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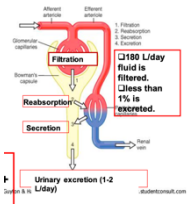
Renal Physiology L5

The functional unit of the kidney

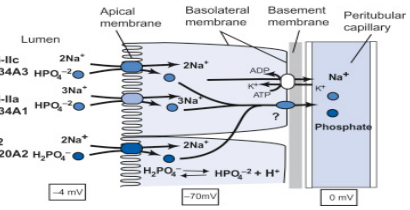
- Basic Mechanisms of Urine Formation
  - Ultrafiltration
    - We have about 180L of fluid filtered daily
  - Reabsorption
    - If there was no reabsorption we will lose the total volume of plasma that we have in a very short time
    - So it's a very important and significant process
    - A lot of substances are going to be reabsorbed in different rates, it's a selective process, very specific and requires energy (high expenditure of energy during this process)



  - Secretion
    - Some of the waste/harmful substances are secreted to eliminate them faster than filtration
  - Excretion
    - What remains in the tubules in the end is called urinary excretion
    - So mathematically
      - Excretion=Filtration-Reabsorption+ Secretion

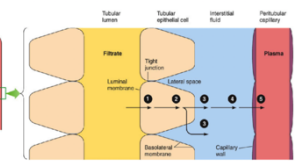
Reabsorption of Water and Solutes

- This picture represent a wall/segment in the proximal tubule
- As you can see the wall of tubule is composed of proximal epithelial cells that have a brush border on the luminal/apical surface which increases the efficiency of reabsorption
- Lets just explain the structure of the proximal tubule cells and make it clear
  - the proximal tubule cells have two sides



    - basal side
      - this is the side towards the peritubular capillaries/ intersitium
    - apical side
      - this is the side towards the proximal tubule lumen

- Lets make a few thing clear before we begin:
  - first of all, remember we talked about filtration and we said that blood enters the glomeruli and its going to get filtered into the bowman's capsule in which anything that is small and we don't want is going to go to the bowman's capsule and then go to the proximal convoluted tubule.
  - Now here in the proximal convoluted tubule reabsorption happens, in which there are going to be some substances that I want/need in this filtrate, so what happens here is basically these

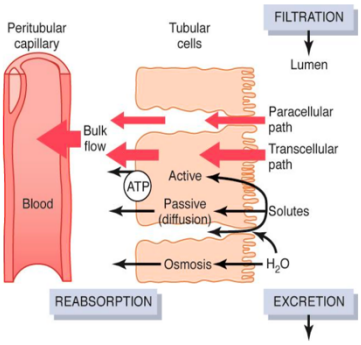


substances like sodium and glucose are going to get reabsorbed by the proximal tubule cells to the send them back into the blood

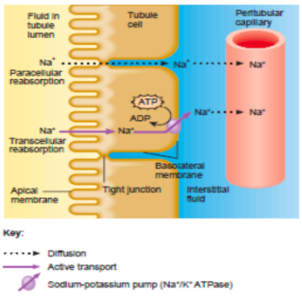
- Okay now that we made that clear, lets continue:
- The way each substance is reabsorbed is different since different substances have different permeabilities due to different factors like their chemical structures
- Routes of flow
    - Paracellular – in between the cells
        - We have paracellular spaces and tight junctions between the epithelial cells but those junctions aren't that tight to allow passage of water and sometimes ions
        - there permeability isn't equal in all nephrons they can be tighter in some nephron segments compared to others.
            - So they are tight junctions but not very tight to allow the paracellular path
        - The substances can enter down their gradient (no channels)
    - Transcellular – through the cells
        - The way they enter through cells is via channels
        - In which here they can move either passively (down their gradient) or actively (against their gradient, required energy)
- When there is reabsorption of solutes (regardless if it's active or passive) the tubular fluid (fluid in the proximal tubule) would have lower osmolarity than the intersitium
        - (remember osmolarity is the measure of the conc. of solutes)
    - And because there is going to be a lower osmolarity in the tubular fluid compared to the intersitium, that will drive osmosis of water across the membrane (from the proximal tubule to the intersitium) by aquaporin channels (water also has a transcellular and paracellular route)
        - Think about it logically, if I have a lower osmolarity in the tubular fluid that means I have less solutes, so more water
        - And if I have a higher osmolarity in the intersitium that means I have more solutes so less water
        - So it makes sense how the water will move (via aquaporin channels or passively) from the proximal tubule to the intersitium (from a higher water potential to a lower water potential via osmosis)
    - Plus water can also carry along other ions like potassium and calcium, this is called Solvent Drag, and ions that don't have selective transporters like potassium and calcium undergo solvent drag in the proximal convoluted tubule.
- Once the substances are in the interstitium they are going to be moved depending on the bulk flow and hemodynamic forces (similar to what happens in the capillary bed, in which we have hydrostatic forces, oncotic, net forces that facilitate the bulk flow into the peritubular capillaries)

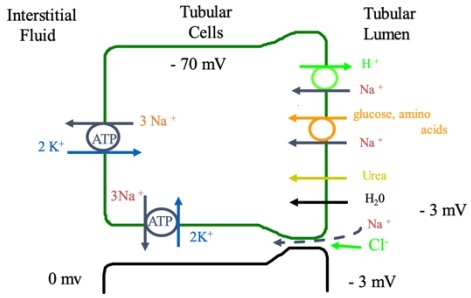
- Reabsorption of Na+ - KEY SUSBTANCE HERE
  - Na+ is a major cation in the extracellular fluid and in the filtered fluid so it's a key element,
  - There are special transporters for sodium to get it reabsorbed, the transporters are called sodium potassium ATPase pumps
  - These pumps are found on the basolateral side (towards the peritubular capillaries)
  - Sodium can also be reabsorbed paracellularly down their gradient
  - How they work
    - It pumps 3 sodium's outside (to the blood) in exchange of 2 potassium inside (to enter the tubule)
    - pumping sodium requires energy so they use ATP (breaking it down)
    - so we keep sodium inside the cell (proximal convoluted tubule cells) very low, so this is a gradient that favors sodium reabsorption form the filtered fluid to the cell
    - So Na+ diffuses from the tubular fluid into the tubular cells and is then pumped out to the interstitium towards the peritubular capillaries.
    - So the sodium-potassium ATPase doesn't just cause a chemical gradient, it also creates negative potential electrical gradient
      - Because when we release 3 sodium in exchange of 2 potassium, so it creates negative potential inside the cell (proximal convoluted cells)
      - So this will drive more sodium to get reabsorbed so there is also an electrochemical gradient favoring sodium reabsorption so the positive goes to the negative to get reabsorbed

Reabsorption of Water and Solutes

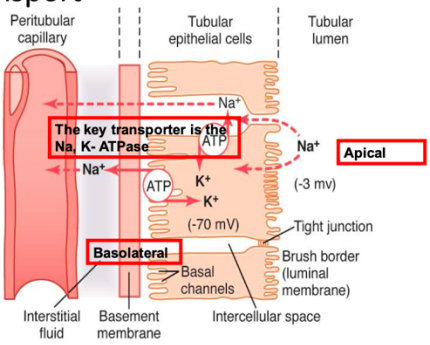


Reabsorption of Water and Solutes

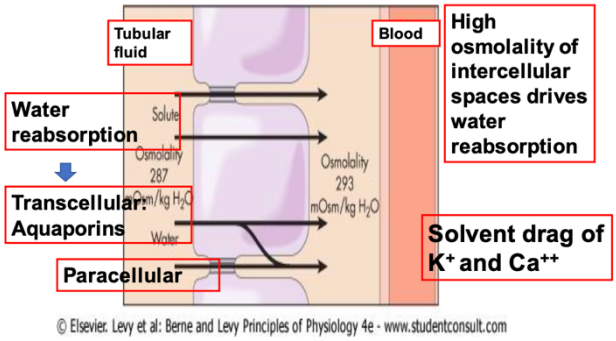




Active Transport

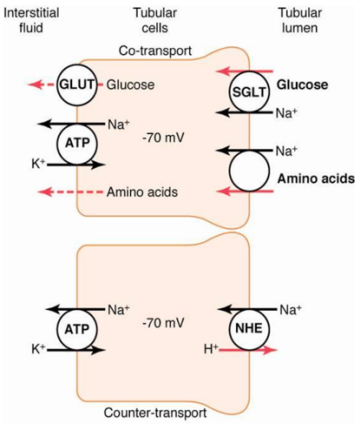


Proximal tubule reabsorption



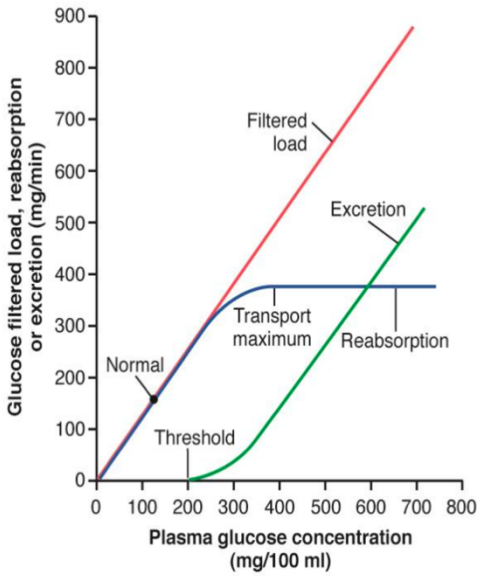
Glucose: Proximal Tubules

- Glucose and amino acids should be completely reabsorbed in the proximal tubules (so all the filtered glucose and amino acids should be reabsorbed)
- How is this achieved
  - Through mainly either facilitated diffusion or secondary active transport
    - We need active transport because facilitated diffusion will just cause the glucose and amino acids concentrations to reach equilibrium, while the secondary active transport will make sure all the amino acids and glucose are reabsorbed since they work against the concentration gradient
      - The secondary active transport is basically the transport of two or more substances using a membrane protein (a carrier molecule) and these substances are transported together across the membrane.
        - As one of the substances (for example ,sodium) diffuses down its electrochemical gradient, the energy released is used to drive another substance (for example, glucose) against its electrochemical gradient.
        - Thus, secondary active transport does not require energy directly from ATP or from other high energy phosphate sources. Rather, the direct source of the energy is that liberated by the simultaneous facilitated diffusion of another transported substance down its own electrochemical gradient.
- Co-transport
  - Glucose
    - The carrier protein that transports glucose and sodium together via secondary active transport is called SGLT, they transport two sodium's down their gradient and use the gradient built by the sodium potassium ATPase pump
  - Amino acids
    - They use the gradient of the sodium to move the amino acids
  - These transporters are called symporters
- Counter transporters
  - Another transporter is the sodium/H+ exchanger (also present in the proximal convoluted tubule) this exchange is found on the luminal/apical surface, in which it uses the gradient of sodium to re-absorb sodium and secrete hydrogen
    - Sodium is reabsorbed down its gradient
    - The hydrogen is secreted against its gradient (since in the lumen of the tubular fluid it has a higher concentration)
      - This is one of the ways we eliminate hydrogen from our system since we already produce a lot of acids



Glucose Transport Maximum

- Because the glucose and amino acids require transporters/carriers
- normally the substances in transport are related directly to the gradient of the substance across the membrane, as the gradient increases the transport also increases
- substances that require transporters like glucose and amino acids, they reach saturation/transport maximum, so if you exceed certain concentration in the blood or plasma, you wont be able to increase the reabsorption rate, because the reabsorption is limited to the number/capacity of the transporters/carriers
- so from the graph you can see that as the plasma glucose concentration increased, in the beginning the amount reabsorbed also increased because the filtered load (amount that is filtered) is higher (red line is higher than blue line)
    - the filtered load is calculated depending on the glomerular filtration rate and on the concentration of the substance in the plasma (GFR x plasma concertation per minute)
    - so as the filter load increases the proximal tubule has to reabsorb it so it increases the reabsorption as it increases but up to an extent which is the transport maximum
    - at this limit ALL the nephrons glucose transporters are saturated so no matter how much glucose you increase in the plasma, the reabsorption wont be able to increase
    - so the glucose that exceeded the transport maximum will get excreted
    - before 200 mg/100ml of glucose in the plasma there is no excretion of glucose since the glucose in the urine is supposed to be zero, so all the glucose is getting reabsorbed, but as soon as we exceed 200 mg/100ml, which is before the transport maximum in a bit, we start seeing glucose in the urine (the 200 mg/100 ml is the threshold)
        - the reason why excretion starts before we reach the transport maximum is because some of the nephrons (not all) have reaches their transport maximum so excretion will occur
        - so the plateau of the transport maximum that we see is the transport maximum for ALL nephrons (all nephrons are saturated)



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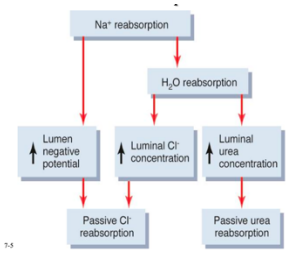
- substances that have a transport maximum are like glucose, phosphate, and amino acids
- sodium can also have a transport maximum but it depends on its location
    - in the beginning of the nephron in the Proximal convoluted tubule
        - the number of transporters available is so high that there is a low possibility of saturation especially that there is leak of sodium that occurs that is then reabsorbed so no saturation occurs here
        - the sodium reabsorption here follows the rule of time and gradient
            - gradient
                - as the concentration gradient increases (which means as the sodium increases in the tubular fluid) the reabsorption will increase
            - time
                - if the tubular flow rate was high the reabsorption would be low since they wont have time to reabsorb
                - As the flow rate is slower, the reabsorption would increase
    - in the distal part of the nephron in the Distal convoluted tubule
        - the amount of transporters isn't a lot so saturation can occur here

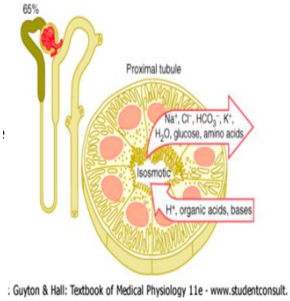
Mechanisms of water, chloride, and urea reabsorption coupled with sodium reabsorption

- What is left is chloride and urea which are now in high concentration and due to water reabsorption, that would increase their concertation even higher
- Chloride
    - The chloride remaining would increase the lumen negative charge which would form a potential to drive chloride via the paracellular route which sodium then follows
    - And since the chloride concentration increases as water get reabsorbed, so depending on the concertation gradient this favors the passive reabsorption of chloride
- Urea
    - As water gets reabsorbed the urea also increases in concertation (has a low reabsorption rate) and this causes passive urea reabsorption but not as good as water reabsorption since its permeability of urea isn't high
    - Urea anyways is a waste so our body in general doesn't want to reabsorb it a lot
    - But 50% of the urea is reabsorbed and 50% is excreted



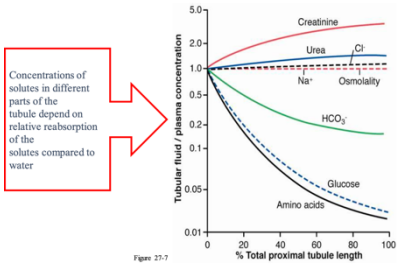
Proximal Tubules

- The proximal tubules reabsorbs about 67% of filtered water, Na+, Cl-, K+, HCO3-
- The proximal tubules reabsorbs almost all glucose and amino acids filtered by the glomeruli.
- The key transporter element is the Na, K- ATPase in the basolateral membrane



Changes in concentration in proximal tubule

- The main point here is that the substances that are reabsorbed higher than water, we will find that their ratio is less than 1 (tubular fluid concertation is less than that of the plasma)
- While the substances that are reabsorbed less than water , we will find that their ratio is more than 1 (so the concertation in the tubular fluid is higher than that in the plasma)
    - E,g urea and creatinine (creatinine being the highest)
- While the substances that have similar reabsorption to water, we will find that their ratio is 1 (which means that their tubular fluid and plasma concertation is similar)



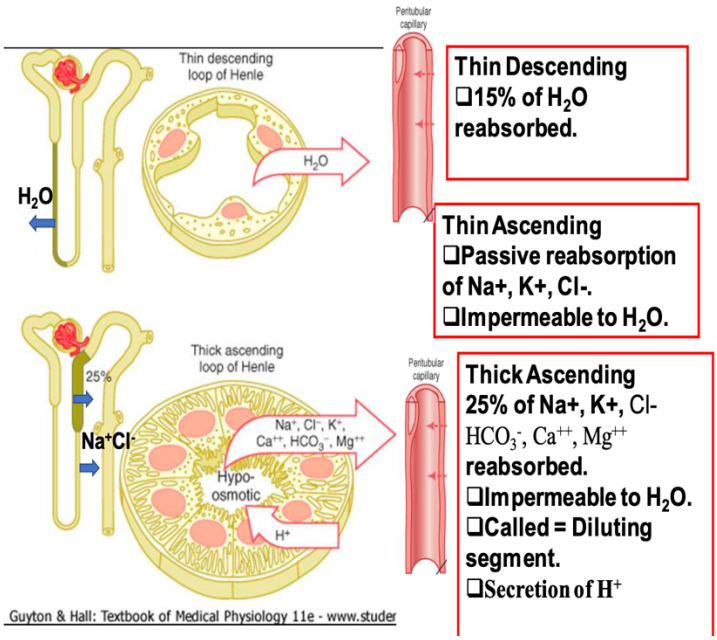
Loop of Henle

- The loop of Henle has 3 main physiologically relevant segments which are (in order)
    - Each of these segments have special characteristics that we need to memorize and understand
    - 1. Thin descending
        - Permeable to water
            - As we go deeper into the medulla, the intersitium becomes more concentrated in osmoles
            - So here as the fluid goes down the interstitium is more concentrated than the fluid
            - And since only water is allowed to be transported so osmosis of water occurs
            - 15% of water is reabsorbed here
        - Impermeable to solute
            - Slight solutes are transported here
            - So by the end of the tin descending tubule the solution is going to be hypertonic since its not permeable to the solutes and only is permeable to water so all the solutes will stay while the water will leave
    - 2. Thin ascending
        - Water is impermeable
            - No water is reabsorbed
            - So no aquaporins or paracellular route
        - Solutes is permeable

- So as the fluid is ascending, its concertation is higher in the tubular fluid than in the interstitium (since as we ascend the concentration of interstitial decreases)

- 3. Thick ascending
  - Its thick since its large cuboidal cells that have a lot of transporters and a lot of energy production and a lot of mitochondria
  - Water is impermeable here too
  - 25 % of Solutes (like Na+, K+, Cl-,HCO3-,Ca2+,Mg2+
    - When reaching the thick ascending, tubercular fluid is isotonic
    - Here there is active transport of the solutes
      - Active reabsorption of Na+
      - K+ and Mg+ are reabsorbed by voltage drag
    - So by the end of the thick ascending tubule the solution will be hypotonic (since you aren't allowing the water to leave, and the solutes are leaving, so its going to be very diluted) so this is called the diluting segment
  - Secretion of H+

- Each of these segments have special characteristics that we need to memorize and understand
- Water reabsorption occurs exclusively in the thin descending limb of Henle via AQP1 water channels.(Aquaporins)
- Reabsorption of NaCl occurs in both thin and thick ascending limb of Henle.
- In thin ascending limb NaCl is reabsorbed passively. However, in thick ascending limb NaCl is reabsorbed through Na+ -K+ ATPase in basolateral membrane ans .
- Ascending limb is impermeable to water.
- Reabsorption of Ca++ and HCO3- occurs also in Loop of Henle.



Thick ascending limb of Henle

- From the picture you can see the different transporters
- On the apical surface
    - Sodium – Potassium ATPASE
        - As we said before its present in the basolateral surface and it decreases the Na+ inside the cells and produces a sodium gradient
    - Sodium -Chloride-Potassium transporter
        - Reabsorbed , sodium, 2 chloride and potassium depending on the gradient that was created by the sodium potassium ATPase channel
    - Sodium- Hydrogen Exchanger
        - Reabsorbs sodium in exchange of the H+ being secreted
            - H+ is made in the cell from the CO2 and H20 and this is facilitated by carbonic anhydrase forming HCO3- and H+
                - H+ is secreted out be excreted in the urine
                - HCO3- is reabsorbed in the blood to buffer the acidity in the blood
    - The accumulation of the positive charges in the proximal cells is going to form something called a voltage drag
        - This facilitates transport of positively charged ions (especially the bivalent ones) across the paracellular route and this is very significant cause it makes up 50% of the transport of the solutes in the thick ascending limb of Henle
        - When potassium accumulates in the cell, part of it leaks out to the tubular fluid and the other part is reabsorbed
            - REMEMBER ITS IMPERMEABLE TO WATAER HERE
    - So there is a drug that has been manufactured called furosemide (a diuretic) which blocks the sodium chloride potassium reabsorption, so these ions are then secreted in the urine
        - So in the other segments, the amount of water that is going to be reabsorbed will be lower because the amount of solute in the tubular fluid is higher than that of the interstitium, so the tube has less water and more in the interstitium so the water will move by osmosis from a region of higher water potential (interstitium) to a region of lower water potential (the tube) → diuretic
        - The problem in it is that it also blocks potassium reabsorption too, so in the long run it causes hypokalemia which is risky and dangerous on the heart function