PHYSIOLOGY

- SHEET NO. 7
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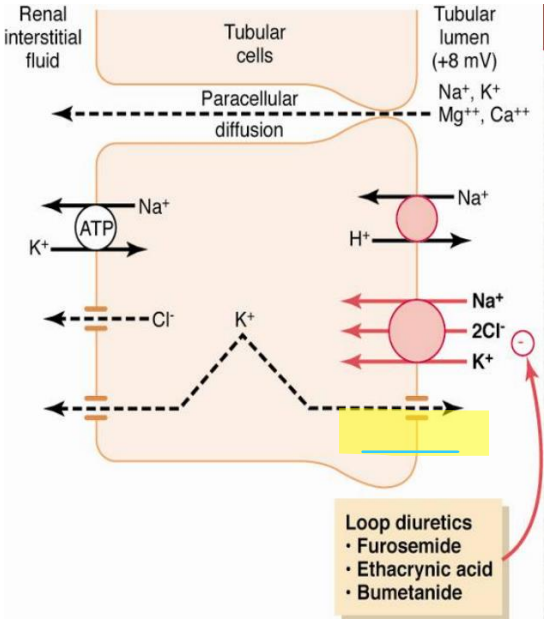
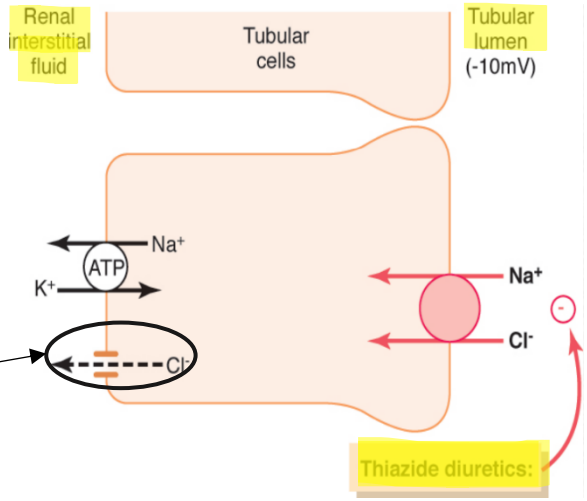
بسم الله الرحمن الرحيم

Recap about the thick ascending limb of Henle:



- **The main transporter** is the sodium chloride potassium channel. This channel transports Na+ & 2Cl- & K+ from the tubular fluid into the tubular cells causing their reabsorption.
- **Loop diuretics (ex. Furosemide):** that blocks the sodium chloride potassium (Na-K-Cl) channel, so more excretion of salts and fluids which will decrease blood volume/the extracellular compartment volume, so blood pressure decreases. BUT it also causes loss of potassium as it prevents its reabsorption causing hypokalemia on the chronic use.
- The thick ascending limb of Henle is the is the **diluting segment** because water permeability is virtually absent.
- **The voltage drag process:** The high density of positive charge causes high repulsion between the positive ions that causes it to be reabsorbed through the paracellular route.
  The positive charge is due to the **leak of potassium** into the lumen mainly because of high intracellular potassium.
  - ➔ So, fluid will flow in the early distal tubule (early segment of distal convoluted tubule) after passing through thick ascending loop Henle. The distal convoluted tubule is divided into early and late segments because they are two functionally distinct segments. The late distal is combined to the collecting tubule as they are characteristically similar. Now lets start with the early distal tubule.

Early Distal Tubule:



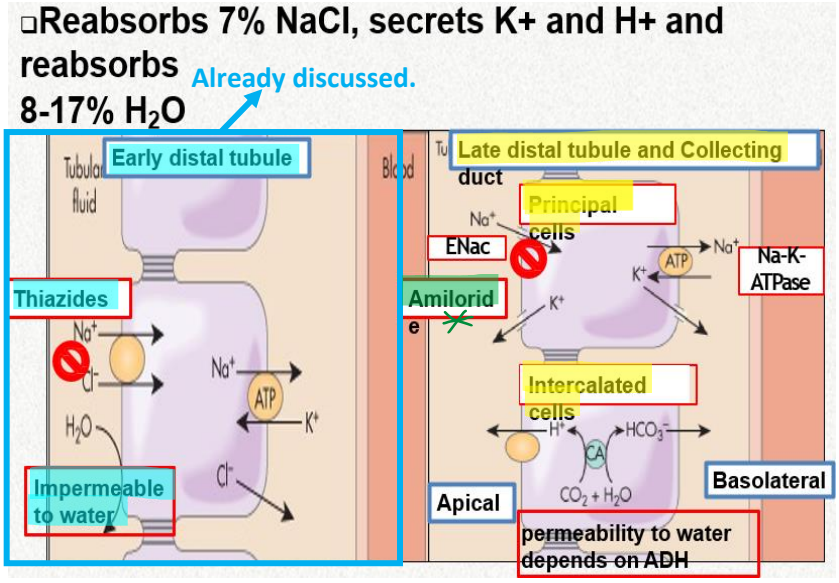
- The first cells in the walls of tubules are the **macula densa cells** which are important in the renal autoregulation (the tubuloglomerular feedback) as part of the juxtaglomerular apparatus.
- The next cells are the classical cells of the early distal tubule that will perform the function of reabsorbing sodium. The main channel present here is the Na+/Cl- channel on the luminal/tubular side it transports Na+/Cl- by using the gradient that is produced by the **Na+/K+-ATPase**, so the Na and Cl are reabsorbed. Chloride is reabsorbed through its **own channels** to the peritubular capillaries.
- There are group of drugs specialized to block this channel called Thiazide diuretics, they selectively block this channel, therefore function as a diuretic, because when they block the Na+ and Cl- reabsorption, a large amount of it will be stuck in tubular fluid, and water follows solute, so diuresis happens (So more sodium chloride and water volume will be lost which will reduce blood pressure).
- Almost 5% of sodium chloride is going to be reabsorbed in early distal tubule.

The early distal tubule is:

- **Functionally similar to thick ascending loop of Henle** (in terms of water reabsorption: impermeable to water).
- **Not permeable to water (also called diluting segment).** This is similar to thick ascending loop of Henle, so the presence of sodium reabsorption in this segment will make the tubular fluid more diluted.
  *So, dilution continues from thick ascending loop of Henle to the early distal tubule.
- **Active reabsorption of Na+, Cl-, K+, Mg++**
- **Contains macula densa.**

Late distal tubule and collecting duct:

Late distal tubule and collecting duct are composed of two functionally and anatomically distinct types of cells: **principal cells & intercalated cells.**



1. **Principal cells:** are characterized by the presence of ENac (Epithelial sodium channels)→ENac channels will cause Na+ reabsorption→the reabsorbed Na+ will be pumped out by Na+/K+ Atpase (present on basal membrane) and at the same time it increases intracellular potassium→this intracellular k+ will build up→ causing its secretion into the tubular fluid/lumen (in other words it will be like there is one transporter that **reabsorbs Na+ and secretes k+,** but actually **it is not just one transporter doing that**, BUT ENac will indirectly causes more K+ secretion to the lumen due to increased Na+ reabsorption).

Aldosterone hormone will stimulate both the **Na+/K+ Atpase** and the **ENac** (Epithelial sodium channels). **When is aldosterone hormone secreted? It has 2 stimulants:**

1- **Hyperkalemia:** increased blood conc of K+ will stimulate aldosterone secretion from adrenal cortex→ acts on principal cells activating Na+/K+ Atpase and the ENac→ increasing Na+ reabsorption as well as K+ secretion→ which will eliminate excess potassium and correct the potassium level in blood.

2- **Angiotensin 2**: Hypotension, hypovolemia, haemorrhage, or low salts will stimulate angiotensin 2 that will stimulate aldosterone secretion thus increasing Na+ reabsorption (remember hypotension→ renin secretion that will convert angiotensinogen to ang 1→Ang1 will be converted to ang2 by ACE → aldosterone secretion by ang 2→ sodium retention→ blood pressure rises).

*Both these 2 stimulants will cause Na+ reabsorption, but aldosterone also increases K+ secretion, **aldosterone is the primary regulator for the potassium** in our body, greater than its role in sodium.

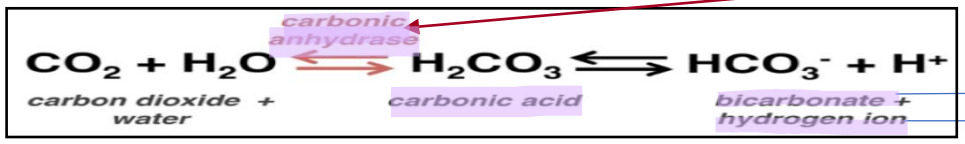
➔ ENac channel is blocked by Amiloride (K+ sparing diuretic), it is a diuretic because it blocks the reabsorption of Na+ (cause diuresis by loss of sodium and fluids), BUT it is also causes **potassium-sparing** because it blocks the secretion of k+ into the tubular fluid. This means it causes diuresis, but it doesn't decrease k+ concentration in blood (K+ sparing).

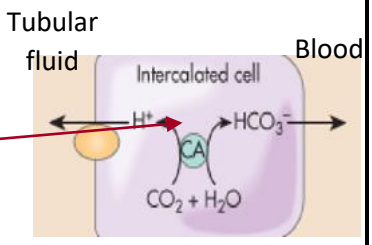
➔ Amiloride inhibits ENac. Aldosterone stimulates ENac.

2. **The Intercalated cells:** Their main function is to maintain acid-base balance in our body fluids. Our body tends to produce acids more than bases so we tend to have acidosis (our plasma secretes a lot of acids), but surely alkalosis may also occur. There are **2 types of intercalated cells** (Type A and Type B):

➢ **Type A: Activated by Acidosis:**

H+ ATPase pumps (present on luminal surface) secrete H+ (needs energy).
H+ is produced by the action of carbonic anhydrase:





Reabsorbed to blood.
Secreted into tubular fluid.

➔ Classically intercalated cells secrete hydrogen to tubular fluid & reabsorb the bicarbonate back to blood to neutralize the acids that the body produced to prevent acidosis.

➢ **Type B: Activated by Alkalosis (more bases):** Here the channels are in an opposed direction → reabsorption of H+ (neutralize bases) and secretion of bicarbonate (get rid of bases).

Permeability to water in late distal and collecting ducts is variable and **depends on antidiuretic hormone (ADH).**

➔ **In the presence of ADH** in late distal and collecting ducts (which is stimulated in dehydration or increased osmolarity in body fluids)→ activation of insertion of aquaporin channels on apical and basal membranes → increase permeability to water in late distal and collecting ducts → water become able to reabsorbed by osmosis to peritubular capillaries from tubular fluid → **decreasing urine volume, concentrating the urine, preserving body fluids, and increasing blood pressure** (if its already low, it can be increased). So ADH prevents the high volume of urine & increases the extracellular fluids and blood pressure.

➔ **In the absence of ADH** in late distal and collecting ducts: There is almost no permeability for water (or very low). We know that the fluids coming from the early distal tubule are very diluted, so if the late distal and collecting ducts are also impermeable to water then the **urine will be very diluted with low osmolarity and high volume of urine** because there is no or very low reabsorption of water.

*Remember: in thick ascending and early distal tubule → impermeable to water →tubular fluid is diluted.

Early and Late Distal Tubules and Collecting Tubules: Collecting tubules have 2 parts: cortical or medullary (collecting ducts also can have medullary).

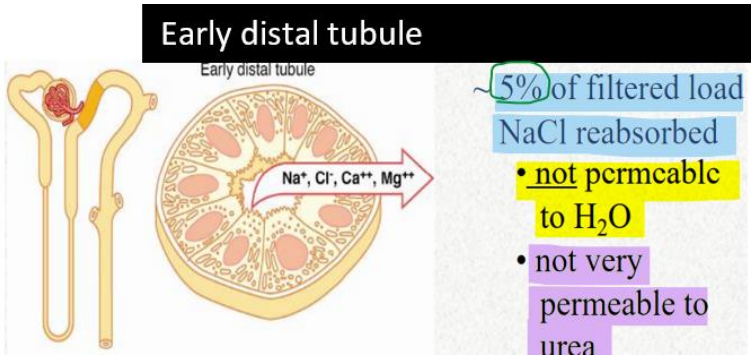
➔ They differ in **urea permeability**: **cortical collecting tubules have very limited/poor permeability to urea, but medullary collecting tubules/ducts is permeable to urea.**

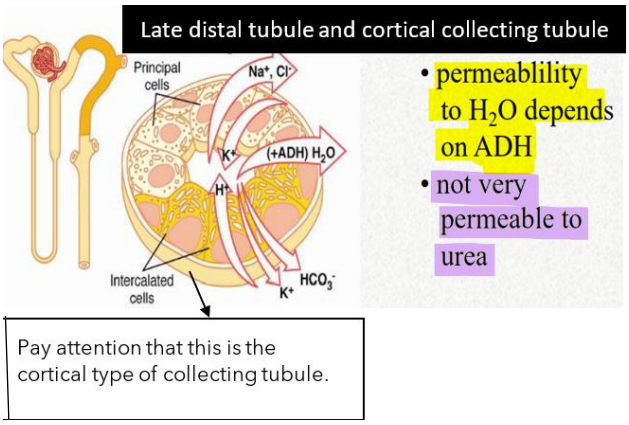
Urea reabsorption in medullary collecting ducts:

This characteristic gives the kidney the capability of **concentrating urine** which will increase interstitial osmotic pressure in medulla.

➔ So, as we go down in medulla→ more interstitial osmotic pressure → more capability of water reabsorption in presence of ADH.

This is a characteristic especially to the juxtamedullary nephron (most of their collecting tubules are in the medulla).





Pay attention that this is the cortical type of collecting tubule.

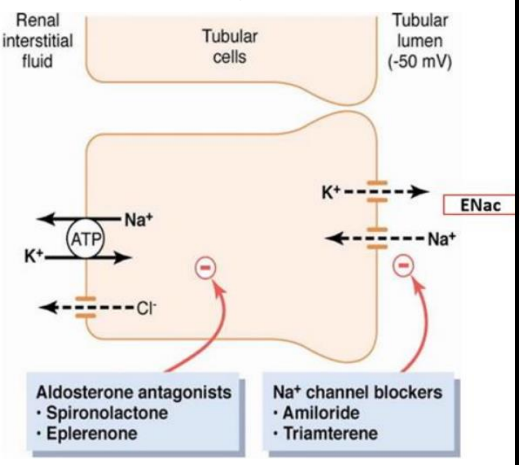
Both are not very permeable to urea; this is opposite to medullary collecting ducts.

Late Distal and Cortical Collecting Tubules Principal Cells – Secrete K+:

The main characteristic in these cells is their ENac channels which **reabsorb Na+** and cause **K+ secretion** into tubular fluid. Notice that when amiloride blocks ENac, it blocks the Na+ reabsorption (diuresis function) & blocks K+ secretion (preserves K+ inside the body). This is the opposite of what happens in the other diuretic types we discussed which do not preserve K+.

➔ Aldosterone antagonists (also diuretics), that block mineralocorticoids receptors (aldosterone receptors). If aldosterone stimulates Na+-K+ atpase and ENac in principal cells, so blocking aldosterone will result in **sparing of K+ and diuresis** (ex. Spironolactone), (almost the same action of Amiloride).

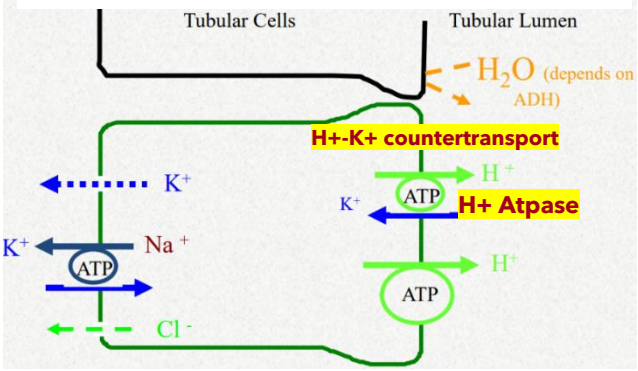
Demonstrating principal cells



Late Distal and Cortical Collecting Tubules Intercalated Cells –Secrete H+:

Main function of intercalated cells: Acid-base balance in both acidosis and alkalosis.

Demonstrating intercalated cells



Types of transporters in intercalated cells:

- **H+ Atpase pump:** How different is this pump from the Na+/H+ exchanger in thick ascending limb and the proximal tubule?

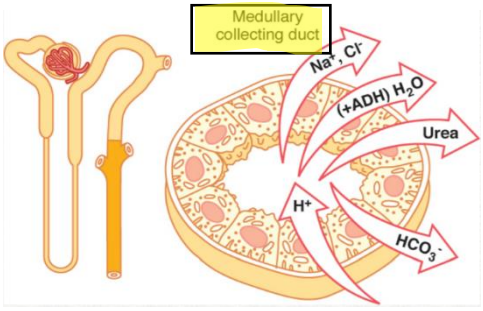
1- No exchange with sodium in H+ Atpase pump present in intercalated cells.

2- More effective in secreting H+ than Na+/H+ exchanger in TAL and the proximal tubule (more powerful in secreting H+ against its gradient).
   - Na+/H+ exchanger in thick ascending limb and the proximal tubule → can secretes H+ against its concentration gradient only 10 times.
   - BUT, here the H+ Atpase pump in intercalated cells → secretes H+ even though against gradient 1000 times more! This makes the intercalated cells have a much greater ability in acid-base balance compared to proximal tubules or thick ascending tubules.

- **H+-K+ countertransport:** reabsorption of K+ and secretion of H+

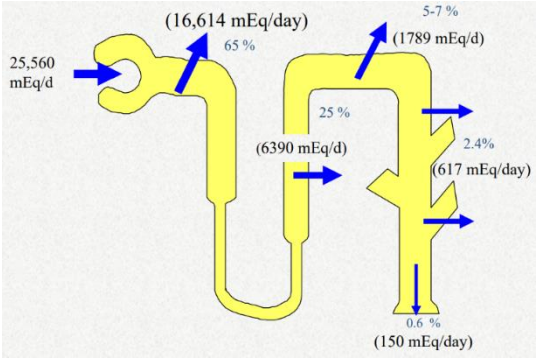
Transport characteristics of medullary collecting ducts:

As discussed before: In medullary specifically there is urea reabsorption (so there is permeability to urea compared to cortical collecting tubules which has no urea permeability), its concentration increases in the matrix. So, if ADH is activated, urine becomes more concentrated, water is highly reabsorbed to get the water back from the tubular fluid.



Normal Renal Tubular Na+ Reabsorption:

If we look at sodium reabsorption in all parts of nephron→ Firstly, in the proximal tubule (about 65% of the tubular Na+ reabsorbed), after that in the thick ascending limb (25% from filtered Na+ is reabsorbed), after that in early distal (5%), and in late distal and collecting ducts (2.4%). Finally excreted Na+ (0.6%). **Less than 1% from filtered Na+ is excreted.**



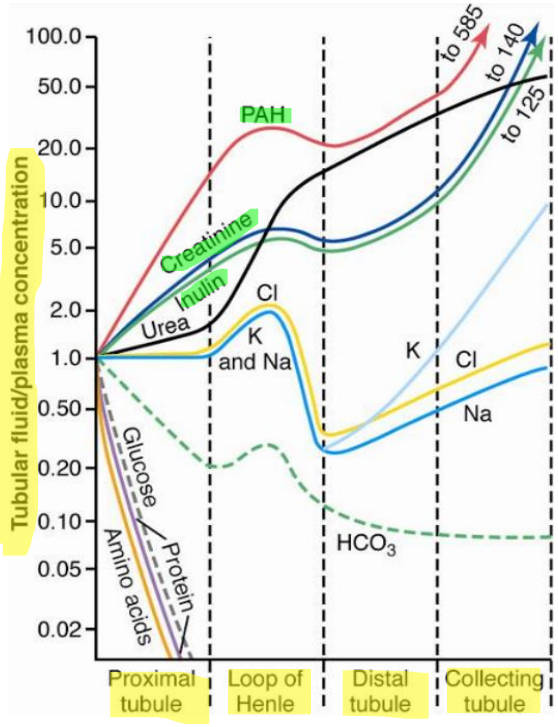
Changes in concentrations of substances in the renal tubules:

The graph on the right depicts the changes in concentrations of different substances in different segments of the renal tubule (In different segments we can notice different concentration percentages).

Remember: the different concentrations are measured as Tubular Fluid Concentration of the substance divided by Plasma Concentration of the same substance (tubular fluid conc/plasma conc ratio).

Changes in this ratio are due to tubular fluid concentration changes not plasma concentration.

The ratio can be more than one, less than one, or around one (substances around 1 ratio is mainly in the proximal convoluted tubule and may vary in its ratio)



Concentrations of solutes in different parts of the tubule depend on:

➔ Relative reabsorption of the solutes compared to water.

If water is reabsorbed to a greater extent than the solute, the ratio is more than one because the solute has poor reabsorption so it will become more concentrated in the tubule, it may also be secreted in addition to filtration to give a higher ratio (e.g. creatinine, urea, inulin, PAH: para-aminohippuric acid).

If water is reabsorbed to a lesser extent than the solute (the solute is reabsorbed to a much higher extent than water reabsorption), the ratio here is less than one because the solute will become less concentrated in the tubule (e.g. glucose and amino acids especially in the proximal convoluted tubule, bicarbonate, and also sodium may be reabsorbed more than water in some segments).

➔ So that's why the different concentrations of solutes between segments can be explained by the different permeabilities of water.

Note from the Book for better understanding: Whether a solute will become concentrated in the tubular fluid is determined by the relative degree of reabsorption of that solute versus the reabsorption of water. If a greater percentage of water is reabsorbed, the substance becomes more concentrated. If a greater percentage of the solute is reabsorbed, the substance becomes more diluted.

- **Inulin** is an **exo**genous polysaccharide substance, if given experimentally, it will be freely filtered as water, but it will not undergo neither reabsorption nor secretion, and will be excreted unchanged (so its filtration rate equals its excretion rate, and its clearance is the same as the GFR so it is used for GFR calculation, this point will be more discussed in the next lecture).

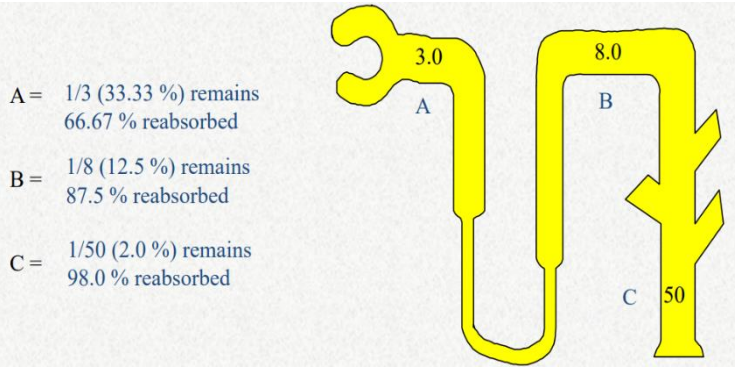
  ➔ So, if inulin is not reabsorbed nor secreted (constant amount), but its concentration across the nephron is increasing, what does this reflect?
  That there is **water reabsorption**, this will help us to measure the water reabsorption in different segments (see the example on the next page). So, changes in inulin concentration at different points along the renal tubule, therefore, reflect changes in the amount of water present in the tubular fluid.

- **Creatinine** concentration is little higher than inulin this is because it undergoes secretion.

- **PAH (para-aminohippuric acid)** is also an exogenous substance, but when given to a person, it is freely filtered BUT is extensively secreted because it has a much higher concentration than inulin which is not secreted nor reabsorbed. It has a very high secretion to an extent that its excretion rate is equal to plasma flow rate in kidney (renal blood flow), that's why it's used in measuring renal blood flow.

Using Inulin in calculating water reabsorption in different segments:

➔ **Example:** The figure below shows the concentrations of inulin at different points along the tubule, expressed as the tubular fluid/plasma (TF/P_{inulin}) concentration of inulin. If inulin is not reabsorbed by the tubule, what is the percentage of the filtered water that has been reabsorbed or remains at each point? What percentage of the filtered water has been reabsorbed up to that point?



Tubular Fluid/Plasma Inulin Concentration Ratio Can Be Used to Measure Water Reabsorption by the Renal Tubules. Once Inulin is filtered, its tubular fluid conc/plasma conc ratio is 1 **(*In general plasma conc is constant but tubular fluid conc is changeable).**

Point A: The tubular fluid/plasma concentration ratio for inulin rises to about 3.0 at the end of the proximal tubules, indicating that inulin concentration in the tubular fluid is three times greater than in the plasma and in the glomerular filtrate. Because inulin is not secreted or reabsorbed from the tubules, a tubular fluid/plasma concentration ratio of 3.0 means that only one third of the water (33.33%) that was filtered remains in the renal tubule and that two thirds (66.67%) of the filtered water has been reabsorbed as the fluid passes through the proximal tubule. So this change is due to the diluent/solvent change by reabsorption and not from inulin, because inulin hasn't changed (not reabsorbed nor secreted).

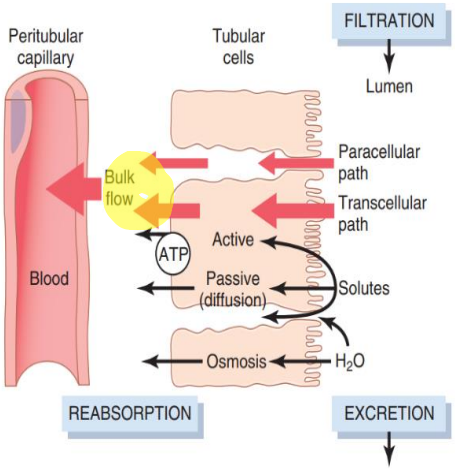
Point B: The Inulin ratio becomes 8 → so 1/8 (12.5%) of water remains, and the rest (87.5%) is reabsorbed.

Point C: The Inulin ratio becomes 50 → so 1/50 (2%) of water remains, and the rest (98%) is reabsorbed.

Diuretic type	Channel involved	Present in	Mechanism summary
Loop-acting Ex. Furosemide (Lasix)	Blocks sodium chloride potassium (Na-K-Cl) channel	Thick ascending limb of Henle (PCT)	Inhibits Na+ reabsorption → water follows solute so H2O reabs. ↓ = diuresis
Thiazide	Blocks Na+/Cl- channel	Early distal tubule	Inhibits Na+ and Cl- reabs. → solute remains in tubular fluid → water follows solute = diuresis
Potassium-sparing Ex. Amiloride Triamterene	Blocks epithelial sodium potassium channel (ENac)	Principal cells in late distal tubules and collecting ducts	Inhibits Na+ reabs.... = diuresis Blocks K+ secretion into tubular fluid so K+ is spared from excretion
Aldosterone antagonists Ex. Spironolactone Eplerenone	ENac Note: aldosterone stimulates ENac, aldosterone antagonists inhibit aldosterone	Principal cells in late distal tubules and collecting ducts	Aldosterone stimulates ENac→ inc. Na+ reabs., inc. K+ secretion into tubular fluid = prevent diuresis. Antagonist inhibits this (does the opposite).

Before moving to another topic, this is a useful table from 2019 that summarize diuretics.

Regulation of Tubular Reabsorption



We mentioned in the previous lectures the importance of GFR regulation, and now we will talk about regulation of reabsorption because at the end we need balance between both of them to achieve renal homeostasis.

Recap ➞ we said that the tubular reabsorption mechanism is the transport of the desired nutrients from the tubular lumen into the tubular cells. Then, the nutrients pass to the Interstitium and complete passing until reaching the peritubular capillaries and the nutritional passage into the peritubular capillaries is called BULK FLOW, which depends on:

1- **Glomerulotubular Balance** (achieved by hemodynamic forces)
(intrinsic adjustment of reabsorption rate that results from changes of GFR)
If GFR increased and we couldn't control it or it was controlled and decreased down to a certain level but was still considered high→ tubular reabsorption increases to avoid excessive urine loss.

2- **Peritubular Physical Forces** (Hydrostatic and colloid osmotic forces govern the rate of reabsorption across the peritubular capillaries)

3- **Hormones** (the strongest factor and each one acts selectively on different substances). See the table below.
- aldosterone
- angiotensin II
- antidiuretic hormone (ADH)
- natriuretic hormones (ANF)
- parathyroid hormone

4- Sympathetic Nervous System
5- Arterial Pressure (pressure natriuresis)
6- Osmotic factor (e.g If a substance has a high osmotic pressure and it's filtered → this will cause changes in reabsorption process)

This table is extra, From Guyton

It's useful though 😉

Table 28-3 Hormones That Regulate Tubular Reabsorption

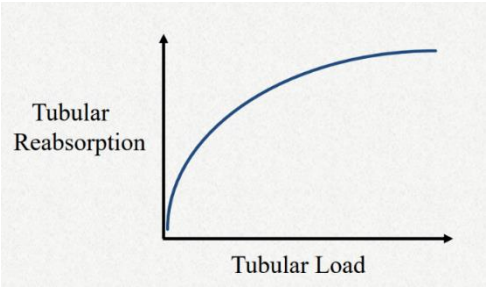
Hormone	Site of Action	Effects
Aldosterone	Collecting tubule and duct	↑ NaCl, H_2O reabsorption, ↑ K^+ secretion, ↑ H^+ secretion
Angiotensin II	Proximal tubule, thick ascending loop of Henle/distal tubule, collecting tubule	↑ NaCl, H_2O reabsorption, ↑ H^+ secretion
Antidiuretic hormone	Distal tubule/collecting tubule and duct	↑ H_2O reabsorption
Atrial natriuretic peptide	Distal tubule/collecting tubule and duct	↓ NaCl reabsorption
Parathyroid hormone	Proximal tubule, thick ascending loop of Henle/distal tubule	↓ PO_4^- reabsorption, ↑ Ca^{++} reabsorption

Note that each hormone acts selectively on different substances.

Glomerulotubular balance

The graph on the right depicts the relationship between Tubular load and Tubular Reabsorption.

➔ We can notice that as the concentration of the substance that has been filtered (Filter/ Tubular Load) increases, the tubular reabsorption also increases (up to a limit/ reaches plateau at the end) in an attempt to adjust the tubular reabsorption to an extent to become compatible with the increase in the Tubular load that was due to the increase in the filtration load (GFR).



Tubular load → filtered amount of renal plasma fluid (represents GFR)

The Importance of Glomerulotubular balance in minimizing the changes that can take place in urine volume due to changes in the Glomerular Filtration Rate.

In the previous lectures, we discussed the importance of Tubuloglomerular feedback/Balance.

➔ The **tubuloglomerular** feedback is the feedback that can change/ modify glomerular filtration rate while the **Glomerulotubular balance** is the balance that takes place between the GFR and tubular reabsorption (notice that **reabsorption** is the thing that is going to be modified here).

Kidneys regulate this salt excretion by modulating the rapport between glomeruli and tubules. The tubules respond to glomeruli with Glomerulotubular balance, whereas glomeruli respond to tubules through tubuloglomerular feedback.

Referring to this table in the case of "No Glomerulotubular Balance":

➔ If the GFR increased from 125 ml/min (normal value) to 150 ml/min, and reabsorption did not change (stayed as 124), because there was no Glomerulotubular balance ⟶ the urine volume will rise from 1 to 26 ml/min.

GFR	Reabsorption	Urine Volume	% Reabsorption
	no glomerulotubular balance		
125	124	1.0	99.2
150	124	26.0	82.7
	"perfect" glomerulotubular balance		
150	148.8	1.2	99.2

➔ If we calculate the percentage of reabsorption in the normal case 124/125 *100 = **99.2 %** (this percentage indicates that from the filtration, 99.2% was reabsorbed back).

➔ But when there is no Glomerulotubular balance (loss of filtered substances occurs) , and the reabsorption is not increased upon the increase in the GFR → the reabsorption percentage will be reduced because there is no adjustment or modification for the reabsorption→ 124/150 *100 = **82.7 %**

Referring to the previous table in the case of "Perfect Glomerulotubular Balance":

➔ When the GFR increased from 125 to 150, the reabsorption is also adjusted to increase from 124 to 148.8 → the urine volume will be 1.2 and the percentage of reabsorption equals 99.2%

This represents the case of "**Perfect Glomerulotubular Balance**", meaning that there was an adjustment for the reabsorption, in order to prevent any changes in the urine volume (the urine volume stays at the same value present when the GFR and Reabsorption values are normal).

- So again.. if hypertension raised GFR to 180 → Autoregulation is achieved and GFR is decreased down to 150→ Also, reabsorption increases from 124 to 148.8 as a compensatory mechanism (Glomerulotubular balance is achieved) to avoid excessive urine loss.

The **perfect situation** is : when GFR increases → GFR autoregulation + compensatory increase in tubular reabsorption /glomerulotubular balance

Regulation in both GFR and tubular reabsorption.

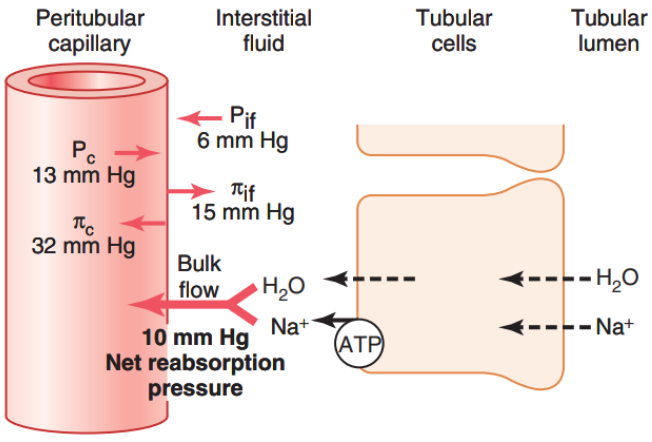
Peritubular capillary reabsorption

Remember: we have talked previously about the forces that govern the glomerular filtration.

NOW, we will discuss the forces that govern the Peritubular Capillary Reabsorption / BULK FLOW.

➔ After reabsorption and transport take place, all absorbed water and solutes will flow from interstitium to capillaries as bulk flow.

The type of forces is the same, but here we are talking about tubular cells (that form the wall of the tubules) and peritubular capillaries.



Notice that the values of the forces here are different from that of the glomeruli or Bowman's Capsule, BUT the direction of the forces are the same.

These hemodynamic forces are:

1- **Capillary Hydrostatic Pressure** = 13 mmHg, and the direction of this pressure is to the outside of the capillary.
2- **Interstitial Hydrostatic Pressure** = 6 mmHg, it is found in the hydrostatic fluid and it is directed into the capillaries.
3- **Capillary Oncotic Pressure** = 32 mmHg, it is directed toward the inside of the capillary.
4- **Interstitial Fluid Oncotic Pressure** = 15 mmHg, and it is directed toward the outside of the capillary

- Since the processes occurring in the Peritubular capillaries are reabsorption processes NOT filtration process (as in the glomeruli), and therefore when we want to calculate the Net Reabsorption Pressure, we consider that any force toward reabsorption is POSITIVE, and any force against reabsorption is NEGATIVE.

  → Capillary Hydrostatic Pressure and the Interstitial Fluid Oncotic Pressure → NEGATIVE pressures
  → Interstitial Hydrostatic Pressure and Capillary Oncotic Pressure → POSITIVE pressures.

- The **net reabsorption** pressure is the process of water and sodium reabsorption represented by the BULK FLOW or diffusion into the peritubular capillaries.

  → The NET REABSORBTION PRESSURE = +6 +32 -13 -15 = 10 mmHg

- This is the normal reabsorption value and there is small leakage that exists normally.
  - But if any changes took place to these forces → net reabsorption would be affected

    For example if the oncotic capillary pressure decreases → net reabsorption decreases → accumulation of bulk flow → back leak of fluids and return back through the intercellular junction into tubular fluid → **decreases the whole reabsorption process**

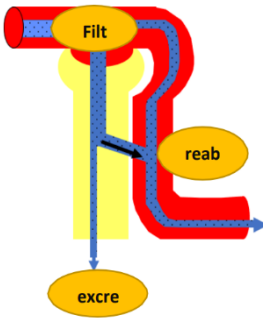
  - So reabsorption doesn't depend only on transporters (in tubular cells) but also on hemodynamic forces(in peritubular capillaries and interstitium).

اللهم صل على سيدنا محمد

Filtration rate and Excretion rate

When Excretion is less than Filtration (**Excret s < Filt s**)

Part of the substance is Reabsorbed.



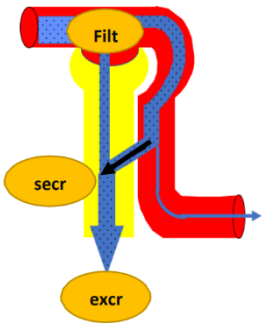
measure the **Tubular Reabsorption Rate.**

Reabsorption = Filtration – Excretion

If reabsorption was **negative** → secretion has occurred

When Excretion is more than Filtration (**Excret s > Filt s**)

The substance had undergone a net Secretion



measure the **Tubular Secretion Rate.**

Secretion = Excretion - Filtration

Filt s = GFR x Ps

(Ps = Plasma conc of s)

We can calculate the Filtration Rate [filtered load] for a particular substance by multiplying the GFR (Glomerular Filtration Rate) by the concentration of the substance in plasma.

Excret s = Us x V

(Us = Urine conc of s

V = urine flow rate)

In order to calculate the excretion rate, multiply the concentration of the substance (that we are measuring its reabsorption) in the urine by the urine flow rate.

- The **Glomerular Filtration Rate** is a function in the Glomeruli that does not depend on the type of the substance = 125 ml/min
  The **concentration** of the substance is measured in mg/ml.
  ➔ The **Filtration rate** is measured in mg/min.

- The **Urine concentration** of a substance is measured in mg/ml.
  The **urine flow rate** is measured in ml/min.
  ➔ The **excretion rate** is measured in mg/min.

Example: **Given the following data, calculate the rate of Na+ filtration, excretion, reabsorption, and secretion.**

GFR =100 ml/min (0.1 L/min)

PNa= 140 mEq/L

urine flow = 1 ml/min (.001 L/min)

urine Na conc = 100 mEq/L

Be careful to the units while solving.

➢ Answer:
We know that the Na is reabsorbed, but in case we don't know, we first need to calculate the filtration and excretion, then we see which one is higher in order to decide whether absorption or secretion occurred.

Filtration Na = GFR x PNa = 0.1 L/min x 140 mEq/L = 14 mEq/min

Excretion Na = Urine flow rate x Urine Na conc = 0.001 L/min x 100 mEq/L = 0.1 mEq/min

Now, we can see that the filtration is much higher than the excretion:

➔ Reabsorption occurs.

Reabsorption Na = Filtration Na - Excretion Na = 14.0 - 0.1 = 13.9 mEq/min

➔ Secretion Na = There is no net secretion of Na since Excret Na < Filt Na

The Concept of Transport Maximum

As we mentioned earlier when we discussed glucose transport, some substances have a maximum rate of tubular transport due to saturation of carriers, limited ATP, etc.

➔ Transport Maximum: Once the transport maximum is reached for all nephrons (the transporters are saturated with the substance), further increases in tubular load (concentration of this substance in the tubular fluid) is not going to be reabsorbed instead they are going to be **excreted** through urine.

Transport maximum is the maximum amount of substance that can be reabsorbed based on the number of transport proteins available

➔ Threshold: is the tubular load (concentration of the substance) at which transport maximum is exceeded in some nephrons. This is not exactly the same as the transport maximum of the whole kidney because some nephrons have lower transport max's than others.

In other words, there might be a certain concentration of a substance in the tubular fluid, and some nephrons reach their transport maximum at this concentration, but the rest of the nephrons are still not reaching their transport maximum.

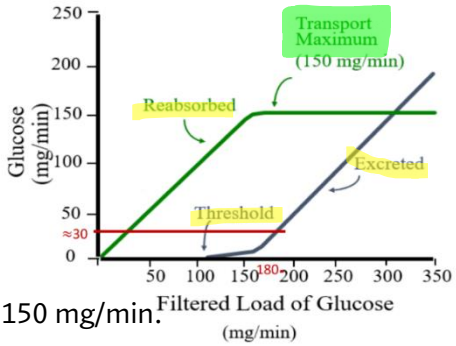
At the threshold we notice an increase in the excretion of a certain substance, but some other nephrons can still reabsorb this substance.

- Transport maximum and Threshold are related terms, but they are not the same.
- Transport maximum is related to substances that are actively reabsorbed through their own transporters.
- The following are examples of substances having a transport maximum and a threshold: **glucose, amino acids, phosphate, sulphate, lactate.**

MCQ QUESTION: A uninephrectomized patient (having one kidney) with uncontrolled diabetes has a GFR of 90 ml/min, a plasma glucose of 200 mg% (2mg/ml), and a transport max (Tm) shown in the figure. What is the glucose excretion for this patient?

A. 0 mg/min B. 30 mg/min C. 60 mg/min D. 90 mg/min

E. 120 mg/min



Answer: From the figure we can see that the Transport maximum equals 150 mg/min.

We first calculate the tubular load/ filtered load of the patient using the GFR and the plasma glucose level. GFR = 90 ml/min , Plasma Glucose = 2 mg/ml

→ The tubular load/ filtered load = 2 x 90 = 180 mg/min

→ The excreted = 180 – 150 = 30

Notice that the transport maximum is 150 mg/min, meaning that the transporters found in the kidney can only transport 150 mg/min, but the tubular load is 180 mg/min → so there will be a remaining of 30 mg/min that are going to be excreted. Referring to the figure, we can notice that at a filtered load of 180, the transport maximum was already achieved, and that's why the remaining 30 mg/ml are going to be excreted. Therefore, the answer is B.

So again…

We can see that at the threshold, we did not reach the transport maximum for all the nephrons. And since the 150 mg/min is the transport maximum for all the nephrons→ at this level of glucose filtered load, all the nephrons are saturated→ and the excess is excreted.

At the threshold, some nephrons reached their transport maximum before the other nephrons, and that is why we can notice the excretion after the threshold value at 120 or 130 mg/ml (look at the figure in the previous page) → in other words, at the threshold we start noticing glucose in the urine, although we did not reach the transport maximum in all the nephrons.

Guyton Questions:

1) Which of the following tends to decrease potassium secretion by the cortical collecting tubule?

A) Increased plasma potassium concentration
B) A diuretic that decreases proximal tubule sodium reabsorption
C) A diuretic that inhibits the action of aldosterone (e.g., spironolactone)
D) Acute alkalosis
E) High sodium intake

2) Because the usual rate of phosphate filtration exceeds the transport maximum for phosphate reabsorption, which statement is true?

A) All the phosphate that is filtered is reabsorbed
B) More phosphate is reabsorbed than is filtered
C) Phosphate in the tubules can contribute significantly to titratable acid in the urine
D) The "threshold" for phosphate is usually not exceeded
E) Parathyroid hormone must be secreted for phosphate reabsorption to occur

3) Use the following clinical laboratory test results to answer
Urine flow rate = 1 ml/min
Urine inulin concentration = 100 mg/ml
Plasma inulin concentration = 2 mg/ml
Urine urea concentration = 50 mg/ml
Plasma urea concentration = 2.5 mg/ml

What is the net urea reabsorption rate?

A) 0 mg/min
B) 25 mg/min
C) 50 mg/min
D) 75 mg/min
E) 100 mg/min

4) If a patient has a creatinine clearance of 90 ml/min, a urine flow rate of 1 ml/min, a plasma K^+ concentration of 4 mEq/L, and a urine K^+ concentration of 60 mEq/L, what is the approximate rate of K^+ excretion?

A) 0.06 mEq/min
B) 0.30 mEq/min
C) 0.36 mEq/min
D) 3.6 mEq/min
E) 60 mEq/min

5) In normal kidneys, which of the following is true of the osmolarity of renal tubular fluid that flows through the early distal tubule in the region of the macula densa?

A) Usually isotonic compared with plasma
B) Usually hypotonic compared with plasma
C) Usually hypertonic compared with plasma
D) Hypertonic, compared with plasma, in antidiuresis

6) Which of the following changes would be expected from a patient with diabetes insipidus due to a lack of ADH secretion?

	Plasma Osmolarity Concentration	Plasma Sodium Concentration	Plasma Renin	Urine Volum
A)	↔	↔	↓	↑
B)	↔	↔	↑	↑
C)	↑	↑	↑	↑
D)	↑	↑	↔	↔
E)	↓	↓	↓	↔

7) When the dietary intake of K^+ increases, body K^+ balance is maintained by an increase in K^+ excretion primarily by which of the following?

A) Decreased glomerular filtration of K^+
B) Decreased reabsorption of K^+ by the proximal tubule
C) Decreased reabsorption of K^+ by the thick ascending limb of the loop of Henle
D) Increased K^+ secretion by the late distal and collecting tubules
E) Shift of K^+ into the intracellular compartment

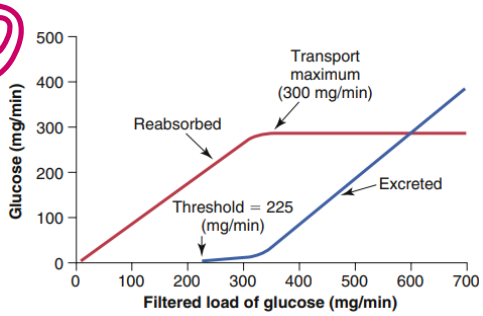
8) What would cause the greatest degree of hyperkalemia?

A) Increase in potassium intake from 60 to 180 mmol/day in a person with normal kidneys and a normal aldosterone system
B) Chronic treatment with a diuretic that inhibits the action of aldosterone
C) Decrease in sodium intake from 200 to 100 mmol/day
D) Chronic treatment with a diuretic that inhibits loop of Henle Na^+-$2Cl^-$-K^+ co-transport
E) Chronic treatment with a diuretic that inhibits sodium reabsorption in the collecting ducts

9) If distal tubule fluid creatinine concentration is 5 mg/100 ml and plasma creatinine concentration is 1.0 mg/100 ml, what is the approximate percentage of the water filtered by the glomerular capillaries that remains in the distal tubule?

A) 5%
B) 10%
C) 20%
D) 50%
E) 80%
F) 95%

10



A 32-year-old man reports frequent urination. He is overweight (280 pounds [127 kilograms], 5 feet 10 inches [178 cm] tall). After measuring the 24-hour creatinine clearance, you estimate his GFR to be 150 ml/min. His plasma glucose level is 300 mg/dl. Assuming that his renal transport maximum for glucose is normal, as shown in the figure above, what would be this patient's approximate rate of urinary glucose excretion?

A) 0 mg/min
B) 100 mg/min
C) 150 mg/min
D) 225 mg/min
E) 300 mg/min
F) Information provided is inadequate to estimate the glucose excretion rate

11

Which of the following tends to increase potassium secretion by the cortical collecting tubule?

A) A diuretic that inhibits the action of aldosterone (e.g., spironolactone)
B) A diuretic that decreases loop of Henle sodium reabsorption (e.g., furosemide)
C) Decreased plasma potassium concentration
D) Acute metabolic acidosis
E) Low sodium intake

12

A 62-year-old woman has previously had a unilateral nephrectomy after diagnosis of renal carcinoma. Her GFR (estimated from creatinine clearance) is 50 ml/min, her urine flow rate is 2.0 ml/min, and her plasma glucose concentration is 200 mg/100 ml. If she has a kidney transport maximum for glucose of 150 mg/min, what would be her approximate rate of glucose excretion?

A) 0 mg/min
B) 50 mg/min
C) 100 mg/min
D) 150 mg/min
E) 200 mg/min
F) 300 mg/min
G) Glucose excretion rate cannot be estimated from these data

13

Furosemide (Lasix) is a diuretic that also produces natriuresis. Which of the following is an undesirable side effect of furosemide due to its site of action on the renal tubule?

A) Edema
B) Hyperkalemia
C) Hypercalcemia
D) Decreased ability to concentrate the urine
E) Heart failure

14

Which of the following would likely lead to hyponatremia?

A) Excessive ADH secretion
B) Restriction of fluid intake
C) Excess aldosterone secretion
D) Administration of 2 liters of 3% NaCl solution
E) Administration of 2 liters of 0.9% NaCl solution

15

If a person has a kidney transport maximum for glucose of 350 mg/min, a GFR of 100 ml/min, a plasma glucose level of 150 mg/dl, a urine flow rate of 2 ml/min, and no detectable glucose in the urine, what would be the approximate rate of glucose reabsorption, assuming normal kidneys?

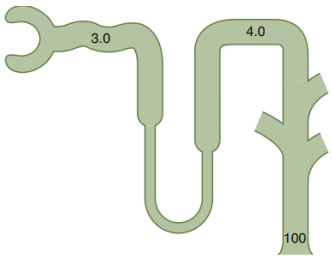
A) Glucose reabsorption cannot be estimated from these data
B) 0 mg/min
C) 50 mg/min
D) 150 mg/min
E) 350 mg/min

16

Which diuretic inhibits Na^+-$2Cl^-$-K^+ co-transport in the loop of Henle as its primary action?

A) Thiazide diuretic
B) Furosemide
C) Carbonic anhydrase inhibitor
D) Osmotic diuretic
E) Amiloride
F) Spironolactone

17



The above figure shows the concentration of inulin at different points along the renal tubule, expressed as the tubular fluid/plasma ratio of inulin concentration. If inulin is not reabsorbed, what is the approximate percentage of the filtered water that has been reabsorbed prior to the distal convoluted tubule?

A) 25%
B) 33%
C) 66%
D) 75%
E) 99%
F) 100%

18

The principal cells in the cortical collecting tubules

A) Are the main site of action of the thiazide diuretics
B) Have sodium-chloride-potassium co-transporters
C) Are highly permeable to urea during antidiuresis
D) Are an important site of action of amiloride
E) Are the main site of action of furosemide

19

If the cortical collecting tubule tubular fluid inulin concentration is 40 mg/100 ml and plasma concentration of inulin is 2.0 mg/100 ml, what is the approximate percentage of the filtered water that remains in the tubule at that point?

A) 0%
B) 2%
C) 5%
D) 10%
E) 20%
F) 100%

Answers and explanation:

1) **C)** Aldosterone stimulates potassium secretion by the principal cells of the collecting tubules. Therefore, blockade of the action of aldosterone with spironolactone would inhibit potassium secretion. Other factors that stimulate potassium secretion by the cortical collecting tubule include increased potassium concentration, increased cortical collecting tubule flow rate (as would occur with high sodium intake or a diuretic that reduces proximal tubular sodium reabsorption), and acute alkalosis.

2) **C)** Phosphate excretion by the kidneys is controlled by an overflow mechanism. When the transport maximum for reabsorbing phosphate is exceeded, the remaining phosphate in the renal tubules is excreted in the urine and can be used to buffer hydrogen ions and form titratable acid. Phosphate normally begins to spill into the urine when the concentration of extracellular fluid rises above a threshold of 0.8 mmol/L, which is usually exceeded.

3) **D)** The net urea reabsorption rate is equal to the filtered load of urea (GFR [50 ml/min] × plasma urea concentration [2.5 mg/ml]) − urinary excretion rate of urea (urine urea concentration [50 mg/ml] × urine flow rate [1 ml/min]). Therefore, net urea reabsorption = (50 ml/min × 2.5 mg/ml) − (50 mg/ml × 1 ml/min) = 75 mg/min.

$$GFR = C_{inulin} = \frac{U_{in} \times V}{P_{in}}$$

This law will be mentioned in lec 8 (x3)

4) **A)** K^+ excretion rate = urine K^+ concentration (60 mEq/L) × urine flow rate (0.001 L/min) = 0.06 mEq/min.

5) **B)** As water flows up the ascending limb of the loop of Henle, solutes are reabsorbed, but this segment is relatively impermeable to water; progressive dilution of the tubular fluid occurs so that the osmolarity decreases to approximately 100 mOsm/L by the time the fluid reaches the early distal tubule. Even during maximal antidiuresis, this portion of the renal tubule is relatively impermeable to water and is therefore called the diluting segment of the renal tubule.

6) **C)** In the absence of ADH secretion, a marked increase in urine volume occurs because the late distal and collecting tubules are relatively impermeable to water. As a result of increased urine volume, there is dehydration and increased plasma osmolarity and high plasma sodium concentration. The resulting decrease in extracellular fluid volume stimulates renin secretion, resulting in an increase in plasma renin concentration.

7) **D)** Most of the daily variation in potassium excretion is caused by changes in potassium secretion in the late distal tubules and collecting tubules. Therefore, when the dietary intake of potassium increases, the total body balance of potassium is maintained primarily by an increase in potassium secretion in these tubular segments. Increased potassium intake has little effect on GFR or on reabsorption of potassium in the proximal tubule and loop of Henle. Although high potassium intake may cause a slight shift of potassium into the intracellular compartment, a balance between intake and output must be achieved by increasing the excretion of potassium during high potassium intake.

8) **B)** Inhibition of aldosterone causes hyperkalemia by two mechanisms: (1) shifting potassium out of the cells into the extracellular fluid, and (2) decreasing cortical collecting tubular secretion of potassium. Increasing potassium intake from 60 to 180 mmol/day would cause only a very small increase in plasma potassium concentration in a person with normal kidneys and normal aldosterone feedback mechanisms (see TMP13 **Figs. 30-7 and 30-8**). A reduction in sodium intake also has very little effect on plasma potassium concentration. Chronic treatment with a diuretic that inhibits loop of Henle Na^+-$2Cl^-$-K^+ co-transport would tend to cause potassium loss in the urine and hypokalemia. However, chronic treatment with a diuretic that inhibits sodium reabsorption in the collecting ducts, such as amiloride, would have little effect on plasma potassium concentration.

9) **C)** Because water is reabsorbed by the renal tubules whereas creatinine is not reabsorbed, the concentration of creatinine in the renal tubular fluid will increase as fluid flows from the proximal to the distal tubule. An increase in the concentration from 1.0 mg/100 ml in the proximal tubule to 5.0 mg/100 ml in the distal tubule means that only about one fifth (20%) of the water that was in the proximal tubules remains in the distal tubule.

10) **C)** The filtered load of glucose in this example is determined as follows: GFR (150 ml/min) × plasma glucose (300 mg/dl) = 450 mg/min. The transport maximum for glucose in this example is 300 mg/min. Therefore, the maximum rate of glucose reabsorption is 300 mg/min. The urinary glucose excretion is equal to the filtered load (450 mg/min) minus the tubular reabsorption of glucose (300 mg/min), or 150 mg/min.

11) **B)** Potassium secretion by the cortical collecting ducts is stimulated by (1) aldosterone, (2) increased plasma potassium concentration, (3) increased flow rate in the cortical collecting tubules, and (4) alkalosis. Therefore, a diuretic that inhibits aldosterone, decreased plasma potassium concentration, acute acidosis, and low sodium intake would all tend to decrease potassium secretion by the cortical collecting tubules. A diuretic that decreases loop of Henle sodium reabsorption, however, would tend to increase the flow rate in the cortical collecting tubule and therefore stimulate potassium secretion.

12) **A)** The filtration rate of glucose in this example is GFR (50 ml/min) × plasma glucose concentration (200 mg/100 ml, or 2 mg/ml) = 100 mg/min. Because the transport maximum for glucose in this example is 150 mg/min, all of the filtered glucose would be reabsorbed and the renal excretion rate for glucose would be zero.

13) **D)** Furosemide (Lasix) inhibits the Na^+-$2Cl^-$-K^+ co-transporter in the ascending limb of the loop of Henle. This action not only causes marked natriuresis and diuresis but also reduces the urine-concentrating ability. Furosemide does not cause edema; in fact, it is often used to treat severe edema and heart failure. Furosemide also increases the renal excretion of potassium and calcium and therefore tends to cause hypokalemia and hypocalcemia rather than increasing the plasma concentrations of potassium and calcium.

14) **A)** Excessive secretion of ADH increases water reabsorption by the renal collecting tubules, which reduces extracellular fluid sodium concentration (hyponatremia). Restriction of fluid intake, excessive aldosterone secretion, or administration of hypertonic 3% NaCl solution would all cause increased plasma sodium concentration (hypernatremia), whereas administration of 0.9% NaCl (an isotonic solution) would cause no major changes in plasma osmolarity.

15) **D)** In this example, the filtered load of glucose is equal to GFR (100 ml/min) × plasma glucose (150 mg/dl), or 150 mg/min. If there is no detectable glucose in the urine, the reabsorption rate is equal to the filtered load of glucose, or 150 mg/min.

16) **B)** Furosemide is a powerful inhibitor of the Na^+-$2Cl^-$-K^+ co-transporter in the loop of Henle. Thiazide diuretics primarily inhibit NaCl reabsorption into the distal tubule, whereas carbonic anhydrase inhibitors decrease bicarbonate reabsorption in the tubules. Amiloride inhibits sodium channel activity, whereas spironolactone inhibits the action of mineralocorticoids in the renal tubules. Osmotic diuretics inhibit water and solute reabsorption by increasing osmolarity of the tubular fluid.

17) **D)** The tubular fluid–plasma ratio of inulin concentration is 4 in the early distal tubule, as shown in the figure. Because inulin is not reabsorbed from the tubule, this means that water reabsorption must have concentrated the inulin to four times the level in the plasma that was filtered. Therefore, the amount of water remaining in the tubule is only one fourth of what was filtered, indicating that 75% of the water has been reabsorbed prior to the distal convoluted tubule.

18) **D)** The principal cells of the collecting tubules are an important site of action of amiloride, which blocks entry of sodium into sodium channels. Thiazide diuretics inhibit Na^+-Cl^- co-transport in the early distal tubule. The collecting tubule cells are not very permeable to urea. Furosemide inhibits the Na^+-Cl^--K^+ co-transporter in the thick ascending loop of Henle.

19) **C)** Because inulin is not reabsorbed or secreted by the renal tubules, increasing concentration of inulin in the renal tubules reflects water reabsorption. Thus, an increase of inulin concentration from a level of 2 mg/100 ml in the plasma to 40 mg/100 ml in the cortical collecting tubule implies that there has been a 20-fold increase in concentration of inulin. In other words, only 1/20th (5%) of the water that was filtered into the renal tubule remains in the collecting tubule.

وَمَن يَتَّقِ اللَّهَ يَجْعَل لَّهُ مَخْرَجًا وَيَرْزُقْهُ مِنْ حَيْثُ لَا يَحْتَسِبُ وَمَن يَتَوَكَّلْ عَلَى اللَّهِ فَهُوَ حَسْبُهُ إِنَّ اللَّهَ بَالِغُ أَمْرِهِ قَدْ جَعَلَ اللَّهُ لِكُلِّ شَيْءٍ قَدْرًا