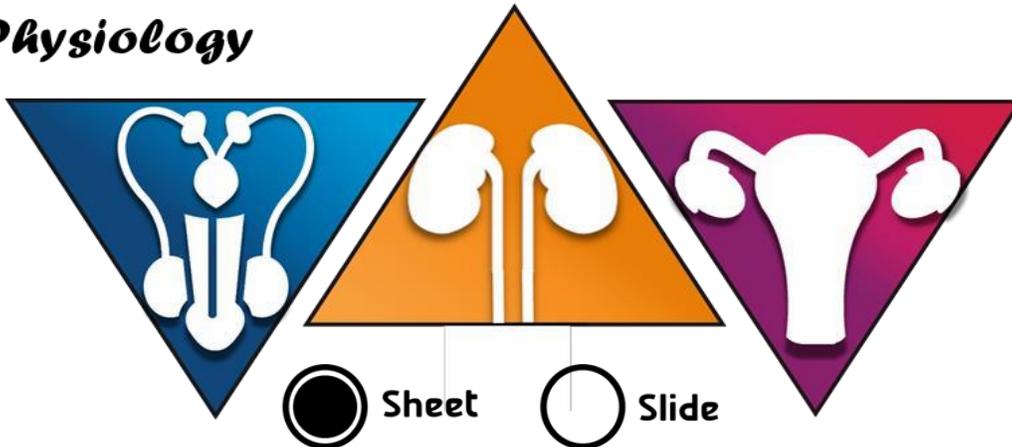




Urogenital system

Physiology



Sheet



Slide

Number:

Physiology – Dr.najeeb Online
Lecture

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Why kidneys sometimes make diluted urine/ concentrated urine

notes: -

- Normal osmolarity of blood is 290 mosm/L
- One function of the kidney is to maintain this blood osmolarity; it does so by changing urine osmolarity
- Waste solutes (metabolic end products) are 600mosm/L which is not affected by the amount of water consumed or excreted through urine .

1-Drinking too much water will tend to dilute body fluids (ICF+ECF) increasing their tendency to become hypo-osmolar. Kidney stops body fluids from becoming hypo-osmolar by increasing water excretion, by doing so urine volume increases; remember that waste solutes are still **600mosm/L** and now they are in a larger urine volume, making urine hypo-osmolar.

2-Not Drinking enough water will tend to concentrate body fluids (ICF+ECF) increasing their tendency to become hyperosmolar. Kidney stops body fluids from becoming hyperosmolar by decreasing water excretion, by doing so urine volume decreases; again, waste solutes are **600mosm/L** and now they are in a smaller urine volume, making urine hyperosmolar.

Notice

- Whenever blood osmolarity is increasing (hyperosmolar) urine osmolarity increases as well.
- Whenever blood osmolarity is decreasing (hypo-osmolar) urine osmolarity decreases as well.

Process Mechanism

Required mechanism from both concentrating and diluting urine: -

1. Corticopapillaryosmolar gradient (hyperosmolar medullary interstitium); note: this works for both diluting and concentrating urine however it best suits concentrating urine.
2. Role of ADH.

3. Notes: -

- Renal cortex osmolarity is 300mosm/L and as you move towards the medulla (papilla) the interstitium fluid osmolarity progressively **increases**.
- Osmolarity is a relative concept for our discussion it is always relative to the blood osmolarity (300) anything more is hyper, and anything less is hypo. Applies to urine as well (if urine osmolarity is > 300 , it is called hypertonic urine , if <300 it is called hypotonic urine , if 300 it is called isotonic urine)
- Descending loop of Henly is only thin.
- Our discussion will involve 1 nephron

1 .Corticopapillaryosmolar gradient

Production of the osmolar gradient by two mechanism: -

1. Loop of Henly as a counter current multiplier.
2. Urea recycling in renal medulla.

A - Loop of Henly as a counter current multiplier

- Tubular fluid at the level of Bowman's capsule has osmolarity of 300 similar to that of blood.
- Two thirds of this fluid is reabsorbed at the level of the proximal tubules. 65% of Na ,65% of H₂O, 65% Cl, 80% HCO₃, 100% of Glucose and amino acids.
- The osmolarity of the tubular fluid leaving PCT and entering the descending loop of Helen is still 300! This is because the PCT is freely permeable to water, so the same ratio of water and solutes has been absorbed from the PCT and by that osmolarity stays the same. (water and solutes absorption at the level of PCT is said to be isosmotic)

Note we will skip descending loop of Henly for now and explain the thick ascending loop of Henly

- Thick ascending loop is water **impermeable**.
- Cells of the thick ascending loop of Helen contain on their basolateral surface: -
 - Na/K ATPase which pumps Na out into the medulla interstitium and K into the cell.
 - K leaky channels which allow K to move into the medulla interstitium.

- Cl- channels which allow Cl to leak into the medulla interstitium.
- On their luminal surface (lumen of the tubule) they contain: -
 - Na/K/2Cl channels which reabsorbs 1 Na, 1K, and 2Cl into the cell from the tubular fluid.
 - K leaky channels which allow K to move into the tubular fluid.
- So, solutes leave the tubular fluid however water doesn't, this means the tubular fluid is becoming more hypo-osmolar (diluted) and the interstitium is becoming hyperosmolar. (acts as a diluter of tubular fluid and a concentrator of the interstitium)
- The thick ascending loop cells are able to create a maximum osmolar gradient of 200 mosm/L between the tubular fluid and interstitium. Example the tubular fluid in the thick ascending loop is 300 osmoles then the interstitium will be 500 osmole gradients is 200.
- The descending loop is permeable to water (20% of water reabsorbed) and the interstitium around it is hyperosmolar (500 osmoles) due to the action of the thick ascending loop; due to this hyperosmolar medullary interstitium water will be leaving the descending loop. This will cause the tubular fluid inside the descending loop to become hyperosmolar and **equal** to that of the interstitium (500)
Remember the tubular fluid that reached the descending had 300 osmolarity.
- Now this tubular fluid with osmolarity of 500 moves to the thick ascending loop which again creates an osmolar gradient of 200, so now the interstitium gets 700; and the previous step repeats but this time the tubular fluid in the descending reaches 700 instead of 500 and the thick will increase the interstitium to 900 the maximum osmolarity of interstitium is **1200**.

So descending loop water lost, thick ascending solutes lost (counter current) and this multiplies medullary interstitium hyperosmolarity.

- The fluid leaving the ascending loop is hypo-osmolar due to loss of solutes that's why it called **medullary diluting segment**.
- the hypo-osmolar tubular fluid moves to the early DCT which is impermeable to water and removes solutes from the tubular fluid similar in function to thick ascending, DCT is called the **cortical diluting segment**.
- Now the tubular fluid moves to the late DCT and its osmolarity is around 60.

Note: furosemide works on thick ascending loop, thiazide works of early DCT water permeable from PCT to thin ascending loop.

water impermeable form thick ascending to early DCT

Water absorption controlled from late DCT to collecting duct.

Urea recycling in renal medulla.

- From the thick ascending till the inner medullary collecting duct (papillary collecting duct) it is impermeable to urea.
- As fluid moves from the thick ascending urea is getting more and more concentrated until it reached the last part of the nephron (papillary collecting duct) which is permeable to urea , but the last part of the papillary collecting duct has urea channels , so some (few) urea will be reabsorbed into the renal medullary interstitium and this will contribute 30%-40% of the medullary interstitium hyperosmolarity
- Urea can reenter the tubular fluid again through PCT, descending, and thin ascending. Urea will cycle back (it **recycles** few times before it gets lost in urine).

Note: ADH works to amplify both countercurrent and urea recycle mechanism.

Blood flow in cortical area is more and faster, as you go towards the medulla the blood flow gets less and slower and this slow flow will help maintain solutes in the medullary interstitium and maintain the hyperosmolarity gradient.

High flow will wash away solutes; slow will not.

Now, how **to maintain** the corticomedullary osmotic gradient which is generated by the countercurrent multiplier system of loop of Henle?

The renal medulla must be supplied with blood to nourish the tissues in this area and to transport water that is reabsorbed by the loops of Henly and collecting ducts back to the general circulation. All of this is done by the action of **vasa recta**, the capillary networks that supply blood to the medulla, are **freely permeable to solute and water**. In doing so, however, it is important that

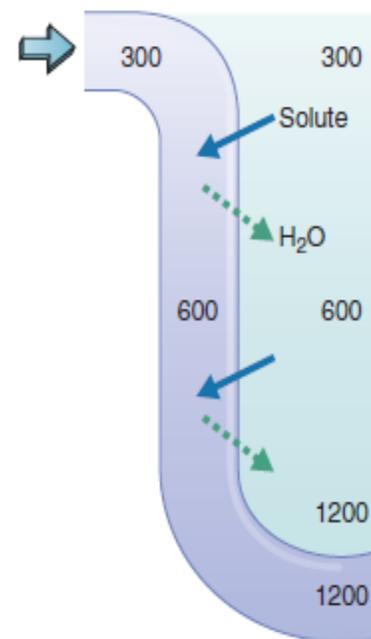
circulation of blood through the medulla does not disturb the corticomedullary osmotic gradient that is established by the loops of Henly.

Vasa recta **maintain** this gradient by the counter current **exchange** system (not multiplier).

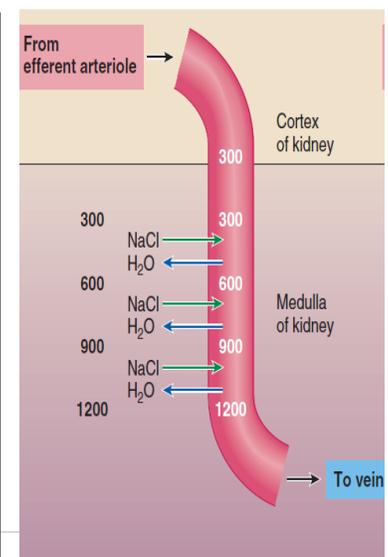
How this system works?

Vasa recta form a loop rather than being straight, and we will explain the cause behind that.

The blood enters the vasa recta(see the figure), at cortical level, with osmolarity of 300 mOsm/L. As blood passes descends down in vasa recta , it becomes surrounded by more and more hyperosmolar interstitial fluid , it will try to equilibrate (it picks up salt and loses H₂O)with the progressively increasing concentration of the surrounding interstitial fluid , until it is very hypertonic by the bottom(1200 mOsm/L). To explain, it enters as 300 mOsm/L and descends down to reach a point where it is surrounded by 600 mOsm/L interstitial fluid. Here, the blood inside the vasa recta freely equilibrates (losing water and gaining salts until they equilibrate) with the 600 mOsm/L.

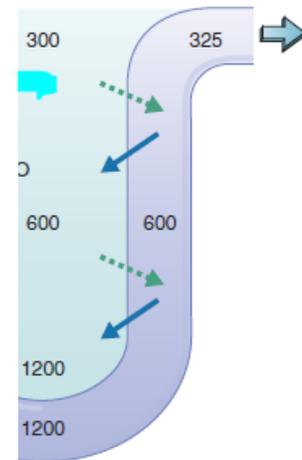


Consider the situation if blood were to flow straight through from the cortex to the inner medulla and then directly into the renal vein as shown in the figure. What happens is that, the isotonic blood entering the medulla, on equilibrating with each medullary level, would leave the medulla very hypertonic at 1200 mOsm/L. It would be impossible to establish and maintain the medullary hypertonic gradient because the salts pumped into the medullary interstitial fluid, by the nephrons, would continuously be carried away by the circulation, which in turn, disturbs the corticomedullary osmotic gradient that is very important to concentrate the urine. This dilemma is avoided by the special structure of the vasa recta which loops back through the concentration gradient in reverse direction to allow the blood to leave the medulla and enter the renal vein essentially isotonic(approximately) to incoming arterial blood, as we will see.



Hypothetical pattern of blood flow

Then, as blood flows up the ascending limb, it becomes surrounded by more and more hypo-osmolar interstitial fluid (see the figure), salt diffuses back out into the interstitial fluid, and H₂O reenters the vasa recta as progressively decreasing concentrations are encountered in the surrounding interstitial fluid until it is approximately isotonic at the venous end. It is actually slightly hyperosmolar (with the osmolarity of 325 mOsm/L at the venous end), meaning that it carries with it some salts to the circulation.



This **passive exchange** (countercurrent multiplier system is active) of solutes and H₂O between the two limbs of the vasa recta and the interstitial fluid is known as **countercurrent exchange**. Unlike countercurrent multiplication, it does not establish the concentration gradient. Rather, **it preserves or maintains** (prevents the dissolution of) the gradient. Because blood enters and leaves the medulla at the same osmolarity as a result of countercurrent exchange, the medullary tissue is nourished with blood, yet the corticomedullary gradient is preserved.

Extra, but important, note: notice that the blood leaving the vasa recta has an osmolarity of 325 mOsm/L, which is slightly higher than the osmolarity of the original blood that entered it. Some of the solute from the corticomedullary osmotic gradient was picked up and will be carried back to the systemic circulation. With time, this process could dissipate the corticomedullary osmotic gradient. The gradient normally does not dissipate, however, because the mechanisms of countercurrent multiplication and urea recycling continuously replace any solute that is carried away by blood flow.

This lecture is concerned with the process of making concentrated urine, and to achieve this, 2 factors are involved:

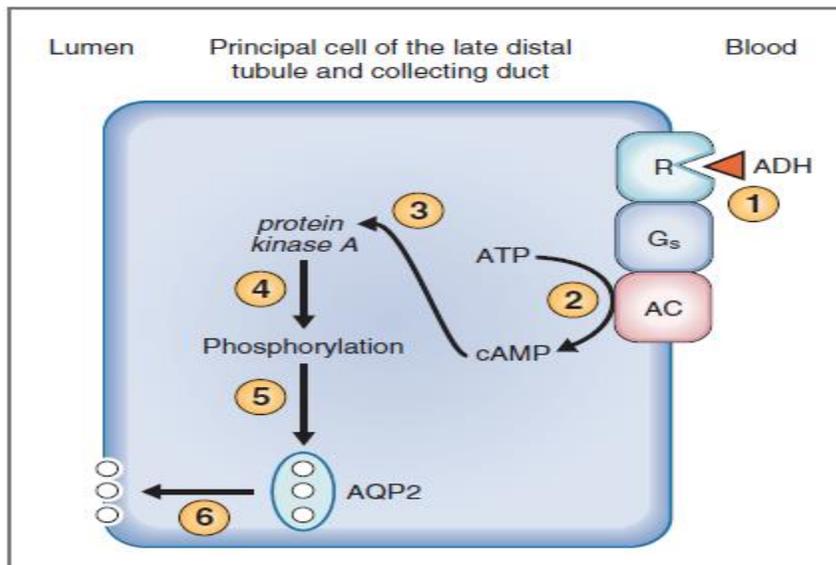
- 1- The corticomedullary gradient (which is established via the countercurrent multiplication and maintained via countercurrent exchange system, as we mentioned).
- 2- The ADH.

How exactly ADH works?

It performs its action by affecting the principal cells of the nephron, which are a special type of cells that can be found in the late DCTs, cortical CDs, and medullary CDs.

These cells are ADH and aldosterone sensitive cells; when they are under the effect of aldosterone, they retain water as well as sodium and secrete potassium. Under the effect of ADH, they **only retain water**.

The following steps are involved in the action of ADH on the principal cells in retaining water. These steps correspond to the circled numbers in the figure (Dr Yanal said that he will not ask about the cascade below):



- 1- ADH is delivered to the principal cells via the peritubular capillary blood. **ADH receptors**, present in the *basolateral* membrane, are coupled to **adenylyl cyclase** via a stimulatory G protein (Gs). (ADH is a **small peptide** which cannot cross the membrane, so it interacts with its receptor on the surface of the membrane. On the other hand, aldosterone, which is a steroid, can easily cross the membrane to interact with its intracytoplasmic or intranuclear receptor.)
- 2- When ADH binds to the receptors, adenylyl cyclase is activated and catalyzes the conversion of ATP to **cAMP**.

- 3- cAMP activates **protein kinase A**.
- 4- Activated protein kinase A then causes **phosphorylation** of intracellular structures. The identity of these structures is uncertain, although possibilities include microtubules and microfilaments, which are involved in intracellular shuttling mechanisms.
- 5- and 6- After the phosphorylation step, vesicles containing water channels(within their membrane) are shuttled to and inserted into the **luminal membrane** of the principal cell, thus increasing its water permeability. The specific waterchannel that is controlled by ADH is **aquaporin 2 (AQP2)**.

To conclude:

In the absence of ADH, the principal cells are impermeable to water. In the presence of ADH, water channels, or aquaporins, are inserted in the **luminal membrane** of the principal cells ,making them permeable to water.

On the basolateral side of the principal cells, there are other types of water channels (**AQP 3 and 4**). And these channels are present all the time which means that the basolateral side of the principal cells is always permeable to water, but the luminal side is under the control of ADH.

We said that the fluid leaving the early DCT is highly dilute, 60mOsm/L. If the cells become permeable to water (ADH action), water flows out of the tubular fluid by osmosis, driven by the osmotic gradient across the cells.

- When ADH is low or absent ,the last parts of the nephron will be impermeable to water; As tubular fluid flows through them, water won't be reabsorbed, causing the urine to be Hyposmotic (diluted large amount of urine).
- When ADH is present, the last parts of the nephron will be highly permeable to water; Water will be reabsorbed (due to ADH-dependant hyperpermeability) until the tubular fluid equilibrates osmotically with surrounding interstitial fluid(it is exposed to the corticomedullary osmotic

gradient). The final urine may reach the osmolarity present at the tip of the medulla, which is 1200 mOsm/L.

The function of ADH is not only to increase the permeability of water in the last parts of the nephron, it also does the following:

- It increases the activity of the **Na⁺-K⁺-2Cl⁻** cotransporter of the thick ascending limb of Henle
- It increases urea permeability in the inner medullary collecting ducts

By these, it has a role in enhancing countercurrent multiplication, and urine recycling. By these, ADH also can make the osmolarity in the inner medulla as high as 1400 mOsm/L to maximize the water reabsorption and the urine concentration.

Let's have an examples:

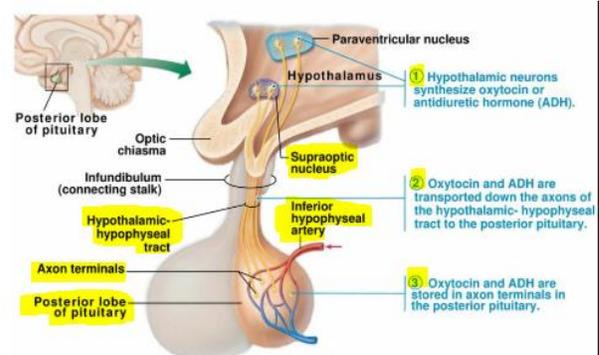
- If a person is lost in the desert without water to drink, and under these conditions, he loses water via sweating, respiratory system and kidney. We expect him to pass a small amount of a very concentrated urine to preserve water. But how does the biological system handle this situation? Losing water without compensation, will make the blood hyperosmolar (more than 300 mOsm/L).

1- This hyperosmolar blood is detected by a special type of receptors, **osmoreceptors**, found in the anterior hypothalamus. These receptors are very sensitive to any minimal change in blood osmolarity.

2- Once osmoreceptors are activated, they activate the **supraoptic nuclei**,

{which synthesize ADH in their cell body and transport it along the axon within vesicles to be stored within the narrow ends(axon terminals) that are found in the posterior pituitary, this is called **supraoptic hypophyseal tract**},

which generate an action potential along the axon of the neuron to



reach the narrow ends and causing ADH vesicles to be secreted into the hypophyseal vessels.

- 3- ADH reaches the circulation and ends in the kidneys(it has other targets), where it functions to insert water channels, or aquaporins, in the **luminal membrane** of the principal cells,making them permeable to water.
- 4- Water is preserved, and urine is very concentrated(as high as 1400 mOsmL).

Desert's rodents can live without drinking too much of water, and the cause behind that is their very long loop of Henle which can concentrate the urine to be 5000 mOsm/L or greater.

- On the other hand, if the person drinks a lot of water, his blood osmolarity will decrease, causing the osmoreceptors to be inhibited, which results in the inhibition of ADH secretion. In the absence of ADH, the principal cells are impermeable to water. So he will excrete diluted urine with osmolarity of 60 mOsm/L.

The last concept which will be discussed in this lecture is the **tubular fluid/ plasma osmolarity** (TF_{osm}/P_{osm} ratio):

Along the nephron, the composition of the fluid changes dramatically as follows:.

- At the bowman capsule; the filtrate has the same osmolarity of the plasma, so, the ratio will be: $TF/P = 300/300 = 1$
- At the end of the proximal tubule; the tubular fluid will have 300 mOsm/L, so, the ratio will be: $TF/P = 300/300 = 1$ (here the same ratio of water: solute is reabsorbed)
- At the end of the descending limb of loop of henle; the tubular fluid will have 1200 mOsm/L, so, the ratio will be: $TF/P = 1200/300 = 4$ (let's say that it is more than 1), as water is being reabsorbed without solutes.

- At the end of the ascending limb of the loop; the tubular fluid will be hypo-osmolar and the ratio is less than 1, as this part is impermeable to water at all.
- The ratio at the last part of the nephron depends on the presence and absence of ADH:
 - 1- When ADH is absent, the ratio will be less than 1, due to 2 factors; the water is not reabsorbed, and the solutes are reabsorbed under the effect of aldosterone, making the urine more diluted.
 - 2- When ADH is present, the ratio will be more than 1, as water is being reabsorbed and urine is being concentrated.