Renal Mechanisms for Regulating Urine Concentration

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Reabsorption is selective

<table>
<thead>
<tr>
<th>Substances</th>
<th>Amount Filtered</th>
<th>Amount Reabsorbed</th>
<th>Amount Excreted</th>
<th>% of Filtered Load Reabsorbed</th>
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<tr>
<td>Glucose (g/day)</td>
<td>180</td>
<td>180</td>
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<td>Bicarbonate (mEq/day)</td>
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<td>Sodium (mEq/day)</td>
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<td>Chloride (mEq/day)</td>
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<td>Potassium (mEq/day)</td>
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<td>Urea (g/day)</td>
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<td>Creatinine (g/day)</td>
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For a substance to be reabsorbed, it must first be transported (1) across the tubular epithelial membranes into the renal interstitial fluid and then (2) through the peritubular capillary membrane back into the blood.
Primary Active Transport Through the Tubular Membrane Is Linked to Hydrolysis of ATP.

The energy for this active transport comes from the hydrolysis of ATP. The primary active transporters that are known include
- sodium-potassium ATPase,
- hydrogen ATPase,
- hydrogen-potassium ATPase,
- calcium ATPase.
The net reabsorption of sodium ions from the tubular lumen back into the blood involves at least three steps:

1. Sodium diffuses across the luminal membrane (also called the apical membrane) into the cell down an electrochemical gradient established by the sodium-potassium ATPase pump on the basolateral side of the membrane.
2. Sodium is transported across the basolateral membrane against an electrochemical gradient by the sodium-potassium ATPase pump.
3. Sodium, water, and other substances are reabsorbed from the interstitial fluid into the peritubular capillaries by ultrafiltration (also called “bulk flow”), a passive process driven by the hydrostatic and colloid osmotic pressure gradients.
The Kidneys Excrete Excess Water by Forming a Dilute Urine

- When there is **excess water in the body** and **body fluid osmolarity is reduced**, the kidney can excrete urine with an osmolarity as low as 50 mOsm/L, a concentration that is only about **one sixth the osmolarity of normal extracellular fluid**.

- Conversely, when there is a **deficit of water** and **extracellular fluid osmolarity is high**, the kidney can excrete urine with a concentration of 1200 to 1400 mOsm/L, **nearly five times the osmolarity of normal extracellular fluid**.

- Equally important, the kidney can excrete a **large volume of dilute urine or a small volume of concentrated urine** without major changes in rates of excretion of solutes such as sodium and potassium.

- When **osmolarity of the body fluids increases above normal** (that is, the solutes in the body fluids become too concentrated), the **posterior pituitary gland secretes more ADH, which increases the permeability of the distal tubules and collecting ducts to water but not sodium and potassium**.
  - This allows large amounts of water to be reabsorbed and decreases urine volume but does not markedly alter the rate of renal excretion of the solutes.
Renal Mechanisms for Excreting a Dilute Urine

When the glomerular filtrate is initially formed, its osmolarity is about the same as that of plasma (300 mOsm/L). To excrete excess water, it is necessary to dilute the filtrate as it passes along the tubule. This is achieved by reabsorbing solutes to a greater extent than water, but this occurs only in certain segments of the tubular system.

Water diuresis in a human after ingestion of 1 liter of water. Note that after water ingestion, urine volume increases and urine osmolarity decreases, causing the excretion of a large volume of dilute urine; however, the total amount of solute excreted by the kidneys remains relatively constant. These responses of the kidneys prevent plasma osmolarity from decreasing markedly during excess water ingestion.
Tubular Fluid Remains Isosmotic in the Proximal Tubule. As fluid flows through the proximal tubule, solutes and water are reabsorbed in equal proportions, so that little change in osmolarity occurs; that is, the proximal tubule fluid remains isosmotic to the plasma, with an osmolarity of about 300 mOsm/L. As fluid passes down the descending loop of Henle, water is reabsorbed by osmosis and the tubular fluid reaches equilibrium with the surrounding interstitial fluid of the renal medulla, which is very hypertonic—about two to four times the osmolarity of the original glomerular filtrate. Therefore, the tubular fluid becomes more concentrated as it flows into the inner medulla.

In the ascending limb of the loop of Henle, especially in the thick segment, sodium, potassium, and chloride are avidly reabsorbed. However, this portion of the tubular segment is impermeable to water, even in the presence of large amounts of ADH. Thus, regardless of whether ADH is present or absent, fluid leaving the early distal tubular segment is hypo-osmotic, with an osmolarity of only about one third the osmolarity of plasma.
Tubular Fluid in Distal and Collecting Tubules Is Further Diluted in the Absence of ADH. As the dilute fluid in the early distal tubule passes into the late distal convoluted tubule, cortical collecting duct, and collecting duct, there is additional reabsorption of sodium chloride. In the absence of ADH, this portion of the tubule is also impermeable to water, and the additional reabsorption of solutes causes the tubular fluid to become even more dilute, decreasing its osmolarity to as low as 50 mOsm/L. The failure to reabsorb water and the continued reabsorption of solutes lead to a large volume of dilute urine.
The Kidneys Conserve Water by Excreting a Concentrated Urine

When there is a water deficit in the body, the kidney forms a concentrated urine by continuing to excrete solutes while increasing water reabsorption and decreasing the volume of urine formed. The human kidney can produce a maximal urine concentration of 1200 to 1400 mOsm/L, four to five times the osmolarity of plasma. Some desert animals, such as the Australian hopping mouse, can concentrate urine to as high as 10,000 mOsm/L.

The basic requirements for forming a concentrated urine are (1) a high level of ADH, which increases the permeability of the distal tubules and collecting ducts to water, thereby allowing these tubular segments to avidly reabsorb water, and (2) a high osmolarity of the renal medullary interstitial fluid, which provides the osmotic gradient necessary for water reabsorption to occur in the presence of high levels of ADH.

ADH binds to specific receptors (V2 receptors) in the late distal tubules, collecting tubules, and collecting ducts, increasing the formation of cyclic AMP and activating protein kinases. This, in turn, stimulates the movement of an intracellular protein, called aquaporin-2 (AQP-2), to the luminal side of the cell membranes. The molecules of AQP-2 cluster together and fuse with the cell membrane by exocytosis to form water channels that permit rapid diffusion of water through the cells.

What is the process by which renal medullary interstitial fluid becomes hyperosmotic?
A Countercurrent Mechanism Produces a Hyperosmotic Renal Medullary Interstitium.

The major factors that contribute to the buildup of solute concentration into the renal medulla are:

1. **Active transport of ions from the collecting ducts into the medullary interstitium**
2. Facilitated diffusion of **large amounts of urea from the inner medullary collecting ducts** into the medullary interstitium
3. Diffusion of **only small amounts of water from the medullary tubules into the medullary interstitium**, far less than the reabsorption of solutes into the medullary interstitium
4. **Active transport of sodium ions and co-transport of potassium, chloride, and other ions out of the thick portion of the ascending limb of the loop of Henle** into the medullary interstitium

Because the **thick ascending limb is virtually impermeable to water**, the solutes pumped out are not followed by osmotic flow of water into the interstitium.

The **descending limb of Henle's loop**, in contrast to the ascending limb, is **very permeable to water**, and the tubular fluid osmolarity quickly becomes equal to the renal medullary osmolarity. Therefore, water diffuses out of the descending limb of Henle's loop into the interstitium, and the tubular fluid osmolarity gradually rises as it flows toward the tip of the loop of Henle.
Step 1 – The loop of Henle is filled with fluid with a concentration of 300 mOsm/L.

Step 2 – The active pump of the thick ascending limb on the loop of Henle is turned on; this pump establishes a 200-mOsm/L concentration gradient between the tubular fluid and the interstitial fluid. The limit to the gradient is about 200 mOsm/L because of paracellular diffusion of ions back into the tubule.

Step 3 – The tubular fluid in the descending limb of the loop of Henle and the interstitial fluid quickly reach osmotic equilibrium because of osmosis of water out of the descending limb.

Step 4 – The hyperosmotic fluid formed in the descending limb flows into the ascending limb. Additional ions are pumped into the interstitium, with water remaining behind, until a 200-mOsm/L osmotic gradient is established, with the interstitial fluid osmolarity now rising (at “5” below) to 500 mOsm/L… etc.
The early distal tubule further dilutes the 100 mOsm/L tubular fluid because this segment, like the ascending loop of Henle, actively transports sodium chloride out of the tubule but is relatively impermeable to water. **When there is a high concentration of ADH, the cortical collecting tubule becomes highly permeable to water**, so that **large amounts of water are now reabsorbed** from the collecting tubule into the cortex interstitium, where it is swept away by the rapidly flowing peritubular capillaries. **The fact that these large amounts of water are reabsorbed into the cortex, rather than into the renal medulla, helps to preserve the high medullary interstitial fluid osmolarity.**

As the tubular fluid flows along the **medullary collecting ducts**, there is further water reabsorption from the tubular fluid into the interstitium, but the total **amount of water is relatively small** compared with that added to the cortex interstitium.
Urea Contributes to Hyperosmotic Renal Medullary Interstitium and to a Concentrated Urine

In addition to NaCl, urea contributes about 40 to 50 per cent of the osmolarity (500-600 mOsm/L) of the renal medullary interstitium when the kidney is forming a maximally concentrated urine. Unlike NaCl, urea is passively reabsorbed from the tubule. When there is water deficit and blood concentrations of ADH are high, large amounts of urea are passively reabsorbed from the inner medullary collecting ducts into the interstitium. In the presence of high concentrations of ADH, water is reabsorbed rapidly from the cortical collecting tubule and the urea concentration increases rapidly because urea is not very permeant in this part of the tubule. Then, as the tubular fluid flows into the inner medullary collecting ducts, still more water reabsorption takes place, increasing the concentration of urea. In the inner medullary collecting duct urea diffuses out of the tubule into the renal interstitium. The diffusion of urea is greatly facilitated by specific urea transporters. One of these urea transporters, UT-A1, is activated by ADH. A normal individual still excretes 20-50% of the filtered urea.

The urea reabsorbed from the inner medullary collecting ducts diffuses into the thin loop of Henle, and then passes through the distal tubules, and finally passes back into the collecting duct. This recirculation of urea helps to trap urea in the renal medulla and contributes to the hyperosmolarity of the renal medulla.

Numerical values are in milliosmoles per liter of urea during antidiuresis.
Without a special medullary blood flow system, the solutes pumped into the renal medulla by the countercurrent multiplier system would be rapidly dissipated. How is this maintained?

There are two special features of the renal medullary blood flow that contribute to the preservation of the high solute concentrations:

1. The medullary blood flow is low, accounting for less than 5 per cent of the total renal blood flow. This sluggish blood flow is sufficient to supply the metabolic needs of the tissues but helps to minimize solute loss from the medullary interstitium.

2. The vasa recta serve as countercurrent exchangers, minimizing washout of solutes from the medullary interstitium.

Countercurrent exchange in the vasa recta. Plasma flowing down the descending limb of the vasa recta becomes more hyperosmotic because of diffusion of water out of the blood and diffusion of solutes from the renal interstitial fluid into the blood. In the ascending limb of the vasa recta, solutes diffuse back into the interstitial fluid and water diffuses back into the vasa recta.
Relative Rates at Which Solutes and Water Are Excreted Can Be Assessed Using the Concept of "Free-Water Clearance."

*Free-water clearance* \((C_{H_2O})\) is calculated as the difference between water excretion (urine flow rate, \(V\)) and osmolar clearance:

\[
C_{H_2O} = V - C_{osm} = V - \frac{(U_{osm} \times V)}{(P_{osm})}
\]

The rate of free-water clearance represents the rate at which solute-free water is excreted by the kidneys. When free-water clearance is positive, excess water is being excreted by the kidneys; when free-water clearance is negative, excess solutes are being removed from the blood by the kidneys and water is being conserved.

*Whenever urine osmolarity is greater than plasma osmolarity, free-water clearance will be negative, indicating water conservation.*
Renal Potassium Excretion

Potassium is **reabsorbed in the proximal tubule** and in the **ascending loop of Henle**, so that only about 8 per cent of the filtered load is delivered to the distal tubule. Secretion of potassium into the late distal tubules and collecting ducts adds to the amount delivered, so that the **daily excretion is about 12 per cent of the potassium filtered at the glomerular capillaries**. Most of the day-to-day regulation of potassium excretion occurs in the **late distal and cortical collecting tubules**, where potassium can be either reabsorbed or secreted, depending on the needs of the body.

**Extracellular fluid potassium concentration normally is regulated precisely at about 4.2 mEq/L**, seldom rising or falling more than ± 0.3 mEq/L. This precise control is necessary because many cell functions are very sensitive to changes in extracellular fluid potassium concentration. For instance, an **increase in plasma potassium concentration of only 3 to 4 mEq/L can cause cardiac arrhythmias**, and **higher concentrations can lead to cardiac arrest or fibrillation**.
Renal Potassium Excretion

There are **three mechanisms** by which increased extracellular fluid potassium concentration raises potassium secretion by the cortical collecting tubules:

1. **Increased extracellular fluid potassium concentration stimulates the sodium-potassium ATPase pump**, thereby increasing potassium uptake across the basolateral membrane. This in turn increases intracellular potassium ion concentration, causing potassium to diffuse across the luminal membrane into the tubule.

2. **Increased extracellular potassium concentration increases the potassium gradient from the renal interstitial fluid to the interior of the epithelial cell**; this reduces backleakage of potassium ions from inside the cells through the basolateral membrane.

3. **Increased potassium concentration stimulates aldosterone secretion by the adrenal cortex**, which further stimulates potassium secretion.

**Aldosterone stimulates the sodium-potassium ATPase pump** that transports sodium outward through the basolateral membrane of the cell and into the blood at the same time that it pumps potassium into the cell.

A second effect of aldosterone is to **increase the permeability of the luminal membrane for potassium**, further adding to the effectiveness of aldosterone in stimulating potassium secretion.
Renal Potassium Excretion

1. **K⁺ intake**
   - Increases plasma K⁺ concentration
   - Aldosterone production

2. **Plasma K⁺ concentration**
   - Stimulates K⁺ secretion in cortical collecting tubules

3. **K⁺ secretion**
   - Cortical collecting tubules

4. **K⁺ excretion**

Angiotensin II Increases Sodium and Water Reabsorption. Angiotensin II is perhaps the body's most powerful sodium-retaining hormone.

1) **Angiotensin II stimulates aldosterone secretion**, which in turn increases sodium reabsorption.

2) **Angiotensin II constricts the efferent arterioles**, which has two effects on peritubular capillary dynamics that raise sodium and water reabsorption.

   • First, efferent arteriolar constriction reduces peritubular capillary hydrostatic pressure, which increases net tubular reabsorption, especially from the proximal tubules.

   • Second, efferent arteriolar constriction, by reducing renal blood flow, raises filtration fraction in the glomerulus and increases the concentration of proteins and the colloid osmotic pressure in the peritubular capillaries; this increases the reabsorptive force at the peritubular capillaries and raises tubular reabsorption of sodium and water.

3) **Angiotensin II directly stimulates sodium reabsorption in the proximal tubules, the loops of Henle, the distal tubules, and the collecting tubules**. One of the direct effects of angiotensin II is to **stimulate the sodium-potassium ATPase pump** on the tubular epithelial cell basolateral membrane.
Sympathetic Nervous System Activation Increases Sodium Reabsorption

sympathetic nervous system stimulation increases renin release and angiotensin II formation, which increases tubular reabsorption and decrease renal excretion of sodium.