Renal Control of Sodium Homeostasis

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ABSTRACT

The mechanisms involved in the maintenance of sodium homeostasis are reviewed. Emphasis is placed on localization of sodium reabsorption, effects of physical factors on glomerular ultrafiltration and tubular reabsorption, and action of certain hormones. Responses to arterial hypovolemia and hypervolemia are reviewed.

Introduction

The renal control of sodium homeostasis is dependent upon multiple factors. Renal blood flow, filtration of solute and water at the glomerulus, intrinsic tubular reabsorptive rates, modification of reabsorption by physical factors such as hydraulic and protein oncotic pressures, effects of various hormones, and renal autonomic nervous function all play important roles in the renal regulation of sodium balance.

Renal Blood Flow

For the kidneys to modulate sodium homeostasis, there must be sufficient quantities of solute and water delivered to the kidneys. Ordinarily, about 600 ml of plasma reaches the kidneys of a healthy young adult each minute. If cardiac output is not impaired, this volume with its suspended cellular components is kept quite constant throughout a wide range of perfusion pressures. Thus, the same renal blood flow pertains when mean blood pressure is as low as 60 mmHg or as high as 160 mmHg. This autoregulation of renal blood flow occurs secondary to the intrinsic ability of the myocytes of the afferent arterioles of the kidney to regulate their tone (myogenic regulation). If pressure in the arteriole increases, vasoconstriction occurs, resulting in constancy of blood flow. Conversely, if pressure falls, afferent arteriolar vasodilation preserves blood flow.

Although renal autonomic innervation is extensive, and nerve endings have been demonstrated in afferent arterioles and larger arteries as well as tubular basement membrane, there is no evidence that renal nerves play a role in the autoregulation of renal blood flow. Nonetheless, these nerves probably play some role in overall regulation of renal sodium reabsorption, since electrical stimulation of renal nerves results in an antinatriuresis.

Autoregulation of renal blood and plasma flows is maintained during fluctuations in renal perfusion pressure. However, when cardiac output is reduced, renal blood flow generally decreases. There is an attempt to maintain renal...
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blood flow through afferent arteriolar dilatation; but, as cardiac output falls further, renal flow also falls. However, even when renal plasma flow has begun to decrease, glomerular filtration rate (GFR) is preserved until renal perfusion falls even further. The consequences of preservation of GFR in the face of falling blood flow are important for the preservation of overall homeostasis for it allows filtration and excretion of nonreabsorbable toxic substances. Additionally, as will be described, the changing balance between GFR and plasma flow also allows greater retention of filtered salt and water to restore cardiac output or arterial volume back toward normal while the kidneys are excreting toxins maximally.

Regulation of Glomerular Filtration Rate

The mechanism by which GFR may be maintained in the face of falling perfusion is related to the usual mechanisms of ultrafiltration at the glomerular capillary. Ordinarily a virtually protein-free ultrafiltrate of plasma is formed as the result of the difference between the hydraulic pressure gradients and oncotic pressure gradients across the capillary wall. Thus, the single nephron glomerular filtration rate (SNGFR) is determined by the following:

\[
\text{SNGFR} = K_f (P_{gc} - P_T) - (\Pi_{gc} - \Pi_T)
\]

where:

- \(K_f\) = the ultrafiltration coefficient of the capillary wall, i.e., the intrinsic property of the endothelium, basement membrane, and endothelial cell layer to allow fluids to be filtered;
- \(P_{gc}\) = the hydraulic pressure in the capillary lumen;
- \(P_T\) = the hydraulic pressure in the tubules and in Bowman's Space of the glomerulus;
- \(\Pi_{gc}\) = the oncotic pressure in the glomerular-capillary, determined primarily by the albumin concentration; and
- \(\Pi_T\) = the oncotic pressure in tubules and in Bowman's Space.

The driving force for filtration, therefore, is the hydraulic pressure (blood pressure) in the capillary lumen and, ordinarily, this force is sufficient to cause about 20 percent of all water and filterable solutes flowing through the capillaries each minute to be ultrafiltered.

When renal plasma flow falls, it is necessary for intracapillary hydraulic pressure to be maintained at a level sufficient to maintain GFR. This is accomplished by constriction of the efferent arterioles which are distal to the glomerular capillaries. Thus, the capillaries are strategically placed between two vascular resistances in series. The afferent arterioles are pre-glomerular, and the efferent arterioles are post-glomerular. When dilatation of the former is insufficient to maintain intracapillary pressure, constriction of the latter then results in sufficient resistance to flow that the intracapillary hydraulic pressure is maintained at a level sufficient to maintain ultrafiltration at a normal rate. Constriction of the efferent vessels is brought about through the vasoconstrictor properties of circulating catecholamines and the intrarenal generation of angiotensin II.

Regulation of Proximal Tubular Reabsorption

In the low-cardiac output or volume-depleted states, the consequences on subsequent tubular reabsorption of this new balance between GFR and plasma flow are considerable. It is necessary to recall that the ultrafiltrate is almost protein free. Thus, in the normal state of a total renal plasma flow of 600 ml per min, 120 ml of protein-free filtrate are formed per min. The result is that all the serum proteins leaving the glomeruli are now suspended in 480 ml, i.e., they have been concentrated by a factor of 600/480 = 1.25. If a pathophysiologic state occurs which causes renal plasma flow to fall to 400 ml per min with maintenance of GFR at 100 ml per min, the protein will be concentrated to 400/300 = 1.33 times that present in the afferent arteriole. The result is that the oncotic pressure in the peritubular
capillaries which branch from efferent arterioles will be higher than in the normal state. Additionally, flow through these capillaries will also be decreased with an accompanying decrease in hydraulic pressures in the capillaries which surround the tubules. The result of this combination of increased oncotic pressure and decreased hydraulic pressure in the capillaries is increased resorption of fluid from the renal cortical interstitium which results in decreased interstitial fluid pressure.

The reduced renal interstitial fluid pressure plays a major role in modulating net reabsorption of solute and water by the renal proximal tubules. Under normal circumstances, the proximal tubules reabsorb about 60 percent of the glomerular filtrate. The net reabsorptive rate is equal to the amount of solute and water actually reabsorbed minus a fairly large backflux of fluid from the interstitium into the tubular lumens. This backflux occurs through the paracellular spaces between tubular cells and is determined by the quantity of fluid in the interstitium or by interstitial fluid pressure. In the volume-depleted state, for the reasons outlined previously, there is relatively less interstitial fluid, and the backflux is reduced. Thus, net reabsorption is increased since:

Net Reabsorption =

Actual Reabsorption minus Backflux

Under these circumstances, more than 60 percent of GFR is reabsorbed by the proximal tubules.

In states of volume expansion, the converse set of circumstances exists, i.e., plasma flow increases to a greater extent than does GFR, resulting in decreased protein concentration and increased hydraulic pressures in the post-glomerular blood vessels. This results in decreased reabsorption from the renal interstitium causing increased interstitial fluid volume and increased passive backflux of fluid into the tubular lumen. Net proximal tubular reabsorption, therefore, is decreased in the volume-expanded (i.e., high cardiac output, increased arterial filling) state. Less than 60 percent of GFR is reabsorbed by the proximal tubules under these circumstances.

Angiotensin II may also play an important role in the chronic regulation of tubular sodium reabsorption. When the angiotensin converting enzyme of dogs is inhibited chronically while the dogs are receiving a low-sodium diet, they tended to excrete more sodium than did the controls receiving the same diet. This occurred even though their filtration rates and blood pressures were lower than those of the controls. However, since the renal plasma flows of the dogs were actually increased, it is possible that the relative natriuresis observed was secondary to changes in the relationship between total plasma flow and filtration as discussed previously. Nonetheless, a chronic effect of angio-tensin on tubular epithelial reabsorption per se could not be ruled out—especially since such effects have been acutely observed.

Mechanisms of Proximal Reabsorption

Whatever quantity of tubular contents is reabsorbed by the proximal tubules, the reabsorbate is always isotonic so that neither concentration nor dilution of the tubular contents occurs. However, the reabsorbate does not have the same individual solute concentrations as does plasma. In the proximal one-third or so of the proximal tubule, about 90 percent of filtered HCO₃⁻ is reabsorbed, almost all filtered glucose is reabsorbed, almost all filtered amino acids are reabsorbed, and most phosphate is reabsorbed. Sodium is reabsorbed actively either in cotransport with the previous compounds or as sodium chloride; water follows passively. The result is an isonatremic, isotonic solution left in the tubular lumen, but the chloride concentration is elevated since other anions have been reabsorbed. Reabsorption in the remainder of the proximal tubule occurs isotonically as well, some
being passive but most driven by active transport.2

**Sodium Reabsorption in the Loop of Henle**

There is no reabsorption of sodium in the descending limb of Henle’s Loop. Instead, water is passively reabsorbed secondary to the osmotic differences between the luminal contents and the hypertonic interstitium of the renal medulla. However, sodium chloride is actively reabsorbed in the thick segment of the ascending limb. The evidence to date indicates that chloride is actively transported in this segment and sodium follows passively.1,15 There is equivocal evidence that deep, juxtamedullary nephrons may alter their fractional sodium chloride reabsorptive rates in the loop depending upon the organism’s volume status, i.e., increased reabsorption (or decreased net delivery to collecting ducts) in volume contraction or low cardiac output and, conversely, decreased reabsorption (or increased delivery to collecting ducts) in states characterized by arterial hypervolemia.10 This concept is currently under considerable debate.10

**Reabsorption in the Distal Nephron**

Reabsorption in the distal convoluted tubule per se appears to be by means of active sodium transport. Sodium reabsorption in the cortical connecting tubule (that portion which connects true distal convolution with cortical collecting tubule) is also active. Much of sodium reabsorption in the cortical connecting and collecting tubules is under the influence of aldosterone. Aldosterone stimulates active sodium reabsorption, creating an electronegative potential difference with the lumen being negative to the cell. This electrical gradient allows potassium and probably hydrogen ion as well to flow down their electrochemical gradients. This mechanism accounts for much of the kaliuresis and hydrogen ion excretion induced by aldosterone.

Once the formative urine leaves the cortical collecting tubules, it enters the medullary collecting ducts. There is currently much debate as to whether or not the collecting ducts are actively involved in the process of preservation of sodium homeostasis.10 Considerable experimental evidence indicates that the collecting ducts are capable of conserving sodium chloride in states of volume depletion.10 This process may be modulated by a low molecular weight peptide natriuretic substance.3,13 It should be recognized that the concept of the collecting ducts playing an active role in the process of sodium homeostasis is debated strongly.10 Nonetheless, it seems logical to assume that they must do so since the final urine which passes through the collecting ducts can be rendered virtually sodium-free in many pathophysiologic states. There is some fairly extensive body of evidence to indicate that distal portions of the nephron, perhaps collecting ducts, alter their function before that of the proximal tubules is changed in early salt retention or in early saline diuresis.12,17

**Prostaglandins**

Sodium reabsorption can be affected by hormones other than aldosterone. Considerable evidence exists to support the concept that certain prostaglandins (especially PGE2) play an important role in the maintenance of renal blood flow in salt-depleted, low cardiac output, or stressed states.16 Thus, inhibition of prostaglandin cyclo-oxygenase in these states results in a reduction of renal blood flow and enhancement of sodium reabsorption.16 Patients receiving such inhibitors (non-steroidal anti-inflammatory agents) frequently show elevations of blood urea nitrogen and an inability to excrete a salt load. Currently, considerable investigation is being directed toward any effects of prostaglandins on the intrinsic sodium reabsorptive capacity of tubular epithelium.
Summary of Factors Affecting Sodium Homeostasis

From the previous material, it is obvious that the maintenance of sodium homeostasis is accomplished through the interplay of many factors which are summarized in table I. There is no question that the intimately linked interrelationship between renal perfusion and proximal tubular reabsorption plays an important role, since this portion of the nephron is responsible for the largest bulk of sodium reabsorbed. However, the effects of changing loop or collecting duct function and the chronic action of aldosterone on cortical collecting structures play important roles in modulating the total amount of sodium returned to the blood or excreted. It is the combination of gross changes proximally and fine adjustments distally which allows the kidneys to perform one of their most important functions,—the maintenance of arterial blood volume through the maintenance of sodium and water homeostasis.

References

2. CHANTRELLE, B. and RECTOR, F. C., Jr.: Active and passive components of volume reabsorp-

*Glomerular filtration rate.