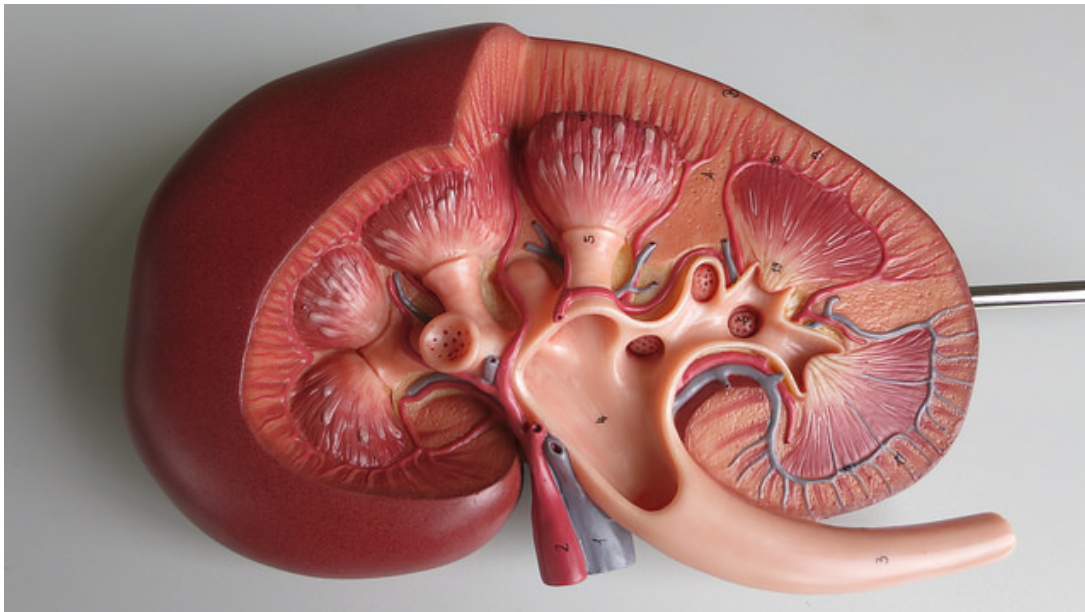


## Renal Physiology — Renal Clearance, Tubular Transport and the RAAS

[See online here](#)

**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 first to be aware of the anatomical structure of the kidney, especially the nephrons. Each kidney has an afferent arterial and efferent venous vasculature, as well as a uriniferous tubular system. Each nephron consists of a glomerulus and tubule.

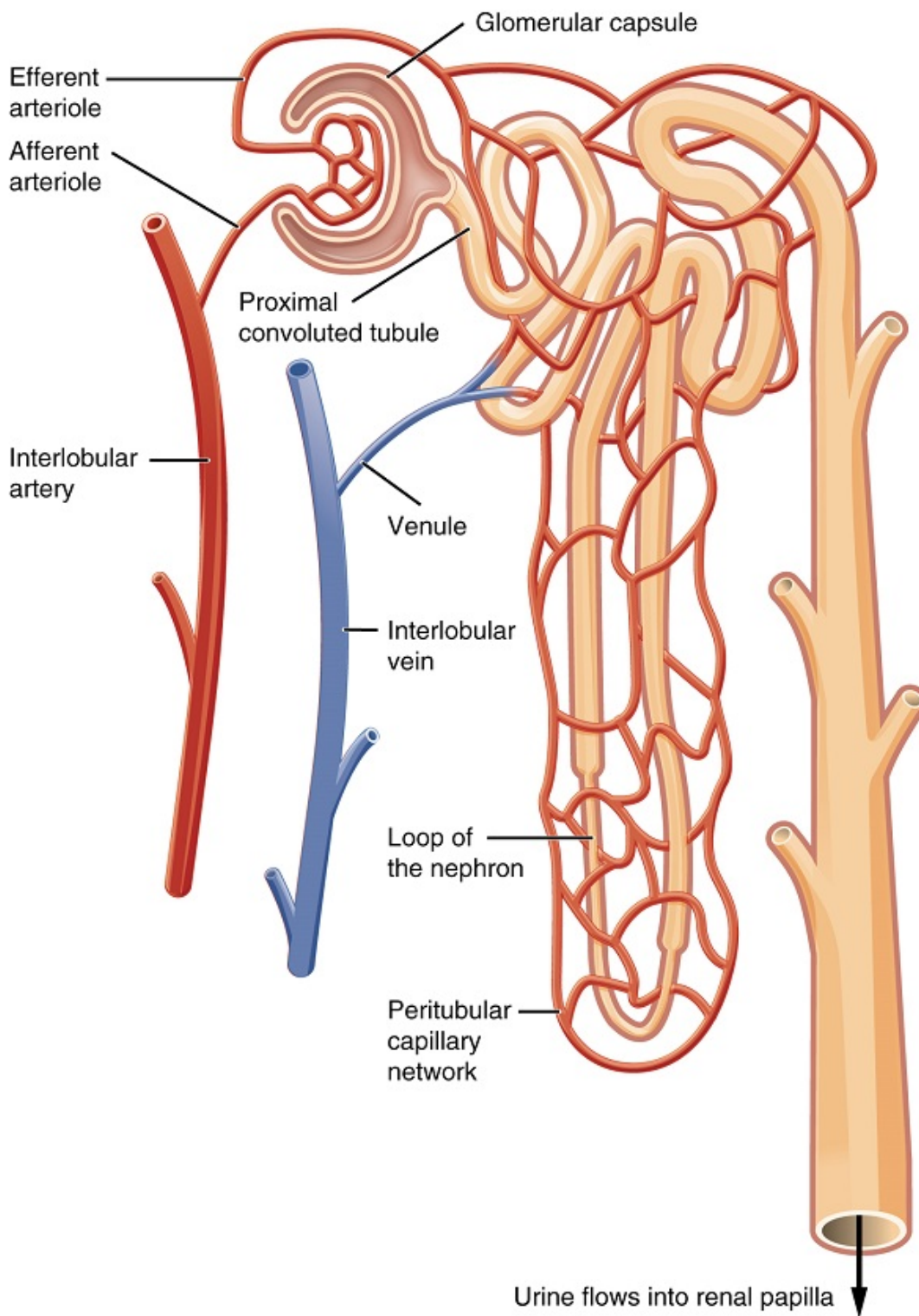


Image: Detail: Blood flow in the nephron. By Phil Schatz, License: [CC BY 4.0](https://creativecommons.org/licenses/by/4.0/)

The operating principle is simple: The filtration process takes place in the glomeruli. The serum is expelled from the glomerular capillaries due to the **effective filtration pressure**. Thus, **primary urine or ultrafiltrate** is produced and accumulates within the Bowman capsule. From here, primary urine flows inside a sequence of tubules. Vessels run alongside the tubules, and substances absorbed from the tubules enter these vessels. Conversely, substances can actively be removed from the peritubular capillaries and secreted into the tubules, which means that the composition and volume of the primary urine are not equal to that of the final urine!

The **glomerular filtration rate (GFR)** indicates the volume of primary urine filtered in the glomerulus per time unit. It is often expressed as mL/min and lies in the range of 85–135 mL/min in healthy kidneys. It is quoted in standardized terms with reference to 1.73 m<sup>2</sup> of body surface area. In many [kidney diseases](#), its measurement is important as a parameter of kidney function, as decreased GFR can become very dangerous.

Flow amount per minute (mL)	Calculation	
<b>Renal blood flow</b>	1050	5000 * 0.21 = 1050 mL blood/min
<b>Renal plasma flow</b>	578	1050 * 0.55 = 578 mL plasma/min
<b>Glomerular filtration rate</b>	110	578 * 0.19 = 110 mL filtration/min
<b>Urine</b>	1296 mL/day	110 * 0.8 = 0.9 mL urine/min. Multiply urine/min with 60 minutes and 24 hours to obtain daily urine production. 0.9 * 60 * 24 = 1296 mL/daily urine

**Table:** Calculating urine formation per day. 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 around 48 mm Hg, from the blood towards the filter. The second component is the pressure in the Bowman's capsule  $P_{\text{bow}}$  of around 13 mm Hg, which 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, thus attracting water and ions out of the Bowman capsule and toward the blood. This results in:

$$P_{\text{eff}} = P_{\text{cap}} - P_{\text{bow}} - \pi_{\text{cap}} = 48 - 13 - 25 = 10 \text{ mm Hg}$$

A  $\pi_{\text{cap}}$  increases sharply along the capillary because as water is removed from the blood, protein concentration rises. Once it reaches a value of 35 mm Hg,  $P_{\text{eff}}$  drops to 0, and the **filtration equilibrium** is reached, which means filtration no longer occurs. If the renal blood flow increases, the point of the filtration equilibrium is shifted further towards 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**. When the blood flow to the kidneys is reduced, such as during heart failure or renal artery stenosis, the filtration must, therefore, be increased to perform the routine tasks of the kidney in balancing fluid and electrolytes in the body. This increase in filtration is reflected by a high filtration fraction, showing that the kidneys have to work more with the fluid they are receiving.

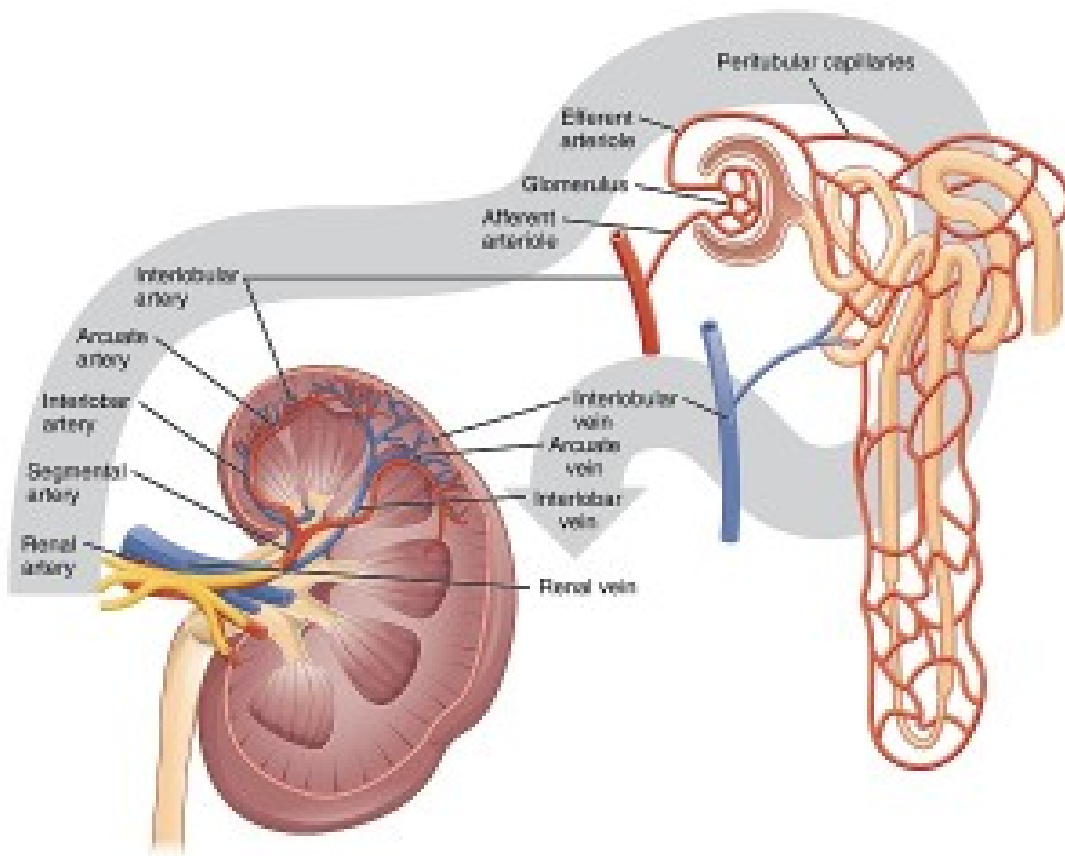


Image: Detail: Nephrons and vessels. By Phil Schatz, License: [CC BY 4.0](https://creativecommons.org/licenses/by/4.0/)

## Renal Clearance

The concept of **renal clearance** arises from the function of the kidney as an organ of detoxification. It describes the amount of plasma volume completely cleared of a particular substance per time unit. Here, other processes in addition to filtration are at play, such as absorption (removal from the tubules and transferred to the blood), secretion (removal from the blood and transferred to the tubules), excretion, or passage through and out of the tubule and 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:

- **Absorption**
- **Excretion**
- **Metabolic degradation**

The formula which is used for the clearance  $C$  is  $C = K_{urine} \times V_{urine} / K_{plasma}$ , which refers to the concentrations in urine and plasma and the volume flow of urine.

Clearance can be used to determine the GFR, and thus, the renal function. For this purpose, a substance that cannot be secreted, absorbed, or metabolized, but can be freely filtered has to be found. **Inulin** meets these requirements. If a patient is infused with inulin, and then plasma and urine concentration of inulin are measured, the

clearance can be calculated, and the GFR can be surmised. The following applies: Inulin - Clearance curve = GFR.

GFR determination using inulin is very laborious. For routine checks and follow-ups, determination using creatinine clearance is usually sufficient. Its presence in plasma is relatively constant, except during high muscle activity. In case of a drop in GFR, the creatinine concentration in the plasma increases. Unfortunately, there is a so-called **blind area**. In some instances, creatinine concentration in plasma may only rise by 20% after a significant reduction of GFR.

The concept of **fractional excretion (FE) or renal clearance ratio** is also noteworthy. It describes the fraction of the excreted amount to the filtered amount per time unit, i.e. **clearance of a substance X/inulin clearance**. Therefore,  $FE = 1$  applies for inulin and creatinine. For substances that are absorbed in the tubular lumen,  $FE < 1$ , and for substances which are secreted  $FE > 1$ . An example of a very high fractional excretion is p-aminohippurate (PAH). It can have an FE of 5, i.e. 500%. It is actively secreted and, thus, excreted extremely fast.

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

$$FE_{Na} = 100 \times \frac{\text{spot urinary sodium} \times \text{plasma creatinine}}{\text{plasma sodium} \times \text{spot urinary creatinine}}$$

plasma sodium x spot urinary creatinine

Value	Category	Description
Below 1%	Prerenal disease	The physiologic response to a decrease in renal perfusion is an increase in sodium reabsorption to control hyponatremia, often caused by volume depletion or decrease in effective circulating volume (e.g., low output heart failure).
Above 2% or 3%	Acute tubular necrosis or other kidney damage (postrenal disease)	Either excess sodium is lost due to tubular damage or the damaged glomeruli leads to hypovolemia, resulting in the normal response of sodium wasting
Intermediate	Either disorder	In renal tract obstruction, 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.

## Clinical application of creatinine (Cr)

- The breakdown product of skeletal muscle
- Constant release into the bloodstream: released in a rate proportional to muscle mass
- Renal handling: freely filtered across glomerulus; not reabsorbed; slightly secreted

- Creatinine clearance (CCr): because of slight secretion, CCr is slightly greater than GFR; used as an approximation of GFR in practice

Do clinicians routinely measure creatinine clearance? Rarely, because it requires a timed urine collection, and it is generally considered a nuisance. Instead, they typically use plasma creatinine concentration as a surrogate marker of creatinine clearance and, therefore, of GFR.

- Basic idea:  $Cr \propto 1/GFR$  or  $GFR \propto 1/Cr$
- Very roughly, a “normal”  $Cr \approx 1$  and a normal  $GFR \approx 100$  mL/min
- $Cr$  of 2 implies a  $GFR$  that is half-normal, or roughly 50 mL/min
- $Cr$  of 3 implies a  $GFR$  in a range of 33 mL/min
- $Cr$  of 4 implies a  $GFR$  of roughly 25 mL/min

But, because  $Cr$  and  $GFR$  are inversely proportional, an increase in  $Cr$  from 1 to 2 represents a much more significant drop in renal function than an increase from 4 to 5.

- $Cr$  rise of 1 to 2 implies a 50% drop in  $GFR$  of  $100 \rightarrow 50$  mL/min
- $Cr$  rise of 4 to 5 implies a 20% drop in  $GFR$  of  $25 \rightarrow 20$  mL/min
- $Cr$  of 4 or 5 are almost clinically equivalent

Recall that as  $GFR$  drops, a greater proportion of  $Cr$  is excreted by secretion (rather than filtration). As  $GFR$  drops, creatinine clearance or any estimate of  $GFR$  based on  $Cr$  becomes less accurate.

### Creatinine clearance (CCr) of 24-hour urine collection

Correlates with  $GFR$

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

$$C_{Cr} = \frac{U_{cr} V_{cr}}{P_{cr}}$$

C = Clearance | U = Urine (mg/dL)

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

**Normal adult  $C_{Cr}$  is 97 to 137 mL/min.** In general,  $C_{Cr} < 100$  mL/min is abnormal.  $C_{Cr} < 10$  mL/min indicates renal failure. **Elderly patients normally have a decrease in  $C_{Cr}$ .** It is important to calculate the dose and dose interval for nephrotoxic drugs (e.g., aminoglycosides) to avoid precipitating acute renal failure due to nephrotoxic acute tubular necrosis.

### Causes of increased and decreased $C_{Cr}$

Cause	Discussion
<b>Increased <math>C_{Cr}</math></b>	
Normal pregnancy	A normal increase in plasma volume causes an increase in the $GFR$ leading to an increase in $C_{Cr}$ ; highest at the end of the 1st trimester
Early diabetic glomerulopathy	Efferent arteriole becomes constricted due to hyaline arteriosclerosis causing an increase in $GFR$ and $C_{Cr}$
	Increased $GFR$ damages the glomerulus ( <b>hyperfiltration injury</b> )

Decreased $C_{cr}$	
Elderly people	GFR typically decreases with age causing a corresponding decrease in the $C_{cr}$ ; dangerous when using nephrotoxic drugs
Acute and chronic renal disease	Acute renal failure due to acute tubular necrosis; chronic renal failure due to diabetic glomerulopathy

### Experimental calculations of renal function

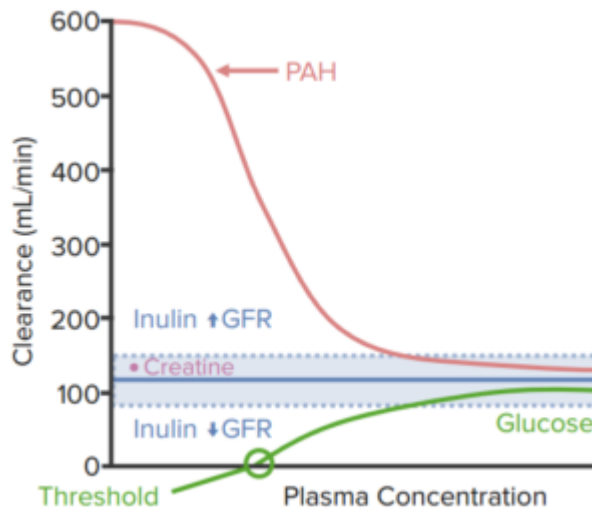


Image: Clearance. By Lecturio

Renal Blood Flow (RBF):

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

$RPF = \text{Renal Plasma Flow} \mid Hct = \text{Hematocrit}$

Filtration Fraction(FF) =  $GFR/RPF$

- $FF = C_{inulin} / C_{PAH}$
- $FF = 15\text{-}20\%$

## Renal blood flow

As compared to other organs in the body, the kidney is very heavily supplied with blood. Each minute, about 1.2 L blood passes through it (25% of our blood volume), and this is referred to as **renal blood flow**. As filtration takes place in the glomeruli that are in the cortex, most of the blood only reaches the cortex, which makes sense in terms of filtration. Oxygen consumption is directly linked to ATP-dependent  $Na^+$ -resorption.

Renal blood flow can be determined by measuring the PAH mentioned above. Since **PAH is filtered freely and strongly secreted**, it can be assumed that the **renal plasma flow** corresponds to the PAH clearance. Because about 90% of PAH is excreted (filtered plus secreted),  $RPF = V_U \times U_{PAH} / (0.9 \times P_{PAH})$ .

The hematocrit can be used to calculate the RBF from the RPF. Accordingly, the following equation results:  $RBF = RPF / (1 - Hct)$ . The determination of renal blood flow can be useful in many diseases.



The blood flow of the kidneys can be autonomously controlled by the kidneys themselves, called **renal autoregulation**. RBF is kept constant at a mean arterial pressure of 80–170 mm Hg, which is attributed to an increase in renal flow resistance. GFR also remains within this range.

Change in GFR	NaCl Absorption	Role of adenosine triphosphate(ATP) and adenosine/Role of nitric oxide (NO)	Impact on GFR
Increased GFR	Tubular NaCl increased	ATP and adenosine increased, which leads to vasoconstriction	Vasoconstriction slows down the GFR
Decreased GFR	Tubular NaCl decreased	ATP and adenosine decreased, which leads to vasodilation	Vasodilation increases GFR
Increased GFR	Tubular NaCl increased	NO increased, which leads to vasodilation	Vasodilation increases GFR
Decreased GFR	Tubular NaCl decreased	NO decreased, which leads to vasoconstriction	Vasoconstriction decreases GFR

**Table:** Paracrine mechanisms controlling glomerular filtration rate. 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**. The myogenic response is defined as vasoconstriction of the interlobular arteries with increasing pressure. Thus, the increase in blood pressure ordinarily does not affect the afferent arterioles of the glomerulus.

The part of the kidney responsible for tubuloglomerular feedback is the **macula densa**, which lies between the distal tubule and the glomerulus. If high amounts of sodium chloride flow past the macula densa in the distal tubule, filtration in the glomerulus is limited by a reduction of RBF or GFR via the release/withhold of ATP, adenosine, or NO.

## Tubular Transport

The tubular system, which joins the glomerulus, consists of the proximal tubule, descending limb, the loop of Henle, ascending limb, and the distal tubule, followed by the **collecting duct** and the **papillary duct, that ends in the renal papilla**. Molecules important for the body are reabsorbed along with these systems, whereas harmful substances are secreted to be eliminated as quickly as possible.

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



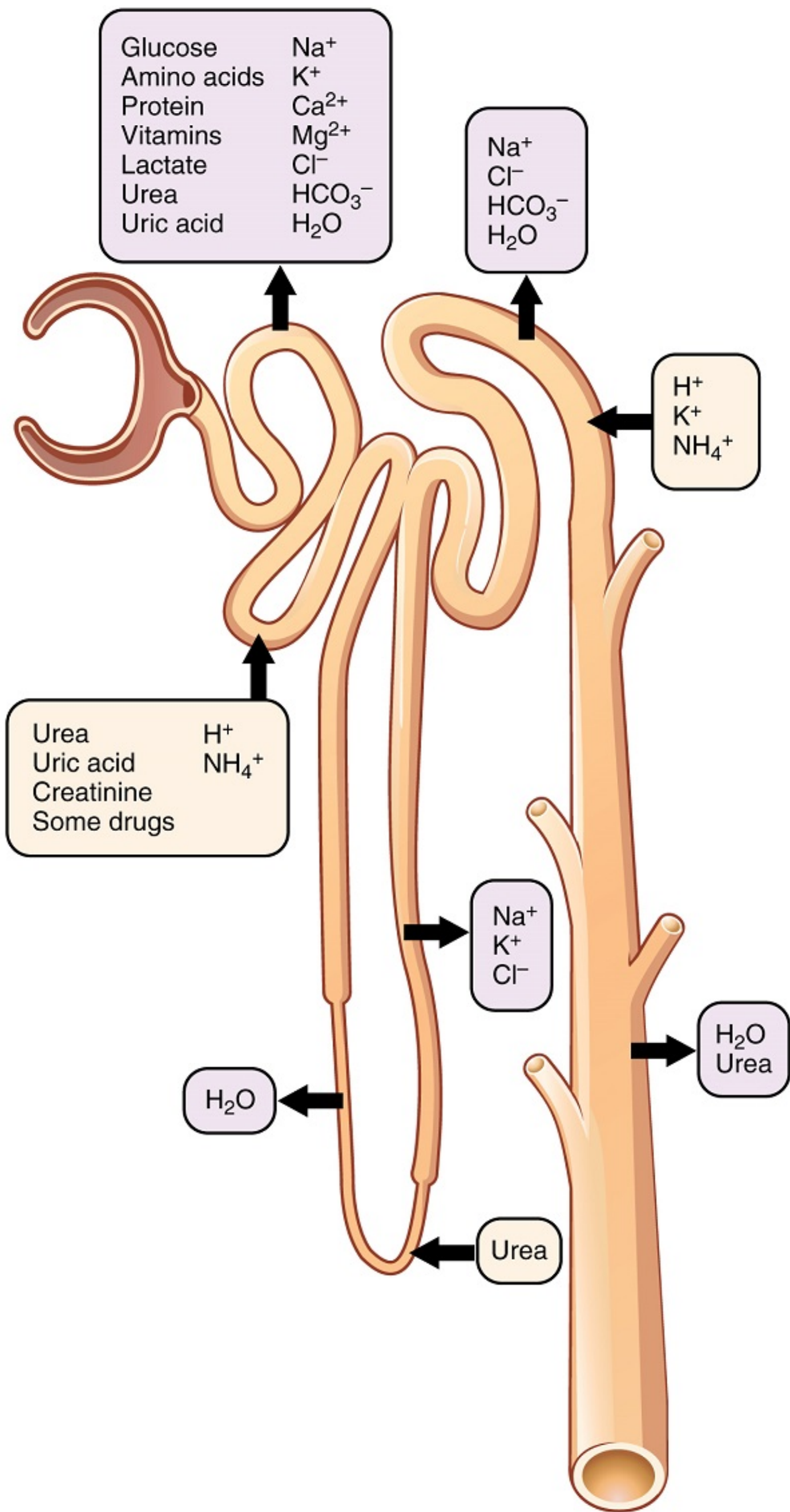


Image: Detail: Tubular reabsorption. By Phil Schatz, License: [CC BY 4.0](https://creativecommons.org/licenses/by/4.0/)

## Proximal tubule

The proximal tubule has a strongly defined brush border that creates an extensive area, ideal for 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 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 ( $Cl^-$ ) is resorbed after a quarter of the proximal tubule. Due to the negative charge of  $Cl^-$ , a **lumen-positive transepithelial potential** arises, resulting in paracellular resorption of cations.

The basolateral side has numerous  $Na^+/K^+$ -ATPases. Thus, sodium is repeatedly removed from the equilibrium of the cell. Electrical and chemical gradient builds up, which is crucial for the regulated transport. It is also important to note that aquaporins, small water channels, are built into both the luminal as well as the basolateral side for water transport.

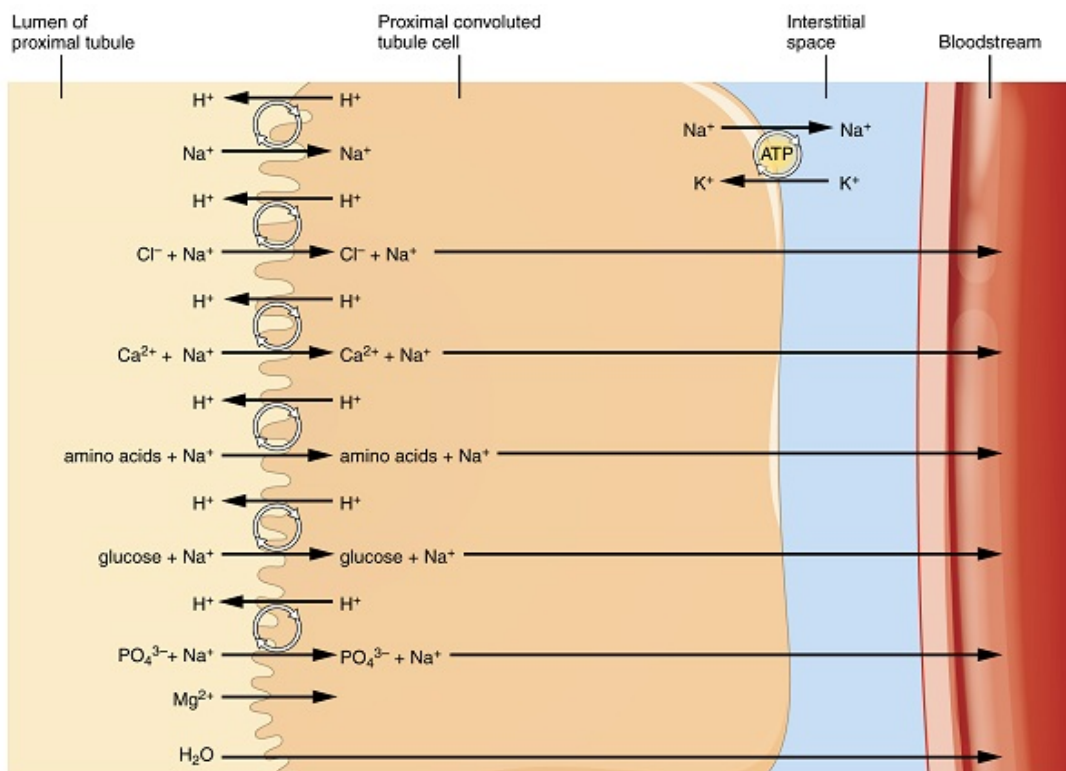


Image: Reabsorption and secretion in the PCT. By Phil Schatz, License: [CC BY 4.0](https://creativecommons.org/licenses/by/4.0/)

## Henle's Loop

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

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

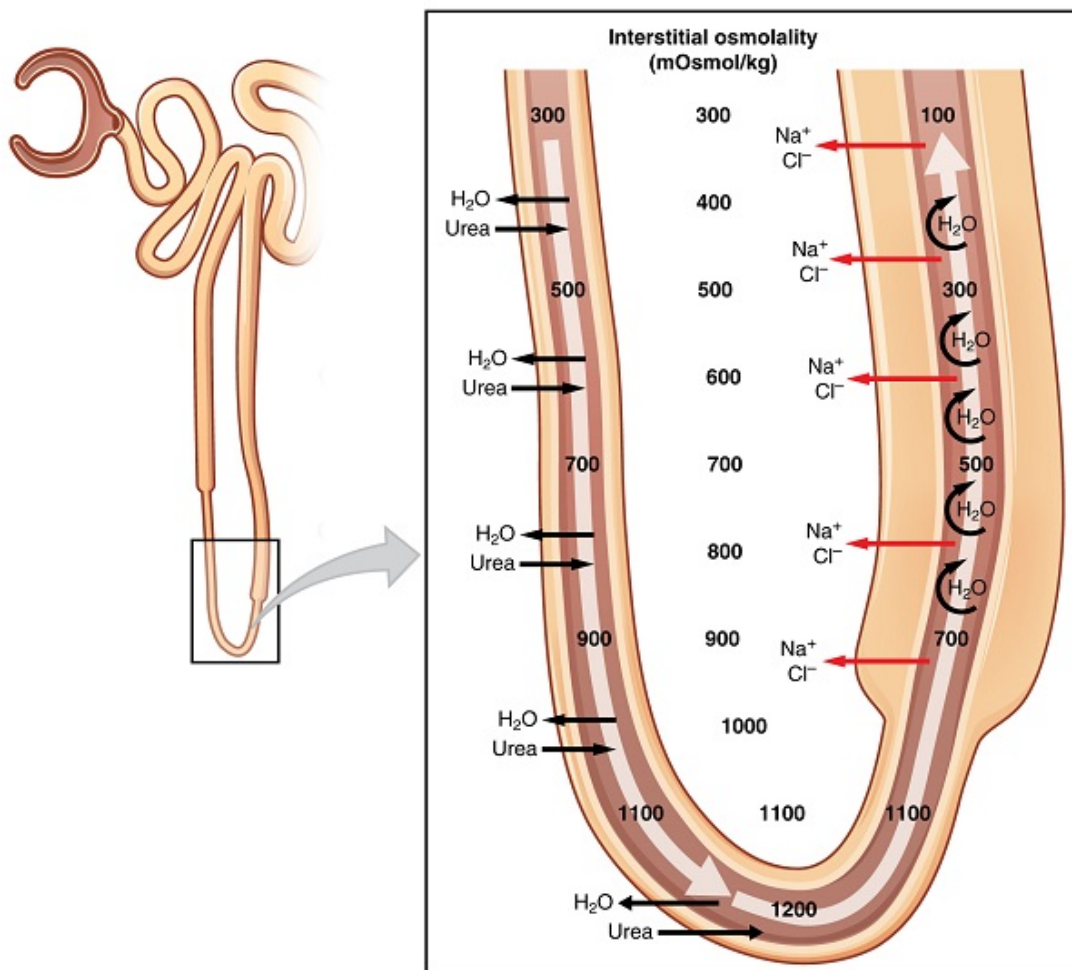
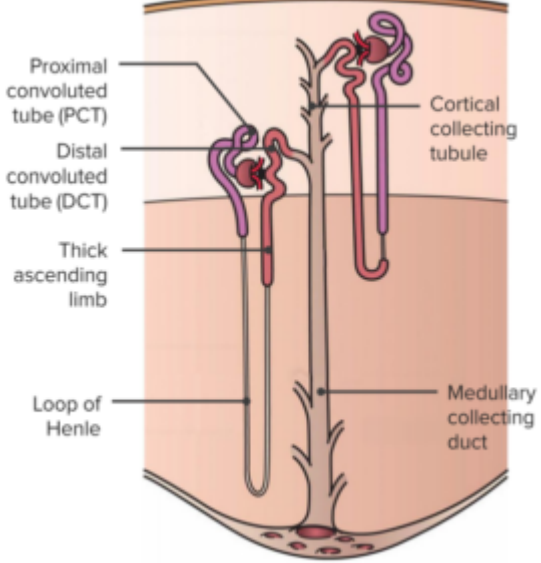


Image: Countercurrent multiplier system. By Phil Schatz, License: [CC BY 4.0](https://creativecommons.org/licenses/by/4.0/)

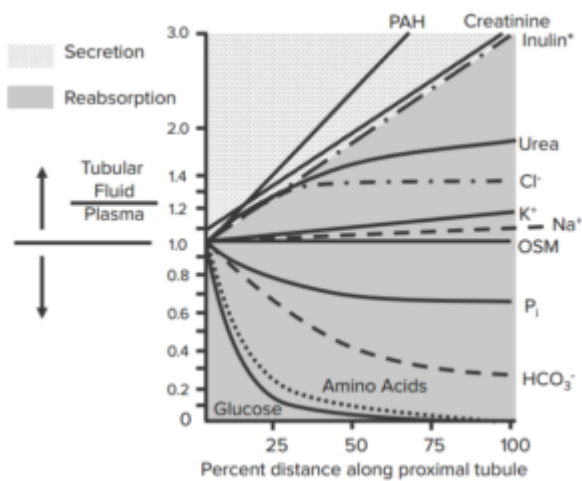
## The distal tubule

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

## Tubular transport by nephron segment: proximal vs. distal nephron

Proximal	Distal	
<ul style="list-style-type: none"> <li>• Proximal convoluted tubule</li> <li>• Thin portion of the loop of Henle</li> </ul>	<ul style="list-style-type: none"> <li>• Thick ascending limb</li> <li>• Distal convoluted tubule</li> <li>• Cortical collecting tubule</li> <li>• Medullary collecting duct</li> </ul>	

## Proximal convoluted tubular mechanics



\*Neither secreted nor reabsorbed; concentration increases as water is reabsorbed.

Tubular **creatinine and inulin** increases in concentration (but not amount) along the proximal tubule due to water reabsorption. Cl<sup>-</sup> reabsorption occurs at a **slower rate** than sodium in the proximal one-third of the proximal tubule, and then matches the rate of Na<sup>+</sup> reabsorption more distally. Its relative concentration increases before it plateaus. **Na<sup>+</sup> reabsorption** drives H<sub>2</sub>O reabsorption, so it nearly matches osmosis.

## Correlation of nephron cotransporters and pumps with electrolyte disorders

### Proximal renal tubule:

A. Primary site for Na<sup>+</sup> reabsorption:

(1) Na<sup>+</sup> reabsorption is increased when cardiac output is decreased

a) ↓ EABV → ↑ FF → P<sub>o</sub> > P<sub>H</sub>

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

b) Examples: congestive heart failure, cirrhosis, hypovolemia

(2)  $\text{Na}^+$  reabsorption is decreased when cardiac output is increased

a)  $\uparrow \text{EABV} \rightarrow \downarrow \text{FF} \rightarrow P_H > P_o$

b) Examples: mineralocorticoid excess, isotonic gain in fluid

**B. Primary site for reclamation of bicarbonate ( $\text{HCO}_3^-$ ):** Mechanism for reabsorbing some of the filtered  $\text{HCO}_3^-$  back into the blood

(1) Hydrogen ions ( $\text{H}^+$ ) in tubular cells are exchanged for  $\text{Na}^+$  in the urine

(2)  $\text{H}^+$  combines with filtered  $\text{HCO}_3^-$  to form  $\text{H}_2\text{CO}_3$  in the brush border of the proximal tubules

(3) Carbonic anhydrase dissociates  $\text{H}_2\text{CO}_3$  to  $\text{H}_2\text{O}$  and  $\text{CO}_2$ .  $\text{CO}_2$  and  $\text{H}_2\text{O}$  are reabsorbed into proximal renal tubular cells.

(4)  $\text{H}_2\text{CO}_3$  is re-formed in the proximal renal tubular cells.  $\text{H}_2\text{CO}_3$  dissociates into  $\text{H}^+$  and  $\text{HCO}_3^-$

(5)  $\text{HCO}_3^-$  is reabsorbed into the blood.

(6) A  $\text{Na}^+/\text{K}^+$ -ATPase pump moves  $\text{Na}^+$  into the blood

### Decreased effective arterial blood volume

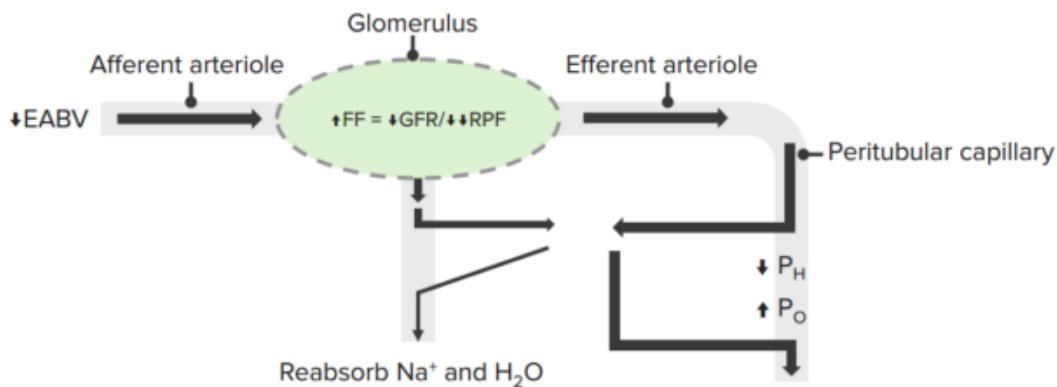


Image by Lecturio

### Increased effective arterial blood volume

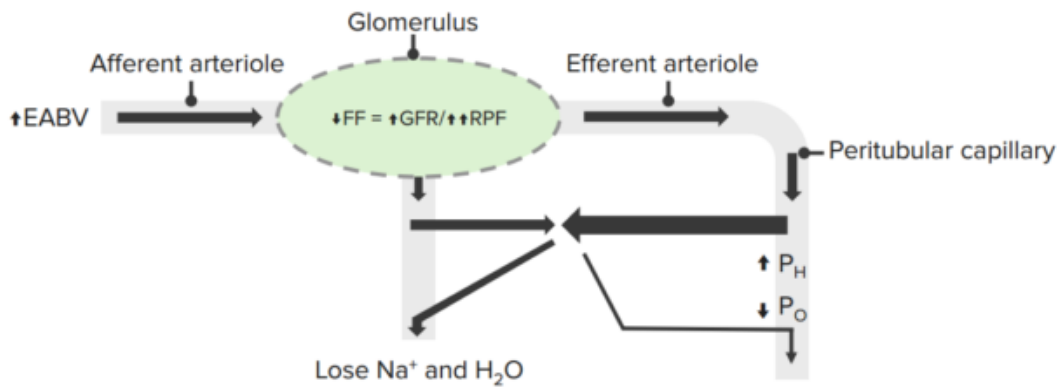


Image by Lecturio

## Thick Ascending Limb of the Distal Tubule

The primary function is to reabsorb water separately from sodium, which increases osmolarity in the medulla via a countercurrent mechanism.

## The collecting duct and the papillary duct

The so-called ENaC, an epithelial  $\text{Na}^+$  channel, is a membrane-bound ion channel that is selectively permeable to **Na<sup>+</sup> ions**, and that is assembled as a heterotrimer composed of 3 homologous subunits  $\alpha$  or  $\delta$ ,  $\beta$ , and  $\gamma$ . These subunits are encoded by 4 genes: SCNN1A, SCNN1B, SCNN1G, and SCNN1D. It is primarily involved in the reabsorption of sodium ions in the collecting ducts of the nephrons. It can be stimulated by aldosterone and antidiuretic hormone (ADH). Amiloride, atrial natriuretic peptide (ANP), and prostaglandins can inhibit it. Inflowing sodium from the lumen causes a lumen negative potential. Therefore,  $\text{K}^+$  is secreted, and  $\text{Cl}^-$  is transported paracellularly.

Here, the resorption of water is controlled by **ADH**. This hormone is released during water deficiencies and 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 are secreted: organic cations and anions, including bile salts and uric acid. Substances being secreted enter the interstitial space from the peritubular capillaries. They are transported by organic transporters in the basolateral membrane into the cytoplasm of tubular epithelial cells. They are carried out of cells and into tubular lumen by luminal membrane transporters.

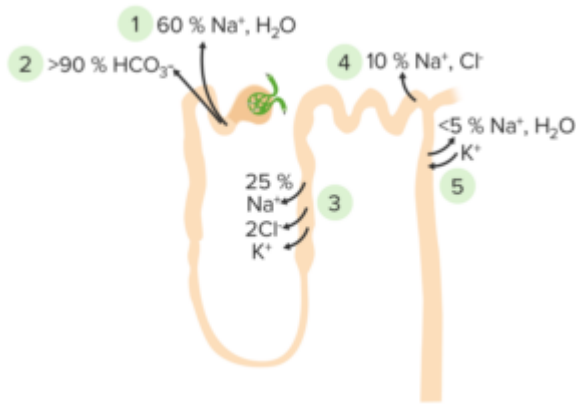


Image by Lecturio

### 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 must gain access to the tubular lumen to act. They are highly **protein-bound** and are thus, not freely filtered through the glomerulus. They are transported into the tubular lumen via **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. Large doses of diuretics must be given to overcome this competition for tubular secretion.

## Countercurrent Multiplier Theory

Henle's Loop plays a crucial role in urine concentration. The **countercurrent multiplier theory** between Henle's loop and the vasa recta of the renal medulla is important. The osmolality increases strongly in the direction of the loop apex. Through this **corticomedullary gradient**, water is withdrawn from the arterial blood flowing 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 Henle's Loop is the active  $\text{NaCl}$  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 Henle's loop decreases, whereas the osmolality of the interstitium increases due to the inflowing  $\text{NaCl}$ . To compensate for this, water is resorbed from the descending part of the loop. Thus, the concentration of  $\text{NaCl}$  is highest at the apex of the loop, so that the resorption in the ascending part can take place passively.



This pumping system is kept in motion through a principle called **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 collecting duct concentrate the urine further, as strong resorption of water takes place here. This part is impermeable to urea. Urea can only be resorbed further down in the collecting ducts in the presence of ADH and contributes to the total osmolality of the interstitium, which is crucial for the maintenance of the gradients.

The 'single effect' theoretical approach helps visualize the step-by-step process of the countercurrent multiplier formation. Once the corticopapillary osmotic gradient is established, it can be modified but does not need to be reestablished.

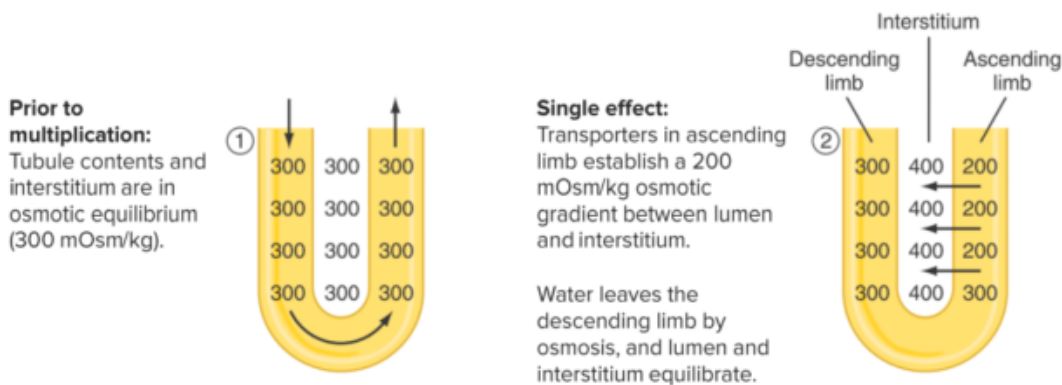


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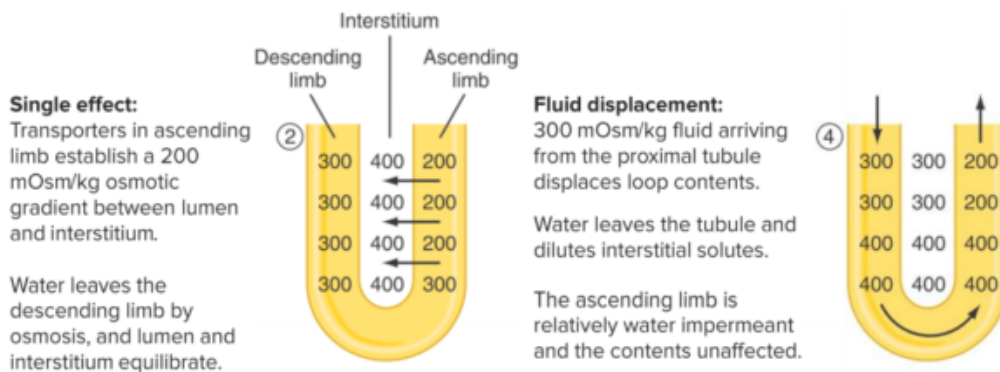
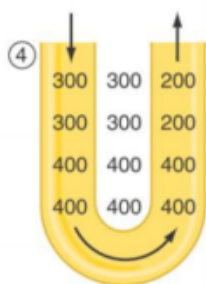


Image by Lecturio

**Fluid displacement:**  
 300 mOsm/kg fluid arriving from the proximal tubule displaces loop contents.  
 Water leaves the tubule and dilutes interstitial solutes.  
 The ascending limb is relatively water impermeant and the contents unaffected.



**Single effect:**  
 Transporters in the ascending limb reestablish the 200 mOsm/kg gradient.

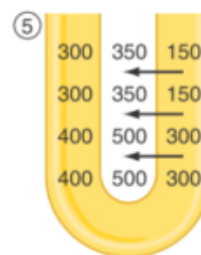


Image by Lecturio

## The Renin-Angiotensin-Aldosterone System—RAAS

Granulosa cells of the juxtaglomerular apparatus produce the enzyme **renin**. It proteolytically cleaves angiotensinogen into angiotensin (Ang) I, which is hydrolyzed by the angiotensin-converting enzyme (ACE) to **angiotensin II**. Rise in ANG II leads to the production of **aldosterone** in the cortex of the adrenal gland. The system serves to maintain blood pressure and can sense drops 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 is not a hormone in itself but affects hormone production, **erythropoietin (EPO)** 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 case of hypoxia.

## Pathophysiology

### The Bartter syndrome

If one of the transporters in the ascending limb of Henle's loop fails due to a **loss-of-function mutation**, the so-called **Bartter syndrome** takes place. Thereby, resorption of  $\text{Na}^+$ ,  $\text{Mg}^{2+}$ ,  $\text{Cl}^-$ , and  $\text{Ca}^{2+}$  is disturbed. Although this can be partially or even completely reversed in later sections, it is associated with increased  $\text{K}^+$  and  $\text{H}^+$  secretion. Signs are  $\text{Na}^+$ - 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 epithelial sodium channel (ENaC) in the collecting ducts. It 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

Pseudohypoaldosteronism presents the opposite clinical picture of Liddle's syndrome. It is characterized by hypovolemia, hypotension, hyperkalemia, and acidosis and is based on a loss-of-function mutation of ENaC.

## Diabetes insipidus

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

The distinction is made between **diabetes insipidus centralis** and **diabetes insipidus renalis**. The former is associated with damage to the pituitary gland or hypothalamus, which results in the disruption of ADH production. In the 2nd variant, ADH cannot function sufficiently due to defects in the region of the collecting tube.

### Renal tubular acidosis (RTA or Necrosis, RTN)

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

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

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