REGULATION OF EXTRACELLULAR FLUID VOLUME BY INTEGRATED CONTROL OF SODIUM EXCRETION

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The ability of the kidneys to regulate extracellular fluid volume by altering sodium excretion is important for maintaining adequate volume within the vascular system. Sodium excretion is controlled by integrating physical, neural, and hormonal regulatory systems. The major systems involved in retaining sodium include the renin-angiotensin-aldosterone and sympathetic systems, whereas natriuretic factors such as atrial natriuretic peptide and nitric oxide are important in promoting sodium excretion. In response to increased sodium intake, the sodium-retaining systems are inhibited and natriuretic hormones are activated. Pressures and flows within the microcirculation of the kidney, in concert with neural and hormonal systems, interact to regulate sodium excretion. The quantitative importance of each of these systems in regulating sodium balance is variable and is determined by the physiological or pathiophysiological condition.

EXTRACELLULAR FLUID VOLUME IS DETERMINED BY BALANCE BETWEEN SODIUM INTAKE AND RENAL EXCRETION OF SODIUM

The ability of the kidneys to regulate extracellular fluid volume by altering sodium excretion is important for maintaining adequate volume within the vascular system. This ensures that appropriate tissue perfusion occurs under various physiological conditions. Provided that the antidiuretic and thirst systems are functional, changes in the balance between sodium intake and sodium output determined the total *quantity* of sodium in the body and the volume of the extracellular compartment (11, 12). For example, when sodium intake exceeds sodium output by the kidneys, total body sodium (not Na^+ concentration) and extracellular fluid volume increases. Conversely, when renal excretion of sodium exceeds sodium intake, total body sodium and extracellular fluid volume decrease. Thus the maintenance of a constant extracellular fluid volume depends on the body's ability to regulate the amount of NaCl in the compartment. The body achieves this important regulatory function by varying sodium excretion to match the level of sodium intake.

CHANGES IN SODIUM BALANCE ARE SENSED BY VOLUME-DEPENDENT RECEPTORS

To maintain a constant extracellular fluid volume, the body monitors the volume of this compartment by sensors or receptors in different regions of the body (11, 12). In response to the sensory output, effector mechanisms are activated to make appropriate adjustments in the renal output of sodium. The portion of the extracellular fluid compartment that is sensed by these receptors is plasma volume. Plasma volume determines the magnitude of various hemodynamic variables that are sensed by volume and/or pressure receptors. For example, changes in plasma volume can cause changes in the distending pressures in certain regions of the cardiovascular system. Volume

receptors are located in the low- and high-pressure portions of the cardiovascular system.

The low-pressure receptors are found in the pulmonary vasculature and in the atria. An increase in atrial pressure in response to an increase in plasma volume activates two effector mechanisms that enhance sodium excretion (10, 11, 12). An increase in atrial pressure decreases renal sympathetic nerve activity via a neural reflex mechanism and increases the release of atrial natriuretic peptide (ANP) from atrial myocytes (3, 4). Conversely, a decrease in plasma volume reduces atrial pressure, which leads to enhanced renal sympathetic nerve activity and decreased ANP secretion.

Under certain conditions, an increase in plasma volume leads to increases in arterial pressure. Changes in arterial pressure are sensed by high-pressure receptors located in the aortic arch and the carotid sinus (3). Increases in arterial pressure result in baroreceptor-mediated reductions in renal sympathetic nerve activity, whereas a decrease in arterial pressure leads to enhanced renal sympathetic nerve activity and sodium retention.

Changes in plasma volume can also be sensed by two different types of intrarenal volume-dependent receptors (10, 11, 12). Changes in arterial pressure are sensed by pressure receptors located in the afferent arterioles. Decreases in arterial pressure at the level of the afferent arteriole lead to renin secretion and enhanced formation of angiotensin II (ANG II), which is a sodium-retaining hormone. Changes in plasma volume can also lead to alterations in NaCl delivery to macula densa cells, which in turn alters renin secretion. Increases in plasma volume lead to an increase in sodium delivery [via a decrease in proximal tubule reabsorption and/or increase in glomerular filtration rate (GFR)] to macula densa cells, which in turn suppresses renin release. Conversely, a decrease in plasma volume leads to a decrease in sodium delivery to macula densa cells and enhanced renin secretion and angiotensin formation.

Thus changes in extracellular fluid volume are detected by various sensors in the body, which activate effector mechanisms that adjust sodium excretion appropriately to return extracellular fluid volume to normal levels. The effector mechanisms involved in adjusting sodium excretion involve neural and hormonal factors. These factors alter the rate of sodium excretion by influencing the main determinants of sodium excretion, GFR, and tubule sodium reabsorption. The quantity of sodium excreted is determined by the difference between the filtered load of sodium and the amount of sodium reabsorbed along the nephron. Thus an increase in sodium excretion can occur via an increase in glomerular filtration or a decrease in sodium reabsorption. Conversely, a decrease in sodium excretion can occur via a decrease in glomerular filtration or an increase in sodium reabsorption. The remaining part of this brief review will focus on how specific neurohormonal effector mechanisms regulate sodium excretion via alterations in glomerular filtration and tubular sodium reabsorption.

CHANGES IN PERITUBULAR CAPILLARY PHYSICAL FACTORS INFLUENCE SODIUM REABSORPTION BY ALTERING INTERSTITIAL HYDROSTATIC PRESSURE

An imbalance between hydrostatic and colloid osmotic forces governs the rate of reabsorption across the peritubular capillaries, just as these physical forces control filtration in the glomerular capillaries (11, 12). Thus changes in renal hemodynamics and colloid osmotic pressure can alter peritubular capillary fluid and solute reabsorption, interstitial fluid hydrostatic and colloid osmotic pressure, and, ultimately, reabsorption from the renal tubules. Likewise, primary changes in tubular reabsorption also influence the hydrostatic and colloid osmotic forces of the interstitial compartment and, ultimately, peritubular capillary reabsorption. Thus the hydrostatic and colloid osmotic forces of the renal interstitium provide an important link between circulatory function and renal tubular reabsorption (7). Interstitial fluid volume (and, therefore, interstitial fluid hydrostatic pressure) is determined by the difference between the rate of volume inflow to the interstitium due to tubular reabsorption and outflow due to peritubular capillary reabsorption. In the steady state, peritubular capillary reabsorption must equal renal tubular reabsorption. Thus, from anatomic considerations alone, it is clear that physical forces in the peritubular capillaries and renal interstitium influence renal tubular reabsorption.

Expansion of the extracellular fluid volume compartment results in an increases in peritubular capillary hydrostatic pressure (due to renal vasodilation and/or increases in arterial pressure) and a decrease in colloid osmotic pressure (due to a decrease in filtration fraction). These changes result in a reduced rate of sodium and water reabsorption in the proximal tubules (7, 11, 12). Conversely, when extracellular fluid volume is contracted, decreases in peritubular capillary hydrostatic pressure and increases in colloid osmotic pressure enhance the rate of sodium reabsorption in the proximal tubule.

Changes in peritubular capillary physical forces are thought to influence sodium reabsorption by changes in renal interstitial volume or hydrostatic pressure (see Fig. 1). Numerous physiological perturbations that increase sodium excretion such as increases in renal perfusion pressure or extracellular fluid volume expansion are associated with significant elevations in renal interstitial hydrostatic pressure (RIHP) (6, 7). Furthermore, renal vasodilators that cause natriuresis also increase RIHP (7). In contrast, renal vasodilators, such as secretin, that do not increase sodium excretion also do not increase RIHP (7). Finally, when RIHP is
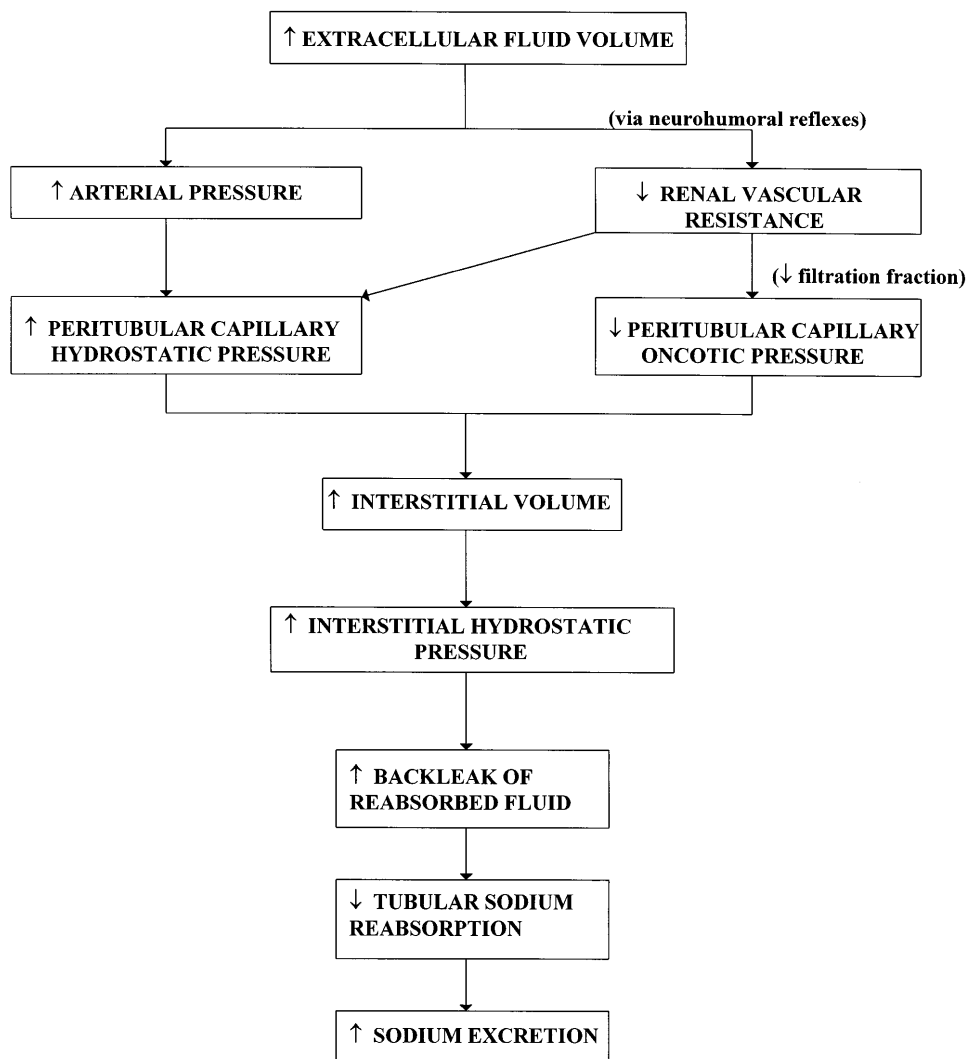

FIG. 1.
Mechanism whereby renal interstitial hydrostatic pressure reduces sodium reabsorption in response to extracellular fluid volume expansion.

prevented from increasing during renal vasodilatation or acute saline volume expansion, natriuresis is markedly attenuated or even abolished (7). Thus RIHP appears to link changes in peritubular capillary hemodynamics to sodium reabsorption.

Although the exact mechanism whereby RIHP influences the reabsorption of sodium and water is unclear, it is thought that RIHP decreases sodium absorption in the proximal tubule by inhibiting passive sodium and water transport (7). One hypothesis is that increased renal interstitial volume and/or pressure raises the permeability of the tight junctional complexes of the proximal tubule. This effect would, in turn, increase the back leak of sodium from the interstitium into the tubule lumen. The net effect would be a reduction of sodium and water reabsorption across the proximal tubule. Conversely, a decrease in RIHP would reduce back leak of sodium from the interstitium and enhance proximal tubule sodium reabsorption.

CHANGES IN MEDULLARY BLOOD FLOW INFLUENCE SODIUM REABSORPTION IN LOOP OF HENLE

In addition to the influence of the cortical peritubular microcirculation on sodium reabsorption, it has been shown that alterations in medullary hemodynamics affect passive sodium transport in the loop of Henle (10, 11, 15). An increase in medullary blood flow leads to a washout of medullary interstitial hypertonicity (see Fig. 2). Consequently, water abstraction out of the thin descending limb of Henle's loop, which is relatively impermeable to sodium, is reduced. Thus an increased volume of fluid with the same quantity of sodium but decreased sodium concentration is delivered to the water-impermeable thin ascending limb of Henle's loop. The reduced sodium concentration decreases sodium reabsorption in that nephron segment, and more sodium is delivered to the distal tubules and eventually excreted.

In contrast, reductions in medullary blood flow would decrease sodium excretion by increasing medullary interstitial tonicity, water abstraction out of the thin descending loop of Henle, and sodium concentration in the thin ascending limb of Henle's loop. The
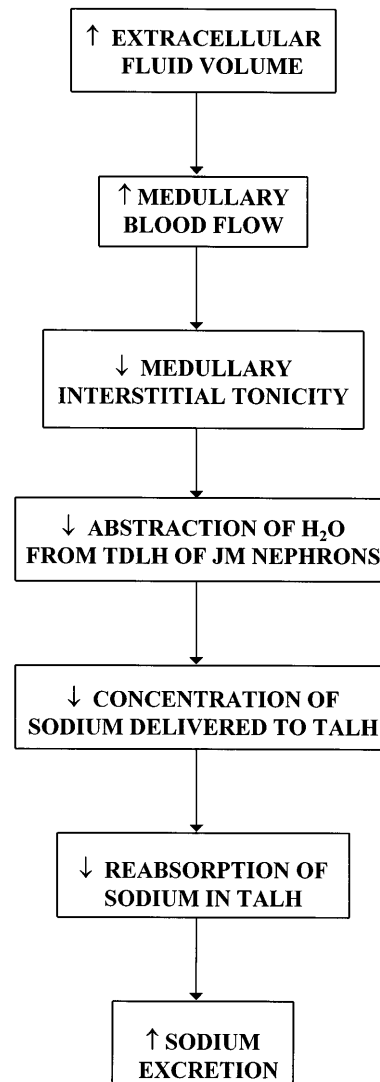
FIG. 2.
Mechanism whereby increases in medullary blood flow decreases sodium reabsorption and enhances sodium excretion. TDLH, thin descending limb of loop of Henle; JM, juxtamedullary; TALH, thick ascending limb of loop of Henle.

increased sodium concentration would increase passive sodium reabsorption in this nephron segment.

A variety of neurohumoral factors, such as angiotensin, norepinephrine, and ANP, and local autocoid factors, such as prostaglandins and nitric oxide (NO), influence medullary blood flow (15). Thus the effects

of these factors on sodium excretion could, in part, be due to alterations in medullary hemodynamics.

CHANGES IN RENAL ARTERY PRESSURE INFLUENCE SODIUM REABSORPTION VIA ALTERATIONS IN INTRARENAL HEMODYNAMICS

Increases in renal perfusion pressure enhance sodium excretion, a phenomenon commonly referred to as renal pressure natriuresis (2, 6, 8). 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 GFR and the filtered load of sodium are usually well autoregulated. Although renal pressure natriuresis plays a critical role in the long-term regulation of extracellular fluid volume and arterial pressure, the mechanisms whereby changes in renal perfusion pressure influence sodium excretion and, specifically, sodium reabsorption, have not been fully elucidated (2, 8, 10). Research investigations during recent years, however, have provided new insights into possible mechanisms of pressure natriuresis and have suggested that physical factors, especially renal interstitial pressure, may be primary mediators of pressure natriuresis (7).

Some investigators have argued against a role for RIHP in mediating pressure natriuresis, because renal blood flow and/or peritubular capillary hydrostatic pressure is usually autoregulated in response to changes in renal perfusion pressure (7). Direct measurement of RIHP, however, indicates that increased RIHP may occur despite efficient autoregulation of whole kidney renal blood flow and peritubular capillary hydrostatic pressure (7). Moreover, preventing RIHP from increasing in response to increased renal perfusion pressure markedly attenuates pressure natriuresis (7). Direct increases in RIHP, comparable to those measured in response to increased renal perfusion pressure, also significantly decrease proximal tubular sodium reabsorption and increase sodium excretion.

Because pressure natriuresis can occur in the absence of discernible changes in renal blood flow and peritubular capillary hydrostatic and oncotic pressures, the mechanisms responsible for sustained increased RIHP have been unclear. Recent studies, however, have provided evidence that renal medullary hemodynam-

ics are closely linked to changes in RIHP (7). Increases in renal perfusion pressure raise vasa recta flow and hydrostatic pressure, possibly reducing fluid uptake across the vasa recta capillary wall and increasing medullary interstitial volume and medullary interstitial hydrostatic pressure (see Fig. 3). The increase in medullary interstitial hydrostatic pressure is then thought to be transmitted throughout the kidney, including the cortex (15).

Why papillary plasma flow increases when renal perfusion pressure is elevated and cortical blood flow is effectively autoregulated is unknown. It is possible that endothelial (NO) or interstitial factors (ANG II, prostaglandins, kinins) are released into the medulla with increased renal perfusion pressure (7, 15). Once released, these intrarenal factors could then alter medullary hemodynamics and override intrinsic autoregulatory mechanisms in the inner medulla.
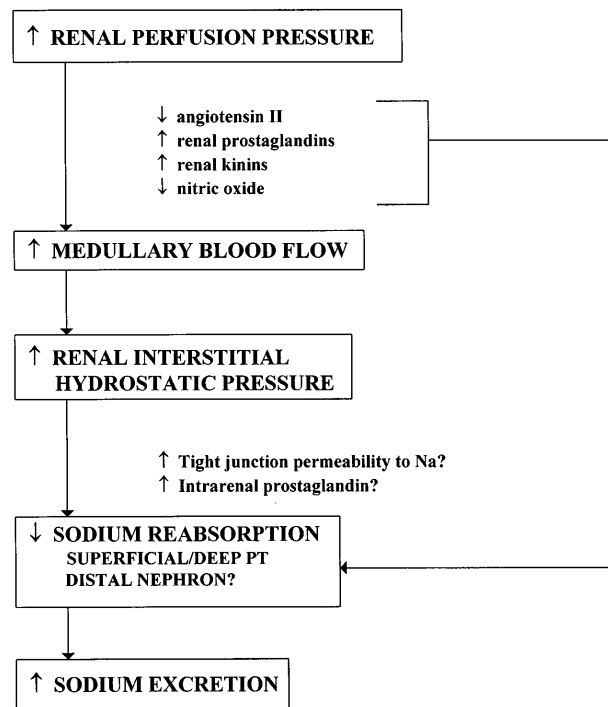

FIG. 3.
Mechanisms whereby increases in renal perfusion pressure enhances sodium excretion. PT, proximal tubule.

ACTIVATION OF RENAL SYMPATHETIC NERVOUS SYSTEM REDUCES SODIUM EXCRETION BY DECREASING GFR AND ENHANCING SODIUM REABSORPTION

Because the kidneys receive extensive sympathetic innervation, alterations in renal nerve traffic are believed to play an important role in the regulation of sodium excretion and extracellular fluid volume (3, 10, 11, 12). The renal sympathetic nervous system is activated via peripheral and central reflex mechanisms. In response to acute reductions in extracellular fluid volume, for example, intrathoracic volume/pressure receptors are thought to initiate a neural reflex that, in turn, enhances renal sympathetic nerve

activity and reduces sodium excretion. Conversely, increases in central volume lead to a reduction in renal nerve traffic and natriuresis.

Direct renal nerve stimulation reduces sodium excretion, whereas acute renal denervation enhances pressure natriuresis (3). Increases in renal sympathetic nerve activity could reduce sodium excretion by increasing tubular reabsorption or decreasing the filtered load of sodium (see Fig. 4). Renal nerves are known to act directly on the tubule to increase sodium reabsorption via an α-adrenergic receptor. In addition, increases in renal sympathetic nerve activity influence tubule reabsorption by activating the renin
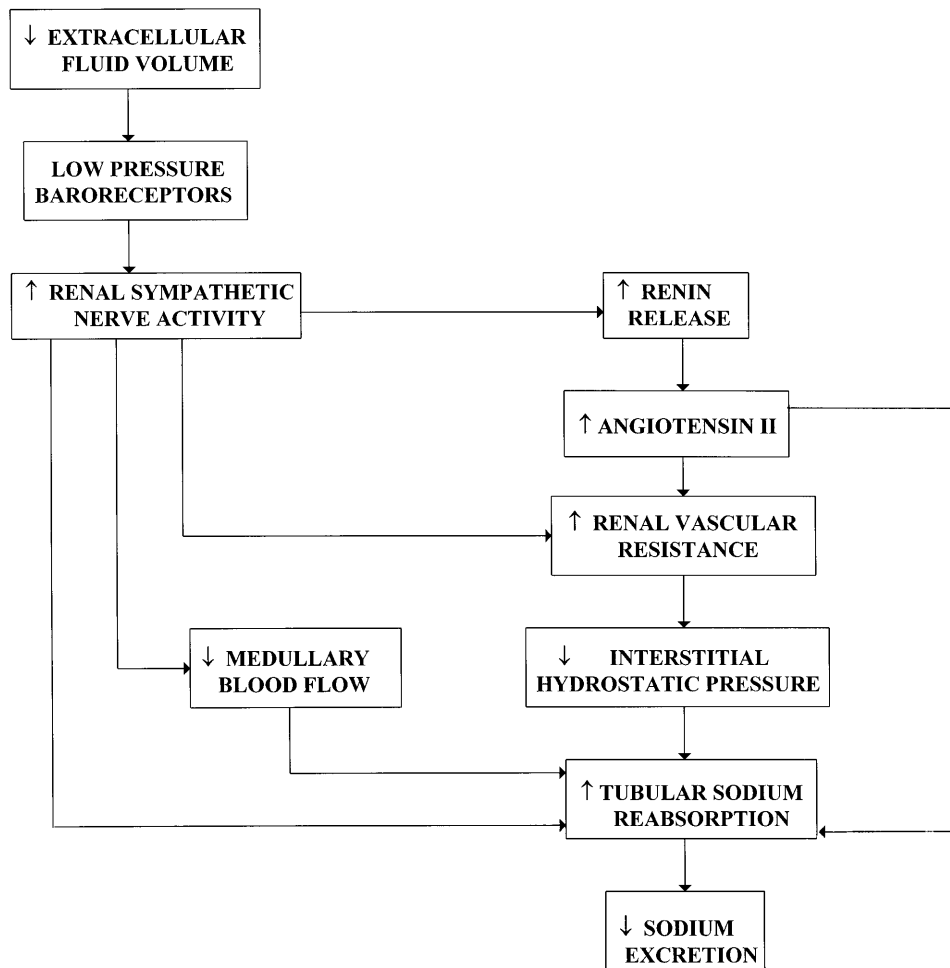

FIG. 4.
Mechanism whereby activation of sympathetic nervous system reduces sodium excretion in response to extracellular fluid volume contraction.

angiotensin system. Marked increases in renal sympathetic nerve activity may also raise renal vascular resistance and decrease GFR, medullary blood flow, and renal interstitial pressure, changes that could all contribute to the sodium-retaining effects of renal nerve activation.

Most of the experimental evidence suggests that this system plays a role in regulating sodium excretion under conditions associated with marked sodium retention, such as in congestive heart failure, cirrhosis, and a low-sodium diet (3, 10, 11, 12). There is also evidence to suggest that excessive activation of the sympathetic nervous system may play a role in the pathogenesis of certain forms of hypertension such as in obesity-related hypertension.

ALDOSTERONE ENHANCES SODIUM REABSORPTION IN CORTICAL COLLECTING DUCT

Aldosterone is a potent sodium-retaining hormone that is synthesized in the zona glomerulosa of the adrenal cortex. Although several factors (plasma K^+ and Na^+, ACTH, and ANP) influence its secretion, ANG II is the most important in controlling aldosterone secretion in response to changes in extracellular fluid volume. Increases in plasma ANG II enhance aldosterone secretion, whereas reduced plasma ANG II decreases aldosterone secretion. There is also a strong inverse relationship between sodium intake and plasma aldosterone concentration. A low-sodium diet is associated with high levels of plasma aldosterone. Conversely, plasma aldosterone concentration approaches zero in individuals with a high sodium intake.

Aldosterone decreases sodium excretion by enhancing renal sodium reabsorption. Aldosterone increases sodium reabsorption in principal cells of the collecting duct by increasing the sodium permeability of the luminal membrane and by stimulating Na^+-K^+-ATPase activity. Aldosterone permeates the cell membrane of the principal cells and binds to a cytosolic receptor (11). The aldosterone/receptor complex is translocated into the nucleus, where it activates the transcription of specific mRNA. The newly formed proteins called aldosterone-induced proteins are involved in mediating the increase in sodium permeability of the luminal membrane and Na^+-K^+-ATPase activity. Spi-

ronolactone, an aldosterone receptor antagonist, is used clinically to promote sodium loss in sodium retaining states such as congestive heart failure, cirrhosis, and hyperaldosteronism.

ANG II ENHANCES SODIUM REABSORPTION VIA A DIRECT EFFECT ON TUBULE TRANSPORT AND BY INDIRECT HEMODYNAMIC MECHANISMS

The renin-angiotensin system is the most thoroughly studied, and perhaps most important, system primarily responsible for the regulation of sodium excretion (9). During extracellular fluid volume contraction, renin is released from the kidneys. Renin acts on a substrate to release ANG I, which is rapidly converted to ANG II by a converting enzyme located in the pulmonary circulation and in the kidney itself.

For many years ANG II was thought to affect sodium excretion solely through the release of aldosterone, which acts on the cortical tubules to enhance sodium reabsorption (9). However, more recent studies have provided evidence that ANG II can stimulate sodium reabsorption through a direct action on ANG II receptors located on the renal tubules and by reducing medullary blood flow and renal interstitial hydrostatic pressure (see Fig. 5).

The importance of the renin-angiotensin-aldosterone system in regulating sodium excretion has been elucidated with the use of a specific receptor antagonist to ANG II and converting-enzyme inhibitors that block the formation of ANG II (9). ANG II appears to play a role in controlling sodium excretion over a wide range of physiological and pathophysiological conditions. For example, suppression of renin release and reduced ANG II formation in response to increases in dietary sodium intake has been shown to play a critical role in allowing the body to maintain sodium balance without increasing arterial pressure (9). ANG II also has powerful vasoconstrictor effects, which, in combination with the sodium-retaining actions of ANG II, play a crucial role in regulating extracellular fluid volume and arterial pressure. Receptor antagonists to ANG II and converting-enzyme inhibitors are widely used in clinical situations that are associated with abnormalities in volume regulation such as in hypertension and congestive heart failure.
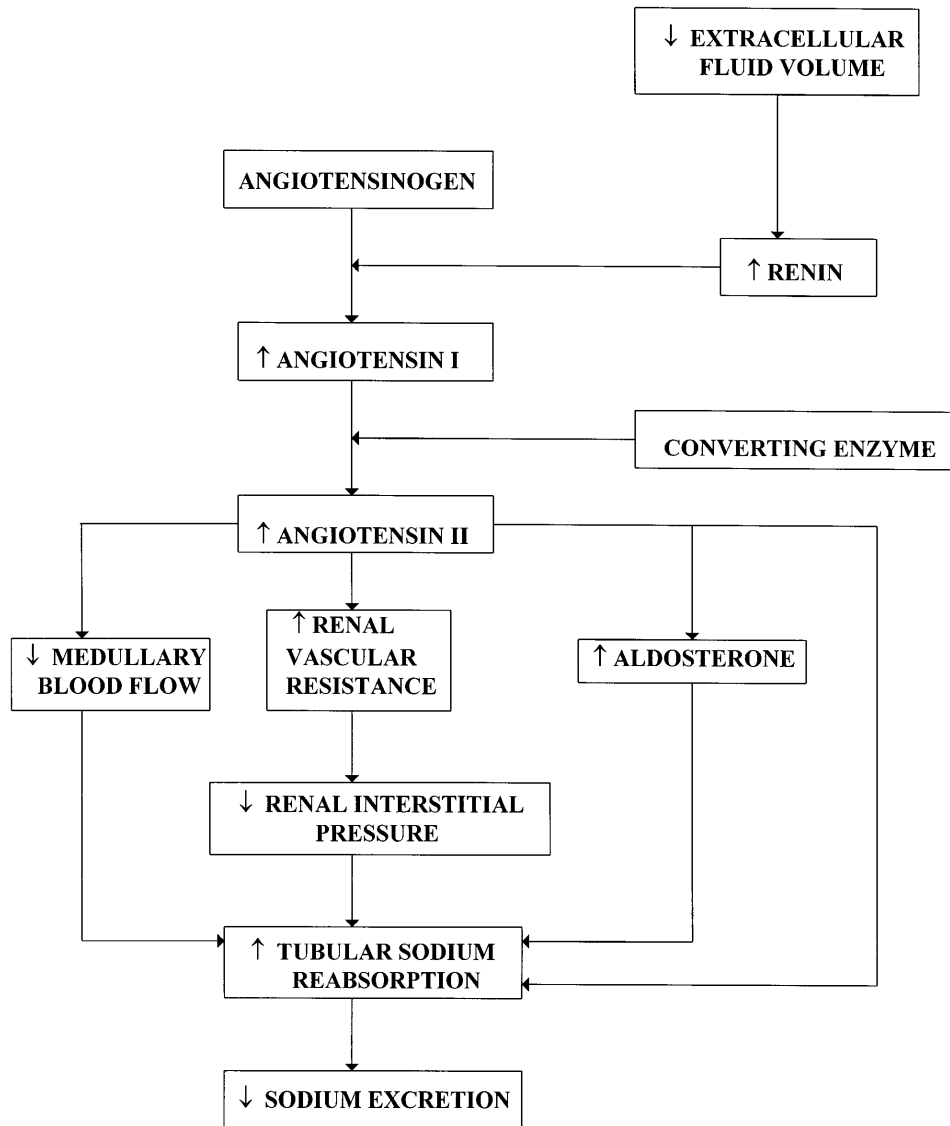
FIG. 5.
Mechanism whereby activation of renin-angiotensin system reduces sodium excretion in response to extracellular fluid volume contraction.

IN RESPONSE TO ATRIAL DISTENTION, THE HEART RELEASES A HORMONE THAT ENHANCES SODIUM EXCRETION

ANP is a 28-amino acid peptide hormone that is synthesized by atrial myocytes and secreted in response to increased atrial distention. Conversely, ANP secretion is reduced in response to reductions in atrial pressure (1, 3, 5).

Figure 6 shows pathways whereby ANP is released and then acts through direct and indirect mechanisms to enhance sodium excretion. ANP increases sodium excretion by increasing GFR and reducing sodium reabsorption; however, an increase in GFR is not essential for the natriuresis. Inhibition of sodium reabsorption occurs through direct and indirect effects on the renal tubules. ANP directly inhibits
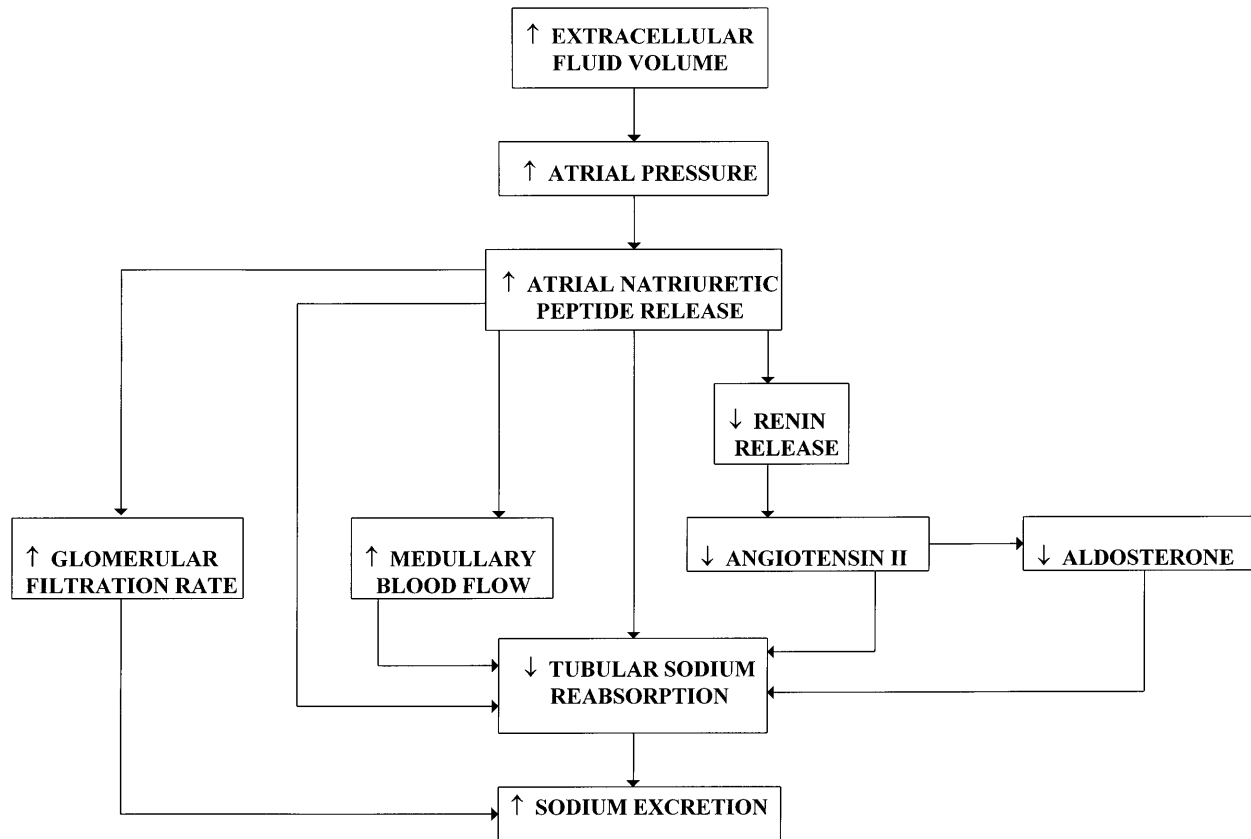
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FIG. 6.

Mechanism whereby atrial natriuretic peptide enhances sodium excretion in response to extracellular fluid volume expansion.

Boxes: ↑ GLOMERULAR FILTRATION RATE; ↑ MEDULLARY BLOOD FLOW; ↓ ANGIOTENSIN II; ↓ ALDOSTERONE; ↓ TUBULAR SODIUM REABSORPTION; ↑ SODIUM EXCRETION

sodium reabsorption in the collecting duct via a cGMP-mediated reduction in sodium permeability. ANP decreases sodium reabsorption indirectly by increasing medullary blood flow and inhibiting the formation of ANG II and aldosterone.

The quantitative importance of ANP in controlling sodium excretion is uncertain due to the lack of effort via experimental tools to block the synthesis or effector site of ANP. Increases in dietary sodium intake result in relatively small increases in plasma ANP concentration. Thus its importance in regulation sodium balance in response to increments in sodium intake is unclear. ANP is thought to play an important role in controlling sodium excretion under conditions of severe volume overload such as congestive heart failure. Under these conditions ANP is believed to play a role in protecting the body from severe volume retention and edema formation.

NITRIC OXIDE IS SYNTHESIZED BY RENAL ENDOTHELIAL AND TUBULE CELLS AND PROMOTES SODIUM EXCRETION

NO is synthesized from the amino acid L-arginine in endothelial as well as other renal tubule cells by the action of NO synthase (13, 14). The characterization and cloning of constitutive and inducible NO-synthesizing enzymes and the development of specific inhibitors of the L-arginine-NO pathway have provided powerful tools to examine the role of NO in the regulation of renal hemodynamics and sodium excretion (13, 14, 16). NO is believed to enhance sodium excretion by increasing glomerular filtration and by
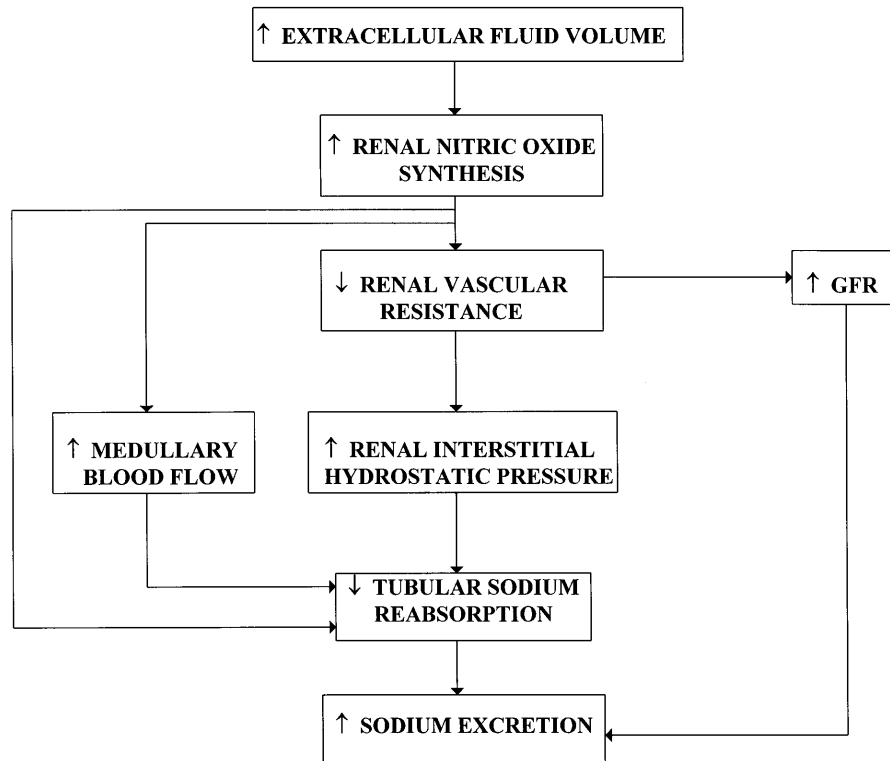
FIG. 7.
Mechanism whereby nitric oxide increases sodium excretion in response to extracellular fluid volume expansion. GFR, glomerular filtration rate.

inhibiting tubular sodium reabsorption (see Fig. 7). NO directly inhibits sodium transport in the collecting duct (13, 16). In addition, NO decreases tubular reabsorption by enhancing medullary blood flow ad increasing renal interstitial hydrostatic pressure (13, 16). NO may also decrease tubular odium reabsorption by antagonizing the renal tubular actions of ANG II studies (13, 16).

Recent studies indicate that NO may be important in the regulation of sodium excretion (13, 16). All three isoforms of NO synthase are found in the kidney, and there is evidence to suggest that NO synthesis increases in response to increases in sodium intake and other stimuli that increase sodium excretion such as increases in renal perfusion pressure.

The mechanism whereby increases in extracellular fluid volume increase NO production, however, has yet been fully elucidated. Blockade of endogenous NO formation reduces sodium excretion. In addition,

chronic blockade of NO synthesis results in a salt-sensitive form of hypertension. Thus it appears that NO is involved in the normal regulation of extracellular fluid volume and arterial pressure.

SODIUM EXCRETION RESPONSE TO ELEVATIONS IN SODIUM INTAKE INVOLVES INTEGRATION OF NEURAL, HORMONAL, AND PHYSICAL FACTORS

The integration of control systems regulating sodium excretion under normal conditions can be summarized by examining the homeostatic response to progressive increases in dietary sodium intake (see Fig. 8). The primary purpose of the homeostatic response is to enhance sodium excretion and maintain a balance between sodium intake and renal sodium output. As sodium intake is increased, sodium output initially lags behind intake. This time delay in sodium excretion results in a positive cumulative sodium balance and an increase, albeit small, in extracellular
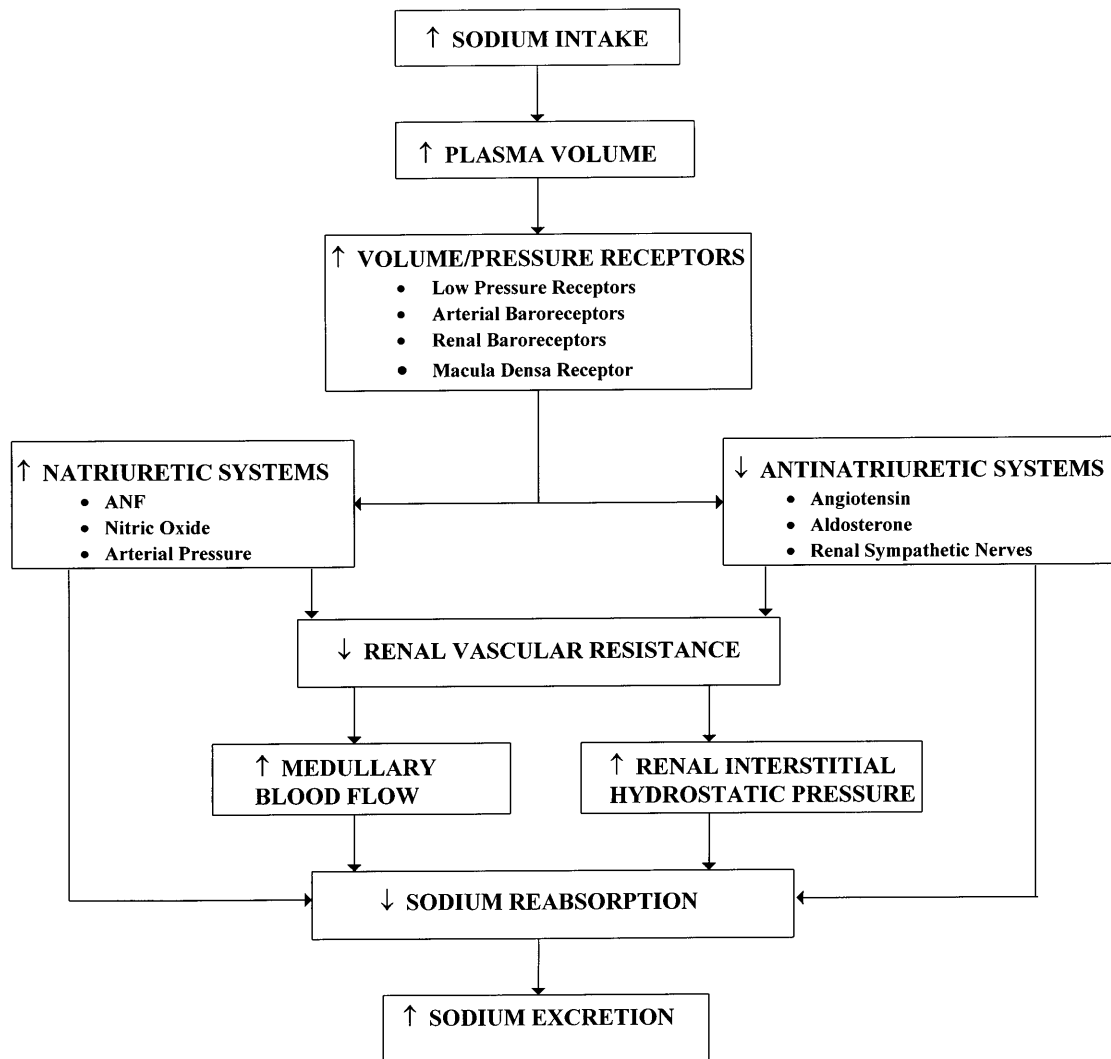
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│ ↑ VOLUME/PRESSURE RECEPTORS      │
│   • Low Pressure Receptors       │
│   • Arterial Baroreceptors       │
│   • Renal Baroreceptors          │
│   • Macula Densa Receptor        │
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↑ NATRIURETIC SYSTEMS
  • ANF
  • Nitric Oxide
  • Arterial Pressure

↓ ANTINATRIURETIC SYSTEMS
  • Angiotensin
  • Aldosterone
  • Renal Sympathetic Nerves

↓ RENAL VASCULAR RESISTANCE

↑ MEDULLARY BLOOD FLOW

↑ RENAL INTERSTITIAL HYDROSTATIC PRESSURE

↓ SODIUM REABSORPTION

↑ SODIUM EXCRETION

FIG. 8.
Integrated response to increases in dietary sodium intake. ANF, atrial natriuretic factor.

fluid volume. It is this small increase in extracellular fluid volume that triggers various volume and/or low-pressure receptors in the body to increase sodium excretion. Activating these receptors suppresses sodium-retaining systems and activates sodium-losing systems. Under normal conditions, progressive increases in sodium intake reduce renin release, ANG II formation, and aldosterone secretion. The elevation in extracellular fluid volume may also lead to a reduction in renal sympathetic nerve activity. In contrast to the sodium-retaining systems, natriuretic systems, such as the ANP and NO systems, are likely to be activated during progressive increases in dietary sodium intake.

The combined activation of natriuretic systems and suppression of sodium-retaining systems leads to an increase in sodium excretion, partly through reductions in sodium reabsorption and increases in glomerular filtration. These systems act on the kidneys to decrease sodium reabsorption directly by inhibiting sodium transport and indirectly by increasing RIHP and medullary blood flow. Maintaining sodium balance during chronic increases in sodium intake normally occurs without marked increases in renal perfusion pressure. Thus the neural and hormonal systems are sufficiently effective under normal conditions to maintain sodium balance without marked increases in

renal perfusion pressure. Thus the neural and hormonal systems are sufficiently effective under normal conditions to maintain sodium balance without excessive volume retention and hypertension. However, when a derangement in an important regulatory system occurs, activation of other natriuretic mechanisms, such as a rise in arterial pressure, becomes an important compensatory mechanism for maintaining sodium balance.

The importance of pressure/natriuresis can be illustrated in the homeostatic response to increased sodium intake when ANG II production is unable to be suppressed. Because ANG II is unable to respond to further increments in sodium intake, more sodium is retained, causing increases in extracellular fluid volume and arterial pressure that help to restore sodium balance. Another possible factor for maintaining sodium balance may be the release of natriuretic factors, such as atrial natriuretic factor (ANF). Circulatory levels of this natriuretic substance are elevated under these conditions; however, its quantitative importance in achieving sodium balance has not been determined.

Thus sodium excretion is controlled by integrating physical, neural, and hormonal regulatory systems. The major systems involved in retaining sodium include the renin-angiotensin-aldosterone and sympathetic systems, whereas natriuretic factors such as ANP and NO are important in promoting sodium excretion. In response to increased sodium intake, the sodium-retaining systems are inhibited and natriuretic hormones are activated. Pressures and flows within the microcirculation of the kidney, in concert with neural and hormonal systems, interact to regulate sodium excretion. The quantitative importance of each of these systems in regulating sodium balance is variable and is determined by the physiological or pathophysiological condition.

References

1. **Burnett, J. C., Jr., J. P. Granger, and T. J. Opgenorth.** Effects of synthetic atrial natriuretic factor on renal function and renin release. *Am. J. Physiol.* 247 (*Renal Fluid Electrolyte Physiol.* 16): F863–F866, 1984.
2. **Cowley, A. W., Jr.** Long-term control of arterial blood pressure. *Physiol. Rev.* 72: 231–300, 1992.
3. **DiBona, G. F.** The functions of the renal nerves. *Rev. Physiol. Biochem. Pharmacol.* 94: 76–181, 1982.
4. **Genest, J., and M. Cantin.** Regulation of body fluid volume: the atrial natriuretic factor. *News Physiol. Sci.* 1: 3–5, 1986.
5. **Granger, J. P.** Inhibitors of ANF metabolism: potential therapeutic agents in cardiovascular disease. *Circulation* 82: 313–315, 1990.
6. **Granger, J. P.** Pressure-natriuresis: role of renal interstitial hydrostatic pressure. *Hypertension* 19: I9–I17, 1992.
7. **Granger, J. P.** Role of renal interstitial hydrostatic pressure in the regulation of sodium excretion. *Federation Proc.* 45: 840–844, 1986.
8. **Guyton, A. C., T. G. Coleman, A. W. Cowley, Jr., K. W. Scheel, R. D. Manning, and R. A. Norman.** Arterial pressure regulation: overriding dominance of the kidneys in long-term regulation and in hypertension. *Am. J. Med.* 52: 584–594, 1972.
9. **Hall, J. E.** Control of sodium excretion by angiotensin II: intrarenal mechanisms and blood pressure regulation. *Am. J. Physiol.* 250 (*Regulatory Integrative Comp. Physiol.* 19): R960–R972, 1986.
10. **Hall, J. E., and J. P. Granger.** Role of sodium and fluid excretion in hypertension. In: *Textbook of Hypertension*, edited by J. D. Swales. Oxford, UK: Blackwell Scientific, 1994, p. 360–387.
11. **Knox, F. G., and J. P. Granger.** Control of sodium excretion: an integrative approach. In: *Handbook of Renal Physiology*, edited by E. Windhager. New York: Oxford Univ. Press, 1992, p. 927–967.
12. **Knox, F. G., and J. P. Granger.** Control of sodium excretion: the kidney produces under pressure. *News Physiol. Sci.* 2: 26–29, 1987.
13. **Kone, B. C., and C. Baylis.** Biosynthesis and homeostatic roles of nitric oxide in the normal kidney. *Am. J. Physiol.* 272 (*Renal Physiol.* 41): F561–F578, 1997.
14. **Moncada, S., R. M. J. Palmer, and E. A. Higgs.** Nitric oxide: physiology, pathophysiology and pharmacology. *Pharmacol. Rev.* 43: 109–142, 1991.
15. **Roman, R. J., and A.-P. Zou.** Influence of the renal medullary circulation on the control of sodium excretion. *Am. J. Physiol.* 265 (*Regulatory Integrative Comp. Physiol.* 14): R963–R973, 1993.
16. **Schnackenberg, C. G., K. Kirchner, A. Patel, and J. P. Granger.** Nitric oxide, the kidney, and hypertension. *Clin. Exp. Pharmacol. Physiol.* 24: 600–606, 1997.