Renal Physiology

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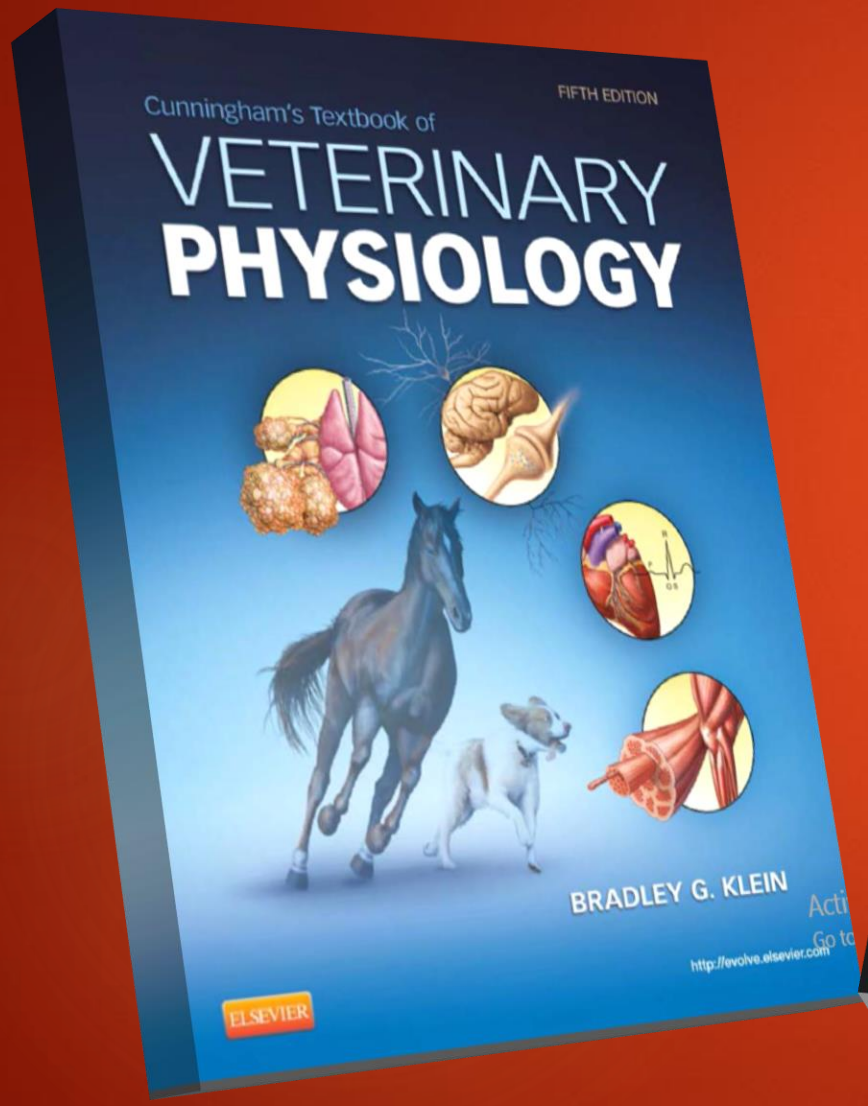
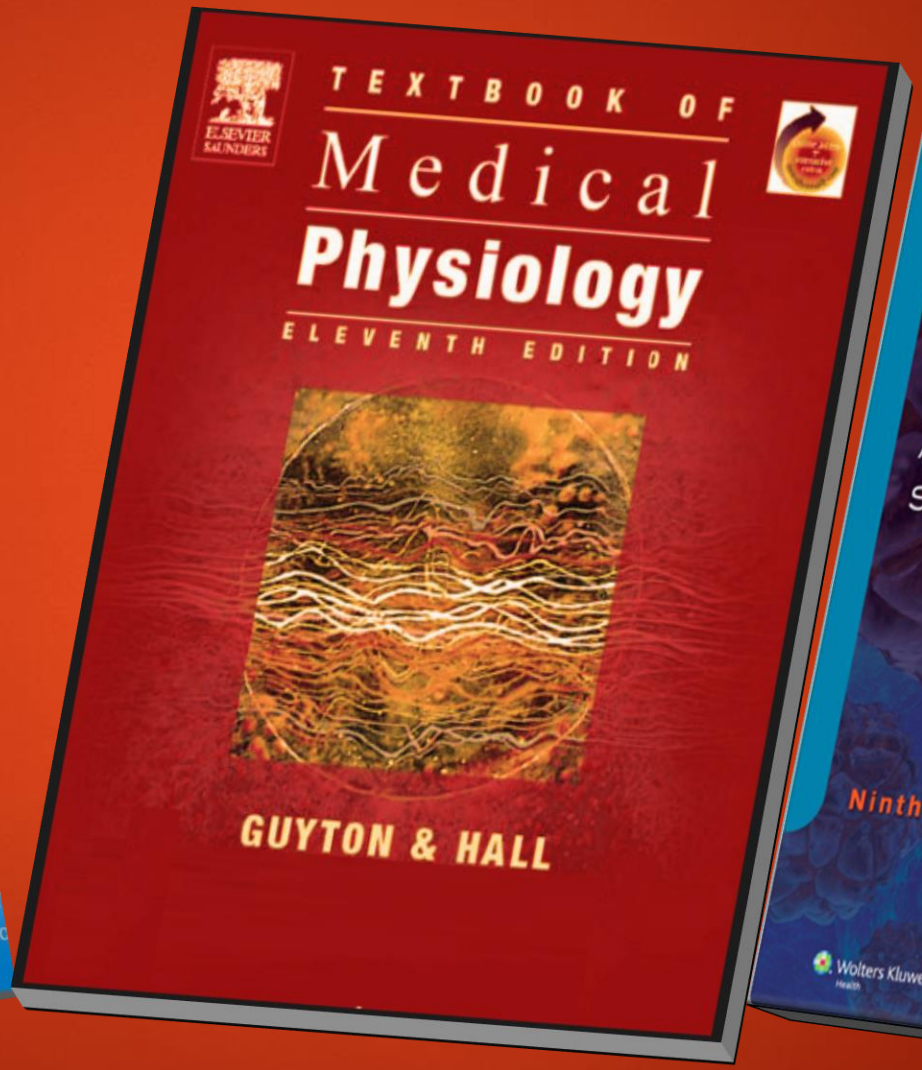
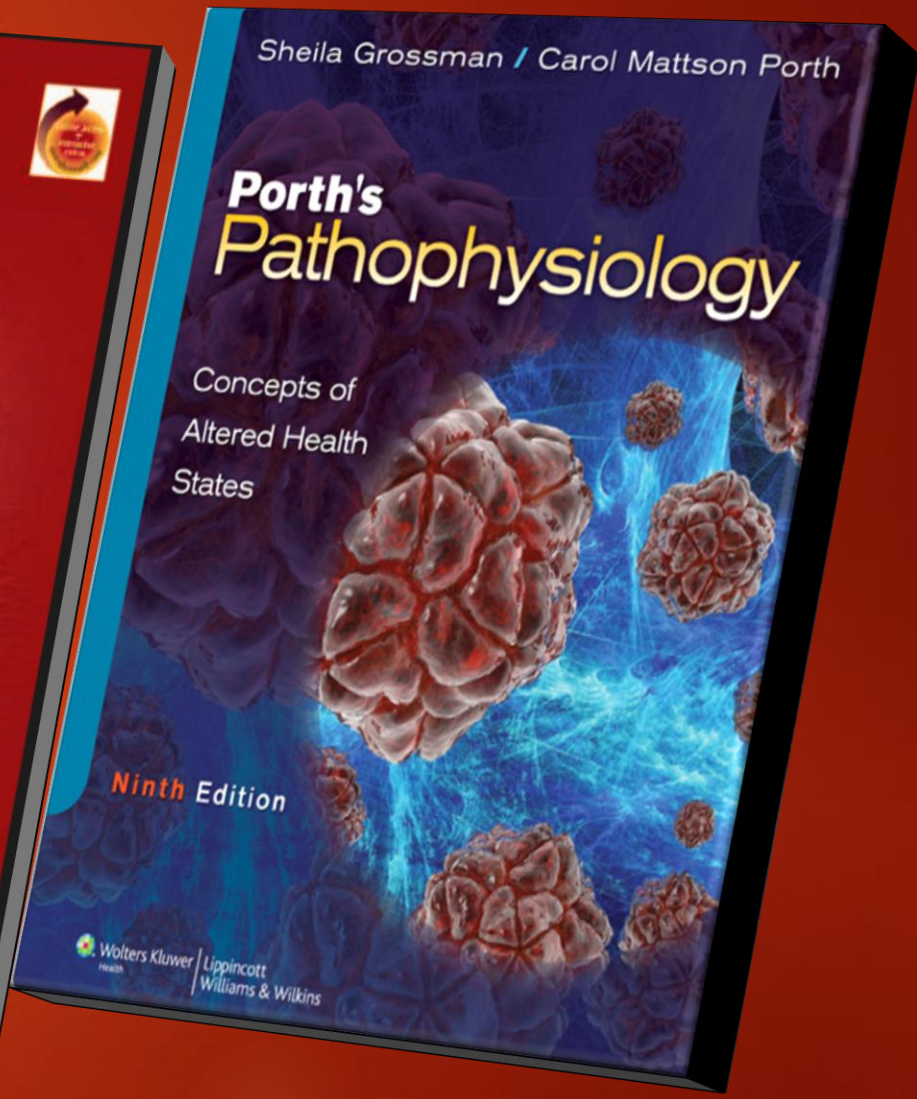
References







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Section 1:

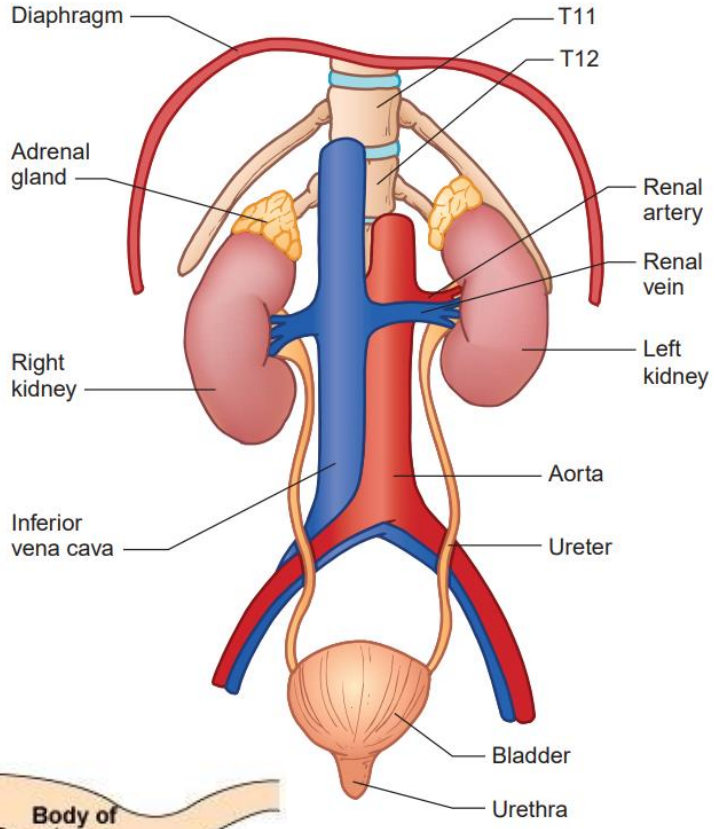
Structure and Function of the kidney

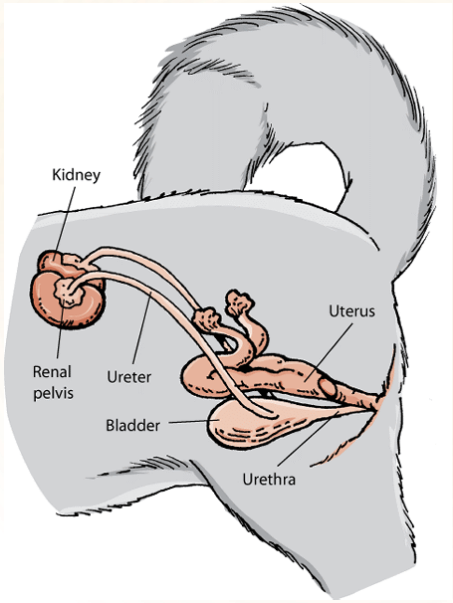
Functions of the kidney

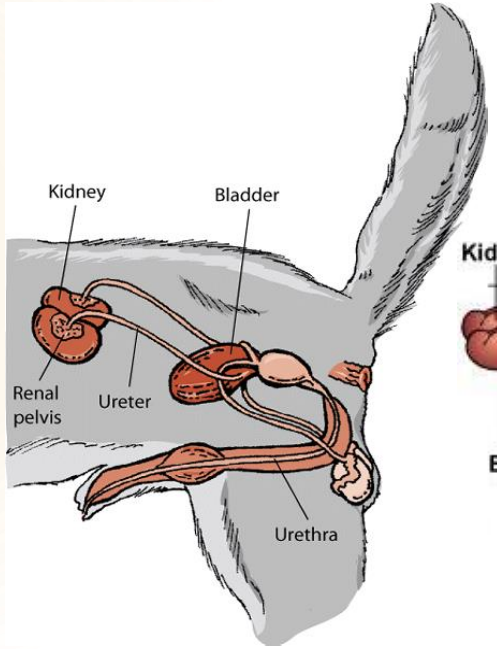
- The kidney has diverse roles in maintaining homeostasis:
  - filtering the blood and thereby excrete metabolic waste, while retrieving filtered substances that are needed by the body, including water, glucose, electrolytes, and low–molecular-weight proteins.
  - maintaining the proper osmolarity of body fluids
  - maintaining proper plasma volume
  - helping to maintain proper acid-base balance
  - producing erythropoietin and renin
  - converting vitamin D to an active form
- The kidneys respond to water, electrolyte, and acid-base disturbances by specifically altering the rate of reabsorption or secretion of these substances.

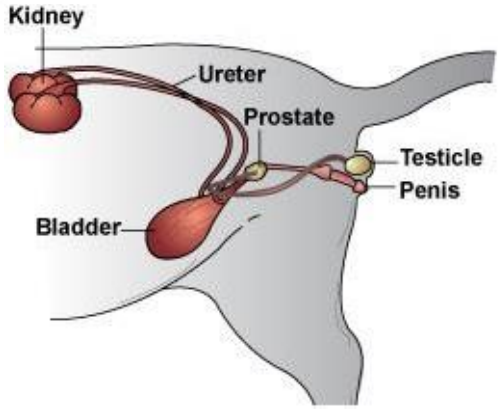
Structure of the Kidney

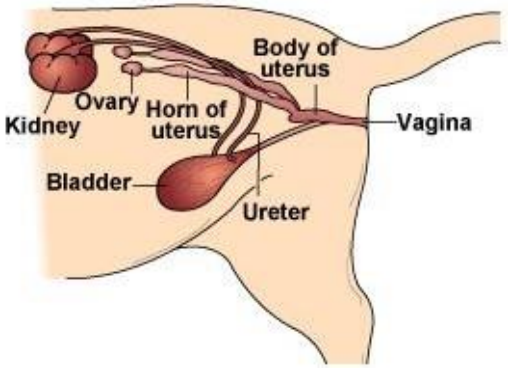
- The kidneys are paired, bean-shaped organs that lie outside the peritoneal cavity in the back of the upper abdomen, one on each side of the vertebral column



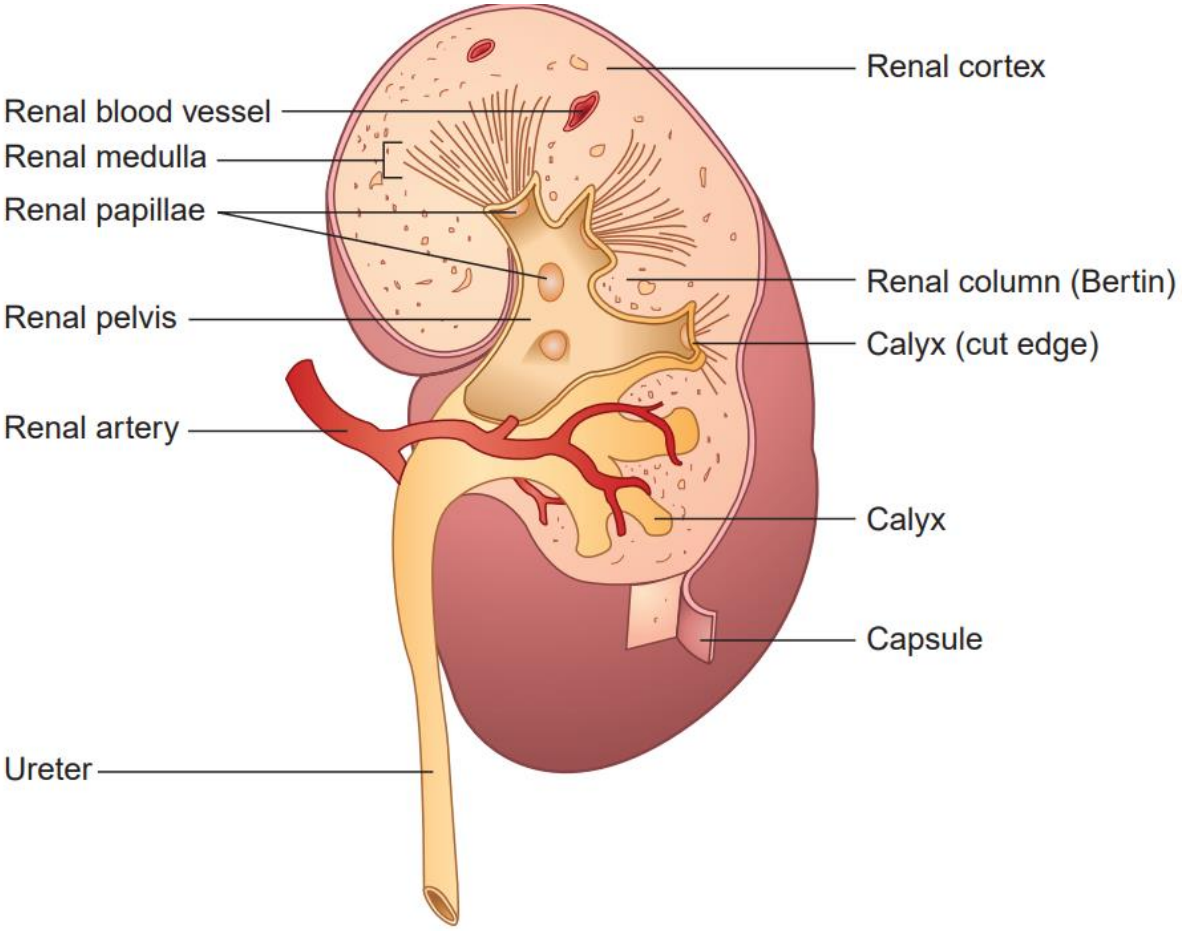


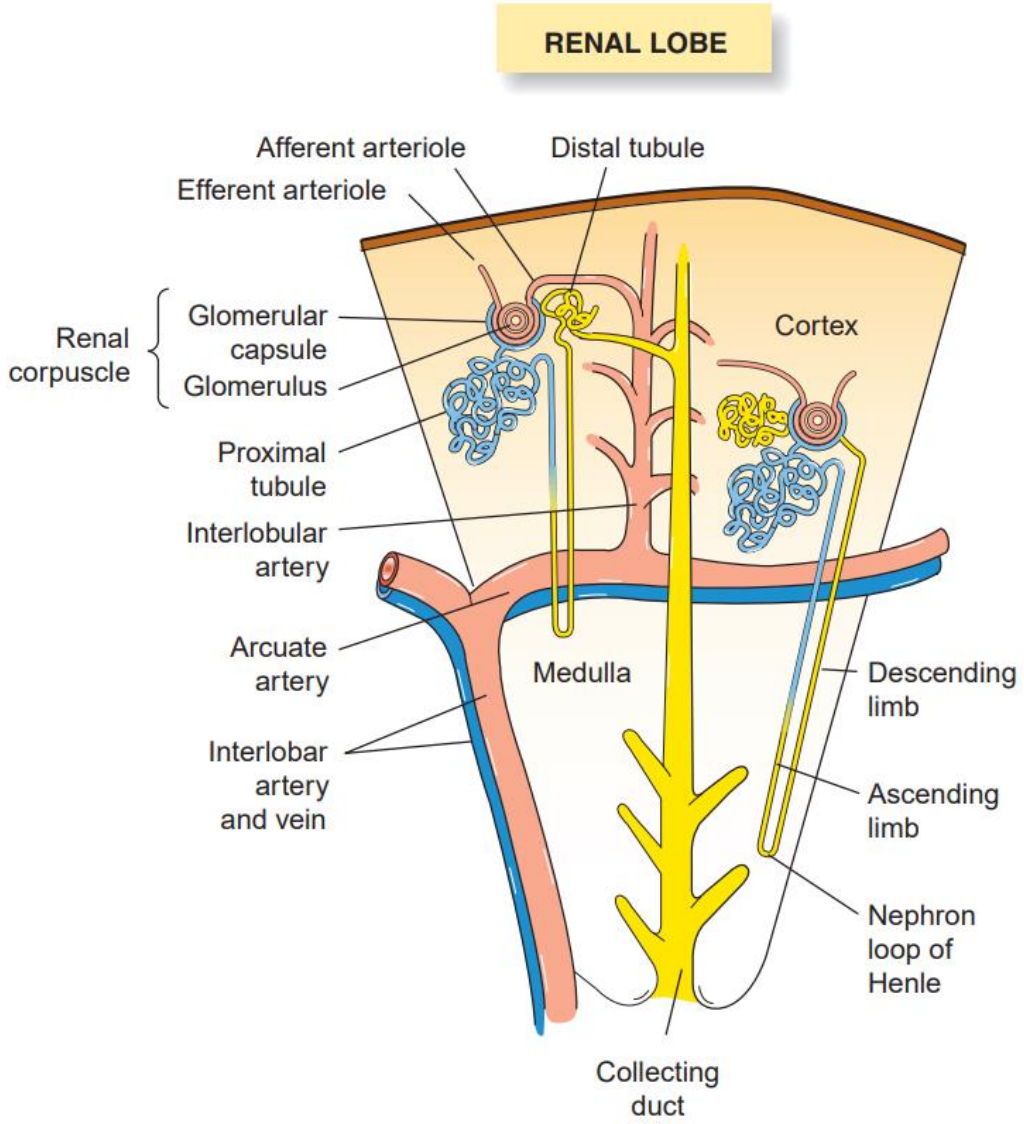




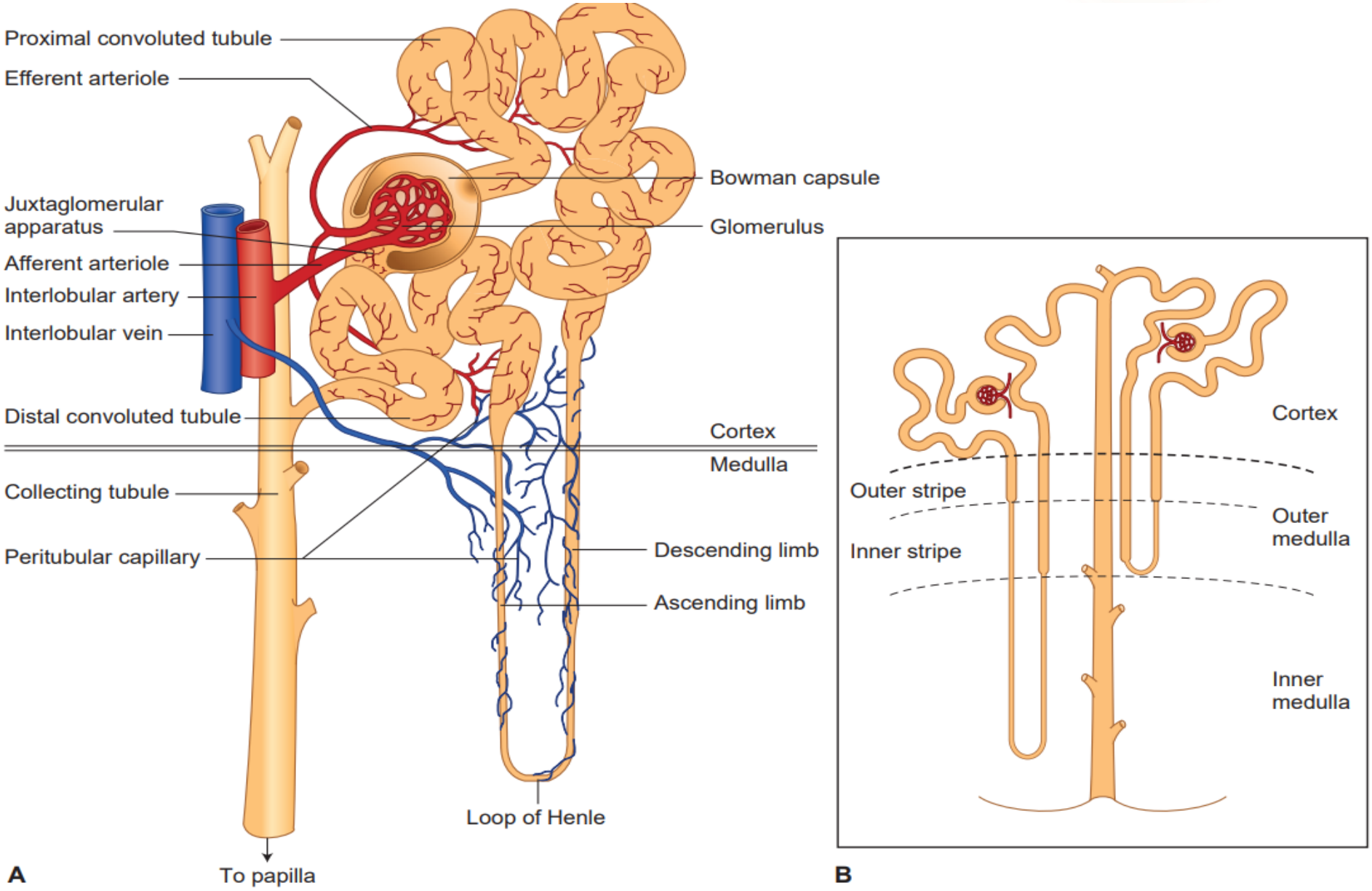


Structure of the Kidney





The Nephron

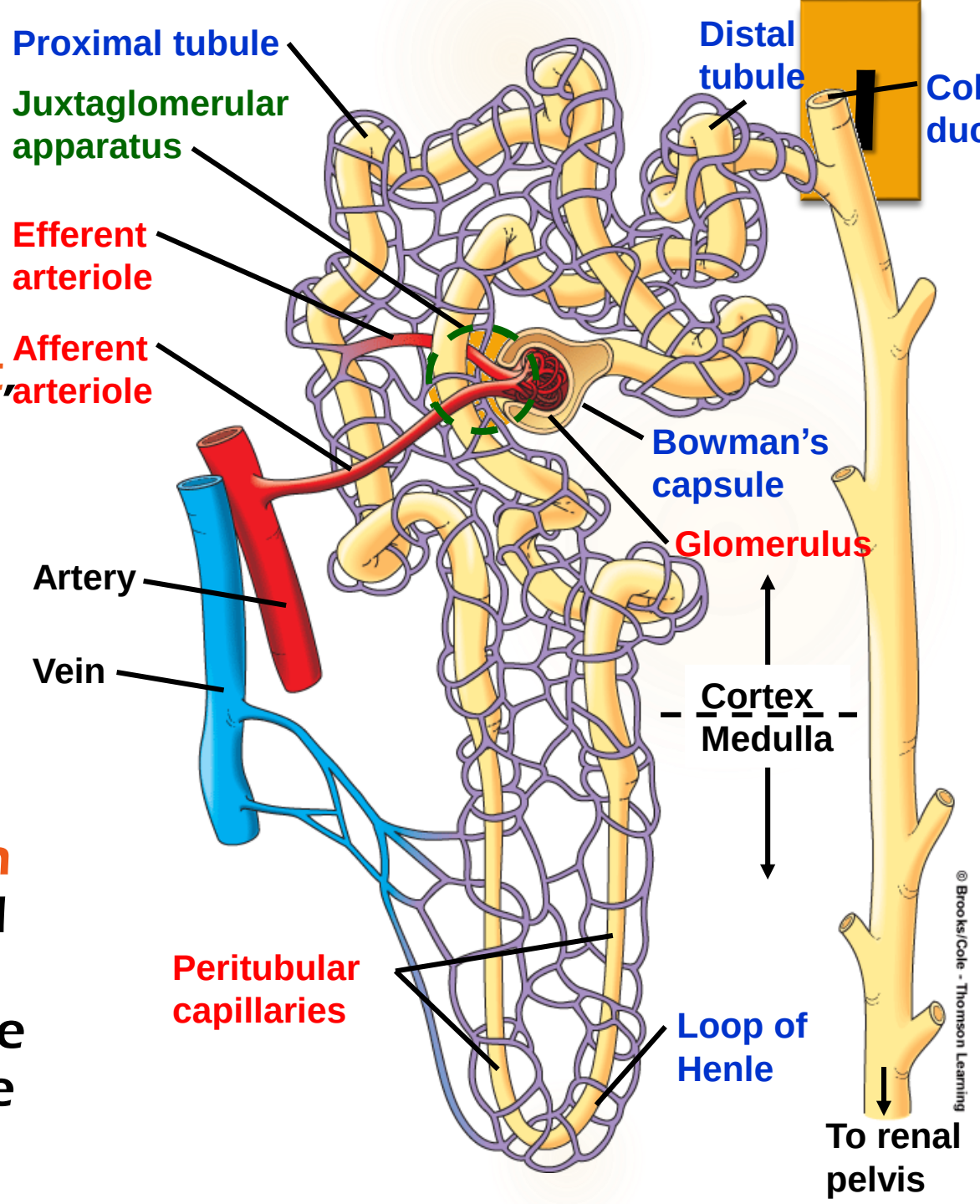

Proximal convoluted tubule
Efferent arteriole
Bowman capsule
Juxtaglomerular apparatus
Glomerulus
Afferent arteriole
Interlobular artery
Interlobular vein
Distal convoluted tubule
Cortex
Medulla
Collecting tubule
Peritubular capillary
Descending limb
Ascending limb
Loop of Henle
To papilla
A
Cortex
Outer stripe
Outer medulla
Inner stripe
Inner medulla
B

The Nephron

- Each kidney is composed of more than approximately 1 million tiny, closely packed functional units called nephrons
- The kidney has no ability to regenerate nephrons. Therefore, with aging, there is a generalized decrease in functioning nephrons.
- Each nephron consists of a glomerulus, a proximal convoluted tubule (PCT), a loop of Henle, a distal convoluted tubule (DCT), and a collecting duct. Blood is filtered in the glomerulus.
- In the proximal tubule, loop of Henle, distal tubule, and collecting duct, water, electrolytes, and other substances needed to maintain the constancy of the internal environment are reabsorbed into the bloodstream, while other unneeded materials are secreted into the tubular filtrate for elimination.

The Nephron

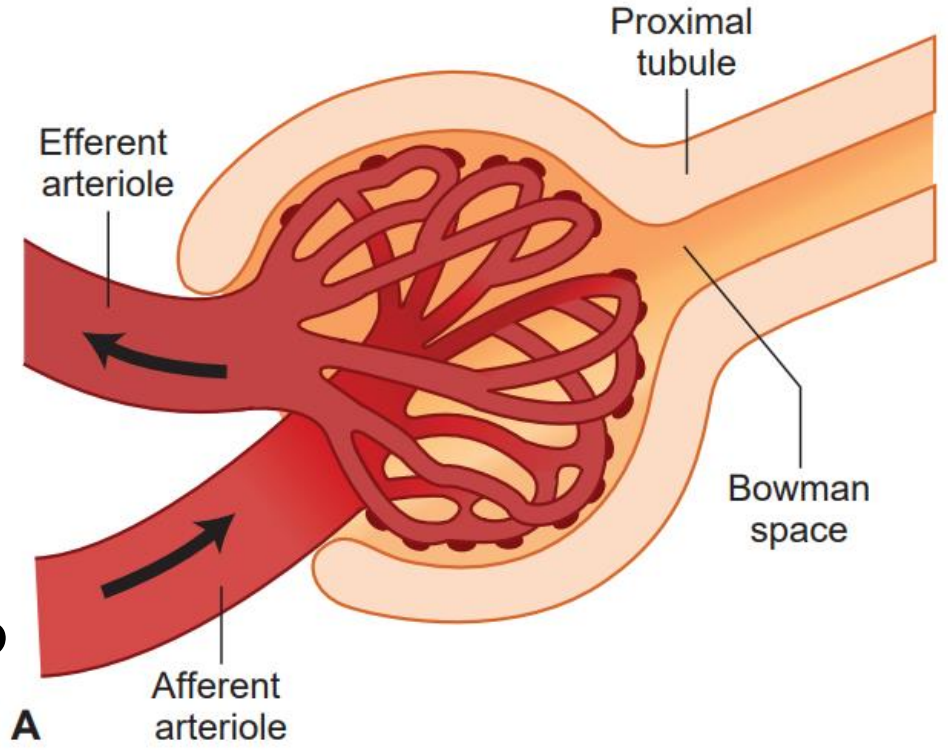
- The nephron, which is the functional unit of the kidney, is composed of a vascular component, which connects to the circulatory system, and a tubular component, which has connections to both the circulatory system and the elimination functions of the kidney
- The tubular portion of the nephron processes the glomerular filtrate (urine), facilitating the reabsorption of substances from the tubular fluid into the peritubular capillaries and the secretion of substances from the peritubular capillaries into the urine filtrate



The Glomerulus

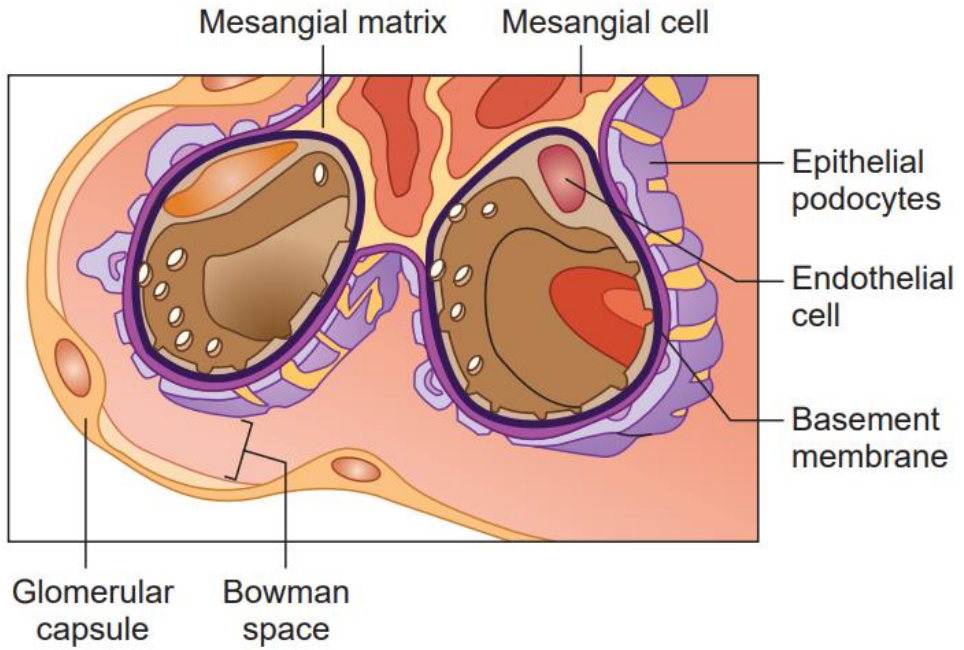
1

- The glomerulus consists of a compact tuft of capillaries encased in a thin, double-walled capsule called Bowman capsule.
- Blood flows into the glomerular capillaries from the afferent arteriole and flows out of the glomerular capillaries into the efferent arteriole, which leads into the peritubular capillaries.
- Fluid and particles from the blood are filtered through the capillary membrane into a fluid-filled space in Bowman capsule, called Bowman space.
- The portion of the blood that is filtered into the capsule space is called the filtrate



The Glomerulus

- The glomerular capillary membrane is composed of three layers:
  - 1. Capillary endothelial layer
  - 2. Basement membrane
  - 3. Single-celled capsular epithelial layer
- The endothelial layer contains many small perforations called fenestrations.
- The cells of the epithelial layer have unusual octopus-like structures that possess a large number of extensions, or foot processes (i.e., podocytes), which are embedded in the basement membrane These foot processes form slit pores through which the glomerular filtrate passes.



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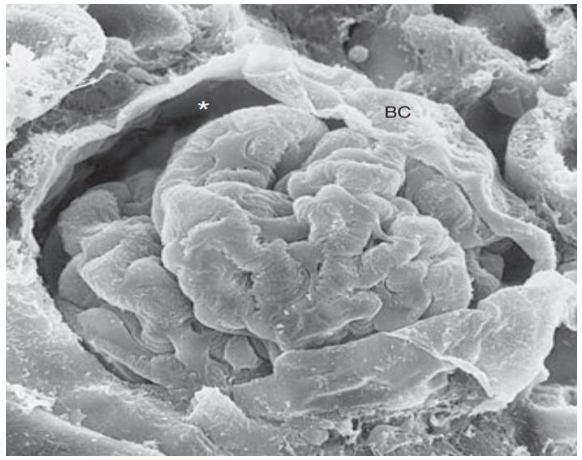
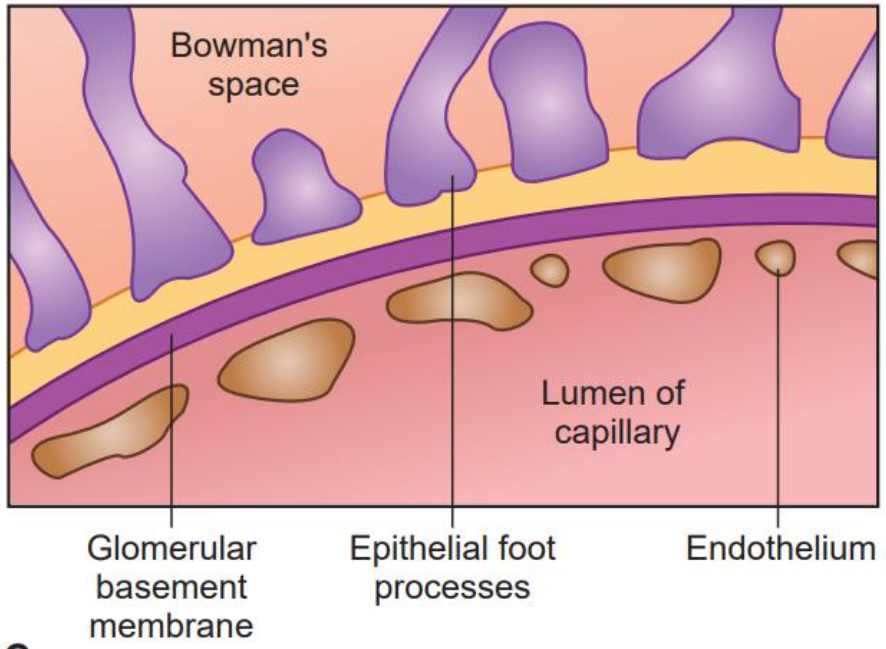
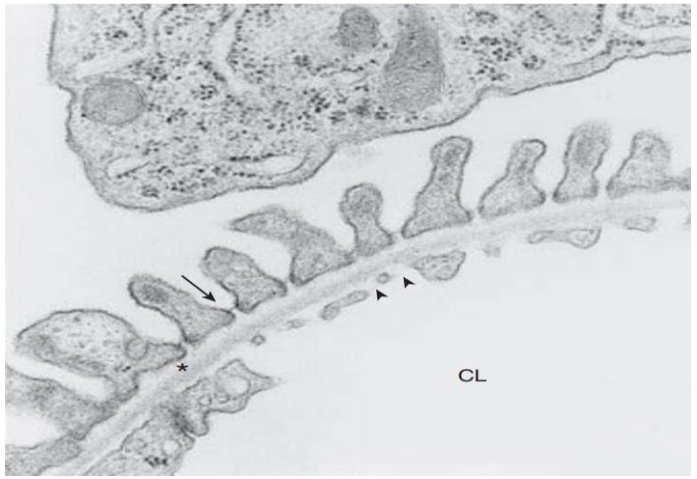


The Glomerulus

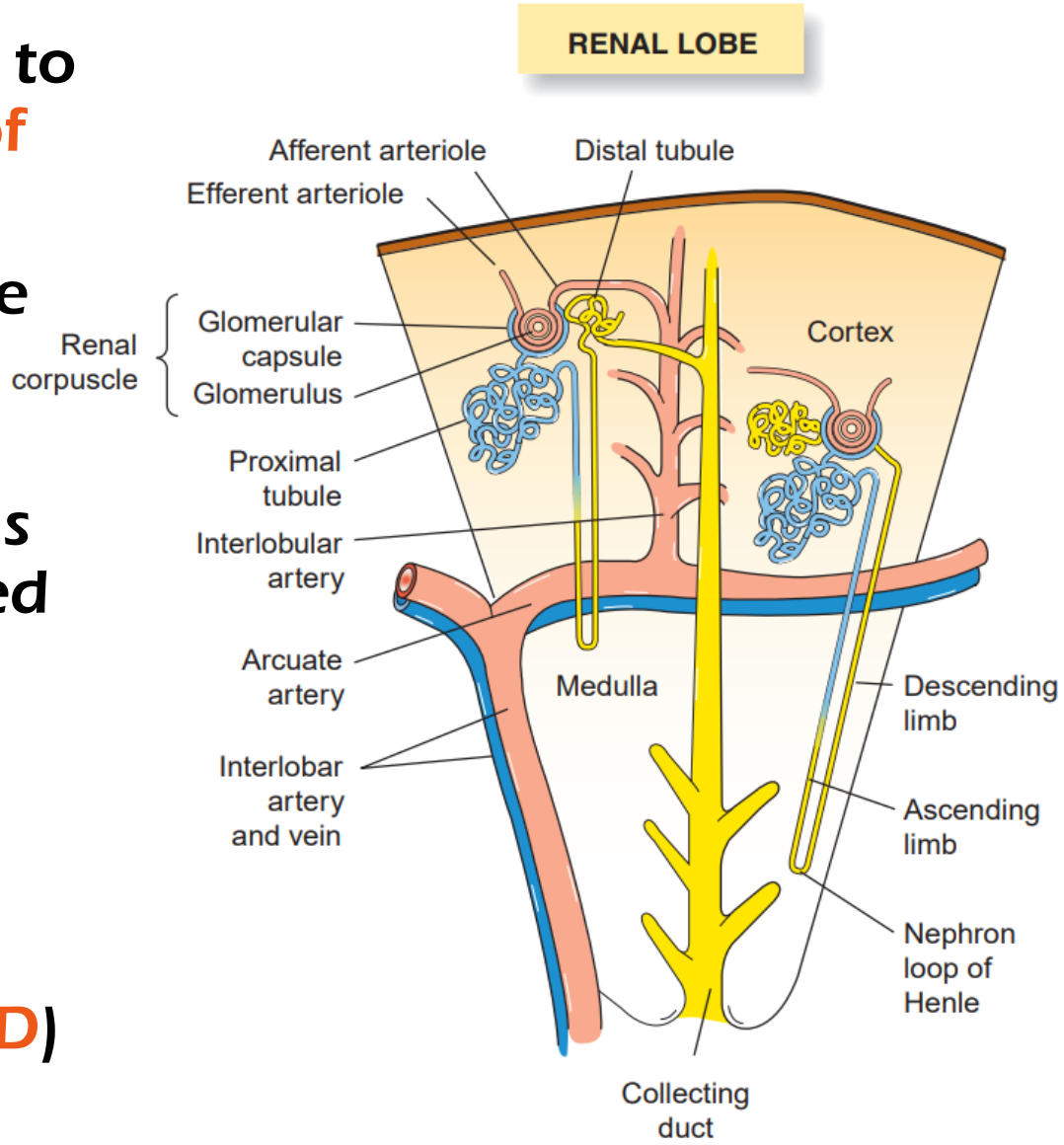
- The size of the pores in the basement membrane normally prevents red blood cells and plasma proteins from passing through the glomerular membrane into the filtrate.
- Alterations in the structure and function of the glomerular basement membrane are responsible for the leakage of proteins and blood cells into the filtrate that occurs in many forms of glomerular disease.
- The mesangial cells possess phagocytic properties and remove macromolecular materials that enter the intercapillary spaces.





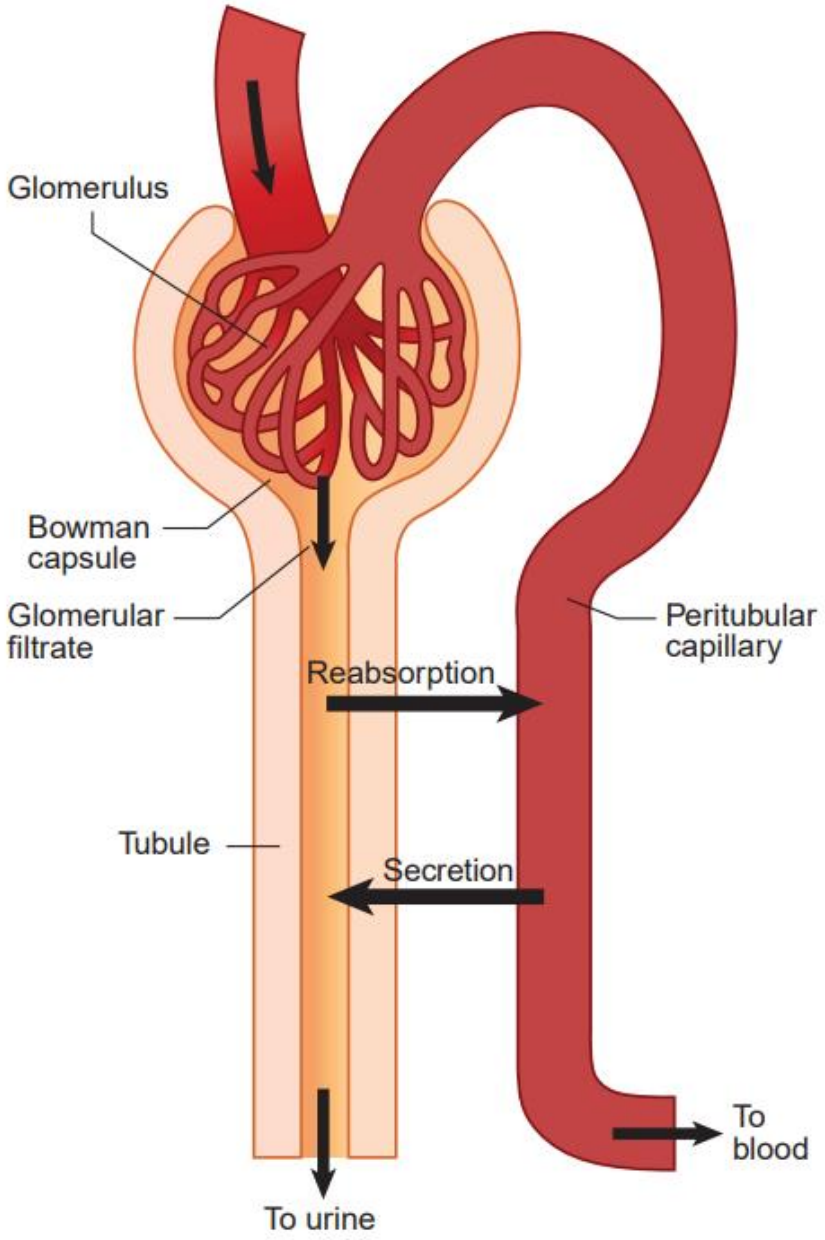
Tubular Components of the Nephron

- The proximal tubule is a highly coiled structure that dips toward the renal pelvis to become the descending limb of the loop of Henle.
- The ascending loop of Henle returns to the region of the renal corpuscle, where it becomes the distal tubule.
- The distal convoluted tubule, which begins at the juxtaglomerular apparatus, is divided into two segments—the diluting segment and the late distal tubule.
- The late distal tubule fuses with the collecting duct. Like the distal tubule, the collecting duct is divided into two segments—the cortical collecting duct (CCD) and the medullary collecting duct (MCD).



Urine Formation

- Urine formation involves:
  - the filtration of blood by the glomerulus to form an ultrafiltrate of urine
  - the tubular reabsorption of electrolytes and nutrients needed to maintain the constancy of the internal environment
  - eliminating waste materials by secreting them to the filtrate
- The final urine is affected by two other processes:
  - Water balance
  - Acid-Base balance

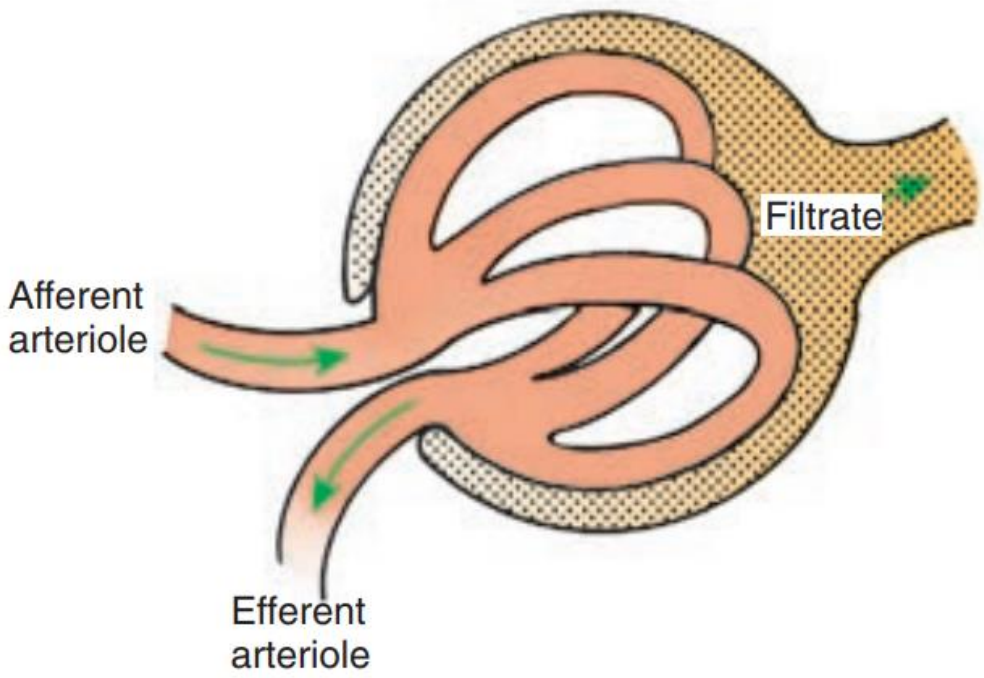


Section 2:

Glomerular Filtration

Glomerular Filtration

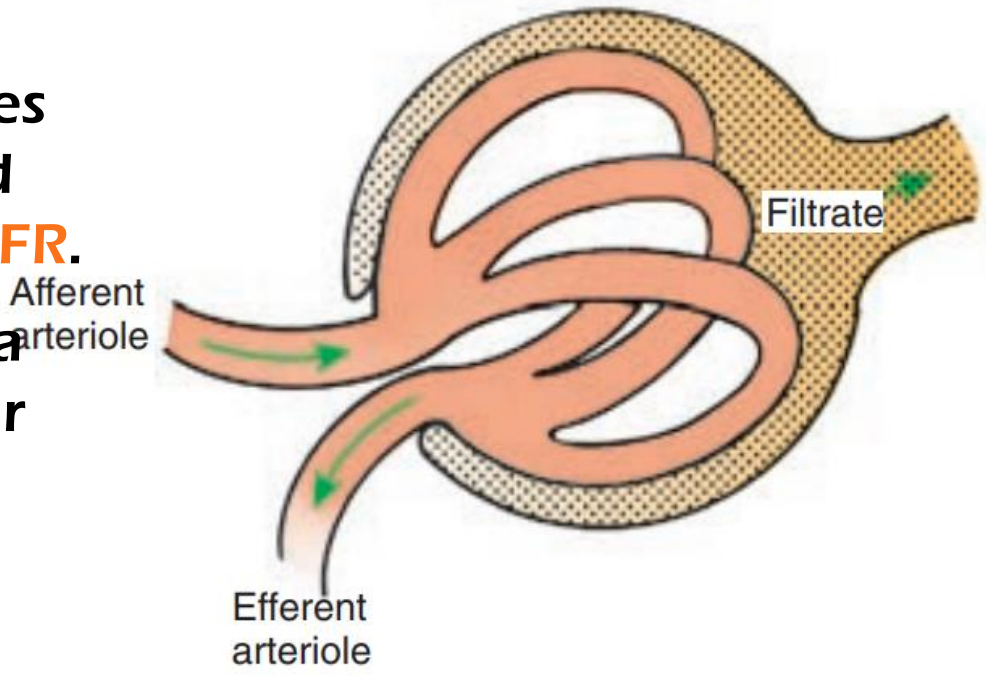
- Urine formation begins with the filtration of essentially protein-free plasma through the glomerular capillaries into Bowman space.
- It depends on:
  - capillary filtration pressure,
  - colloidal osmotic pressure,
  - capillary permeability
- Approximately 125 mL of filtrate is formed each minute. This is called the glomerular filtration rate (GFR).



Glomerular Filtration

II

- The filtration pressure and the GFR are regulated by the constriction and relaxation of the afferent and efferent arterioles.
  - Constriction of the efferent arteriole increases resistance to outflow from the glomeruli and increases the glomerular pressure and the GFR.
  - Constriction of the afferent arteriole causes a reduction in the renal blood flow, glomerular filtration pressure, and GFR.
- The afferent and the efferent arterioles are innervated by the sympathetic nervous system and are sensitive to vasoactive hormones, such as angiotensin II, as well.



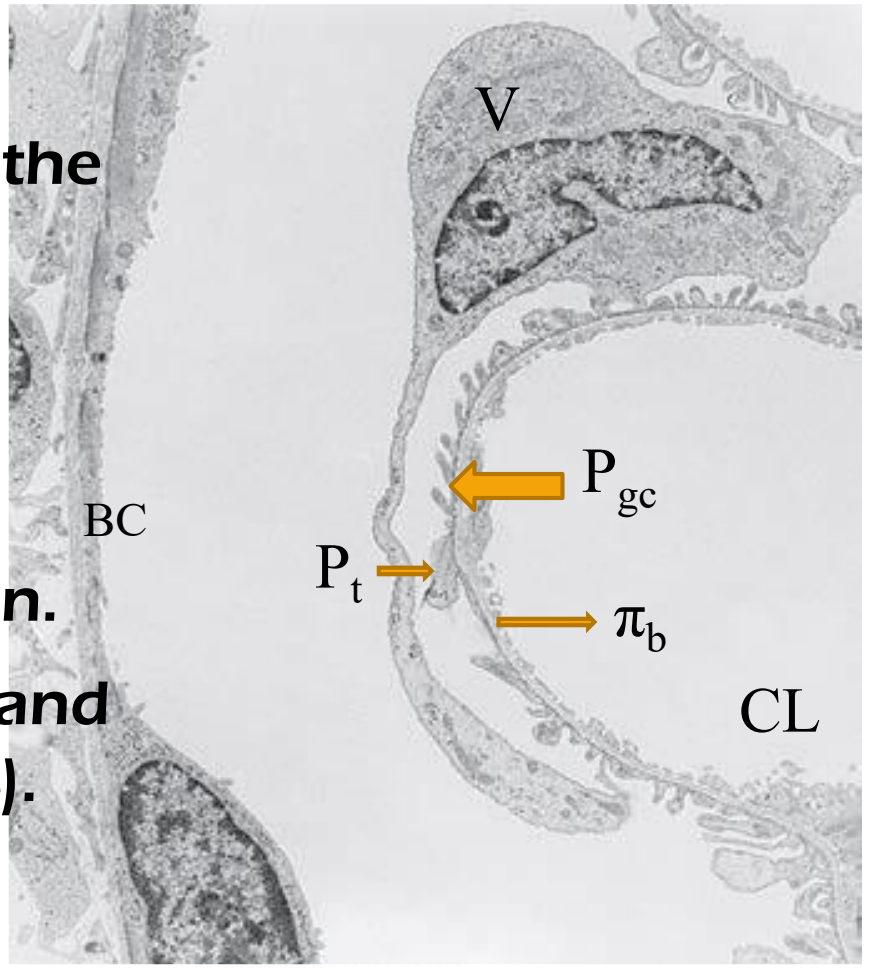
Glomerular Filtration

- The main driving force for filtration is the glomerular capillary hydrostatic pressure (P_{gc}).
- Forces opposing filtration are the plasma oncotic pressure (Π_b)within the glomerular capillary and the hydrostatic pressure in Bowman's space (P_t).

$$P_f = P_{gc} - (\pi_b + P_t)$$

- The GFR is the product of the mean net filtration pressure (P_f), the permeability of the filtration barrier, and the surface area available for filtration.
- The product of the filtration barrier permeability and its surface area is the ultrafiltration coefficient (K_f).

$$GFR = P_f \times K_f \ (ml/min/kg)$$



Glomerular Filtration

II

- Permeability of glomerulus depends on:
  - The size of the molecule:
    - substances with a molecular radius of 4 nm or more are not filtered, whereas molecules with a radius of 2 nm or less are filtered without restriction
  - The net electrical charge of a molecule:
    - The cations are more freely filtered than the neutral form, which is more freely filtered than the anionic form of the same molecule
    - These differences are caused by a charge-selective barrier in the glomerular capillary with negatively charged residues of glycoproteins
  - The shape and deformability of the molecule:
    - The more flexible molecule, the higher rate of glomerular filtration

The GFR Regulation

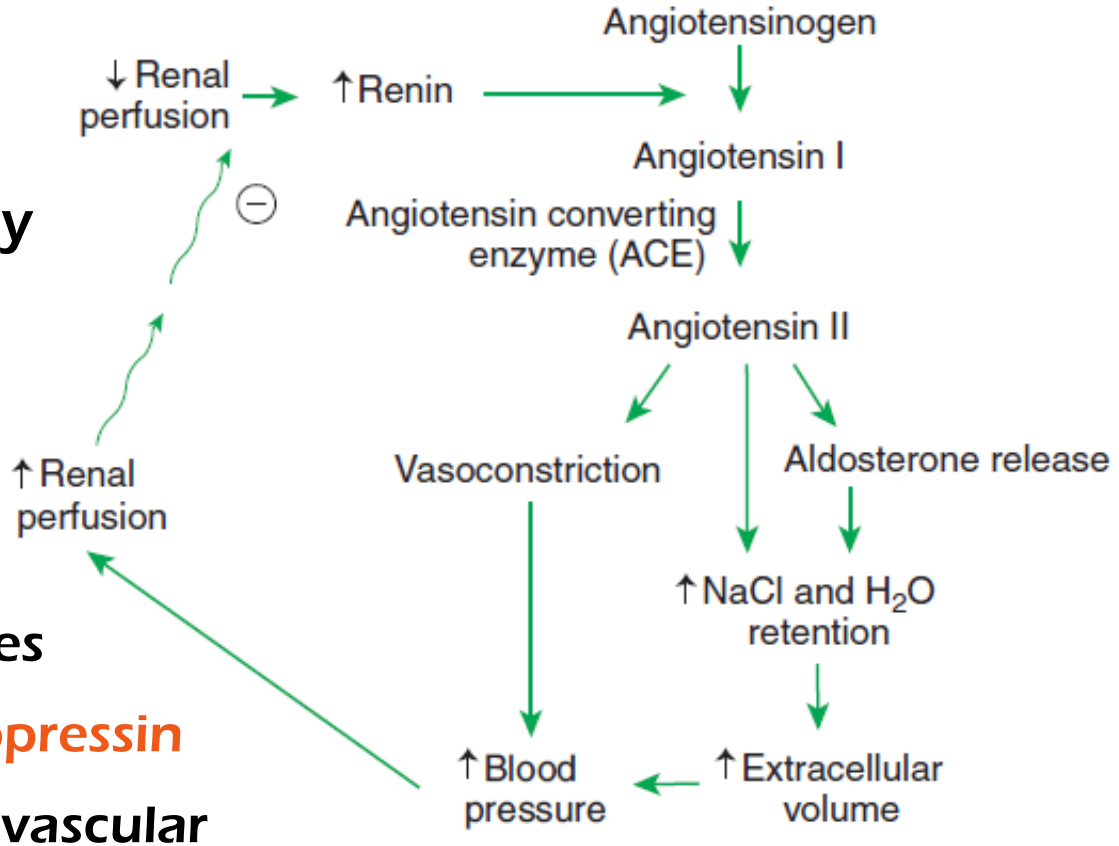
- The kidney normally maintains the GFR at a relatively constant level despite changes in systemic blood pressure and renal blood flow

$$\uparrow P_f = \uparrow P_{gc} - (\pi_b + P_t) \qquad \uparrow GFR = \uparrow P_f \times K_f \ (ml/min/kg)$$

- The GFR is kept within the physiological range by renal modulation of:
  1. Control of systemic blood pressure and volume
     - The renin-angiotensin-aldosterone system (RAAS)
  2. Intrinsic control of glomerular capillary perfusion
     - The myogenic reflex
     - Tubuloglomerular feedback (TGF)

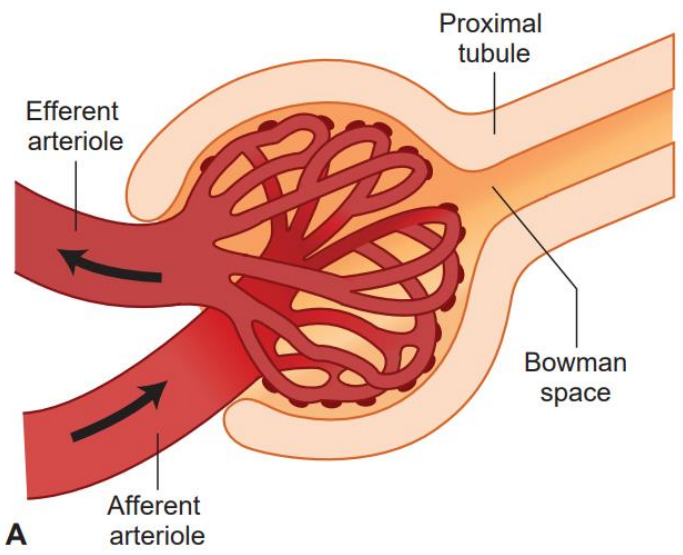
The renin-angiotensin-aldosterone system (RAAS) II

- Renin is a hormone produced by juxtaglomerular cells
  - stimulated by a decrease in renal perfusion pressure, most often caused by systemic hypotension
  - catalyzes angiotensinogen to angiotensin I.
- Angiotensin I is converted to angiotensin II by angiotensin converting enzyme (ACE), in the vascular endothelium of the lung
- Angiotensin II:
  - Is a potent vasoconstrictor
  - activates sodium uptake in several renal tubules
  - stimulates the release of aldosterone and vasopressin
  - Thus, increases salt and water retention, intravascular volume, and vascular resistance, to increased systemic blood pressure and renal perfusion pressure.



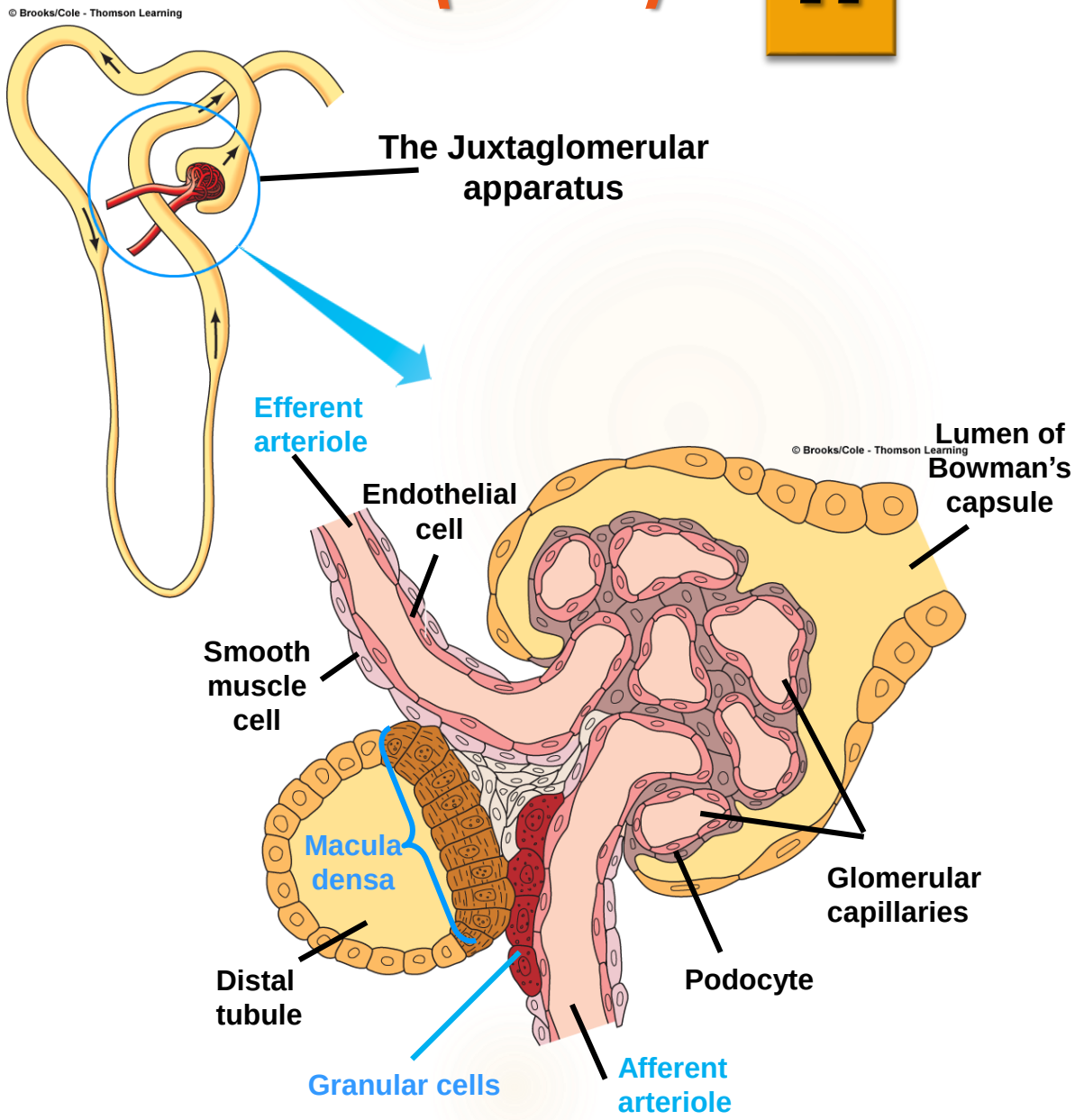
The myogenic reflex

- The myogenic reflex is an autoregulatory mechanism triggered by changes in glomerular perfusion
- The myogenic reflex regulates renal blood flow and GFR by almost immediate afferent arteriolar change in diameter.
  - constriction after an increase in arteriolar wall tension, thus increasing resistance to blood flow in response to increased perfusion pressure.
  - dilation after a decrease in arteriolar wall tension, thus reducing resistance to flow when vascular perfusion pressure decreases.
- These changes in vascular resistance contribute to maintenance of GFR and renal blood flow at a constant level, despite marked alterations in the blood pressure in the renal artery



The Tubuloglomerular Feedback (TGF)

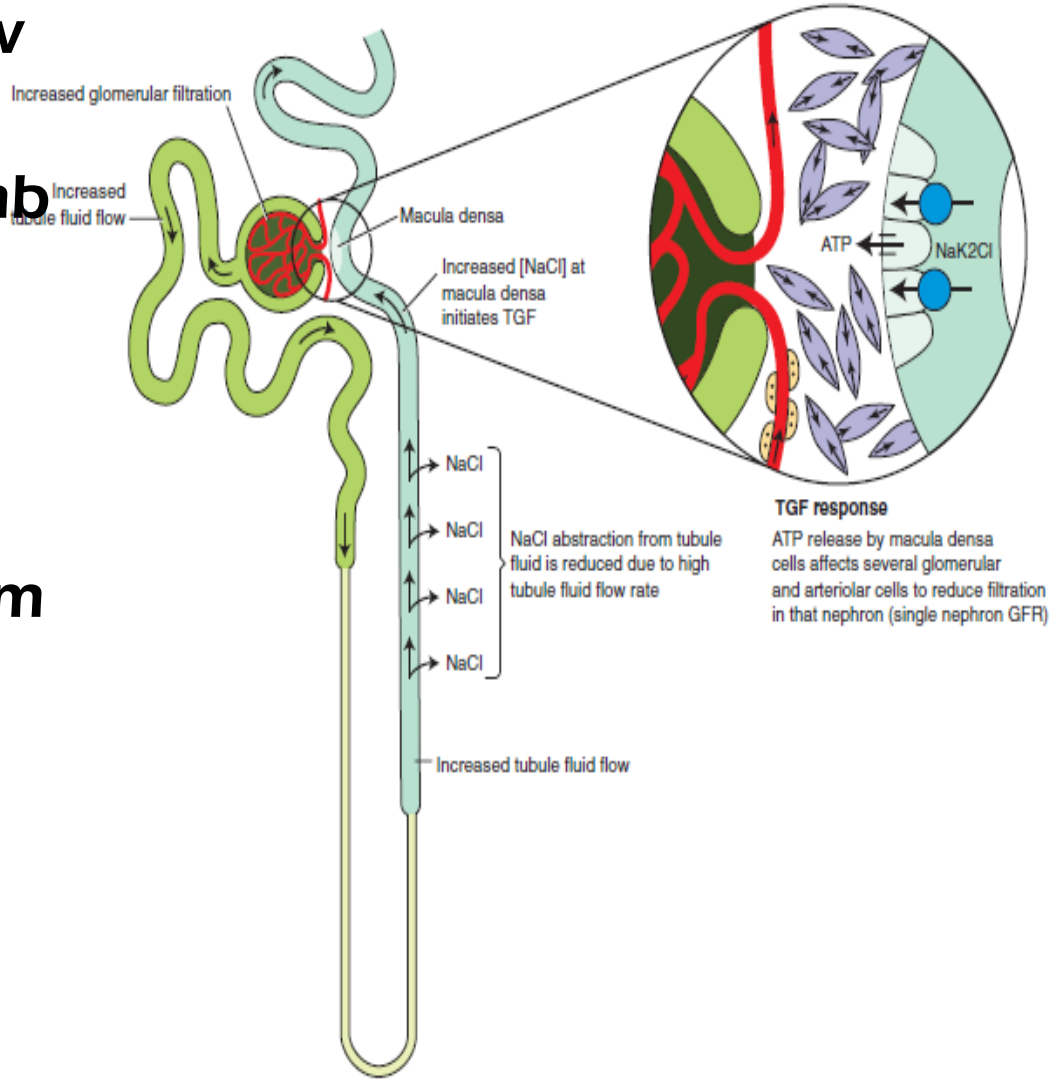
- The juxtaglomerular apparatus
  - The *afferent* arteriole
  - The *efferent* arteriole
  - The *macula densa*
  - The *granular cells*



The Tubuloglomerular Feedback (TGF)

II

- Increased GFR increases tubule fluid flow rate;
- increased flow in the thick ascending limb (TAL) increases NaCl delivery to the macula densa (MD);
- increased NaCl uptake at the MD causes basal ATP release;
- ATP release suppresses renin release from juxtaglomerular (JG) cells in the afferent arteriole, causes afferent arteriolar constriction, mesangial cell contraction and thereby decreased K_f.
- The result is decreased single-nephron GFR.



Glomerular Filtration Measurement

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- In experimental settings and in clinical practice, GFR is one of the most important parameters of renal function.
- Determination of GFR relies on the concept of clearance, that is, the rate the plasma is cleared of a substance.
- The rate of clearance is measured by the rate of elimination of a substance divided by its plasma concentration

$$C_X = (U_X V)/P_X$$

  - C_X: the volume of plasma cleared of substance X per unit time,
  - U_X: the urine concentration of substance X,
  - V: is the volume of urine collected divided by the time period of the collection,
  - P_X: the plasma concentration of substance X

Glomerular Filtration Measurement

II

- Clearance rate = Filtration – Reabsorption + Secretion
- This is neatly done by using inulin as the substance for the measurement of clearance.
  - Inulin is freely filtered by the glomerulus but is neither reabsorbed nor secreted by the renal tubule cells

$$GFR = C_{inulin} = (U_{inulin} V)/P_{inulin}$$

- In clinical situations the most widely used measure of glomerular filtration is endogenous creatinine clearance
- In practice, a 24-hour urine collection is done and urine volume and mean urine and plasma creatinine are measured

$$C_{creatinine} = U_{creatinine} V/P_{creatinine}$$

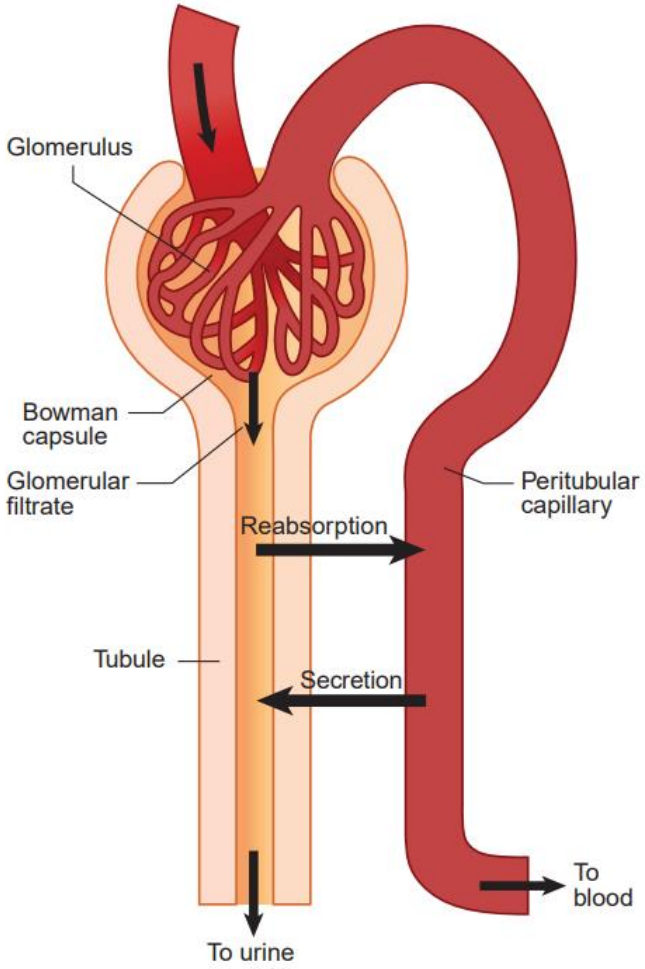
- In clinical practice, the serum creatinine level alone is frequently used to assess renal function

Section 3:

Tubular Reabsorption and Secretion

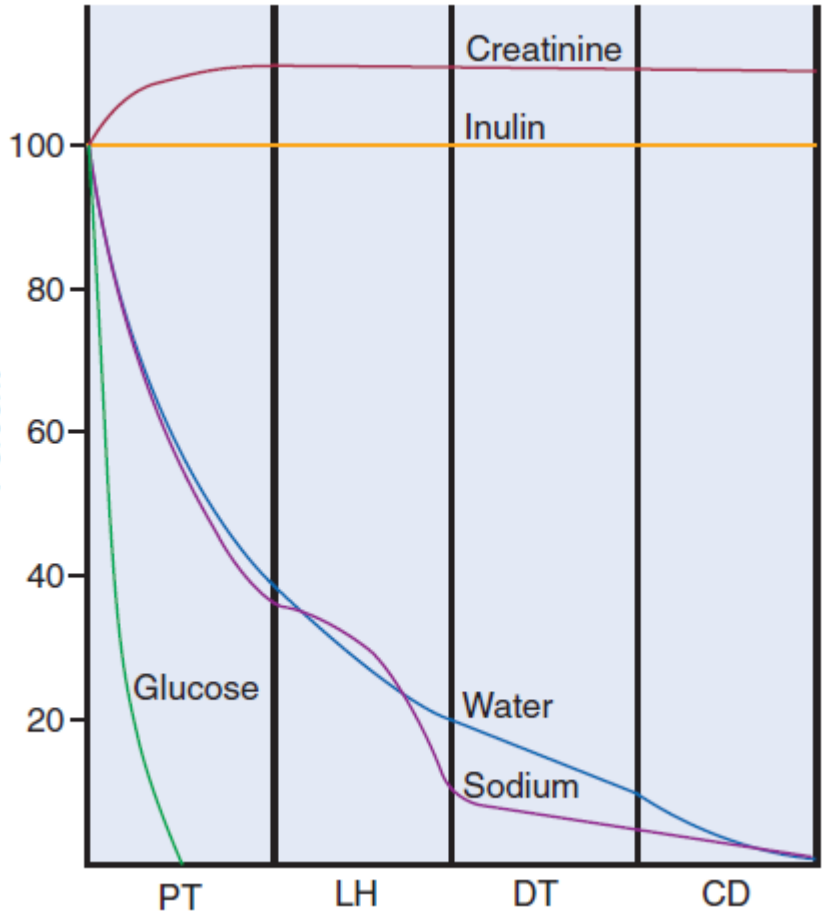
Tubular Reabsorption and Secretion

- Tubular transport can result in reabsorption of substances from the tubular fluid into the peritubular capillaries or secretion of substances into the tubular fluid from the blood in the peritubular capillaries
- The basic mechanisms of transport across the tubular epithelial cell membrane are:
  - Primary active transport
  - Carrier-mediated secondary active transport
  - Solvent drag
  - Passive diffusion
    - Osmosis



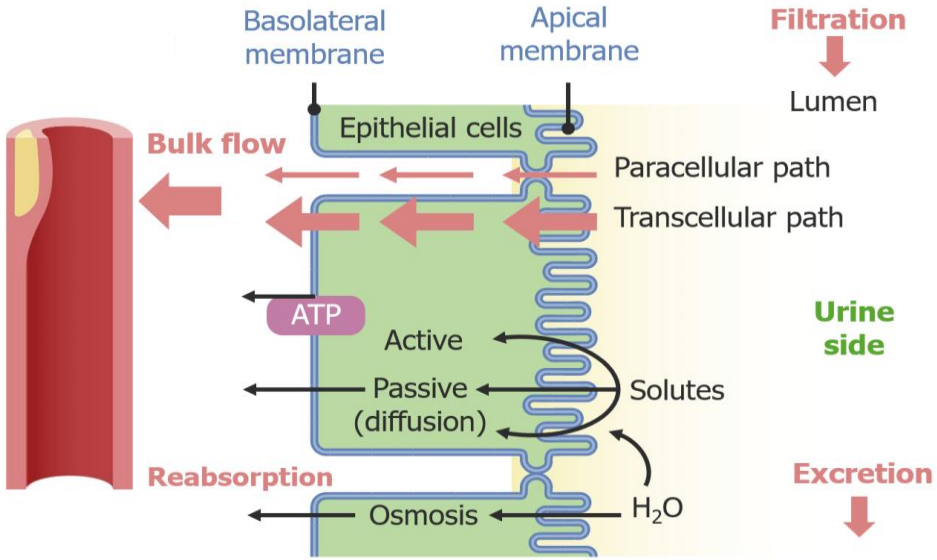
Tubular Reabsorption and Secretion

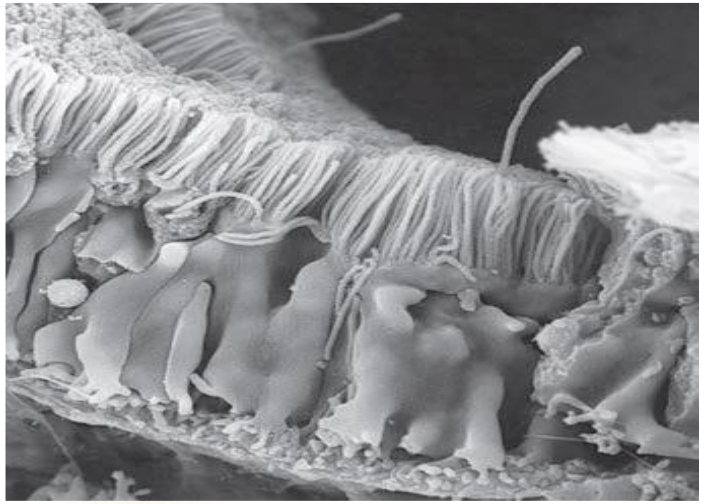
- The rate of reabsorption and secretion of filtered substances varies among segments of the renal tubule.
  - In general, the proximal convoluted tubule (PCT) reabsorbs more of the ultrafiltrate than the other tubule segments combined, at least 60% of most filtered substances
  - In the distal tubule (DCT) and collecting ducts (CD), the remaining filtrate would be tuned to correct the final urine concentration with the regulation of hormones.
- One hundred percent of the filtered glucose is reabsorbed by the proximal tubule; by the time the final urine is formed in the terminal collecting duct, approximately 99% of the filtered water and sodium has been retrieved.



Tubular Reabsorption and Secretion - PCT

- The outside membrane that lies adjacent to the interstitial fluid is called the basolateral membrane, and the side that is in contact with the tubular lumen and tubular filtrate is called the luminal (apical) membrane.
- The movement of tubule fluid components into the blood is done through two pathways: the transcellular pathway and the paracellular pathway.
- The apical plasma membrane has extensive microprojections, called microvilli, which collectively create the brush border.

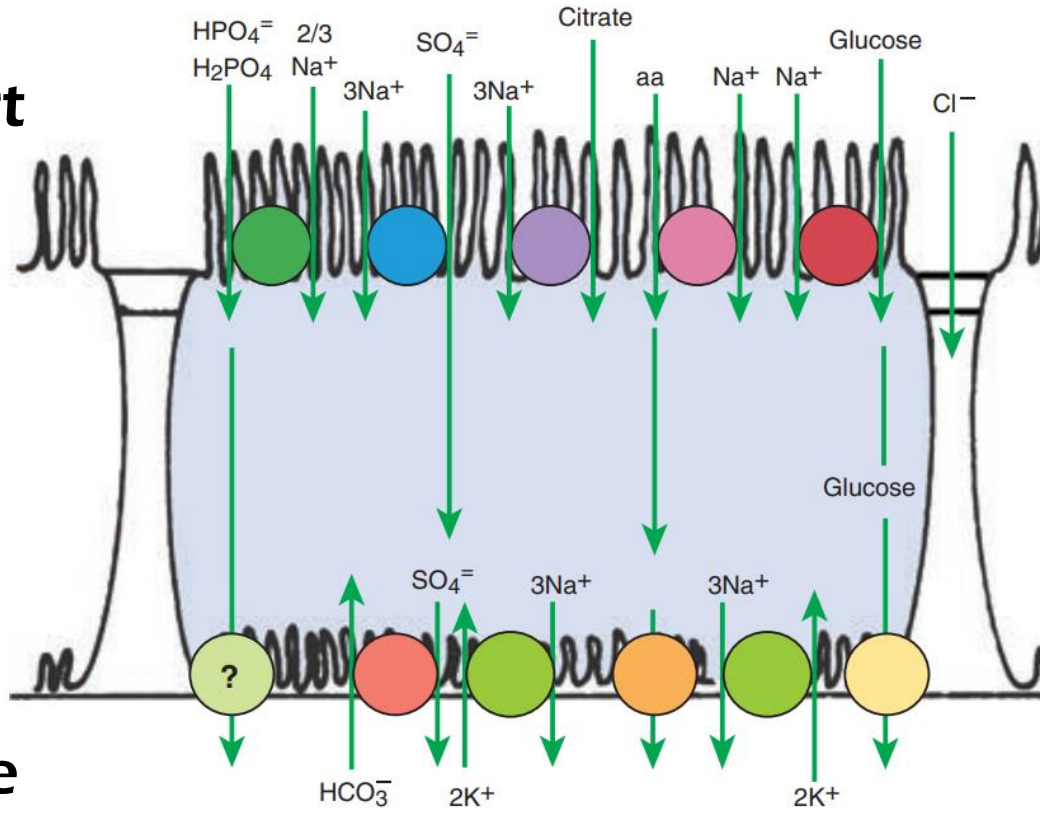




Tubular Reabsorption and Secretion - PCT

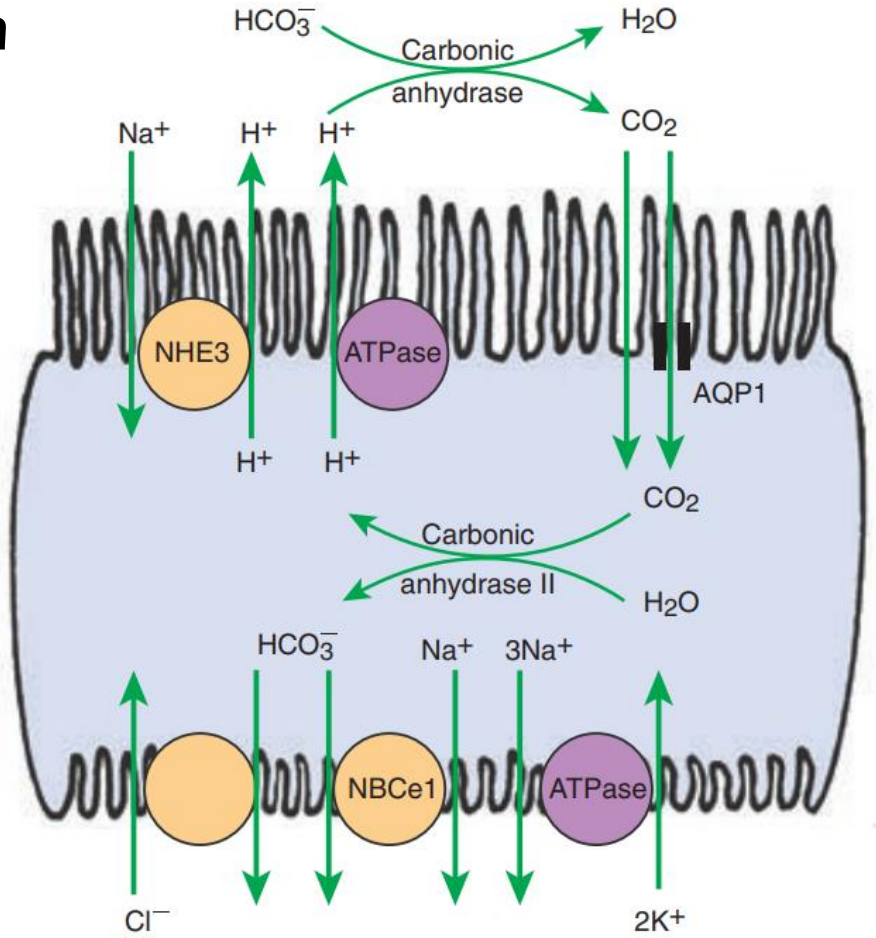
III

- In the proximal tubule, most solute reabsorption is driven by the active transport of sodium ions (Na^+) by the (Na^+/K^+ ATPase) pump, which is located in the basolateral plasma membrane.
- (Na^+/K^+ ATPase) activity reduces the intracellular Na+ concentration and makes the cell interior electrically negative relative to the exterior.
- Specific Na^+-dependent transporters mediate the uptake from the proximal tubule fluid by the mechanism of secondary active transport.



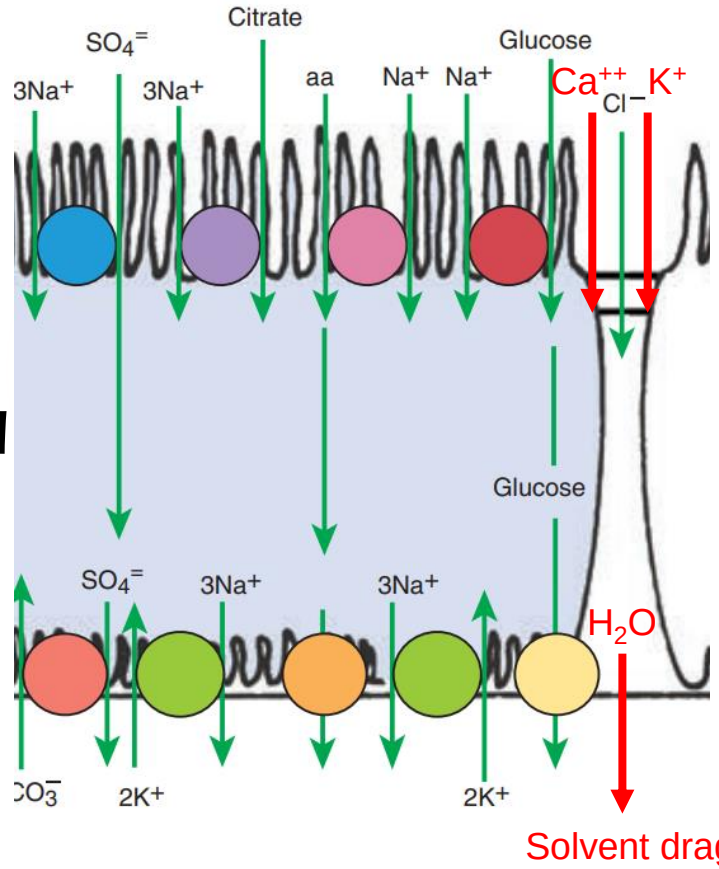
Tubular Reabsorption and Secretion - PCT

- Bicarbonate ($HCO3^-$) reabsorption in the proximal tubule is also driven by the Na^+ gradient, although indirectly.
  - The chemical gradient for Na^+ drives Na^+ and H^+ counter-transport across the apical plasma membrane through a Na^+/H^+ exchanger.
  - Secreted H^+ combines with filtered $HCO3^-$ in the tubule fluid to form water H_2O and CO_2, catalyzed by the enzyme carbonic anhydrase in the apical plasma membrane of proximal tubule cells.
  - CO_2 enters the cell and cytoplasmic carbonic anhydrase catalyzes the hydroxylation of CO_2 with OH^- donated from H_2O, forming H^+ and $HCO3^-$ in the cell.
  - $HCO3^-$ crosses the basolateral plasma membrane through a $Na^+/3$-($HCO3^-$) co-transporter and $HCO3^-/Cl^-$ exchanger.



Tubular Reabsorption and Secretion - PCT

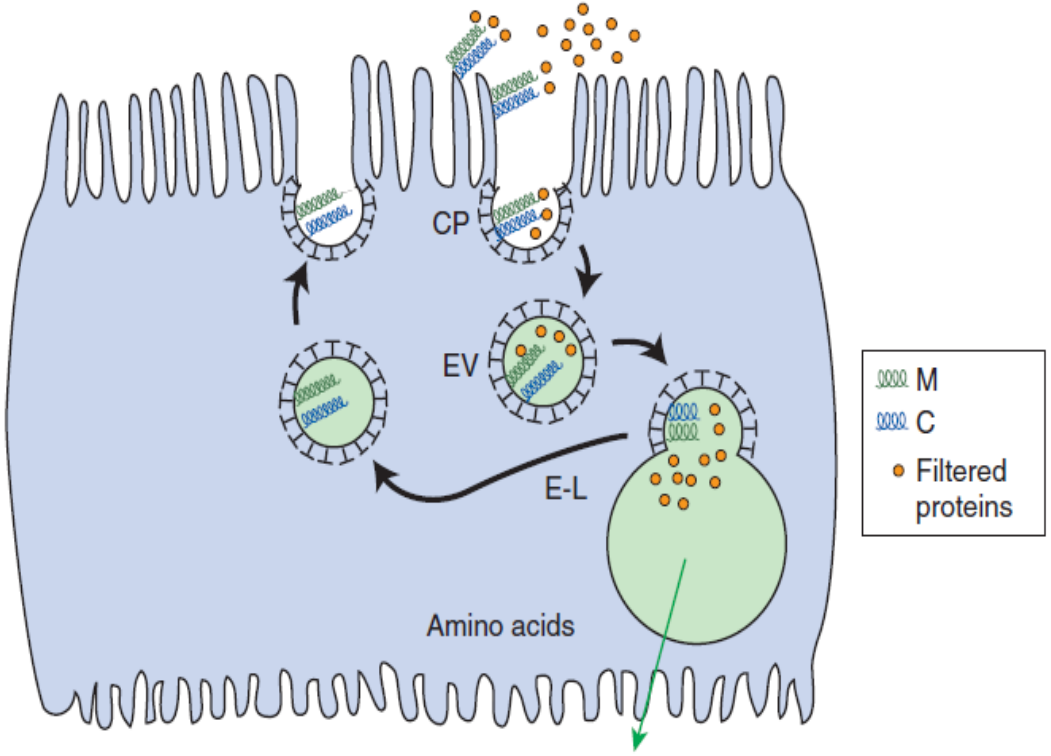
- Chloride ion (Cl^-) reabsorption in the proximal tubule is also indirectly powered by the Na^+,K^+-ATPase pump and occurs through both paracellular and transcellular.
  - Cl^- diffuses across the zonula occludens into the lateral intercellular spaces down its electrochemical gradient.
- potassium (K^+) and calcium (Ca^{2+}) ions are reabsorbed by the proximal tubule.
  - Approximately 65% of filtered Ca^{2+} is reabsorbed in the proximal tubule.
  - About 90% of the Ca^{2+} uptake in the proximal tubule is paracellular because of a favorable electrochemical gradient in the late proximal tubule and solvent drag.
  - The majority of K^+ reabsorption in the proximal tubule also occurs by passive mechanisms, primarily through the paracellular route.



65% Ca^{++} reab. In prox.
90% paracellular

Tubular Reabsorption and Secretion - PCT

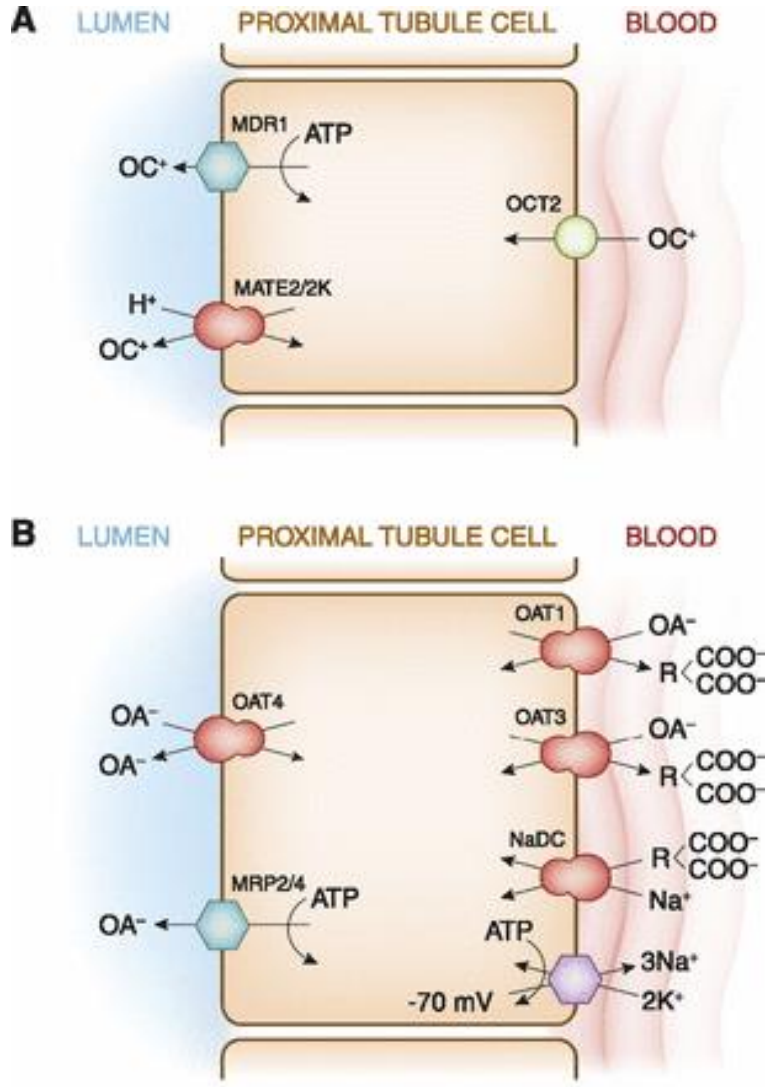
- **Low–molecular-weight proteins** are avidly reabsorbed by the proximal tubule, but by a different mechanism.
  - Filtered proteins such as insulin, glucagon, parathyroid hormone, and many more are taken up at the apical plasma membrane by **receptor-mediated endocytosis**
- The proteins bind receptors (megalin and cubilin) in the plasma membrane, are endocytosed, and delivered by the endocytic vesicles to intracellular organelles called lysosomes while the receptors are recycled to the apical plasma membrane.



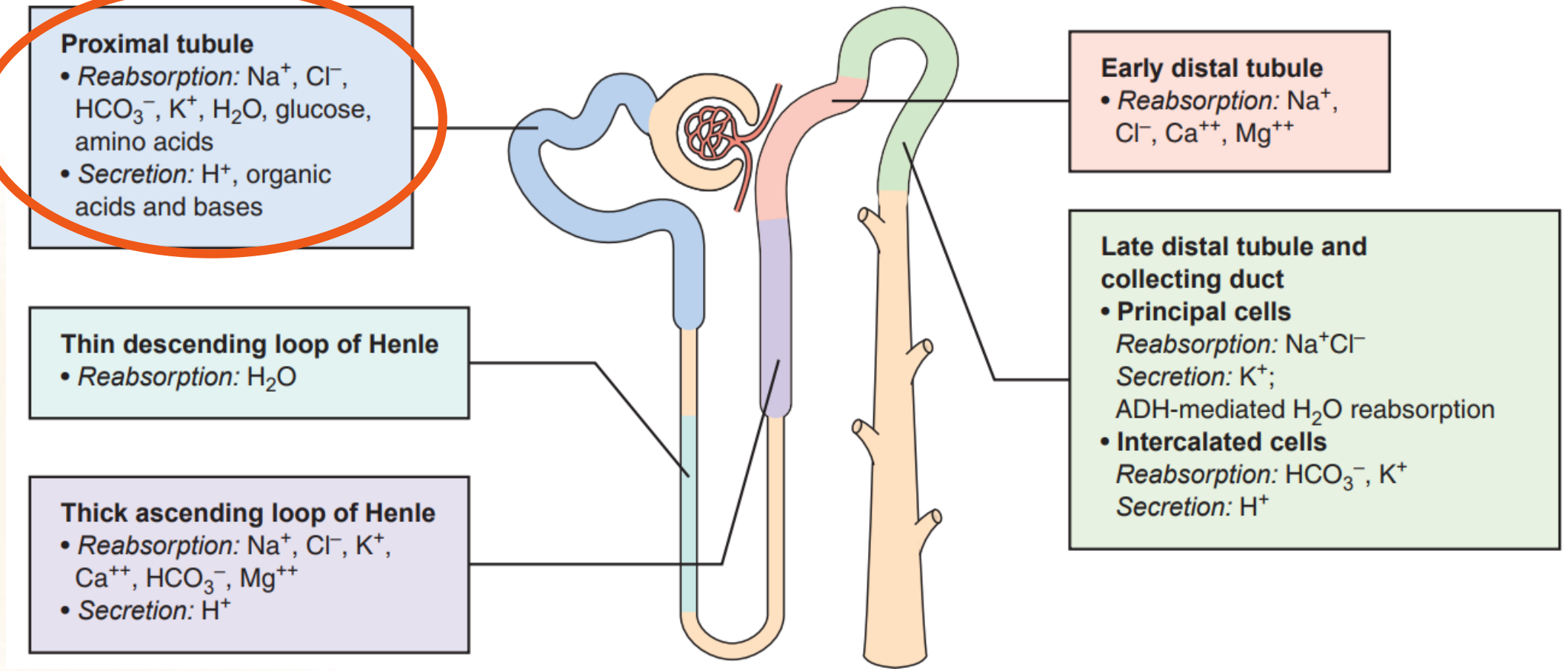
Tubular Reabsorption and Secretion - PCT

III

- The proximal tubule secretes a wide variety of organic ions into the tubule fluid.
  - endogenous waste products
  - exogenous drugs or toxins
- Transporters involved include organic anion transporters (OAT) and organic cation transporters (OCT).
- Endogenous waste products:
  - bile salts, oxalate, urate, creatinine, prostaglandins, epinephrine, . . .
- Exogenous drugs or toxins
  - antibiotics (e.g., penicillin G), diuretics (e.g., chlorothiazide, furosemide), antiviral agents (e.g., acyclovir, ganciclovir) and analgesics, . . .

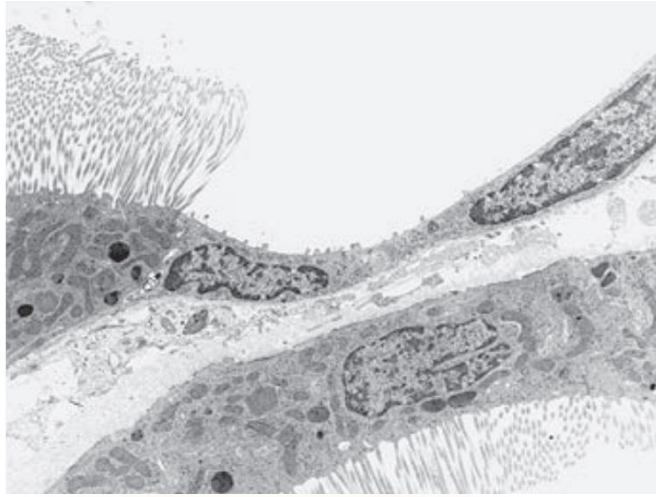


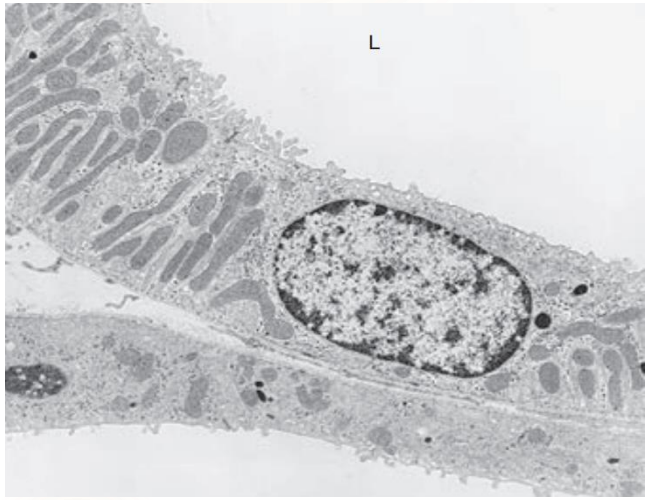
Tubular Reabsorption and Secretion - PCT



Tubular Reabsorption and Secretion - LH

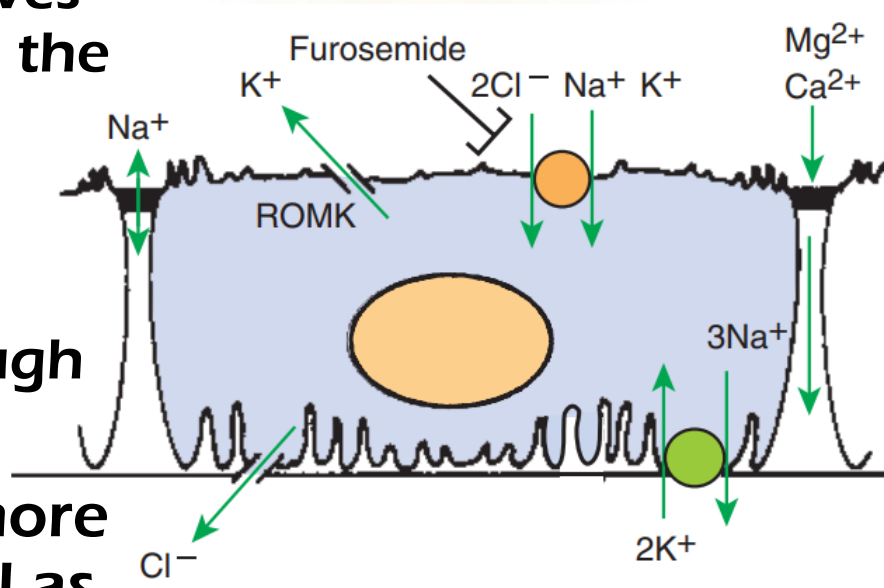
- Immediately downstream from the straight portion of the proximal tubule is the thin limb of Henle's loop, which is a low epithelium with few mitochondria and few membranous infoldings.
  - The function of the thin limb is passive reabsorption of water in the medulla which will be discussed in the 'water balance' chapter.
  - In the ascending limb of Henle's loop, the epithelium is cuboidal with many mitochondria and protein pumps in basolateral membrane for active transport.
  - The thick ascending limb of Henle's loop (TAL) and the distal convoluted tubule (DCT) reabsorb Na^+, Cl^-, and the divalent cations Ca^{2+} and Mg^{2+}.



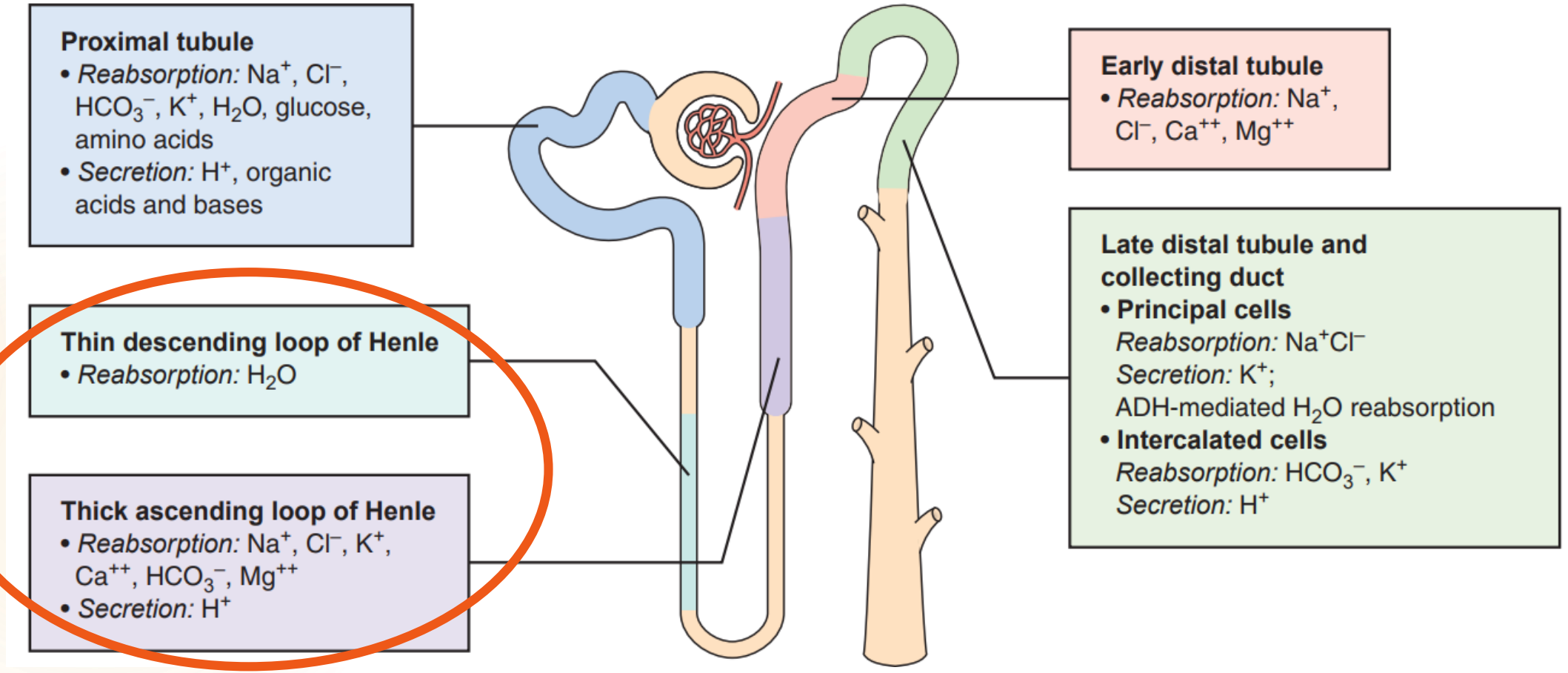


Tubular Reabsorption and Secretion - LH

- Salt reabsorption in the TAL and DCT is driven by Na^+,K^+-ATPase in the basolateral plasma membrane.
  - In the TAL, the electrochemical gradient for Na^+ established by basolateral Na^+,K^+-ATPase activity drives ion uptake through the $Na^+,K^+,2Cl^-$ co-transporter in the apical plasma membrane.
  - Intracellular Cl^- diffuses down its chemical gradient into the interstitial fluid through Cl^-channels.
  - The K^+ moves down its concentration gradient through apical K^+ channels, thus is recycled to the lumen.
- The Cl^- absorption and K^+ secretion cause lumen more positive than interstitium, so Ca2+ and Mg^{2+} as well as Na^+ can diffuse through paracellular pathways.
- loop diuretics (such as furosemide) inhibit $Na^+,K^+,2Cl^-$ co-transporter and thus increase K^+ excretion.

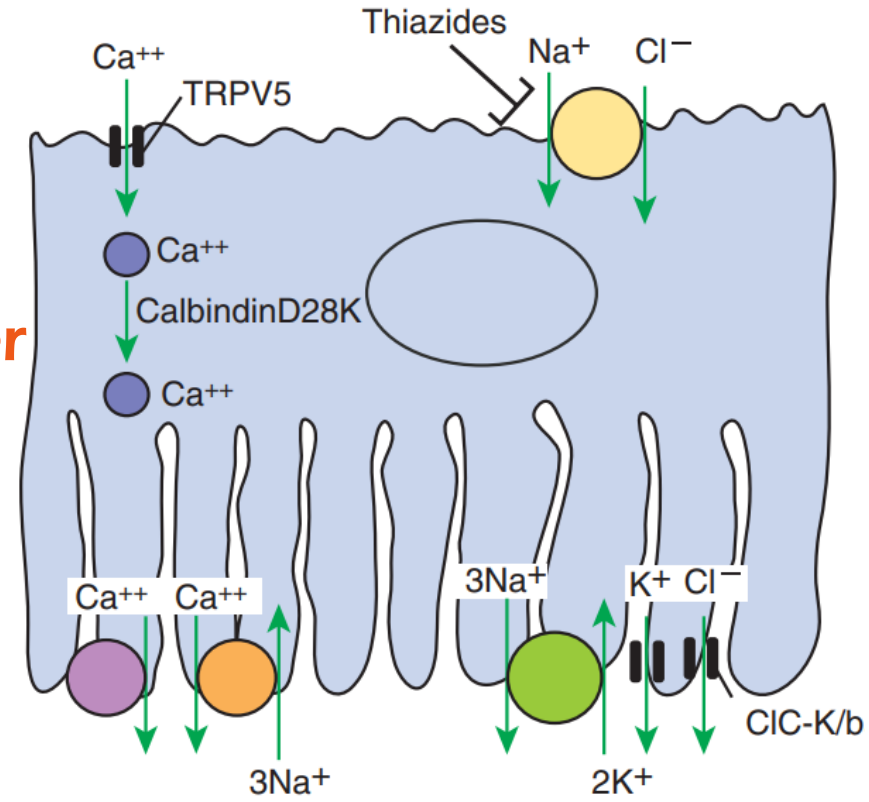


Tubular Reabsorption and Secretion - LH

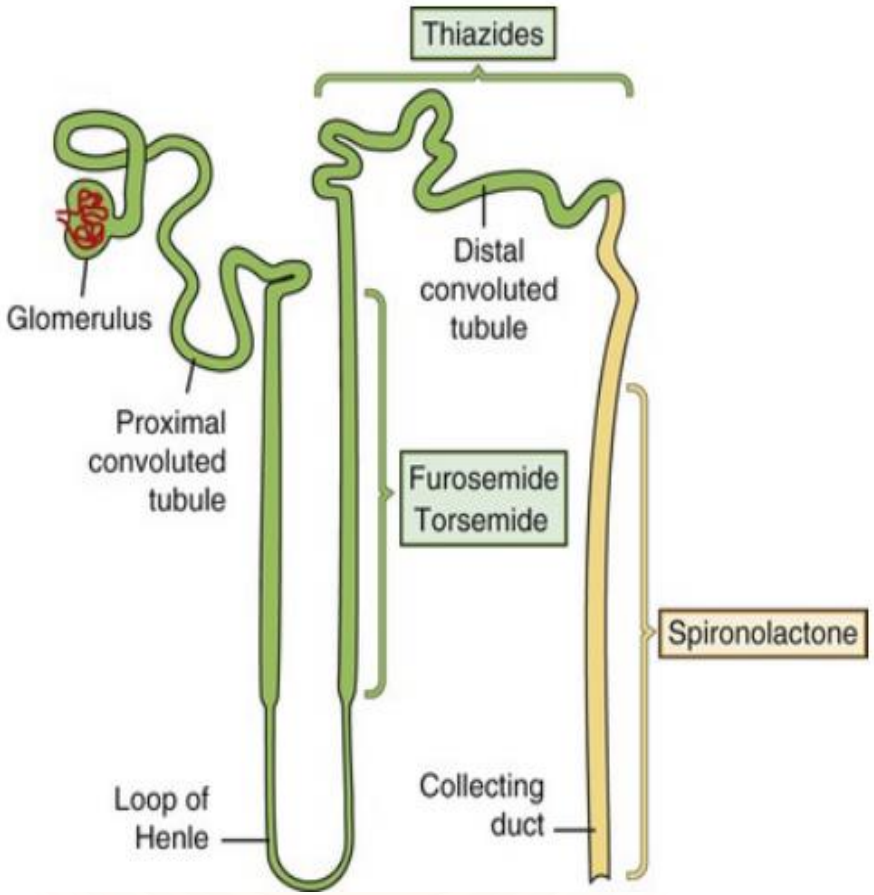


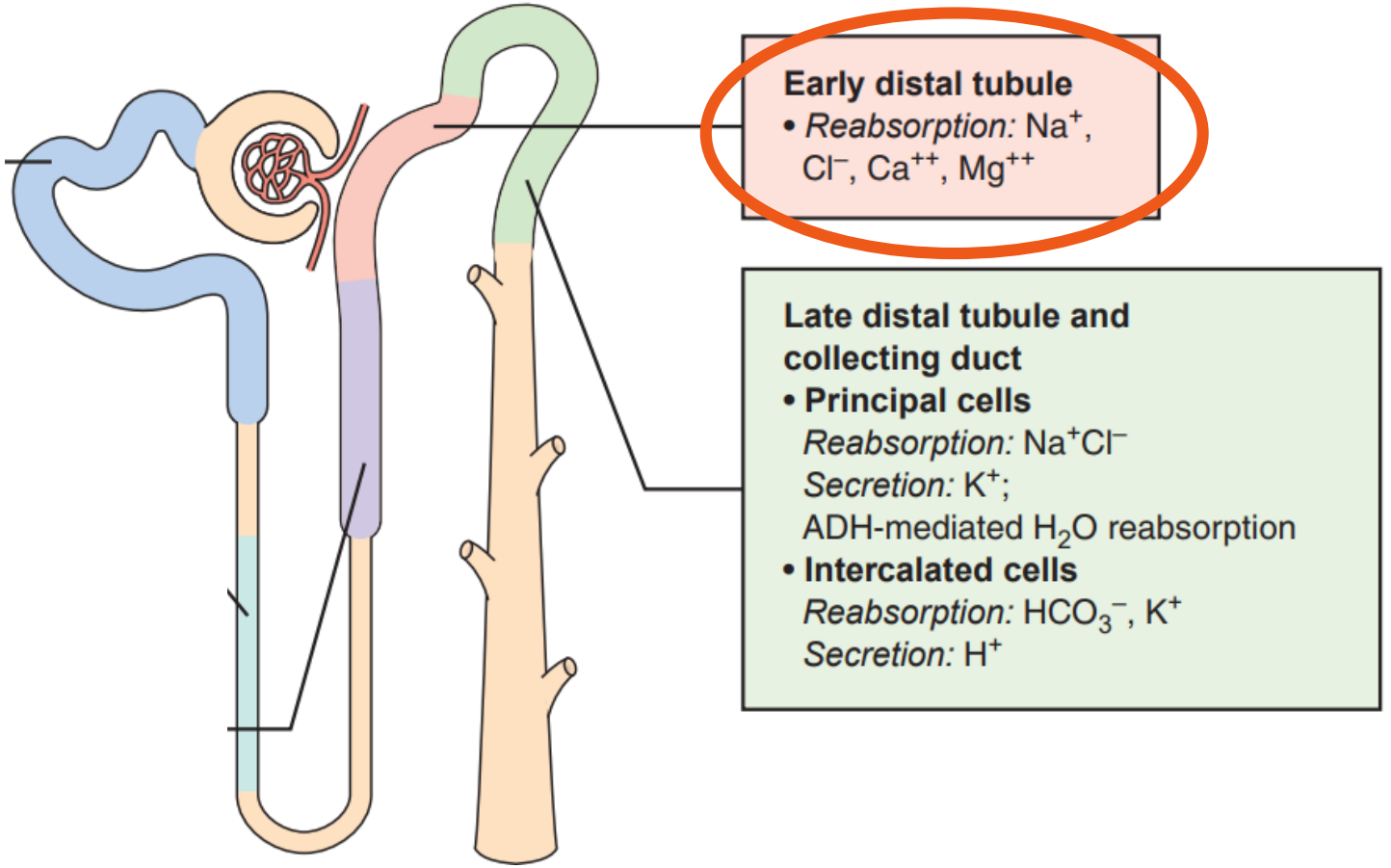
Tubular Reabsorption and Secretion - DCT

- Sodium reabsorption occurs through a Na^+,K^+-ATPase and Na^+/Cl^- cotransport mechanism.
  - Approximately 5% of filtered sodium chloride is reabsorbed in this section of the tubule.
- Unlike the thick ascending loop of Henle, neither Ca^{++} nor Mg^{++} is passively absorbed in this segment of the tubule. Instead, Ca^{++} ions are actively reabsorbed in a process that is largely regulated by parathyroid hormone and possibly by vitamin D.
- The thiazide diuretics exert their action by inhibiting sodium chloride reabsorption in this segment of the renal tubules



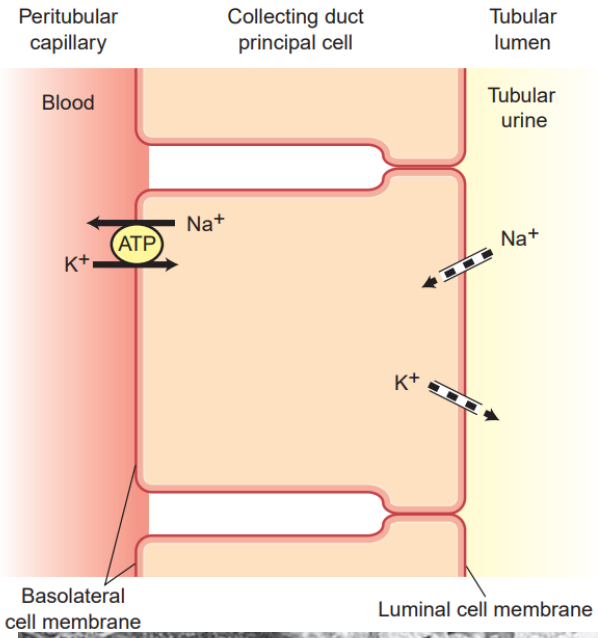
Tubular Reabsorption and Secretion - LH

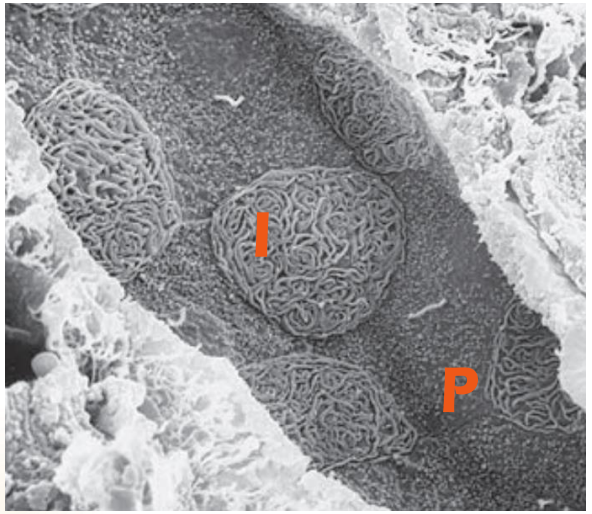




Tubular Reabsorption and Secretion – DCT/CCD

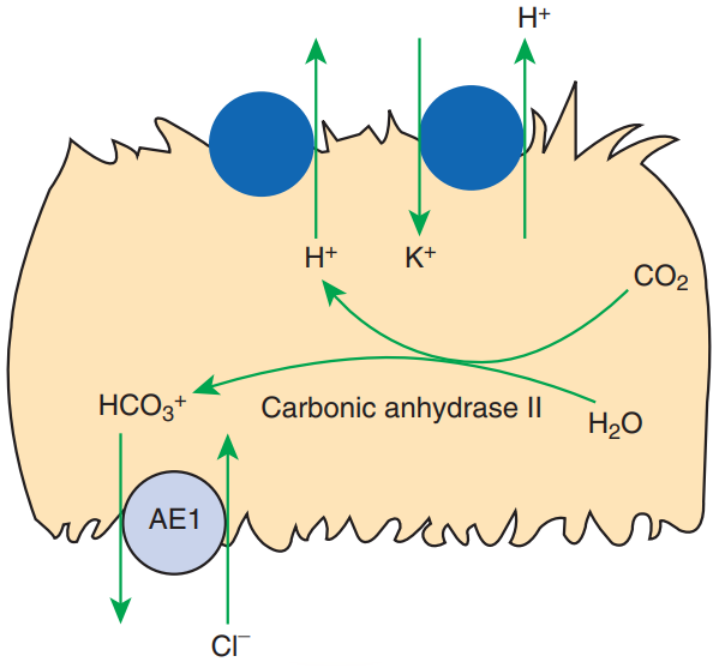
- In the late distal tubule and the cortical collecting duct sodium reabsorption and potassium secretion and elimination is done by the regulation of aldosterone.
  - Although responsible for only 2% to 5% of sodium chloride reabsorption, this site is largely responsible for determining the final sodium concentration of the urine.
  - When the body is confronted with a potassium excess, as occurs with a diet high in potassium content, the amount of potassium secreted at this site may exceed the amount filtered in the glomerulus.
- This tubular segment is composed of two types of cells, the intercalated cells, where potassium is reabsorbed and hydrogen is secreted, and the principal cells, where aldosterone exerts its action.

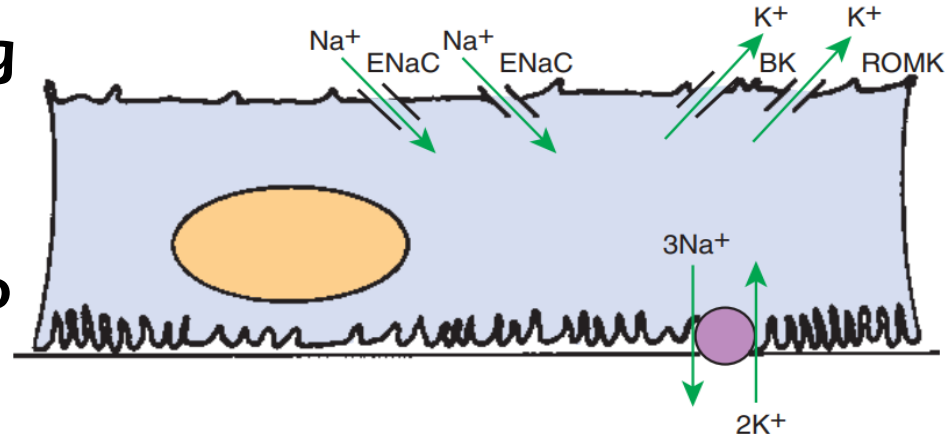




Tubular Reabsorption and Secretion – DCT/CCD

- The secretion of H^+ ions into the tubular fluid by the intercalated cells is accompanied by the reabsorption of HCO_3^- ions.
  - The intercalated cells can also reabsorb K^+ ions.
- The principal cells reabsorb Na^+ and facilitate the movement of K^+ into the urine filtrate.
  - Under the influence of aldosterone, sodium moves from the urine filtrate into principal cells; from there, it moves into the surrounding interstitial fluid and peritubular capillaries.
  - Potassium moves from the peritubular capillaries into the principal cells and then into the urine filtrate.



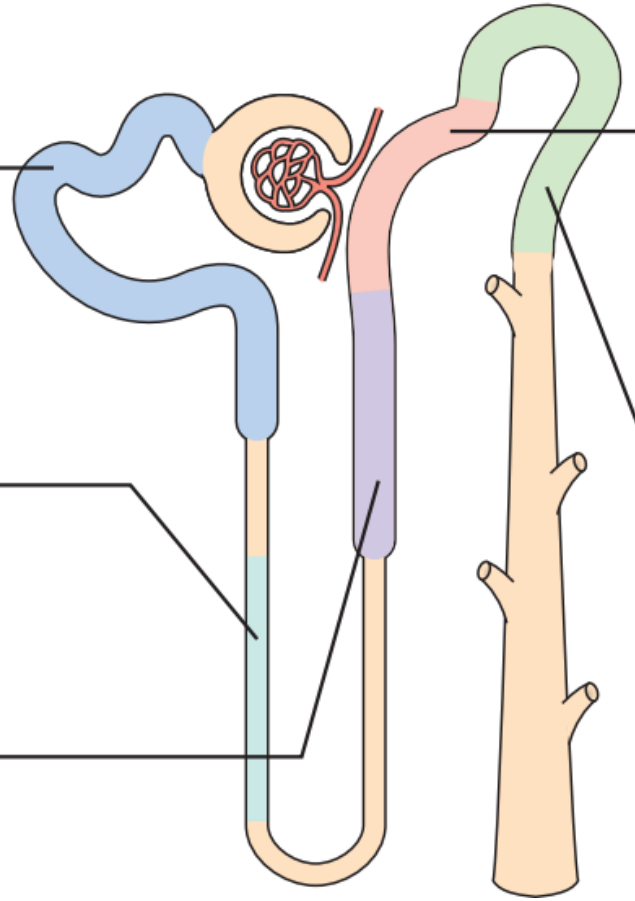


Tubular Reabsorption and Secretion - LH

Proximal tubule
- *Reabsorption:* Na^+, Cl^-, HCO_3^-, K^+, H_2O, glucose, amino acids
- *Secretion:* H^+, organic acids and bases

Thin descending loop of Henle
- *Reabsorption:* H_2O

Thick ascending loop of Henle
- *Reabsorption:* Na^+, Cl^-, K^+, Ca^{++}, HCO_3^-, Mg^{++}
- *Secretion:* H^+



Early distal tubule
- *Reabsorption:* Na^+, Cl^-, Ca^{++}, Mg^{++}

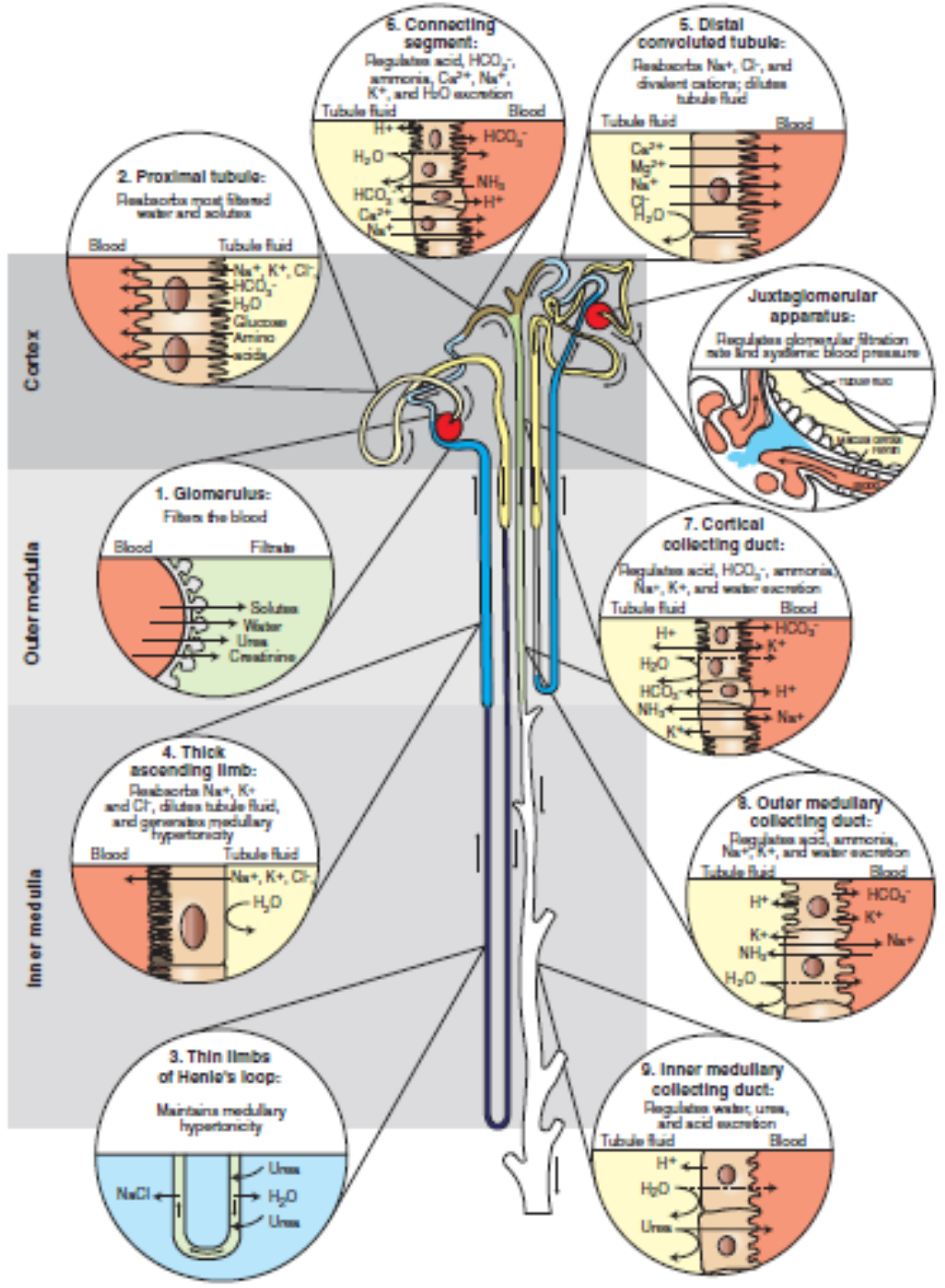
Late distal tubule and collecting duct
- **Principal cells**
  Reabsorption: Na^+Cl^-
  Secretion: K^+;
  ADH-mediated H_2O reabsorption
- **Intercalated cells**
  Reabsorption: HCO_3^-, K^+
  Secretion: H^+

Solute Transport Regulation

- In the proximal tubule, most filtered solutes and water are reabsorbed regardless of the animal's physiological state, but the rate of reabsorption of sodium, chloride, phosphate, and other solutes is regulated by specific hormones.
- The distal tubule and collecting duct control the ultimate rate of excretion of electrolytes and water to maintain homeostasis despite variations in dietary intake and extrarenal losses of salts and water.
- The specific homeostatic responses of these segments are controlled in large part by several hormones, including angiotensin II, aldosterone, antidiuretic hormone, endothelin-1, atrial natriuretic peptide, parathyroid hormone, 1α,25-$(OH)_2$–vitamin D_3, and calcitonin.

Solute Transport Regulation

- Angiotensin II, (Direct Na^+ reabsorption)
- Aldosterone, (Na^+ reabsorption and K^+ secretion)
- Antidiuretic hormone, (H_2O reabsorption)
- Endothelin-1, (NaCl and H_2O secretion)
- Atrial natriuretic peptide, (Stimulated by atrial distention., inhibits aldosterone and renin release, increase Na^+ excretion)
- Parathyroid hormone, (decrease $HPO4^-$ uptake, increase urinary $HPO4^-$ excretion, Ca reuptake in PCT and ascending loop of hele and DCT)
- 1α,25-$(OH)_2$–vitamin D3, (enhance Ca reabsorption in DCT and CCD)
- Calcitonin, (Ca^{2+} reabsorption in DCT and CCD)


6. Connecting segment:
Regulates acid, HCO_3^-, ammonia, Ca^{2+}, Na^+, K^+, and H_2O excretion
Tubule fluid
Blood
H^+
HCO_3^-
H_2O
NH_3
HCO_3^-
H^+
Ca^{2+}
Na^+
5. Distal convoluted tubule:
Reabsorbs Na^+, Cl^-, and divalent cations; dilutes tubule fluid
Tubule fluid
Blood
Ca^{2+}
Mg^{2+}
Na^+
Cl^-
H_2O
2. Proximal tubule:
Reabsorbs most filtered water and solutes
Blood
Tubule fluid
Na^+, K^+, Cl^-
HCO_3^-
H_2O
Glucose
Amino acids
Juxtaglomerular apparatus:
Regulates glomerular filtration rate and systemic blood pressure
Cortex
Outer medulla
Inner medulla
1. Glomerulus:
Filters the blood
Blood
Filtrate
Solutes
Water
Urea
Creatinine
7. Cortical collecting duct:
Regulates acid, HCO_3^-, ammonia, Na^+, K^+, and water excretion
Tubule fluid
Blood
H^+
HCO_3^-
K^+
H_2O
HCO_3^-
H^+
NH_3
Na^+
K^+
4. Thick ascending limb:
Reabsorbs Na^+, K^+ and Cl^-; dilutes tubule fluid, and generates medullary hypertonicity
Blood
Tubule fluid
Na^+, K^+, Cl^-
H_2O
8. Outer medullary collecting duct:
Regulates acid, ammonia, Na^+, K^+, and water excretion
Tubule fluid
Blood
H^+
HCO_3^-
K^+
K^+
Na^+
NH_3
H_2O
3. Thin limbs of Henle's loop:
Maintains medullary hypertonicity
Urea
NaCl
H_2O
Urea
9. Inner medullary collecting duct:
Regulates water, urea, and acid excretion
Tubule fluid
Blood
H^+
H_2O
Urea

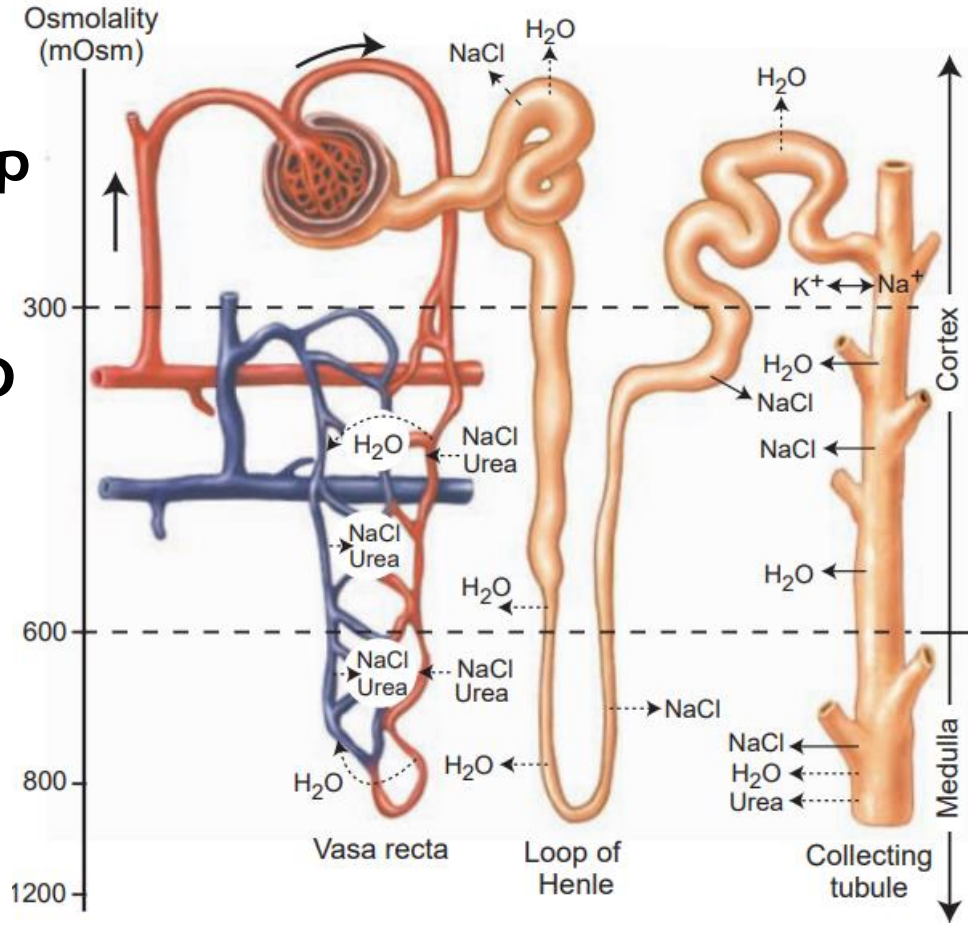
Section 4:

Water Balance

Water Balance

IV

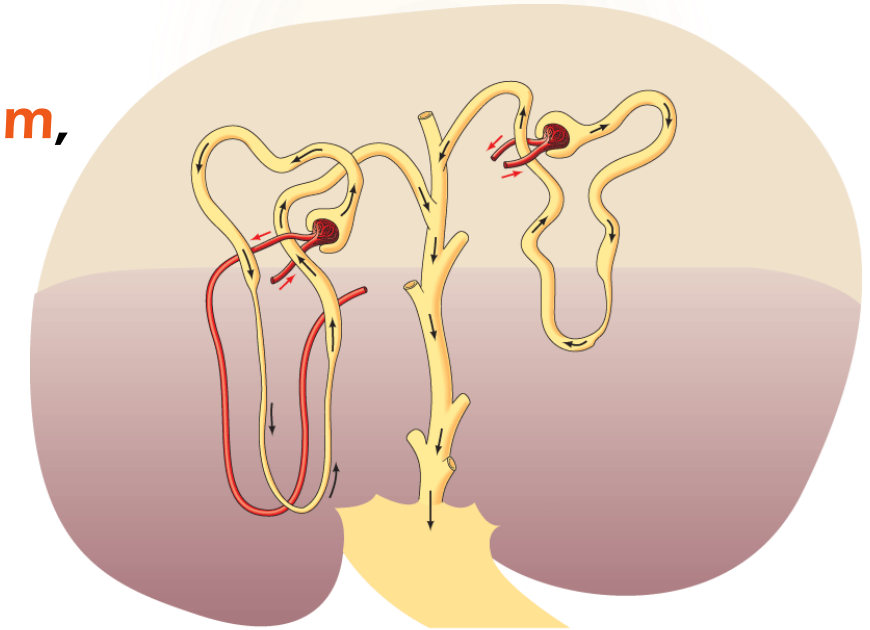
- The Kidney Maintains Water Balance
  - In normal condition: 99% of filtered H_2O reabsorbs
  - A water-deprived dog can concentrate urine up to 2000 mOsmol/kg H_2O
  - In water overload condition: dog can excrete hypotonic urine as low as 100 mOsmol/kg H_2O
- The Proximal Tubule Reabsorbs More Than 60% of Filtered Water
  - Na^+,K^+-ATPase pump actively transports Na^+
  - Water reabsorbs through the osmosis phenomenon
  - The high OP and low HP in the peritubular capillaries favor the movement of water and solute to the blood.



Water Balance

IV

- An elegant system has evolved in the mammalian kidney that allows excretion of either concentrated or diluted urine as needed.
- This system has three main components:
  1. Generation of a hypertonic medullary interstitium, which allows excretion of concentrated urine;
  2. Dilution of the tubule fluid by the thick ascending limb and the DCT, which allows excretion of dilute urine;
  3. Variability in the water permeability of the collecting duct in response to antidiuretic hormone (ADH, vasopressin), which determines the final urine concentration.



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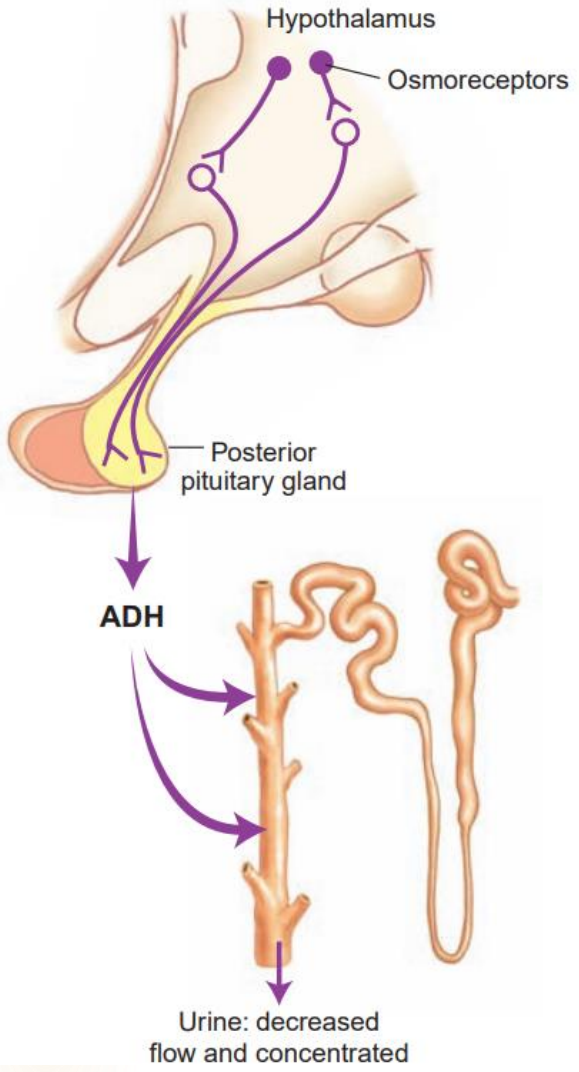
Medullary Hypertonicity

IV

- Excretion of concentrated wastes conserves water and thus reduces the volume of water that must be consumed to prevent dehydration.
- Two factors that are responsible for the formation of concentrated urine:
  - generation of a hypertonic medullary interstitium
  - enhanced water permeability in the collecting duct in the presence of ADH
- The hypertonicity of the medullary interstitium is produced and maintained primarily by
  1. the reabsorption of osmotically active substances by tubules in the medulla
  2. the removal of water from the medullary interstitium by the vasa recta.

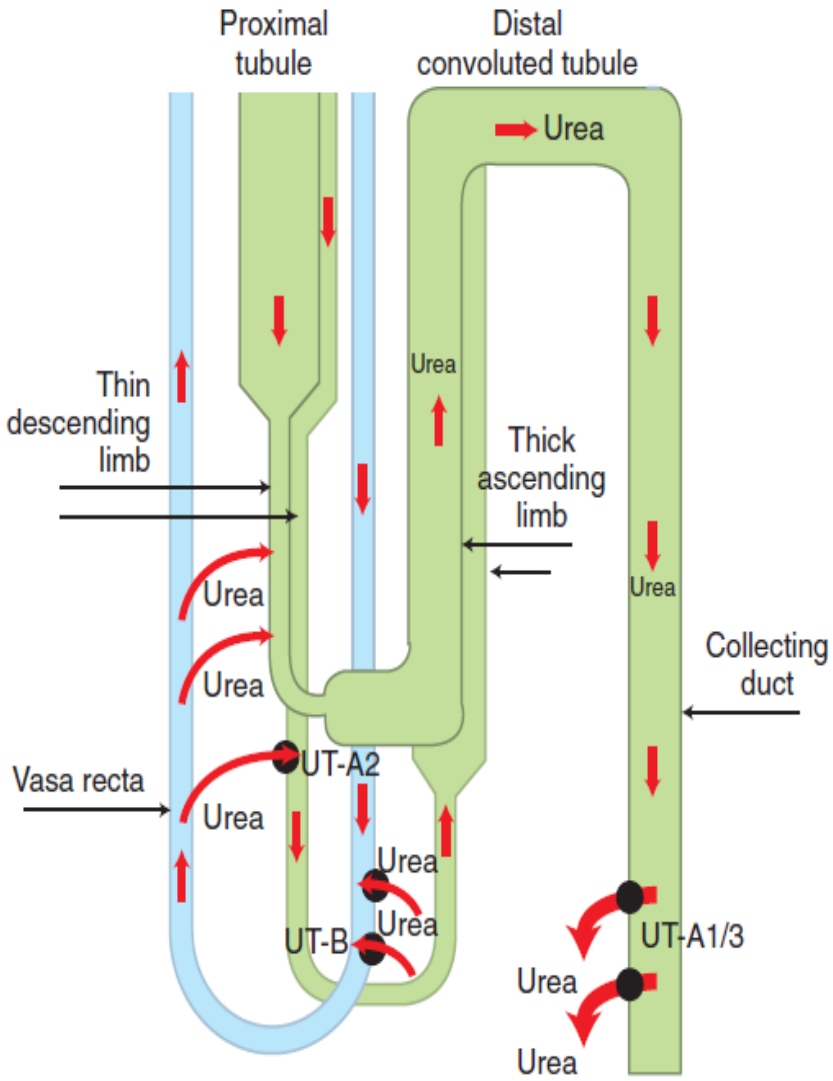


Medullary Hypertonicity

IV

1. Urea Reabsorption and Recycling:

- The terminal IMCD is highly permeable to urea. Thus, urea remains in the tubule fluid until it reaches the terminal IMCD deep in the medulla.
  - Filtered urea is reabsorbed in the IMCD by facilitated diffusion.
  - Then diffuses down into the vasa recta.
  - Then diffuses out and returns into the thin limbs of Henle's loop.
  - Urea reabsorption in the IMCD is enhanced by ADH.
- Accumulation of urea in the medullary Interstitium:
  - Make medullary interstitum hypertonic
  - Promotes water reabsorption

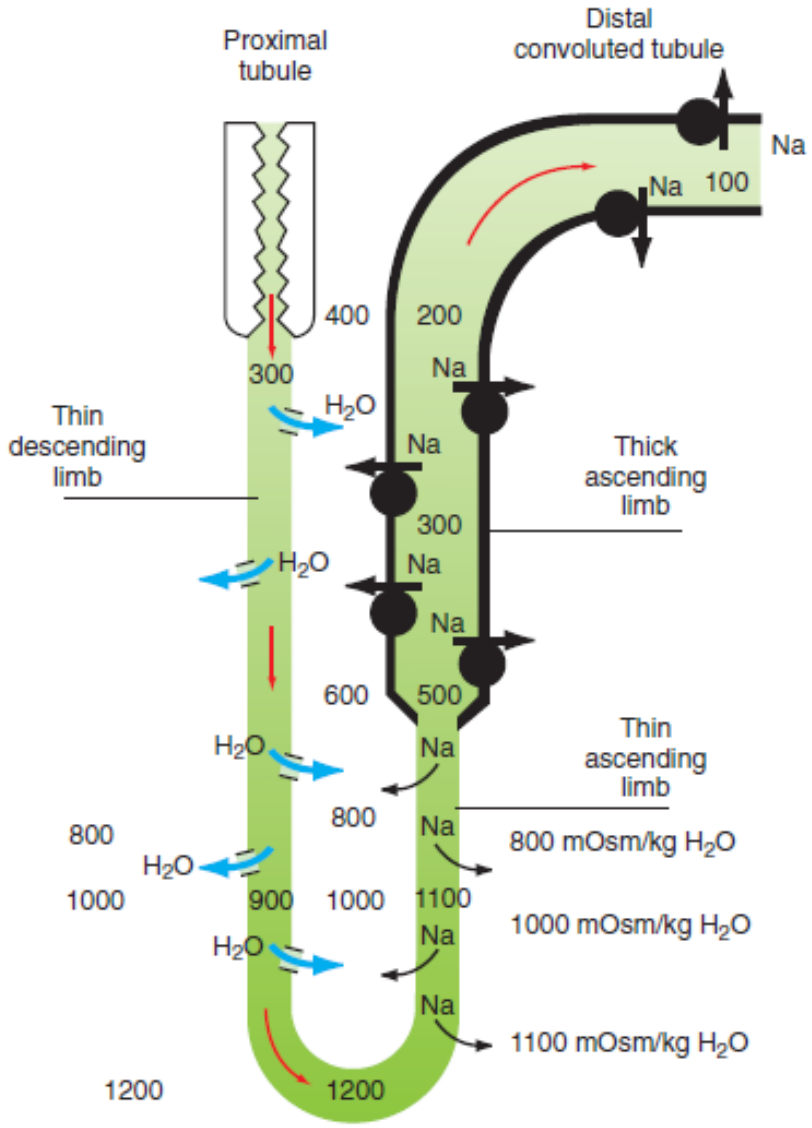


Medullary Hypertonicity

IV

2. The Countercurrent Mechanism in Henle's loop

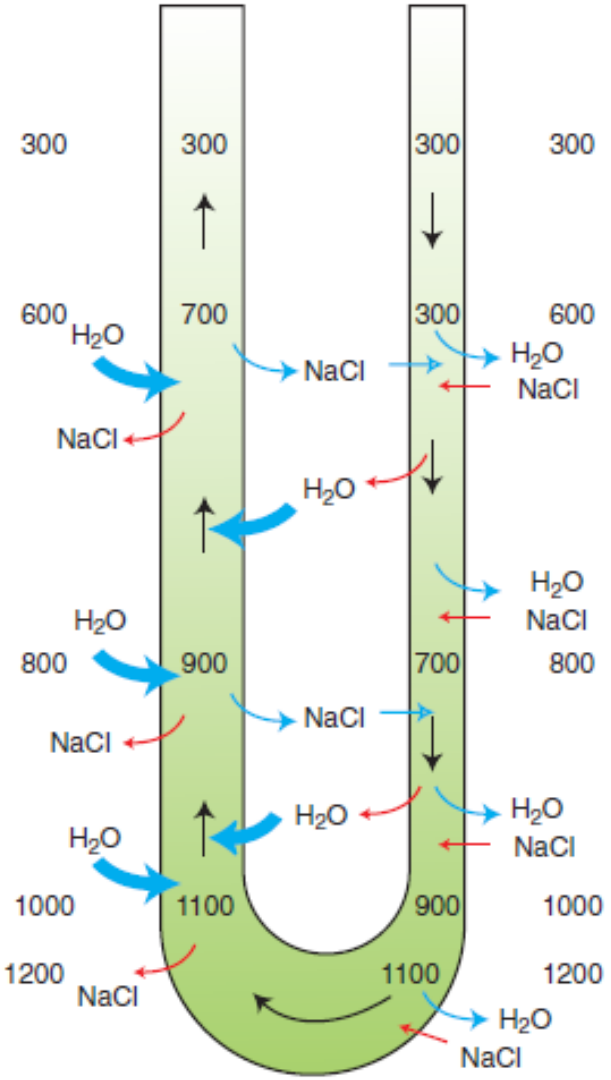
- The thick ascending limb of Henle's loop actively transports NaCl into the interstitium without water
  - Diluting the tubule fluid and raising the medullary interstitial tonicity
- Thin descending limbs are impermeable to Na^+ but are permeable to H_2O
- Ascending thin limb is impermeable to water but is permeable to sodium, the gradient draws luminal sodium into the interstitium.
- The countercurrent arrangement preserve the medullary interstitial concentration gradient or medullary hypertonicity.



Medullary Hypertonicity

IV

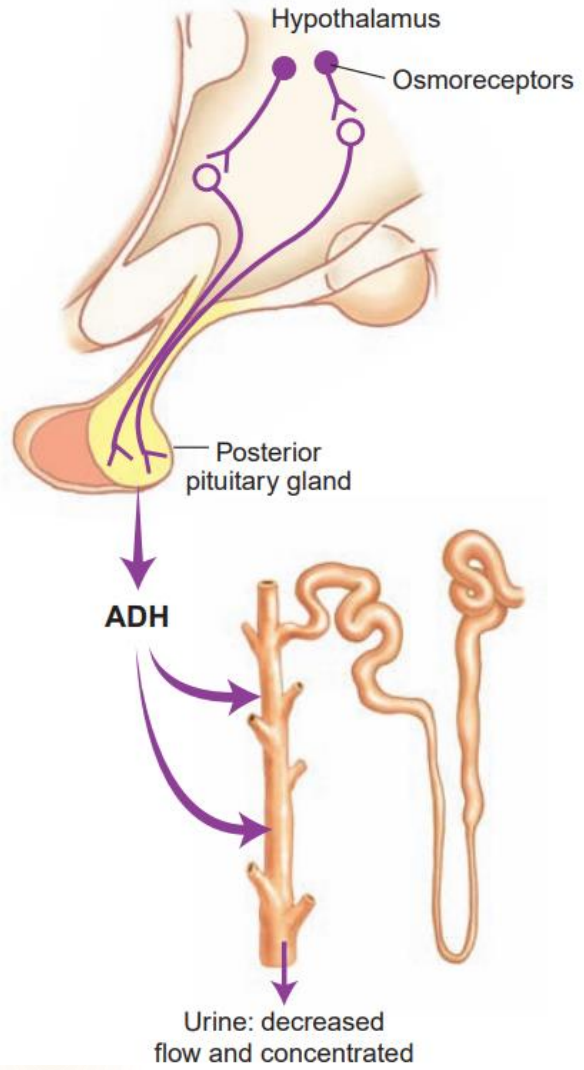
- **Countercurrent Exchange in the Vasa Recta vessels**
- This mechanism removes water from the medullary interstitium without reducing medullary interstitial hypertonicity.
  - The walls of the vasa recta are permeable to water and salt (NaCl)
  - Plasma osmolality progressively increases entering the inner medulla.
  - Water diffuses out and NaCl enters the blood through concentration gradient in the descending vasa recta
  - In the ascending vasa recta, as the vessel passes through hypotonic interstitum, NaCl leaves and H_2O enters the blood
- There is net removal of water from the interstitium because of the relatively low HP and relatively high OP in the vasa recta.



Determining the Final Urine Osmolality

IV

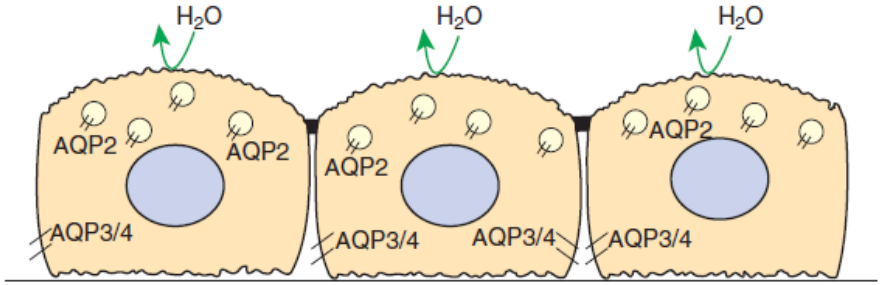
- The generation of medullary hypertonicity and dilution of the tubule fluid in the distal nephron segments set the stage for the elimination of either concentrated or dilute urine, as warranted by the fluid volume status, plasma tonicity, and blood pressure of the animal.
- The water permeability of the collecting duct, which is regulated by ADH, determines the osmolality of the excreted urine.



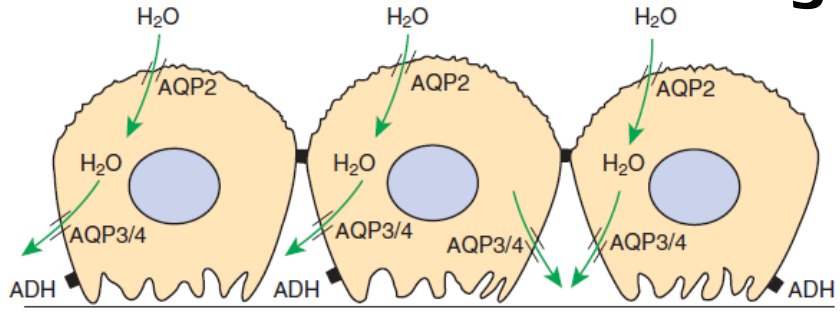
Determining the Final Urine Osmolality

IV

- During water overload, ADH is absent, and the collecting duct is relatively impermeable to water. The tubule fluid delivered by the distal convoluted tubule remains hypotonic because the water is retained in the collecting duct lumen. Thus, in the absence of ADH, dilute urine is formed, and excess water is excreted



- When ADH is present, water flows from the dilute tubule fluid into the cell and then the interstitium down the concentration gradient, producing structural alterations that include cell swelling and dilation of the intercellular spaces



Section 5:

Acid-Base Balance

Acid-Base Balance

V

Definitions:

- Acid: substance that can donate hydrogen ions
  - hydrochloric acid (HCl) dissociates in water to form hydrogen (H^+) and chloride (Cl^-) ions
- Base: substance that can accept hydrogen ions
  - the bicarbonate ion ($HCO3^-$), is a base because it can combine with H+ to form carbonic acid (H_2CO_3).
- Most of the body's acids and bases are weak acids and bases
  - the most important being H_2CO_3, which is a weak acid derived from carbon dioxide (CO_2), and bicarbonate ($HCO3^-$), which is a weak base.
- Reduced pH (elevated hydrogen ion concentration) equals acidemia)
- Increased pH (reduced hydrogen ion concentration equals alkalemia)
- Process that lowers pH = acidosis
- Process that increases pH = alkalosis

Acid-Base Balance

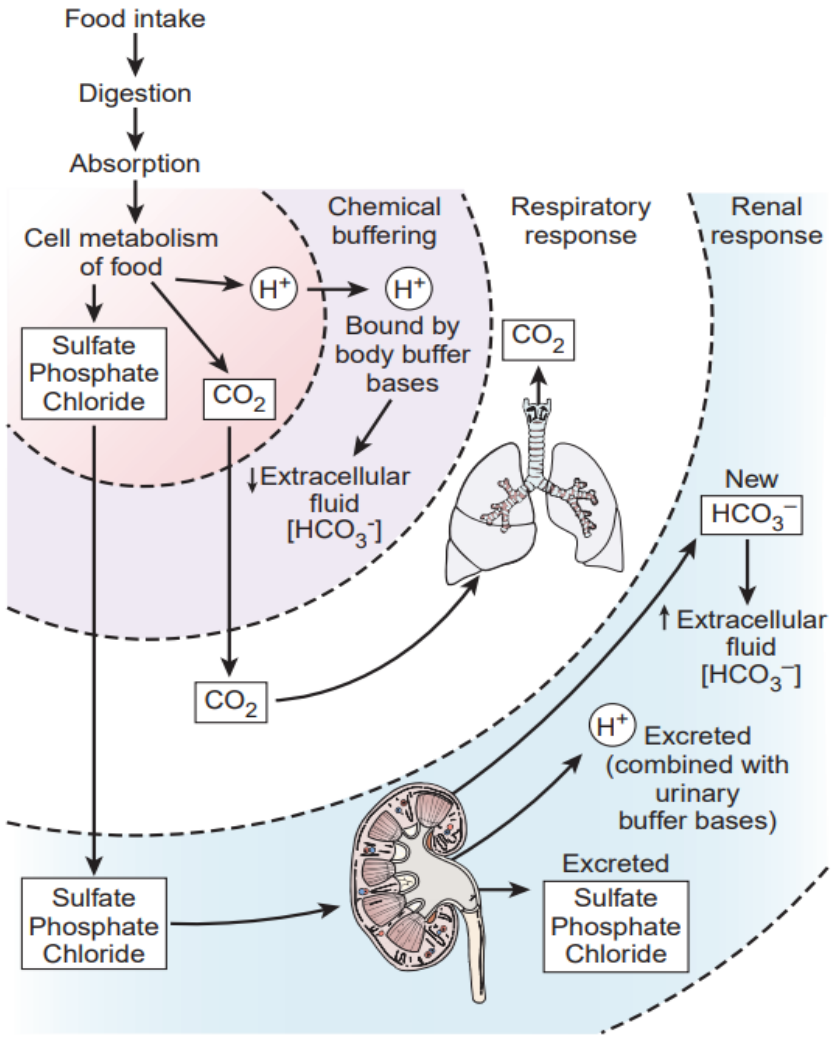
V

- Acids and bases exist as buffer pairs or systems—a mixture of a weak acid and its conjugate base or a weak base and its conjugate acid.
- When an acid (HA) is added to water, it dissociates reversibly to form H+ and its conjugate anion (A^-).
  - An example of this is $HA \longrightarrow H^+ + A^-$.
- The degree to which an acid dissociates and acts as an H^+ donor determines whether it is a strong or weak acid.
  - Strong acids, such as sulfuric acid, dissociate completely. Weak acids, such as acetic acid, dissociate only to a limited extent. The same is true of a base and its ability to dissociate and accept an H+.
- Specifically, pH represents the negative logarithm (log_{10}) of the H^+ concentration expressed in milliequivalents per liter (mEq/L). Thus, a pH value of 7.0 implies an H^+ concentration of 10^{-7} (0.0000001 mEq/L).
  - Because the pH is inversely related to the H^+ concentration, a low pH indicates a high concentration of H^+, and a high pH indicates a low concentration.

Acid-Base Balance

V

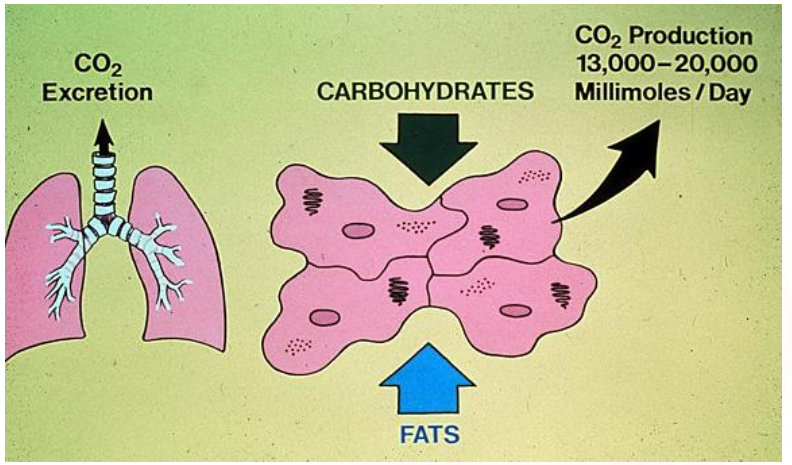
- Acids are continuously generated as by-products of metabolic processes.
- Physiologically, these acids fall into two groups:
  - the volatile acid H_2CO_3 and all other nonvolatile or fixed acids.
- The difference between the two types of acids arises because H_2CO_3 is in equilibrium with CO2 ($H_2CO_3 \leftrightarrow CO_2 + H_2O$), which is volatile and leaves the body by way of the lungs. Therefore, the lungs and their capacity to exhale CO_2 determine H_2CO_3 concentration.
- The lungs do not eliminate fixed or nonvolatile acids (e.g., sulfuric, hydrochloric, phosphoric). Instead, they are buffered by body proteins or extracellular buffers, such as $HCO3^-$, and then eliminated by the kidney

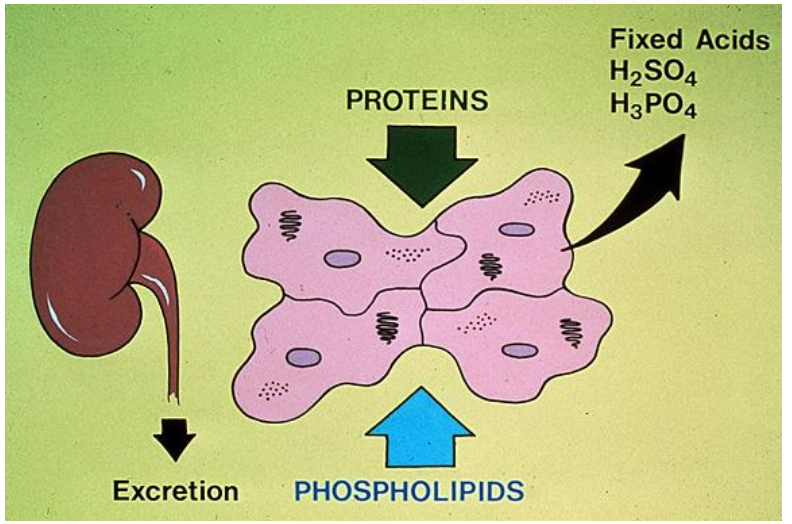


Regulation of pH

V

- Normal blood pH : 7.4 (7.35-7.45)
- The pH of body fluids (or change in H^+ concentration) is regulated by three major mechanisms:
  1. Chemical buffer systems of the body fluids, which immediately combine with excess acids or bases to prevent large changes in pH
  2. The lungs, which control the elimination of CO_2
  3. The kidneys, which eliminate H+ and both reabsorb and generate new HCO^{3-}





1. Chemical Buffer Systems

V

- A buffer system consists of a weak base and its conjugate acid pair or a weak acid and its conjugate base pair.
- In the process of preventing large changes in pH, the system trades a strong acid for a weak acid or a strong base for a weak base.
- The three major buffer systems that protect the pH of body fluids are
  - 1a - The bicarbonate buffer system
  - 1b - Proteins
  - 1c - The transcellular H^+/K^+ exchange system

Buffer Pair	H^+ Acceptor	H^+ Donor
Bicarbonate (ECFV)	HCO_3^-	H_2CO_3
Phosphate (urine)	$H_2PO_4^{2-}$	H_2PO_4
Ammonia (urine)	NH_3	NH_4^+
Protein	Protein	Protein

Chemical Buffer Systems

V

- Bone represents an additional source of acid–base buffering.
- Excess H^+ ions can be exchanged for Na^+ and K^+ on the bone surface, and dissolution of bone minerals with release of compounds such as sodium bicarbonate ($NaHCO_3$) and calcium carbonate ($CaCO_3$) into the ECF can be used for buffering excess acids.
  - It has been estimated that as much as 40% of buffering of an acute acid load takes place in bone.
- The role of bone buffers is even greater in the presence of chronic acidosis.
- The consequences of bone buffering include demineralization of bone and predisposition to development of kidney stones because of increased urinary excretion of calcium. Animals with chronic kidney disease are at particular risk for reduction in bone calcium due to acid retention.

1a - Bicarbonate Buffer System

- The HCO_3^- buffer system, which is the most powerful ECF buffer, uses H_2CO_3 as its weak acid and a bicarbonate salt such as sodium bicarbonate ($NaHCO_3$) as its weak base.
- It substitutes the weak H_2CO_3 for a strong acid such as hydrochloric acid ($HCl + NaHCO_3 \rightarrow H_2CO_3 + NaCl$) or the weak bicarbonate base for a strong base such as sodium hydroxide ($NaOH + H_2CO_3 \rightarrow NaHCO_3 + H_2O$).
- The bicarbonate buffer system is a particularly efficient system because its components can be readily added or removed from the body.
- Metabolism provides an ample supply of CO_2, which can replace any H_2CO_3 that is lost when excess base is added, and CO_2 can be readily eliminated when excess acid is added. Likewise, the kidney can conserve or form new HCO_3^- when excess acid is added, and it can excrete HCO_3^- when excess base is added.

$$(HCO3^- + H^+ \leftrightarrow H_2CO_3 \leftrightarrow CO_2 + H_20)$$

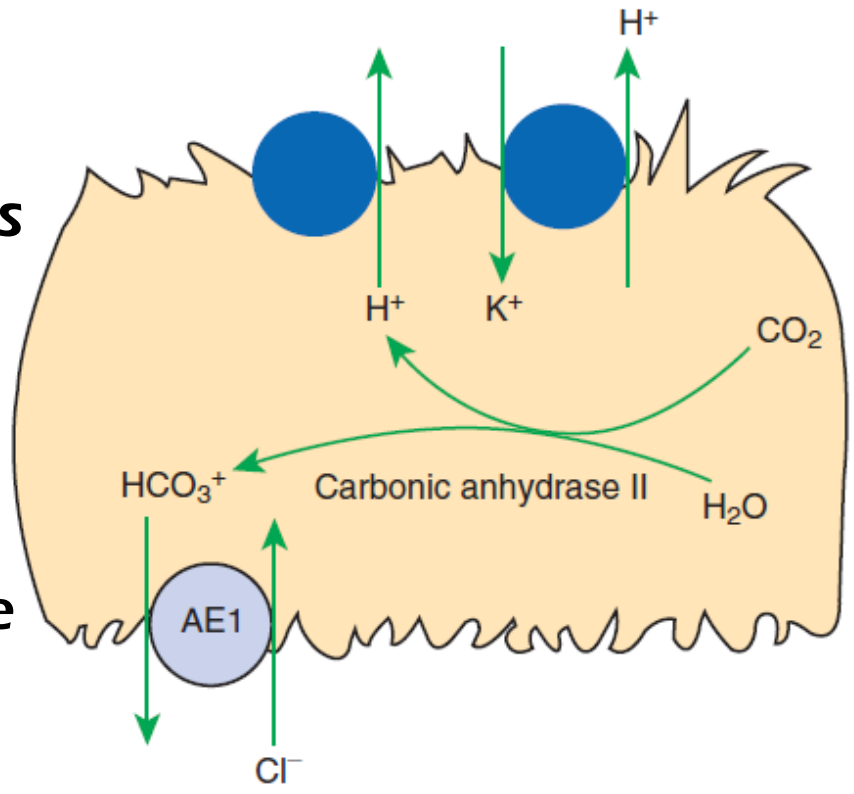
1b - Protein Buffer Systems

- Proteins are the largest buffer system in the body.
- Proteins are amphoteric, meaning that they can function either as acids or bases. They contain many ionizable groups that can release or bind H^+.
- The protein buffers are largely located in cells, and H^+ ions and CO_2 diffuse across cell membranes for buffering by intracellular protein
- Albumin and plasma globulins are the major protein buffers in the vascular compartment.

Buffer systems (primarily bicarbonate)	ECF	Immediate ($HCO_3^- + H^+ \leftrightarrow H_2CO_3 \leftrightarrow CO_2 + H_2O$)
Increased rate and depth of breathing to decrease CO_2	Lungs	Minutes to hours
Buffer systems (phosphate, bicarbonate, protein)	Intracellular fluid	2-4 hours
Hydrogen ion excretion, bicarb reabsorption, & bicarb generation	Kidneys	Hours to days

1c - Hydrogen–Potassium Exchange buffer V

- The transcompartmental exchange of H^+ and potassium ions (K^+) provides another important system for regulation of acid–base balance.
- Both ions are positively charged, and both ions move freely between the ICF and ECF compartments.
  - When excess H^+ is present in the ECF, it moves into the ICF in exchange for K^+, and when excess K^+ is present in the ECF, it moves into the ICF in exchange for H^+ .
  - Thus, alterations in potassium levels can affect acid–base balance, and changes in acid–base balance can influence potassium levels.



Buffer Mechanisms in Tubular fluid

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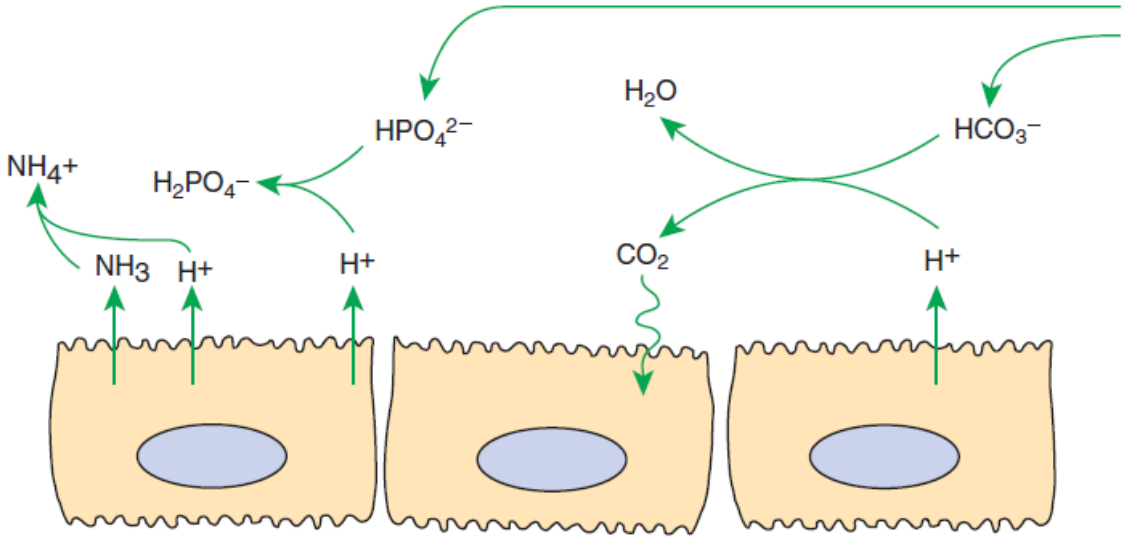
- In the proximal tubule, buffering by filtered bicarbonate (HCO_3^-) predominates because of the relatively high concentration of HCO_3^-
- In the cortical collecting duct, buffering by filtered, nonbicarbonate buffers, such as HPO_4^{2-}, predominates.
- NH_3 secretion in the collecting duct, in basal conditions and particularly in response to acidosis, increases luminal buffering in the collecting duct, which enhances acid secretion.



Renal Ammonia Metabolism

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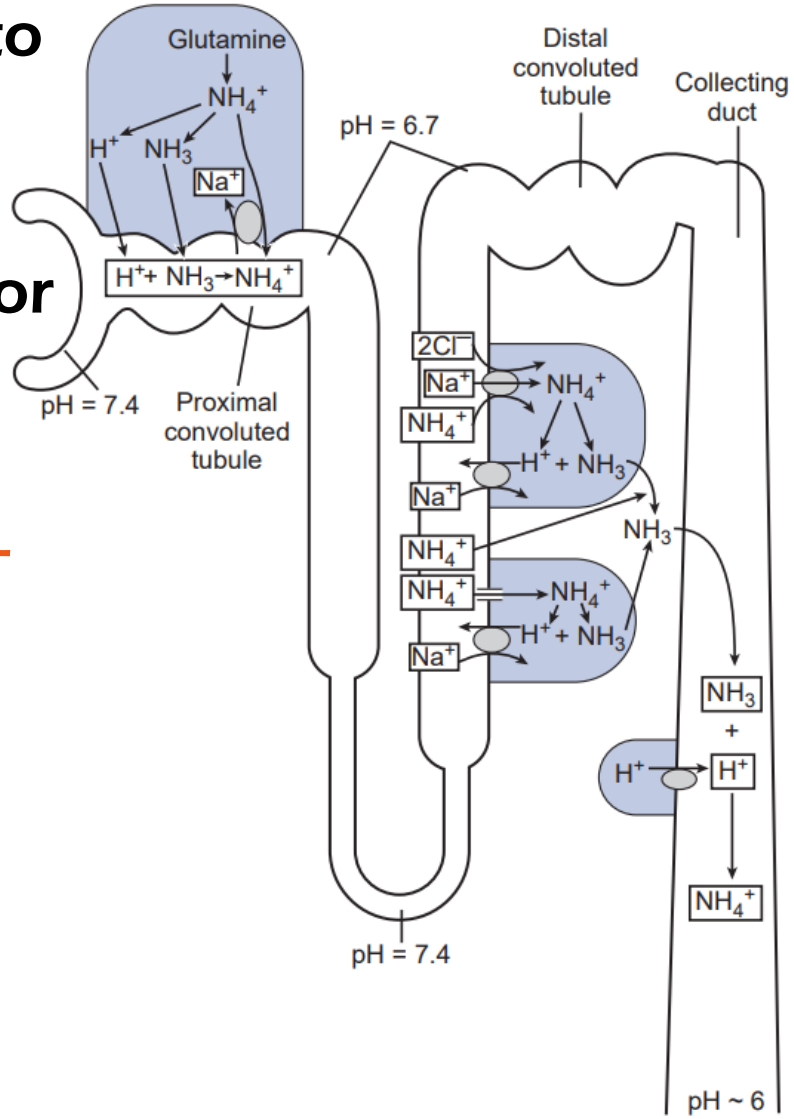
- In the proximal tubule, glutamine is catabolized to generate ammonium ion (NH_4^+) and bicarbonate (HCO_3^-)
- $NH4^+$ is secreted into the lumen by substitution for H^+ on the Na^+/H^+ exchanger
- Ammonium ion recycles in the thick ascending limb, by substitution for K^+ on the $Na^+/K^+,2Cl^-$ co-transporter in the apical membrane
- NH_4^+ is transported by specific ammonia transporters in the collecting duct and by substitution of NH_4^+ for K^+ on Na^+,K^+-ATPase in the inner medullary collecting duct, and is excreted in the urine.



2. Respiratory Control Mechanisms

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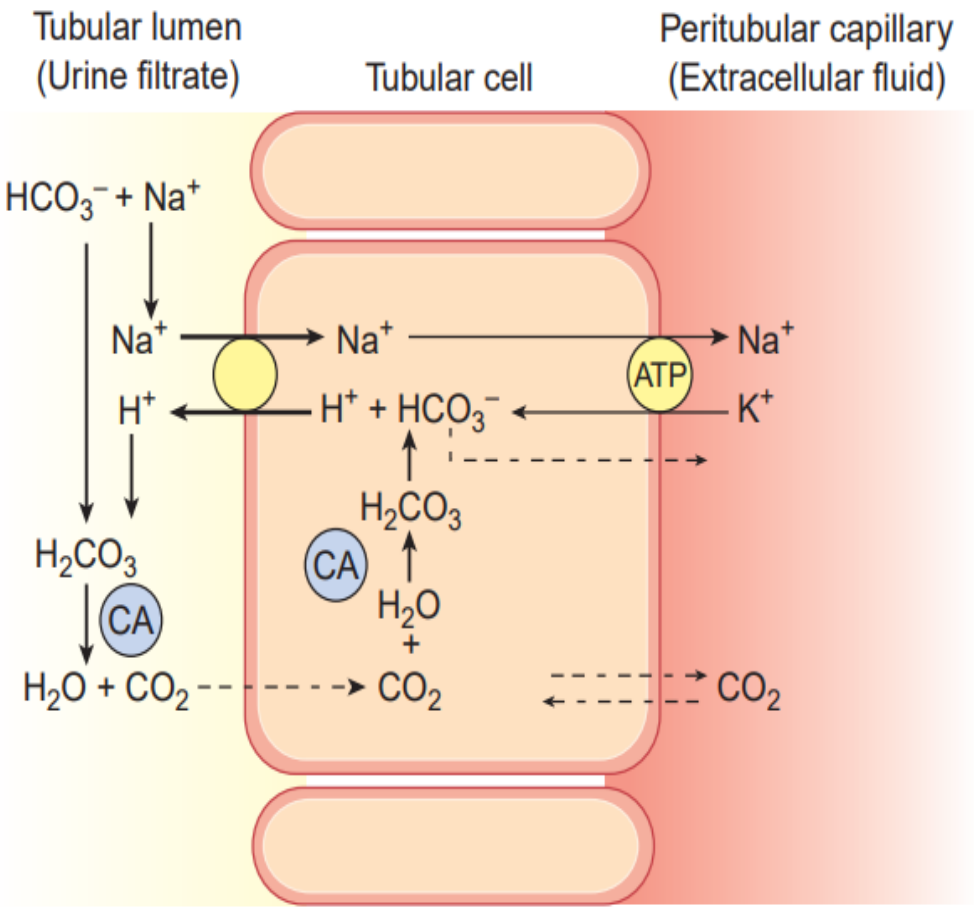
- The second line of defense against acid–base disturbances is the control of extracellular CO_2 by the lungs
  - Increased ventilation → PCO_2 ↓
  - Decreased ventilation → PCO_2 ↑
- Chemoreceptors in the brain stem and the peripheral chemoreceptors in the carotid and aortic bodies sense changes in PCO_2 and pH and alter the ventilatory rate.
- When the H^+ concentration is above normal, the respiratory system is stimulated resulting in increased ventilation
  - Although the respiratory response is rapid, it does not completely return the pH to normal.

3. Renal Control Mechanisms

- The kidneys play three major roles in regulating acid–base balance:
  a. Excretion of H^+ from fixed acids that result from protein and lipid metabolism
  b. Potassium–Hydrogen Exchange which is a response to the concentration of potassium in the plasma by regulation of H^+ secretion to the urine
  c. Chloride–Bicarbonate Exchange in response to chloride ion depletion
- These mechanisms begin to adjust the pH in hours and continue to function for days until the pH has returned to normal or near-normal range

3a - Excretion of H^+ From Fixed Acids

- The process begins with a coupled Na^+/H^+ transport system in which H^+ is secreted into the tubular fluid and Na^+ is reabsorbed into the tubular cell
- The secreted H^+ combines with filtered HCO_3^- to form H_2CO_3 . The H_2CO_3 then decomposes into CO_2 and H_2O, catalyzed by a brush border carbonic anhydrase
- Inside the cell, the reactions occur in reverse to form HCO_3^- and H^+. The HCO_3^- is then reabsorbed into the blood along with Na^+ , and the newly generated H^+ is secreted into the tubular fluid to begin another cycle.



3b - Potassium–Hydrogen Exchange

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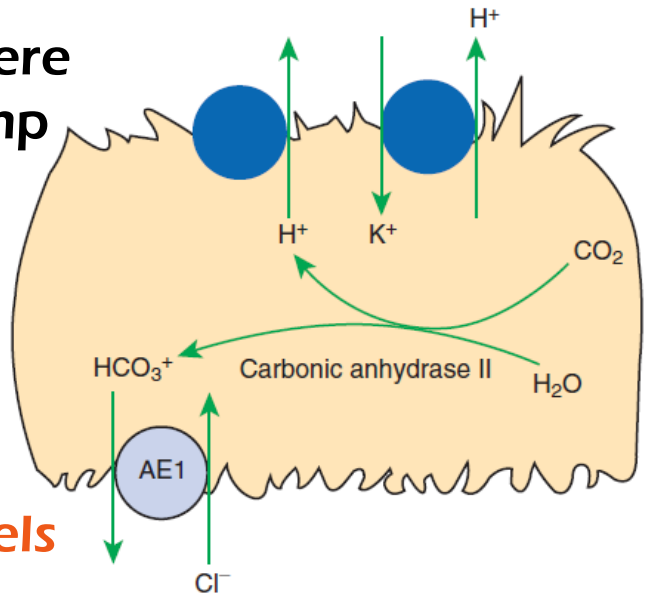
- Plasma K+ levels influence renal elimination of H+ and vice versa.
- Hypokalemia is a potent stimulus for H+ secretion and HCO3 – reabsorption.
  - When plasma K+ levels fall, there is movement of K+ from the ICF into the ECF compartment and a reciprocal movement of H+ from the ECF into the ICF compartment.
  - A similar process occurs in the distal tubules of the kidney, where the H+ /K+ -adenosine triphosphatase (ATPase) exchange pump actively reabsorbs K+ as well as secretes H+
- Hyperkalemia has the opposite effect.
- Plasma K+ levels are similarly altered by acid–base balance.
  - Acidosis tends to increase H+ elimination and decrease K+ elimination, with a resultant increase in plasma potassium levels
  - Alkalosis tends to decrease H+ elimination and increase K+ elimination, with a resultant decrease in plasma K+ levels



3c - Chloride–Bicarbonate Exchange

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- Chloride–bicarbonate anion exchange occurs in association with Na^+ reabsorption to regulate the concentration of HCO_3^-
- Normally, Cl^- is absorbed along with Na^+ throughout the tubules.
- In situations of volume depletion due to vomiting and chloride depletion, the kidneys are forced to substitute HCO_3^- for the Cl^- anion, thereby increasing its absorption of HCO_3^- .
  - Hypochloremic alkalosis refers to an increase in pH induced by excess HCO_3^- reabsorption due to a decrease in Cl^- levels,
  - hyperchloremic acidosis refers to a decrease in pH because of decreased HCO_3^- reabsorption due to an increase in Cl^- levels.

Acid-Base Balance Disorders

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Metabolic Disorders:

- Processes that directly alter bicarbonate concentration
  - Metabolic acidosis: decreased bicarbonate
  - Metabolic alkalosis: increased bicarbonate

Respiratory Disorders:

- Processes that directly alter CO_2
  - Respiratory acidosis: increased CO_2
  - Respiratory alkalosis: decreased CO_2

Buffer effect:

- slightly increased HCO_3 with respiratory acidosis.
- Slightly decreased HCO_3 with respiratory alkalosis.

V

Disorder	pH	HCO_3^-	pCO_2	Comment
Metabolic acidosis	↓	↓ (primary)	↓(compensatory)	All 3 markers go in same direction
Metabolic alkalosis	↑	↑ (primary)	↑(compensatory)	All 3 markers go in same direction
Resp. acidosis	↓	↑ (compensatory)	↑ (primary)	pH goes opp. other 2 markers
Resp. alkalosis	↑	↓ (compensatory)	↓ (primary)	pH goes opp. other 2 markers

Acid-Base Balance

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Good Luck