Renal Physiology — Renal Clearance, Tubular Transport, and the Renin-Angiotensin-Aldosterone System

The kidney's physiology is an extremely complex issue in medicine, which is, therefore, a popular topic in exams. Since the kidney fulfills many vital functions in the body in addition to its role as an excretory organ, it can be referred to as a multifunctional organ. The physiology of the kidney is a function of its anatomical structures, especially the nephrons.

Complete renal failure leads to death. Apart from its well-known function as an excretory organ of the body, the kidney performs many essential functions, including:

- Excretion of urine
- Blood pressure regulation—the renin-angiotensin-aldosterone system (RAAS)
- Homeostasis of the acid-base balance
- Regulation of water and electrolyte metabolism
- Hormone production

Glomerular Filtration

To understand the principle of glomerular filtration, it is necessary to first understand the structure of the kidney, especially that of the nephrons. Each kidney has afferent arterial and efferent venous vessels, as well as a uriniferous tubular system. Each nephron consists of a glomerulus and tubule.
The operating principle of the kidney is simple. The filtration process occurs in the glomeruli. Serum is expelled from the glomerular capillaries due to the effective filtration pressure, and primary urine or ultrafiltrate is produced, which accumulates within the Bowman capsule. From the Bowman capsule, primary urine passes through a sequence of tubules. Vessels run alongside the tubules, and substances absorbed from the tubules enter these vessels. Conversely, substances can actively be reabsorbed from the peritubular capillaries into the tubules. Thus, the composition and volume of the primary urine are not equal to those of the final urine.
The glomerular filtration rate (GFR) indicates the volume of primary urine filtered in the glomerulus per unit time. It is often expressed as mL/min and ranges from 85-135 mL/min in healthy kidneys. It is expressed in standardized terms with reference to 1.73 m² body surface area. In many kidney diseases, GFR is an important parameter of kidney function, as decreased GFR is an undesirable condition.

<table>
<thead>
<tr>
<th>Flow per minute (mL)</th>
<th>Calculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal blood flow</td>
<td>1050</td>
</tr>
<tr>
<td>Renal plasma flow</td>
<td>578</td>
</tr>
<tr>
<td>Glomerular filtration rate</td>
<td>110</td>
</tr>
<tr>
<td>Urine</td>
<td>1296 mL/day</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Calculation</th>
<th>mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>5000 × 0.21 = 1050</td>
<td>Blood/min</td>
</tr>
<tr>
<td>1050 × 0.55 = 578</td>
<td>Plasma/min</td>
</tr>
<tr>
<td>578 × 0.19 = 110</td>
<td>Filtration/min</td>
</tr>
<tr>
<td>110 × 0.008 = 0.9</td>
<td>Urine/min</td>
</tr>
</tbody>
</table>

Table: Calculating daily urine formation. By: Phil Schatz, License: CC BY 4.0

The driving pressure gradient is essential for the filtration process. This effective filtration pressure \( P_{\text{eff}} \) is the sum of various components. The first component is the capillary blood pressure \( P_{\text{Cap}} \) of about 48 mm Hg, which the blood exerts on the filter. The second component is a pressure of about 13 mm Hg in the Bowman capsule \( P_{\text{bow}} \), and this pressure acts in the opposite direction.

The third component is the colloid osmotic or oncotic pressure \( \pi_{\text{Cap}} \) of about 25 mm Hg, which is due to plasma proteins that cannot pass through the filter. This pressure moves water and ions out of the Bowman capsule and toward the blood. \( P_{\text{eff}} \) is calculated as follows:

\[
P_{\text{eff}} = P_{\text{Cap}} - P_{\text{bow}} - \pi_{\text{Cap}} = 48 - 13 - 25 = 10 \text{ mm Hg}
\]

\( \pi_{\text{Cap}} \) sharply increases along the glomerular capillary because as water is expelled from the blood, the protein concentration rises. Once \( \pi_{\text{Cap}} \) reaches a value of 35 mm Hg, \( P_{\text{eff}} \) drops to 0 and the filtration equilibrium is reached, which means that filtration can no longer occur. If the renal blood flow increases, the point of the filtration equilibrium is shifted further toward the end of the capillary, and a more extended segment of the glomerular capillary can be utilized for filtration. Thus, GFR depends on renal blood flow. Therefore, when the blood flow to the kidneys is reduced, such as during heart failure or in renal artery stenosis, the filtration must be increased to balance fluid and electrolytes in the body. This increased filtration is reflected by a high filtration fraction (FF), showing that the kidneys have to work more with the fluid they are receiving.
Renal Clearance

The concept of **renal clearance** arises from the function of the kidney as an organ of detoxification. Renal clearance describes the amount of plasma volume that is completely cleared of a particular substance per unit time. Here, in addition to filtration, other processes are at play. These processes include reabsorption (substances are removed from the tubules and transferred to the blood), secretion (substances are removed from the blood and transferred to the tubules), and excretion (passage of substances through the tubule and out into the collecting duct).

The amount of substance in the tubular lumen *increases* through:

- Secretion
- Formation of new products of metabolism
- Glomerular filtration

The amount of substance in the tubular lumen *decreases* through:

- Reabsorption
- Excretion
- Metabolic degradation

The formula for calculating renal clearance, \( C \), is \( \frac{K_{\text{urine}} \times V_{\text{urine}}}{K_{\text{plasma}}} \), which refers to the concentrations (K) of a substance in urine \( (K_{\text{urine}}) \) and plasma \( (K_{\text{plasma}}) \) and the volume (V) of urine \( (V_{\text{urine}}) \).

Clearance can be used to determine GFR, and thus, renal function. Therefore, to estimate renal function using renal clearance, it is important to identify a substance that cannot be
secreted, reabsorbed, or metabolized, but can be freely filtered. **Inulin** meets these requirements. If a patient is infused with inulin and the plasma and urine concentrations of inulin are measured, the renal clearance of inulin can be calculated and the GFR can be surmised. The following formula applies: \[ \text{Inulin Clearance curve} = \text{GFR} \]

However, GFR determination using inulin is very laborious. For routine checks and follow-ups, GFR determination using creatinine clearance is usually sufficient. The amount of creatinine in plasma is relatively constant, except during periods of high muscle activity. Plasma creatinine concentration increases when there is a decrease in GFR. However, in some instances, plasma creatinine concentration may only rise by 20% after a significant reduction of GFR. This is called the **creatinine blind area**.

The concept of **fractional excretion (FE) or renal clearance ratio** should also be understood. The FE of a substance describes the fraction of the excreted amount to the filtered amount per unit time, i.e. **the clearance of a substance X/inulin clearance**. Therefore, for inulin and creatinine, \( \text{FE} = 1 \); for substances that are absorbed in the tubular lumen, \( \text{FE} < 1 \), and for substances that are secreted, \( \text{FE} > 1 \). An example of a substance with a very high FE is p-aminohippurate (PAH). PAH can have an FE of 5, i.e. 500%. It is actively secreted and is excreted very rapidly.

 Absolute urinary excretion can be distinguished from FE. Absolute excretion refers to the actual excreted volume of a substance in a 24-hour collection of urine, whereas the FE of sodium (\( \text{FE}_{\text{Na}} \)) is the percentage of sodium that is filtered by the kidney and excreted in the urine. \( \text{FE}_{\text{Na}} \) is measured in terms of plasma and urine sodium, rather than by urinary sodium concentration alone, because absolute urinary sodium concentrations can vary with water reabsorption. The following example of the care of a critically ill patient demonstrates the use of \( \text{FE}_{\text{Na}} \): A sick, elderly patient has had no urinary output for 24 hours. Is the patient experiencing acute renal failure or does he have a postrenal problem or a low blood volume due to dehydration (a prerenal problem)?

\[
\text{FE}_{\text{Na}} = 100 \times \frac{\text{spot urinary sodium}}{\text{plasma creatinine}}
\]

<table>
<thead>
<tr>
<th>Value</th>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Below 1%</td>
<td>Prerenal disease</td>
<td>The physiologic response to a decrease in renal perfusion is an increase in sodium reabsorption to control hyponatremia, which is often caused by volume depletion or a decrease in effective circulating volume (e.g., low-output heart failure).</td>
</tr>
<tr>
<td>Above 2% or 3%</td>
<td>Acute tubular necrosis or other kidney damage (postrenal disease)</td>
<td>Excess sodium is lost due to tubular damage or through the damaged glomeruli leading to hypovolemia and the normal response of sodium wasting.</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Either disorder</td>
<td>In renal tract obstruction, ( \text{FE}_{\text{Na}} ) values may be either higher or lower than 1%. The value is lower in early disease, but with kidney damage from the obstruction, the value becomes higher.</td>
</tr>
</tbody>
</table>

**Clinical application of creatinine (Cr)**

- **Cr** is the breakdown product of skeletal muscle metabolism
- **Cr** is constantly released into the bloodstream. The rate of its release is proportional to the muscle mass
- Renal handling: **Cr** is freely filtered across the glomerulus; it is not reabsorbed,
but a small amount is secreted

- Creatinine clearance (C\text{Cr}): Because of the slight secretion, C\text{Cr} is slightly greater than GFR. In practice, C\text{Cr} is used as an approximation of GFR.

Clinicians do not routinely measure C\text{Cr} because C\text{Cr} measurement requires a timed urine collection, and the test is considered inconvenient. However, plasma creatinine concentration is typically used as a surrogate marker of C\text{Cr} and, therefore, of GFR.

- Basically, Cr \propto 1/GFR or GFR \propto 1/Cr
- Very roughly, a “normal” Cr level is \approx 1 and a normal GFR is \approx 100 mL/min
- A Cr level of 2 mg/dL implies a half-normal GFR (roughly 50 mL/min)
- A Cr level of 3 mg/dL implies a GFR in a range of 33 mL/min
- A Cr level of 4 mg/dL implies a GFR of roughly 25 mL/min

However, because Cr and GFR are inversely proportional, an increase in Cr level from 1-2 mg/dL represents a much more significant decrease in renal function than an increase from 4-5 mg/dL.

- Increase in Cr level from 1-2 mg/dL implies a 50% decrease in GFR (100 \rightarrow 50 mL/min)
- Increase in Cr level from 4-5 mg/dL implies a 20% decrease in GFR (25 \rightarrow 20 mL/min)
- Cr levels 4 and 5 mg/dL are almost clinically equivalent

Note that as GFR decreases, a greater proportion of Cr is excreted by secretion (rather than by filtration). As GFR decreases, C\text{Cr} or any Cr-based estimation of GFR becomes less accurate.

**C\text{Cr} assessment using 24-hour urine collection**

C\text{Cr} correlates with GFR

- Annual 1 mL/min decrease in C\text{Cr} after 50 years of age
- Useful in detecting renal dysfunction

\[
C = \frac{U_{cr} \cdot V_{cr}}{P_{cr}}
\]

V = Volume (mL/min) | P = Plasma (mg/dL)

**Normal adult C\text{Cr} is 97-137 mL/min.** Generally, C\text{Cr} < 100 mL/min is considered abnormal. C\text{Cr} < 10 mL/min indicates renal failure. **Elderly patients normally have decreased C\text{Cr}**. In patients receiving nephrotoxic drugs (e.g., aminoglycosides), it is important to calculate the dose and dose interval of the drug to avoid acute renal failure due to nephrotoxic acute tubular necrosis.

**Causes of increased and decreased C\text{Cr}**

<table>
<thead>
<tr>
<th>Cause</th>
<th>Discussion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Increased C\text{Cr}</strong></td>
<td></td>
</tr>
<tr>
<td>Normal pregnancy</td>
<td>A normal increase in plasma volume causes an increase in GFR leading to an increase in C\text{Cr}. C\text{Cr} is highest at the end of the 1st trimester</td>
</tr>
</tbody>
</table>
Early diabetic glomerulopathy

The efferent arteriole becomes constricted due to hyaline arteriosclerosis causing increased GFR and C\textsubscript{cr}.
The increased GFR leads to glomerular injury (hyperfiltration injury)

Decreased C\textsubscript{cr}

Elderly people

GFR typically decreases with age causing a corresponding decrease in C\textsubscript{cr}. The use of nephrotoxic drugs is dangerous in this population.

Acute and chronic renal disease

Acute renal failure is due to acute tubular necrosis, while chronic renal failure is due to diabetic glomerulopathy.

Experimental calculations of renal function

Renal blood flow (RBF):

- \( RBF = RPF + \text{Non-plasma blood} \)
- \( RBF = \frac{RPF}{(1 - \text{Hct})} \)
- \( RPF = \text{Clearance of a substance in a single pass} \)
- \( RPF = \text{Clearance of PAH} \)

\[ RPF = \text{Renal plasma flow} \mid \text{Hct} = \text{Hematocrit} \]

\[ FF = \frac{GFR}{RPF} \]

- \( FF = \frac{C\text{\textsubscript{inulin}}}{C\text{\textsubscript{PAH}}} \)
- \( FF = 15\text{–}20\% \)

Renal blood flow

Compared to other organs of the body, the kidney is very heavily supplied with blood. Each minute, about 1.2 L of blood passes through the kidneys (25% of the total blood volume); this is referred to as the RBF. Because filtration occurs in the glomeruli, which are in the renal cortex, most of the blood that enters the kidneys only reaches the cortex. Oxygen consumption is directly linked to ATP-dependent Na\textsuperscript{+}-resorption.

RBF can be determined by measuring PAH, as mentioned above. Since PAH is freely filtered and is strongly secreted, it can be assumed that RPF corresponds to PAH.
clearance. Because about 90% of PAH is excreted (via filtration and secretion), \( RPF = \frac{V_{U \times U_{PAH}}}{0.9 \times P_{PAH}} \).

Hematocrit can be used to calculate RBF from RPF. Accordingly, the following equation is applied: \( RBF = \frac{RPF}{1 - Hct} \). Determining RBF is useful in many diseases.

The RBF can be autonomously controlled by the kidneys. This is called renal autoregulation. RBF is maintained at a mean arterial pressure of 80–170 mm Hg, which is influenced by an increase in renal flow resistance. GFR also remains within this range.

<table>
<thead>
<tr>
<th>Change in GFR</th>
<th>NaCl Absorption</th>
<th>Role of adenosine triphosphate (ATP) and adenosine/Role of nitric oxide (NO)</th>
<th>Impact on GFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased GFR</td>
<td>Tubular NaCl increases</td>
<td>ATP and adenosine increase, which leads to vasoconstriction</td>
<td>Vasoconstriction slows down GFR</td>
</tr>
<tr>
<td>Decreased GFR</td>
<td>Tubular NaCl decreases</td>
<td>ATP and adenosine decrease, which leads to vasodilation</td>
<td>Vasodilation increases GFR</td>
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**Table:** Paracrine mechanisms that control GFR. By: Phil Schatz, License: [CC BY 4.0](https://creativecommons.org/licenses/by/4.0)

Two principles can be attributed to autoregulation: myogenic response or Bayliss effect and tubuloglomerular feedback. Myogenic response is defined as the vasoconstriction of the interlobular arteries with increasing pressure. Thus, increase in blood pressure does not typically affect the afferent arterioles of the glomerulus.

The macula densa is the part of the kidney that is responsible for tubuloglomerular feedback, and it lies between the distal tubule and the glomerulus. If high amounts of NaCl flow past the macula densa in the distal tubule, filtration in the glomerulus would be limited by a reduction of RBF or GFR via the release/suppression of ATP, adenosine, or NO.

**Tubular Transport**

The tubular system which joins the glomerulus consists of the proximal tubule, the descending limb, the loop of Henle, the ascending limb, and the distal tubule. This is followed by the collecting duct which transitions into the papillary duct and ends in the renal papilla. Molecules important for body functioning are reabsorbed along these structures, while harmful substances are secreted for elimination as quickly as possible.

Each section of the tubular system is equipped with specific transport proteins and channels that ensure the regulation of substances that are absorbed and secreted. Generally, tubular cells possess a luminal side which is toward the lumen and a basolateral side which communicates with the bloodstream.
Proximal tubule

The proximal tubule has a strongly defined brush border that creates an extensive area that is ideal for the absorption of water and salt. In the 1st stage, sodium ions are reabsorbed and hydrogen ions (H\(^+\)) are secreted via a Na\(^+\)-H\(^+\)-exchanger, while glucose, galactose, amino acids, and other substances are reabsorbed through a Na\(^+\)-symporter. Through the transport of a positive charge into the cells, a lumen-negative transepithelial potential is created.

Due to osmosis, substance transport causes water resorption through the relatively leaky epithelium. The water, in turn, drags dissolved molecules with it, a mechanism known as solvent drag. In the 2nd stage, a lot of chloride ions (Cl\(^-\)) are resorbed after a quarter of the length of the proximal tubule. Because of the negative charge of Cl\(^-\), a lumen-positive transepithelial potential arises, resulting in paracellular resorption of cations.

The basolateral side of tubular cells has numerous Na\(^+\)/K\(^+\)-ATPases. Thus, sodium is repeatedly removed from the equilibrium of the cell. Electrical and chemical gradients build up, which is crucial for the regulated transport. It should be noted that aquaporins (small water channels) are built into both the luminal and basolateral sides of tubular cells for water transport.

The loop of Henle

When studying the loop of Henle, it is important to note that while water is absorbed in the descending part of the loop, NaCl is not. In the ascending section, the exact opposite occurs. In this part, water absorption does not take place, but there is resorption of NaCl (and other ions). This is a crucial mechanism of urine concentration and an important task.
of the loop of Henle.

In the luminal side of the loop of Henle, certain Na⁺-K⁺-2Cl⁻ cotransporters can be found. These carriers are targets for loop diuretics, such as furosemide. The basolateral side contains specific Cl⁻ transporters, which can only be found in the kidney and the inner ear, and which contain a functional subunit, called Barttin.

The distal tubule

In the distal tubule, NaCl is resorbed, and this process takes place via a NaCl cotransporter that is sensitive to thiazide and aldosterone. While thiazides can inhibit NaCl cotransporter activity, NaCl cotransporter is stimulated by aldosterone. A Na⁺/K⁺-ATPase is embedded in the basolateral side of the distal tubule and maintains the gradient.

Tubular transport by nephron segments: proximal vs. distal nephron
Proximal convoluted tubular mechanics

Tubular creatinine and inulin increase in concentration (but not amount) along the proximal tubule due to water reabsorption. Cl⁻ reabsorption occurs at a slower rate than Na⁺ reabsorption in the proximal one-third of the proximal tubule, and the rate of Cl⁻ reabsorption matches the rate of Na⁺ reabsorption more distally. Its relative concentration increases before it plateaus. Na⁺ reabsorption drives H₂O reabsorption, so it nearly matches osmosis.

Relationship between nephron cotransporters and pumps and electrolyte disorders

Proximal renal tubule:

A. Primary site for Na⁺ reabsorption:

1. Na⁺ reabsorption is increased when cardiac output is decreased
a) ↓ EABV → ↑ FF → P_0 > P_H

EABV=Effective arterial blood volume, FF=Filtration fraction, P_0=Peritubular capillary oncotic pressure, P_H=Peritubular capillary hydrostatic pressure

b) Examples: congestive heart failure, cirrhosis, and hypovolemia

(2) Na^+ reabsorption is decreased when cardiac output is increased

a) ↑ EABV → ↓ FF → P_H > P_0

b) Examples: mineralocorticoid excess and isotonic gain in fluid

B. Primary site of bicarbonate (HCO_3^-) reclamation: Mechanism of partial reabsorption of filtered HCO_3^- into the blood

(1) Hydrogen ions (H^+) in tubular cells are exchanged for Na^+ in the urine

(2) H^+ combines with filtered HCO_3^- to form H_2CO_3 in the brush border of the proximal tubules

(3) Carbonic anhydrase dissociates H_2CO_3 to H_2O and CO_2. CO_2 and H_2O are reabsorbed into the proximal renal tubular cells.

(4) H_2CO_3 is re-formed in the proximal renal tubular cells. H_2CO_3 dissociates into H^+ and HCO_3^-.

(5) HCO_3^- is reabsorbed into the blood.

(6) A Na^+/K^+-ATPase pump moves Na^+ into the blood

Decreased effective arterial blood volume

Increased effective arterial blood volume
Thick ascending limb of the distal tubule

The primary function of the thick ascending limb of the distal tubule is to reabsorb water without reabsorbing sodium, which increases the osmolarity in the medulla via a countercurrent mechanism.

The collecting duct and the papillary duct

The ENaC, an epithelial Na\(^+\) channel, is a membrane-bound ion channel that is selectively permeable to Na\(^+\) ions. ENaC is assembled as a heterotrimer composed of three homologous subunits α or δ, β, and γ. These subunits are encoded by 4 genes: SCNN1A, SCNN1B, SCNN1G, and SCNN1D. ENaC is primarily involved in the reabsorption of sodium ions in the collecting ducts of the nephrons. ENaC can be stimulated by aldosterone and antidiuretic hormone (ADH). Amiloride, atrial natriuretic peptide, and prostaglandins can inhibit ENaC. Inflowing sodium from the lumen causes a lumen-negative potential. Therefore, K\(^+\) is secreted and Cl\(^-\) is transported paracellularly.

In the collecting duct and papillary duct, the resorption of water is controlled by ADH. This hormone is released in settings of water deficiency and it causes the incorporation of aquaporins in the luminal membrane. The resorption of water in the collecting duct is mostly independent of sodium absorption.

Tubular secretion

Several substances such as organic cations and anions, including bile salts and uric acid, are secreted in the tubules. The secreted substances enter the interstitial space from the peritubular capillaries and are transported by organic transporters in the basolateral membrane into the cytoplasm of tubular epithelial cells. The secreted substances are transported out of cells and into the tubular lumen by luminal membrane transporters.
Sites of drug action

1. Mannitol
2. Carbonic anhydrase inhibitors
3. Loop diuretics
4. Thiazides
5. Potassium-sparing diuretics

Tubular secretion and diuretics

Most diuretics have to gain access to the tubular lumen in order to exert their effects. Diuretics are mostly protein-bound and are, thus, not freely filtered through the glomerulus. Diuretics are transported into the tubular lumen by organic ion transporters.

Clinical correlate

Loop diuretics are not very useful in individuals with renal failure because other organic ions accumulate in renal failure and compete with diuretics for transport. Thus, large doses of diuretics must be administered to overcome this competition before tubular secretion can occur.

Countercurrent Multiplier Theory

The loop of Henle plays a crucial role in urine concentration. The countercurrent multiplier theory between the loop of Henle and the vasa recta of the renal medulla is important. Osmolality increases strongly in the direction of the loop apex. Through this corticomedullary gradient, water is withdrawn from the arterial blood towards the apex, and this water is released back into the hyperosmolar venous vessels leaving the medulla.

Thus, a wash-out effect of the osmotic gradient at the apex of the loop in the renal medulla is avoided. The driving force of the countercurrent multiplier theory in the loop of Henle is the active NaCl resorption in the ascending portion of the loop, in combination with a lack of water resorption due to the mostly watertight epithelium.

Thus, the osmolality of the urine in the lumen of the ascending portion of the loop of Henle decreases, whereas the osmolality of the interstitium increases due to the inflowing NaCl. To compensate for this, water is resorbed from the descending part of the loop. Thus, the concentration of NaCl is highest at the apex of the loop, so that the resorption
in the ascending part can occur passively.

This pumping system is kept in motion through a principle called the **countercurrent multiplier theory**. In the thick ascending segment of the loop of Henle, sodium is actively reabsorbed and discharged into the interstitium and this causes water reabsorption in the descending part, increasing the osmolarity of the urine.

The distal tubule and the collecting duct concentrate the urine further, as strong resorption of water takes place in these regions, which are impermeable to urea. Urea can only be resorbed further down in the collecting ducts in the presence of ADH, and the resorbed urea contributes to the total osmolality of the interstitium, which is crucial for the maintenance of the gradients.

The ‘single effect’ theoretical approach helps to visualize the step-by-step process of the countercurrent multiplier formation. Once the corticopapillary osmotic gradient is established, this gradient can be modified but it does not need to be reestablished.
The Renin-Angiotensin-Aldosterone System—RAAS

Granulosa cells of the juxtaglomerular apparatus produce the enzyme, renin. Renin proteolytically cleaves angiotensinogen into angiotensin (Ang) I, which is hydrolyzed by angiotensin-converting enzyme (ACE) to angiotensin II. An increase in Ang II levels leads to the production of aldosterone in the cortex of the adrenal gland. The RAAS system serves to maintain blood pressure and can detect a decrease in blood pressure as small as 10–15 mm Hg. ACE is a target for ACE inhibitors used for the treatment of elevated blood pressure.

Renal hormone production

In addition to renin, which affects hormone production, erythropoietin is another important product of the kidney. It is a glycoprotein formed in the endothelial cells of the capillaries. It affects the formation of red blood cells in the bone marrow and is released in settings of hypoxia.

Pathophysiology

The Bartter syndrome

If one of the transporters in the ascending limb of the loop of Henle is defective due to a loss-of-function mutation, the so-called Bartter syndrome occurs. In this syndrome, resorption of Na⁺, Mg²⁺, Cl⁻, and Ca²⁺ is disturbed. Although this can be partially or completely reversed in later sections of the loop, it is associated with increased K⁺ and H⁺ secretion. Signs of the Bartter syndrome are Na⁺ and volume depletion, hypocalcemia, and hypokalemic alkalosis.

Gitelman syndrome

A genetic defect in the transporter of the distal tubule leads to Gitelman syndrome. The clinical signs are similar to those of Bartter syndrome but milder.

Liddle syndrome

In Liddle syndrome, a gain-of-function mutation leads to a permanently open state of the ENaC in the collecting ducts. Liddle syndrome is accompanied by hypervolemia, hypertension, hypokalemia, and alkalosis, and can be compared to symptoms of high aldosterone secretion. Therefore, it is also called pseudohyperaldosteronism.
Pseudohypoaldosteronism type 1

The clinical picture in pseudohypoaldosteronism is opposite that of Liddle’s syndrome. Pseudohypoaldosteronism is characterized by hypovolemia, hypotension, hyperkalemia, and acidosis, and is based on a loss-of-function mutation of ENaC.

Diabetes insipidus

In diabetes insipidus, ADH is absent or has limited effect, and therefore, there is no incorporation of aquaporins in the collection tube. The resorption of water is also disturbed, which leads to a greatly increased urinary excretion of 5–25 L per day.

**Diabetes insipidus centralis** and **diabetes insipidus renalis** have important differences. The former is associated with damage to the pituitary gland or hypothalamus, which results in the disruption of ADH production, while in the latter, ADH cannot function sufficiently due to defects in a region of the collecting tube.

Renal tubular acidosis or renal tubular necrosis

Hypoxia or toxic drugs can lead to selective damage to the proximal or distal tubule, causing loss of bicarbonate (damage to the proximal tubule) or loss of hydrogen ion secretion (damage to the distal tubule).

References

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**Correct answers:** 1A, 2B, 3A

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