increased Rantes, a chemotoxic protein, in the vasculature and perivascular fat. These observations were confirmed by Crowley et al. using a model very similar to the RAG-1–/– mice.[121] They reported that ANGII hypertension, renal injury, left ventricular hypertrophy, and cardiac fibrosis were prevented in SCID mice lacking T cells.

Although there is growing evidence that the immune system may play a role in the progression of hypertension, the mechanisms by which hypertension stimulates an immune response remain unclear, but might involve the formation of neoantigens that activate adaptive immunity. Moreover, although findings in experimental models of hypertension are intriguing, the importance of the immune system in the pathogenesis of essential hypertension in humans remains to be determined.

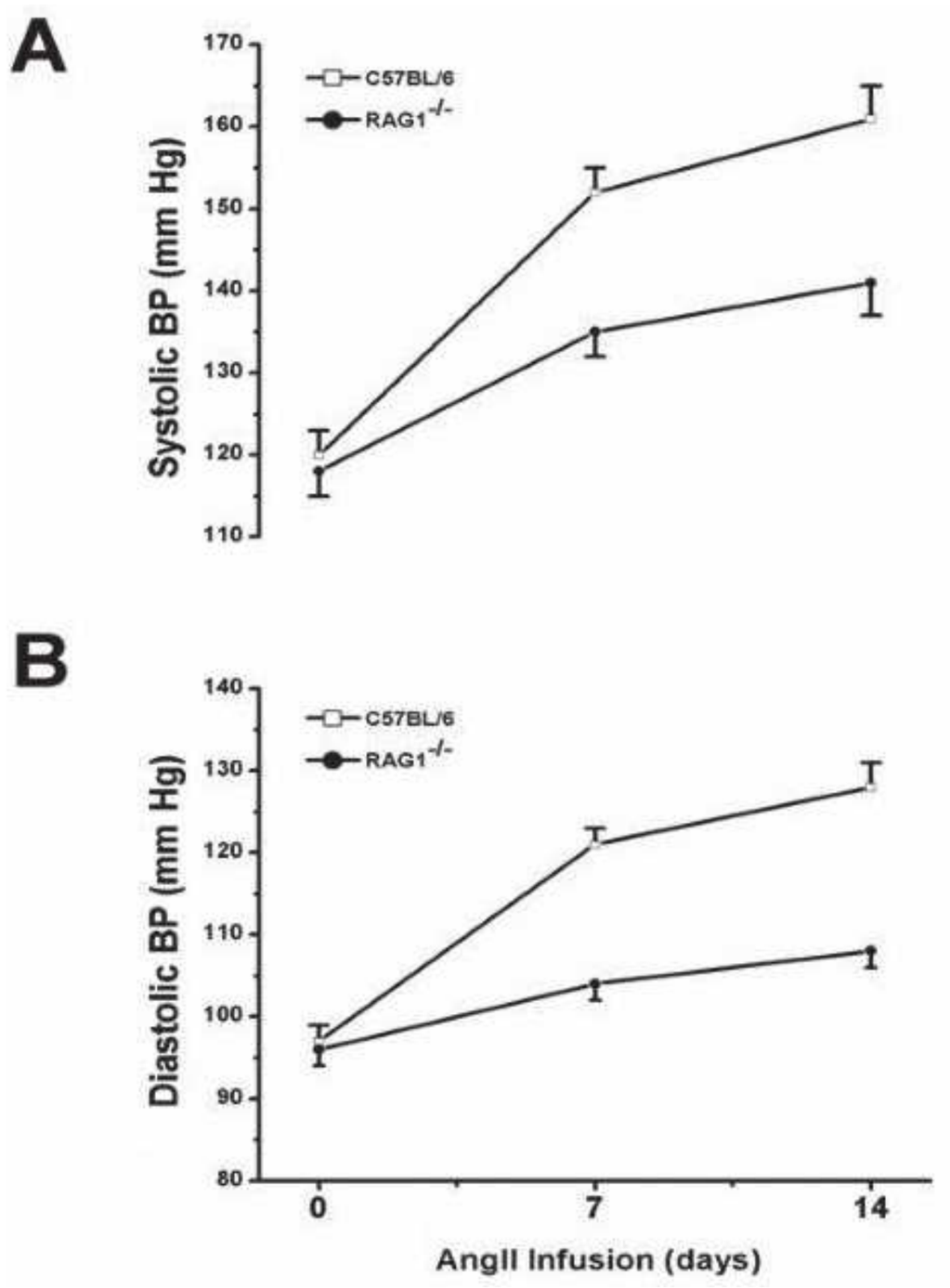

FIGURE 39.23 C57BL/6 and RAG-1–/– mice were treated for 14 days with 490 ng/min/kg angiotensin II, which was administered subcutaneously via osmotic minipump. (Redrawn from Guzik TJ, Hoch NE, Brown KA, et al. Role of the T cell in the genesis of angiotensin II induced hypertension and vascular dysfunction. *J Exp Med*. 2007;204:2449–2460.)

Vascular Endothelial Growth Factor

Although vascular endothelial growth factor (VEGF or VEGF-A) is known to regulate angiogenesis and arteriogenesis, experimental studies over the last decade have suggested that VEGF may also affect renal function and BP regulation.[123,124] VEGF belongs to a family of secreted glycoproteins, including VEGF-B, C, D, and placenta growth factor (PlGF). VEGF signaling is mediated via two receptors, VEGFR1/Flt1 and VEGFR2/Flk1. An array of VEGF pathway inhibitors have been developed to block formation of tumor blood vessels and cause tumor regression. Although hypertension appears to be one of the most common side effects of VEGF inhibitors, the mechanisms underlying the increase in BP in response to VEGF pathway inhibitors have not been fully elucidated.[125,126] Because the endothelium is a major target for the actions of VEGF, it is likely that decreases in the production of endothelium-derived relaxing factors such as NO or enhanced production of vasoconstricting factors such as endothelin play a role in the hypertensive response to drugs that block the VEGF pathway (Fig. 39.24). Facemire and colleagues reported that administration of a specific antibody against the major VEGF receptor, VEGFR2, to normal mice caused a rapid and sustained increase in BP that was associated with reductions in expression of endothelial and neuronal NO syntheses in the kidney (Fig. 39.25).[127] They also reported that L-NAME administration abolished the difference in BP between the vehicle- and anti-VEGFR2–treated groups.[127] These findings suggest that VEGF, acting via VEGFR2, plays a critical role in influencing basal levels of BP control by enhancing NOS expression and NO activity. Moreover, the results suggest that reducing NO production and/or availability may be one mechanism underlying hypertension caused by anti-angiogenic agents targeting VEGF.[122]

Another important endothelial-derived factor that may play a role in mediating the hypertension produced by VEGF inhibition is the vasoconstrictor ET-1.[122] A study by Murphy et al. suggests an important role of ET-1 in mediating the hypertension in a model of preeclampsia that has elevated levels

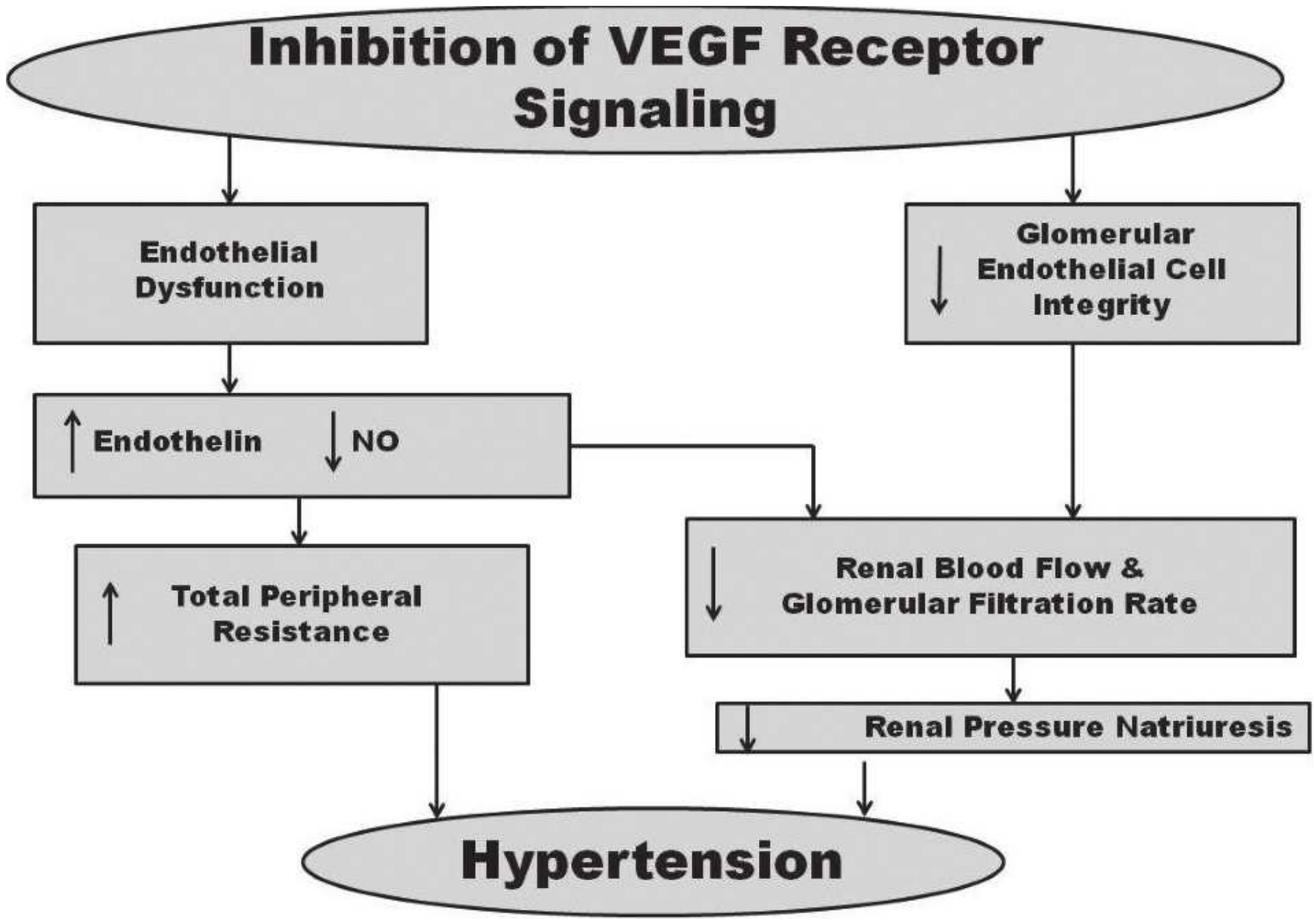

FIGURE 39.24 Potential mechanisms whereby inhibitors of vascular endothelial growth factor (VEGF) receptor signaling raise blood pressure. Blockade of VEGF receptors results in endothelial dysfunction leading to decreased production of endothelium-derived relaxing such as nitric oxide and prostaglandin or enhanced production of vasoconstrictor factors such as thromboxane and endothelin. Inhibitors of VEGF signaling may also result in alterations in glomerular structure and function. These changes may elevate blood pressure by reducing renal blood flow and GFR and impairing the kidney's ability to excrete sodium and water (depicted by a decrease in the pressure natriuresis relationship).

of the soluble VEGF receptor antagonist, sFlt-1.[128] Kappers et al. also reported that sunitinib, an inhibitor of tyrosine kinases including the VEGF receptor, induces a reversible rise in BP in patients and in rats associated with activation of the endothelin-1 system and generalized microvascular dysfunction.[129] Finally, deBeers and colleagues recently reported that VEGF inhibition with sunitinib in pigs results in endothelin-mediated hypertension.[130] Thus, another potential mechanism whereby VEGF blockade could increase BP is by enhancing ET-1 synthesis.[122,131]

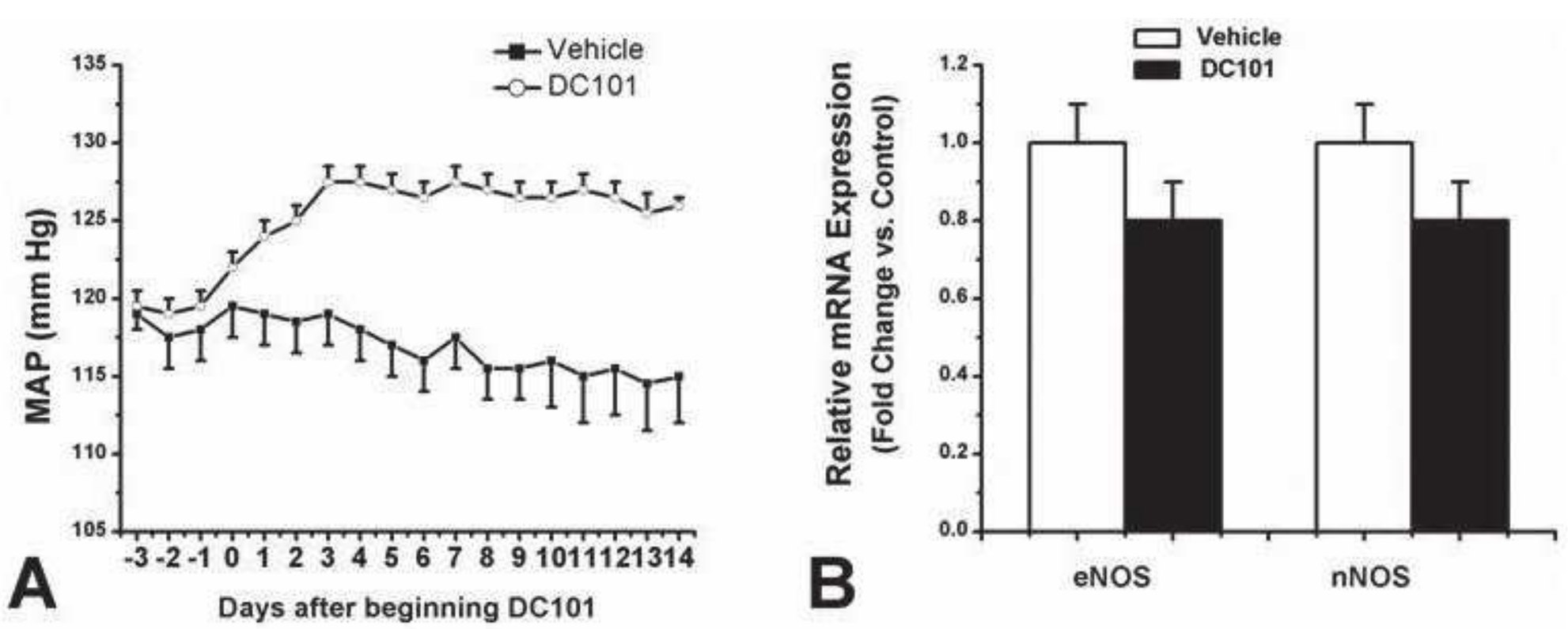

FIGURE 39.25 Effect of vascular endothelial growth factor receptor 2 inhibition on mitogen-activated protein and nitric oxide synthase mRNA expression in kidney in mice. (Redrawn from Facemire CS, Nixon AB, Griffiths R, et al. Endothelial growth factor receptor 2 (VEGFR2) controls blood pressure by regulating nitric oxide synthase expression. *Hypertension*. 2009;54(3):652–658.)

Although it is thought that the blockade of VEGF-A signaling pathway plays a critical role in the hypertension produced by VEGF inhibitors, a study by Machnik and colleagues suggests a role for VEGF-C.[132] The authors propose that macrophages regulate salt-dependent volume and BP by a VEGF-C dependent buffering mechanism. They suggest that VEGF-C, which is produced by macrophages, stimulates lymphatic vessel growth, creating a third fluid compartment that buffers the increased total body sodium and volume and buffers the high BP in response to increases in sodium intake.[132] This novel mechanism could potentially serve as an additional extrarenal mechanism that prevents changes in BP in response to increases in sodium intake. Moreover, loss or abnormalities in this putative sodium buffering pathway could be another potential mechanism for salt-sensitive hypertension. Indeed, Machnik and colleagues reported that macrophage depletion or inhibition of VEGF-C signaling increased BP in response to a high-sodium diet. The authors suggested that increase in BP was due to a decrease in lymphatic vessel growth and a reduction in the fluid compartment.[132] However, the fact that macrophage depletion or inhibition of VEGF-C signaling caused a chronic increase in BP indicates that inhibition of VEGF-C signaling also reduces the kidney's ability to excrete sodium and water. Future studies will be necessary to discern the renal mechanisms whereby macrophage depletion or inhibition of VEGF-C signaling alters the pressure natriuresis relationship.

CONCLUSION

Experimental and theoretical evidence strongly support a central role for the kidneys in the long-term regulation of body fluid volume and arterial pressure. A pivotal part of the renal–body fluid feedback control system for long-term BP regulation is the renal-pressure natriuresis mechanism. Increases in renal perfusion pressure lead to significant increases in sodium and water excretion, an effect that is thought to be mediated by increases in medullary blood flow and renal interstitial pressure. Renal pressure natriuresis is abnormal in all types of experimental and clinical hypertension. Hypertension is an important compensatory mechanism that allows maintenance of sodium balance when renal pressure natriuresis is impaired. Impaired renal pressure natriuresis and chronic hypertension can be caused by factors that either reduce GFR and/or increase tubular reabsorption. A shift of pressure natriuresis can occur as a result of intrarenal abnormalities such as enhanced formation of angiotensin II, ROS, and endothelin (via ET_A receptor activation) or decreased synthesis of NO or natriuretic prostanoids. In other instances, the altered kidney function is caused by extrarenal disturbances, such as increased SNS activity or excessive formation of antinatriuretic hormones such as aldosterone.

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