

Chapter 1 / Capítulo 1

*Electrolyte and Internal Environment Imbalances in
Emergencies (English Edition)*

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Composition and functions of the internal environment. Renal physiology

Composición y funciones del medio Interno. Fisiología renal

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Objectives:

- Understand renal physiology
- Describe the mechanisms of renal filtration and excretion
- Understand the physiological mechanisms of glomerular filtration

INTRODUCTION

In his work *From Fish to Philosopher*, Smith describes with remarkable clarity how the evolutionary processes that guided the transition of primitive aquatic organisms shaped the complex renal physiology that characterizes vertebrates today. During the shift of proto-vertebrates from a marine environment to freshwater habitats, the osmotic pressure of the new medium imposed a fundamental biological challenge: the need to eliminate excess water and maintain internal homeostasis. In response to this adaptive demand, a specialized vascular tuft –the glomerulus– emerged, whose primary function consisted of filtering plasma in order to counteract the hypotonic dilution of the external environment.

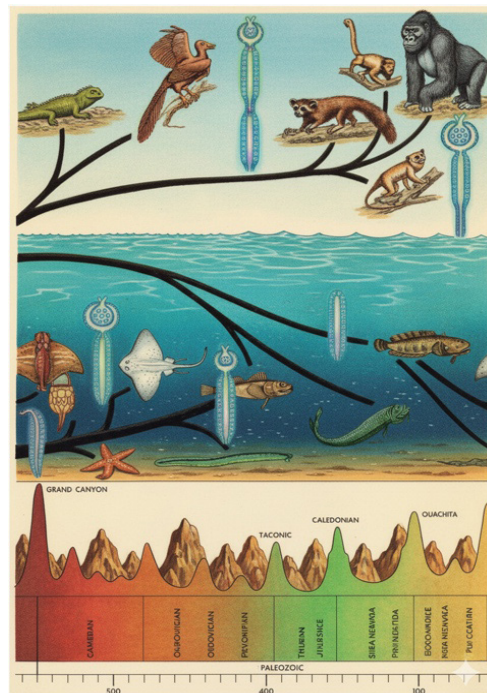


Figure 1.1. Evolution of the nephron adapted from: Smith, Homer W. *From Fish to Philosopher*

As evolution progressed, the appearance of reptiles and, later, mammals brought about a new physiological reconfiguration. Upon conquering terrestrial environments, these organisms faced a setting characterized by relative water scarcity, which required more efficient mechanisms for water conservation and electrolyte balance. From this adaptive process arose the convoluted tubules of the nephron, highly specialized structures that optimized the reabsorption of water and solutes and that today constitute one of the cornerstones of renal physiology in higher vertebrates, making the kidney a true laboratory for filtering and conserving the internal environment (figure 1.1).

The internal environment and its disorders can lead to an acute, life-threatening pathological condition, and these must be recognized and treated at the first point of contact with the patient. An effective treatment strategy is linked to the understanding of renal function, since this organ is one of the most important in maintaining hydroelectrolytic and acid-base homeostasis in the human body.

RENAL PHYSIOLOGY

The kidneys perform three main functions:

- a) Maintenance of the extracellular environment, through the excretion of waste products (urea, creatinine, uric acid), water, and electrolytes.
- b) Secretion of hormones involved in hemodynamic regulation (renin, angiotensin II, aldosterone), red blood cell production (erythropoietin), and mineral metabolism (calcitriol and 1,25-dihydroxyvitamin D).
- c) The kidneys regulate acid-base balance, by excreting either acidic or alkaline urine. The excretion of acidic urine reduces the amount of acid in the extracellular fluid, whereas the excretion of alkaline urine removes bases from this extracellular fluid.

Mechanisms

The kidneys regulate the concentration of H^+ in the extracellular fluid through three basic mechanisms:

- secretion of H^+
- reabsorption of filtered HCO_3^-
- production of new HCO_3^-

Each day, the kidneys filter approximately 4 320 mEq of HCO_3^- ($180 \text{ L/day} \times 24 \text{ mEq/L}$), and under normal conditions, almost all of it is reabsorbed by the tubules in order to preserve the principal buffering system of the extracellular fluids.

The reabsorption of HCO_3^- and the excretion of H^+ are carried out through the process of H^+ secretion in the tubules. Because HCO_3^- must react with the secreted H^+ to form H_2CO_3 before it can be reabsorbed, 4 320 mEq of H^+ must be secreted each day to allow for the complete reabsorption of filtered HCO_3^- .

An additional 80 mEq of H^+ must be secreted to eliminate the nonvolatile acids produced each day, which brings the total daily H^+ secretion into the tubular lumen to approximately 4 400 mEq.

Relationship between filtration and excretion

Glomerular filtration averages 130 to 145 L/day (90 to 100 mL/min) in women and 165 to 180 L/day (115 to 125 mL/min) in men. Therefore, the filtered sodium load is approximately 25 200 mEq. Considering that the sodium concentration in the extracellular fluid is 140 mEq/L and that daily sodium intake ranges from 80 to 250 mEq, this means that the kidney has an extraordinarily high capacity for sodium reabsorption. This capacity for filtration, reabsorption, and excretion occurs in the different segments of the nephron (table 1.1).

Table 1.1. Sites and mechanisms of sodium reabsorption

Tubular segment	Percentage of Na^+ reabsorption	Mechanism of Na^+ entry	Main regulatory factors
Proximal tubule	50-55 %	$\text{Na}^+ - \text{H}^+$ exchange, cotransport with glucose, amino acids, phosphate, and other organic solutes	Angiotensin II; norepinephrine; glomerular filtration rate
Loop of Henle	35-40 %	$\text{Na}^+ - \text{K}^+ - 2 \text{Cl}^-$ cotransport	Flow-dependent
Distal tubule	5-8 %	$\text{Na}^+ - \text{Cl}^-$ cotransport	Flow-dependent
Collecting tubules	2-3 %	Na^+ channels	Aldosterone; atrial natriuretic peptide

Source: Own elaboration

General mechanism of transtubular reabsorption

Sodium reabsorption from the tubular lumen to the peritubular capillary occurs in two phases, the first phase is the movement of sodium from the tubular lumen into the tubular cell, and the second phase is the movement of sodium from the tubular cell into the capillary.

Tubular reabsorption takes place through membrane transporters or sodium channels, which have different characteristics and functions in each tubular segment of the nephron, as described below:

Sodium reabsorption in the proximal tubule

PEARL:

SGLT2 inhibitors (e.g., dapagliflozin) block the Na^+ –Glucose cotransporter.

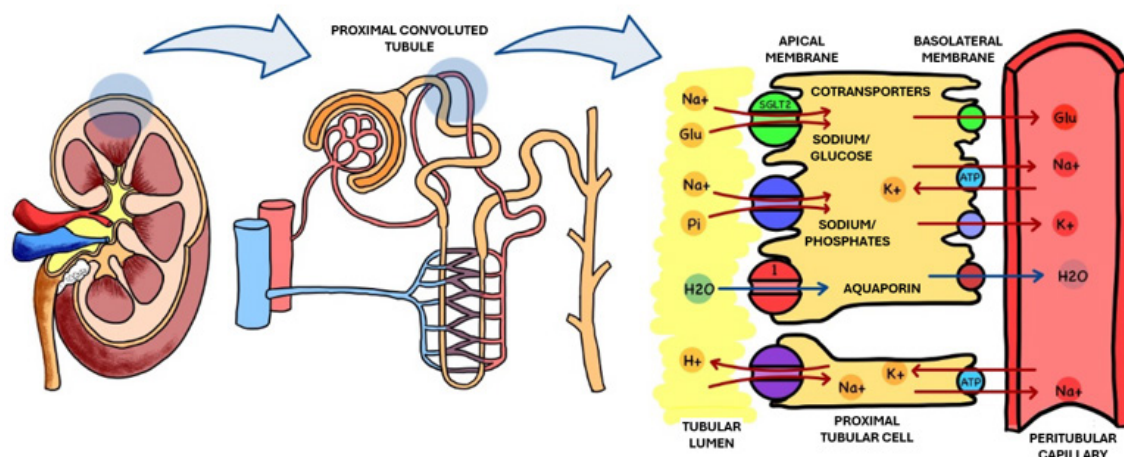


Figure 1.2. Transtubular reabsorption in the proximal tubule

In the proximal tubule of the nephron, 50 % to 55 % of the filtered sodium and water are reabsorbed through the following mechanisms (figure 1.2):

- Transport of sodium (Na^+) from the tubular lumen into the tubular epithelium through cotransporters (e.g., glucose + Na^+ , sodium-citrate, sodium-phosphate, and sodium-amino acid).

- Transport of Na^+ from the tubular lumen into the tubular epithelium via the sodium-hydrogen (Na^+/H^+) exchanger, which swaps Na^+ for H^+ at the epithelial membrane.
- Osmotic gradient facilitated by aquaporins, which allow water transport across the apical membrane of the tubular epithelium.
- Transport of Na^+ from the epithelium to the capillaries through the $3\text{Na}^+-2\text{K}^+$ ATPase pump.
- Transport of K^+ from the epithelium to the capillaries through a transporter driven by the electrochemical gradient generated.

Sodium reabsorption in the Loop of Henle

In the Loop of Henle, 35 % to 40 % of the sodium is reabsorbed, however, this segment is impermeable to water due to the absence of aquaporins. The mechanisms are the following (figure 1.3):

- Transport of Na^+ from the tubular lumen into the epithelium through the $\text{Na}^+-\text{K}^+-2\text{Cl}^-$ cotransporter.
- Transport of K^+ from the epithelium back into the tubular lumen through a transporter driven by the electrochemical gradient (necessary for the reabsorption of Na^+ , Ca^{2+} , and Mg^{2+}).
- Passive transport of Na^+ , Ca^{2+} , and Mg^{2+} from the tubular lumen into the capillaries through the tight junctions, driven by the electrochemical gradient generated by K^+ in the tubular lumen.
- Transport of Na^+ from the epithelium into the capillaries via the $3\text{Na}^+-2\text{K}^+$ ATPase pump.

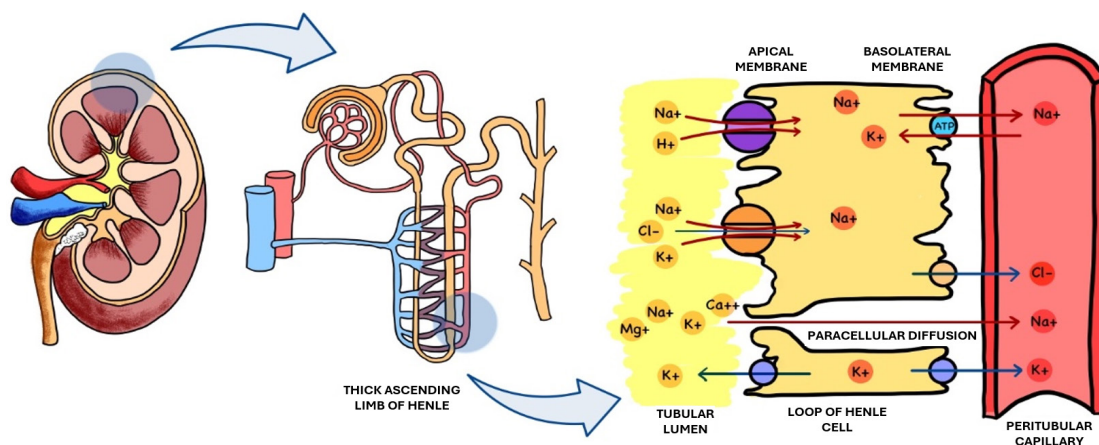


Figure 1.3. Transtubular reabsorption in the loop of Henle. Adapted from Rennke et al. Renal Pathophysiology

Sodium reabsorption in the distal tubule

In the distal tubule, between 5 % and 8 % of the filtered sodium is reabsorbed. As in the Loop of Henle, this segment is also impermeable to water (figure 1.4).

- Transport of Na^+ from the tubular lumen into the epithelium through the Na^+/Cl^- cotransporter.
- Reabsorption of Ca^{2+} occurs in this segment and is facilitated by the electrochemical gradient that creates a negative charge inside the tubular cell due to the activity of the $3\text{Na}^+-2\text{K}^+$ pump. Calcium transport is mediated by a vitamin D-dependent calcium-binding protein.

- Transport of Na^+ from the tubular epithelium into the capillaries via the $3\text{Na}^+-2\text{K}^+$ ATPase pump.
- Transport of Ca^{2+} from the tubular epithelium into the capillaries through a Ca^{2+} ATPase pump and the $\text{Ca}^{2+}-3\text{Na}^+$ exchanger.

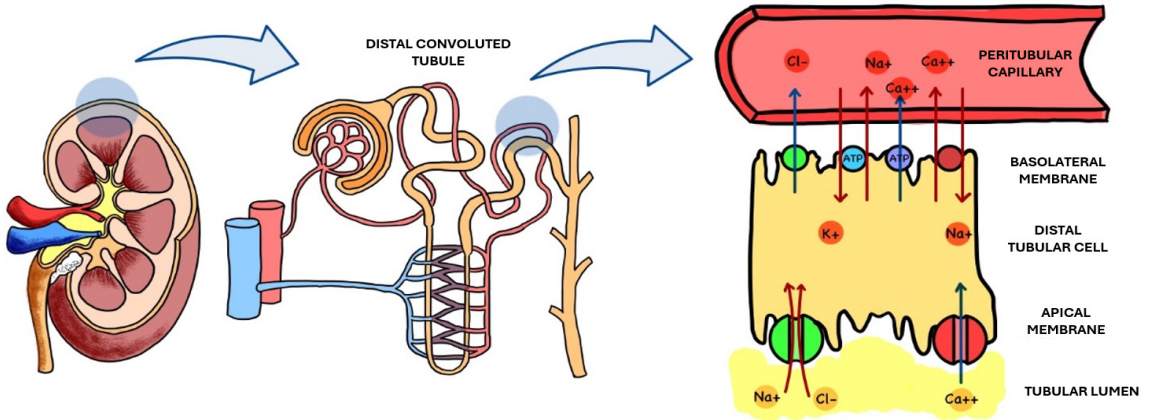


Figure 1.4. Transtubular reabsorption in the distal tubule. Adapted from Rennke et al. Renal Pathophysiology

Collecting tubule

In the collecting tubule, between 2 % and 3 % of the sodium is reabsorbed through the following mechanisms:

- Selective Na^+ channels, which are stimulated by aldosterone and by atrial natriuretic peptide (ANP) in the cortical and medullary cells, respectively.
- The entry of Na^+ into the tubular cells also promotes the exit of K^+ into the tubular lumen.
- Aquaporin-2 is expressed in the apical membrane of the tubular cells in response to cyclic GMP and protein kinase, stimulation triggered by antidiuretic hormone (ADH), which also promotes the insertion of aquaporins 3 and 4 into the basolateral membrane toward the capillaries (figure 1.5).

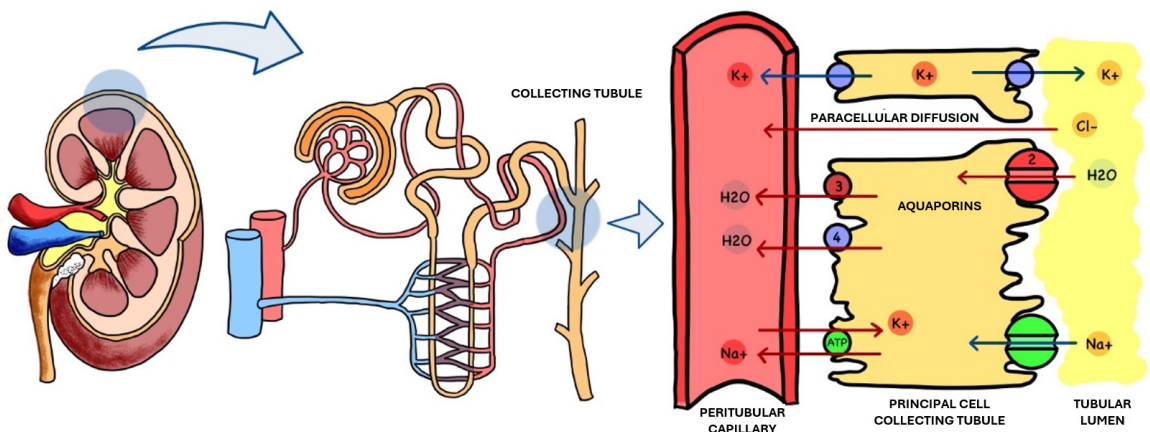


Figure 1.5. Reabsorption and transport in the collecting tubule. Adapted from Rennke et al. Renal Pathophysiology

Countercurrent mechanism

This mechanism allows variability in urinary osmolarity by enabling water conservation (urine concentration) or water elimination (urine dilution). It occurs due to the “U-shaped” configuration of the Loop of Henle, where changes in urinary osmolarity are generated. It is generated by:

- The Loop of Henle has two limbs: a descending limb (permeable to water) and an ascending limb (permeable to sodium and impermeable to water).
- As the fluid descends through the descending limb, water is reabsorbed and the urine becomes more concentrated.
- Then, as it ascends through the ascending limb, electrolytes (such as sodium and chloride) are reabsorbed but water is not, causing the urine to become more diluted.
- This exchange creates a concentration gradient in the renal medulla, which allows the kidneys to reabsorb water later (in the collecting tubules) and thus produce concentrated urine (figure 1.6).

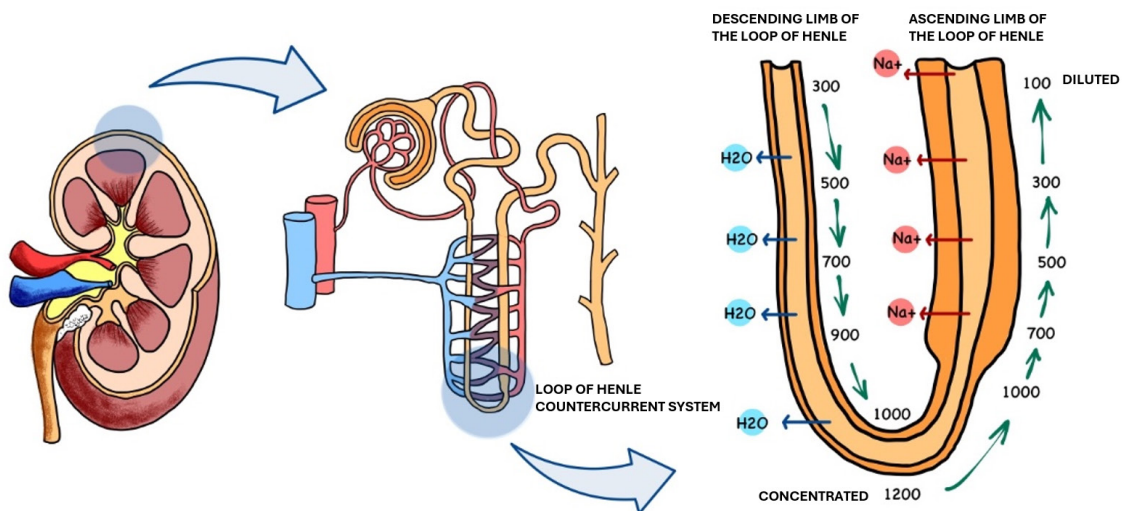


Figure 1.6. Countercurrent mechanism. Adapted from Rennke et al. Renal Pathophysiology

Understanding the nephron as a key functional structure in hydroelectrolytic balance is very important to understand patients with disorders of the internal environment. The nephron carries out these functions through the reabsorption of Na⁺ and water, when extracellular volume decreases, through the activation of compensatory mechanisms that increase the reabsorption of both Na⁺ and water. When there is excess volume and/or glucose, the drugs used to counteract this excess exert their mechanisms of action on various electrolyte transporters and cotransporters in different segments of the nephron. The nephron also plays a highly active role in water metabolism through the production of diluted or concentrated urine by means of the countercurrent mechanism. Acids handling: the kidneys filter approximately 4 320 mEq of HCO₃⁻ (180 L/day × 24 mEq/L) and, under normal conditions, almost all of it is reabsorbed by the tubules in order to preserve the main buffering system of the extracellular fluids.

The reabsorption of HCO₃⁻ and the excretion of H⁺ occur through the process of tubular H⁺ secretion. Because HCO₃⁻ must react with the secreted H⁺ to form H₂CO₃ before it can be reabsorbed, 4 320 mEq of H⁺ must be secreted each day to allow full reabsorption of the filtered HCO₃⁻.

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