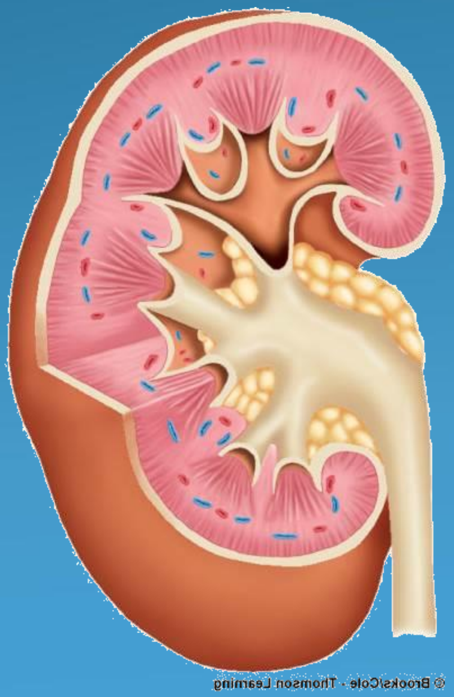
The Urinary System part two



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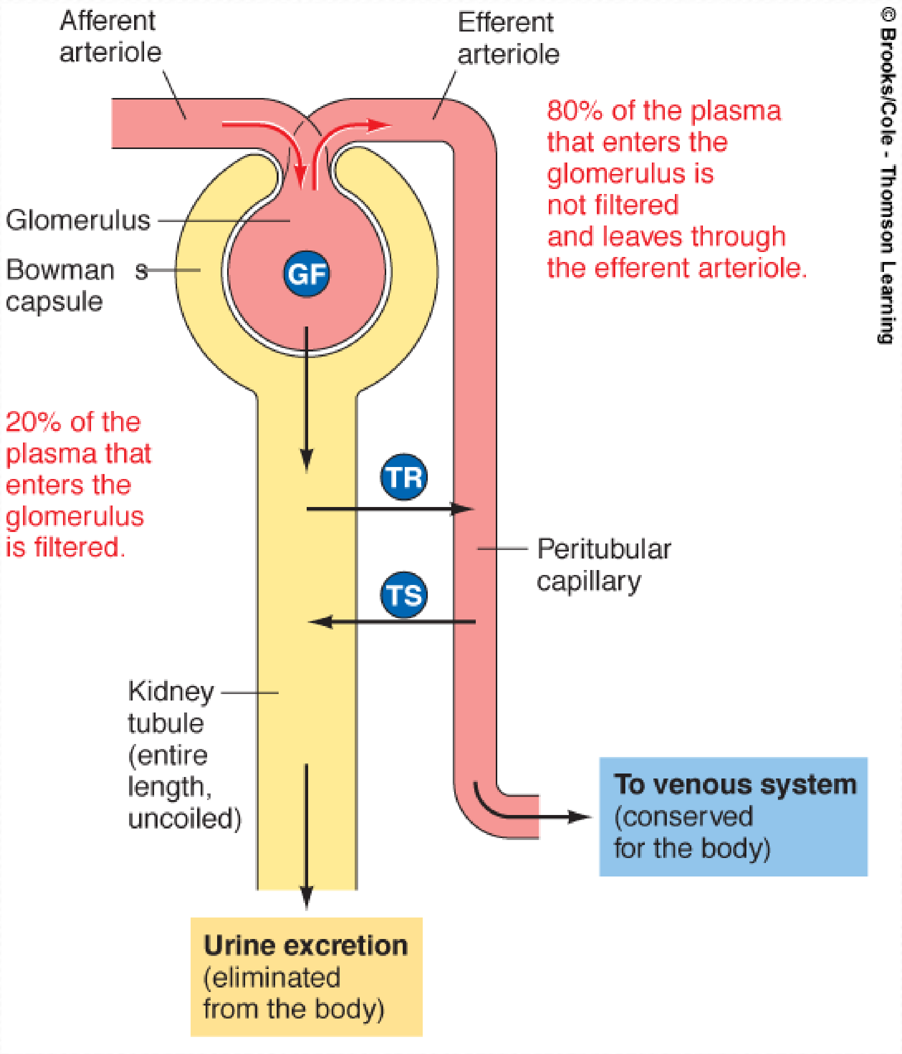
Tubular Reabsorption
Tubular Secretion

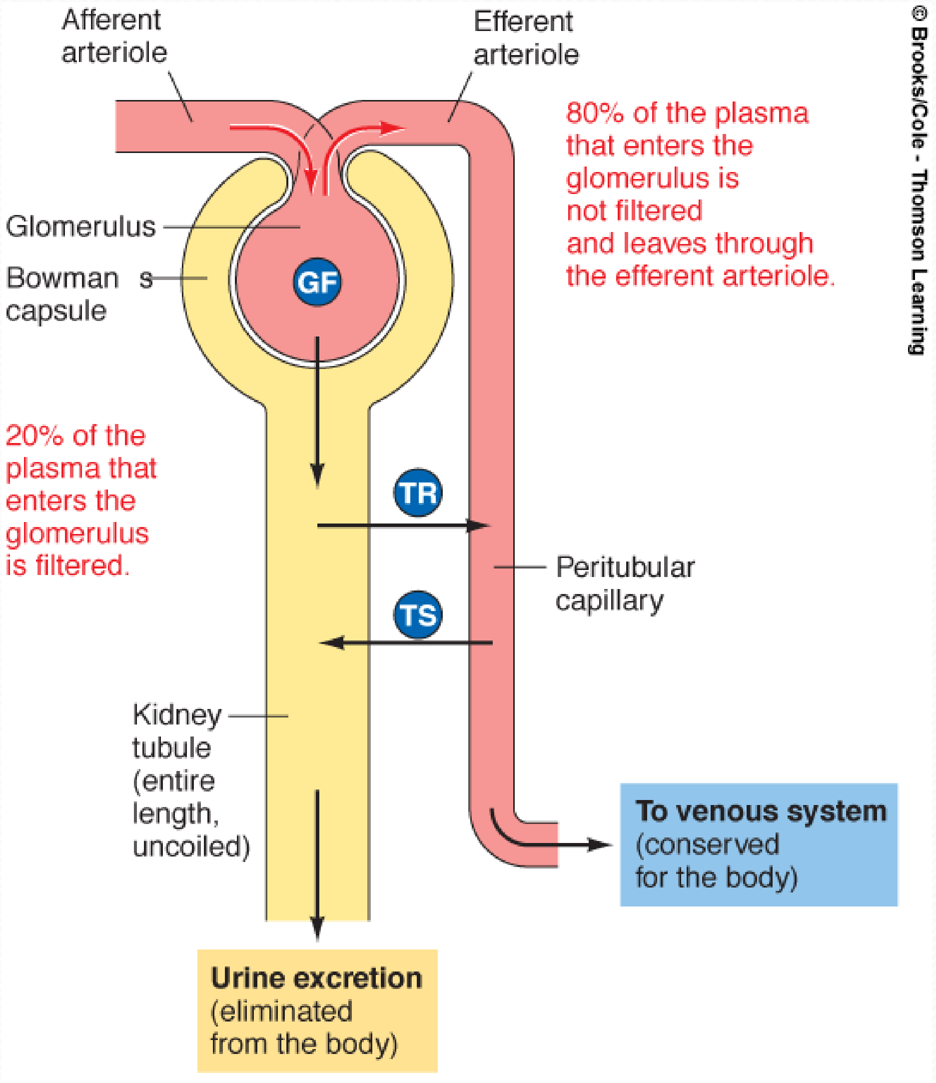
TUBULAR REABSORPTION

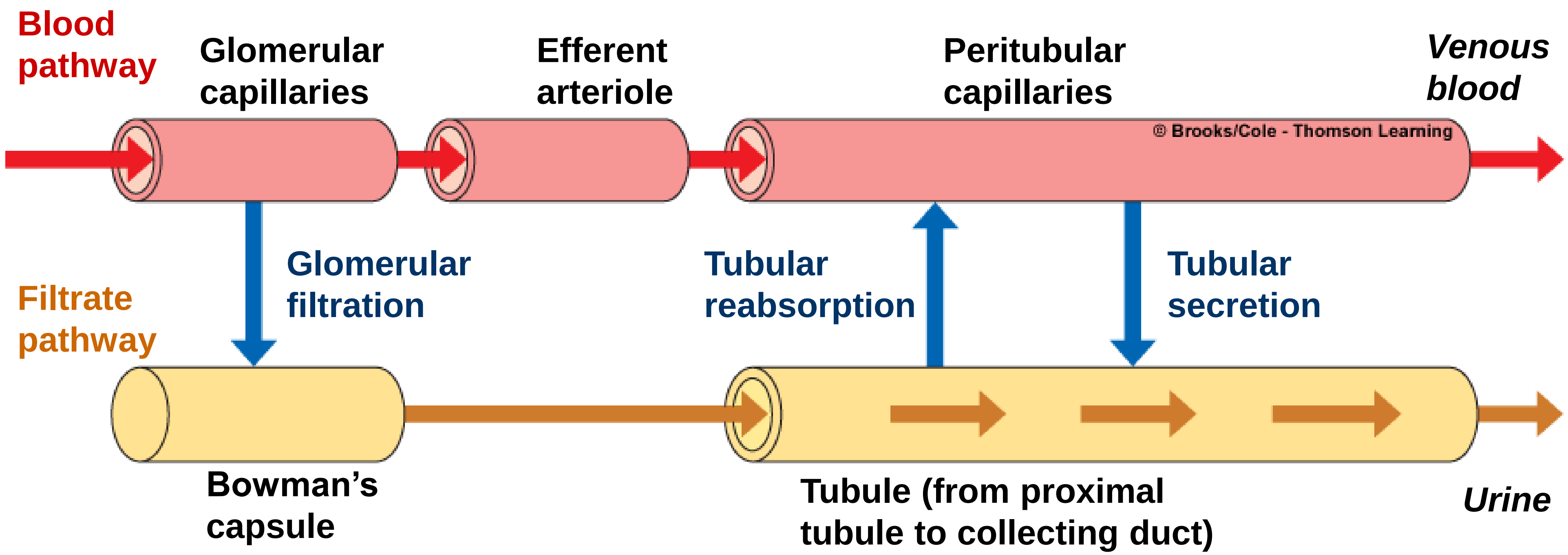
- By tubular reabsorption, filtered substances move from the inside of the tubular part of the nephron into the blood of the peritubular capillaries. The reabsorption rates of most substances are very high.



Basic Urinary processes

- **Tubular secretion** is a selective process by which substances from the peritubular capillaries enter the lumen of the nephron tubule.
- The 80% of the plasma not filtered passes into the efferent arteriole and through the peritubular capillaries.
- Urine excretion results from these three processes.





Blood pathway
Glomerular capillaries
Efferent arteriole
Peritubular capillaries
Venous blood
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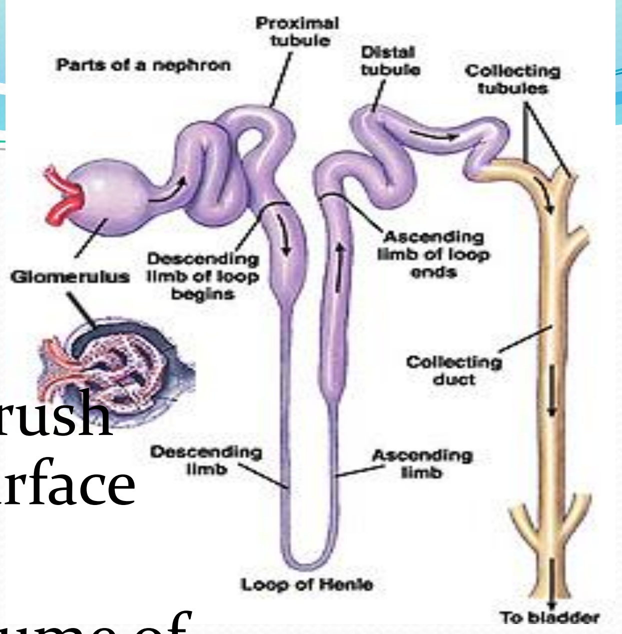
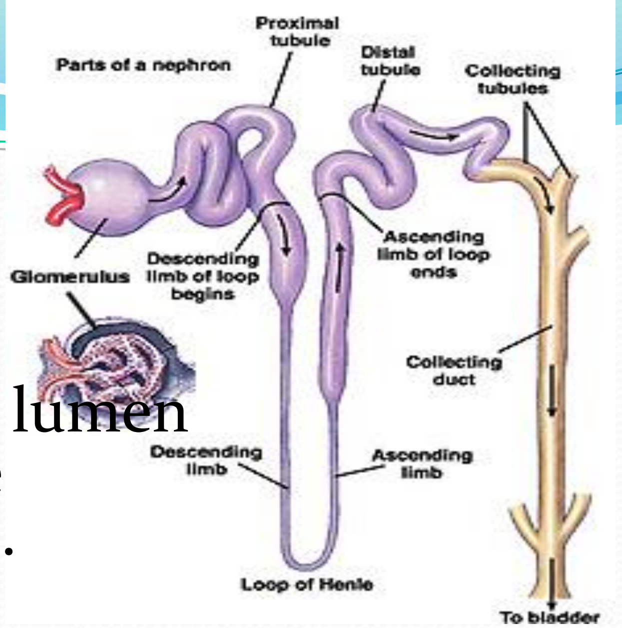
Glomerular filtration
Tubular reabsorption
Tubular secretion
Filtrate pathway
Bowman's capsule
Tubule (from proximal tubule to collecting duct)
Urine

Proximal tubule



- **<u>Morphology:</u>** 15 mm long and 55 µm in diameter; epithelium cells have a striate brush border (projections), which enlarge the surface for the reabsorption.
- **<u>Function:</u>** Reabsorption of the largest volume of solution filtered in glomerular apparatus.
  - 75 - 80 % water
  - Na^+, Cl^-, HCO_3^-, K^+, Ca^{2+}, Mg^{2+}, HPO_4^{2-}
  - Glucose
- **Results in ISOOSMOTIC SOLUTION**
- Fluid in the filtrate entering the proximal convoluted tubule is reabsorbed into the vasa recta, including approximately 2/3 of the filtered salt and water and all filtered organic solutes (primarily glucose and amino acids).

Proximal tubule



- This is driven by sodium transport from the lumen into the blood by the Na+/K+ ATPase in the basolateral membrane of the epithelial cells.
- Much of the mass movement of water and solutes occurs in between the cells through the tight junctions.
- The solutes are absorbed isotonically: the osmotic potential of the fluid leaving the proximal tubule is the same as that of the initial glomerular filtrate.
- Glucose and amino acids are absorbed actively via cotransport channels driven by the sodium gradient out of the nephron.

TUBULAR REABSORPTION-prox

- Approximately 99% of the filtered water and sodium, and 100% of glucose has been retrieved.

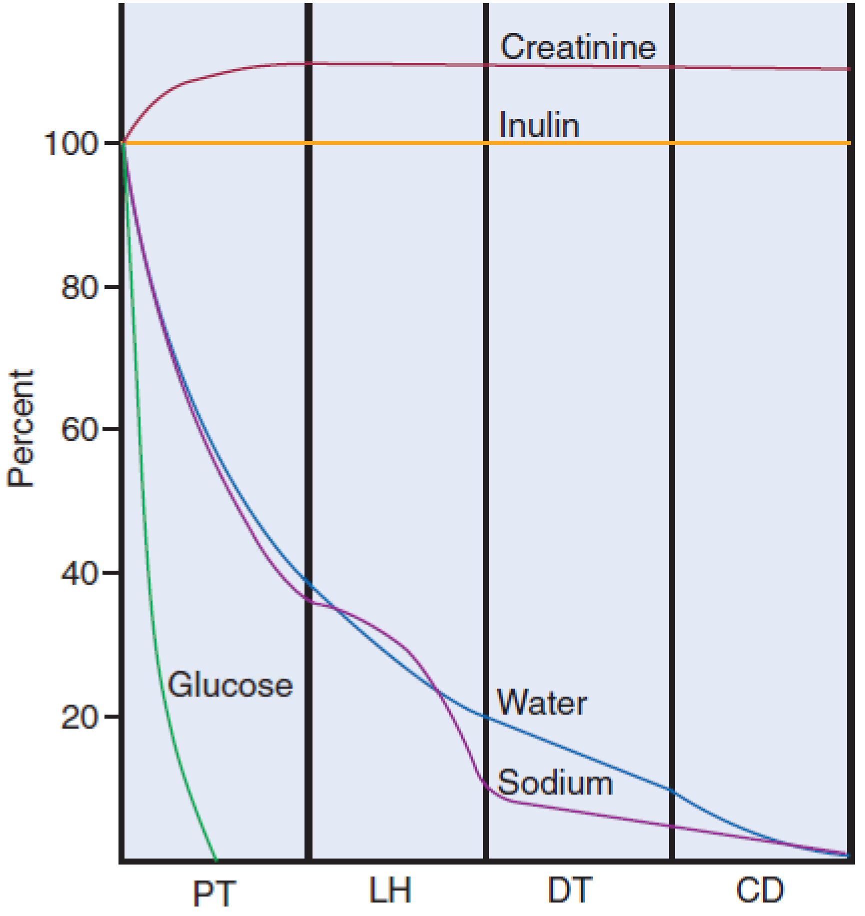
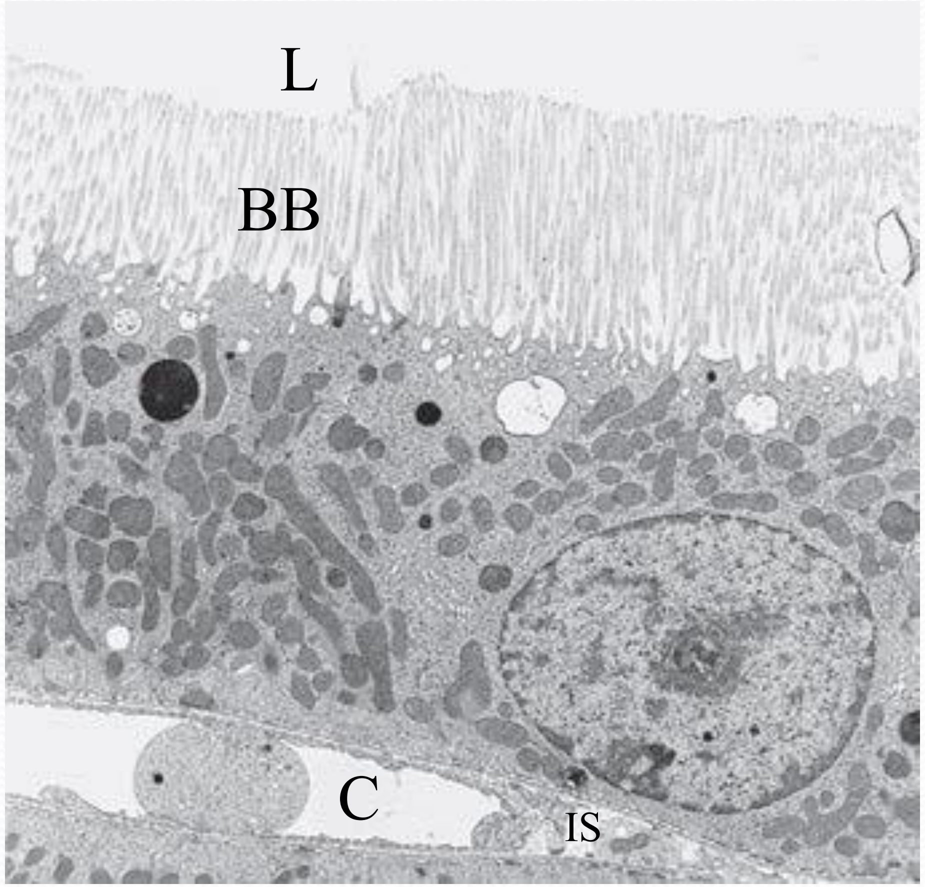


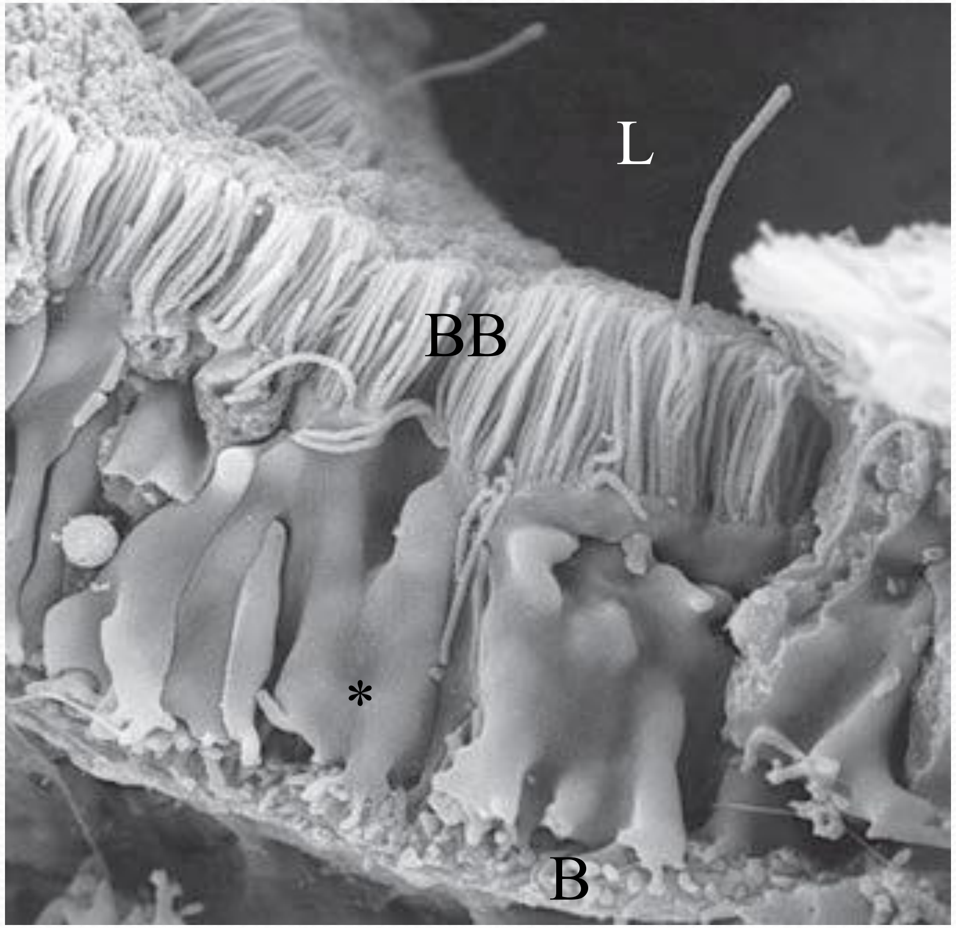
Illustration of the percentage of filtered substances $[(U_x/P_x) \times 100/(U_{inulin}/P_{inulin})]$ remaining in the tubule fluid in various tubule segments. In some species, creatinine is secreted by the proximal tubule and is excreted at a greater rate than the reference substance, inulin. *CD,* Collecting duct; *DT,* distal tubule; *LH,* loop of Henle; *PT,* proximal tubule.

TUBULAR REABSORPTION-prox



The brush border *(BB)* of the apical plasma membrane extends from the epithelial cells into the tubule lumen *(L),* where it is bathed by the tubule fluid. On the basal side of the cell is the interstitial space *(IS)* and the peritubular capillary *(C)*.

TUBULAR REABSORPTION-prox

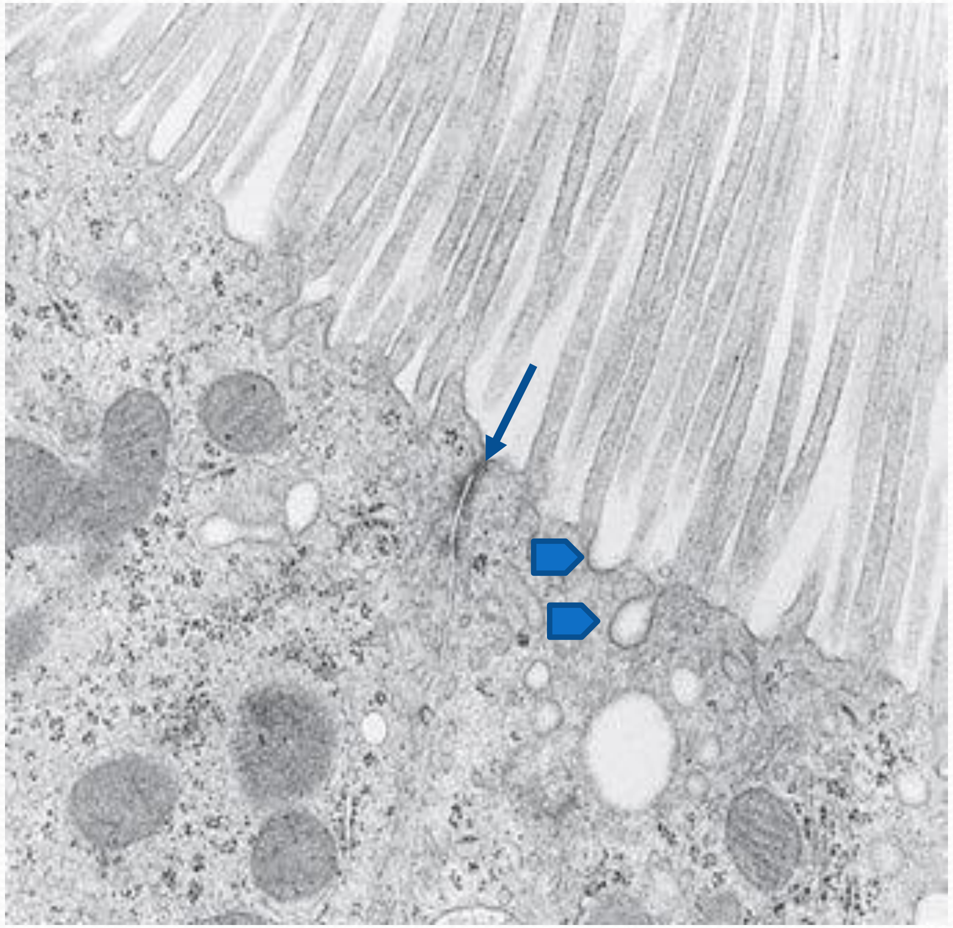


Scanning electron micrograph of rat proximal tubule, viewed from the lateral intercellular space. The lush brush border *(BB)* carpets the luminal aspect *(L)*. Lateral cellular processes *(asterisk)* interdigitate with those of neighboring cells. The surface of the basal plasma membrane *(B)* is amplified by extensive membrane infoldings, creating numerous processes called *micropedici* ("tiny feet").

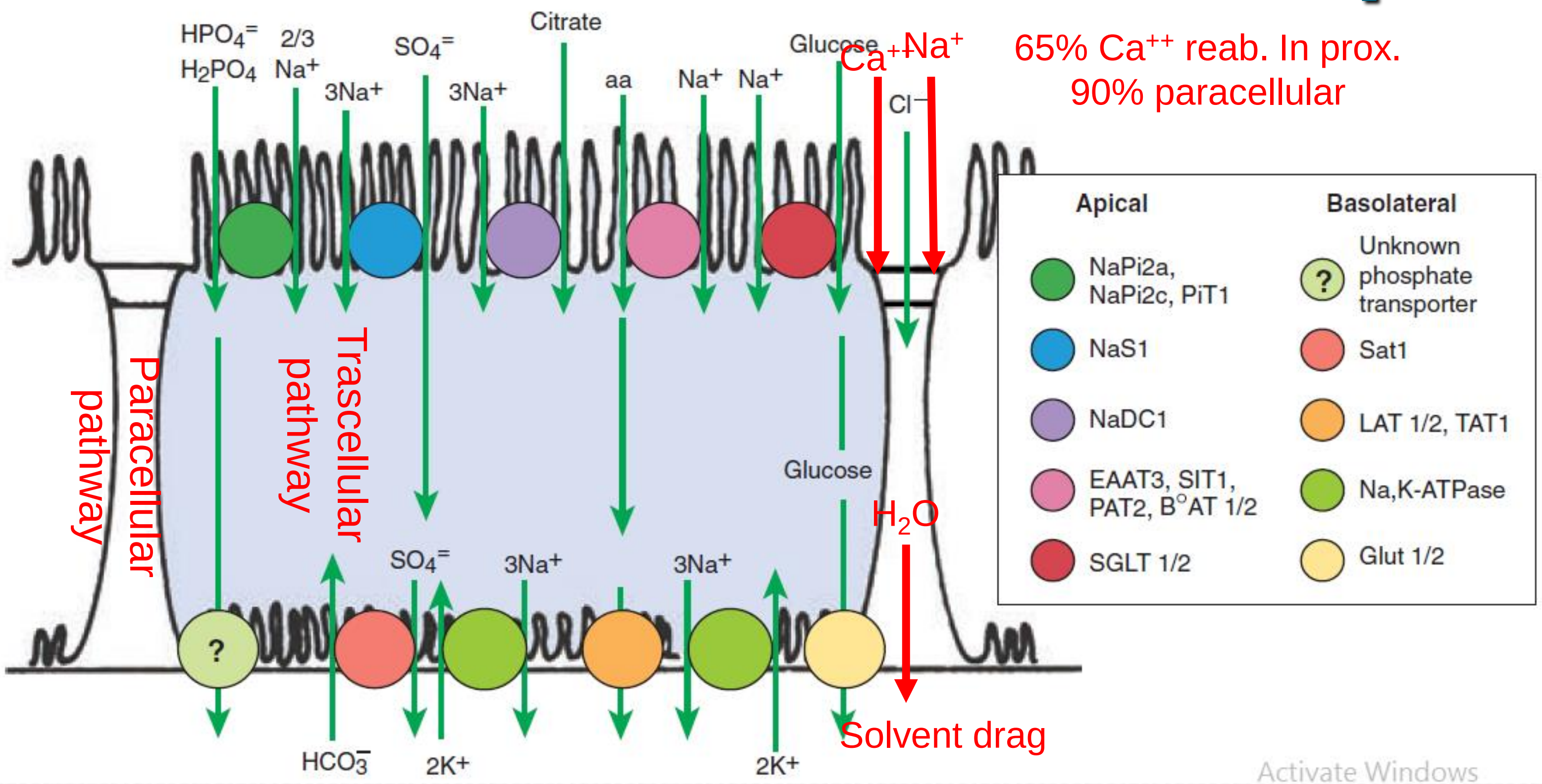
TUBULAR REABSORPTION-prox

Transmission electron micrograph of apical region of rat proximal tubule viewed in cross section. The zonula occludens *(arrow)* joins adjacent proximal tubule cells. The zonula occludens divides the apical plasma membrane from the basolateral plasma membrane and separates the tubule fluid from the fluid of the lateral intercellular space.

Also seen are coated pits *(arrowheads)* that contain the binding sites for substances reabsorbed by receptor-mediated endocytosis.



TUBULAR REABSORPTION-prox



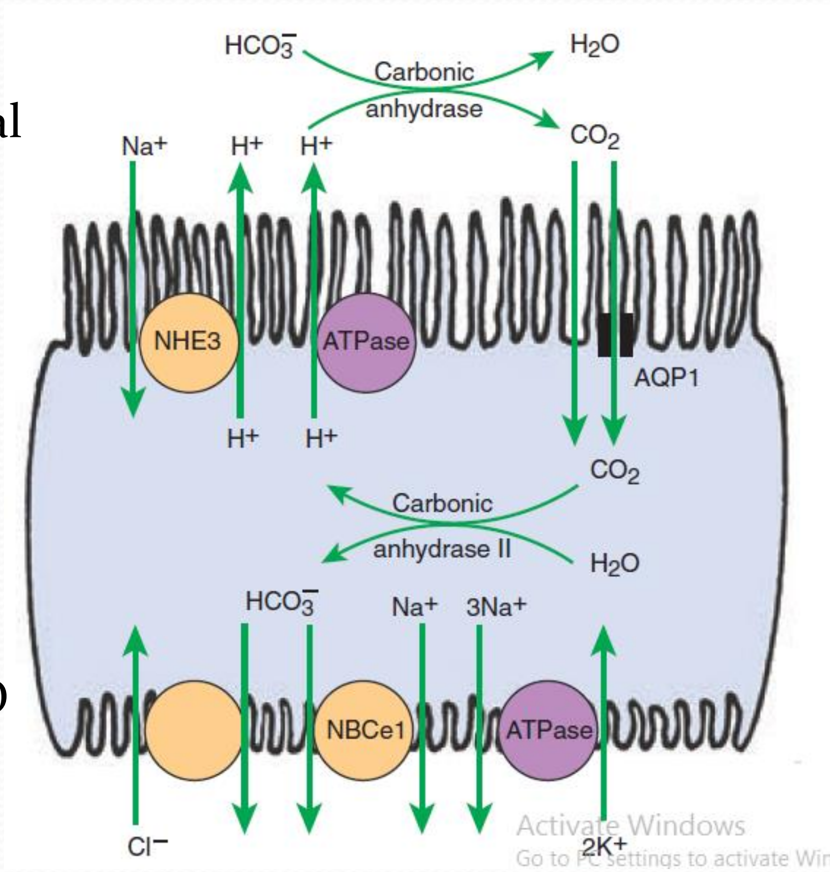
Schematic illustration of transport processes in the **proximal tubule** epithelial cell. Virtually all transport is believed to be driven by active reabsorption of Na^+ by the Na^+,K^+-ATPase located in the basolateral plasma membrane. Glucose, phosphate, sulfate, citrate, and amino acids *(aa),* and other solutes enter the cell by Na^+-coupled secondary active transport on solute specific transporters, driven by the low intracellular Na^+ concentration resulting from the active transport of Na^+ out of the cell. Cl^- diffuses across the zonula occludens into the lateral intercellular spaces down its electrochemical gradient.

TUBULAR REABSORPTION-prox

Schematic illustration of **bicarbonate** (HCO_3^-) reabsorption and acid secretion in the proximal tubule.

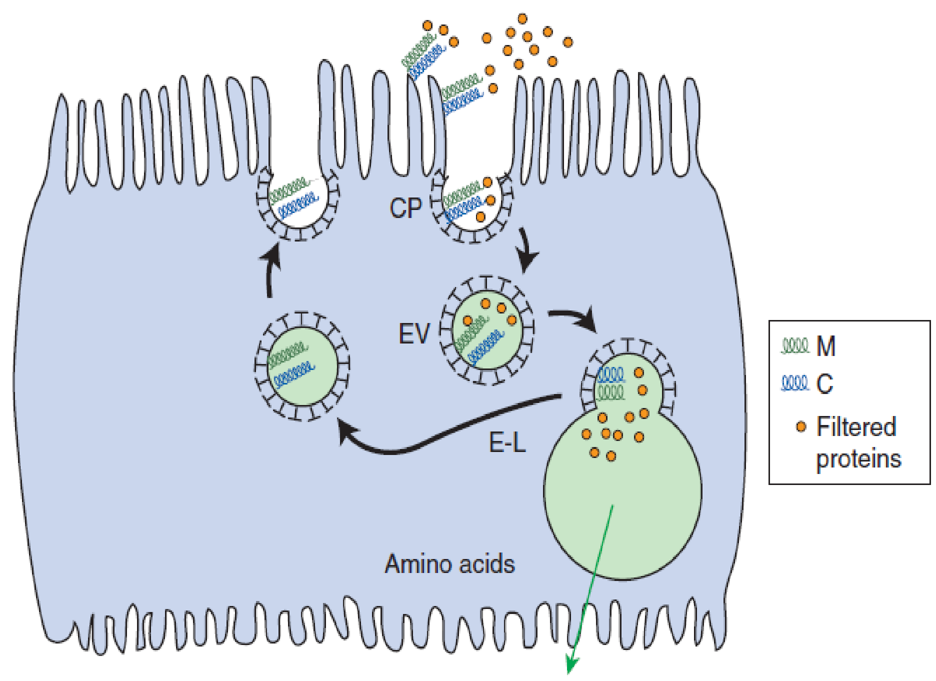
The active reabsorption of Na^+ by the basolateral Na+,K+-ATPase pump drives the secretion of H^+ through the Na+/H+ exchanger (NHE3) in the apical plasma membrane; apical H+ATPase also contributes to proximal tubule proton secretion. In the lumen the secreted H^+ and filtered HCO_3^- form H_2O and CO_2, catalyzed by apical membrane–associated carbonic anhydrase.

The CO_2 crosses the apical plasma membrane into the cell, facilitated by AQP1 channels. Intracellular CO_2 combines with intracellular H_2O to form H^+ and HCO_3^-, catalyzed by cytoplasmic carbonic anhydrase II. The H^+ is secreted into the tubule fluid, and the HCO_3^- is transported to the blood side of the cell through co-transport with Na+ (NBCe1) or counter-transport with Cl–.



60-85% of filtered bicarbonate reabsorbs in prox. tubules

TUBULAR REABSORPTION-prox



Filtered **proteins** bind with receptors, megalin *(M)* and cubilin *(C)*, in the membrane of coated pits *(CP)* in the apical plasma membrane.

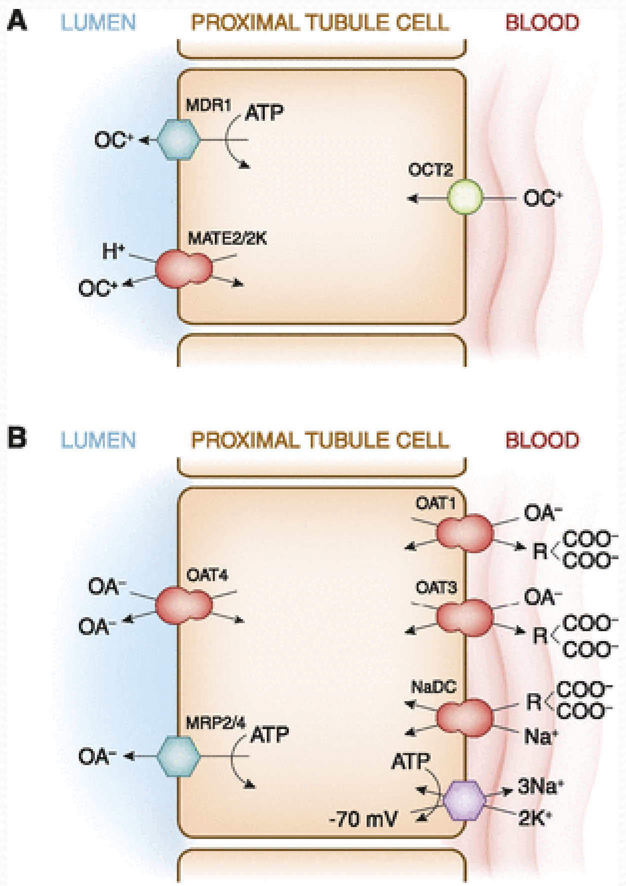
The coated pits invaginate and form endocytic vesicles *(EV)* that transport the proteins to the endosomal-lysosomal system *(E-L)*.

The proteins are degraded and the amino acids transported to the interstitium; megalin and cubilin are recycled to the apical plasma membrane.

TUBULAR SECRETION-prox

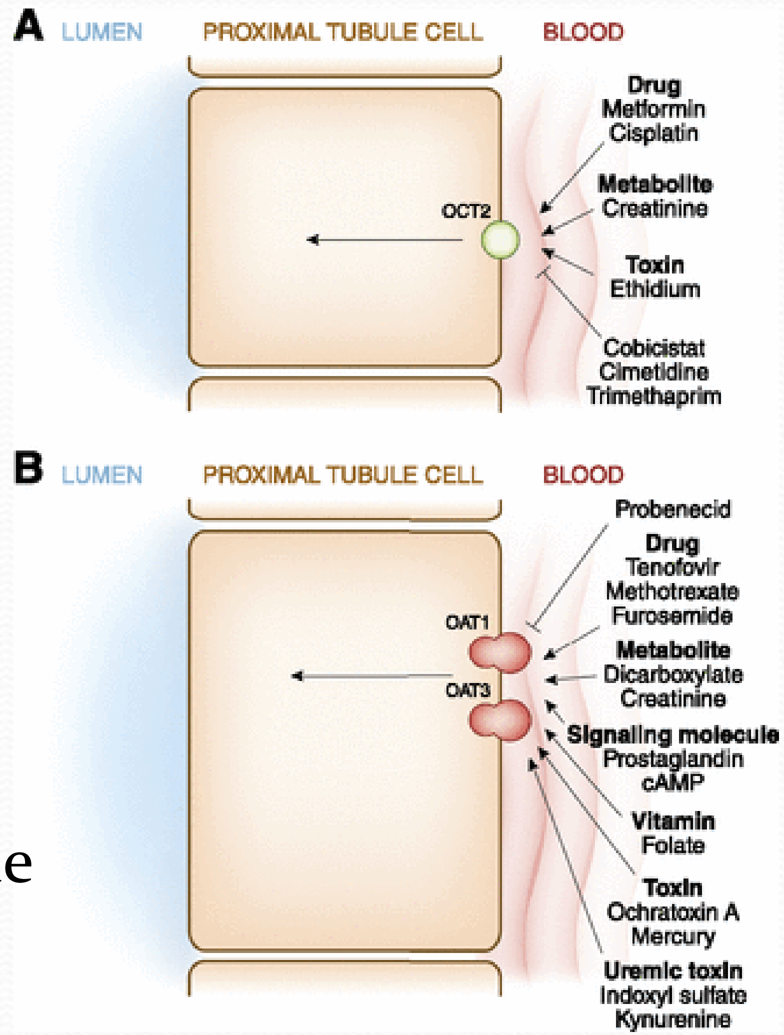
- Endogenous waste products
- exogenous drugs or toxins
  - protein bound
  - poorly filtered by the glomerulus

- organic anion transporters (OA^-)
- organic cation transporters (OC^+)



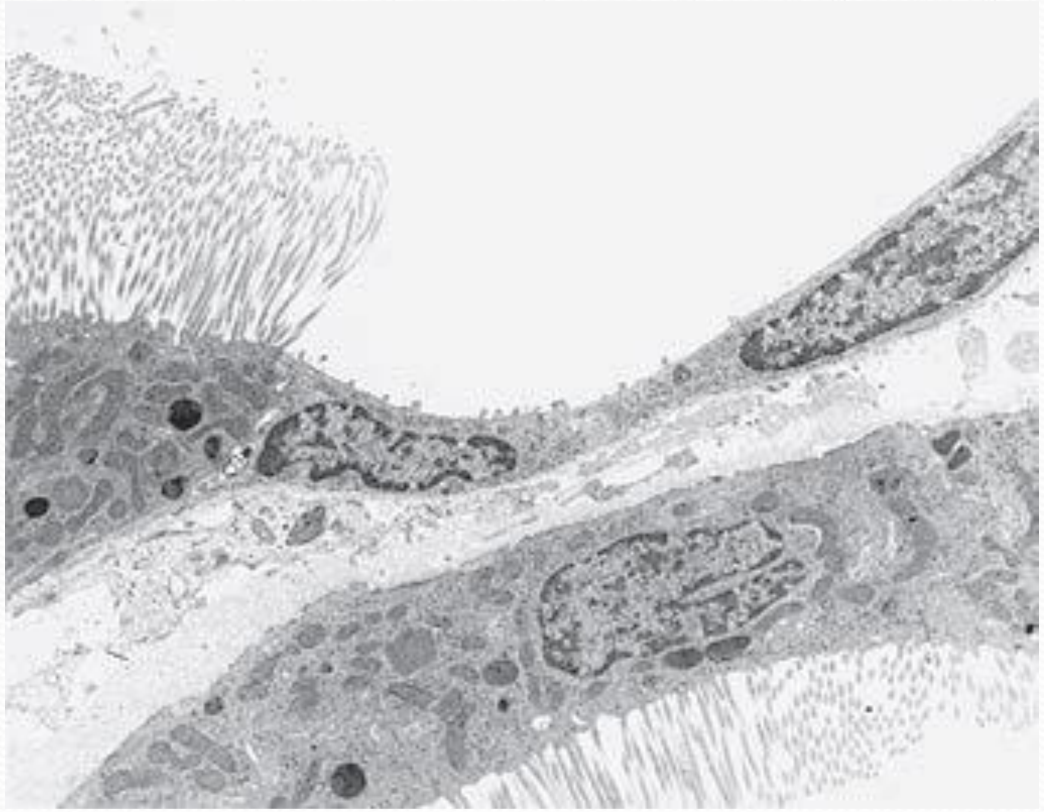
TUBULAR SECRETION-prox

- Endogenous organic compounds
  - bile salts, oxalate, urate, creatinine, prostaglandins, epinephrine, and hippurates.
- Drugs
  - antibiotics (e.g., penicillin G, trimethoprim), diuretics (e.g., chlorothiazide, furosemide), antiviral agents (e.g., acyclovir, ganciclovir), the analgesic morphine and many of its derivatives, the potent herbicide paraquat, and many more.



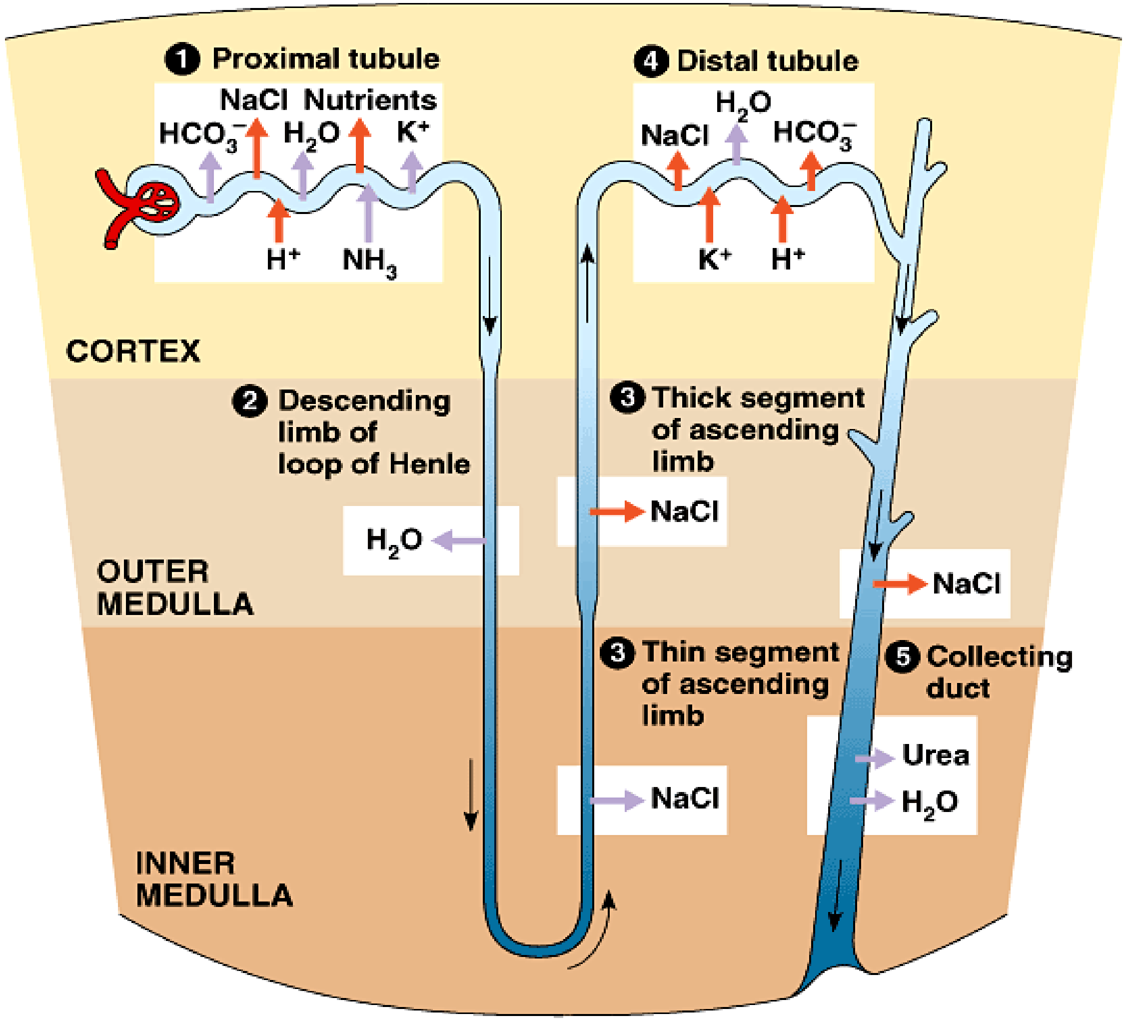
TUBULAR REABSORPTION

Desc. Loop of Henle

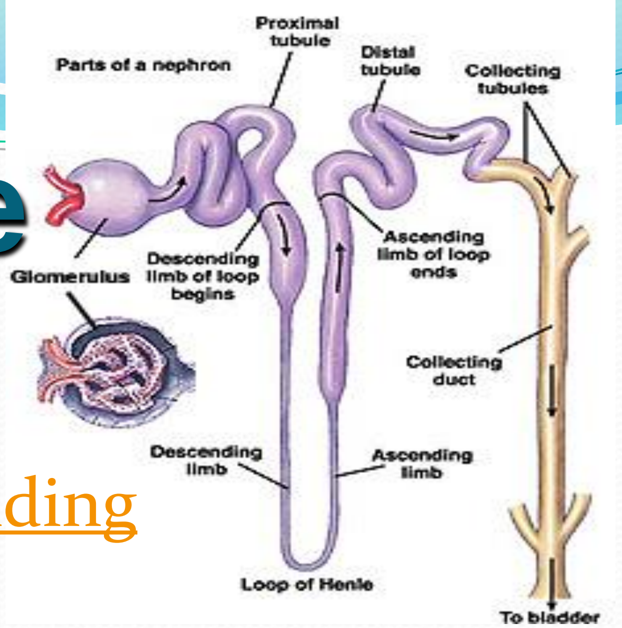


Transmission electron micrograph of rat kidney illustrating the transition from the proximal tubule to the thin descending limb of Henle's loop. The tall epithelium of the proximal tubule with the extensive brush border and abundant mitochondria abruptly changes to the low epithelium of the thin limb of Henle's loop. Epithelial cells of the thin limb have a smooth, simple plasma membrane surface and few mitochondria, which is consistent with the apparent absence of significant active transport.

Water and ion transport

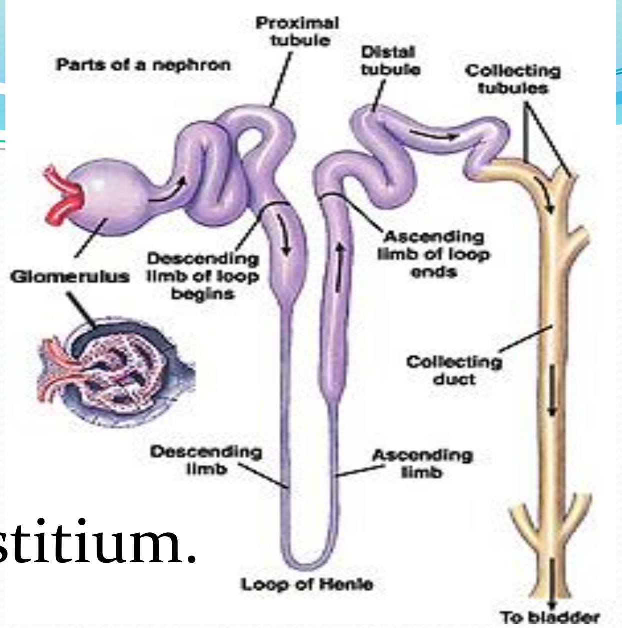


Loop of Henle



- A U-shaped tube that consists of a descending limb (thin part) and ascending limb (thin and thick part) .
- Begins in the cortex, receiving urine from the proximal convoluted tubule, extends into the medulla, and then returns to the cortex to empty into the distal convoluted tubule.
- Its primary role is to concentrate the salt in the interstitium, the tissue surrounding the loop.

Loop of Henle - Descending limb



- Permeable to water, and thus only indirectly contributes to the concentration of the interstitium.

- As the filtrate descends deeper into the hypertonic interstitium of the renal medulla, water flows freely out of the descending limb by osmosis until the tonicity of the filtrate and interstitium equilibrate.

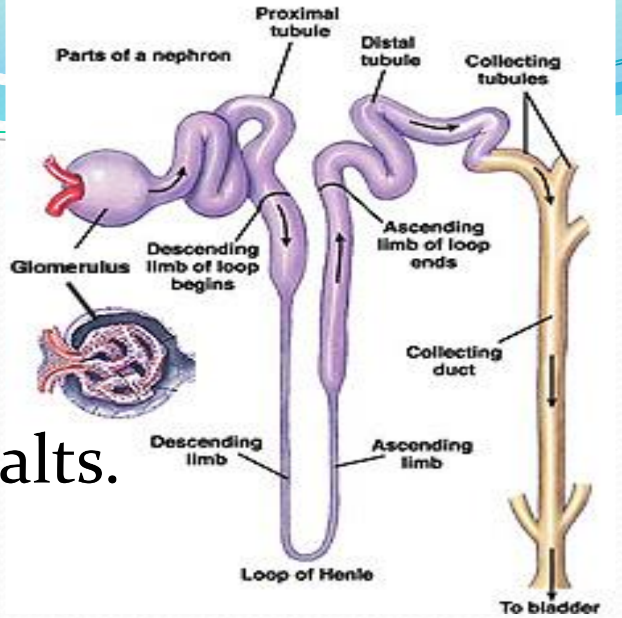
- Longer descending limbs allow more time for water to flow out of the filtrate, so longer limbs make the filtrate more hypertonic than shorter limbs.
- **Results in hypertonic solution in tubuli.**

TUBULAR REABSORPTION

Asce. Loop of Henle

Transmission electron micrograph of thick ascending limb of Henle's loop in the rat. In accordance with its important role in active Na+ reabsorption, the thick ascending limb is a tall epithelium, with extensive basolateral plasma membrane infoldings and numerous mitochondria. A collecting duct is adjacent to the basolateral aspect of the thick limb.

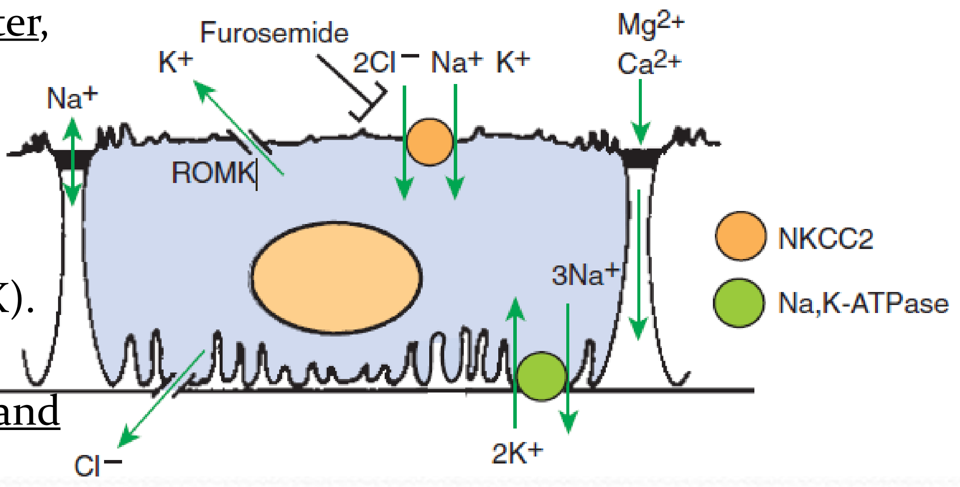
Loop of Henle - Ascending limb



- Impermeable to water, permeable for salts.
- Actively pumps sodium out of the filtrate, generating the hypertonic interstitium that drives countercurrent exchange.
- **Results in hypotonic solution in tubuli.**
- This hypotonic filtrate is passed to the distal convoluted tubule in the renal cortex.

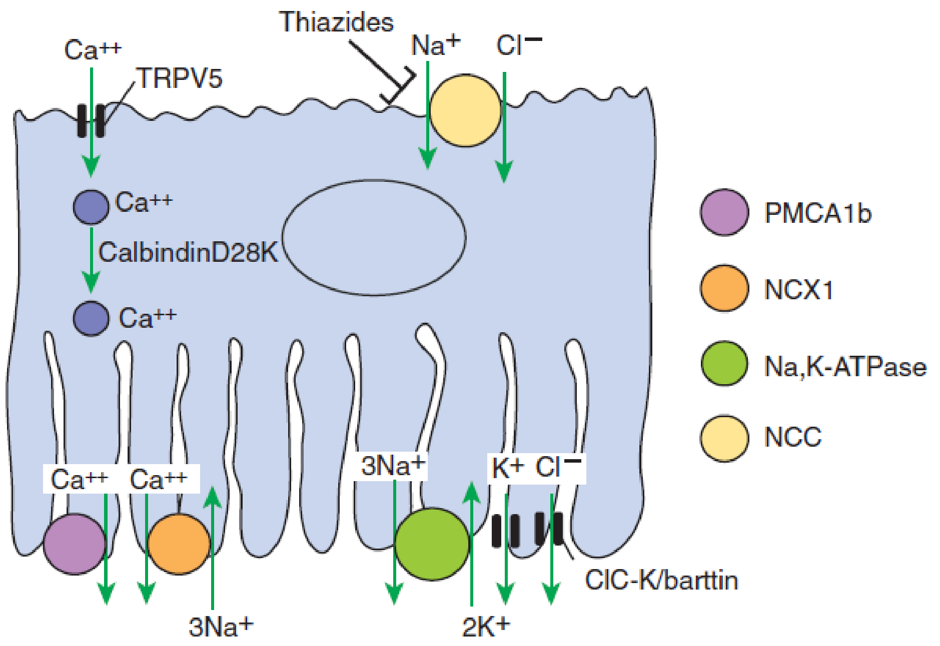
TUBULAR REAB./SECR. Asce. Loop of Henle

- Basolateral Na+,K+-ATPase pump.
  - Na+ actively reabsorbs
- Na+, K+, and Cl– enter the cell from the luminal fluid through secondary active co-transport via the Na+, K+, 2 Cl– co-transporter, NKCC2.
- Cl– exits through basolateral Cl– channels formed from ClC-K and barttin subunits.
- K+ leaves the cell down its concentration gradient through apical K+ channels (ROMK).
- A lumen-to-blood gradient for cations is established and drives reabsorption of Ca2+and Mg2+ through cation-selective paracellular channels in the tight junction formed by claudins.
- Na+ also crosses paracellular channels, initially from lumen to blood, but as the tubule fluid becomes more dilute, paracellular Na+ back-leak occurs. Loop diuretics, such as furosemide, inhibit NKCC2.

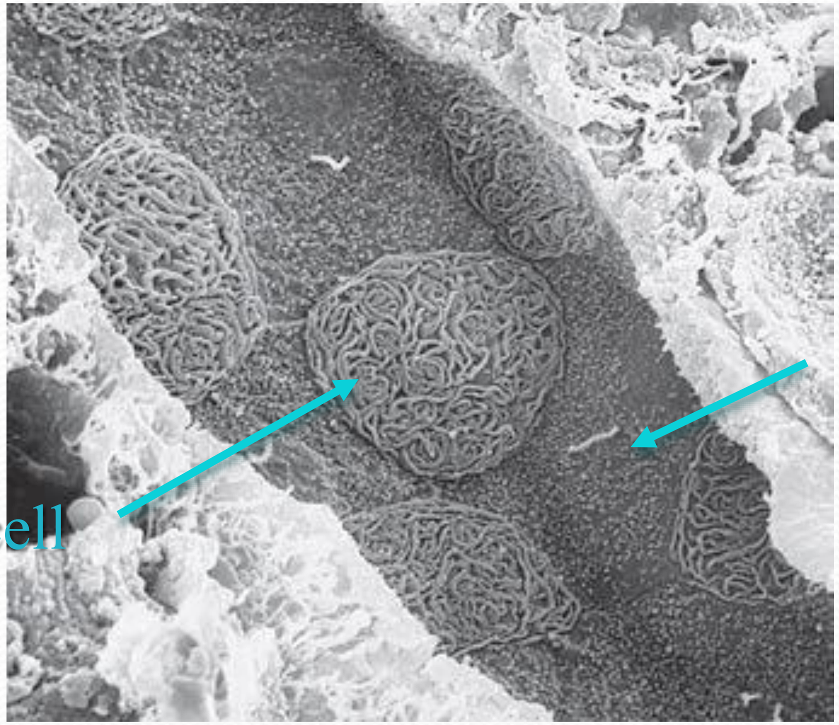


TUBULAR REABSORPTION-dist

- Na+ is actively reabsorbed by the basolateral Na+,K+-ATPase pump.
- Na+ and Cl− enter the cell from the luminal fluid through secondary active co-transport via the thiazidesensitive Na+, Cl− co-transporter, NCC.
- Cl− exits through basolateral ClC-K/barttin Cl− channels.
- K+ is recycled to the interstitium through basolateral K+ channels.
- Calcium uptake is driven by basolateral Ca2+ATPase (PMCA1b) and Na+,K+-ATPase, which drive Ca2+ uptake through the basolateral Na+/Ca2+ exchanger (NCX1) and apical Ca2+ channel (TRPV5).
- Calbindin 28k facilitates diffusion of Ca2+ from the apical to the basolateral cytoplasm.

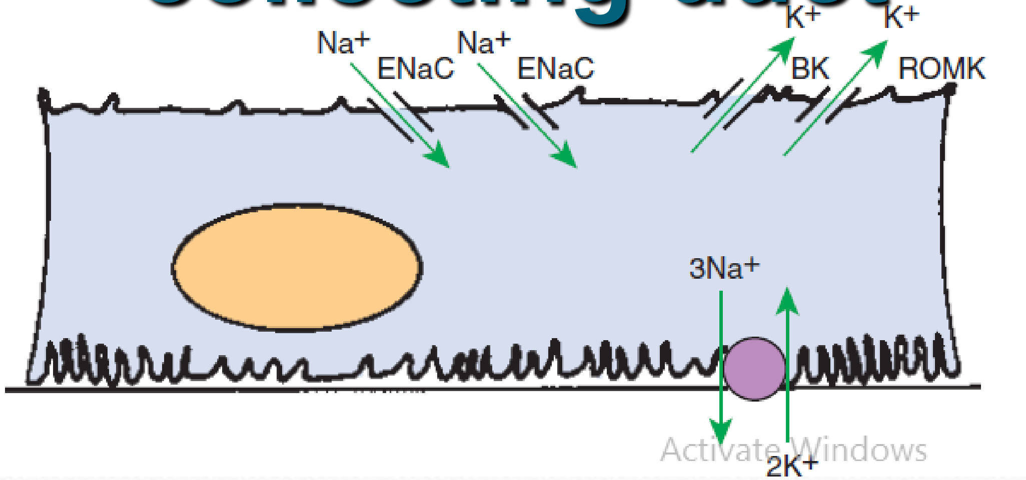


TUBULAR REAB./SECR.
collecting duct



Two cell types are evident: the principal cell, with short, small projections over the apical surface and a single central cilium; and the intercalated cell, with extensive, complex membrane folds (microplicae) over the apical surface.

TUBULAR REAB./SECR. collecting duct



- Basolateral Na^+,K^+-ATPase actively transports Na^+ and drives passive diffusion of Na^+ from the tubule lumen into the cell through a Na^+-selective channel, ENaC, in the apical plasma membrane.
- K^+-selective channels (ROMK, BK) in the apical plasma membrane enable K^+ secretion into the tubule fluid.
- The hormone aldosterone enhances Na^+,K^+-ATPase and ENaC channel activity and increases K^+ permeability of the apical plasma membrane,
- thus enhancing Na^+ reabsorption and K^+ secretion.

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.

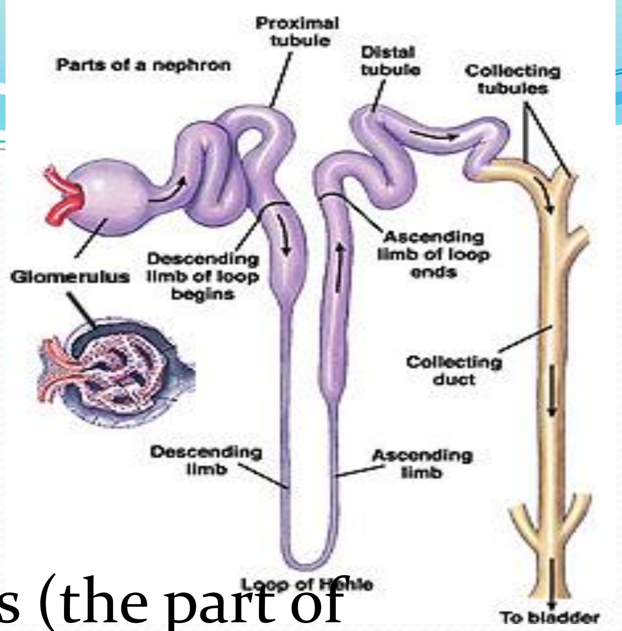
- The **distal** tubule and **collecting duct** control the ultimate rate of excretion of electrolytes and water to maintain homeostasis despite variations in dietary intake and extrarenal losses of salts and water.

Solute transport regulation

The specific homeostatic responses of distal and col. Duct are controlled in large part by several hormones, including:

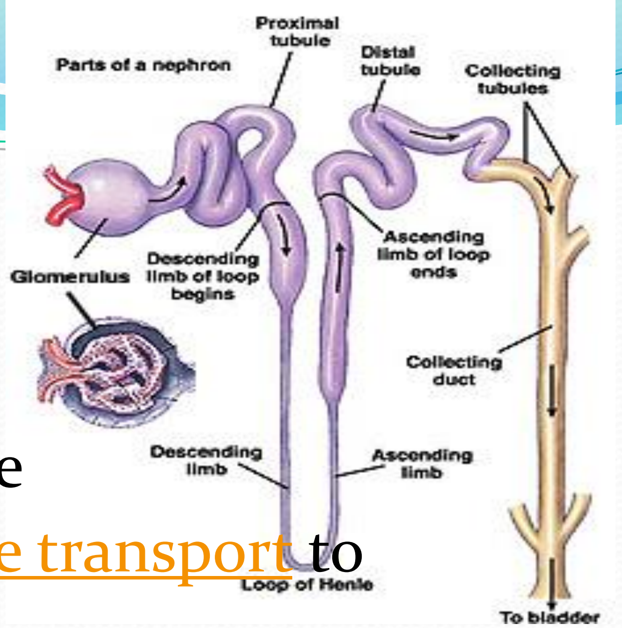
- **angiotensin II**, (Direct Na reabsorption)
- **aldosterone**, (Na reabsorption and K secretion)
- **antidiuretic hormone**, (H_2O reabsorption)
- **endothelin-1**, (NaCl and H_2O secretion)
- **atrial natriuretic peptide**, (Stimulated by atrial dist., inhibits ald. And renin release, increase Na excretion)
- **parathyroid hormone**, (decr. HPO_4 uptake, incr. urinary HPO_4 excretion, Ca reuptake in prox., Asc. And dist.)
- **1α,25-(OH)2–vitamin D3**, (enhance Ca reab. In dist.& col)
- **calcitonin**. (Ca reabsorption in dist. And collect. Ducts)

Distal tubule



- **Morphology:** continuation of the thick ascending limb of the Loop of Henle in the cortex of kidneys – direct part.
- Convolute part – Juxtaglomerular apparatus (the part of distal tubule near the glomerular apparatus) = special cells = **MACULA DENSA** (thin cells very tight next to each other) Large nucleus, secretion of **RENIN**
- **Reabsorption:**
  - Water
  - Na^+
- **Results in ISOOSMOTIC SOLUTION**
- After traveling the length of the distal convoluted tubule, only 3% of water remains, and the remaining salt content is negligible.
- 97.9% of the water in the glomerular filtrate enters the convoluted tubules and collecting ducts by osmosis.

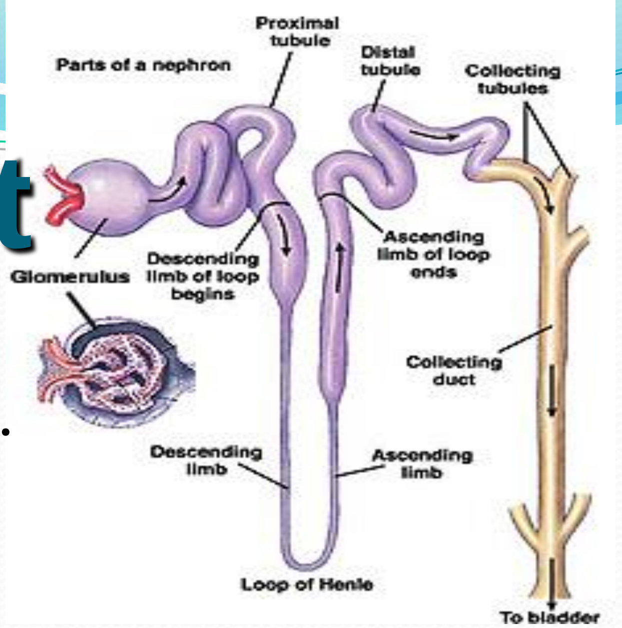
Distal tubule



- The distal convoluted tubule is similar to the proximal convoluted tubule in structure and function. Cells lining the tubule have numerous mitochondria, enabling active transport to take place by the energy supplied by ATP.

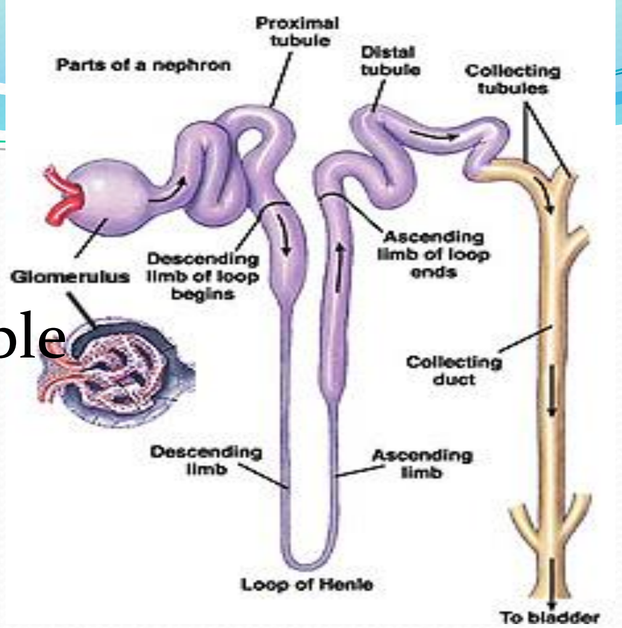
- Much of the ion transport taking place in the distal convoluted tubule is regulated by the endocrine system.
  - In the presence of parathyroid hormone, the distal convoluted tubule reabsorbs more Ca^{2+} and excretes more phosphate.
  - When aldosterone is present, more Na^{+} is reabsorbed and more K^{+} excreted.
  - Atrial natriuretic peptide causes the distal convoluted tubule to excrete more Na^{+} .
- In addition, the tubule also secretes hydrogen and ammonium to regulate pH.

Collecting duct



- Collects about 10 distal tubules, continues as medullary pyramides (about 2700 nephrons).
- Final adjustment
- **Results in HYPERTONIC SOLUTION**
- Each distal convoluted tubule delivers its filtrate to a collecting duct, most of which begin in the renal cortex and extend deep into the medulla.
- As the urine travels down the collecting duct, it passes by the medullary interstitium which has a high sodium concentration as a result of the loop of Henle's.

Collecting duct



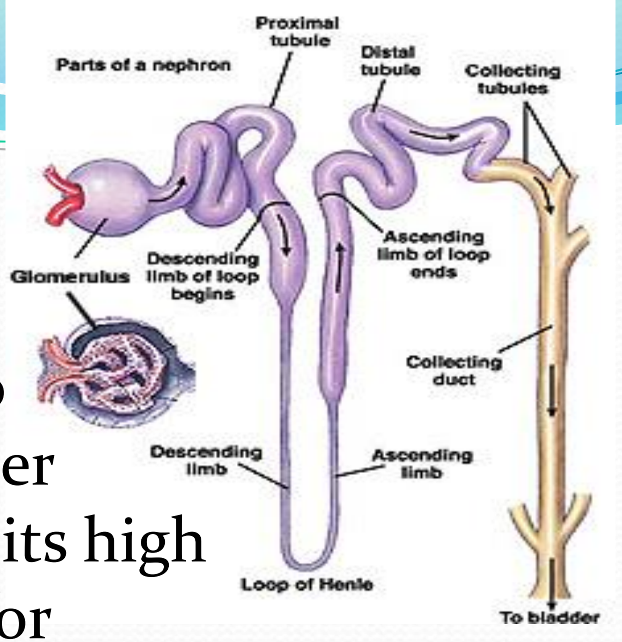
- The collecting duct is normally impermeable to water, it becomes permeable under the actions of antidiuretic hormone (ADH).

- As much as 3/4 of the water from urine can be reabsorbed as it leaves the collecting duct by osmosis.

- The levels of ADH determine whether urine will be concentrated or dilute.

- Dehydration results in an increase in ADH, while water sufficiency results in low ADH allowing for diluted urine.

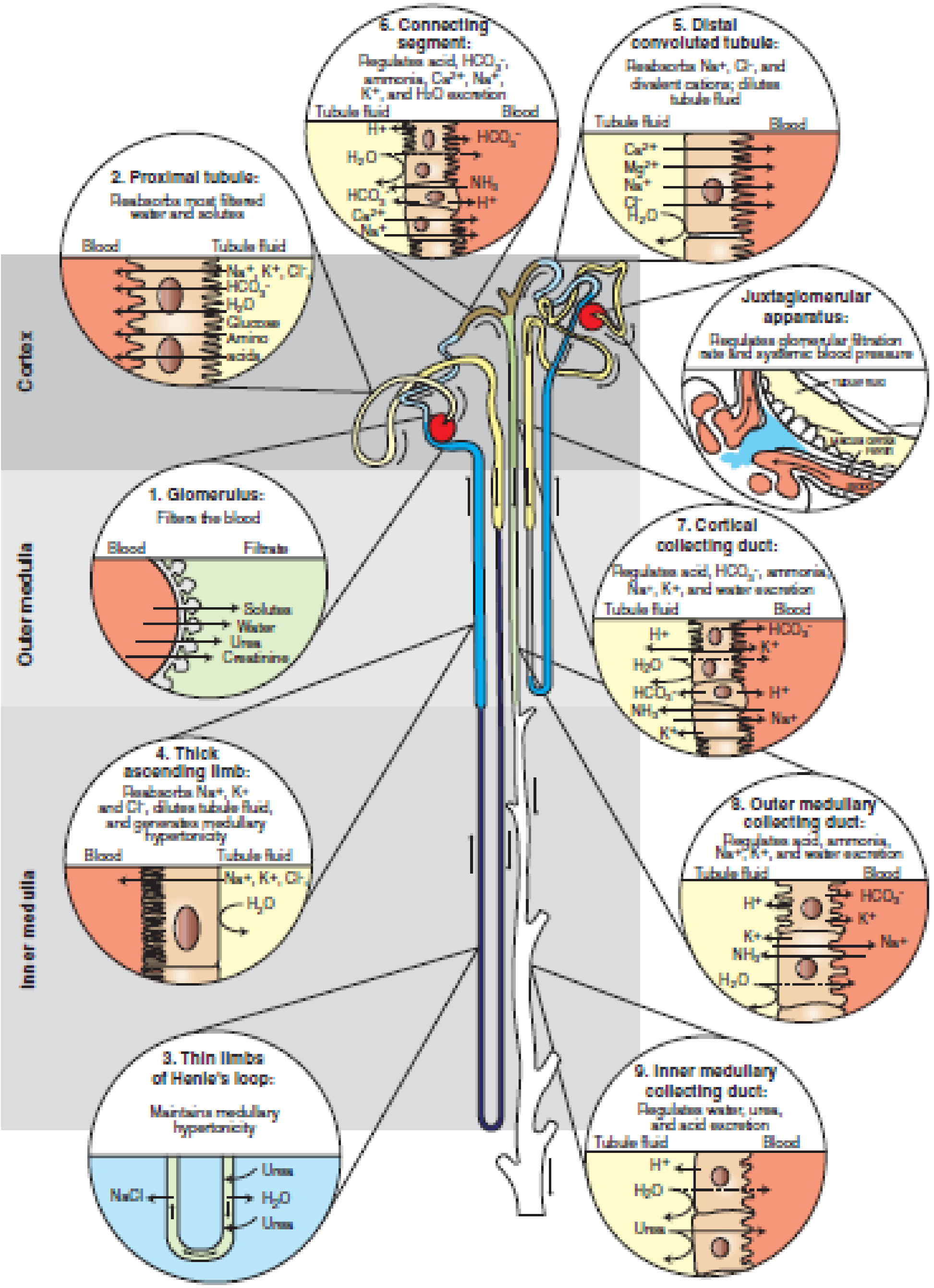
Collecting duct



- Lower portions of the collecting duct are also permeable to urea, allowing some of it to enter the medulla of the kidney, thus maintaining its high ion concentration (which is very important for the nephron).

- Urine leaves the collecting duct through the renal papilla, emptying into the renal calyces, the renal pelvis, and finally into the bladder via the ureter.

- Because it has a different embryonic origin than the rest of the nephron (the collecting duct is from endoderm whereas the nephron is from mesoderm), the collecting duct is usually not considered a part of the nephron proper.



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

Water Balance

Water Balance

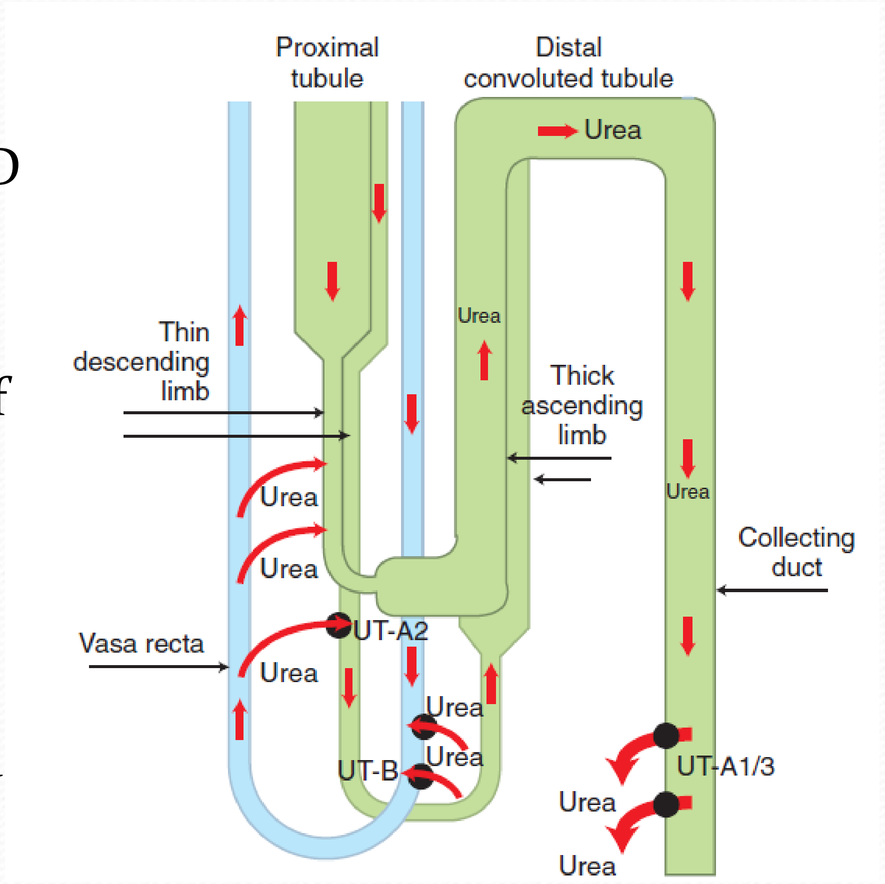
- **The Kidney Maintains Water Balance**
  - In normal condition: 99% of filtered H_2O reabsorbs
  - A water-deprived dog can concentrate urine up to 2000 mOsmol/kg H_2O
  - In water overload condition: dog can excrete hypotonic urine as low as 100 mOsmol/kg H_2O
- **The Proximal Tubule Reabsorbs More 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

- **Concentrated or Diluted Urine:**
  - the mammalian kidney has evolved to excrete concentrated/diluted urine as needed:
    - hypertonic medullary interstitium, excretion of concentrated urine
    - dilution of the tubule fluid by the thick ascending limb and the DCT, excretion of dilute urine
    - variability in the water permeability of the collecting duct in response to ADH, which determines the final urine concentration.

Medullary Hypertonicity

1. Urea recycling

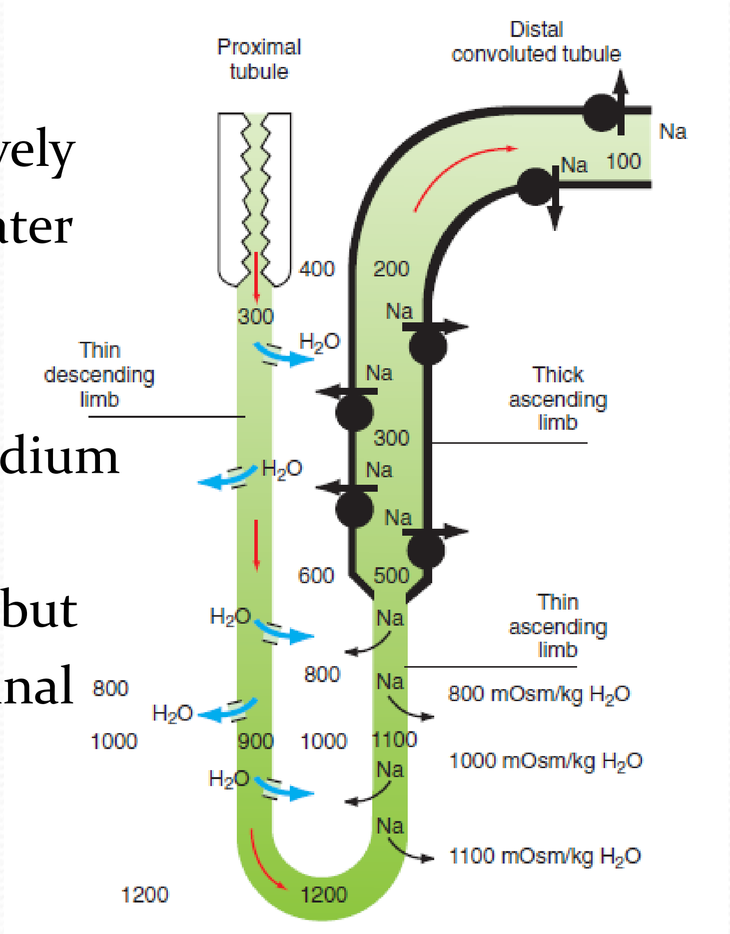


- Filtered urea is reabsorbed in the IMCD by facilitated diffusion.
- Then diffuses down into the vasa recta.
- Then diffuses out into the thin limbs of Henle's loop.
- Urea reabsorption in the IMCD is enhanced by ADH

- Accumulation of urea in the medullary Interstitium:
  - Make medullary interstitum hypertonic
  - Promotes water reabsorption

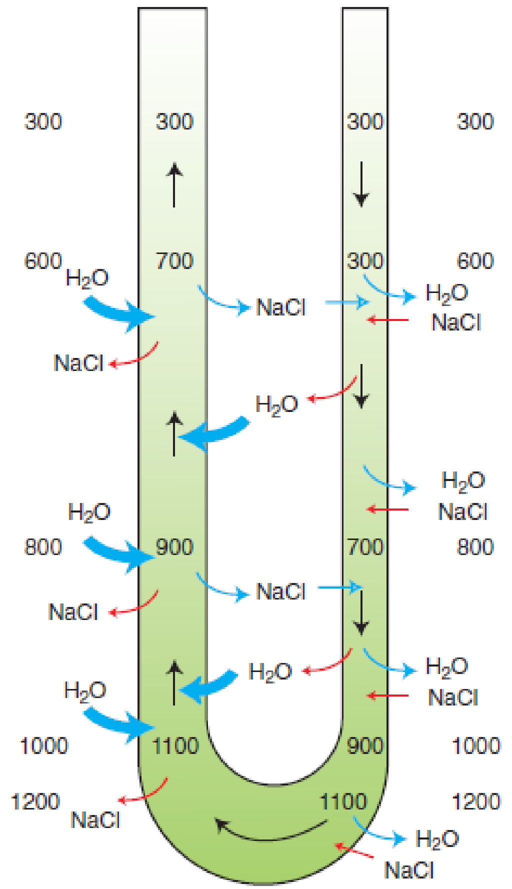
Medullary Hypertonicity

2. The Countercurrent Mechanism



- 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 sodium *(Na)* but are permeable to water *(H2O)*
- 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

Medullary Hypertonicity

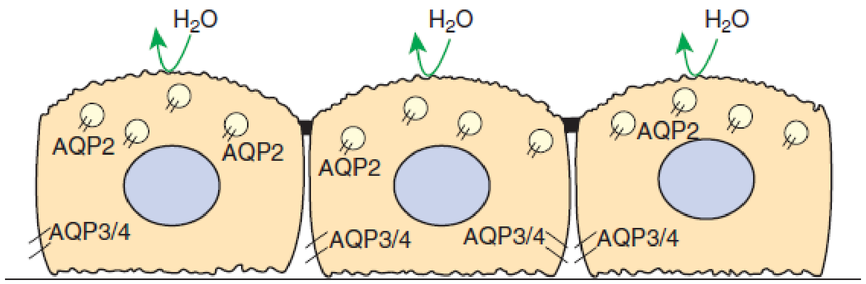


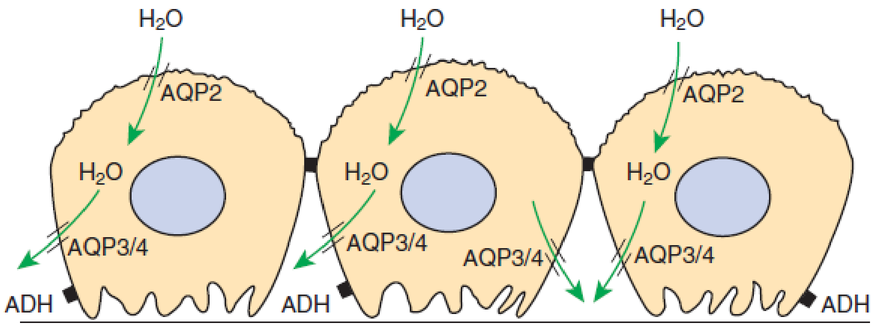
- **Countercurrent Exchange in the Vasa Recta**
- The walls of the vasa recta are permeable to water and salt *(NaCl)*
- Plasma osmolality progressively increases entering the inner medulla.
- Water diffuses out and NaCl enters the blood through concentration gradient in the descending vasa recta
- In the ascending vasa recta, as the vessel passes through hypotonic interstitum, NaCl leaves and H2O enters the blood
- This system prevents the dissipation of the medullary concentration gradient
- there is net removal of water from the interstitium because of the relatively low HP and relatively high OP in the vasa recta.

Medullary Hypertonicity

3. ADH Regulates Collecting Duct Water Permeability

- When ADH is absent, the apical plasma membrane is impermeable to water, and dilute urine is excreted.





- ADH stimulates the insertion of aquaporin-2 *(AQP2)* water channels into the apical plasma membrane, which enhances its water permeability. Water rushes into the cells and across the basolateral plasma membrane via aquaporin-3 and -4 *(AQP3, AQP4)* into the lateral intercellular spaces.

Acid-Base Balance

Acid-Base Balance

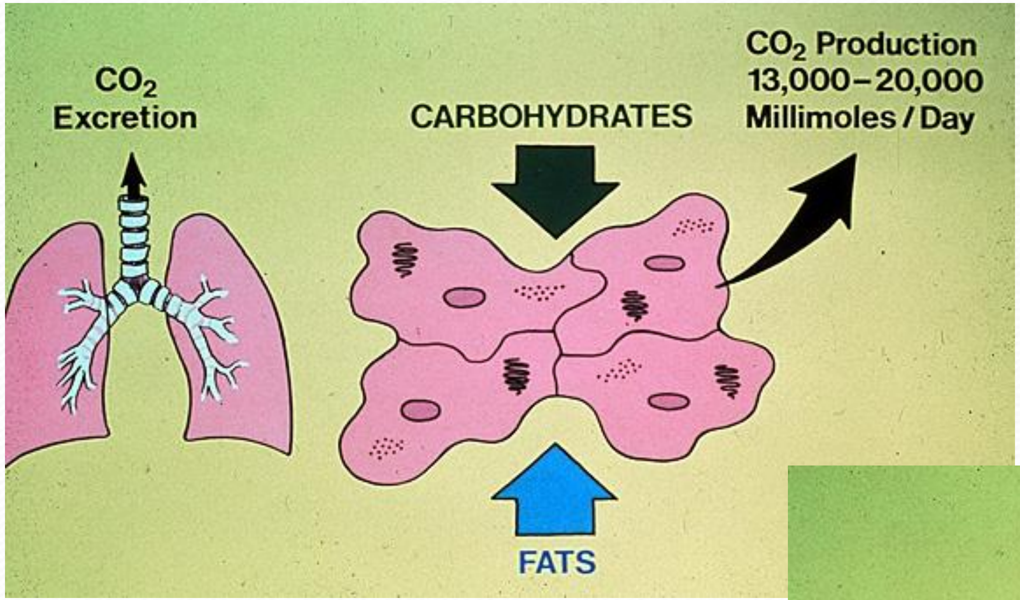
- Definition:
  - Acid: substance that can donate hydrogen ions
  - Base: substance that can accept hydrogen ions
  - Reduced pH (elevated hydrogen ion concentration) equals acidemia
  - Increased pH (reduced hydrogen ion concentration equals alkalemia)
  - Process that lowers pH = acidosis
  - Process that increases pH = alkalosis

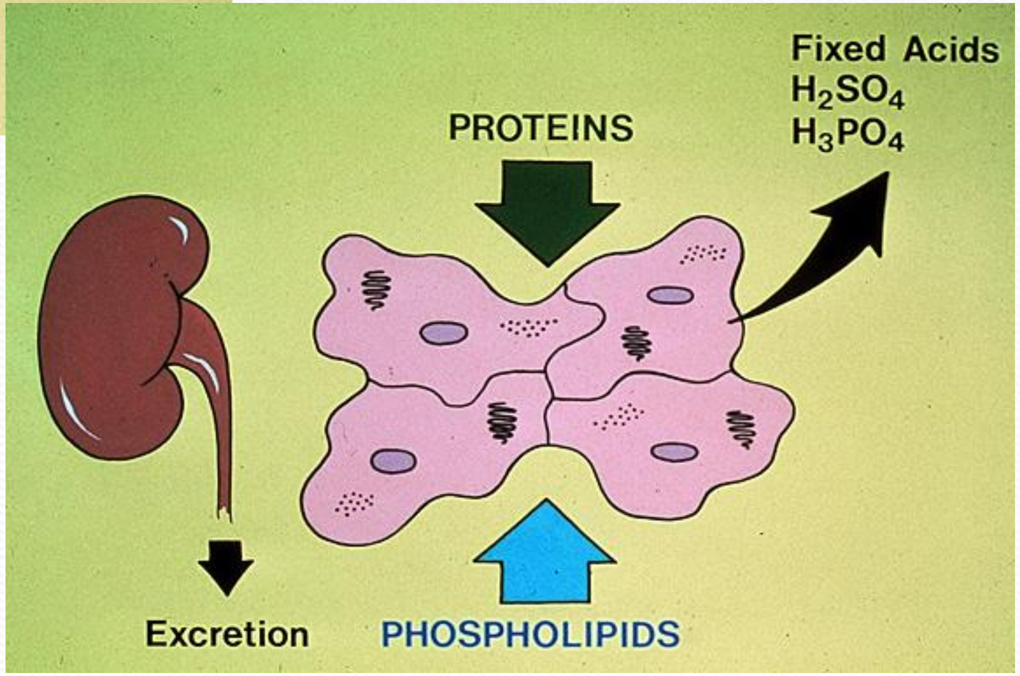
Acid-Base Balance

- Normal blood pH : 7.4 (7.35-7.45)
- Rapid correcting systems of pH:
  - Extracellular and intracellular buffers
  - The lungs

- Slow acid-base homeostasis:
  - The kidneys

Acid-Base Balance





Buffers

- Hemoglobin and other proteins
- Carbonate in bone
- Phosphate
- Bicarbonate

- These buffers rapidly normalize the pH after acute changes in the acid load, unless the buffering capacity is exceeded.
- During chronic metabolic acidosis, bone provides a reservoir of buffer that is mobilized to help normalize systemic pH.
- Excess H^+ and low HCO_3^- in the extracellular fluid promote physicochemical as well as osteoclast-mediated dissolution of bone, releasing carbonate, which buffers H^+. In chronic acidosis, this can lead to abnormally low bone mineral density.

Buffers

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

Mechanisms that Buffer an Acid Load

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

Buffers

- **Metabolic Disorders:**

  Processes that directly alter bicarbonate concentration

  - Metabolic acidosis: decreased bicarbonate
  - Metabolic alkalosis: increased bicarbonate

- **Respiratory Disorders:**

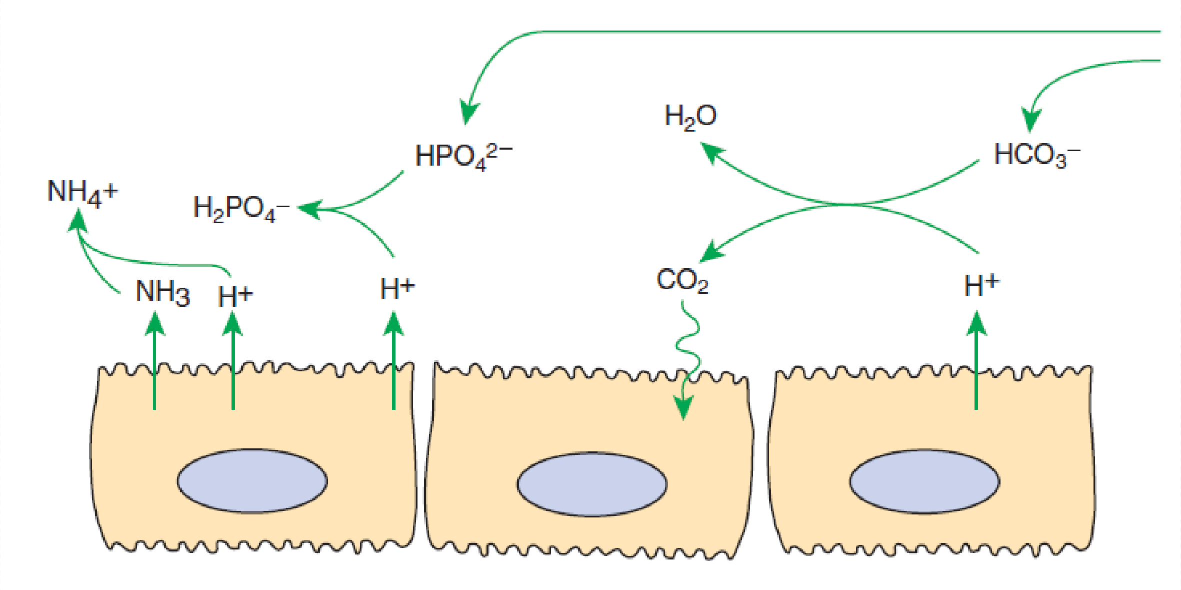
  Processes that directly alter CO_2

  - 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.

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

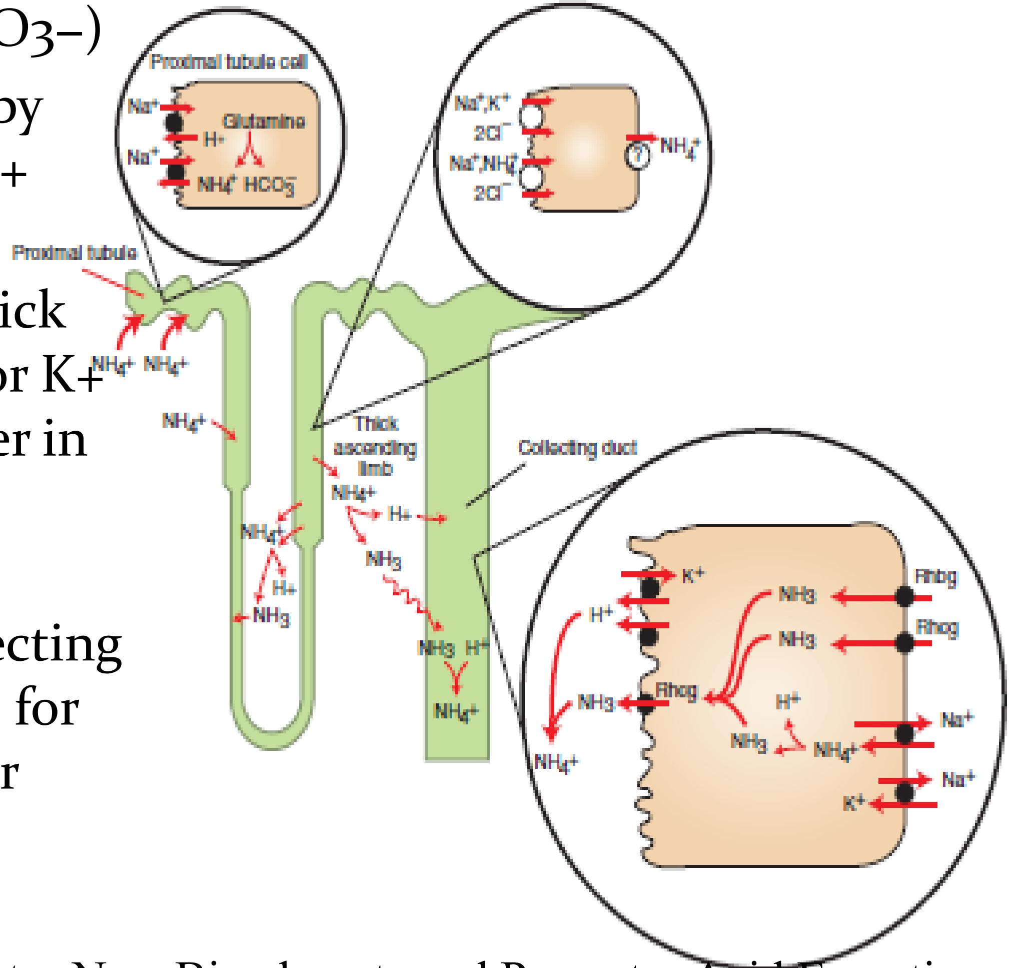
Buffer mechanism in tubule fluid



- In the proximal tubule, buffering by filtered bicarbonate (HCO3–) predominates because of the relatively high concentration of HCO3–
- In the cortical collecting duct, buffering by filtered, nonbicarbonate buffers, such as HPO42–, predominates.
- NH3 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

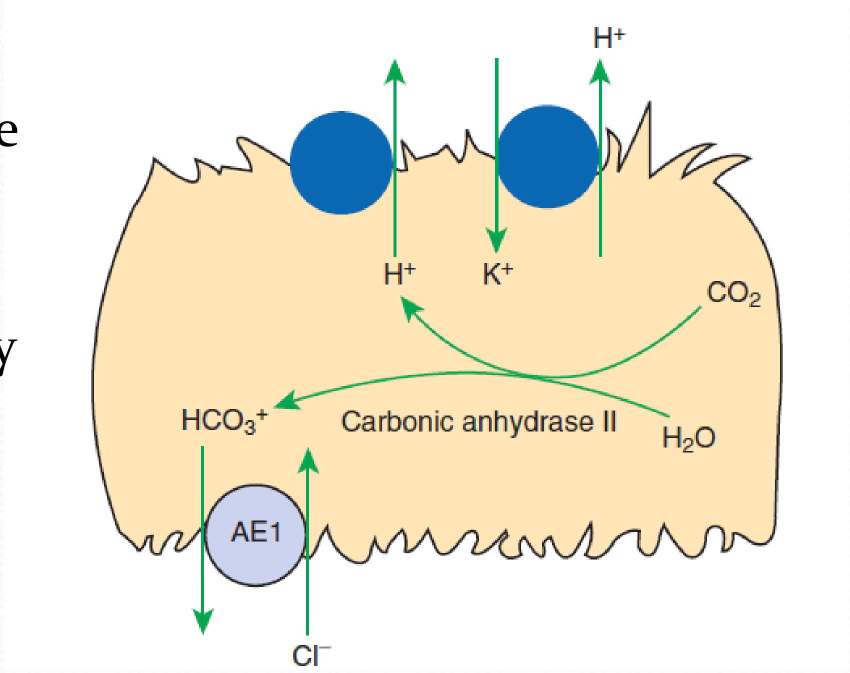
- In the proximal tubule, glutamine is catabolized to generate ammonium ion *(NH_4^+)* and bicarbonate (HCO_3^-)
- NH_4^+ is secreted into the lumen by substitution for H^+ on the Na^+/H^+ exchanger
- Ammonium ion recycles in the thick ascending limb, by substitution for K^+ on the $Na^+/K^+,2Cl^-$ co-transporter 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.



- Renal Ammonia Metabolism Generates New Bicarbonate and Promotes Acid Excretion

H+ secretion and HCO3– reabsorption in the intercalated cells in collecting duct

- The electrogenic proton pump, H+-ATPase
- electrically neutral H+,K+-ATPase pump.
- The intracellular formation of H+ and HCO3– from CO2 and H2O is catalyzed by cytoplasmic carbonic anhydrase.
- basolateral plasma membrane contains a Cl–/HCO3– exchanger (AE1) that allows HCO3– reabsorption.



Acid-Base Balance

Transportation of the substances

- **Pasive transport**
  - Simple – only Na^+
  - Co-transport – with Cl^-, glucose, aminoacids, phosphates
  - Anti-transport - Na^+ inside, H^+ or Ca^{2+} out
- **Active transport**
  - Na^+/K^+- pump – dependent on ATP energy

Transportation of the substances

- **Organic substances**
  - Substances which have **KIDNEY'S THRESHOLD** = like **GLUCOSE** – physiologically not in urine, when the level of glucose in plasma is higher than the threshold of kidneys reabsorption, than we can see glucose in the urine.
  - Substances without kidney's threshold = physiologically in urine
- **GLUCOSE**
  - Secondary active transport = it is secondary dependent on ATP. It means that glucose transport is together with Na+ as co-transport, and the ATP-dependent natrium-kalium pump helps to keep the gradient of natrium

Function - Excretion of waste products

- The kidneys excrete a variety of waste products produced by metabolism, for example, urea (from protein catabolism) and uric acid (from nucleic acid metabolism).
- **UREA**
  - filtered in glomerular apparatus → increase urea concentration in proximal tubule, because of the reabsorption of water → reabsorption of urea later in proximal tubule → back into the Loop of Henle (helps to keep the hypertonic interstitium) → out again in the collecting ductus

Function - Homeostasis

- **Acid-Base Balance**
  - The kidneys regulate the pH, mineral ion concentration, and water composition of the blood.
  - By exchanging hydronium ions (cation H_3O^+) and hydroxyl ions (OH), the blood plasma is maintained by the kidney at pH 7.4.
  - Urine, on the other hand, becomes either acidic at pH 5 or alkaline at pH 8.
- **Water Balance**
  - Aldosterone
- **Plasma Volume**
  - ADH

Aldosterone

- A steroid hormone (mineralocorticoid) synthesized from cholesterol by the enzyme aldosterone synthase.
- It is formed in the outer-section (zona glomerulosa) of the adrenal cortex of the adrenal gland.
- It helps regulate the body's electrolyte balance by acting on the mineralocorticoid receptor (MR).
- It diminishes the excretion of Na^+ ions and therefore water, and stimulates the excretion of K^+ ions by the kidneys.
- Aldosterone is synthesized in reaction to increases of angiotensin II or plasma potassium, which are present in proportion to sodium deficiencies.

Control of aldosterone release

- The role of baroreceptors
  - **Baroreceptors** in the human body detect the pressure of blood flowing though them, and can send messages to the central nervous system to increase or decrease total peripheral resistance and cardiac output.
- The role of the juxtaglomerular apparatus
- The role of sympathetic nerves
- The role of the renin-angiotensin system

ADH (VASOPRESSIN)

- A human hormone that is mainly released when the body is low on water.
- It causes the kidneys to conserve water by concentrating the urine.
- **If there is not enough water in the body**
  - The osmotic activity of the EC solution is increased → stimulation of the **OSMOTIC RECEPTORS** in the hypothalamus → stimulation of posterior lobe of the pituitary gland → activation of **VASOPRESSIN** → increase of the permeability of collecting ductus for the water → reabsorption → **HYPERTONIC URINE**
- **If there is too much water in the body**
  - The increase volume stimulates **VOLUME RECEPTORS** in the heart and big veins and arteries → decrease of the activation of **VASOPRESSIN** → decrease of the permeability of collecting ductus for the water → water is not reabsorbed → **ISO- or HYPOOSMOTIC URINE**

Renin-angiotensin system

- A hormone system that helps regulate long-term blood pressure and blood volume in the body.
- The system can be activated when there is a loss of blood volume or a drop in blood pressure (such as in a hemorrhage).
- If the perfusion of the juxtaglomerular apparatus in the kidneys decreases, then the juxtaglomerular cells release the enzymatic hormone renin.
- **Activation:**
  - from **VOLUME RECEPTORS** in afferent arteriole → decrease in perfusion → decrease in tonus of afferent arteriole
  - from **CHEMORECEPTORS** in macula densa → decrease of NaCl in macula densa cells

Renin-angiotensin system

- Renin activates the renin-angiotensin system by cleaving angiotensinogen, produced in the liver, to yield angiotensin I, which is further converted into angiotensin II by specialized cells of the lung capillaries.
- Angiotensin II then constricts blood vessels, increases the secretion of ADH and aldosterone, and stimulates the hypothalamus to activate the thirst reflex, all these actions leading to increased blood pressure.

Renin

- Also known as **angiotensinogenase**, is a circulating enzyme released mainly by juxtaglomerular cells of the kidneys in response to low blood volume or low body NaCl content.
- **Actions of renin**:
  - Vasoconstriction in efferent arteriole (increase of glomerular filtration)
  - Peripheral vasoconstriction (increase in blood pressure)
  - Secretion of aldosterone (reabsorption of Na^+ and water)

Kinin-kallikrein system

- A **kinin** is any of various structurally related polypeptides, such as bradykinin and kallikrein, that act locally to induce vasodilation and contraction of smooth muscle.
- A role in inflammation, blood pressure control, coagulation and pain.
- Produced and stored in distal tubule
- **Function:**
  - vasodilatation
  - secretion of prostaglandins (PGE2)
  - decrease of vasoconstriction and antidiuretic effects of angiotenzin II.
  - increase of vasodilatation and diuretic effect of kinins

Prostaglandins

- A **prostaglandin** is any member of a group of lipid compounds that are derived from fatty acids and have important functions in the animal body.
- Every prostaglandin contains 20 carbon atoms, including a 5-carbon ring.
- Hormone-like substances
- **Function:**
  - Vasodilatation
  - Increase of perfusion
  - Decrease of water reabsorption
  - Decrease of active Na^+ transport in tubules

Parathyroid hormone

- PTH is secreted by the parathyroid glands
- **Function:**
  - regulation of calcium and phosphates excretion by urine
  - increase of Ca^{2+} reabsorption in distal tubule and collecting ductus
  - inhibition of phosphates reabsorption in proximal and distal tubules (increase of their excretion)
  - decrease in natrium and bicarbonates reabsorption = decrease in water reabsorption