PHYSIOLOGY

- SHEET NO. 5
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We will start this lecture by talking about the 3 mechanisms of the **Autoregulation of GFR and Renal blood flow:**

1- Myogenic autoregulation of renal blood flow
2- Macula dense feedback (tubuloglomerular feedback)
3- Angiotensin II (contributing to GFR but not RBF autoregulation)

2- Macula dense feedback (tubuloglomerular feedback):

- This is one of the main intrinsic regulatory mechanisms that occurs between the macula densa in the wall of the distal convoluted tubule and glomerulus.

- The macula densa cells sense changes in NaCl delivery to the distal tubule and signaling it changes the resistance in the afferent arterioles, so:

  A) If NaCl delivery Is high, this indicates a high GFR. So, there will be a signal to the juxtaglomerular cells to reduce it by reducing NO (causing less vasodilation), or by inhibiting renin (causing less Ang II).

  B) if NaCl delivery is low (like in hypotension), then GFR is low and we should increase it by increasing NO and Ang II causing vasodilation.

- This feedback mechanism is considered **Negative**.

Remember: The juxtaglomerular complex consists of macula densa cells in the initial portion of the distal tubule and juxtaglomerular cells in the walls of the afferent and efferent arterioles. The macula densa is a specialized group of epithelial cells in the distal tubules that comes in close contact and cross-talks with the afferent (MAINLY) and efferent arterioles.

To sum up: notes from 019 sheet

- When GFR is increased, the delivery of NaCl will increase in the filtrated fluid that reaches distal convoluted tubules. More NaCl filtration, distal convoluted tubules will receive more NaCl, macula Densa receives more NaCl.

- Input: Macula Densa sends feedback signals to the juxtaglomerular cells then the juxtaglomerular cells detect the high levels of GFR.

- output: GFR must be reduced

- How can GFR be reduced by affecting juxtaglomerular cells? By increasing the **vasoconstriction** in the afferent arterioles (reducing NO release) to reduce RBF thereby reducing GFR. Angiotensin II plays an important role as well.

- Feedback continues to take place until homeostasis is restored again (NORMAL GFR).

- Remember that autoregulation means internal regulation without nervous or endocrine control.

• Renin release from juxtaglomerular cells:

- What stimulates renin production from these cells?

1. **Low Perfusion Pressure** in afferent arterioles stimulates renin secretion while high perfusion inhibits renin secretion, if the blood flow is reduced (hypotension) in the afferent arterioles this will stimulate JG cells to secrete renin, if the perfusion is high (hypertension) JG cells will be inhibited.
2. **Activation of the sympathetic nerve fibers** in the afferent arterioles (In case of severe hemorrhage for example) increases renin secretion and the production of angiotensin II.
3. **NaCl delivery to macula Densa**: When NaCl is decreased, Renin secretion is stimulated and vice versa (tubuloglomerular feedback).

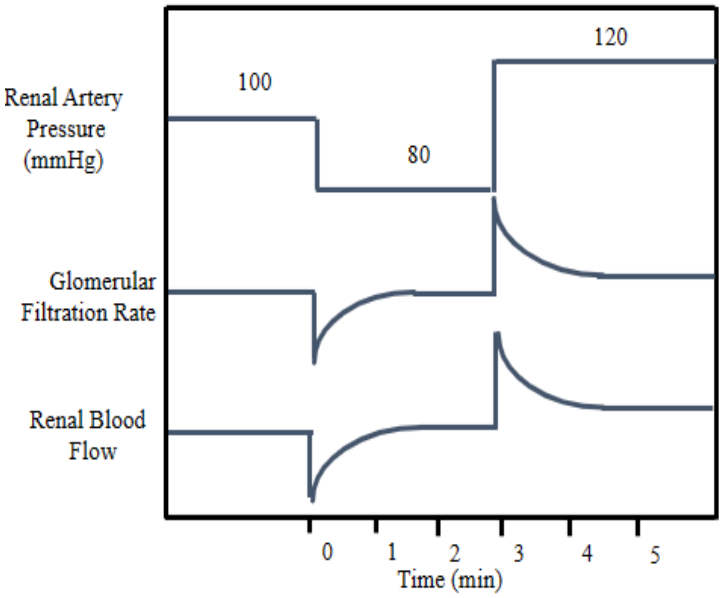
- Note that the secretion of renin is the rate limiting step in the production of Ang II.

Now we are going to study Renal Auto-regulation in details, starting with this experiment:

Firstly, when the **RAP** is **normal** (100 mmHg), **GFR** and **RBF** are going to be **normal** as well.

Then, there will be a sudden and **transient drop** in the **GFR** and **RBF** when the **RAP** is **reduced**. However, they will return back to normal within a minute even if the GFR is still reduced.

Same thing happens if the **RAP** is **increased**, both **GFR** and **RBF** are going to **increase transiently** then return back to normal within a minute even if the GFR is still increased.



So, we have a resistance to changes in GFR and RBF even if the RAP is changed.

This is called The Renal Autoregulation in which the change (increase or decrease) is transient and followed by a correction.

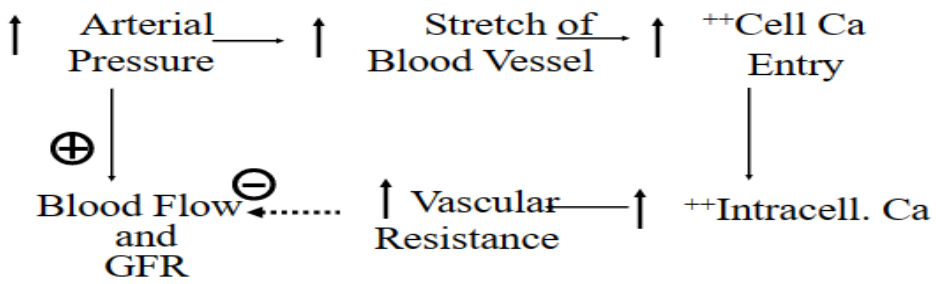
- Remember that we have 3 mechanisms of Renal Autoregulation:

1- Myogenic autoregulation of renal blood flow
2- Macula dense feedback (tubuloglomerular feedback)
3- Angiotensin II (contributing to GFR but not RBF autoregulation)

1. Myogenic autoregulation of renal blood flow:

- It describes the ability of blood flow in the glomerulus to be plateaued and sustained regardless of the changes in the systemic arterial pressure.
- When the arterial pressure is increased, the vascular wall is going to be stretched to allow the movement of calcium ions from the ECF into the cell causing the smooth muscle cells to contract so the diameter will decrease.

- This contraction will prevent excessive stretching of the vessel and in the same time it will prevent the excessive increase in the renal blood flow and GFR by raising the vascular resistance.
- The myogenic autoregulation is very fast, faster than the renal autoregulation, and it is believed to protect glomerulus from the sudden increase in blood pressure.
- This mechanism is **not** very effective in protecting the glomerulus from the decrease in blood pressure.



2. Macula dense feedback (tubuloglomerular feedback):

Before we start we should know:

- The kidneys have a special feedback (tubuloglomerular feedback) that links changes in NACL conc.
- In macula densa with the control of renal arteriolar resistance and autoregulation of GFR, this Feedback helps to ensure a relatively constant delivery on of NACL to the distal tubule and helps prevent spurious fluctuations in renal excretion that would otherwise occur.

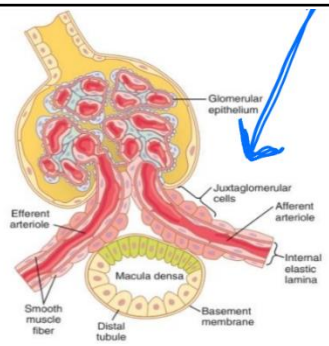
The Tubuloglomerular feedback mechanism has two components that act together to control GFR:

(1) An Afferent arteriolar feedback mechanism.

(2) An Efferent arteriolar feedback mechanism.

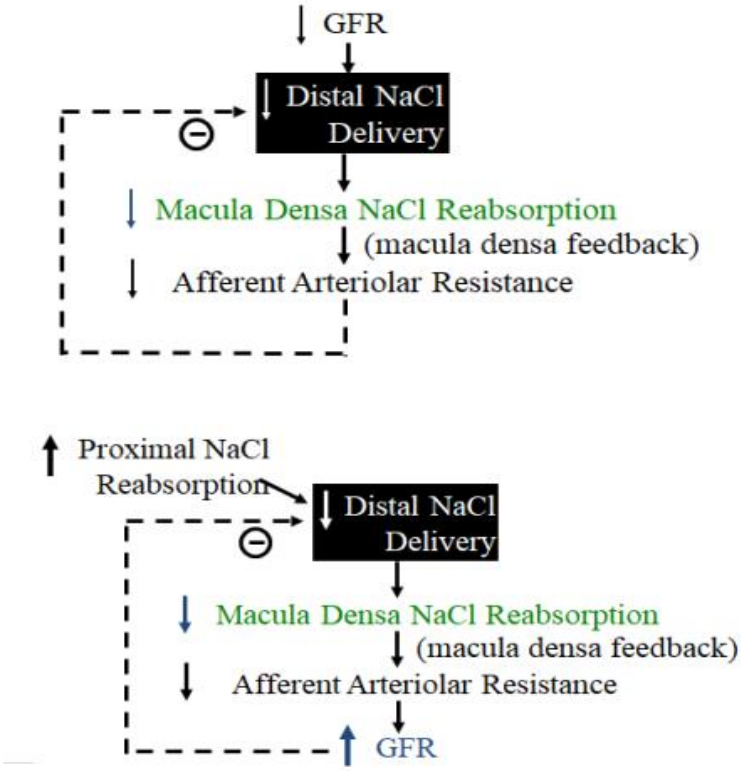
Remember

The juxtaglomerular complex consists of macula densa cells in the initial portion of the distal tubule and juxtaglomerular cells in the walls of theafferent and efferent arterioles



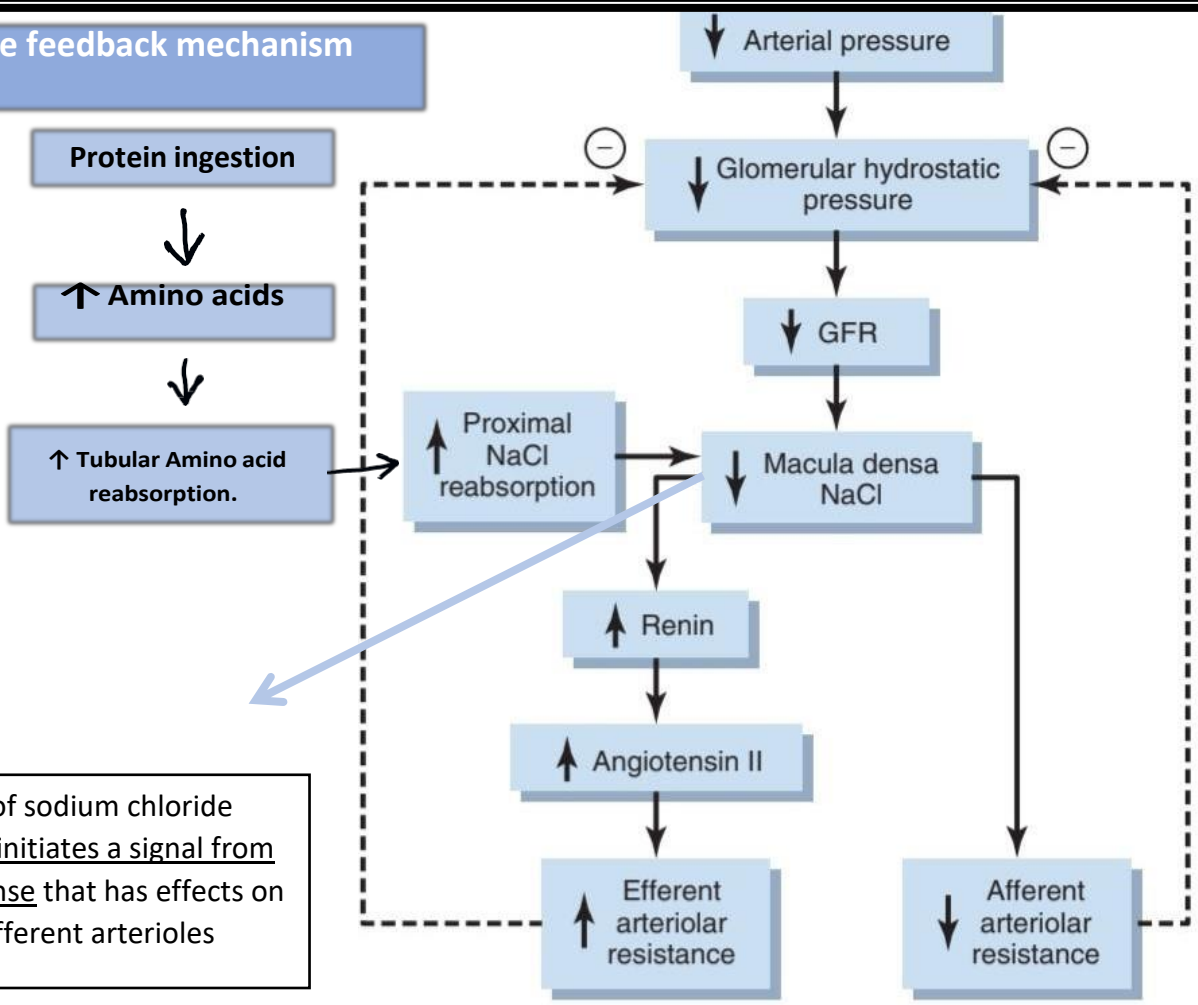
- **Macula dense feedback** is one of the most important autoregulatory mechanisms for the renal regulation of GFR.

- Decreased GFR causes decreased macula dense [NACL] that results in vasodilation (decreasing the resistance) of afferent arterioles and increase Renin release.



Macula dense feedback mechanism

So, protein ingestion leads to GFR.



This decrease of sodium chloride <u>concentration initiates a signal from the macula dense</u> that has effects on Efferent and Afferent arterioles

❖ Now, how the signals from macula densa affect afferent and efferent arterioles:

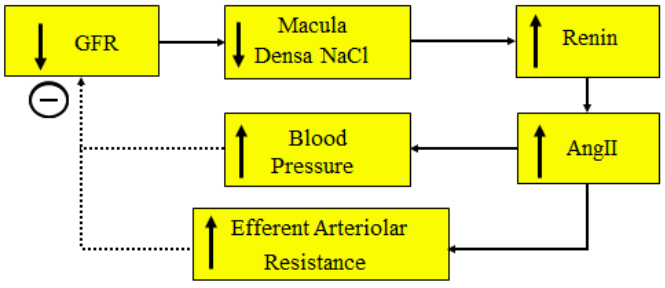
1. **Afferent arterioles**

   It stimulates **nitric oxide** synthesis in endothelial cells, then the nitric oxide is considered a vasodilator for the afferent arterioles so its resistance to blood flow decrease, which raises glomerular hydrostatic pressure and helps return GFR toward normal.

2. **Efferent arterioles**

   It increases **Renin** release from the juxtaglomerular cells of the afferent and efferent arterioles, which are the major storage sites for renin. Renin released from these cells to blood then functions as an enzyme to increase the formation of angiotensin I, which is converted to angiotensin II.

   Finally, the angiotensin II constricts the efferent arterioles, so the resistance increases and then increasing glomerular hydrostatic pressure and helping to return GFR toward normal.

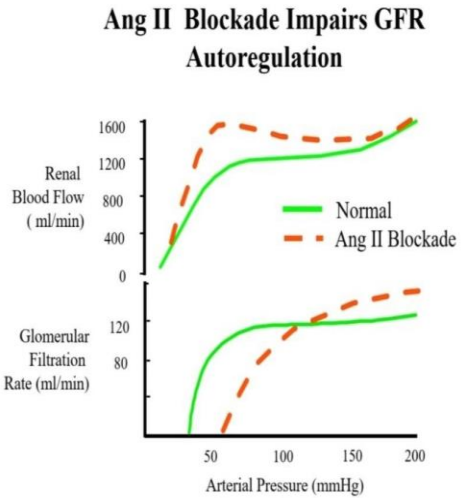


- **Note that Ang II has two effects:**

1- Ang II will increase blood pressure directly by inducing vasoconstriction in the whole system except in kidneys in which it acts preferentially to increase the efferent arteriolar resistance and maintain a normal GFR.

2- By increasing blood pressure directly in the whole system, the blood flow to the kidney is improved.

- **Angiotensin II blockade impairs GFR autoregulation:**



- Some of the drugs hypertensive patients take inhibit angiotensin II synthesis (such as ACE inhibitors), or inhibits the binding between angiotensin II and its receptor.

- When we create a blockade for angiotensin II, we are impairing the plateau that is created naturally, instead, these patients will have severe changes in GFR. This will cause impairment of autoregulation.

- **Very important:** Ang II blockade impairs GFR but not the renal blood flow (actually it is increased) because normally, it is decreased by the action of Ang II.

- **Other factors that influence GFR:**

1- Fever, pyrogens: increases GFR (more urinary excretion when you have fever).
2- High dietary proteins: increases GFR
3- Low dietary protein: Decreases GFR
4- Glucocorticoids (cortisol): increases GFR and reabsorption.
5- Aging: Decreases GFR (every decade after 40 years results in a 10% decrease in GFR function.
6- Hyperglycemia: increases GFR (diabetes mellitus) (Osmotic effect of glucose).

- **People with hyperglycemia and high dietary protein have an increased GFR, why?**

  Amino acids and glucose are reabsorbed along with sodium, so when their blood concentration is increased, their filtered load is increased as well, causing their reabsorption along with sodium.

  More reabsorption of sodium means less delivery of sodium to macula densa, so macula densa thinks that the GFR is low and needs to be increased.

Importance of GFR auto-regulation in preventing extreme changes in renal excretion:

In reality, changes in arterial pressure usually exert much less of an effect on urine volume for two reasons:

(1) Renal autoregulation prevents large changes in GFR that would otherwise occur.

(2) There are additional adaptive mechanisms in the renal tubules to cause them to increase their reabsorption rate when GFR rises (what we will discuss in next lectures).

Arterial Pressure	GFR	Reabsorption	Urine Volume
Poor Autoregulation + no change in tubular reabsorption			
100	125	124	1.0 → normal
120	150	124	26.0 = 37.4 L/day!
Good Autoregulation + no change in tubular reabsorption			
120	130	124	5.0
Good Autoregulation+adaptive increase in tubular reabsorption			
120	130	128.8	1.2

- **If arterial pressure is normal**, the GFR is supposed to be at a value of around 125, the normal reabsorption rate is 124ml/min, which give us a urine volume of 1ml/min (filtration – reabsorption)

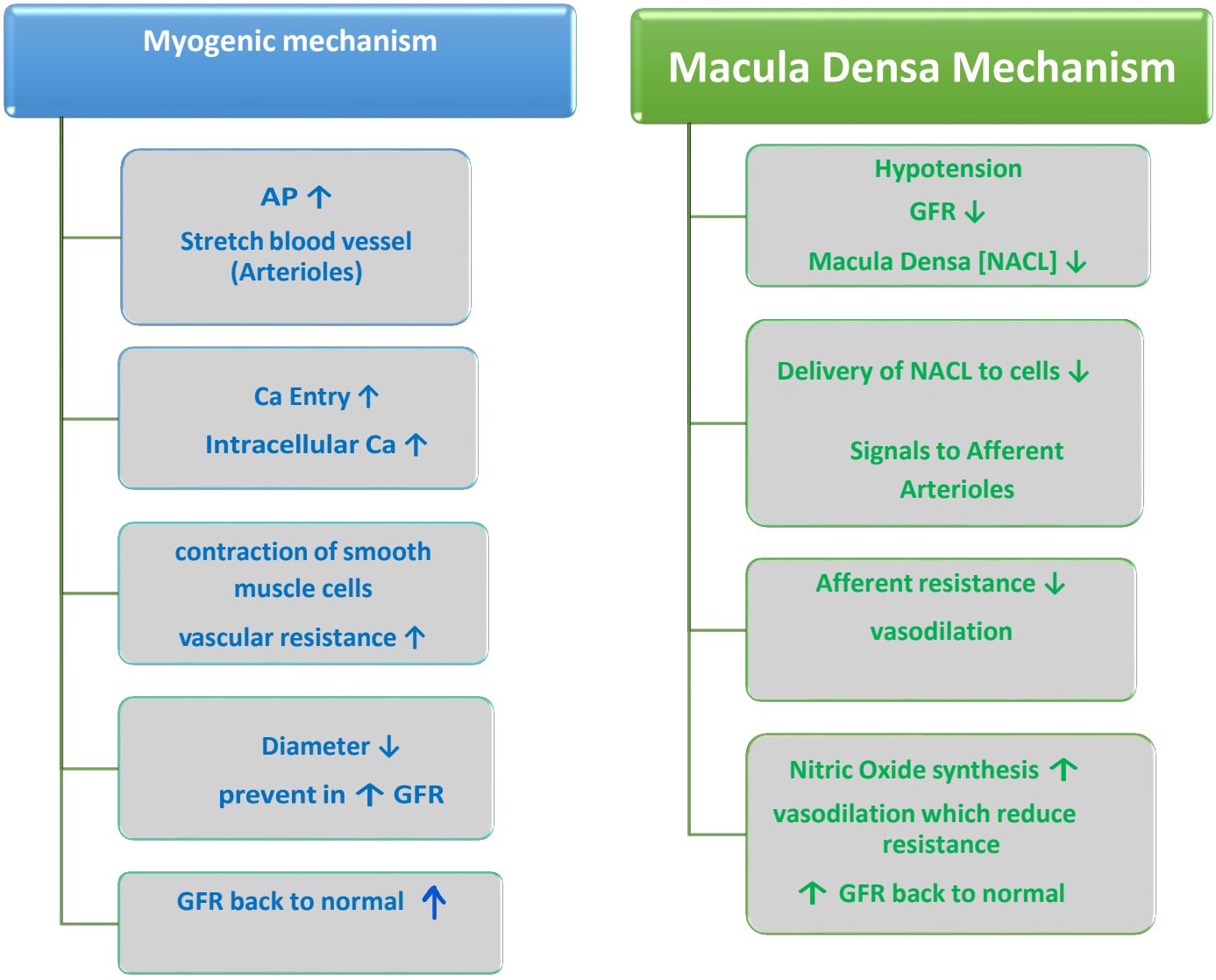
- In the case of **increased arterial pressure with poor autoregulation** and **constant** tubular reabsorption GFR will be 150, while reabsorption rate will remain 124ml/ min and the urine output will be 26ml/min!!!

- While in the case of **increased arterial pressure with good autoregulation** and **constant** tubular reabsorption, GFR will be 130, while reabsorption rate will remain 124ml/ min and the urine output will be 5ml/min.

- In the case of **increased arterial pressure, good autoregulation and adaptive tubular reabsorption**, GFR will be 130, while reabsorption rate will change to 128.8ml/ min and the urine output will be 1.2ml/min (which is close to normal).

We are done with the first topic of this lecture!!!

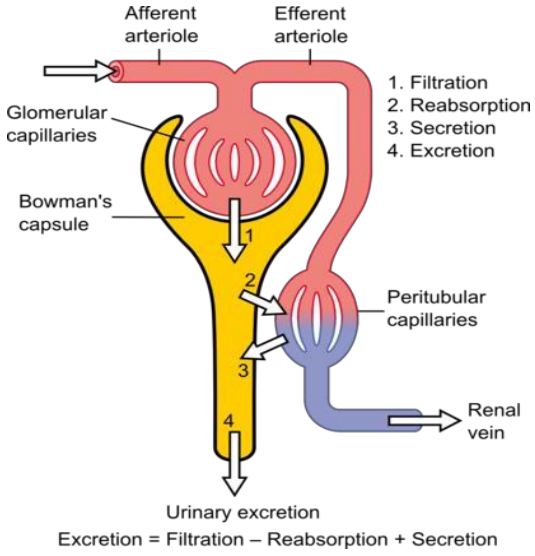
Now check this summary:



Quick recap:

- In the previous lectures, we talked about 3 basic mechanisms of urine formation, all of which occur in the functional unit of the kidney (the nephron, a microstructure presents in the kidney).
- The afferent arteriole from where the blood comes into the nephron contains smooth muscle cells, while the glomerulus consists only of a single layer of endothelial cells. This different structure is due to the difference in function since the filtration process occurs across the wall of the glomerulus and the endothelial cells of the glomerulus have fenestrations making the filtration process more effective
- Filtered fluid will enter the Bowman's capsule (the capsular space) and then it will travel into a tubular system starting from the proximal convoluted tubule, to the loop of Henle, the Distal convoluted tubule, the connecting tubule, and lastly the collecting duct
- The filtered fluid will empty through the renal papilla into the major and minor calyces and then into the renal pelvis to reach the ureters
- **Now, we will discuss (Reabsorption & Secretion).**

- **Actually, reabsorption is as important as filtration.**
- **Filtration without reabsorption = losing your 3 liters of plasma within an hour (dehydration)!**
- **So, we need to reabsorb most of the filtered fluid in order to maintain hemostasis in our body.**



- Filtration is a passive and non-selective process that filtrates substances based on their sizes, and charges, while reabsorption is a highly selective process. So, the reabsorption rate will be different for each substance.

- The valuable substances that are important for our body such as glucose and amino acids will have a high reabsorption rate while the waste substance such as urea, creatinine, andammonia will have a poor reabsorption rate to be excreted.

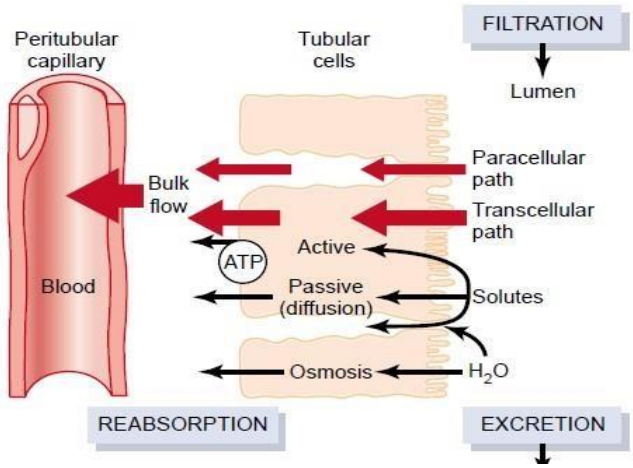
- The secretion process (the third process of urine formation) is an active process through which waste substances are removed from the circulation (peritubular capillaries) into the filtered fluid in the tubular system and finally to the urine at a higher rate than the filtration rate.

- Whatever is left in the tubules after the end of those three processes will be eliminated through a process called the urinary excretion
- Excretion = Filtration – Reabsorption + Secretion
- From 180 L filtered daily, less than 1% is excreted (1-2 L/day)

What are the mechanisms of reabsorption?

- There are hemodynamic forces (starling forces) favoring reabsorption just like those favoring filtration but in the opposite direction (creating a bulk flow into the peritubular capillaries).

- Starting from the proximal convoluted tubules and along the rest of the tubular system the wall is made of a single layer of epithelial cells. The substance should pass through the epithelial cells either **across** their plasma membranes or in **between** to be reabsorbed into the peritubular capillaries.



- There are 2 main paths for reabsorption:

1- Paracellular path:

(through the tight junctions, the intercellular space, the interstitial fluid, and across the capillary wall into the lumen), in that path, water pull whatever solutes dissolved in it.

2- Transcellular path:

(Across the plasma membrane by endocytosis, exocytosis…etc.), the mechanism by which substances cross the plasma membrane of the endothelial cells depends on their nature (ions pass through specific channels, water passes through aquaporins, glucose needs transporters…etc.).

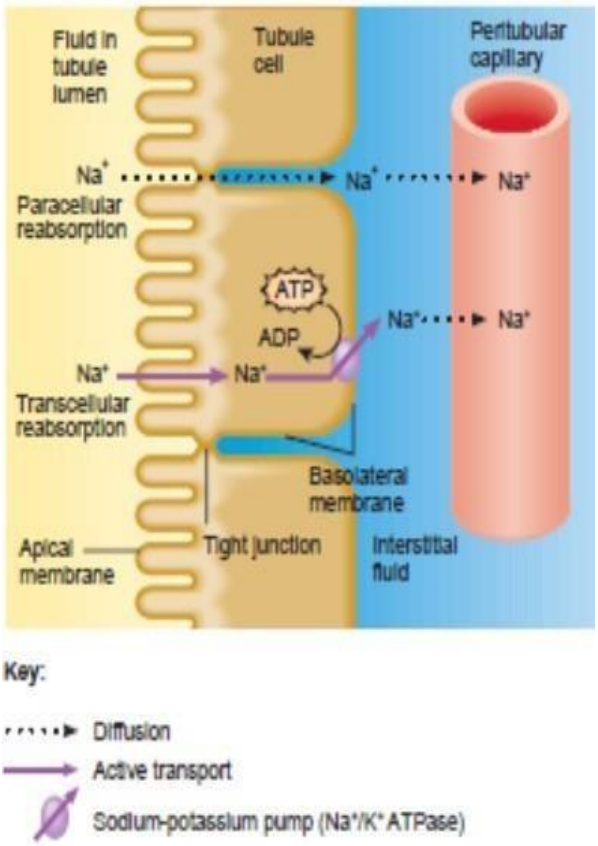
– In the transcellular path solutes can pass either through active (against gradient) or passive (toward gradient) processes (such as NaCl).

– Na+ and other solutes can be transported through both routes (paracellular when found dissolved in fluids, and transcellular using certain channels when found as separate ions).

– Depending on the gradient, solutes can be transported transcellularly either by passive (down their gradient) or active diffusion (against their gradient).

– Water can be transported through **the osmosis process** passively from the hypotonic area to the hypertonic area using both transcellular (aquaporins) and paracellular paths.

– Keep in mind that the transport of water and solutes from the interstitial fluid into the peritubular capillaries occurs by **ultrafiltration (bulk flow).**



– The main player in sodium reabsorption is **the NA+/K+ ATPase channel** (sodium outside – potassium inside), it keeps Na+ intracellularly very low that favors sodium reabsorption down its gradient (from the tubular fluid into the intracellular lumen and then into the interstitial fluid). Paracellular reabsorption also depends on the gradient.

– As you can see, the basal membrane of the proximal convoluted tubule is near the capillary and the apical membrane faces the tubular lumen. The apical membrane has microvilli called the **Burch border** to increase the surface area of reabsorption.

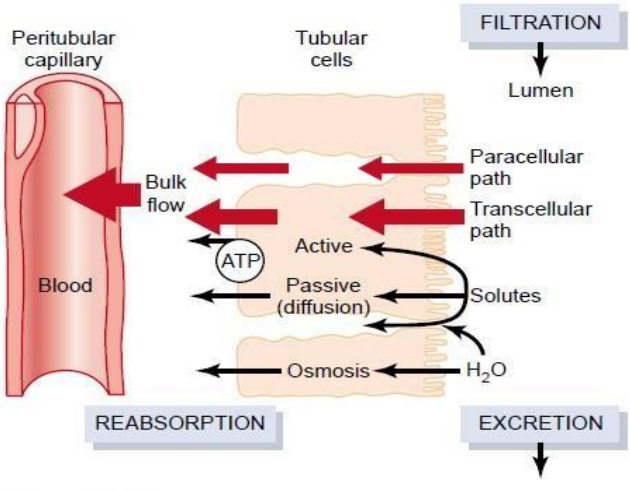


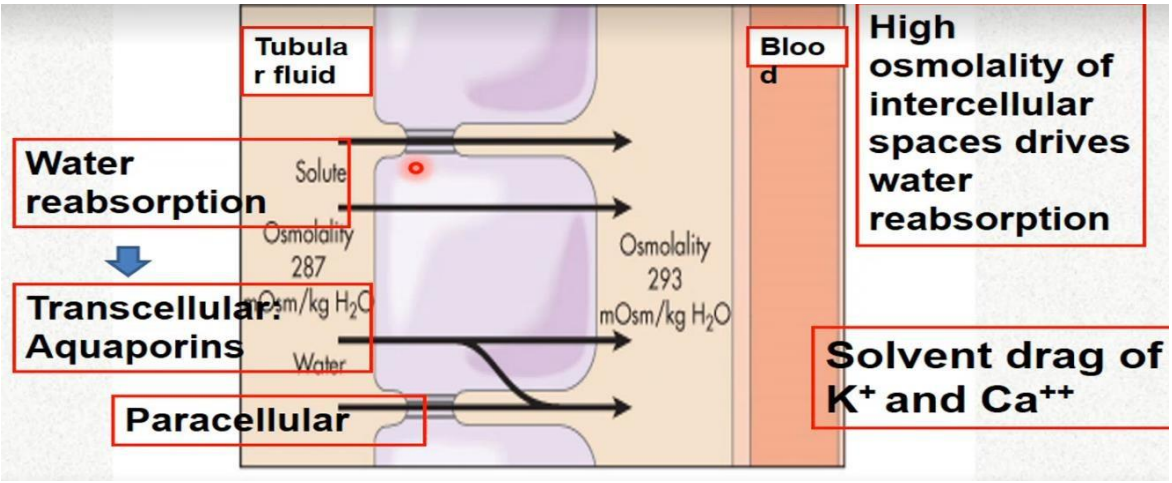
Figure 27–1

Reabsorption of filtered water and solutes from the tubular lumen across the tubular epithelial cells, through the renal interstitium, and back into the blood. Solutes are transported through the cells (transcellular route) by passive diffusion or active transport, or between the cells (paracellular route) by diffusion. Water is transported through the cells and between the tubular cells by osmosis. Transport of water and solutes from the interstitial fluid into the peritubular capillaries occurs by ultrafiltration (bulk flow).

– The Na+/K+ ATPase is located mainly on the lateral membrane (in addition to the basal membrane), **Basolateral ATPase**.

– Na+/K+ ATPase creates an electrochemical gradient that drives the reabsorption of Na+ towards the peritubular capillaries by either trans- or para- cellular paths.

- Remember that this pump requires energy.



- In the proximal convoluted tubule, the extensive transport of Na+ causes changes in the osmolality (the osmolality in the tubular fluid will be less than the osmolality in the interstitial fluid driving the movement of water toward the blood capillaries. This change in the osmolality is caused by the activity of the Na+/k+ ATPase.

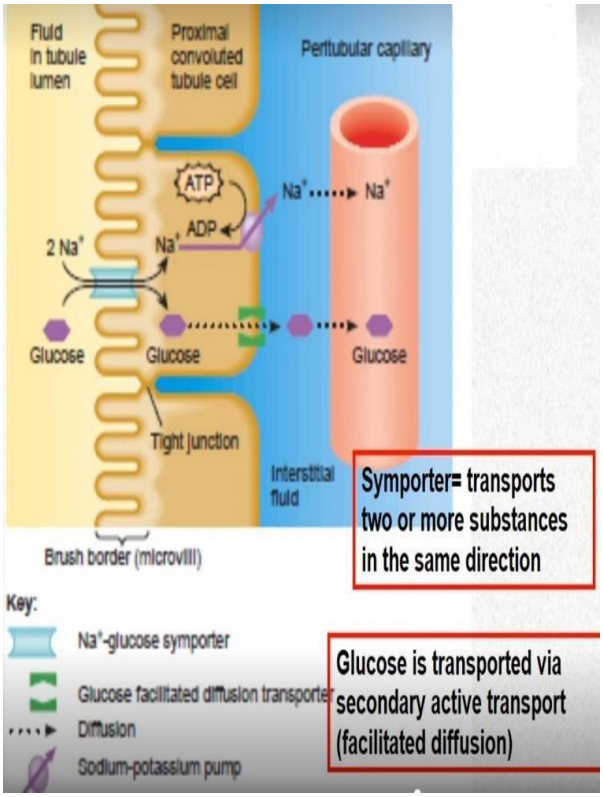
- **Water follows solute**, so in the proximal convoluted tubule there is extensive osmosis of water by either trans- or para- cellular paths.

- In the **paracellular** path, the **solvent drag** of K+ and Ca+ happens which means that water itself has ions dissolved within which contributes to the reabsorption of many ions particularly K+ and Ca+ ions (ions with no selective transporter).

- In the proximal convoluted tubules, 100% of filtrated glucose and amino acids is going to be reabsorbed! In other words, they need to be completely reabsorbed.

- This happens through:

1- Co- transportation (using symporters), also called **secondary active transport.**



- Secondary because we benefit from the gradient created by the NA+/K+ ATPase -that uses the ATP- to move sodium to the inside of the cell and simultaneously transporting glucose through the symporter against its gradient.

2- Then the glucose is transported from the high gradient area (inside the cell) into the low gradient one (outside the epithelial cell) through the **facilitated diffusion** using a certain carrier**.** (The same mechanism applies to theamino acids but with different specific transporters).

- It's abnormal to see glucose or amino acids in urine.

- Both co – transports and counter-transporters are used in the secondary active transport but the direction of transportation of the substances is different.

- Co – transports are used in the reabsorption of glucose and amino acids. SGLT co-transports Na+ and glucose down the Na+ gradient into the cell then they are diffused out.

- Counter-transporters like the Na+/H+ exchanger, uses the transport of Na+ down its gradient to secrete H+ against its gradient (not reabsorption)! Our body uses these transporters to get rid of the extra acids produced during different metabolic processes.

The end!