

# Renal Physiology- Lecture notes-1

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## Important Medical Terms

Before studying renal physiology we have to understand some important medical terms , related to the renal system.

### Renal Physiology

refers to the science that deals with the physiological processes of the renal system , which involves both kidneys , ureters , urinary bladder , and urethra . As far as the kidney fulfills the major functions of this system , it is called renal system ( ren means kidney in latin language).

### Nephrology

refers to an internal medicine specialization , which deals with the diseases of the kidney from a point view of diagnosis , treatment , prevention , and others ( nephro- : is a prefix , which means kidney in ancient Greek language ).

### Urology

refers to a surgical specialization , which deals with the surgical diseases of the urinary system , and male reproductive system as well .

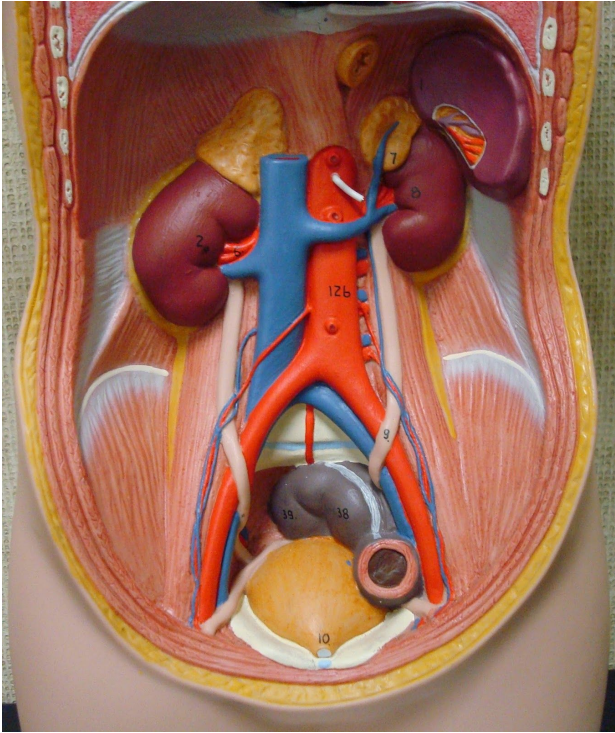
## Functions of the renal system

The renal system has many essential functions that contribute to maintaining homeostasis , such as:

- Urine formation : A process of three steps : Glomerular filtration , tubular reabsorption , and tubular secretion . Thankful to this process our kidney filters the blood , reabsorbs essential nutrients and molecules , and gets rid of metabolic waste products and toxic substances out of organism.
- Contribution to the regulation of arterial blood pressure (intermediate-term , and long-term regulation, most of which has been discussed during cardiovascular section)
- Contribution to acid-base balance .
- Contribution to fluid-electrolytes balance .
- Endocrine function : the kidney produces and releases biologically active substances , including hormones like : erythropoietin , renin , and contributes to formation and activation of Vitamin D3 .
- Contribution to hematopoiesis, as far as most of erythropoietin is produced by the kidney.

## Physiologic anatomy of the renal system

1. Kidneys : We have two kidneys , that are located in the posterior abdominal cavity ( paravertebrally and retroperitoneally ) . The right kidney is slightly located lower than the left one because of the mass of the liver, that is located in the right side of the abdomen , while the left one is more medially located.



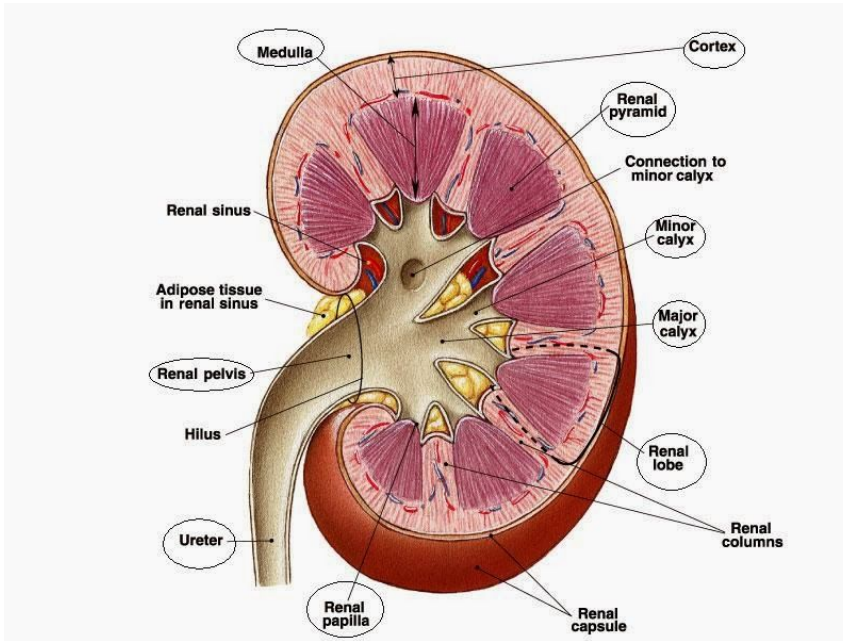
Kidney is a bean shaped organ with concave and convex surfaces. The hilum of the kidney is the concave surface through which the renal artery enters the kidney and the renal vein and ureter leave. Each kidney weighs about 150 grams in male , and 135 grams in female . It is protected by many protective layers that protect the kidney from physical stress and invading microorganisms and other threatening factors. These layers surround the kidney as follows :

- a. renal capsule : composed of tough fibrous tissue.
- b. perinephric fat :
- c. renal fascia
- d. paranephric fat .

In addition to the mentioned protective layers , the anterior border of the kidney is covered by the peritoneum , while the posterior one is covered by fascia transversalis . The floating ribs assure an additional protection too.

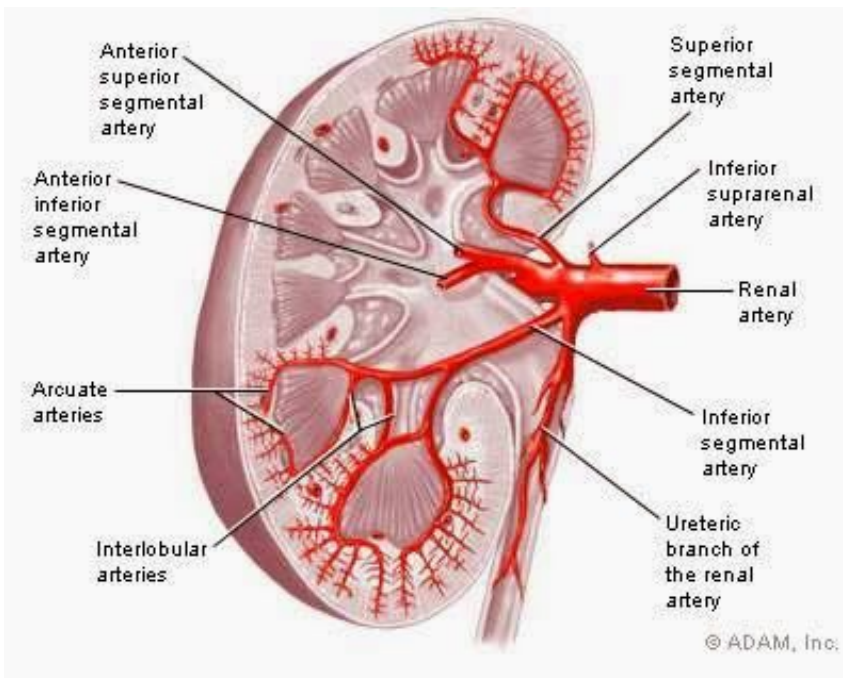
### **Histology of the kidney**

The parenchyma of the kidney is subdivided into superficial cortex and deep medulla . The parenchyma is subdivided into 8-18 lobes, each lobe is composed of a part of the cortex ( renal column) , surrounding a segment of medulla , called pyramid , which tip empties in a minor calyx , the later empties in a major calyx , and the major calyces ( calyces : Pl. of calyx) empty in the renal pelvis. The renal pelvis empties in the ureter.



### Blood supply of the kidney

- Kidney is supplied with blood by the renal artery, which is a branch of the abdominal aorta. Renal artery is subdivided into segmental arteries. Segmental arteries are subdivided into interlobar arteries that penetrate the renal capsule, run between the pyramids on the renal columns, and then subdivided into arcuate arteries between the cortex and medulla. Arcuate arteries are then divided into interlobular arteries, that fade into the afferent arterioles.



- Venous drainage : Venous drainage from the kidneys occurs as follows: Interlobular veins --> arcuate veins ---> interlobar vein ----> renal vein . Left renal vein is longer than the right

one, due to the fact that the left pass longer distance . Left renal vein also receives from left testicular vein and from left suprarenal vein and others.

- Lymphatics: The lymphatic supply of the kidney is abundant and drain into renal circulation via the thoracic duct.
- The kidneys receive about 1.1 litres of blood each minute (22% of cardiac output).
- Renal Plasma flow is about 625 ml/ min. 125 ml/min of this plasma is filtered in the glomeruli (glomerular filtration rate, while the remaining 500 ml/min passes via the efferent arterioles to the peritubular capillaries and then via the renal venules and veins to the circulation.
- The pressure in renal artery is similar to that in the arterial system. In glomerular capillaries, pressure is about 45 mm Hg, while the pressure in renal vein is about 4 mm Hg. Pressure in renal blood vessels is regulated by autonomic nervous system and by local regulatory mechanism as we will see later.

### **Innervation**

Kidney receives sympathetic innervation by the renal plexus , which branches run with renal artery. The parasympathetic innervation is provided by the branches of the vagus nerve.

### **Functional unit of the kidney (Nephron)**

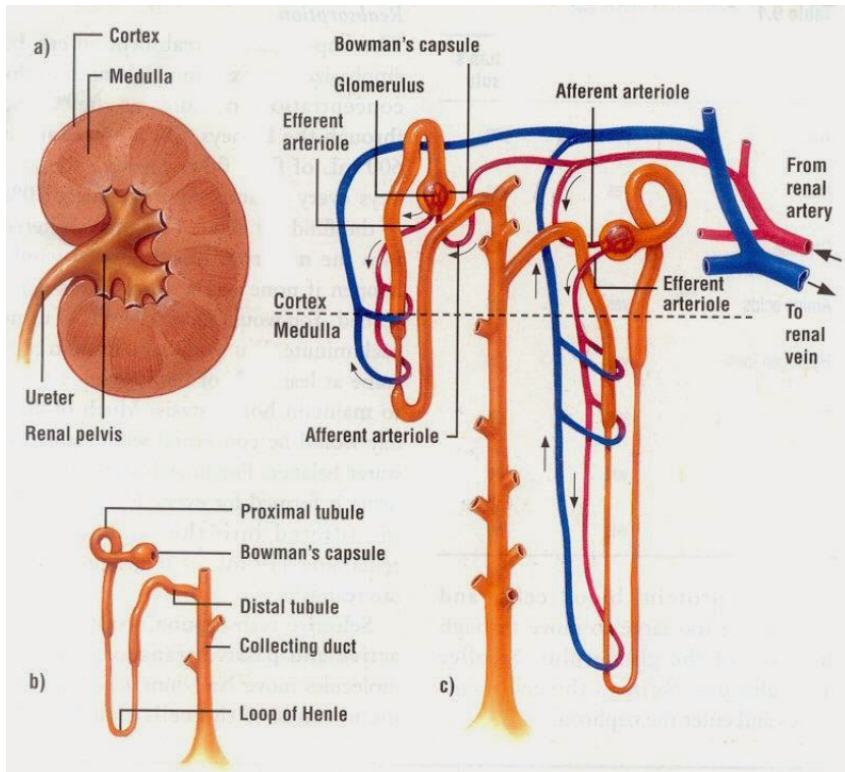
Nephron is the functional unit of the kidney , where the processes of urine formation take place . There are about 1-1.3 million of nephrons in each kidney.

After age of 40 , nephrons are decreased 10% each 10 years due to aging . When there is only 30 % of nephrons remained ,renal failure may develop .

Nephron is composed of :

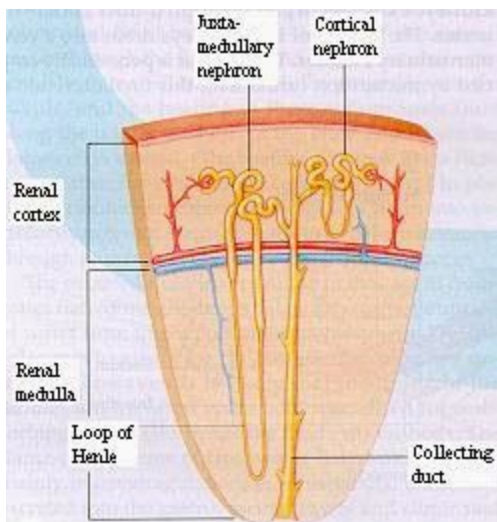
1. Vascular component : Afferent arteriole , glomerular capillaries , efferent arteriole , and peritubular capillaries . Glomerular capillaries and Bowman's capsule together are called renal corpuscle . The efferent arteriole has lesser diameter than that of the afferent arteriole. This is an important factor in glomerular filtration as we will see later.
2. Tubular component : Glomerular capillaries are involved in Bowman's capsule , which continues in the proximal tubule , loop of Henle , distal tubule , collecting tubule , and collecting duct .multiple nephrons may share the same collecting duct .
  - The tubular wall is formed of single layer of cells , with different morphology in different parts of the tubular system . single cell
  - Proximal convoluted tubule is about 15 mm long. Its wall is composed of single layer of cells interdigitated and connected to each others by tight junctions. The apical membrane of the tubular cells has a brush border surface to increase reabsorptive area, a plenty of mitochondria is found in the cytosol.
  - Limbs of loop of Henle are the thin descending and a short thin ascending, and thick ascending one. The cells of thin descending are thin and permeable to water ones. The cells of the thick ascending are permeable to electrolytes and have a lot of mitochondria. The limb of Henle reaches the glomerulus.
  - Distal Nephron : starts with convoluted tubule (5mm long), which starts in macula densa between the afferent and efferent arteriole. The distal tubules coalesce to form collecting duct (20 mm) which will empty into the renal Pelvis. The cells of collecting ducts involve two distinct types of cells: Principal cells, and intercalated cells, that play different role in reabsorptive and secretory functions as we will see later.





There are two types of nephrons :

- Cortical (superficial) nephrons : Found in the superficial layer of the renal cortex , and forms about 80% of the whole nephrons. These nephrons have shorter loop of Henle that does not dip into the medulla .
- Juxtamedullary nephrons : Also found in the renal cortex , but close to the medulla . They form about 20% of the whole nephrons. They dip deeply in the medulla . The loop of Henle of juxtamedullary nephron is surrounded by a special peritubular capillaries that are straight and known as Vasa Recta .



**Juxtaglomerular apparatus:**

Specialized cells that involves: Granular cells of afferent arteriole( Renin-secreting cells), macula densa of distal nephron ( sensitive cells to sodium chloride concentration) closed to afferent and efferent arterioles and lacis cells (extraglomerular mesangial cells) .

The cells of juxtaglomerular apparatus play important role in renal autoregulation as we will see later.

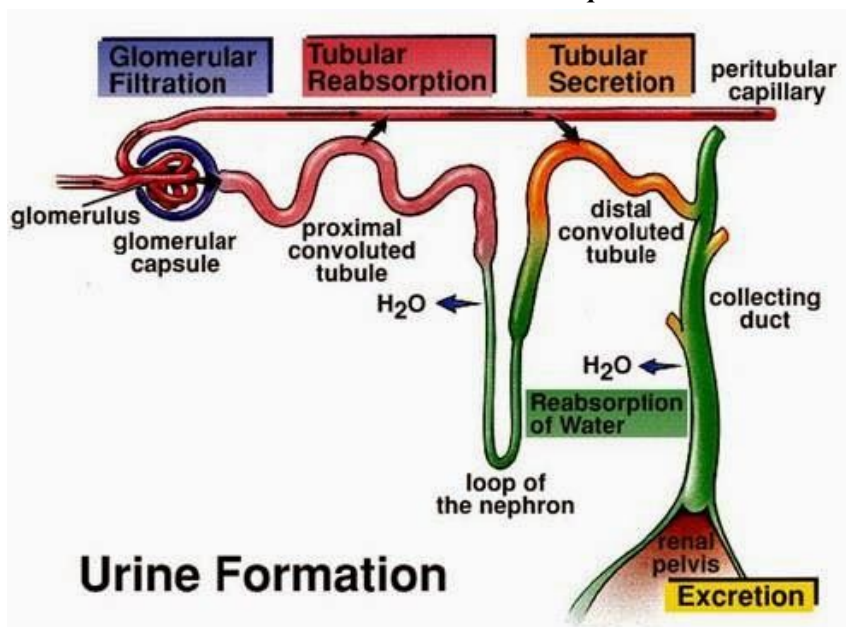
## Basic Functions of the Kidney

As we mentioned before, kidney is a vital organ without which we would not be able to survive. If the kidney's functions are impaired we will die within few days, due to the accumulation of toxic metabolic products inside our organism in addition to impaired fluid-electrolytes and acid-base balance, impaired regulation of arterial blood pressure, and impaired hematopoiesis.

The kidney rescues our life by filtration our blood, reabsorption (retaining) of beneficial for our organism substances, and excretion the waste products. This occurs by the processes of urine formation that takes place in the following steps:

- Glomerular filtration (GF): which means non-selective movement of constituents of plasma except the plasma proteins from the glomerular capillaries into the Bowman's capsule.
- Tubular reabsorption (TR): A selective process, by which some substances of the filtrate are retained back to the blood.
- Tubular Secretion (TS): A selective process by which some substances, that have not been filtered are secreted from the peritubular capillaries into the tubules.
- Whatever left over these three processes will be excreted in form of urine, so

$$\text{Excretion} = \text{Filtration} - \text{Reabsorption} + \text{Secretion}$$

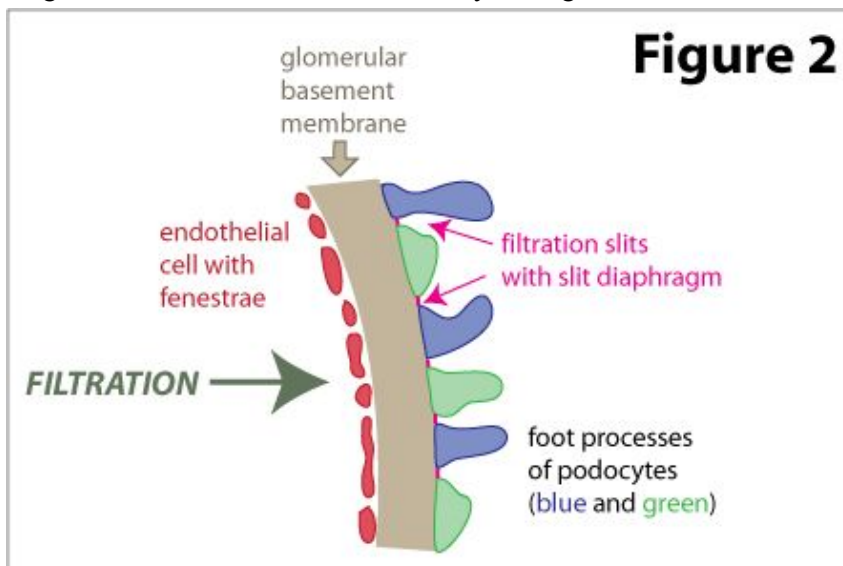


### I. Glomerular filtration

- Kidneys receive about 22-25% of cardiac output, this is called Renal Blood Flow (RBF) which is approximately 1.1-1.3 L of blood in a minute. Plasma in this flow is about 625 ml. It is called Renal Plasma Flow (RPF).
- About 20% of Plasma entering the glomerular capillaries is filtered into the Bowman's capsule.
- Glomerular filtration rate is about 125 ml/min (which means 7.5 L/hr and thus 180 L/day) This means that the kidney filters about 180 liters of plasma every day.

- The urine flow is about 1 ml/min ( about 1.5 liter /day) This means that kidney reabsorbs about 178.5 liters every day .
- Filtration occurs through the filtration unit , which includes :
  1. endothelial cells of glomerular capillaries , which are fenestrated . Fenestrae are quite small so they prevent filtration of blood cells and most of plasma proteins .
  2. Glomerular basement membrane : contains proteoglycan that is negatively charged and repels the negatively charged plasma proteins that may pass the fenestrae due to their small molecular weight like albumin . so the membrane plays an important role in impairing filtration of albumin . Podocytes are specialized cells , which interdigitate to form slits. They surround the endothelial cells along with the basement membrane.
- Between basement membrane and endothelial cells there are specialized cells, that are called mesangial cells that secrete the extracellular matrix and take up immune complexes and contribute to regulation of glomerular filtration as well.
- The basement membrane allow the passage of substances that diameter is 4 -8 nm, and exclude substances mor
- 3. Epithelial cells of Bowman`s capsule

The figure below illustrates the different layers of glomerular filtration membrane



- Many **forces** drive the glomerular filtration (Starling's forces) , which are :
  1. Hydrostatic pressure of the capillary blood , which favours filtration . It is about 55 mmHg .
  2. Oncotic pressure of the plasma proteins in the glomerular capillary ( opposes filtration ) . It is about 30 mm Hg .
  3. Hydrostatic pressure of the Bowman's capsule , which also opposes filtration. It is about 15 mmHg .
- The net pressure is as follows :
- *Hydrostatic pressure of glomerular capillaries - ( Oncotic pressure of glomerular capillaries + Hydrostatic pressure of the Bowman capsule):*

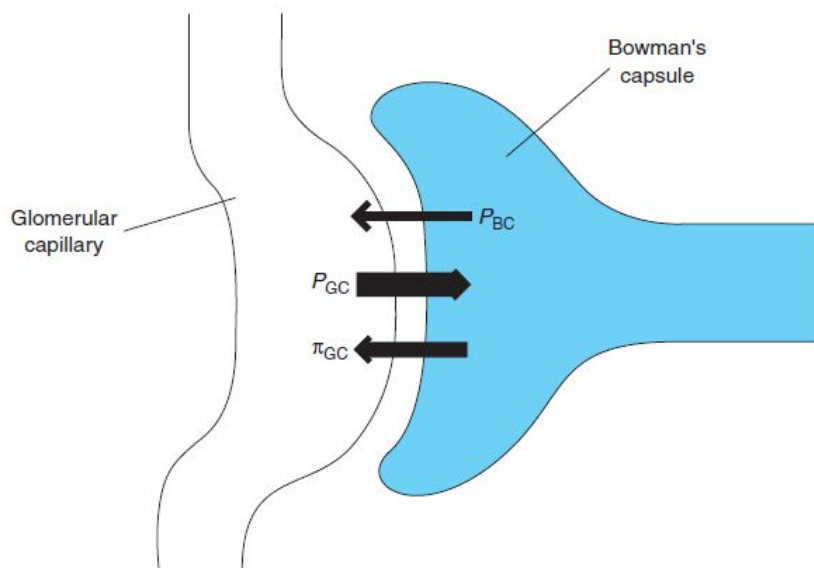
$$55 - (35 + 10)$$

$$= 55 - 45$$

$$= 10 \text{ mmHg .}$$



- The glomerular filtration rate does not depend only on the net pressure, but also on an other values, known as **filtration coefficient (K<sub>f</sub>)**. The later depends on the surface area of the glomerular capillaries and the hydraulic conductivity of the glomerular capillaries (permeability)
- Permeability of glomerular capillaries is high (about 50 times that of capillaries of skeletal muscles). It depends on the diameter of substances as well as their charge.
- Neutral substances less than 4 nm in diameter are always filtered, while substances more than 8 nm in diameter are never filtered.
- In addition to the diameter of substances, permeability also depends on the electrical charge of substances. Negatively charged substances are filtered more difficult than the positively charged ones.
- The surface area of capillaries is affected by mesangial cells that are contractible cells. When they contract they decrease the surface area available for filtration.

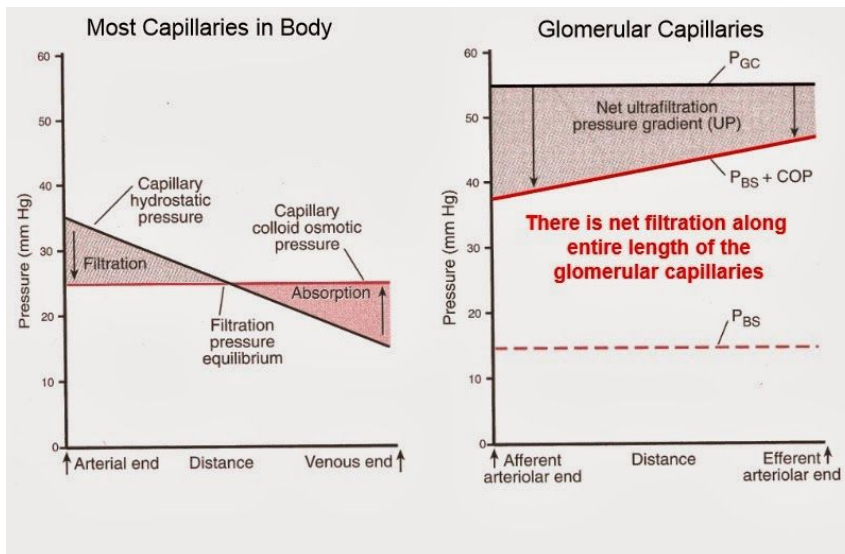


**Question:** Why filtration only occurs in the glomerular capillaries and not reabsorption as in the systemic capillaries?

This occurs thankful to many factors:

- Hydrostatic pressure in the glomerular capillaries is higher than that in the systemic capillaries. This is due to the lesser diameter of the efferent arteriole compared to the afferent arteriole.
- Hydrostatic pressure is almost constant due to the nature of the glomerular capillaries (multiple parallel loops).
- Due to filtration of huge amount of fluid, the oncotic pressure in the capillaries increases, while the hydrostatic pressure in Bowman's capsule does not increase gradually as in the interstitium of the systemic capillaries.

Compare this to the systemic capillaries as we discuss during the lecture.



### Factors , affecting glomerular filtration rate

Any factors that may influence the different pressure forces , or the filtration coefficient will affect the glomerular filtration rate . let's have some example :

1. Dehydration : Causes decrease hydrostatic pressure , and thus decreases GFR.
2. Liver diseases that may decrease the plasma proteins and decrease the oncotic pressure , and thus increases glomerular filtration rate . But please pay attention here! Decrease plasma proteins increase filtration in systemic capillaries which will lead to decrease renal blood flow and thus decrease glomerular filtration rate as a net result.
3. Sympathetic stimulation : will decrease the diameter of afferent arteriole and thus decreases glomerular filtration rate.
4. Renal diseases : Nephrotic syndrome for example decreases the number of working nephrons and thus decreases the filtration coefficient and thus decreases the glomerular filtration rate. Glomerulonephritis will causes thickening of the glomerular basement membrane and thus decreases the glomerular filtration rate by decreasing the filtration coefficient too.

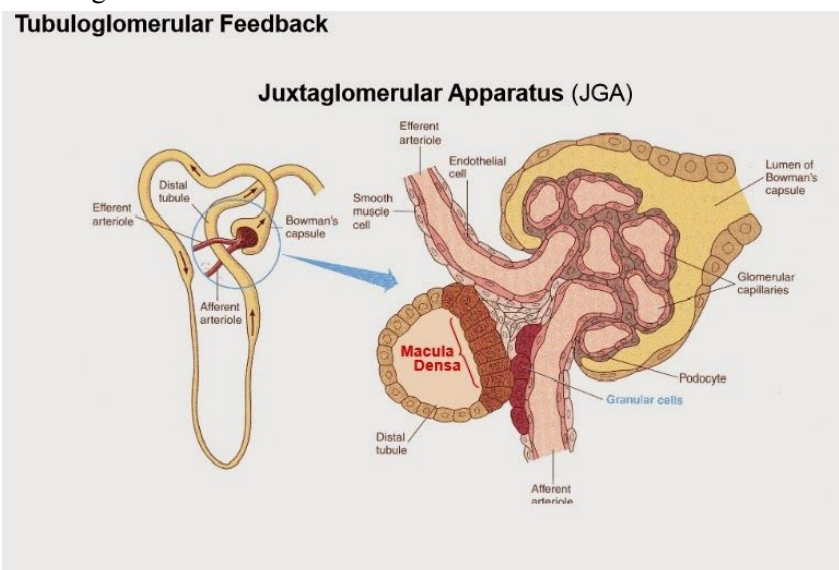
### Regulation of glomerular filtration

1. Extrinsic regulation : occurs by :
  - Neural regulation : sympathetic and parasympathetic nervous system which causes vasoconstriction or vasodilation respectively . Sympathetic nerves causes constriction of afferent arteriole and decreases GFR but this effect is mild at rest. It is remarkable in some pathological situation like hemorrhage.
  - Humoral regulation : Vasoactive substances may affect the GFR as follows:
    - vasoconstrictive substances like endothelin ( derived from damaged vascular endothelial cells)
    - Angiotensin II : Regarding Angiotensin: it preferably constrict efferent arteriole and considered to increase GFR but it also decrease blood flow to peritubular capillaries and increases reabsorption of water and salt, and thus: maintains optimal blood pressure.
    - Norepinephrine and epinephrine: similar to sympathetic effect

- prostaglandin F2 may constrict the afferent arteriole and thus decrease GFR , while the vasodilative agents like dopamine ,
  - NO : vasodilation and decrease in vascular resistance, and thus it increases GFR
  - ANP : Increases GFR by decreasing vascular resistance.
  - Prostaglandins E2 may dilate the afferent arteriole and thus increase the filtration rate
- .
- Dopamine : Causes vasodilation and increases GFR
  - High protein diet increases oncotic pressure and decreases GFR

2. Intrinsic regulation : Occurs by :

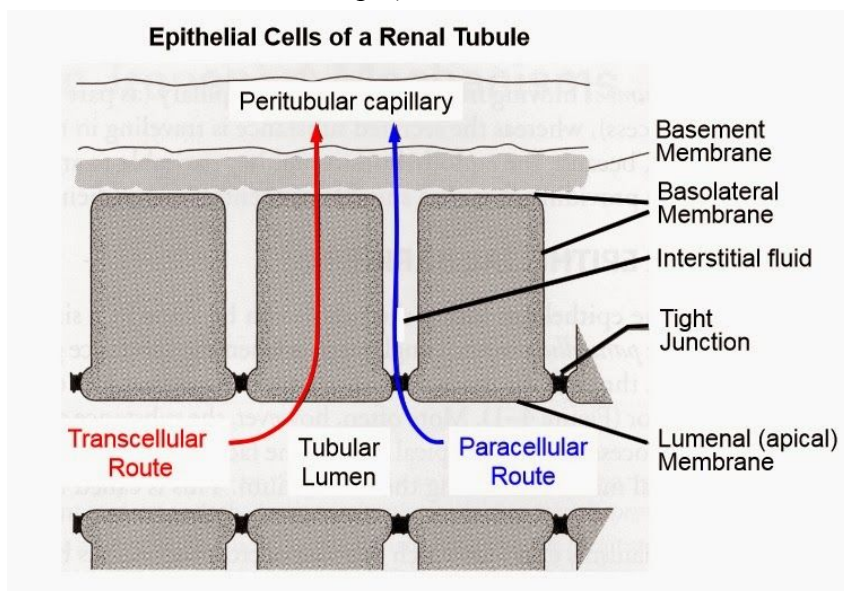
- Myogenic theory ( as in the intrinsic regulation of cardiac output. Please read them again) .
- Tubuloglomerular feedback: occurs by cells of the juxtaglomerular apparatus that is composed of specific cells of the distal tubules when it passes between afferent and efferent arterioles ( macula densa cells ) , these cells sense changes in flow inside the tubules and inform specific cells in the afferent arteriole and cause their dilation. They also affect the (granular cells ) , the later secrete Renin and start activation of RAAS which will activate angiotensin II that will dilate the afferent arteriole and constrict the efferent.



## II. Tubular reabsorption

Remember the following principles before proceeding :

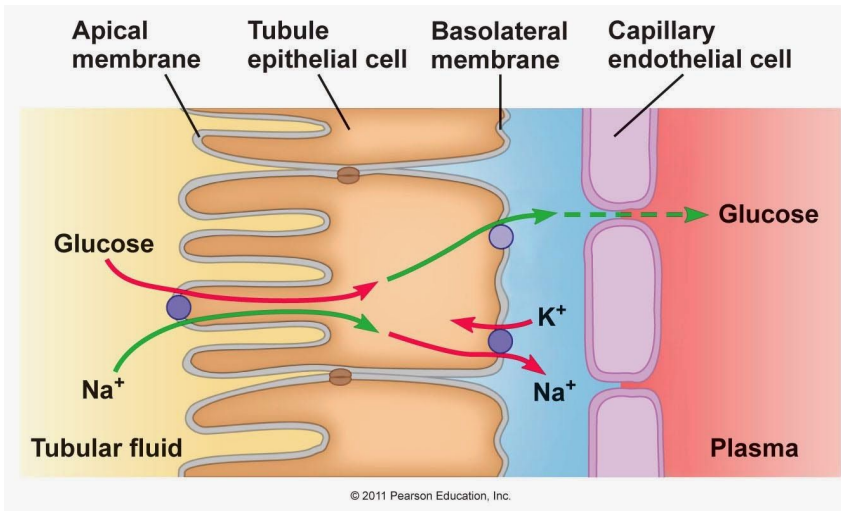
- Reabsorption occurs for most of substances that have been previously filtered.
- The direction of reabsorption is from the tubules to the peritubular capillaries.
- All of transport mechanism are used here (passive and active transport)..
- Different morphology of the cells of different parts of the tubules contribute to reabsorption of different substances.
- There are two routes of reabsorption: Paracellular and transcellular : Paracellular reabsorption depends on the tightness of the tight junction which varies from region to region in the nephrons .Transcellular depends on presence of transporters ( carriers and channels for example).



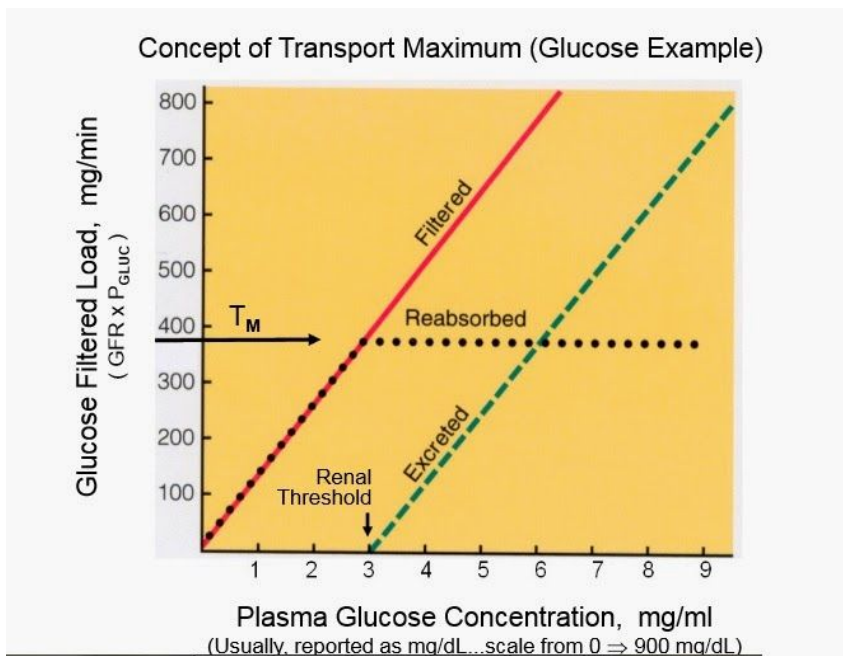
### 1. Reabsorption of glucose , amino acids , and proteins

- Transport of glucose occurs in the proximal tubule .
- Cells of proximal tubules are similar to those of the intestinal mucosa as the apical membrane has brush border form to increase the surface area for reabsorption , the cells have plenty of mitochondria which inform us that high amount of energy is required for active transport , and the basolateral membrane of the cells contain sodium -potassium pumps , while the apical membrane contains a lot of carrier and channels .
- The tight junction between the tubular cells of the proximal tubules are not that (tight) which allow paracellular transport.
- Reabsorption of glucose starts by active transport of Na by the pumps on the basolateral membrane . This will create Na gradient which will cause Na<sup>+</sup> to cross the apical membrane down its concentration gradient .
- Glucose also passes the membrane up its concentration gradient using sodium -glucose symporter as a secondary active transport.

The concentration of glucose will be increased in the cell and this will enable the glucose to pass down concentration gradient to the interstitium by glucose uniporter . Glucose will then pass to the peritubular capillaries by simple bulk flow.



- Remember: Glucose reabsorption occurs via transcellular route.
- Glucose transport has transport maximum . In normal situation there is no glucose in the urine , but in uncontrolled diabetes mellitus patients glucose level exceeds its transport maximum (390 mg/dl) and thus will appear in urine .



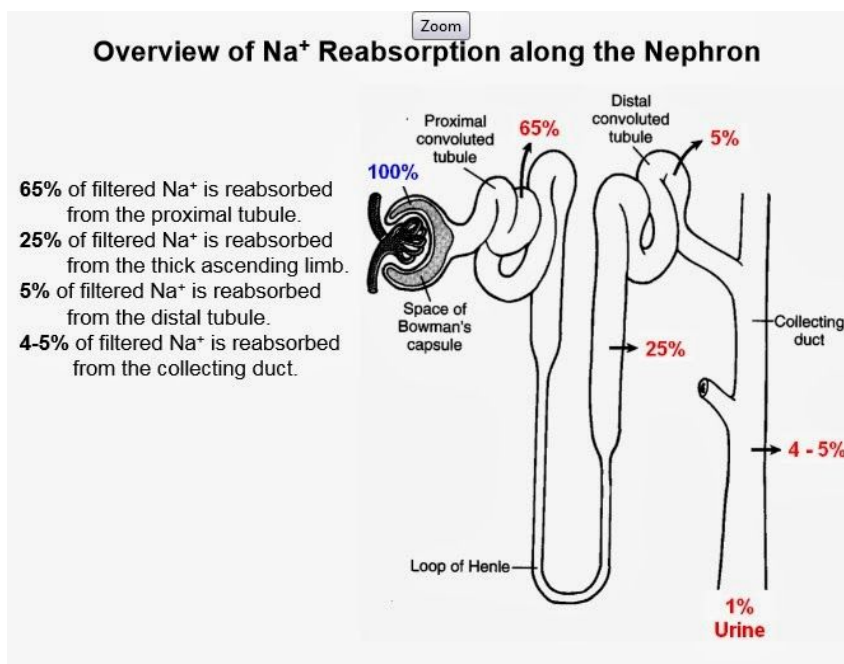
2. Reabsorption of Amino acids : Use secondary active transport mechanism like glucose.
3. Reabsorption of proteins : Plasma proteins are not filtered in Bowman's capsule but some proteins and peptides in blood may pass the filtration membrane and then reabsorbed . Some peptides are reabsorbed paracellularly , while the others bind to the apical membrane and



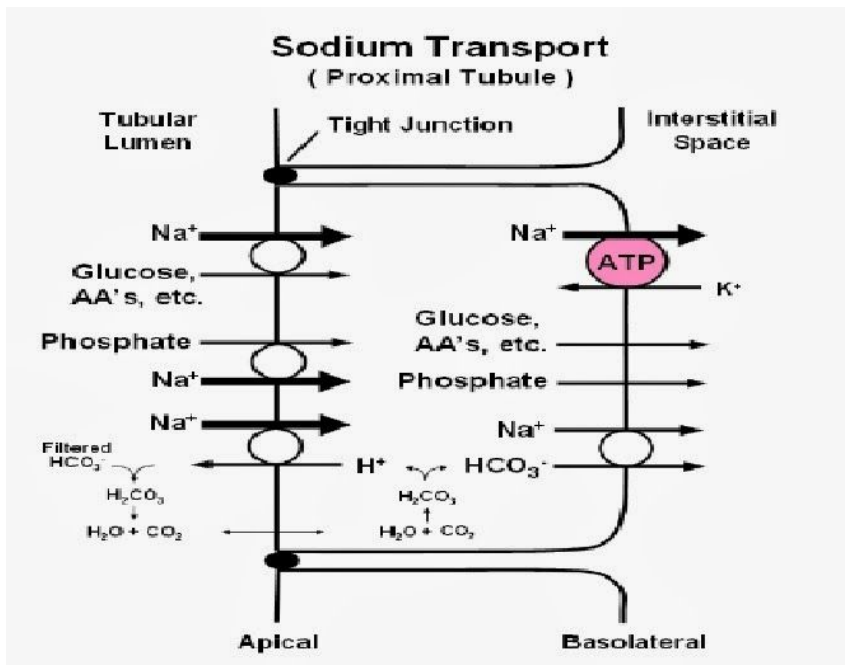
then enter the cells by endocytosis , where they will degraded by peptidase enzymes to amino acids .

#### 4. Renal Handling of Sodium

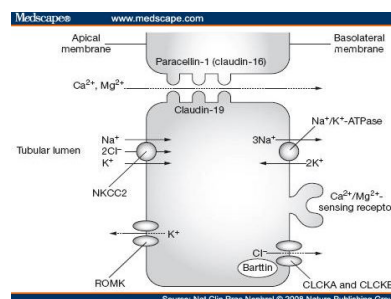
- The daily intake of  $\text{Na}^+$  is about 10.5. 10 g are eliminated by kidney, while the other 0.5g is eliminated by sweat and feces.
- Reabsorption of sodium takes place in different portions of the nephron as follows:
  1. 65 % of sodium is reabsorbed in the proximal tubules ,
  2. 25% are reabsorbed in the thick ascending limb of loop of Henle ,
  3. 9% in the distal and collecting tubules and collecting ducts .
- 90% of sodium reabsorption occurs independently from its plasma level (unregulated) , This is true for sodium reabsorbed in proximal tubule and loop of Henle , while the 9% that is reabsorbed in distal ,collecting tubules and collecting ducts is regulated by Aldosterone.



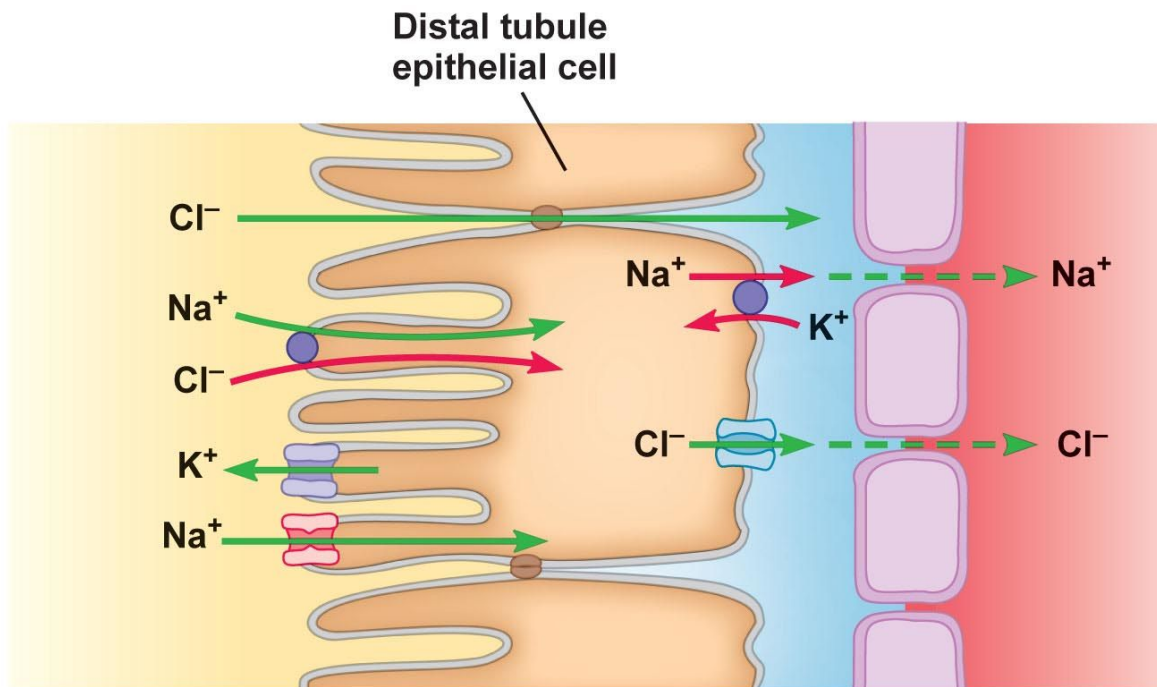
- In proximal tubules, where 65% of sodium is reabsorbed . The initial step occurs by creating sodium gradient by sodium-potassium pump on the basolateral membrane . This will decrease the sodium concentration in the intracellular fluid (12 mEq compared to 140 mEq in the filtrate) and will also create a negative charge inside the cell, thus the sodium will pass from the lumen into the cells down concentration and electrical gradient by sodium -glucose symporter(SGLT1), sodium-amino acid symporter, sodium -phosphate symporter and by sodium- hydrogen antiporter and others . Sodium- hydrogen antiporter accounts for most of sodium reabsorption in the proximal tubule. After crossing the apical membrane, the  $\text{Na}^+$  then passes to the interstitium by  $\text{Na}/\text{K}$  pump and by  $\text{Na}^+/\text{HCO}_3^-$  symporter.



- After reabsorption of sodium, an electrical gradient will be created, then chloride is reabsorbed following the sodium. Chloride diffuses mainly in passive paracellular route, Thus the major cation and anion leave the lumen to the interstitium and thus the water follows by osmosis. 65% of water is reabsorbed in the proximal tubule. The filtrate, leaving the proximal tubule is iso-osmolar.
- Descending limb of loop of Henle is impermeable to electrolytes but avidly permeable to water. 10% of water is reabsorbed in the descending thin limb of loop of Henle, but **NO** sodium is reabsorbed here. The osmolarity of the filtrate is increased due to reabsorption of water.
- The thin ascending limb of loop of Henle is permeable to electrolytes, due to the increased osmolarity, sodium is transported passively here.
- Thick ascending limb of loop of Henle is responsible for reabsorption of 25% of sodium due to presence of  $\text{Na}^2\text{Cl}$  symporter on the apical membrane of its tubular cells. There is also a little contribution of  $\text{Na}^+/\text{H}^+$  antiporter. A paracellular route is also used in sodium reabsorption here, probably due to high conductance of sodium due to positive luminal potential. The thick ascending limb is impermeable of water, so the osmolarity of filtrate is decreased at the end of the limb due to  $\text{Na}^+$  and other electrolytes reabsorption.



- In the distal and collecting tubules and the collecting ducts 9% of sodium is reabsorbed .In distal tubule 5% of sodium is reabsorbed by  $\text{Na}^+/\text{Cl}^-$  symporter and ENaC channels on the apical membrane.



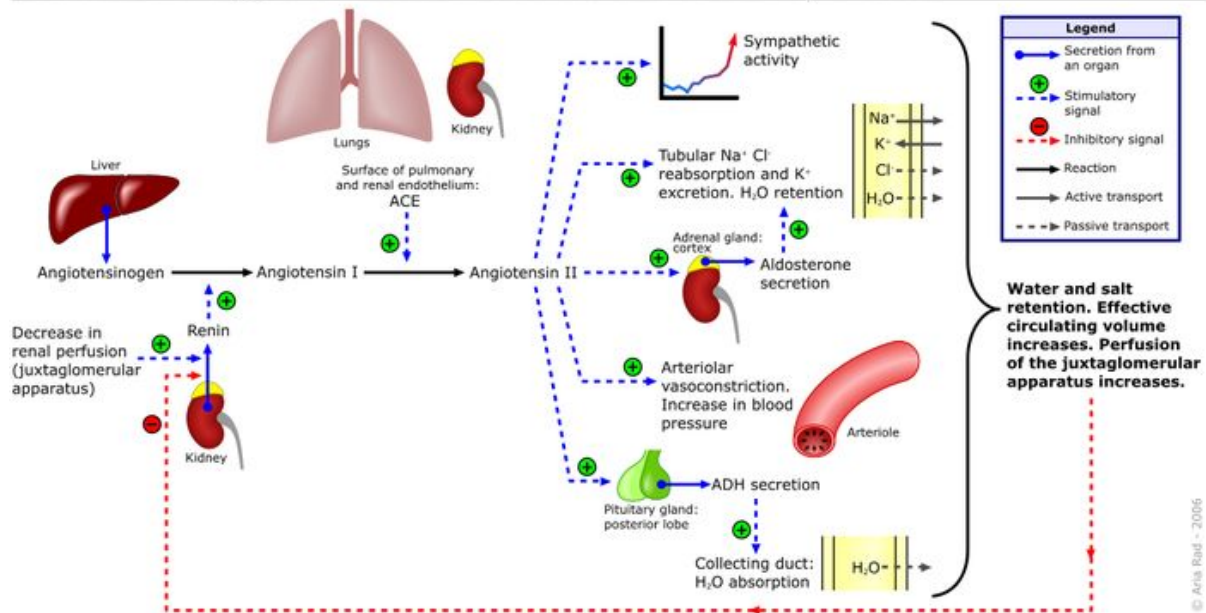
### (b) Sodium reabsorption in the distal tubule

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- In the collecting duct: 4% of sodium is reabsorbed by the principal cells via ENaC sodium channels this occurs under aldosterone control depending on sodium plasma level as follows :  
Aldosterone is a vital hormone that has the following functions :
  1. Reabsorption of sodium in the principal cells of the distal collecting ducts in the kidney, which occurs as follows :
    - On the basal membrane of the tubular cells there are Na/K pump which extrudes three  $\text{Na}^+$  and enter two  $\text{K}^+$  ions and those pumps are up-regulated by aldosterone .As a result of that the intracellular sodium concentration decreases and thus the sodium enter the tubular cell through its epithelial sodium channels found in the apical membrane down its concentration gradient . Aldosterone also up-regulates the epithelial sodium channels and thus increases the permeability for sodium. The water follows sodium , and thus the blood volume increase and the arterial blood pressure increase. Chloride is also reabsorbed to maintain electrochemical balance.
    - 2. Secretion of potassium : The intracellular potassium concentration increases by the effort of Na/K pump and then it is secreted down its concentration gradient out of the tubular cell to the lumen .
    - 3. Secretion of  $\text{H}^+$  : This occurs in the intercalated cells of the collecting ducts in exchange with  $\text{K}^+$  . This contributes to acid -base balance in the organism as we will see later.

- Aldosterone is a part of Renin-Angiotensin- Aldosterone system : Liver produce an inactive protein , known as Angiotensinogen . When the sodium decreases in the blood , the cells of juxtaglomerular apparatus in the kidney sense that and release Renin . Renin converts Angiotensinogen into Angiotensin I . Lungs produce an enzyme , called Angiotensin converting enzyme( ACE) which convert Angiotensin I into the active Angiotensin II . Angiotensin II stimulates aldosterone production and release.

## Renin-angiotensin-aldosterone system



- 1% of sodium is excreted .

### Renal Handling of water - Urine concentration and dilution

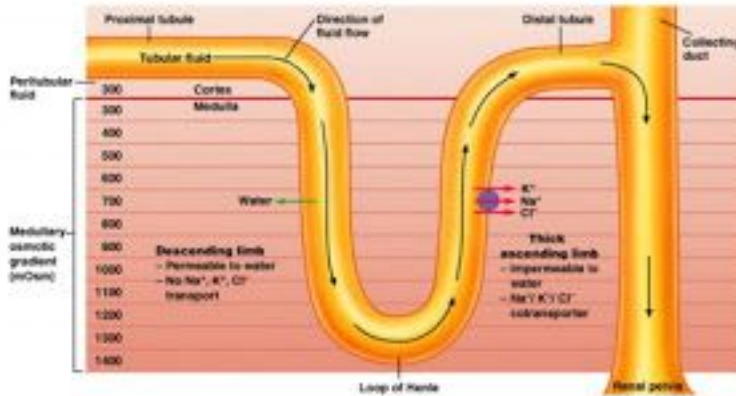
- Daily intake of water is about 2500 ml. 1500 ml as drunk water, 700 ml within the food, and about 300 ml of water is synthesized as an end-product of metabolic processes.
- Water input has to equal water output. So: 1500 ml is excreted in urine, 900 ml of water is eliminated as insensible water loss via respiratory system and skin, and 100 ml is excreted by the stool.
- Kidney is a major route for eliminating fluid from the body to accomplish water balance. Urine excretion is the last step in urine formation. Everyday both kidneys excrete about 1.5 liters of urine.
- After being filtered in the glomerulus, 65% of water is reabsorbed in proximal convoluted tubule, 10% in thin ascending limb of loop of Henle, and the remaining in distal nephron.
- Depending on the hydrated status of the body, kidney either excretes concentrated urine ( if the plasma is hypertonic like in dehydrated status ) or diluted urine ( if the plasma is hypotonic) . This occurs thankful to what is known as countercurrent multiplying system, which functions thankful to establishing large vertical osmotic gradient .To understand this system, lets review the following facts:

1. Descending limb of loop of Henle is permeable to water.

2. Ascending limb of loop of Henle is permeable to electrolytes , but impermeable to water. So fluid will not follow electrolytes by osmosis. and thus Ascending limb creates hypertonic interstitium that will attract water from descending limb.

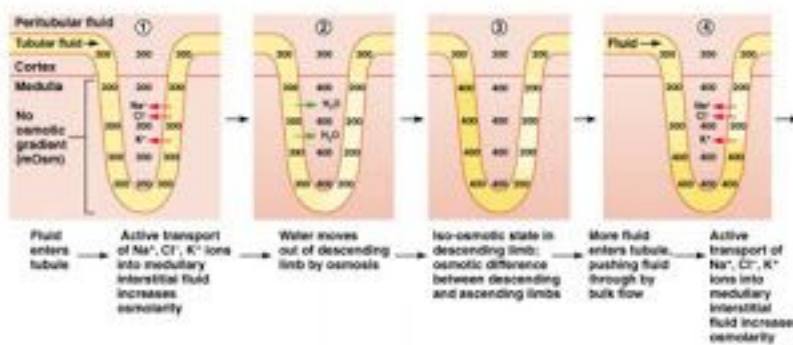
Pumping of electrolytes

3. So: There is a countercurrent flow produced by the close proximity of the two limbs.



4. Losing water by descending limb makes its fluid hypertonic, while losing electrolytes by ascending limb makes its fluid hypotonic. Repeating of these steps will create hypertonic interstitium which will attract fluid and create hypotonic fluid in distal tubules. (see the image)

5. Juxtamedullary nephrons have long loop of Henle that dips deeply in the medulla , so this counter-current system is more obvious and the medullary interstitium is always hypertonic . The countercurrent multiplier system follows the principle proposed by (Kuhn & Ryffel), which states that (osmotic pressure is raised along parallel but opposing flows in nearby tubes that are made contiguous with a hairpin turn). This is true for the juxtamedullary loop of Henle .



6. In addition, peritubular capillaries in the medulla are straight ( vasa recta). There are descending and ascending vasa recta in which blood flow is low and reabsorb solutes and secrete water by descending vasa recta, while reabsorb water and secrete electrolytes by ascending vasa recta, and thus minimize washout of solutes from medullary interstitium, maintaining hypertonic medullary interstitium. This arrangement of blood vessels maintains hypertonic medullary interstitium.(1200-1400 mOsm/l)

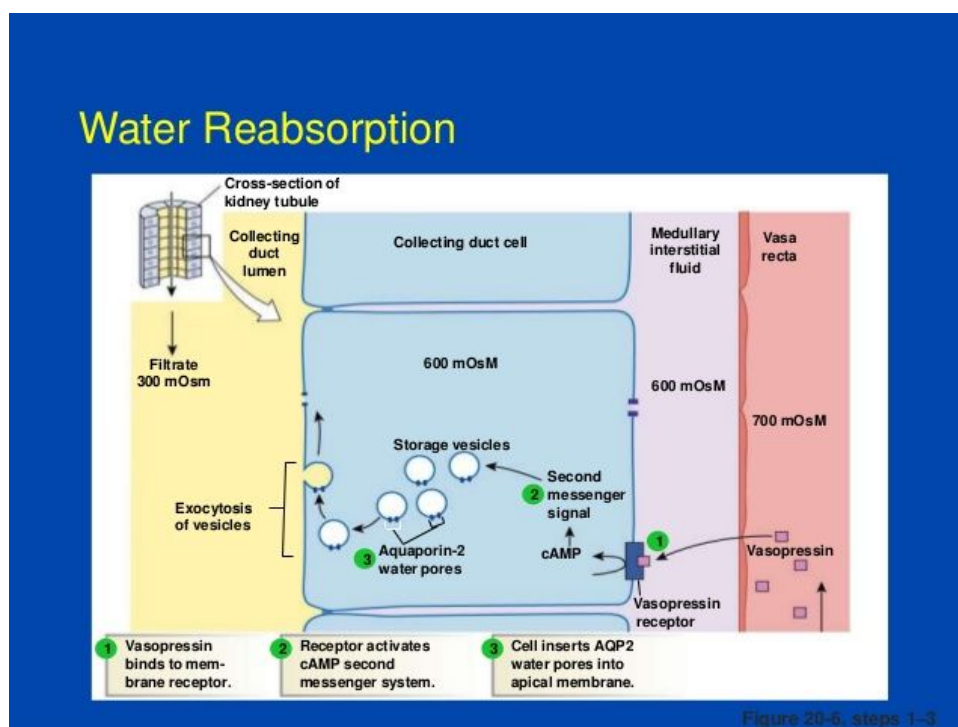
6. As a result: In distal tubules water is diluted. If plasma is hypertonic, this will lead to release of ADH by hypothalamus, which will cause reabsorption of water in collecting tubules and thus excrete



concentrated urine. But: If plasma is hypotonic ADH will be inhibited and the diluted urine in distal tubules will be excreted as diluted urine.

7. Urea contributes to concentrating and diluting of urine as follows: Urea is totally filtered and then 50% of filtered urea will be reabsorbed to the interstitium in proximal convoluted tubule via a paracellular passive diffusion, this will increase the osmolarity of medullary interstitium ( becomes hypertonic ). Those 50% will be secreted in ascending limb of loop of Henle back to tubular fluid to maintain osmolarity of tubular fluid. 55% of urea in distal nephron will be reabsorbed in medullary collecting ducts back to the interstitium ( under the effect of ADH too) . This urea cycle between the limb and collecting ducts additionally maintain hypertonic interstitium.

- If plasma osmolarity is increased ( higher than 290 mOsm/l ), ADH hormone is released by magnocellular cells of hypothalamus (80% by supraoptic nuclei, 20% by paraventricular nuclei) .
- Antidiuretic hormone ( ADH ) or Vasopressin is peptide hormone , that is composed of 9 amino acids . It is released when stimulated by: Increased plasma osmolarity (detected by osmoreceptors in hypothalamus), or by decreased blood pressure or volume ( detected by arterial baroreceptors).
- It acts to increase water permeability in the late distal tubule, cortical and inner medullary collecting ducts of the kidney , and facilitates reabsorption of water and decreases the urine volume( concentrated urine) . This effect is a result of inserting more aquaporins 2 ( water channels) in the apical membrane of late distal tubules and collecting ducts of the kidney . The net result is excretion of more concentrated urine and increasing blood volume and blood pressure. ADH also increases the permeability of inner medullary collecting ducts to urea. ADH receptors in the kidney are V2 receptors. Binding to them ADH affect the target cells via second messenger mechanism .



- If blood volume is increased (hypotonic), the arterial baroreceptors and atrial stretch receptors will be stimulated. They will send signals that inhibit the release in ADH and stimulate the release of ANP (atrial natriuretic peptide).
- This mechanism also contributes to water balance. When plasma osmolarity is increased the osmoreceptors send signals that provoke thirst and stimulate us to drink water.

### **Clinical Physiology**

***1. diabetes insipidus :is a disease , caused either by ADH hormone deficiency ( central diabetes insipidus ) or by resistance in ADH receptors in the distal and collecting tubules ( nephrogenic diabetes insipidus ) . This disease causes dilution in urine and thus increase urine excretion ( polyuria ) , which in turn increases the osmolarity of blood and causes thirst and provokes patient to drink more water ( polydipsia ) .***

***2. Syndrome of inappropriate Antidiuretic Hormone (SIADH): A disease that cause increased secretion of ADH in spite of normal plasma osmolarity. This will lead to impaired water excretion and thus hyponatremia***

### III. Tubular secretion

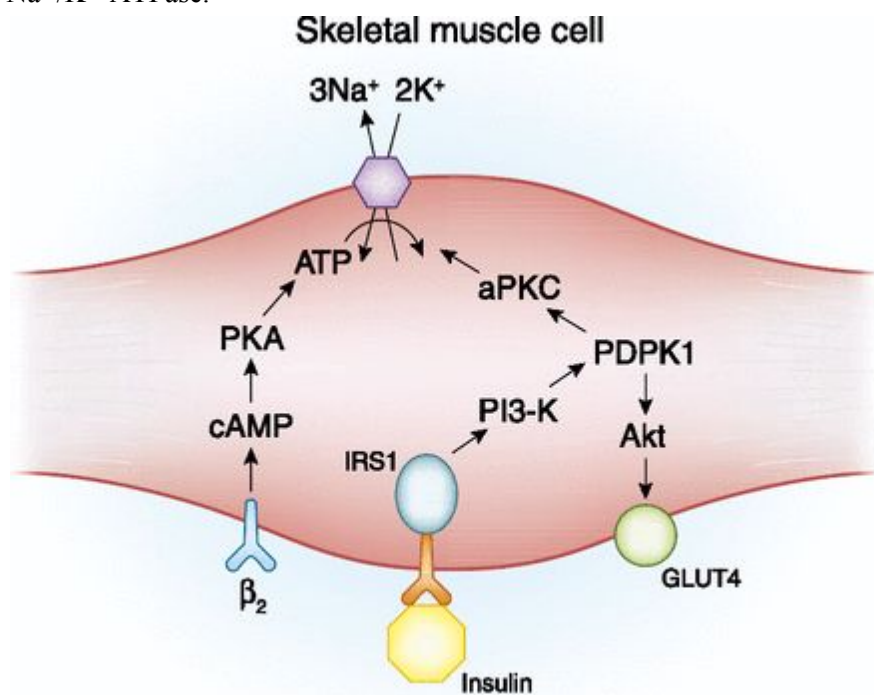
Involves transfer of substances from peritubular capillaries into the tubular lumen. It involves transepithelial transport in a direction opposite to that of tubular absorption.

Renal tubules can selectively add some substances that have not been filtered to the substances that already have been filtered via tubular secretion.

Tubular secretion mostly function to eliminate foreign organic ions, hydrogen ions ( as a contribution to acid base balance ), potassium ions ( as a contribution to maintaining optimal plasma  $K^+$  level to assure normal proceeding of neural and muscular functions), and urea.

Here we will focus on  $K^+$  secretion and will later discuss  $H^+$  secretion in acid base balance. Urea secretion has been mentioned in water balance.

- $K$  is the major intracellular cation. 98% of total body  $K^+$  is intracellular ( about 150 mEq)
- 2% of  $K^+$  is in the ECF. 90% of  $K^+$  is exchangeable, while 10% is unexchangeable.
- $K^+$  in ECF is responsible for maintaining potential difference across the cell membrane (Resting membrane potential) as contributes to neuromuscular excitability and cardiac rhythmicity.
- $K^+$  in ICF is responsible for pH regulation, DNA synthesis, enzyme activity and cellular growth. It also maintains the cell volume (as a major cation)
- $K^+$  daily intake by diet is about 100 mEq.90% is reabsorbed in the intestines, while 5-10% is eliminated by the stool. The reabsorbed  $K^+$  is then distributed between ECF and ICF before being excreted by kidney.
- $K^+$  is distributed between ICF and ECF. Regulation of such distribution is known as : internal  $K^+$  balance. This usually occurs by insulin and catecholamines, both of which affect the  $Na^+/K^+$  ATPase.

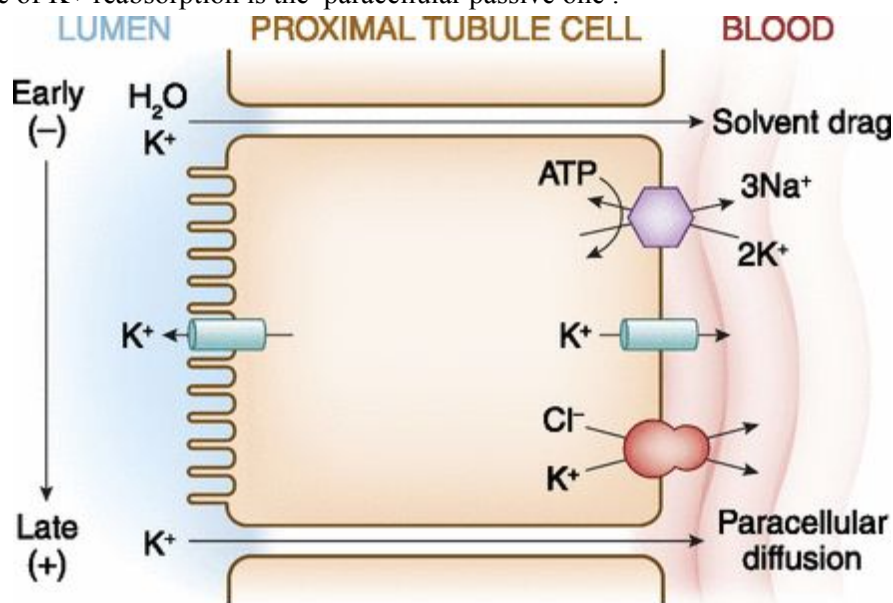


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- Catecholamines activate the  $K^+$  via Beta-receptors in skeletal muscles , while if via alpha receptors they will impair the uptake.

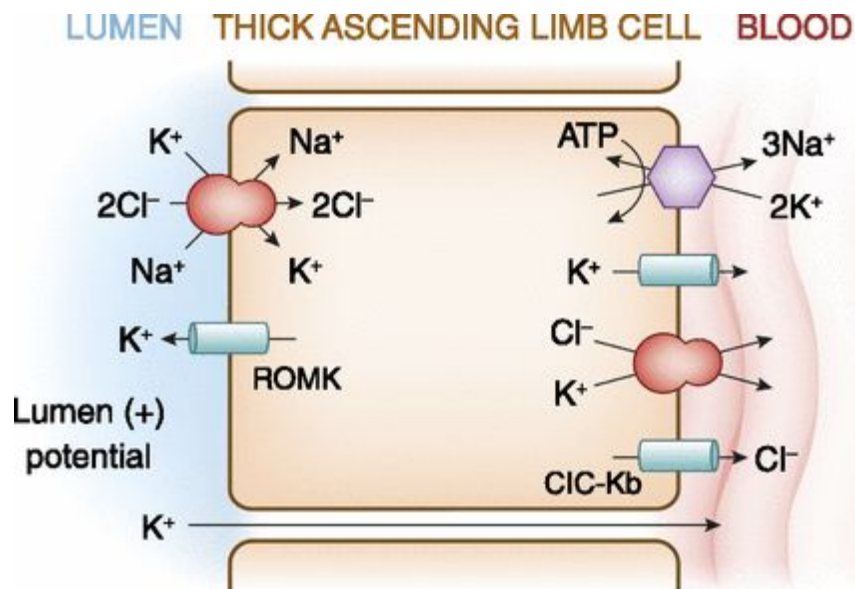
- Aldosterone also increase cellular uptake of  $K^+$  in skeletal muscles.
- Acid base imbalance also affect  $K^+$  level, as metabolic alkalosis decreases the  $K^+$  level in plasma, while metabolic acidosis increases its level .
- Cellular lysis and strenuous exercise also increases  $K^+$  level.
- Finally:  $K^+$  level in plasma has to be kept between 3.5-5.5 mEq/l, any shifting below or above this range may have dangerous consequences.

### Renal Handling of $K^+$

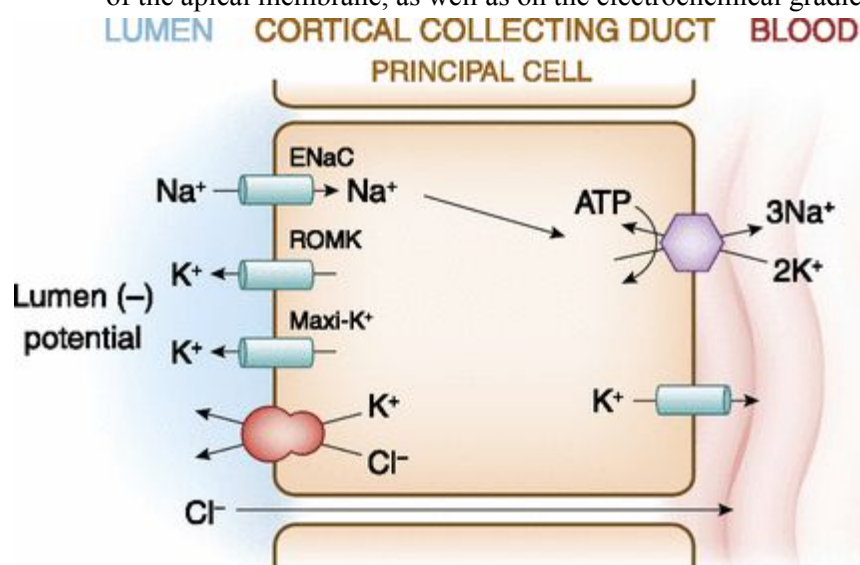
- $K^+$  is filtered in glomerular capillaries and then reabsorbed in proximal convoluted tubules as well as in thick ascending limb of loop of Henle (  $Na^+2Cl^-K^+$  symporter)
- about 67% of  $K^+$  is reabsorbed in proximal tubules by  $K^+/Cl^-$  symporter but the primary route of  $K^+$  reabsorption is the paracellular passive one .



- In thick ascending limb of loop of Henle about 20% of  $K^+$  is reabsorbed. This occurs by the  $Na^+/K^+/2Cl^-$  symporter. The ROMK channels on the apical membrane provide a chance for  $K^+$  recycling between the cell and the lumen, this will create a lumen-positive charge, which create a driving force for paracellular diffusion of  $K^+$  . So : Reabsorption of  $K^+$  in thick ascending limb is both transcellular and paracellular.

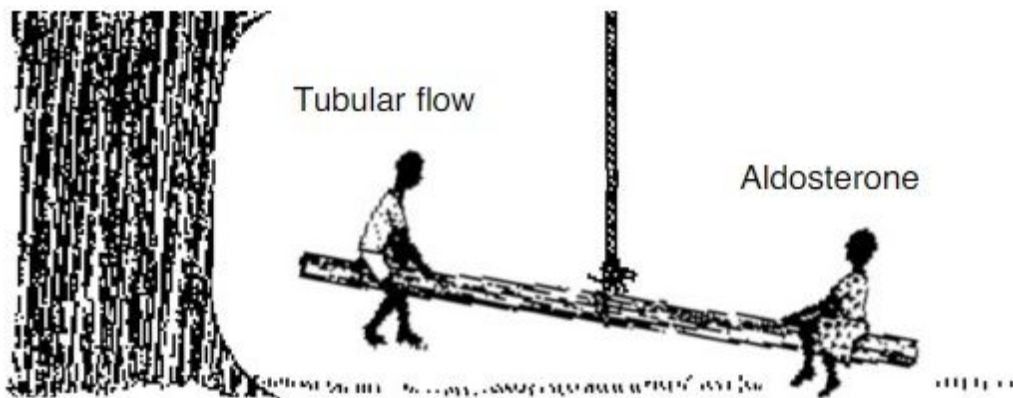


- Distal nephron is able either to reabsorb or secrete K<sup>+</sup>, depending on plasma level of K<sup>+</sup>. This is a hormone-regulated process (mainly cortical collecting ducts and not medullary collecting duct). In early distal convoluted tubule there is Na<sup>+</sup>/Cl<sup>-</sup> cotransporter which is abundant, but it declines in the late convoluted tubules. On the other hand ENaC, ROMK, are gradually increased along the late distal tubule, collecting tubule, and collecting duct.
- Principal cells in collecting tubule and collecting duct are responsible of K<sup>+</sup> secretion. This occurs as follows:
  1. By the activity of Na<sup>+</sup>/K<sup>+</sup> on the basolateral membrane of principal cells, the K<sup>+</sup> enters the cell.
  2. K<sup>+</sup> is the diffuse through the K<sup>+</sup> channels found in the apical membrane against electrochemical gradient. What does causes electrochemical gradient? Sodium enters the cell by ENaC and extruded by the pump. Chloride will follow the sodium paracellularly. This will make the interstitium electrically neutral, and the tubule is negative but less negative
- The process of secretion depends on the activity of Na<sup>+</sup>/K<sup>+</sup> pump, as well as on the permeability of the apical membrane, as well as on the electrochemical gradient.





- Intercalated cells Type A in the distal nephron reabsorb  $K^+$  in exchange with  $H^+$  when plasma level of  $K^+$  is decreased.
- The increased flow rate in the tubule increases  $K^+$  secretion while the decreased flow rate reduces  $K^+$  secretion.
- Aldosterone increases secretion of  $K^+$  by stimulation the activity of  $Na^+/K^+$  ATPase, increasing the  $K^+$  permeability of the apical membrane, and favours the electronegativity of the lumen. **BUT:** The flow rate and aldosterone release are paradoxical, which means that : when the flow rate is increased the aldosterone release is decreased, and vice versa. This is useful, because handling of  $K^+$  remains independent of the plasma volume status.



#### Clinical Physiology :

##### 1. Hypokalemia

- Hypokalemia: A decrease in  $K^+$  below 3.5 results from poor intake, beta agonist drug , rapid cell growth, diuretic use or hyperaldosteronism.
- results in Rhabdomyolysis , cardiac arrhythmia, hypertension and intestinal paralysis.
- Treated by  $K^+$  supplement ( preferably oral ) or as IV supplement.

##### 2. Hyperkalemia:

- An increase in  $K^+$  level above 5.5, which may result from increased intake. renal failure, using of  $K^+$  sparing diuretics, cell death, tumors, using of beta blockers and others.
- Results in muscle weakness, and cardiac arrhythmia.
- Treated by calcium in first place to protect heart, and then decreasing  $K^+$  by inducing  $K^+$  shifting (using insulin and beta agonists) and by promoting renal diuresis.

## Renal Handling of Calcium

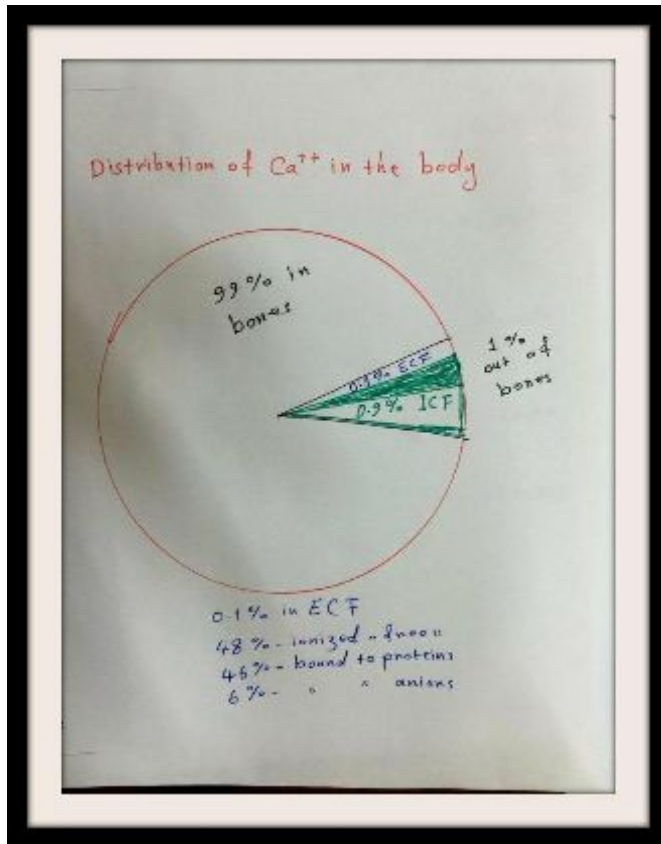
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### I. Functions of calcium

- Formation of bones: Remember that 20% of bones is organic matrix, while 80% is composed of minerals, most of which are calcium phosphate.
- Nerve impulse transmission
- Skeletal muscle contraction
- Cardiac rhythm
- Blood clotting
- Hormone secretion
- Enzyme activity
- Intercellular signalling

### II. Distribution of calcium in the body:

- 99% of calcium is stored in skeleton. 1% of  $\text{Ca}^{++}$  in skeleton is exchangeable with  $\text{Ca}^{++}$  in the extracellular fluid
- 1% of  $\text{Ca}^{++}$  is distributed between intra- and extracellular fluid. Intracellular  $\text{Ca}^{++}$  forms about 0.9% of total body calcium, while extracellular calcium forms only 0.1% of total body calcium.
- 48% of ECF  $\text{Ca}^{++}$  is in ionized form, while the other 46% is bound to plasma proteins and the remaining 6% is bound to anions.



### III. Daily input and output of $\text{Ca}^{++}$

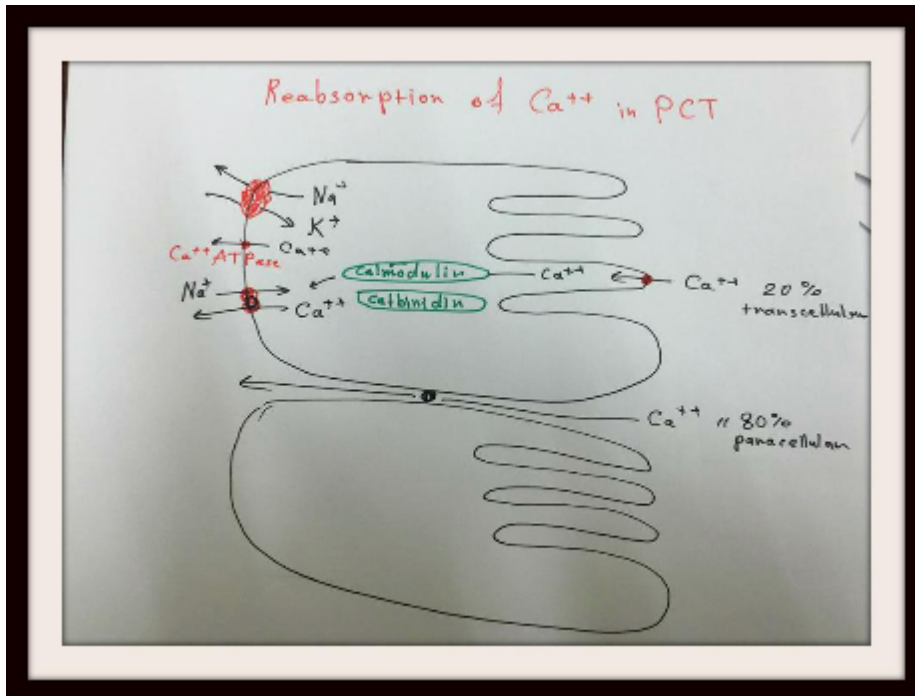
- 1000 mg of  $\text{Ca}^{++}$  is ingested daily: only 400 mg are absorbed in the intestine (duodenum, jejunum, and ileum) . half of the absorbed  $\text{Ca}^{++}$  is secreted by intestinal cells (and thus 800 mg of calcium is eliminated through the feces). 200 mg of  $\text{Ca}^{++}$  are eliminated by kidney each day.
- Absorption of calcium in the intestines occurs through paracellular and transcellular routes
- The predominant route is the passive paracellular route, which is assisted by Vitamin D<sub>3</sub>, that alters the structure of tight junctions between intestinal cells making them more permeable to  $\text{Ca}^{++}$ .
- Active transcellular route occurs by calcium channels in the apical membrane of the intestinal cells. Vit D<sub>3</sub> stimulates formation of such calcium channels and intracellular proteins assists calcium transport from apical to basolateral membrane (microvesicular transport).
- Camodulin- Actin-Myosin I complex and calbindin proteins contribute to microvesicular transport of  $\text{Ca}^{++}$  . After being unloaded as a free ion,  $\text{Ca}^{++}$  is extruded to the interstitium by sodium/calcium exchanger, and then to capillary blood

### IV. Regulation of $\text{Ca}^{++}$ :

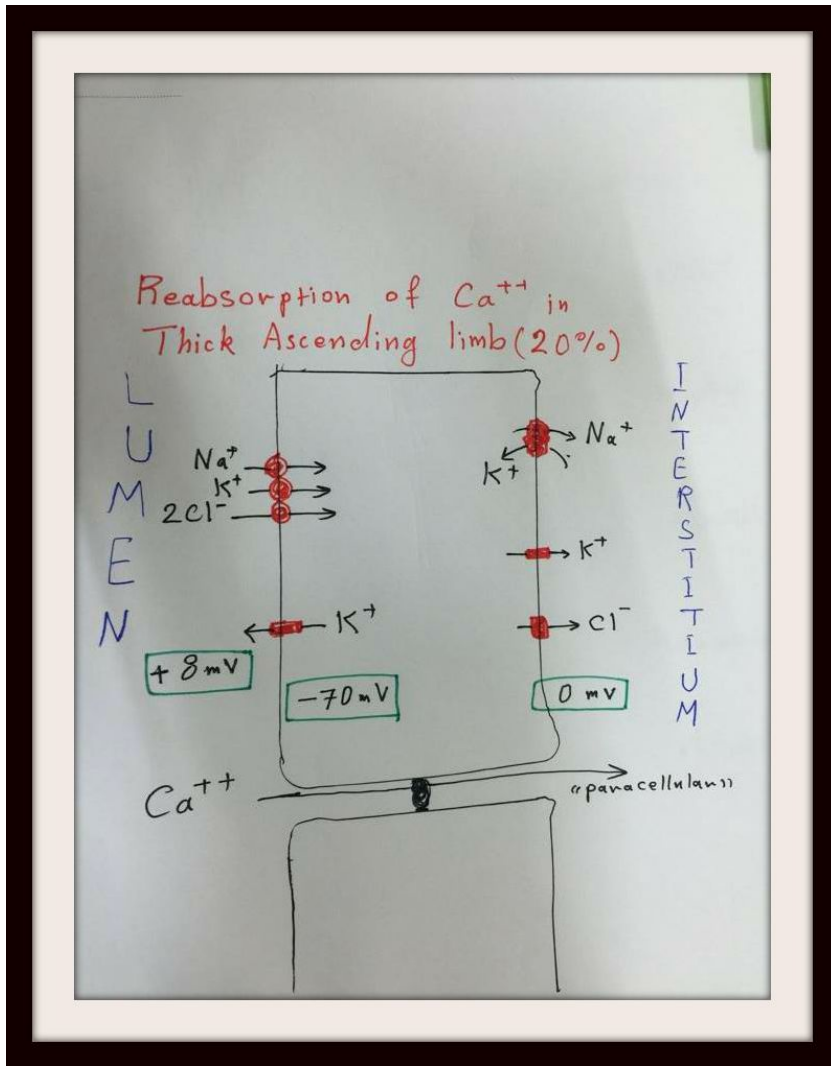
- $\text{Ca}^{++}$  range in plasma is (2.2-2.5 mmol/l) . This range has to be tightly regulated .
- Regulation of  $\text{Ca}^{++}$  occurs by : diet intake, bone resorption, and renal handling.

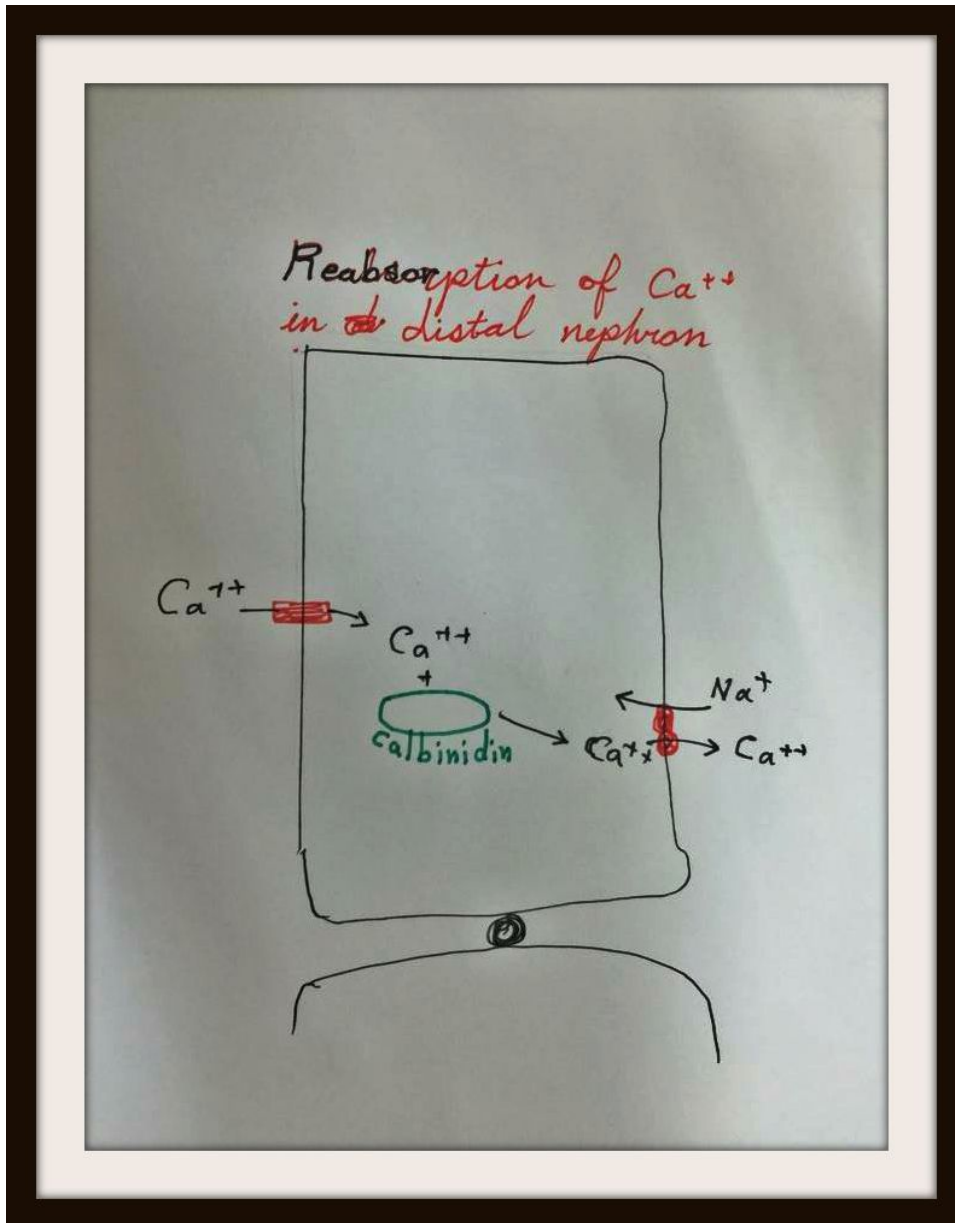
- In kidney: 10 g of  $\text{Ca}^{++}$  is filtered daily. 100-200 mg are excreted, so 98-99% are reabsorbed daily.
- 60-70% of  $\text{Ca}^{++}$  reabsorption occurs in proximal convoluted tubules. 20% is reabsorbed in thick ascending limb of loop of Henle . About 15% of  $\text{Ca}^{++}$  in the distal nephron .
- In proximal convoluted tubules: most of reabsorption of calcium occurs via passive paracellular route . While small amount occurs via active transcellular route. The active one is assisted by Parathyroid hormone mainly.
- In thick ascending limb of loop of Henle calcium reabsorption occurs paracellularly due to lumen-positive transepithelial potential difference.
- In distal nephron, reabsorption of  $\text{Ca}^{++}$  occurs exclusively via active transcellular route because transport occurs against concentration and electrical gradient.  
Reabsorption there occurs through 3 steps:
  1. Transport through the apical membrane : By transient receptor potential vanilloid 5 TRP5 .
  2. Transport of  $\text{Ca}^{++}$  through the cytosol to basolateral membrane by binding to calbindin protein.
  3. Extruding of  $\text{Ca}^{++}$  through the basolateral membrane to the interstitium by sodium-calcium exchanger.
- Different hormones play a role in calcium regulation, which are:
  1. Parathyroid hormone: a polypeptide hormone that is released by parathyroid glands in response to hypocalcemia. PTH regulates calcium level directly and indirectly by affecting three organs: In bones it causes bone resorption, while in kidney it promotes  $\text{Ca}^{++}$  reabsorption (direct effects) . It also activates Vit D3 hormone which will promote the absorption of calcium in intestines and stimulate formation of calcium channels and carriers.
  2. Vitamin D3 : Synthesized in skin under the effect of ultraviolet light, as well as it is ingested in the diet. Both forms are finally activated in the kidney. It is a lipid soluble hormone, which is transported in plasma bound to Vit D binding protein. It crosses the cell membrane and is then transported to the nucleus , where it is mediated by nuclear receptor to stimulate DNA transcription to enhance synthesis of calcium transporter , calcium binding proteins , and  $\text{Ca}^{++}$  ATPase.
  3. Calcitonin : A peptide hormone, released by parafollicular cells of the thyroid gland. It counteracts parathyroid hormone, and thus: it is the only hormone that decreases calcium level by decreasing  $\text{Ca}^{++}$  absorption in the intestine, decreasing  $\text{Ca}^{++}$  reabsorption in the renal tubules, and inhibiting the osteoclasts in bones and thus decreases bone resorption.
- Finally: The level of calcium in blood influences the renal handling of kidney. Increased calcium level in hypercalcemia increases glomerular filtration of  $\text{Ca}^{++}$  and thus increases calcium excretion. Expansion of ECF also increases calcium excretion. Alteration in pH also affects calcium level. In acidosis : calcium excretion is increased, while in alkalosis there is a decrease in calcium level because plasma

proteins dissociate hydrogen ions and expose themselves to calcium, which binding to them decreases its ionized form in plasma.









## V. Clinical physiology

Calcium imbalance is usually expressed as either hyper- or hypocalcemia.

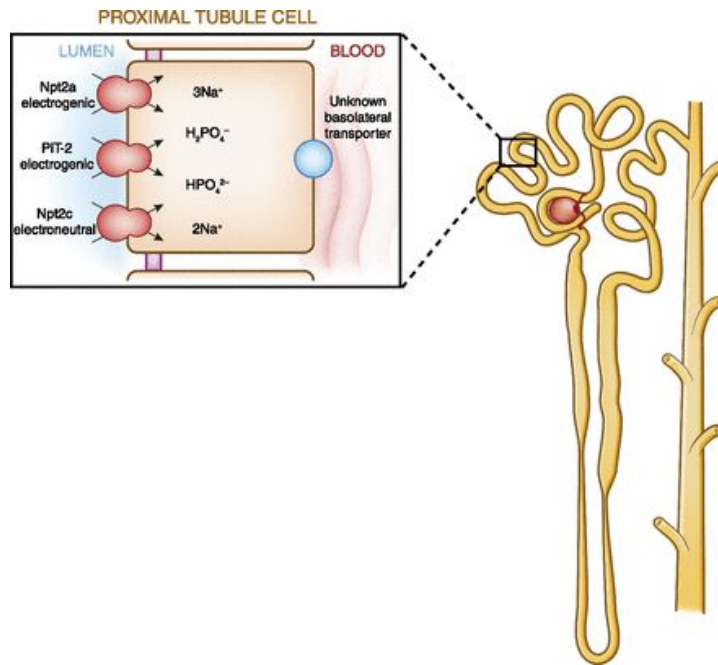
- hypocalcemia : interferes with normal nerve and muscle function , usually represents as convulsion , arrhythmia , tetany and paresthesia and numbness ( CATs go numb)
- hypercalcemia : usually expressed as kidney stones , pain in bone , abdominal pain , nausea and vomiting , polyuria , and psychiatric overtones ( depression , insomnia , anxiety , cognitive problems or even coma)
- Hyperparathyroidism : it could be primary ( due to abnormal increase of PTH production) , or secondary ( due to increased PTH production as a response to hypocalcemia) . In most cases , there are no significant clinical signs

- Hypoparathyroidism : usually due to surgical removing of parathyroid glands or destruction of the glands by autoimmune or other diseases. The clinical manifestations are usually related to hypocalcemia.
- Vitamin D deficiency causes impaired bone mineralization diseases such as Rickets ( in children ) and osteomalacia ( in adults ) . Ricket causes thickening and insufficient mineralization of epiphyseal plate bone and expressed as flat skull , prominent frontal bone , as well as pigeon breast and short deformed limbs. It is a rare disease .Osteomalacia has no symptoms except diffuse bone pain. It is found exclusively in adults.

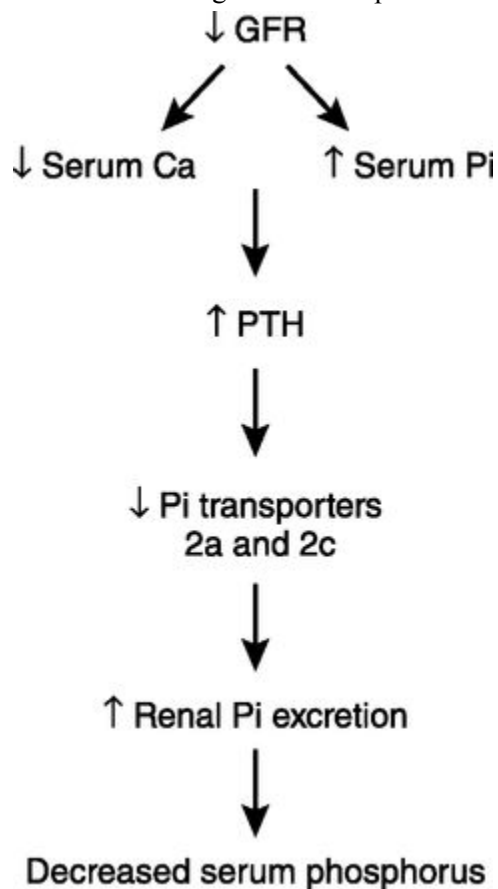
### Renal Handling of Phosphate

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- Phosphate plays important physiological role as :
  1. maintaining energy metabolism
  2. contribution to bone formation
  3. contribution to signal transduction
  4. It is also a constituent of phospholipids and nucleic acids
- Phosphate is ingested by diet as phosphorus, mainly in dairy products (varies from 700-2000 mg/day).
- It is absorbed in the intestine (duodenum, jejunum, and ileum), Its absorption is mediated by type IIb sodium/phosphate cotransporter on the apical membrane of the intestinal cells (NPT2b). It is also regulated by Vit. D3.
- After being reabsorbed it has 1 of 3 fates:
  1. Storage in bone and soft tissue
  2. transport into cells
  3. Elimination by the kidney.
- less than 1% of total phosphate is found in the ECF. It is the target of all regulatory processes. The plasma level of phosphate has to be kept within 2.5-4.5 mg/dl.
- Phosphate is filtered in the glomerulus, and then 75-85% is reabsorbed (depending on phosphate status)
- 85% of reabsorbed phosphate is reabsorbed in the proximal convoluted tubules via the NPT2a, NPT2c, and PiT-2 transporters ( The first two play the most important role in reabsorption) . These transporters are found on the apical membrane and use the energy driven by sodium (secondary active transport). The mechanism by which phosphate cross the basolateral membrane is unknown. As you see in the following figure : NP2a is an electrogenic and transport 3 Na<sup>+</sup> for one divalent phosphate ion. NP2c is an electroneutral and transport 2Na<sup>+</sup> for one divalent phosphate ion. PIT is an electrogenic that prefer transport of monovalent phosphate.



- Regulation of phosphate reabsorption occurs by the following factors:
  1. Dietary phosphate: Increased phosphate in diet remove the three transporters from the apical membrane of the proximal tubule. On the other hand restriction of phosphate in diet increases insertion of transporters on the apical membrane.
  2. Parathyroid hormone decreases the abundance of transporters on the apical membrane by using protein kinases A and C and mitogen activated protein kinase. and other kinases.



3. Fibroblast growth factor-23 : Produced by osteoblast in response to increased plasma phosphate. It decreases the abundance of phosphate transporters on the apical membrane of proximal convoluted tubule as decrease the activity of Vitamin D3 and thus decreased phosphate reabsorption in the intestines.
4. Vitamin D3: increases phosphate absorption in the intestines.
5. Glucocorticoids, Thyroid hormones, estrogen , dopamine also decreases phosphate reabsorption.
  - Reabsorption of the remaining phosphate though the nephron is unknown.

### **Clinical Physiology:**

1. Hypophosphatemia :
  - When phosphate level is below 2.5 mg/dl . It is caused either by decreased phosphate absorption in the intestines, or by shifting of phosphate inside the cells , or increased renal excretion . It may also caused by genetic disorders.
  - Up 1.5 mg/dl hypophosphatemia is asymptomatic . between 1.4- 1 mg/dl causes symptoms like : anorexia, confusion, rhabdomyolysis, paralysis, and seizures. Below 1 mg/dl respiratory paralysis may develop.
  - Treatments is achieved by phosphate supplementation .
2. Hyperphosphatemia:
  - When phosphate level exceeds 4.5 mg/dl. It is caused by either renal insufficiency, hypoparathyroidism, or any cause that increase the ECF phosphate load like phosphate-containing drugs rapid administration.
  - Symptoms involve osteodystrophy and secondary hyperparathyroidism .
  - Treated by phosphate restriction phosphate intake and medications that reduce phosphate absorption in the intestines.

## **Renal Handling of Magnesium**

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- I. Functions of magnesium:
  - Intercellular signaling
  - Bone formation
  - Neuromuscular excitability
  - cardiovascular tone
  - Oxidative Phosphorylation
  - Cofactor for DNA synthesis
- II. Distribution of Magnesium in our body:
  - 99% of body magnesium is intracellular magnesium
  - 1% is extracellular
  - Normal plasma concentration is : 1.4- 2.2 mEq/l (60% ionized, 40% , 10% bound to ions, 30% bound to plasma protein (albumin). A mentioned before : the physiologically active magnesium is the free one.
- III. Clinical sequences of magnesium alteration:

- Hypomagnesemia: when serum magnesium is less than 1.4 mEq/l: Its clinically presentation involves: fatigue , muscle cramps (painful contraction), cardiac arrhythmia, neural symptoms( seizures or numbness).
- Hypermagnesemia : When serum magnesium is higher than 2.2 mEq/l.It is presented as: nausea, vomiting, neurological signs, bradycardia that may be developed to complete heart block if it is severe.

To prevent alteration, magnesium has to be regulated by assuring balance between: magnesium intestinal absorption, bone exchange, and renal handling

1. Intestinal absorption: Intestinal absorption depends on how the diet is rich with magnesium or not. Magnesium rich diet decrease absorption, while magnesium depleted diet increases absorption. Most of magnesium is absorbed in small intestine, while a less amount is absorbed in large intestine.

Magnesium absorption occurs paracellularly and transcellularly ( passive and active pattern respectively). The active absorption occurs by Transient Receptor Potential Melastatin (TRPM6 & TRPM7).

The daily magnesium ingested in diet is about 300 mg/d.

2. Bone exchange : When magnesium serum level is decreased, the bone turnover is increased to replenish serum magnesium level. but the transporters that mediate magnesium transport to and out of bones are unknown.

3. Renal handling of magnesium:

- about 70% of magnesium is filtered in glomeruli( the free and ions bound magnesium only:
- 96% of magnesium is reabsorbed in different components of tubules .
- 10-30% is reabsorbed in PCT by unknown mechanism but it is widely acceptable that passive paracellular transport due to electrochemical gradient is the probable underlying mechanism.
- 40-70% is reabsorbed in thick ascending limb of loop of Henle ( probably paracellularly)
- 5-10% is reabsorbed in distal nephron ( active transcellular reabsorption by TRPM 6).



## Micturition and Micturition reflex

Micturition (urination) is a process, by which the final urine is eliminated out of the body . After being drained into the ureters, urine is stored in urinary bladder until being eliminated. The two ureters transport urine from renal pelvis to the bladder by peristaltic contraction (1-5 per minute). Here let's note that the ureters enter the bladder wall obliquely , and thus do not have sphincter. Contraction of bladder wall prevent urine reflux back to ureters.

Bladder is a hollow muscular organ, which has three layers:

- epithelium : Composed of superficial layer of flat cells and deep layer of cuboidal cells.
- muscular layer : contain smooth muscle fibers, that are arranged in longitudinal, spiral and circular pattern . Detrusor muscle is the main muscle of bladder. The thickening of detrusor muscle forms internal urinary sphincter which is not an actual urinary sphincter. The actual one is the external urinary sphincter, which is composed of striated muscle and is a part of urogenital diaphragm
- adventitia: composed of connective tissue fibers.

There are two phases of bladder function that depend on characteristics of its muscular wall and innervation :

1. Bladder filling : Urine is poured into bladder through the orifices of ureters. The ureter has regular one to five peristaltic contraction per minute . These contraction facilitate moving of urine from the ureter to the bladder as prevent reflux of urine into the ureter.. The capacity of bladder is about 400 ml. But when the bladder start filling its wall extends and thus the pressure is not increased with the increased urine volume.
2. Bladder emptying : When bladder is full stretch receptors in bladder wall are excited , and send signals via the sensory branches of pelvic nerves to the sacral plexus. The first urge to void is felt at a bladder volume of about 150 ml. In sacral portion of spinal cord the sensory signals are integrated and then a motor signal is sent to the urinary bladder muscles through the efferent branches of pelvic nerve itself.

Emptying of bladder is a a result of contraction of circular muscle of bladder (detrusor muscle).

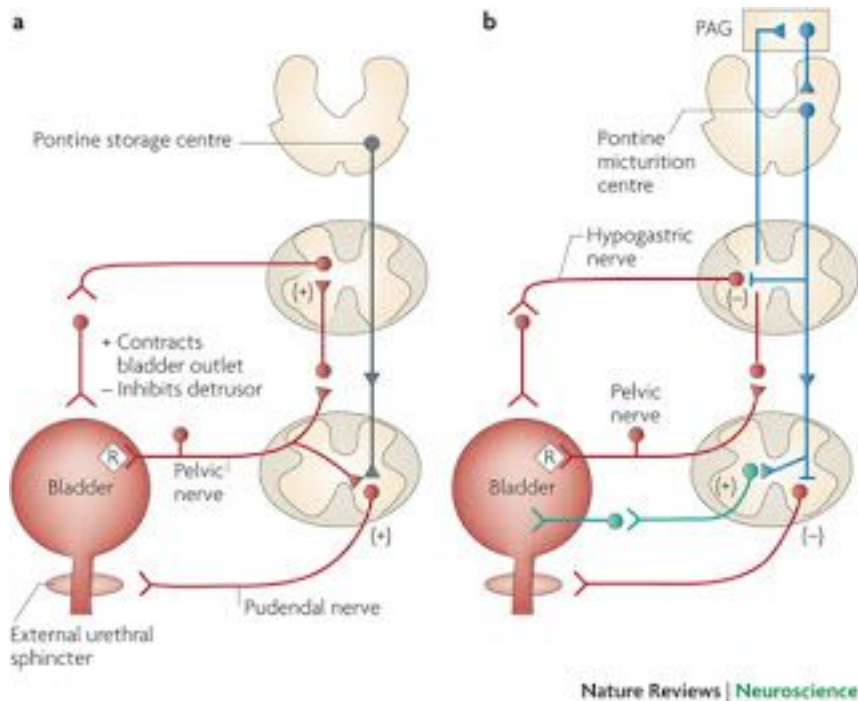
In adult people the neurons in sacral portion is influenced by nerve signals coming from brain ( Micturition center in pons ) that are also influenced by signals coming from cerebral cortex.

So: The sensory signals ,transmitted to the sacral region will also stimulate ascending pathway and the signals be also transmitted to the micturition center in the brain stem and then to the cerebrum to cause conscious desire for urination.

If micturition is not convenient the brain sends signals to inhibit the parasympathetic motor neuron to the bladder via the sacral neurons. It also sends inhibitory signal via the somatomotor pudendal nerve to keep external urinary sphincter contracting.

When micturition is convenient a brain signal via the sacral neurons stimulate the parasympathetic pelvic nerve to cause contraction of detrusor muscle via M-cholinergic receptors and causes relaxation of external urinary sphincter and the micturition occurs.

Sympathetic hypogastric nerve does not contribute that much to the micturition reflex. It plays role in preventing reflux of semen into urinary bladder during ejaculation by contracting bladder muscles.



### Using of Clearance method

Renal clearance is a part of renal function tests, used to evaluate the functioning of kidney. Unfortunately it is a confusing topic for most of medical students although it is a simple method.

- As a definition, renal clearance simply means: A volume of plasma (in ml.) from which a given substance (found in plasma) is removed by the kidney (through the urine) in a given amount of time (one minute).
- To understand the clearance method, let's review that any substance to end up in urine, it is either filtered in glomerulus and not reabsorbed, or is not filtered in glomerulus and then secreted from the peritubular capillaries to the tubules.
- Let's also review that: 1250 ml of blood goes to the kidney every minute (renal blood flow) in this amount of blood plasma forms about 625 ml (renal plasma flow), and that 125 ml of plasma is filtered in the glomerulus per minute (Glomerular filtration rate).

- Remember: The composition of the filtrate in Bowman's capsule is similar to that of plasma (except that no protein is found), but this is not true for urine, because many substances are partially or totally reabsorbed, while others are secreted.
- Let's examine the fate of a substance (let's for now call it X). and let's consider that this substance is totally filtered in glomerulus and then it is not neither reabsorbed nor secreted. This means that 625 ml of plasma containing X go to the kidney/ minute , where 125 ml are filtered per minute and 500 ml go to the peritubular capillaries without being secreted. So the amount of X in the 125 ml filtrate has been removed by the kidney and end up in urine. So the clearance of X is 125ml/minute. It is obvious that the clearance of X is the same as glomerular filtration rate. X does not exist in the body, so a substance that is similar to X (filtered, not reabsorbed, neither secreted) is called INULIN . It is a synthetic substance that is not normally found in body, but a synthetic inulin is injected and its clearance is measured to evaluate if the kidney is properly filtered as its clearance is equal to glomerular filtration rate. Clinically we used the clearance of creatinine ( a metabolic waste product normally found in the body) instead of inulin, although a little amount of filtered creatinine is reabsorbed in the kidney, but it is a good method to estimate the GFR.
- On the hand let's examine the fate of another substance (let's for now call it Y). and let's consider that this substance is filtered , not secreted and then totally reabsorbed by the kidney. This means that 625 ml of plasma containing Y go to the kidney, 125 ml of plasma containing Y has been filtered, and 500 ml of plasma containing Y has gone to peritubular fluid. Then the amount of Y in the 125 ml filtered has been totally reabsorbed back to plasma, so the volume of Plasma from which y is removed by the kidney during 1 minute is equal to 0. So: the clearance of Y is 0. Many substances normally found in the body has the same fate of Y in the kidney (Glucose and amino acids for example). Clearance of glucose is clinically useful, because if there is a glucose in urine (glucosuria) this means that glucose level in plasma is extremely higher than normal (uncontrolled diabetes mellitus).
- Finally let's examine the fate of another substance (Let's call Z for now) that is filtered, not reabsorbed and then totally secreted. This means that 625 ml of plasma containing Z per minute go to the kidney, 125 ml of plasma containing Z are filtered , while 500 ml of plasma containing Z go to the peritubular capillary but Z is secreted from the peritubular capillaries to the tubules So the volume of plasma from which Z has been removed during one minutes equal to  $125+500= 625$  ml. This is equal to 625 ml. This means that clearance of Z is the same as renal plasma flow. Clinically we can use the clearance of plasma to evaluate if the plasma flow is adequate. There is a substance, which is similar to Z. It is called Para amino hippuric acid (PAH).
- If clearance of Urea is 65 ml/ minute. This means that urea is filtered but partially reabsorbed.
- Mathematically we can measure clearance as :  $C= UXV/P$  , where U is the concentration of a given substance in urine, P is the concentration of that substance in plasma, while V is the urine flow per minute.

