PHYSIO

MODIFIED NO. 9-P2

الكُتّاب: ميس سالمان و سُرى علي

المدققين: نغم نعيمات

الدكتور/ة: د.إباء زيادنة

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

Dr. Ebaa M. Alzayadneh, PhD.

Email: e.zayadneh@ju.edu.jo

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Color code

- Slides
- Doctor
- Additional info
- Important

Factors contributing to urine concentrating capability of the kidney

⬆️ High ADH.**(The most important factor)** It **increases reabsorption of water** in the later segments of nephron(late distal tubules and collecting ducts).

⬆️ High osmolarity of medullary interstitial Sodium: which is largely achieved through:

1. **Chloride build up by counter current multiplier (mainly actively)** discussed in previous lecture
2. **Urea build up and recirculation (passively)** which contributes **approximately 40-50%** of the total osmolarity in the medullary interstitium.

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

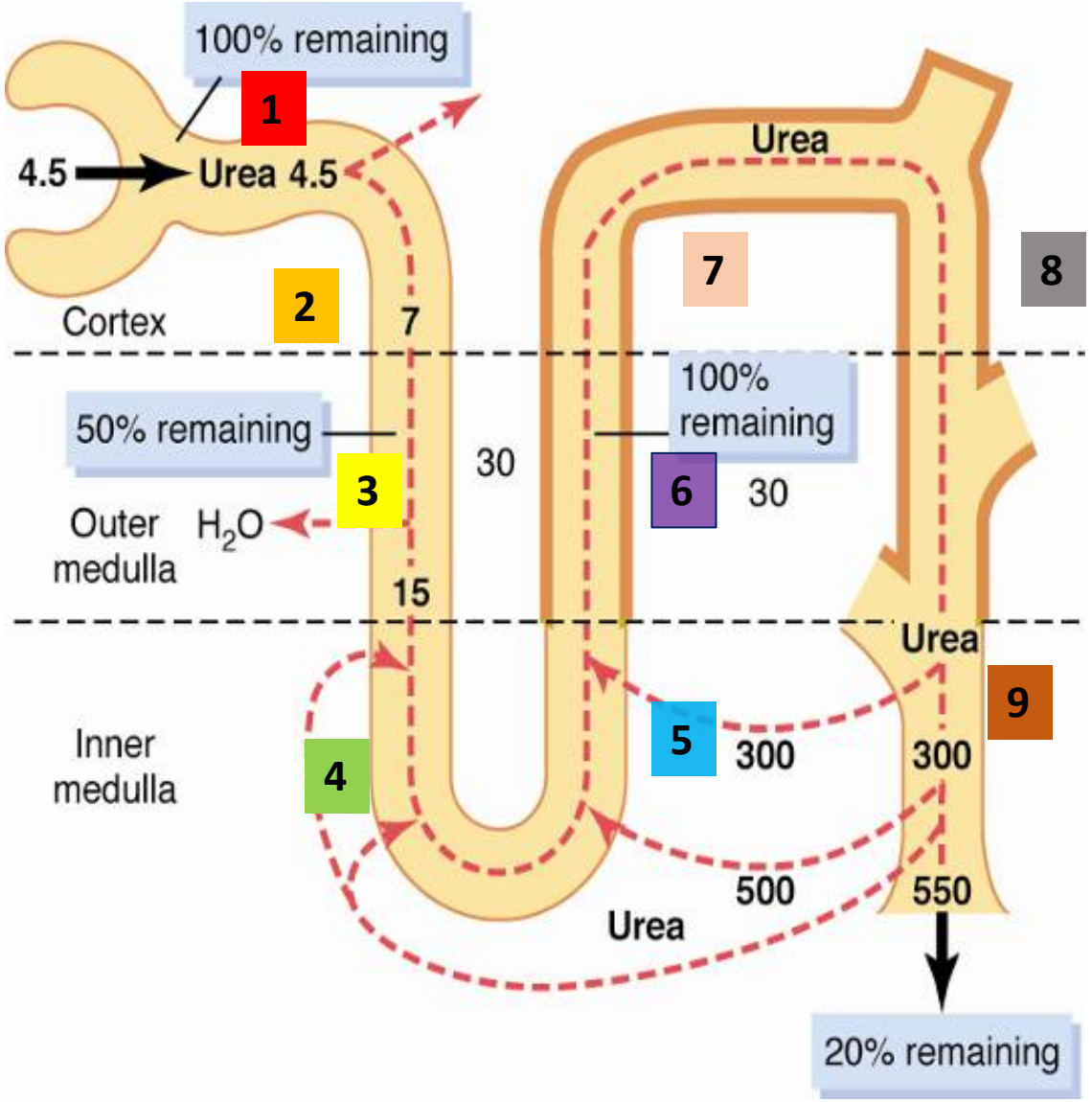


Figure 28-5

- **Importance of urea in making hyperosmotic medullary interstitium**

But first we will discuss **(Recirculation of urea) that is absorbed from the medullary collecting ducts into the interstitial fluid:**

- Urea is filtered at the glomerulus, and at the beginning of the **proximal convoluted tubule 1**, its concentration is about 4.5. Due to reabsorption in the proximal tubule, about **50% of the filtered urea is reabsorbed**, resulting in about 50% of the original urea remaining as it exits the proximal convoluted tubule.

- We see the concentration of urea increasing by the end of proximal convoluted tubule2 , which is due to the **more reabsorption of water that occurs in the proximal convoluted tubules than the reabsorption of urea**.

- REMEMBER In the proximal convoluted tubules, water is reabsorbed more avidly than urea, and that will result in increased concentration of urea at the end of the proximal convoluted tubule.

- يعني even though half of the urea is reabsorbed, the concentration of urea in the tubular fluid increases by the end of the PCT. This is due to **solvent drag** and the fact that water reabsorption concentrates the remaining solutes like urea.

- In the loop of henle, particularly in the **thin descending limb** 3 **(highly permeable for water)**, the concentration of urea increases as water is reabsorbed

- Urea is **secreted** into the tubular fluid 4, 5 from the interstitium, especially in the **inner medullary region** of the loop of Henle because:

•Urea **moves from the interstitium (high concentration)** into the **tubular fluid (low concentration)** this is **urea secretion** into the loop of Henle. **(passive urea diffusion)**, particularly through **UTA2 transporters** located in the **thin descending and thin ascending limbs** 4, 5

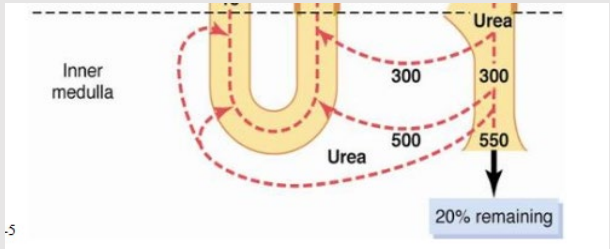
•And that will result in having **100%** remaining of urea. because of this recirculation of urea from the interstitium into the tubular fluid.

- In the **thick ascending limb of the loop of henle** 6 **(impermeable to urea)**, so the urea concentration remains unchanged as the fluid passes through this segment. This lack of permeability continues through the **early distal convoluted tubule** and the **cortical collecting tubules**. (Urea concentration remains **CONSTANT** here)

•However, when the tubular fluid reaches the **inner medullary collecting duct 9**, the **permeability to urea increases significantly**, especially in the presence of **high levels of (ADH)**.

inner medullary collecting duct ➡️ ADH-dependent site

•ADH upregulates **urea transporters (UTA1 and UTA3)**, which facilitate **passive reabsorption of urea** into the medullary interstitium . Because the **inner medullary interstitium has a high urea concentration (osmolarity)**, urea is reabsorbed down its concentration gradient until **equilibrium is reached**.



•**only about 20% of the filtered urea is ultimately excreted in the urine**, while **about 80% is reabsorbed**.

• Some of this reabsorbed urea **accumulates in the medullary interstitium**, contributing to the **medullary osmotic gradient**, and **some re-enters the nephron** at the **thin limbs of the loop of Henle**, especially the **thin ascending limb**, continuing the **urea recycling process**.

Urea Recirculation

SUMMARY!

- 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)

- **Urea recycling is crucial for fluid conservation** in the body. If the kidneys excrete all the urea remaining in the loop of henle and collecting tubules ➡️ this would require a significantly larger amounts of water for its elimination ➡️ **increased obligatory urine output**

- If there is a **fluid scarcity**, this increased water loss would decrease the ability to preserve water.

- The osmolarity of urine, half of it is due to the urea and the other half due to other solutes .

The Vasa Recta Preserve Hyperosmolarity of Renal Medulla

- The vasa recta serve as **countercurrent exchangers**

- Vasa recta blood flow is low (only 1-2 % of total renal blood flow)

🔼 Vasa recta blood flow is low , which means that it doesn't contribute to the washout of solutes!!!

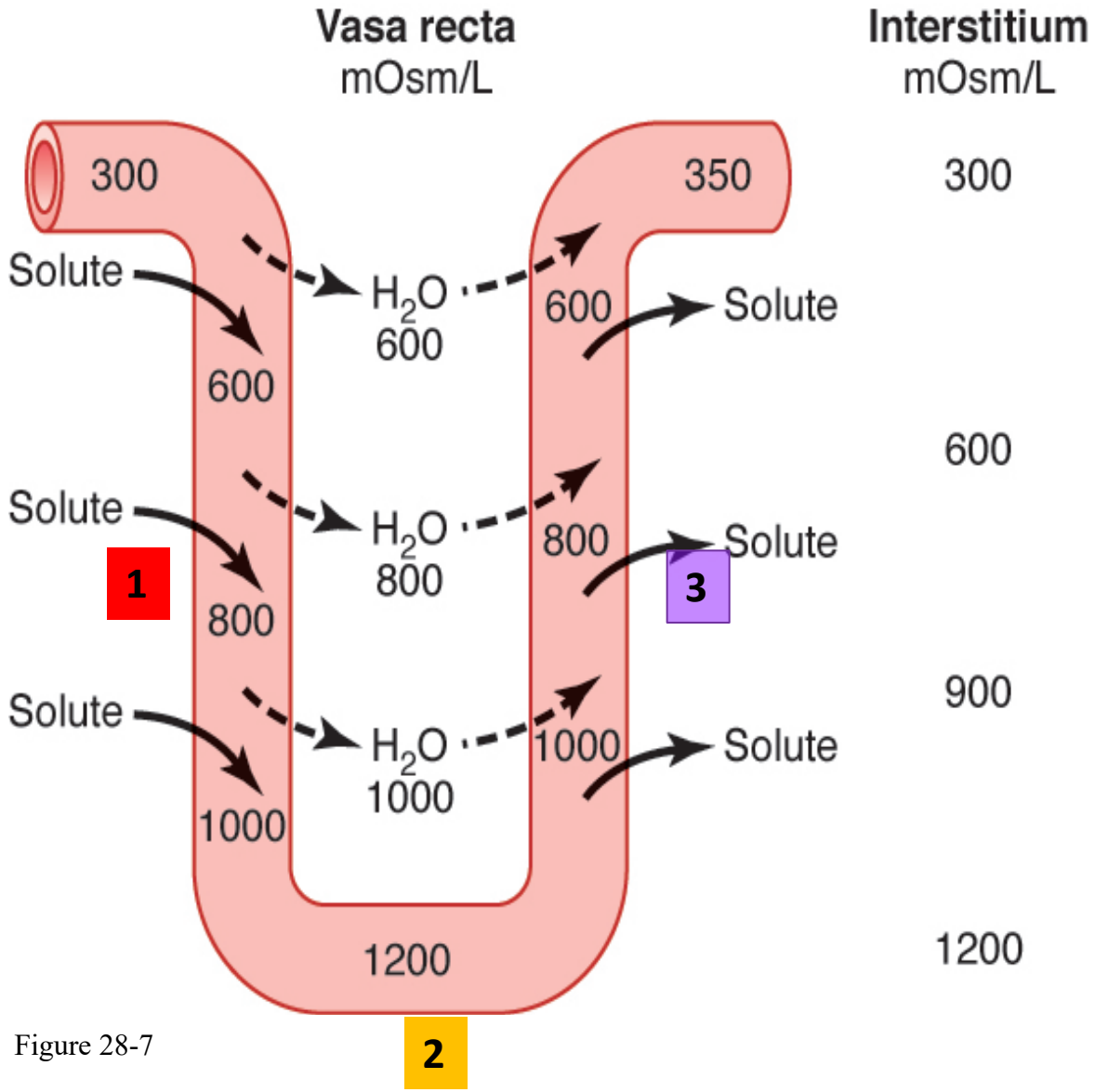


Figure 28-7

VASA RECTA AND GRADIANT

Function of vasa recta?

- **Preservation** of the **hyperosmolarity** in the medullary intersitium
- **Acts as countercurrent exchanger, not multiplier.**

Does vasa recta build the gradient?

❎❎ **NO, it does not build the medullary osmotic gradient.**
The loop of henle, especially in juxtamedullary nephrons generates the gradient via **countercurrent multiplication**

Structure

Sepcialized peritubular capillaries associated with juxtamedullary nephrons.
Runs **parallel to the loop of henle**:

Descending limb of vasa recta ➡️ next to descending limb of loop.
Ascending limb of vasa recta ➡️ next to ascending limb of loop.

Mechanism of Countercurrent Exchange

A) Descending limp pf Vasa Recta 1

- Blood enters with **low osmolarity**
- Passes through the areas of **hyperosmotic medullary interstitium**
- Solutes move **into** the blood
- Water moves **out** into the interstitium
- Blood becomes **more concentrated** as it descends

C) Ascending limb of Vasa Recta 3

- Blood is now **hyperosmotic**
- Blood flows upward through areas of **lower interstitial osmolarity.**
- Solutes **move back** into the interstitium.
- Water **re-enters** the blood.

B) At the tip 2

Blood is **most concentrated** here.

NOTES

- The solutes that enter the blood or exit from the interstitium do so through **paracellular diffusion**, and the **net reabsorption is very small**. As a result, it does **not significantly reduce or take up the gradient** that has been built in the interstitium.

FOR EXAMPLE: If the osmolarity of the blood entering the vasa recta is 300 mOsm, it may rise to about **350 mOsm** as it exits. This shows that while **some solute reabsorption does occur**, it is **not enough to wash out or dilute the high concentration of solutes** that has been established in the medullary interstitium.

🤔 ➡️ This is why we say that the **vasa recta preserves the hyperosmolarity** of the renal medulla. At the same time, **normal reabsorption** occurs between the nephron and the vasa recta in a way that **does not disrupt the medullary gradient**.

(countercurrent exchange system) or more specifically, **(the vasa recta countercurrent exchanger)**. **It does not multiply the gradient** (as the loop of Henle does), and **it does not dilute the interstitium**. It simply facilitates an **EXCHANGE**:
Solutes and water that exit the vasa recta at one point re-enter at another point.
Water that enters the interstitium returns to the blood, and vice versa.

Changes in osmolarity of the tubular fluid

This graph summarizes the effect of ADH on increasing the osmolarity of tubular fluid along different segments of the nephron

- The **highest impact of ADH** occurs in the late distal tubule and the cortical and medullary collecting ducts, where water permeability is increased in the presence of ADH, significantly concentrating the tubular fluid.

- **Note** that the medulla has a high ability for concentrating urine due to its **high osmolarity**, which is established by the **countercurrent multiplier** system and further enhanced by **ADH and urea recycling.**

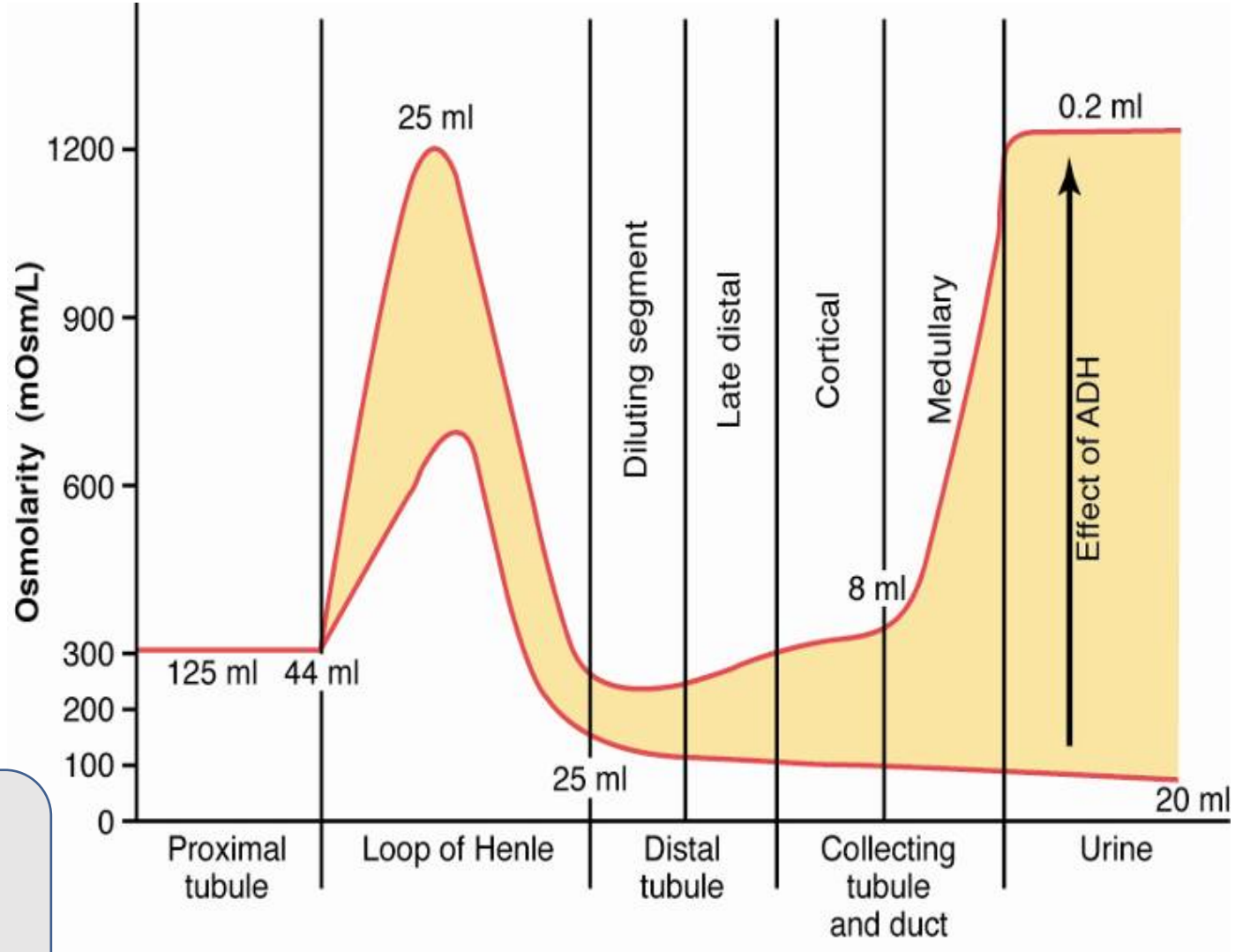


Figure 28-8

ADH mainly acts on the late distal tubule, cortical collecting duct, and medullary collecting duct, resulting in a significant i**ncrease in urine concentration up to 1200 mOsm/L** and a **decrease in urine volume** from about 125 mL/min in the proximal tubule to 0.2 mL/min at the end of the nephron.

The effects observed in the loop of henle (Descending limb) and early distal tubule can be explained by the reabsorption of water in segments that are permeable to water. This reabsorption **increases the intratubular fluid osmolarity**

Summary of water reabsorption and osmolarity in different parts of the tubule

- Proximal Tubule: 65 % reabsorption, isosmotic tubular fluid
- Desc. loop: 15 % reasorption, osmolarity increases
- Asc. loop: 0 % reabsorption, osmolarity decreases because of active reabsorption of solutes
- Early distal: 0 % reabsorption, osmolarity decreases because of continuous solutes reabsorption
- Late distal and coll. tubules: ADH dependent water reabsorption and tubular osmolarity increase
- Medullary coll. ducts: ADH dependent water reabsorption and tubular osmolarity increase

"Free" Water Clearance (C_{H_2O}) (rate of solute-free water excretion)

We can measure free water clearance by measuring the clearance of osmolarities and subtracting it from the urine flow

Free water clearance

$$CH_2O = V - \frac{Uosm \times V}{Posm}$$

where:

Uosm = urine osmolarity
V = urine flow rate
P = plasma osmolarity

If: Uosm < Posm, CH_2O = +

- If the urine flow rate is higher than the clearance of osmoles, this means that dilute urine is being excreted.

If: Uosm > Posm, CH2O = -

- If the clearance of osmoles is higher than the urine flow rate, then the urine is concentrated.

Question

Given the following data, calculate “ free water” clearance :

urine flow rate = 6.0 ml/min
urine osmolarity = 150 mOsm /L
plasma osmolarity = 300 mOsm / L

Is free water clearance in this example positive or negative ?

It can be asked whether the urine is concentrated or diluted.

Answer

$$CH_2O = V - \frac{Uosm \times V}{Posm}$$

$$= 6.0 - \frac{(150 \times 6)}{300}$$

$$= 6.0 - 3.0$$

$$= +3.0 \text{ ml / min (positive)}$$

Diluted urine: water is excreted in excess of solutes

Disorders of Urine Concentrating Ability

- Failure to produce ADH :
  "Central" diabetes insipidus

- Failure of kidney to respond to ADH:
  "nephrogenic" diabetes insipidus

- impaired loop NaCl reabs. (loop diuretics)

- drug induced renal damage: lithium, analgesics

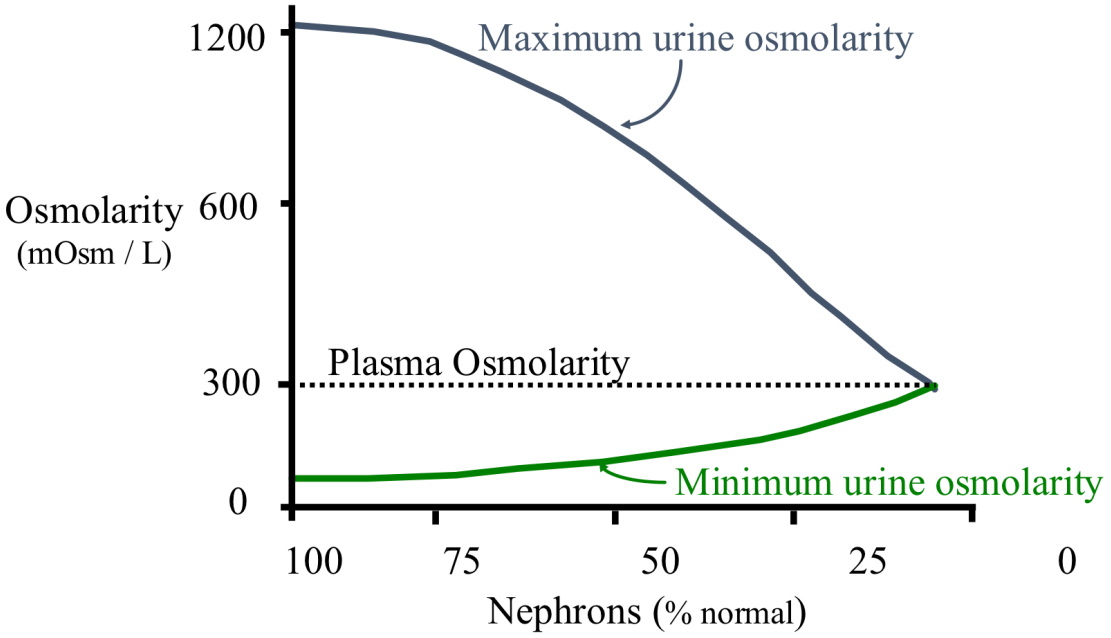
- malnutrition (decreased urea concentration)

- kidney diseases that affect response to ADH: pyelonephritis, hydronephrosis, chronic renal failure

- Low or no protein intake decreases urea concentration in the medullary interstitium, which reduces the kidney's ability to concentrate urine.

Development of Isosthenuria With Nephron Loss in Chronic Renal Failure (inability to concentrate or dilute the urine)

this graph, you can see **the effect of nephron loss on the kidney's ability to concentrate or dilute urine.** Under normal conditions, urine has a minimal osmolarity of 50 to 70 mO/L and a maximal osmolarity of up to 1,200 mOsm/L. As nephron loss increases, the maximal urine osmolarity declines. At the same time, the minimal urine osmolarity increases. Eventually, when less than 20% of nephrons remain, urine osmolarity becomes equal to plasma osmolarity, a condition known as isosthenuria. This condition develops progressively as nephron loss advances, particularly in chronic renal failure.



This slide was not explained by the doctor

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)

Total Renal Excretion and Excretion Per Nephron in Renal Failure

Effect of renal failure on function of nephron

	Normal	75 % loss of nephrons
Number of nephrons	2,000,000	500,000
Total GFR (ml/min	125	40
GFR per nephron (nl/min)	62.5	80
Total Urine flow rate (ml/min)	1.5	1.5
Volume excreted per nephron (nl/min)	0.75	3.0

Total flow rate/no. of nephrons

25% of nephrons are normal

⬇ GFR

⬆ GFR per nephron

Blood will be distributed to less no. of nephrons

↔ urine flow rate

⬆ volume excreated per nephron

Due to loss the ability to concentrate urine as nephron loss increase

Doctor read it all

Osmoreceptor–antidiuretic hormone (ADH) feedback mechanism for regulating extracellular fluid osmolarity.

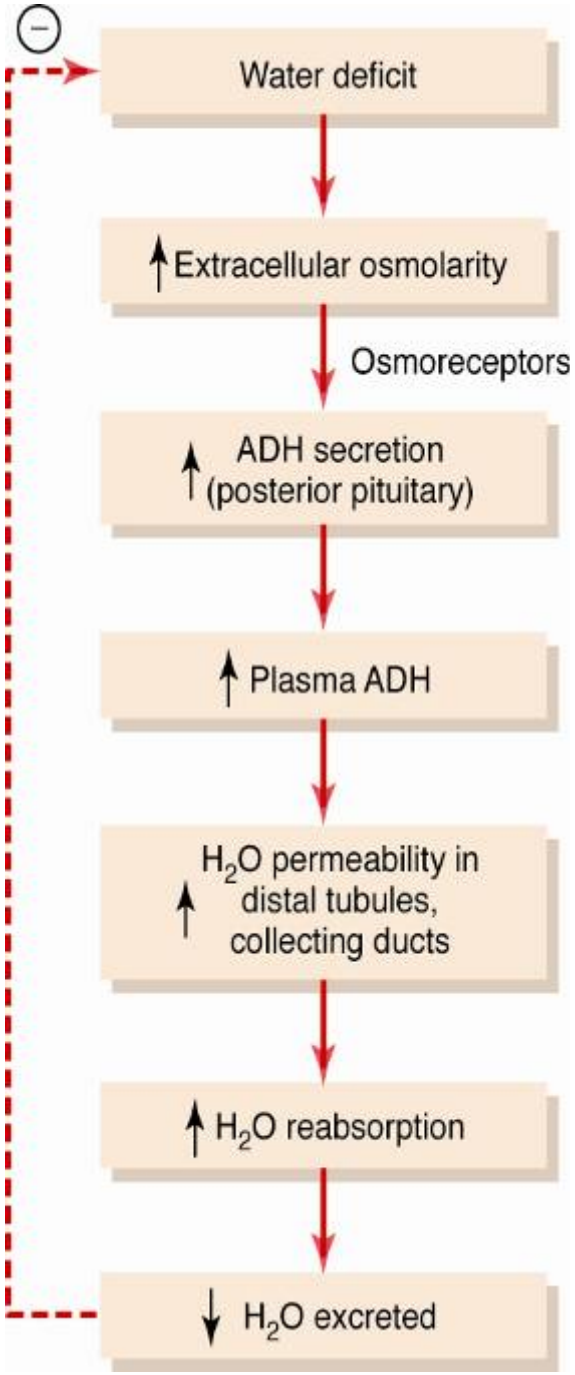


Figure 28-9

ADH synthesis in the magnocellular neurons of hypothalamus, release by the posterior pituitary, and action on the kidneys

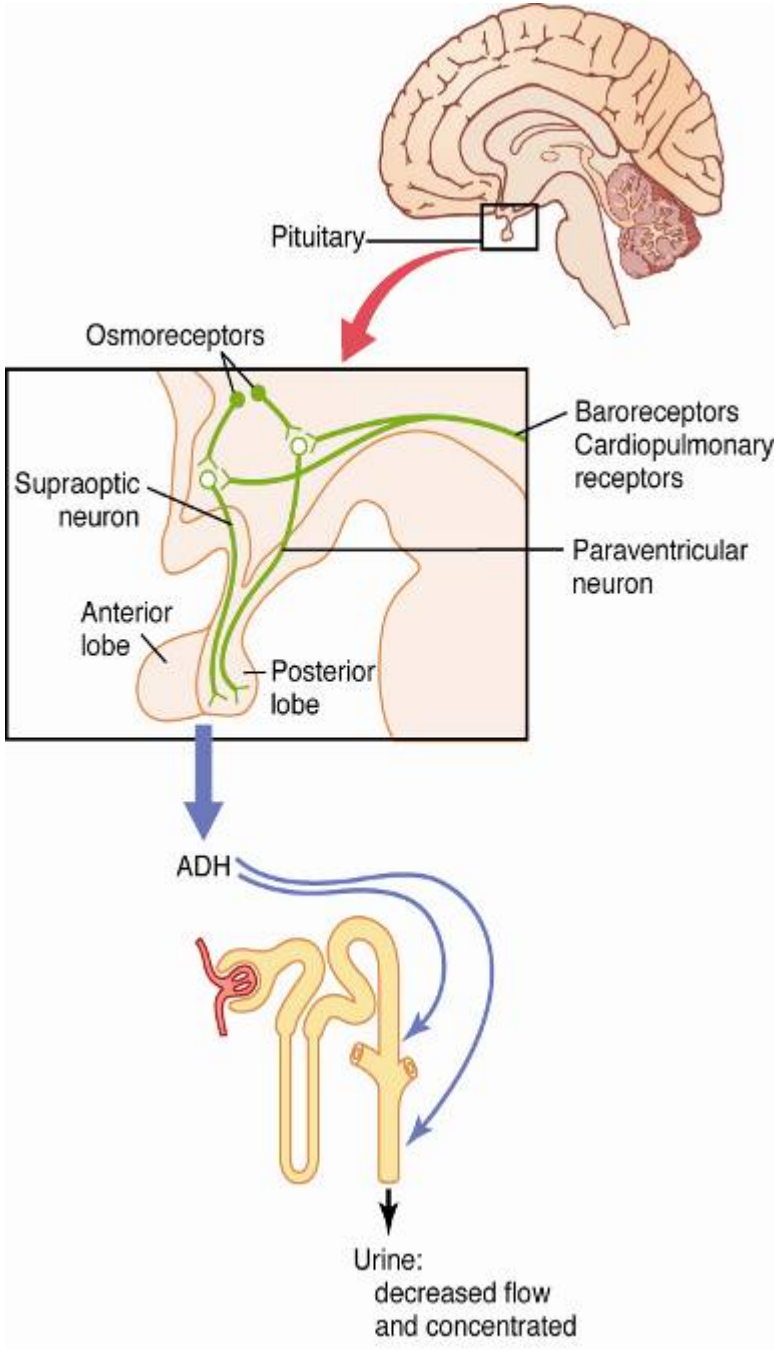


Figure 28-10

Stimuli for ADH Secretion

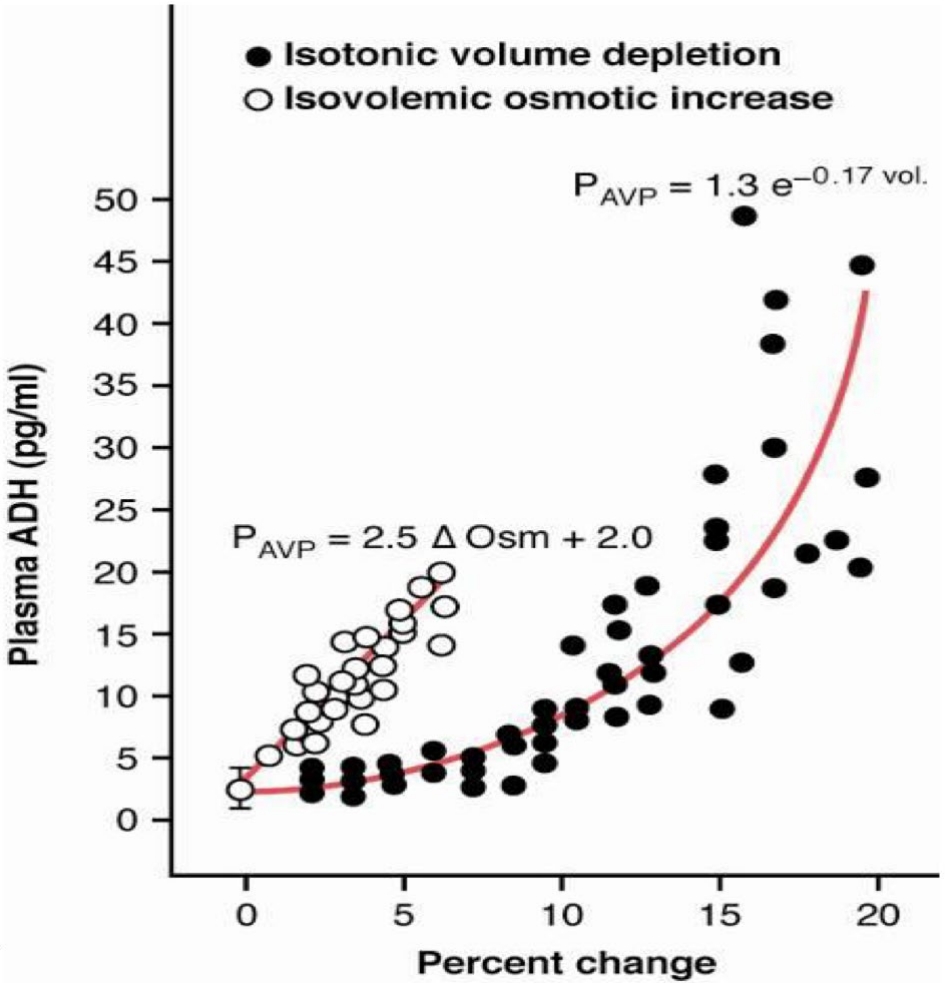
- Increased osmolarity
- Decreased blood volume (cardiopulmonary reflexes)
- Decreased blood pressure (arterial baroreceptors)
- Other stimuli :
  - input from cerebral cortex (e.g. fear)
  - angiotensin II
  - nausea
  - nicotine
  - morphine

When ADH is stimulated, it concentrates the urine and increases water reabsorption.

ADH is triggered more by small changes in osmolarity than by small changes in blood volume. **ADH is highly sensitive to even a 5% change in osmolarity.** In contrast, changes in blood volume do not stimulate ADH secretion **unless the change exceeds 10%.** If there is a 15% change in volume, plasma ADH levels will rise significantly.

- large changes in volume cause a stronger stimulation of ADH release.

The effect of increased plasma osmolarity Vs. decreased blood volume.



ure

Factors That Decrease ADH Secretion

- Decreased osmolarity
- Increased blood volume (cardiopulmonary reflexes)
- Increased blood pressure (arterial baroreceptors)
- Other factors :
  - alcohol
  - clonidine (antihypertensive drug)
  - haloperidol (antipsychotic, Tourette's)

A decrease in ADH causes polyuria and an increase in urine volume

Stimuli for Thirst

Similar to the stimuli for ADH + additional stimuli involved.

- Increased osmolarity
- Decreased blood volume
  (cardiopulmonary reflexes)
- Decreased blood pressure
  (arterial baroreceptors)
- Increased angiotensin II
- Other stimuli:
  - dryness of mouth

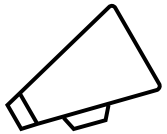
Factors That Decrease Thirst

- Decreased osmolarity
- Increased blood volume
  (cardiopulmonary reflexes)
- Increased blood pressure
  (arterial baroreceptors)
- Decreased angiotensin II
- Other stimuli:
  -Gastric distention Causes temporary inhibition of the thirst sensation.

Maximal Urine flow rate ; water excretion rate

- Max water excretion rate in adults=20-23 L/day, does not exceed 800-1,000 ml/hr
- Then water intake should not exceed 800-1,000 ml / hr to avoid hyponatremia and water intoxication

Water intoxication occurs when water intake exceeds the kidney's ability to excrete it. If too much water is consumed, the excess cannot be eliminated, leading to a decrease in plasma osmolarity. This drop in osmolarity cannot be corrected by the kidneys and results in an electrolyte imbalance, particularly affecting sodium levels.



Link To Recording of The Lecture

https://fisjo-my.sharepoint.com/:v:/g/personal/e_zayadneh_ju_edu_jo/EYUZ_41lxkRJo19TLXEXJbwBuQUW9zUEWB0IeBcYT7m8OA?e=Ee7gGh

١٣٩٣ ـ وَعَنْ أَنَسٍ رضي الله عنه، قَالَ: قَالَ رَسُولُ اللَّهِ ﷺ: «مَنْ خَرَجَ فِي

46

بَابُ فَضْلِ العِلْمِ تَعَلُّماً وتَعْلِيماً لِلَّهِ ٤٦٥

طَلَبِ العِلْمِ؛ فَهُوَ فِي سَبِيلِ اللَّهِ حَتَّى يَرْجِعَ». * رَوَاهُ التِّرْمِذِيُّ [٢٦٤٩]، وَقَالَ: «حَدِيثٌ حَسَنٌ»(١).

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2	15	interstitial osmolarity	intratubular fluid osmolarity
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!