Sheets **Physiology**

Number **4**

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Correction

Recap:

In the previous lectures, Renal blood flow (RBF) and Renal plasma flow (RPF) were discussed and we said that para-aminohippuric acid (PAH) could be used to measure RPF (assuming that it is completely cleared*). When in reality, only 90% is cleared thus underestimating the RPF by 10%. However, measuring RPF enables us to determine the RBF.

* If a substance is to be used in measuring RPF, it must meet the following criteria: (I) freely filtered, (II) not reabsorbed and (III) completely secreted.

We have also talked about the glomerular filtration rate GFR, which can be used as an indicator to assess the quantity of functional nephrons. Inulin is used to measure GFR for research purposes but it's not practically feasible since it's time and effort consuming. Instead, we used creatinine, which meets the criteria of the substances used to measure GFR since its freely filtered, not reabsorbed and not secreted. There is a down side to creatinine since it's secreted by 10%. Even so, we overcame this problem by measuring the plasma creatinine concentration in both forms; free (90%) and bound (10%), so the bound creatinine cancels the secreted creatinine when calculating GFR. Nevertheless, the measurement of creatinine-GFR requires a 24-hour urine collection, so there are some equations that estimate the GFR easily and accurately (95% accurate).
Note: all the mentioned above is explained thoroughly in sheet 3. So if you find any problem just check sheet 3.

- Autoregulation of GFR:

GFR is very important and it must not increase nor decrease. Having high GFR might cause loss of many essential substances like glucose. On the other hand, a decrease in GFR leads to the accumulation of waste and toxic substances. That's why the kidneys ***autoregulate*** the GFR ***regardless*** of the ***blood pressure,*** since it keeps fluctuating during daytime.

Let us review the variation in blood pressure starting from the heart until reaching the kidneys: The blood leaves the heart with a mean arterial pressure of 100 mmHg, which is the BP in the renal artery, then at the beginning of the afferent artery it is 85 mmHg and in the glomerular capillaries it is 60 mmHg and 59 mmHg by the end of the glomerular capillaries. In the efferent arteries, it is 59 at the beginning and 18 at the end. The peritubular capillaries start with 18 and end with 10, then it keeps decreasing as we go from the renal vein towards the right atrium until reaching 0 mmHg.

100	85	85	60	60	59	59	18	18	10	10	0
Renal artery		afferent artery		glomerular capillary		efferent artery		peritubular capillary		renal vein to heart	

We can conclude that most of the renal vascular resistance (≈70%) resides in the afferent and efferent arteries; the BP dropped by 25 in the afferent and 41 in the efferent. Autoregulation of the GFR happens at the levels of the afferent and efferent arteries by (I) either dilating or constricting the afferent, (II) constricting the efferent.

For instance, if someone is bleeding, this will lower their blood pressure and consequently the renal blood flow, resulting in low glomerular capillary hydrostatic pressure and low GFR. When GFR decreases, the amount of sodium and chloride ions reaching the distal parts of the nephron is also decreased. This change in sodium and chloride amounts is sensed by cells that when stimulated send impulses to afferent and efferent neighboring cells known as juxtaglomerular cells or granular cells. These granules contain renin enzyme, and upon stimulation, renin is released into the bloodstream. Renin is a protease, and once it is released into the blood it looks for angiotensinogen, which is a 14-aminoacid peptide. Renin cleaves 4 amino acids converting it to angiotensin I; an inert peptide with no function. In the lungs, angiotensin I is converted to angiotensin II.

- Angiotensin II has four functions:

1- Angiotensin itself is a vasoconstrictor, ↑BP → ↑GFR.

2- It stimulates the secretion of aldosterone from zona glomerulosa of the adrenal gland. Aldosterone is a steroid of 21 carbon atoms. *Estrogen has 18 atoms and testosterone has 19 atoms, while dexamethasone (a synthetic steroid) has 22 carbons*. Steroids work by entering the cells (they are lipid soluble) and binding to their cytoplasmic receptors. This complex then travels to the nucleus where it binds to the DNA and induces transcription of channel proteins (K and Na for example), enzymes needed to generate ATP in order to activate the Na/K pump, and receptors needed in reabsorption. All these actions lead to the secretion of potassium and absorption of sodium and water, thus increasing the BP and GFR. Aldosterone also increases sodium reabsorption in the **distal tubules**.

3- Angiotensin II can directly (not through aldosterone) increase sodium reabsorption in the **proximal tubules.**

4- It has receptors on the **efferent arterioles** which constrict in response to the binding of angiotensin II. Constriction of the efferent arterioles will increase the pressure in the glomerular capillaries.

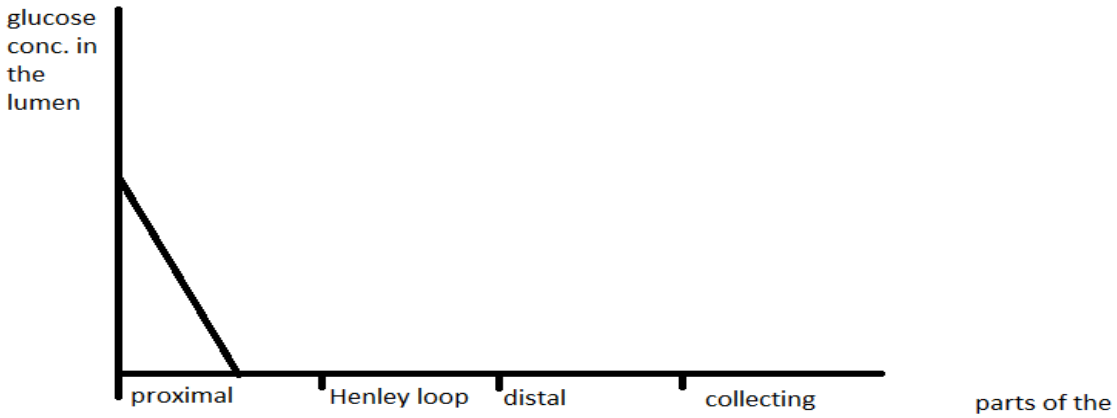
During bleeding, two opposite things must be taken care of, the first one is that I need to get rid of waste products so urine formation must be maintained, and the second thing is that I need to retain as much fluids as possible so urination must be minimized. This conflict is solved by angiotensin II, which constricts the efferent arterioles increasing the pressure in ***the glomerular capillaries*** leading to increased GFR, thus getting rid of waste products. On the other hand, constriction of the efferent arterioles reduces the pressure in ***the peritubular capillaries*** which causes the forces to favor reabsorption over secretion.

-Simply speaking, autoregulation of GFR is to **uncouple** it from the systemic arterial pressure.

➢ The Ultra-filtrate:

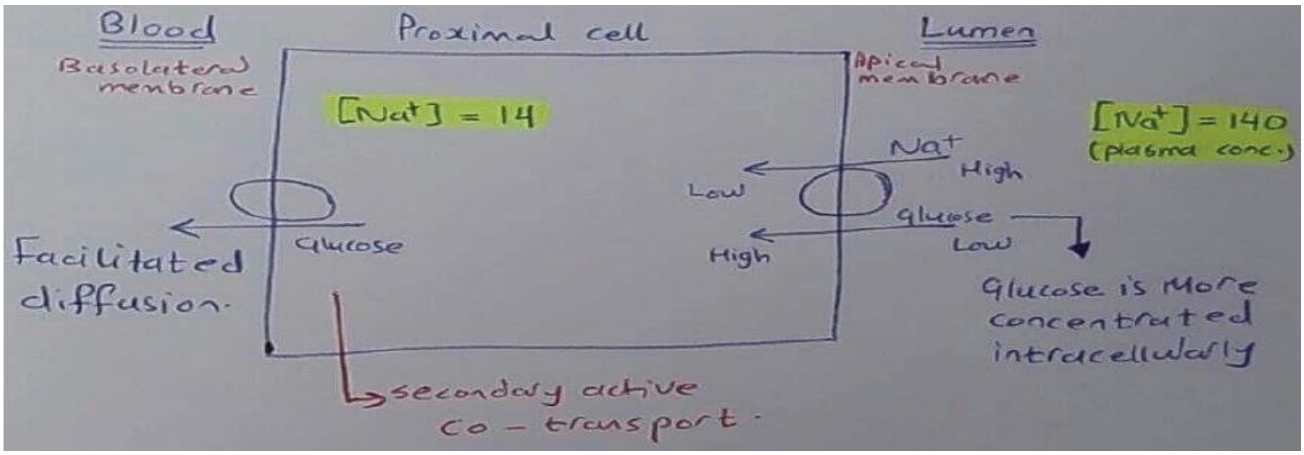
Filtration takes place in the glomerulus and the ultra-filtrate is everything that moves from the plasma to bowman's space. The ultra-filtrate has the same composition as the plasma minus the proteins.
So, **Ultra-filtrate= plasma – proteins.**

Glucose concentration in the plasma is normally 70-110 mg/dl. If the fasting glucose concentration is 126 mg/dl and above, one is said to be diabetic. However, glucose concentration in the urine must be 0. Filtered glucose is completely reabsorbed in the **early proximal tubules**. The same thing applies for amino acids.



this figure illustrates glucose reabsorption

Glucose is absorbed by the help of sodium through secondary active transport. The cells lining the tubules have luminal (brush border) and basolateral sides (rich in mitochondria). The intracellular concentration of Na is 14 while the extracellular (in the lumen) is 140, so Na enters by simple diffusion if its channels are open down its electrochemical gradient. The carriers of Na take advantage of the electrochemical gradient of Na to co-transport glucose against its concentration gradient. Sodium that entered the cell is then pumped actively across the basolateral membrane to the blood via Na/K pump. Glucose crosses the basolateral membrane passively.



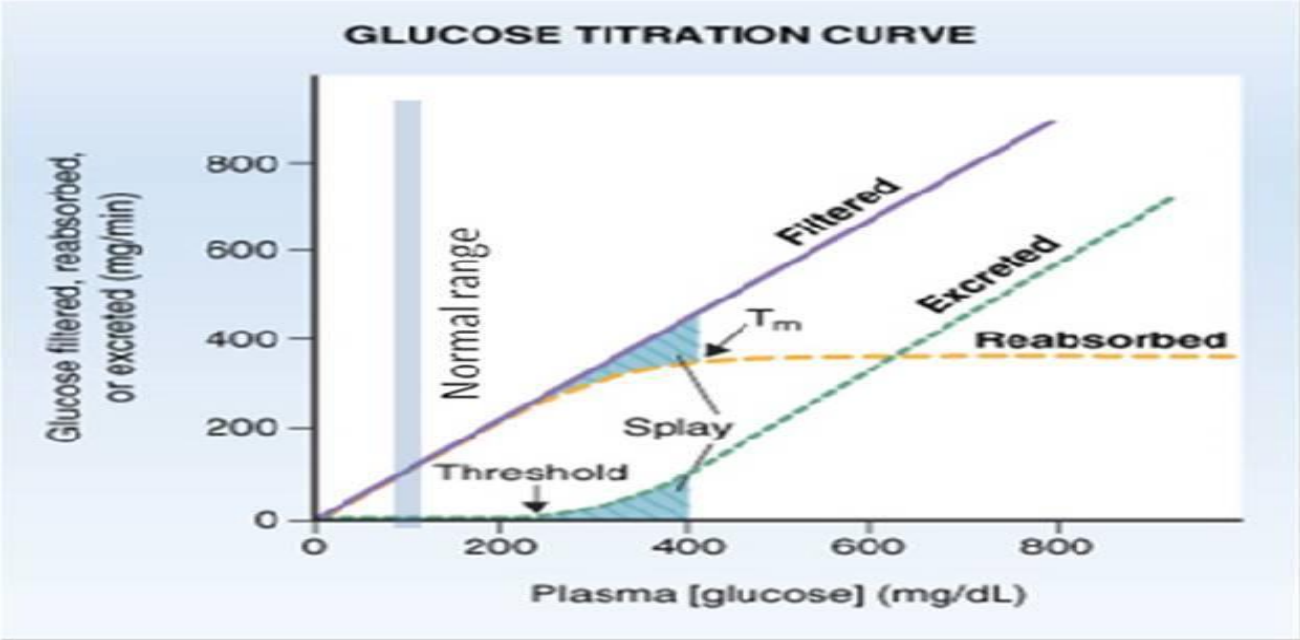
- Tmax and threshold of glucose reabsorption:

Since the glucose is transported in carrier fashion, it has a Tmax. Tmax of glucose is 320 mg/dl. Logically, if glucose concentration increases to any point from 70 up to 320, we should be able to reabsorb it all, but in reality this doesn't happen

What we really need to understand is that Tmax is only exhibited when there is super-saturation of glucose (very high concentrations). So at intermediate concentrations like 190 or 220, we must expect some glucose to escape into urine.

Glucose carriers can catch every glucose particle that is present in the lumen in concentration range of 0-180. Above 180, which is called the threshold, some glucose particles manage to escape the carriers because as we said earlier, Tmax is only exhibited at very high concentrations. So, from 180 to 320, we still reabsorb most of the glucose but not all of it. In order to reabsorb 320 glucose particles the concentration must be very high reaching approximately 1000!
The threshold: it is the concentration at which any increase will cause glucose to start appearing in the urine. It is 180 mg/dl (conc. In plasma) or 220 mg/min (filtered load) for glucose.

"Remember: filtered load is the amount of the substance being filtered per minute and it's calculated by multiplying GFR by the plasma concentration of that substance."



"The numbers in figure are not accurate, just understand the concept"

-**Filtered glucose curve:** ↑Glucose concentration → ↑Filtered glucose.
-**Excretion curve:** Excretion of glucose is absent as long as the concentration is below the threshold. After the threshold, glucose starts to appear in the urine.
- **Reabsorption curve:** Reabsorption becomes constant after reaching Tmax.
-**Splay**: is the deviation of observed curve from predicted curve. Or the appearance of glucose in urine before the Tmax.

If glucose is found in the urine (positive) and its concentration in plasma is above 180 mg/dl, then the patient is said to have ***Diabetogenic Glucosuria***. But if the plasma concentration is within the normal range then the patient is said to have ***Nephrogenic Glucosuria***, meaning that there is a deficit in the kidney which leads to glycosuria. This deficit might be in the carriers, their Tmax or their affinity …etc. Nephrogenic glucosuria is a benign condition that doesn't complicate into another abnormality, so typically we don't tell the patient about his condition.

-Positive glucose test means that there is glucose in the urine and it ranges on a scale from +1 to +4 depending on how much glucose is there in the urine.

GOOD LUCK *_*