PHYSIO

MODIFIED NO. 9-p1

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Welcome to the 9th physiology lecture

You are almost done with mid-term material just 2 lectures to go ☺
It is a nice lecture with many repeated info from previous subjects and systems
Say "بسم الله" and let's start

Color code

- Slides
- Doctor
- Additional info
- Important

Urinary System: Renal Physiology for Medical Students, L9

Chapter 28: Urine Concentration and Dilution;
Regulation of Extracellular Fluid Osmolarity
and Sodium Concentration

Reference: Guyton & Hall, Jordanian first edition

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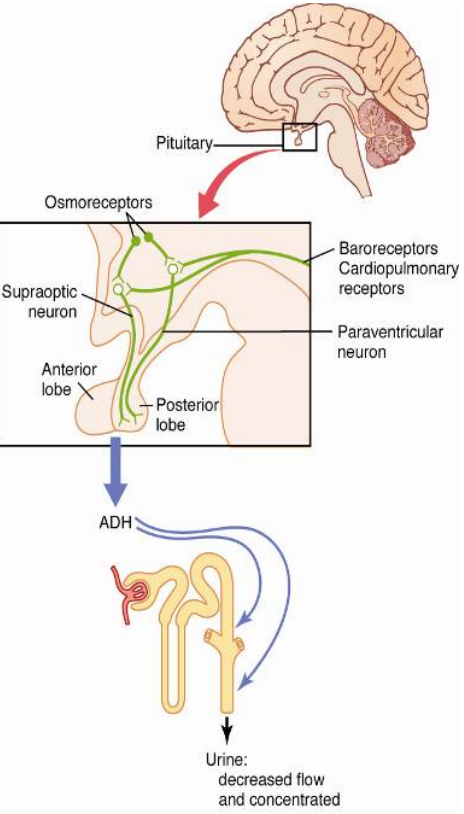
Objectives

- Identify the mechanisms by which the kidney can dilute or concentrate urine
- Understand the concept of Obligatory Urine Volume
- Understand the mechanism of countercurrent multiplier in the loop of Henle and countercurrent exchanger in vasa recta.
- Understand the concept of “Free” Water Clearance.
- Identify the role for urea to the concentrating ability of the kidney.
- Understand the role of ADH and thirst center in kidney function and fluid homeostasis.

Control of Extracellular Osmolarity (NaCl Concentration)



- ADH
- Thirst

⊢ ADH -Thirst Osmoreceptor System

Mechanism:

increased extracellular osmolarity (NaCl) stimulates ADH release, which increases H_2O reabsorption, and stimulates thirst (intake of water)

- **ADH hormone:**
- **is the main controller for extracellular osmolarity,** bcz it restrictively affect H2O reabsorption without affecting solutes excretion
- **Stimulated by high osmolarity in the Extracellular fluid**
- **Synthesized in the hypothalamus & stored in post. Pituitary gland**
- **Released (due to high osmolarity & the power of NH2 stimulation)**
- **It increase the reabsorption of H2O & concentrate urine (site of work: distal convoluted tubules, collecting tubules & duct)**
- => so its function is to control osmolarity

- **Thirst center:**
- we have osmo-receptors in the hypothalamus (stimulated by high osmolarity)
- **This increase water craving & leads to more water drinking (high H2O input)**
- **Thirst => increase H2O input // ADH => decease H2O output == correcting osmolarity**

Concentration and Dilution of the Urine

Urine has wide range of concentration variety based on body's need & homeostasis

- Maximal urine concentration (Highly concentrated)

= 1200 - 1400 mOsm / L

(specific gravity ~ 1.030)

- Minimal urine concentration (Highly diluted)

= 50 - 70 mOsm / L

(specific gravity ~ 1.003)

Specific gravity unit refers to the weight of solutes in the solution, has a direct relationship to osmolarity BUT they are NOT the same

Water diuresis in a human after ingestion of 1 liter of water.

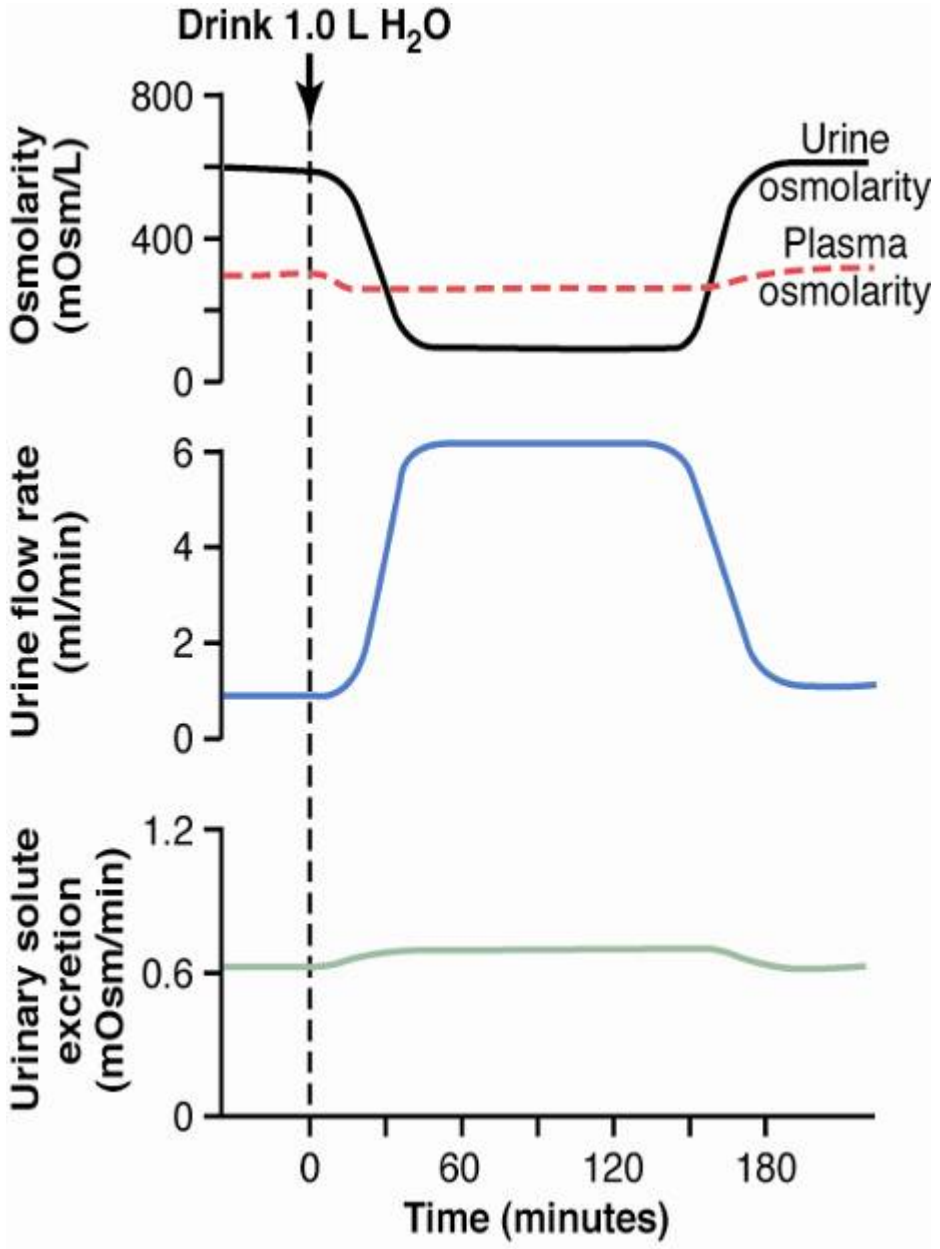


Figure 28-1

This experiment shows what are the consequences of drinking 1L of H2O
=>It aims to understand fluid homeostasis in extracellular fluid

- **The First curve (contains orange color)**
- It shows that when you drink 1L, **osmolarity of urine will drop** (for 2 hrs & then it back to normal)
- While plasma osmolarity (dashed line) there is a **slight drop in plasma osmolarity**
- **This shows that the decrease in urine osmolarity (increase H2O excretion) reduces the changes in the plasma concentration**

- **The second curve (contain blue color)**
- **Urine flow rate (representing the volume of excreted H2O) as in the graph, the normal rate is 1ml/min. After drinking 1L of water the rate increased x6 (6ml/min) & then within 2hrs it will return back to normal**

- **The third curve (contain green color)**
- **You might think that if H2O excretion increased then the excreted solutes should increase but it is not the case**
- **When we look at urinary solutes excretion you find that there's insignificant increase in their excretion**

- So what happened is selective excretion of H2O without affecting solutes excretion
- This **slight drop in plasma osmolarity will inhibit ADH** => this means impermeability of H2O in the distal convoluted ducts
- Once tubular fluid reaches these segments (it is highly diluted but no H2O excretion), **larger volume of urine will be excreted but it will be highly diluted** (this is why the urinary excretion rate increased "urine flow rate") since no H2O reabsorption => higher urine volume/min will be excreted
- This helps to get rid of excess H2O that we drink
- => **the key point here** is that **this selective change in H2O reabsorption wasn't done via changing in solutes reabsorption** (this is the mechanism of action of ADH, affecting H2O selectively)
- **ADH is presented = concentrated urine**
- **ADH is absent = diluted urine (high volume of urine will be excreted)**

Formation of a dilute urine

- Continue electrolyte reabsorption
- Decrease water reabsorption

Mechanism:

Decreased ADH release and reduced water permeability in distal and collecting tubules

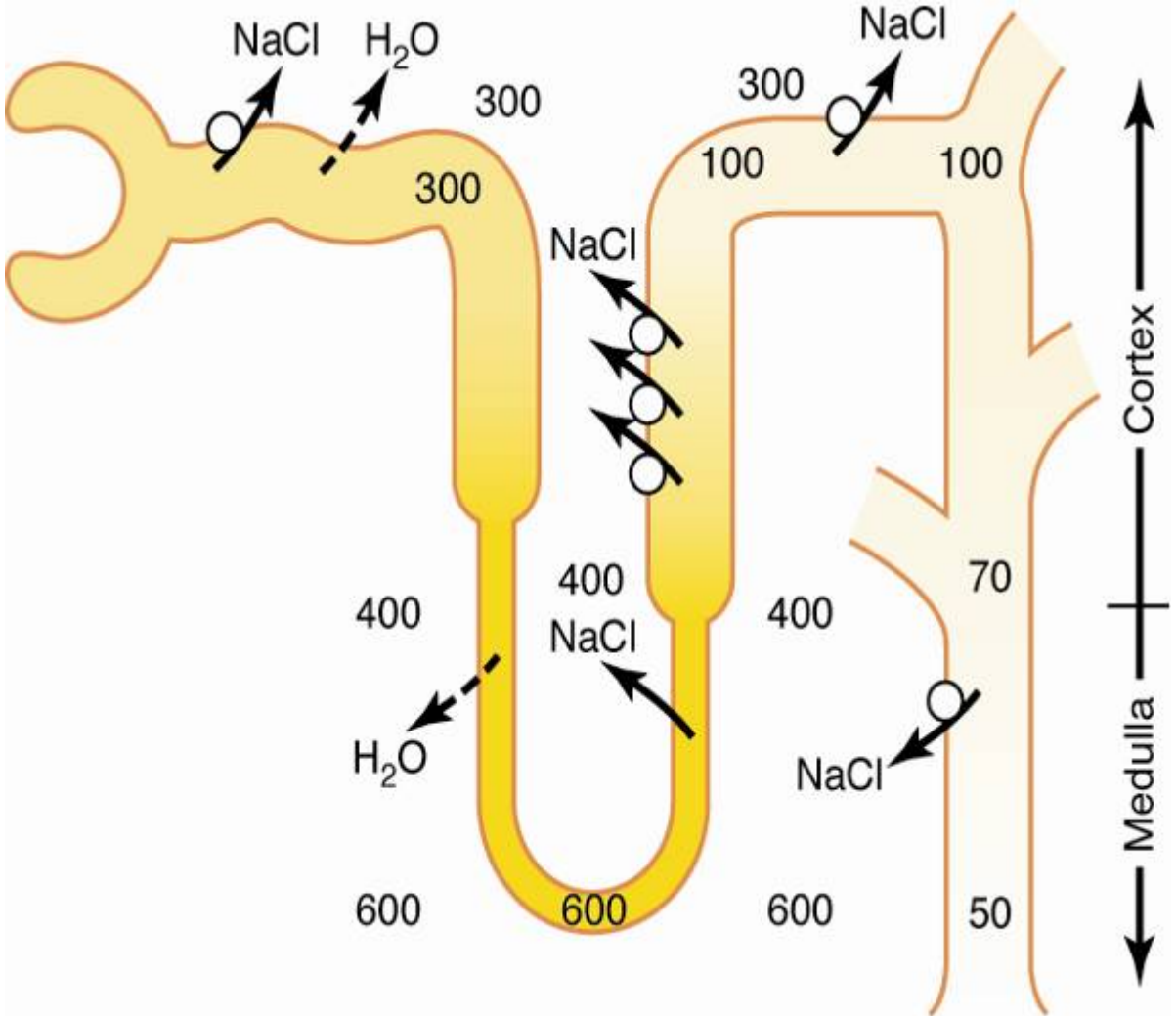


Figure 28-2

- **What is the mechanism of formation diluted urine ?**

=> recall the reabsorption mechanisms in nephrons

1- plasma will filter to **bowman's capsule**- here osmolarity will be as the plasma's =300mOsm/L)

2- In the **proximal convoluted tubules** almost 70% of H2O & solutes will be reabsorbed (so osmolarity will stay the same = 300mOsm/L)

3- At Loope of Henle (we will pass step by step on each part of Loope of Henle)

** as you know kidney has cortex & medulla (moving from cortex to medulla = higher osmolarity in interstitum)

a=> the fluid that is moving down in the **thin descending part of Loope of Henle**[1] (which is permeable to H2O) is considered hypotonic when compared to surrounding interstitum = H2O reabsorption until equilibrium is reached

b=> **at the tip of the Loope**[2] (the fluid will be as interstitial osmolarity= 600 mOsm/L as in previous slide) equilibrium is reached

c=> **the thin ascending part**[3], which is also impermeable to H2O but permeable to solutes, (no active transporters but there's passive reabsorption of NaCl - even at equilibrium), (the opposite will happen here- osmolarity will decrease as we ascend)

d=> now fluid (which is concentrated) now will ascend in **the thick ascending**[4] (=400mOsm/L)
active transporters will work against gradient & reabsorb solutes => this result in diluting the tubular fluid bcz this part is impermeable to H2O (solutes reabsorption without H2O) at the end of the thick ascending part of Henle

- 4- **distal convoluted tubules (early)**
  Continued NaCl reabsorption

- 5- **distal convoluted tubules (late) & collecting ducts and tubules**

  In the absence of ADH, these segments are impermeable to H2O, so this highly diluted urine will not have H2O reabsorption so the solutes reabsorption will continue (active transport works in these segments) this would result in further diluted tubular Fluid (=50 mOsm/L which is the least concentration of urine that can be achieved)

=> absence of ADH + dilution (active reabsorption processes of solutes) = highly diluted (large amounts) of urine

Relationship between urine osmolarity and specific gravity

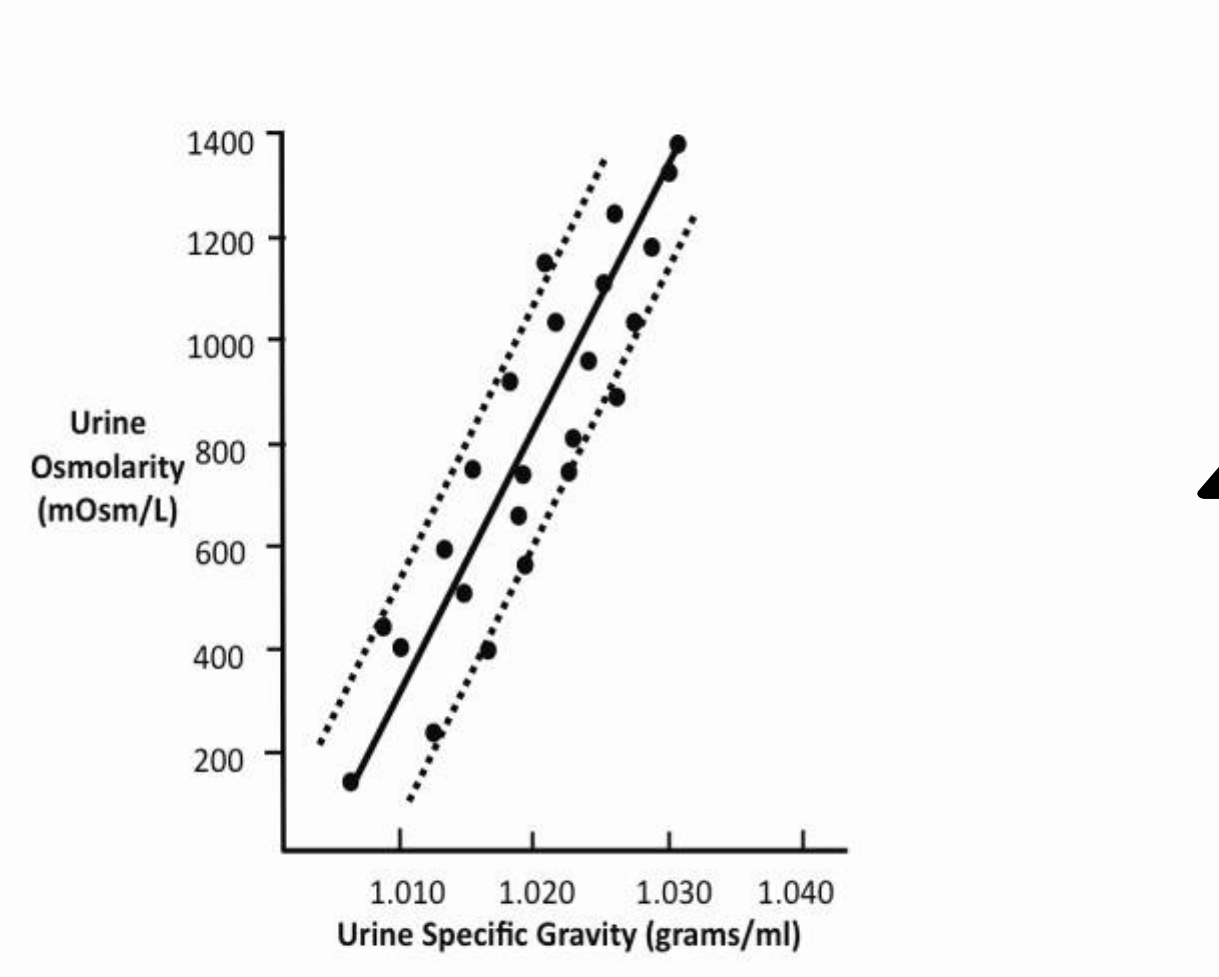


Figure 28-3

- rise by .001 for every 35 to 40 mosmol/kg increase in osmolality.
- 280 mosmol/kg (which is isosmotic to plasma) has a specific gravity of 1.008 or 1.009.

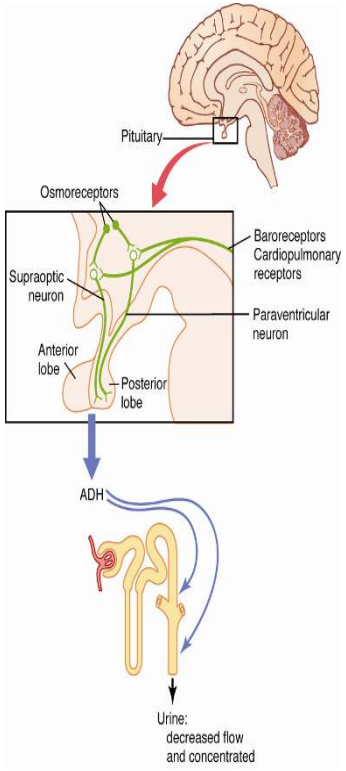
Influenced by

- glucose in urine
- protein in urine
- antibiotics
- radiocontrast media

specific gravity reach 1.030 to 1.050 (falsely suggesting a very concentrated urine), despite a urine osmolality that may be only 300 mosmol/kg.

- This curve describe the relationship between specific gravity & urine osmolarity
- They are related (higher osmolarity = high specific gravity and opposite is right)
- BUT they are not the same; specific gravity is related to molecular weight (also increase with increase number of particles)
- While osmolarity only indicate number of particles
- If urine has large particles (large molecular weight) specific gravity might be either normal or high while osmolarity it is not normal nor high (bcz specific gravity is sensitive to molecular weight while osmolarity is not)
  so there's might be a false indication of them (this happen when particles that shouldn't be in the urine are there like glucose, proteins, antibiotics, etc)
- These 2 measure are indicators if kidney is able to concentrate urine or not BUT we have to be careful if the numbers are incorrect (false number)
- => relatively 35-40 mOsm/kg = specific gravity will increase by 0.001 (generally)

Formation of a Concentrated Urine



- Continue electrolyte reabsorption
- Increase water reabsorption

Mechanism :

- Increased ADH release which increases water permeability in distal and collecting tubules
- High osmolarity of renal medulla
- Countercurrent flow of tubular fluid

- **How can kidney form concentrated urine?**

- First, we need this process when there's a shortage in H2O (preserve H2O) so we control osmolarity to not affect cell status (no shrinkage nor swelling)

- 1- continuous reabsorption of solutes (forming diluted tubular fluid is the first step to make urine concentrated later) first step

- 2- the presence of ADH; which increase H2O permeability by increase water channels (reabsorption) in the distal convoluted tubules, collecting tubules & ducts (so more diluted urine in previous step the more water reabsorption in this step)

  !!... its presence only is not enough (if there's no high osmolarity in interstitum)
  why? Bcz there is no gradient to pull H2O efficiently

- 3- high osmolarity in the renal medullary interstitum (high gradient between tubular fluid & interstitum to draw more H2O to be reabsorbed)
- These 3 factors are important for increasing water osmosis

Formation of a Concentrated Urine when antidiuretic hormone (ADH) are high.

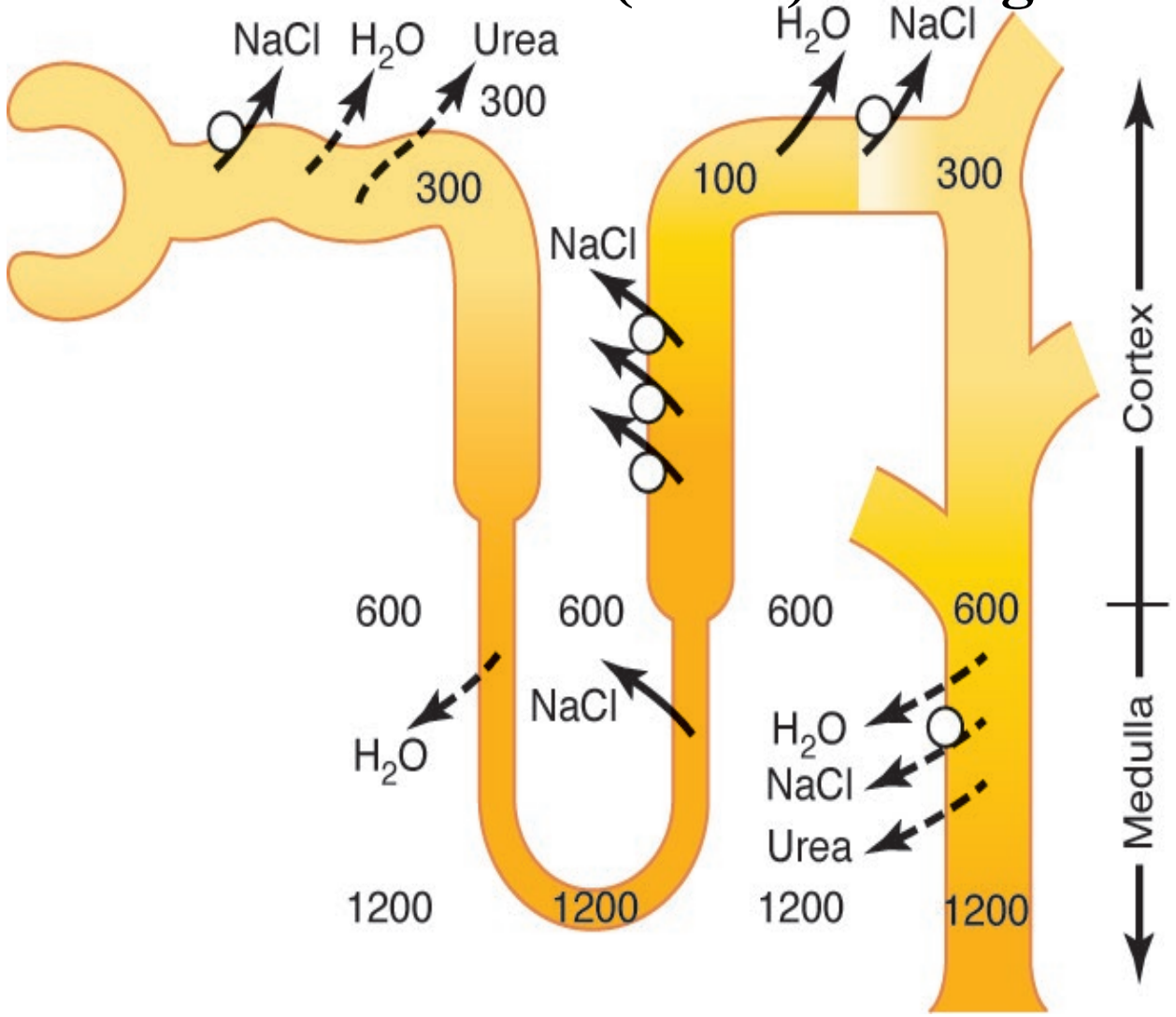


Figure 28-4

Now let's see how does ADH make concentrated urine.

1. At the level of bowman's capsule after filtration, the osmolarity of urine is the same as plasma.
2. In proximal convoluted tubules, reabsorption of electrolytes and water is done to the same extent, so osmolarity is unchanged, and ADH has no effect here.
3. When we descend in the loop of henle, the interstitium gets more concentrated, pulling more water from the urine therefore making urine more concentrated, ADH exaggerates the process of concentration at this level, reaching 1200 mOsm/L
4. As you remember, when we ascend in the loop of henle, there is reabsorption of electrolytes but 0 permeability to water, therefore urine gets dialuted. (Almost 100mOsm/L)
5. When we exit the ascending part to the distal tubules, water permeability get back to normal,so we get back to the process of concentration.
6. In the final part of distal tubule + collecting ducts, we have a special process which is Urea reabsorption, this adds to the reabsorbed solutes making the interstitium more concentrated -> urine more concentrated. ADH increases urea reabsorption at this level.(medullary level)

Obligatory Urine Volume

Definition :The minimum urine volume in which the excreted solute can be dissolved and excreted (Daily)

Example:

If the max. urine osmolarity is 1200 mOsm/L, and 600 mOsm of solute must be excreted each day to maintain electrolyte balance, the obligatory urine volume is:

$$\frac{600\ \text{mOsm/d}}{1200\ \text{mOsm/L}} = 0.5\ \text{L/day, 20 ml/hr}$$

If less Oligurea

If urine volume is less than that, solutes will not be properly dissolved. The minimum for a normal person is 0.5L/day, any less than that is abnormal (oligourea)

Obligatory Urine Volume

In renal disease the obligatory urine volume may be increased due to impaired urine concentrating ability

Example:

- If the max. urine osmolarity = 300 mOsm/L,
- If 600 mOsm of solute must be excreted each day to maintain electrolyte balance
- obligatory urine volume = ?

$$\frac{600\ \text{mOsm/d}}{300\ \text{mOsm/L}} = 2.0\ \text{L/day}$$

So people with impaired kidney function must drink more water to dissolve this amount of solutes.

What helps the build up of osmolarity in the interstitium of renal tubules?

Factors That Contribute to Buildup of Solute in Renal Medulla - Countercurrent Multiplier

- Active transport of Na^+, Cl^-, K^+ and other ions from thick ascending loop of Henle into medullary interstitium
- Active transport of ions from medullary collecting ducts into interstitium
- Passive diffusion of urea from medullary collecting ducts into interstitium, especially with high ADH
- Diffusion of only small amounts of water into medullary interstitium compared to the cortex, so interstitium is less diluted.

Also, the blood flow in the medulla is minimal compared to the cortex, this allows the solutes in the interstitium to get washed out less by blood flow, so solutes stay in the interstitium, therefore we get a high osmolarity interstitium in the medulla. Also, the vasa recta in loop of henle disallows reabsorption of water and solutes (will be explained later).

Summary of Tubules Characteristics

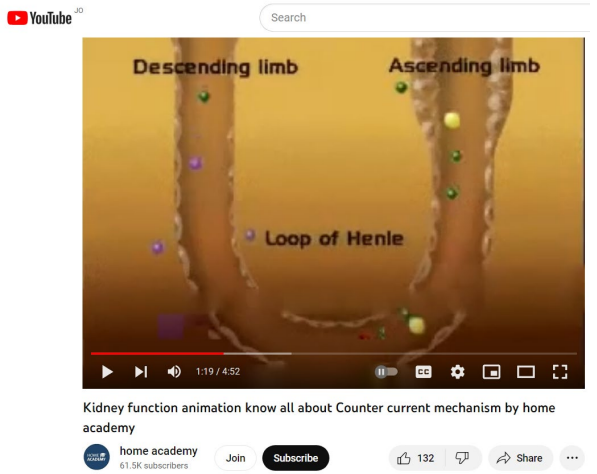
Tubule Segment	Active NaCl Transport	Permeability		
		H_2O	NaCl	Urea
Proximal	++	+++	+	+
Thin Desc.	0	+++	+	+
Thin Ascen.	0	0	+	+
Thick Ascen.	+++	0	0	0
Distal	+	+ADH	0	0
Cortical Coll.	+	+ADH	0	0
Inner Medullary Coll.	+	+ADH	0	+++

You must know these characteristics, they have been explained through the course earlier. Notice where ADH has effect.

Audio-visual Aid

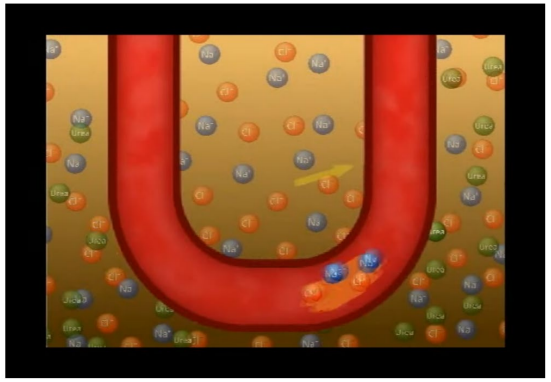
Please check this animation out demonstrating Countercurrent multiplier

[Kidney function animation know all about Counter current mechanism by home academy – YouTube]



and counter current exchanger:

[Countercurrent Mechanism v3 - YouTube]



Now we are going to discuss how the countercurrent flow / horizontal organization (moving between cortex and medulla) affect concentrations in medulla, cortex and tubules in case of water shortage (high ADH) :
Keep up with the figure in the next slide

1. All concentrations are identical at 300 mOsm/L (similar to plasma).
2. In ascending part, there is active reabsorption of solutes from tubules to interstitium, while water reabsorption in blocked, this increases osmolarity in interstitium (400 mOsm/L) compared to urine (200 mOsm/L).
3. Descending part is permeable to water, and it will get affected by the high osmolarity of interstitium now, so water will pass until they both have the same osmolarity, urine in descending (400 mOsm/L) and interstitium (400 mOsm/L).
4. When urine is flowing in the tubules, the (400 mOsm/L) urine in the descending part will move to the ascending, replacing the previous (200 mOsm/L) urine that was there before.
5. Now all concentrations are identical at (400 mOsm/L) so the whole story from step 2 to 4 will be repeated all over again, until we get (500 mOsm/L) then 600 then 700 until we reach 1200 mOsm/L.

This is called the countercurrent multiplier system (it increases osmolarity in each step) facilitated by the active reabsorption of solutes in the ascending part and the passive reabsorption of water in the descending part. This is possible because of the limited blood flow in the medulla that allows the build up of solutes without getting constantly washed out by the blood..
Juxtamedullary nephrons have deeper loops of henle in the medulla, so this system works better.

Countercurrent multiplier system in the loop of Henle

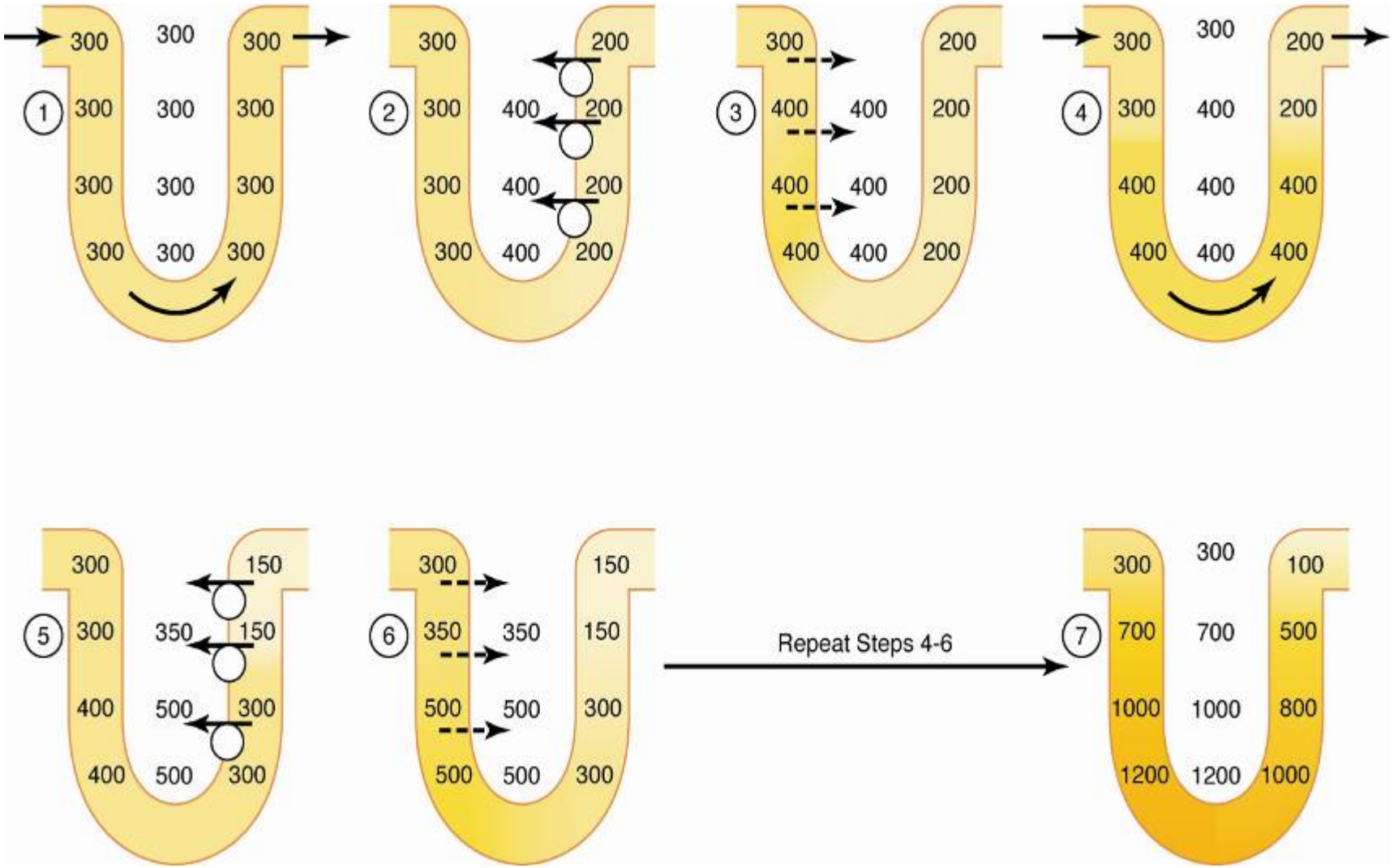


Figure 28-4

Net Effects of Countercurrent Multiplier

1. More solute than water is added to the renal medulla.
   i.e solutes are “trapped” in the renal medulla
2. Fluid in the ascending loop is diluted , in the intertitium more concentrated
3. Most of the water reabsorption occurs in the cortex
   (i.e. in the proximal tubule and in the distal convoluted tubule) rather than in the medulla
4. Horizontal gradient of solute concentration established by the active pumping of NaCl is “multiplied” by countercurrent flow of fluid.

Recirculation of urea absorbed from medullary collecting duct into interstitial fluid.

- Urea also plays an important role in concentrating urine.
- As we know, urea adds to the concentration of the interstitium, so people with low protein intake have low urea, resulting in a low concentrating ability to the urine , because urea is a product of metabolizing protein.

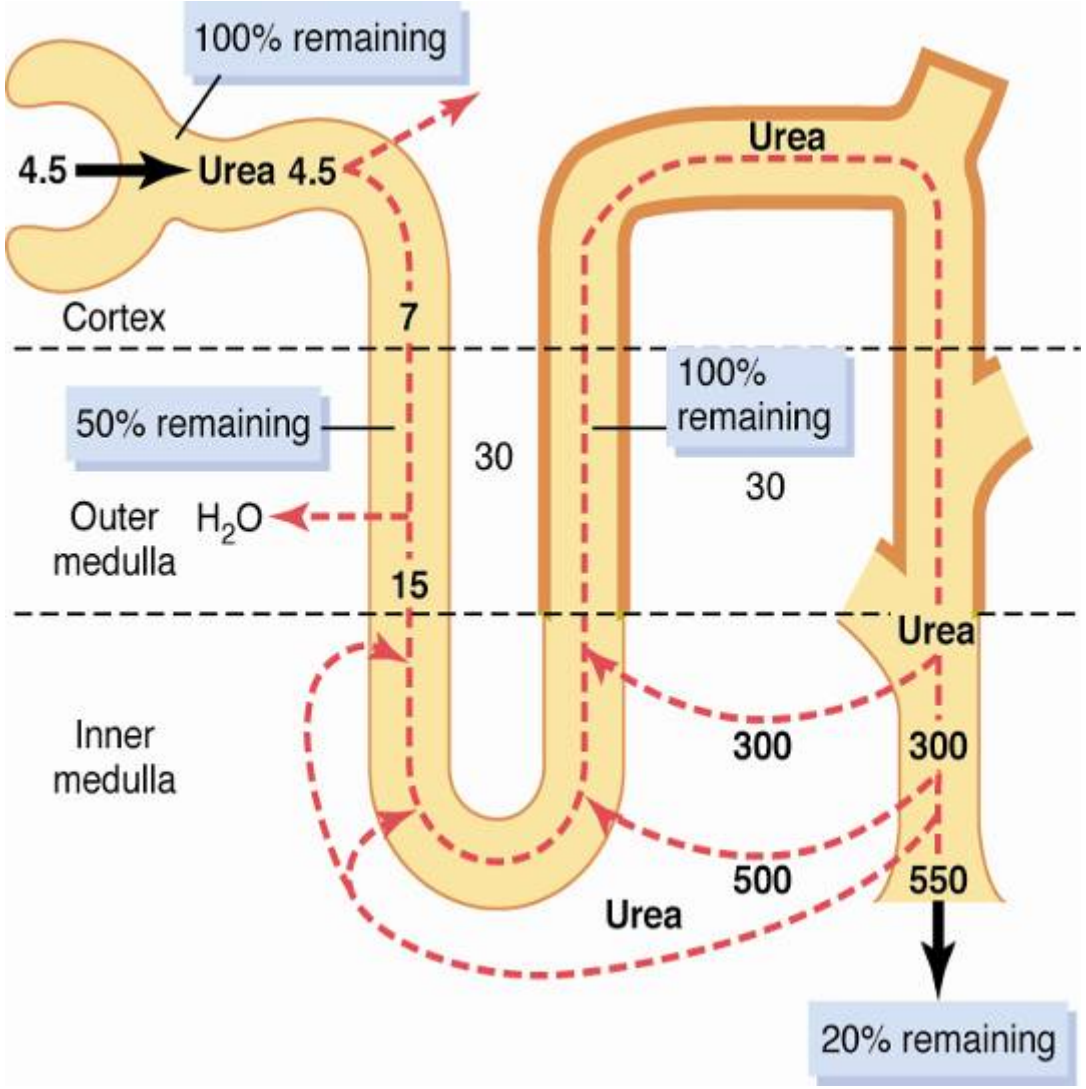


Figure 28-5

- After filtration of plasma, we will have 100% urea concentration in the urine.
- In the descending part of loop of henle, 50% will be reabsorbed and 50% will remain in urine.
- When we reach the descending part of loop of henle (in the medulla), it will be surrounded with interstitium that has high urea concentration (we will now know why), so urea will force it way back into the urine, bringing it back to 100%.
- In the ascending and distal tubule, there is no urea permeability, so the urea is conserved inside the urine at this level (notice that these parts are in the cortex, so no urea will reach the cortical intertitium)
- In the collecting duct (a medullary part) there is a high urea permeability, so 80% of the urea will leak back into the interstitium, adding tho the osmolarity of the medullary interstitium, the remaining 20% will be excreted in the urine.
- This 80% will add to the concentration of the medullary interstitium, and part of it will go back to the descending part (this explains the 3rd step), this is why it is called recirculation.

This process is needed to lower the obligatory urine volume (the minimum needed to dissolve urine solutes), so we use urea to get the right osmolarity, then we reabsorb it back to use it again.
Remember that the function of ADH is to reserve water in the body, so it makes sense to reabsorb more urea. While when we want to lose excess water (low ADH) less urea is reabsorbed.

Urea Recirculation

- Urea is passively reabsorbed in proximal tubule (~ 50% of filtered load is reabsorbed)
- In the presence of ADH, water is reabsorbed in distal and collecting tubules, concentrating urea in these parts of the nephron
- The inner medullary collecting tubule is highly permeable to urea, which diffuses into the medullary interstitium
- ADH increases urea permeability of medullary collecting tubule by activating urea transporters (UT-1)

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2	14	Impermeable	Permeable
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!