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Renal Physiology L2

Last Part of the slides from lecture 1 was explained in lecture 2 so here they are

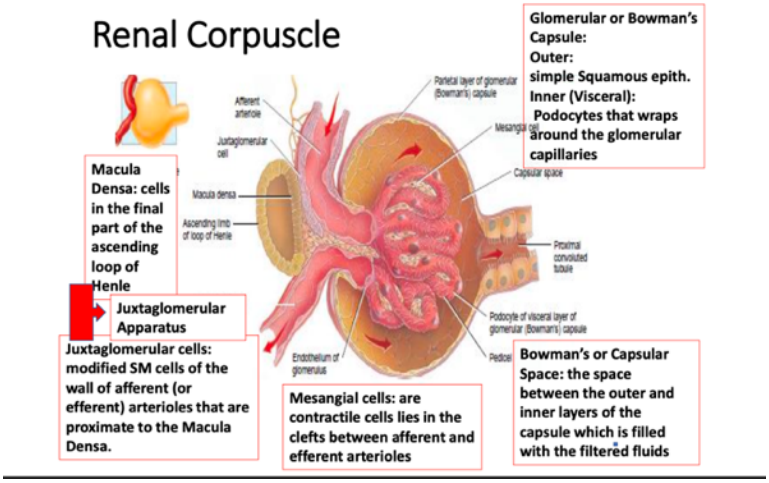
Basic Mechanisms of Urine Formation

- **Filtration** :
  - Passive, somewhat variable (related to size and the charge) , not selective (except for proteins), averages 20% of renal plasma flow
    - No need for energy
    - Its like putting fluid in a strainer and whichever components inside the fluids fits within the pores will get out and whatever stays will stay (this is why glucose is filtered ut)
- (2) **Reabsorption** :
  - highly variable and selective most electrolytes (e.g. Na+, K+, Cl-) and nutritional substances (e.g. glucose) are almost completely reabsorbed; most waste products (e.g. urea) poorly reabsorbed
    - its an active process and that's why its highly variable
    - its highly selective cause it takes place through highly selective transporters
    - electrolytes and nutritional substances CANT be transported by passive transport, so there must be specific transporters to transport them
- (3) **Secretion** :
  - highly variable; important for rapidly excreting some waste products (e.g. H+), foreign substances (including drugs), and toxins
    - active process
    - secretion is highly variable because its depends on the availability of the substances that will be secreted
    - this processes increases the rate of elimination of waste products, so they don't stay for a long time in the body

Renal Corpuscle

- Bowman's capsule consists of 2 layers :
  - Inner Layer - Visceral layer
    - which contain specialized cells called podocytes, these podocytes have processes "pedicles" that wrap the glomerulus
  - Outer Layer – Parietal Layer
    - which contain squamous epithelial cells .

- The space between these two layers contains the filtered fluid which in turn will flow outside the bowman's capsule into the proximal tubules
- You can see the afferent arterioles that bring blood into the renal corpuscle and you will see we have capillaries after the arterioles and these capillaries are covered with podocytes, so you don't see the cells of the capillaries clearly since they're covered in podocytes
- Arterioles have modified smooth muscle cells called juxtaglomerular cells which are located near the distal convoluted tubule–macular densa
    - The juxtamedullary cells also have a unique property in which it secretes the renin enzyme which are secreted depenign on factors like signals from the macula densa and Nitrous oxide
- The last part of the thick ascending loop of Henle is considered part of the juxtamedullary apparatus (in which we said in the last lecture that the last part of the ascending loop of Henle passes between the arterioles) in which the cells lining this part of the tubule is called macula densa, in which their structure is large and wide in colour
    - The macula dense have chemoreceptors in which they sense the delivery of sodium chloride so depending on the rate of delivery of the sodium chloride to the cells it will send signal t the juxtamedullary cells
- Macula Densa + Juxtagolmerular cells <= Juxtaglomerular apparatus is responsible of the autoregulation of the kidney (It is a kind of feedback mechanism between the blood flow that is coming from the afferent arterioles and the composition of filtered fluid that is in this part of the nephron).
    - So you can say that they're involved in the glomeruli filtration process
- There are also Mesangial Cells that is responsible of the control of the surface area; they increase or decrease it by contraction, to adjust the surface area for filtration.

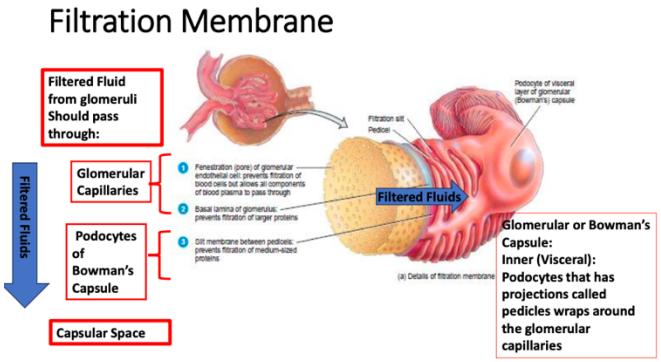


Filtration membrane

- The filtration membrane is composed of the wall of endothelial cells. These walls are composed of a single layer of fenestrated endothelial cells .

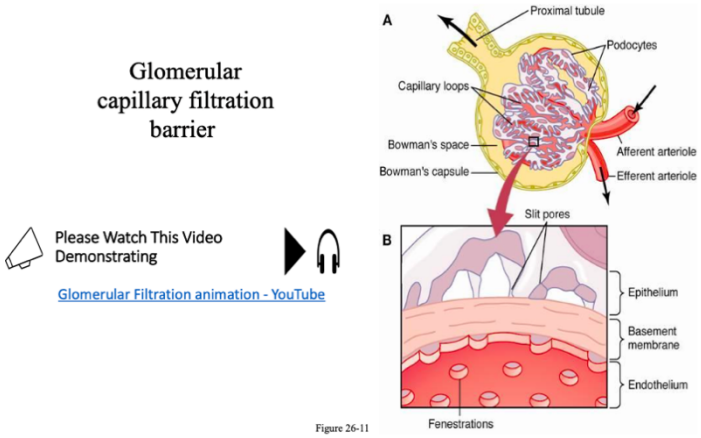
- These endothelial cells are unique since they have fenestrations and pores, and this facilitates the filtration function of the glomerulus. So, they are more permeable than the regular (continuous) capillaries but in the other hand they don't allow to RBC to pass like in sinusoidal capillaries .
- The fenestrations allow a certain size of substances to pass through, and any larger substance will not, so it prevents the filtration of blood cells but allows most of the components to pass through in terms of size.

- The basal lamina is the second barrier.
  - The basal lamina contains negatively charged fibers, so it won't allow negatively charged proteins from passing through, and that is why albumin can theoretically pass through the pores but cannot pass through the basal lamina. Therefore, very little amounts of albumin can be filtered due to this repulsion.
- The last barrier is composed of the inner surface of Bowman's capsule which we call the podocytes.
  - Podocytes are unique cells which have projections wrapping the glomeruli from the outside. Particles can only go through the spaces between these pedicles, and we call these spaces slits. Medium-sized proteins will not pass through them.



Glomerular capillary filtration barrier

- It represents how slits and pores are going to help the filtration process and precent large and medium sized proteins being filtered

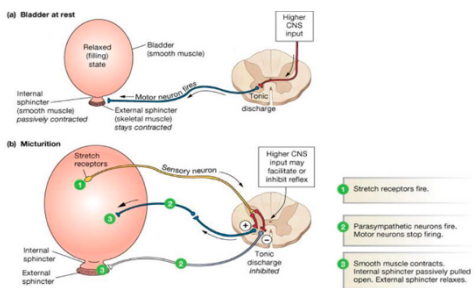


Renal Tubules and Collecting Ducts

- **Proximal Convoluted Tubule (PCT)**:
  - Simple cuboidal epithelial cells with brush borders.
- **Loop of Henle(LH)**:
  - Simple Squamous (thin), Cuboidal(Thick).
- **Distal Convoluted Tubule (DCT)**:
  - simple cuboidal.
- **Last part of DCT and Collecting Duct (CD)**:
  - Simple cuboidal consisting of:
    - 1. Principal Cells: contains receptors for ADH and Aldosterone.
    - 2.Intercalated Cells : Blood PH regulation

Micturition

- From the kidneys urine flows down the ureters to the bladder propelled by peristaltic contraction of smooth muscle. The bladder is a balloon-like bag of smooth muscle = detrusor muscle, contraction of it empties bladder during micturition.
- Voluntary and involuntary muscle contractions.
- Bladder can hold 700-800 ml (differs between males and females)
- Volumes exceeding (200-400)stretch bladder walls and initiate micturition reflex:
  - Spinal reflex (micturition center in the spinal cord)
  - Parasympathetic impulses from the spinal cord causes bladder to contract and the Internal urethral sphincter open.
  - Simultaneously mict. C inhibits the external sphincter (skeletal muscle) and then it relaxes. (This part can be controlled voluntary)
  - In the picture you can see that
    - Normally , both internal and external urethral sphincter are contracted " contraction" Tonic contraction
    - But in micturition urinary bladder will contract and the internal sphincter will relax .
    - AT REST there is a tonic discharge of motor neuron fibers for the internal and external sphincter which keep them contracted ,
    - However , when micturition starts as a result of volume build up, the reflex will start via parasympathetic neurons in order to the urinary muscles to contract , also it inhibits the tonic discharge of the internal sphincter, then the external sphincter will relax also , to excrete the urine.



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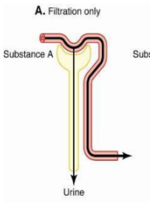
Beginning of Lecture 2

Differential Renal Handling of Water and Solutes

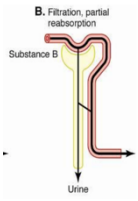
- Does the kidney handle the different substances equally?
- Water
  - From the table you can see that the filtration rate of water is 180L/day in both kidneys, and its rate of reabsorption is 179, so if you calculate it (180-179) only 1 L/day is excreted
  - Now you may ask what do you mean we have 180L of water/fluid in our body that our kidneys filtrate. Well we don't really have 180L of fluid, instead our plasma volume in our body is 3L BUT our body filters its 60 times (3 x 60 = 180L) so this is how the kidneys filters 180L/day.
    - We need to filter it around 60 times to remove the toxins and unwanted products efficiently and to maintain homeostasis of electrolytes ,fluid, blood volume and blood pressure
- Sodium
  - For sodium you can see that 25,560 mmol/day is filtered and 25,410 mmol/day is reabsorbed so by calculating it only 150 mmol/day is excreted (25,560-25,410)
  - Keep in mind sodium is also important to maintain homeostasis
- Glucose
  - For glucose you can see that 180gm/day is filtered and absorbed so there is NO glucose excreted
  - This is important because if there is glucose excreted then it can indicate that someone has diabetes
- Creatine
  - And for Creatine 1.8 gm/day is filtered and zero is reabsorbed so all that is filtered is excreted (you can also sometimes see that the excretion is higher than the filtered)

	Filtration	reabsorption	excretion
L/day Water	180	179	1
Na+ mmol/day	25,560	25,410	150
Glucose gm/day	180	180	0
Creatinine gm/day	1.8	0	1.8

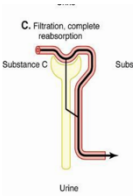
Renal Handling Of Different Substances



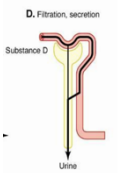
- Scenario A
  - The black line is the substance
  - Substance A is only filtered, in which no reabsorption or secretion occurred here
  - E.g Creatine



- Scenario B
  - Filtration occurred here and part of it was reabsorbed but not complete reabsorption (partial reabsorption) because some of it was excreted
  - E.g Sodium, chloride, potassium, and water



- Scenario C
  - Filtration occurred along with extensive reabsorption in which it was complete reabsorbed, and no excretion occurred

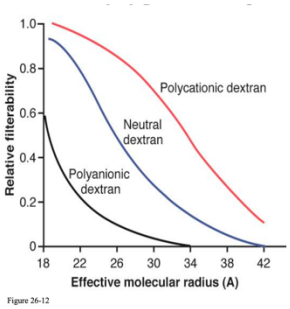


- Scenario D
  - Filtration and secretion occurred
  - You can tell that the body wanted to get rid of the substance quickly
  - E.g toxic substances

Effects of size and electrical charge of dextran on filterability by glomerular capillaries.

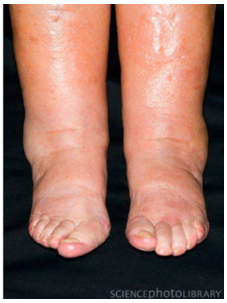
- If we want to do a study on the variability of renal handling of different substances we can perform an experiment of different molecules of different sizes and charges to study the filterability of these different molecules so that we can see what are the factors that affect the filterability across the filtration membrane
- So the chemical that was suitable for this experiment was dextran which is a synthetic substance that we can easily control and change its molecular weight and charge
- So when performing the experiment we separated the dextran into three categories, polycationic dextran, polyanionic dextran and neutral dextran
  - They all have different sizes and so if we say its polyanionic it has different sizes that has different negative charges, if we say polycationic It means different sizes that has different positive charges
  - For neutral dextran, it has different molecular sizes but EQUAL negative and positive charges (hence the name neutral)
- And from the graph you can see that we plotted everything down in which the x axis indicated the molecular size (their radius) and the y axis measured the relative filterability (keep in mind that the relative filterability the highest it can reach is 1, in which it's a ratio, and the highest is water)
  - You can see that for all of them , as the sized (radius) increased the filterability decreased

- You can also see that the polycationic (positively charged) had the highest relative filterability compared to the neutral (equal positive and negative charge) and the polyanionic (negatively charged)
  - So the smaller the size and the more positive the charge is the greater the filterability
    - The reason for the smaller size (logically speaking) is that we know that we have fenestrations (pores) in the filtration membrane, so the smaller the molecule the more likely it is going to get filtered
    - The reason for the positive charge to be more likely to get filtered is, we also mentioned this in the last lecture, we said that one of the barriers of the filtration membrane was the basal lamina and if you recall (you probably don't) , the basal membrane is negatively charged so any negatively charged molecules will get repelled and not get filtered
  - So you can see that the size and charge are important factors in determining the relative filterability



Clinical Application

- What Would happen if Filtration went wrong?



- Causes : For example damage to the podocytes in diabetes or damage to the basement membrane and collagen and proteoglycans got degenerated or damage to the endothelial cells
- Effect: the large proteins that SHOULDN'T pass through (specifically the anionic, like albumin) the filtration membrane will be able to pass through now, and then they're going to be able to be released with urine
  - so when they are in urine, depending on the amount of albumin in urine, we call this albuminuria and in this case the body will lose the plasma proteins which play an important function in the plasma osmotic/ oncotic pressure in which losing the plasma oncotic pressure will cause the fluids to not be able to be reabsorbed again so it will collect in the interstitial and this will cause something called edema
- Edema
- Some kidney diseases result in a damage of the glomerular Capillaries leading to an increase in their permeability to large proteins .
- Hence, Bowman's capsule colloid pressure will increase significantly leading to drawing more water from plasma to the capsule (i.e more filtered fluid).
- Proteins will be lost in the urine causing deficiency in the blood colloid pressure which worsens the situation, blood volume decreases and interstitial fluids increases causing edema.

Microalbuminuria

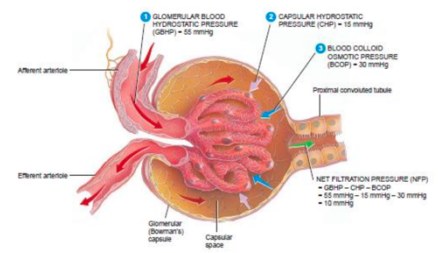
- Definition: urine excretion of > 30 but < 150 mg albumin per day
- Causes: early diabetes, hypertension, glomerular hyperfiltration
- Prognostic Value: diabetic patients with microalbuminuria are 10-20 fold more likely to develop persistent proteinuria

Clinical Significance of Detection of Proteinuria

- Early detection of renal disease in at-risk patients
- hypertension: hypertensive renal disease
- diabetes: diabetic nephropathy
- pregnancy: gestational proteinuric hypertension (pre- eclampsia)
- annual "check-up": renal disease can be silent
- Assessment and monitoring of known renal disease

Glomerular Filtration

- We need to calculate the glomerular filtration rate
- The GFR is the volume of plasma/fluid that has been filtered through ALL the nephron in one minute (how many ml it filtered in one minute) so when they calculated it, the found it to be 180 L/day
- GFR = 125 ml/min = 180 liters/day
- Plasma volume is filtered 60 times per day
    - As we said in the beginning of the lecture , the plasma volume is 3L per day, so it is filtered 60 times per day and this is how they calculated the GFR which is 180L/day (60 x 3)
    - And we said that its filtered 60 times to remove the waste and toxins efficiently and since every time we filter the plasma only 20% of the toxins and waste products are removed, so we need to filter it more than once to make sure all the toxins and waste products are removed so that no toxins accumulate
        - To see the amount that is filtered compared to the renal plasma flow we use a formulae which is GFR/renal plasma flow and this ratio is fixed in which it is 0.2
        - So 20% of the volume of plasma that passes through all the nephrons is filtered
- Glomerular filtrate composition is about the same as plasma, except for large proteins
- Filtration fraction (GFR / Renal Plasma Flow) = 0.2 (i.e. 20% of plasma is filtered)
- The blood when it enters the afferent arterioles has a hydrostatic pressure originating form the force of contraction of the heart so when it enters the afferent arteriole is has a hydrostatic pressure of 55 mmHg
- Inside the glomeruli we have hydrostatic pressure which is also 55 mmHg which is the same as the hydrostatic pressure in the afferent arteriole since it comes from there anyways
- There is going to be fluid that is being filtered and will fill the bowman's capsule, so any fluid in the container will also have hydrostatic pressure, so the hydrostatic pressure in the bowman's capsule is 15 mmHg
- Other pressure available are related to the oncotic/osmotic pressure, the blood in the glomeruli has plasma proteins in which even when filtration occurs they wont get released so these will build an osmotic oncotic pressure, so the blood colloid (oncotic) osmotic pressure is 30 mmHg
- Blood Colloid Osmotic Pressure in the plasma is high due the proteins present that don't leave , exerting a pressure that draw fluids inside the capillaries there



Calculating the net filtration pressure (NGP)

- first of all we need to determine the direction we are calculating so for example we can say that we are calculating the forces towards filtration
- so any force or pressure towards filtration (outside the glomeruli) will be positive and anything inside the glomeruli is considered negative and then we calculate the net
- so you can see from the picture that we have three forces
- the glomeruli hydrostatic pressure
    - its going towards filtration (in which you can see that its going towards the bowman's capsule) so its going to be positive
    - +60 mmHg
- the glomeruli colloid osmotic pressure
    - you can see that its going towards the glomeruli so its against the filtration so its going to be negative
    - -32 mmHg
- bowman's capsule pressure
    - you can see that its also going towards the glomeruli going against the filtration so its going to be negative
    - – 18 mmHg
- So the net filtration =
    - +60 + (-32) + (-18)
    - = + 10 mmHg
        - This means that there is a net of 10mmHg that drives fluid outside the glomeruli to be filtered (remember its positive so that means its towards filtration)
        - If the net decreased , then the filtration would also decrease, so its important to have 10 mmHg since this net filtration forces are related directly to the glomeruli filtration rate

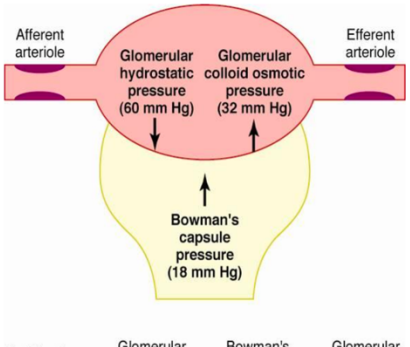


Figure 26-13

Glomerular Filtration Rate (GFR)

- Filtration Fraction (FF)= Fraction of blood plasma in the afferent arterioles that becomes filtrate= 16-20%.
    - It's a fixed ratio as we said before
- GFR =The volume (ml) of fluid filtered through all the corpuscles of both kidneys per minute.
- The volume of fluid filtered daily through all the corpuscles of both kidneys per day = 180 L
- Hence, GFR= 180 L/24hours * (1000 ml/ L)*(1hour/60 min)= 125 ml/min (Males)
- For 125ml/min; renal plasma flow = 625ml/min
    - So we know that 20% of the renal plasma is the GFR then we can calculate the renal plasma flow from the GFR
    - Renal flow x 20/100 = GFR
        - Renal flow x 20/100 = 125
        - Renal flow = 625 ml/min
- FF * PF=GFR, PF= 125/(20%)=625 ml/min
    - Now all of this is in terms of the plasma flow we want to calculate it in terms of the blood flow
    - 55% of the blood is plasma so if we now the plasma flow we can calculate the blood flow
        - Blood flow x 55/100 = Plasma flow
        - Blood flow x 55/100 = 625
            - Blood flow = 1140 ml/min
- 55% of blood is plasma, so blood flow = 1140ml/min 55% * BF= PF; BF= 625ml/min/ (55%)=1140 ml/min
- Renal Blood Flow of 1140 ml/min = (22.8 % of 5 liters) is required to have GFR of 125ml/min.