Renal system

Functions of kidney

Kidneys are essential for life; we can't survive without normal functioning kidneys. They're active organs, they participate in maintaining homeostasis:

- They remove waste products such as urea, Creatinine, ammonia, folic acid, etc.
- They maintain the homeostasis of electrolytes: potassium & sodium.
  - ☒ Renal failure causes hyperkalemia, and hypocalcaemia.
- They regulate extracellular fluid volume.
  - ☒ Renal failure results in expansion of this volume and then edema.
- It controls Acid-base balance.
  - ☒ Renal failure causes metabolic acidosis.
- It regulates blood pressure.
  - ☒ Renal failure causes malignant hypertension.
- It secretes hormones like erythropoietin.
  - ☒ Kidney failure means anemia.
- Activate Vitamin D.

Anatomy of the kidneys

- Kidneys receive the blood through the renal artery, the fifth branch of the aorta.
- Renal artery divides into segmental arteries >> interlobar arteries >> arcuate arteries>> interlobular arteries and then finally the afferent arteriole.
- the afferent arteriole then enters the glomerulus and gives rise to glomerular capillaries which then converge to form the efferent arteriole that leaves the glomerulus (note : the glomerulus is the first part of the nephron which's composed of glomerulus , bowman's capsule , the proximal tubules ,distal tubules and loop of henles) . It starts in the cortex, runs deep down to the medulla, then goes back to the cortex, and finally ends in the medulla .It's 6 cm long. Each afferent arteriole enters a nephron. Each kidney contains a million nephron and thus we have a million afferent arteriole in each kidney).
- Efferent arterioles give rise to peritubular capillaries that surround the tubules. Then they rejoin to form venules and finally the renal vein.

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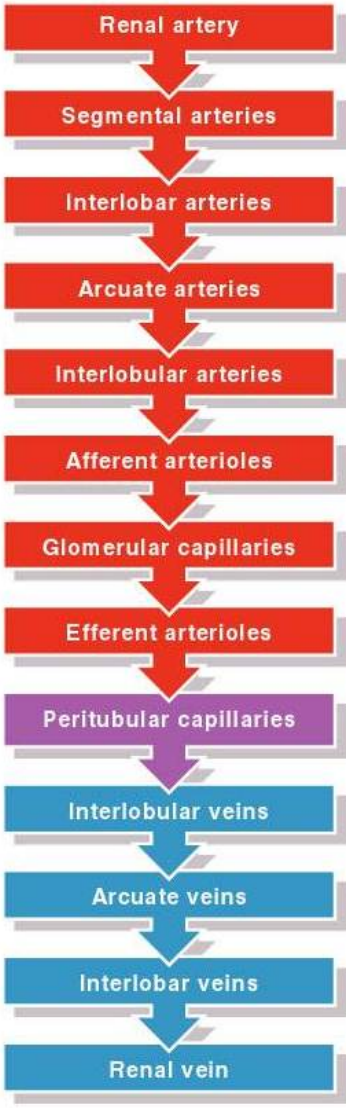

Each kidney has around one million **nephrons**, a nephron is a 4-5 cm long tubule, and we can divide it **anatomically** into glomerulus, Bowman's capsule, the proximal tubules, distal tubules and loop of henles.

But **physiologically** we divide the nephron into two parts:

- **Ultra filtration** device the Glomerular apparatus
- **Epithelium** (The rest of the nephron), which is going to modify the ultra filtration

Modification means taking from the ultra filtrate nephron to capillaries (re absorption) adding to ultra filtrate (secretion

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Conservation of mass

- Some components of the blood that enters the kidney will be extracted as urine and the remaining blood will go to the renal vein. So, the renal artery – urine = renal vein OR renal artery = renal vein + urine. (Conservation of mass).

Renal blood flow (RBF)

- Renal blood flow: volume of blood entering both kidneys per minute.
- The two kidneys receive 25% of the cardiac output (0.25 * 5 ~ **1.25 liters /min**) which is too much .They receive too much blood because blood goes there to change its composition and not only to nourish the kidney and supply it with oxygen . So, kidneys are reconditioning organs that are why they must receive too much blood.
  This makes the A-V O2 difference small *(A-V O2 difference is an indication of how much oxygen is removed from the blood in capillaries as the blood circulates in the body – Wikipedia).*it equals 1.4 . (While it's 6 in skeletal muscles, 6.2 in the brain, 3.4 in the liver, and 0.5 in carotid bodies).

Renal plasma flow (RPF)

- Renal plasma flow : volume of plasma entering both kidneys per minute
- The blood has two components: 45 % cells (hematocrit, Hct) & 55% plasma. We care about plasma not the cells, because they don't participate in kidney function.
- Since the plasma represents 55% of the blood then the renal plasma flow will be 55% of renal blood flow :
  Renal plasma flow = 0.55 * 1200 (RBF) = 660 mL/min ~ **650 mL /min.**

Steps of urine formation

Once the plasma enters the glomerular area:

- 20% of it will be extracted as **filtration**. so , the amount filtered when the renal plasma flow is 650 mL/ min : 650 * 0.2= 125 mL
- The remaining 80 % (525 mL) leave through the efferent arteriole and go to the peritubular capillaries where they undergo one of three options :

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- ✓ Movement of substance from the blood to the tubule (**secretion**) > urine.
- ✓ Movement of substances from the tubule to the blood (**reabsorption**)> back to the renal vein.
- ✓ None of the previous two options >back to the renal vein.

- We have a urine output of 1 mL / minute, 60 mL / hour & 1.5 L / day.
- So, 1 mL of the 650 mL that entered through the renal artery will leave as a urine, and the remaining 649 will go back to the renal vein and then to the circulation (conservation of mass).
- When urine output decreases and becomes less than 1 mL/min we call this **oliguria** and this indicates kidney failure.

How to measure RBF and RPF

(RBF= RPF/ (1-HCT))

- To measure the RBF we have to measure the RPF and then divide it by 0.55.
  Example: if the RPF is 600 mL/ min, how much is RBF?
  600/ 0.55 = 1090 mL / min

But how to measure the RPF? Before we answer this question we have to know what does clearance mean (note that RPF measurement isn't a clinical routine test but we have to understand it).

Clearance

→Clearance is defined as the volume of plasma that provides X for excretion in the urine /minute. (Unit: volume / unit time and NOT a fraction).

Example:

Suppose you have entered 650 mL / minute of plasma to the kidney (RPF). These 650 mL was containing different substances (X, Y & Z) each with concentration of 1 mg/ mL >> so we have 650 mg of each substance.

If there was a 650 mg/mL of X in the urine. This means that all the plasma that entered the kidney was completely cleared from X, and the plasma that get back to the renal vein contained 0 concentration of X. this means that the clearance of X = 650 mL / min.

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Concentration of Y in the urine was 325 mg / mL, which's half of the amount that entered the kidney. So, the clearance of Y = 325 mL/min.

Concentration of Z was zero. So the plasma that entered the kidney was not cleaned at all from Z. so the clearance of Z = zero mL/min.

** Note that in the case of X which was completely cleared from the plasma, the clearance of X was equal to the RPF. So, this makes it a good RPF marker (i.e. can be utilized to measure the RPF).

Do we have such a substance?

PAH meets the criteria we need (para-aminohippuric acid.)

Why did we choose PAH?

PAH is freely filtered, not reabsorbed, completely secreted.

It has also other criteria like: doesn't accumulate in the kidney, not catabolized & not produced by the kidney itself (exogenous substance).

But the first three are the most important and if we have to choose only one we'll choose: completely secreted.

*So, to measure the renal plasma flow we choose a substance that's completely cleared (extracted) from the kidney once it enters it (100% conc. In urine) and ZERO concentration of it reaches the renal vein and goes back to the circulation i.e. its extraction ratio is 100%.

So, 20% of the concentration of the substance will be extracted by filtration, and the remaining 80% are going to be secreted. (Source of PAH in the urine: 20% from the filtrated which is not reabsorbed, 80% from secretion.)

So: **The amount of X provided to the kidney for excretion per minute = the amount of X excreted in urine per minute**

Amount of X provided for excretion = RPF * concentration of X in the plasma.

→We can measure the concentration of X in any sample of plasma

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Amount of X excreted per minute [excretion rate] (mg/min) = urine output (mL/min) * concentration of X in urine (mg/mL)

→We measure the urine output of the patient during the day, then we divide it by 24 (to find the urine output per hour), and then we divide it by 60 (to find the urine output per minute).

→ We measure the concentration of X in the urine from a urine sample.

Since: **the amount of X provided to the kidney for excretion per minute = the amount of X excreted per minute**

This means that: **urine output (mL/min) * concentration of X in urine (mg/mL) = RPF * concentration of X in the plasma.**

In another form: **RPF = [urine output (mL/min) * concentration of X in urine (mg/mL)] / concentration of X in the plasma**

And due to the fact that the excretion is complete then the clearance of PAH will equal the renal plasma flow. So we can use this substance to measure the renal plasma flow but the resultant number will be equal to **585** and not **650** which we have been talking about since the beginning and this result s from the fact that not all the blood entering the kidneys participate in its function; about **10** % of blood will go to nourish the renal capsule and other structures. So the clearance of PAH represent only **90** % of the true renal plasma flow which is called **effective renal plasma flow** which = 585/0.9 that will approximately equal 650

So there is no substance that enter the kidney in a conc. of 100% through the renal artery and its conc. in the renal vein will be equal to zero as not all blood entering the kidney will reach the afferent arterioles but it's more like circulating around the kidney (nourishing related structure) and consequently the **true renal plasma flow** is 10 % more than that of the **effective renal plasma flow**

Example: If the amount of plasma that entered the kidney in one minute was 650 mL and the measured plasma concentration of X was 1mg/ml in the plasma .how much of X has entered the kidney in one minute?

Amount of X that entered the kidney in one minute=RPF* concentration of X in the plasma

650*1 = 650 mg/minute

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- But for more accurate results we have to make sure that the concentration provided of PAH should be less than 80 mg / mL. WHY??

To understand the answer we have to clarify two points:

1. The difference between passive and active processes
2. The "splay".

Active and passive processes

When the process is passive, this means that the more the concentration of a substance you have, the more the transport is (unlimited linear relationship).

However, when the process is active, like in case of carrier-mediated transport, the transport will eventually reach a maximum limit when all transporters are occupied and oversaturated. This means that there's a linear relationship but it's not unlimited. Once you reach a certain concentration called "**Tmax**", an increase in the concentration won't produce an increase in transport (plateau phase).

"Filtration is passive process while secretion is active"

This means that filtration (20%) has a linear unlimited relationship with the concentration while secretion has a limit at Tmax which is 80 mg/mL in the case of PAH.

That's why you should make sure that the amount of PAH reaches the peritubular capillaries isn't more than Tmax (=80mg/mL). Otherwise the substance will accumulate and the kidney won't be able to excrete it fully (the extra amount will get back to the renal vein then to the circulation) and RPF won't be accurate, it'll be **underestimated.**

(Why is it underestimated? there will be an increase in the concentration of PAH in the plasma, while the urine output and PAH concentration in the plasma will remain constant, and according to the equation of RPF we are dividing the product of these two [which remained constant] by a higher value and this will give us a smaller number).

Note >> excretion = filtration +secretion -reabsorption

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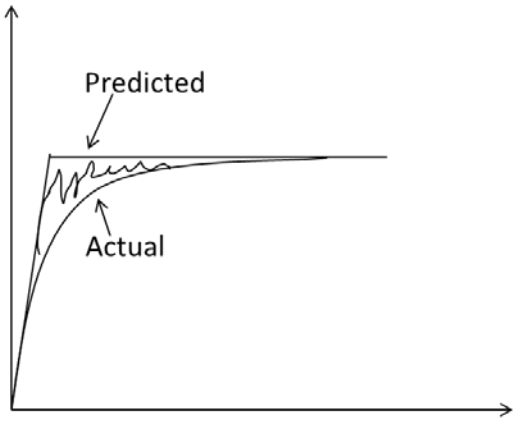
The Splay:

→In the **secretion curve**, they noticed an area that's deviated under predicted around Tmax. They called the space between the predicted curve and the actual curve "splay".

→So, the splay is the difference between actual curve and predicted curve.



→What cause the "**splay**"?

As we said earlier, the **Tmax** for PAH is 80mg/min .this means that if I provided 1000 mg/min they will divide into two parts: 80 mg will be secreted & 920 won't be secreted.

If we provided 800 they'll divide into 80 mg will be secreted & 720 won't be secreted.

If we provided 400 they'll divide into 80 mg will be secreted & 320 won't be secreted. And so on...

BUT, if we provided 100, we expect them to divide into 80 & 20 but this won't happen. They may divide into 75 and 25 for example.

& if we provided 80 we expect them to divide into 80 & 0 but this won't happen. They may divide into 70 & 10 for example.

So, whenever we are around the Tmax concentration we shouldn't expect the affinity of the receptors to be infinity, this means that some receptors may not be able to catch the ligand and this is what causes the splay area.

However, at high concentrations (suprasaturated), if one ligand escaped the other will not & therefore all receptors will be occupied.

So, it's preferred to use small concentrations of PAH to assure 100% excretion of it (before splay area) because at very low concentration if on ligand escaped one receptor it will not escape the others so all the ligands are going to bind the receptors.

والله وليّ التوفيق

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