
# Sheets Physiology

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# *Sodium Homeostasis*

Sodium homeostasis is important in different aspects:

1. **Contributes to the osmolarity of the plasma and controls fluids volume**

   We can predict the osmolarity of the plasma if we know $Na^+$ concentration. In the plasma there are cations and anions, both contribute in osmolarity (in addition to others like sugars). We have the same number of cations and anions. $Na^+$ is not the only cation; we also have $K^+$, $Mg^{++}$, etc. If $Na^+$ was the only cation, we can know the osmolarity by multiplying its concentration by 2; for example, the concentration of $Na^+$ is 140 mEq/L → so the osmolarity=140 X 2=280. But because it is not the only cation we multiply its concentration by 2.1.

   So we can predict the osmolarity using $Na^+$, which means it can tell you how much the extracellular volume is. If you have hypertension, you should eat foods with low $Na^+$ because too much $Na^+$ means too much water and hypertension becomes worse.

2. **Important for excitability of the cells and muscles contraction**

   It is important in depolarization.

3. **Important for secondary active transport of many substances**

   When $Na^+$ is reabsorbed in the kidney, it helps in the absorption of amino acids and glucose. We also have a $Na^+$- $H^+$ exchanger which helps in the counter transport of $H^+$.

4. **Important for concentrating the urine**

   Many diuretics target $Na^+$ specifically but also targets $Cl^-$ and sometimes $K^+$. If you inhibit $Na^+$ reabsorption, it is as if you are inhibiting water reabsorption and you will have diuresis and that's how diuretics work. They inhibit $Na^+$ reabsorption → $Na^+$ remains in the lumen of the tubule and keeps water with it → so you get rid of extra $Na^+$ and water at the end of the day.

- Sodium concentration in plasma = 135-145 mEq/L, its intracellular concentration is 14 mEq (or mM).
- The average sodium intake = 150 mEq/day = Sodium output → ***Sodium Balance***
  - If intake > output → positive balance
  - If output > intake → negative balance

  We need around 4g of $Na^+$/day which corresponds to 150 mEq/day.
- Most of the excreted Na+ is excreted by the kidneys; only 5 mmol/day is excreted by other pathways, such as through the GI secretions or by sweating. The kidneys are the major organs in maintaining Na+ homeostasis.
- **Filtered load of $Na^+$ = GFR X concentration in plasma**

  = 180L/day X 140 mEq/L = 25,200 mEq/day

  25,200 mEq enters bowman's space/day, $Na^+$ concentration in urine is 150 mEq/day. So we need to reabsorb 25,050 mEq/day. So:

$$\text{Percentage of reabsorbed } Na^+ = \frac{25050}{25200} \times 100\% = 99.4\%$$

  99.4% of filtered $Na^+$ is reabsorbed and only 0.6% is excreted in urine. If we doubled the excretion fraction (from 0.6 to 1.2%) the concentration of $Na^+$ in urine will be significantly increased (from 150 to 300).

## Reabsorption of $Na^+$:

- In the proximal tubule → 65% of filtered $Na^+$ is reabsorbed
- In the descending limb of Henle → 0% is reabsorbed (**no $Na^+$ reabsorption**)
- In the thick ascending limb of Henle → 25% of $Na^+$ is reabsorbed with $K^+$ and $2Cl^-$ by **active transport** (electroneutral i.e. 2 +ve charges and 2 –ve charges)
- In the distal tubule → 5% is reabsorbed **under the effect of aldosterone**
- In the collecting duct → 4.5% is reabsorbed
- The remaining 0.5% is excreted in urine

As we go down the tubules, the tubular fluid becomes more concentrated (becomes hyperosmolar) because (as we will see later) water is reabsorbed but $Na^+$ is not.

**Which of these is the most important part in handling $Na^+$??

We can answer this question from different angles. We can say that the proximal part is the most important because it reabsorbs 65% of filtered $Na^+$ (the highest percentage of reabsorbed $Na^+$). We can also say that the distal part is important because it is under control (it can be controlled through aldosterone) which is important for physiologists. For pharmacologists, the most important part is the thick ascending part because it can be controlled by drugs. The descending part can be considered important because it is not permeable to $Na^+$.

## Reabsorption of water:

125ml of water is filtered and 1ml is excreted in urine, so reabsorption is 124ml.

$$\text{Percentage of reabsorbed water} = \frac{124}{125} \times 100\% > 99\%$$

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- In the proximal tubule → 65% is reabsorbed (the same as $Na^+$)
- In the descending limb of Henle → 15% is reabsorbed [compare with $Na^+$]
- In the thick ascending limb of Henle → 0% is reabsorbed [compare with $Na^+$]
  ****This is the only membrane which is NOT permeable to water.**

**the descending limb is permeable to water but not to NaCl and the ascending is permeable to NaCl but not to water.

The more we go up, the more the tubular fluid becomes diluted because we extracted NaCl but not water.

- In the distal tubule → 10% is reabsorbed
- In the collecting duct → 9.3% is reabsorbed **under the control of ADH**
- The remaining is excreted in urine

The ascending limb of Henle is permeable to NaCl but not permeable to water, so in this segment there will be reabsorption of NaCl but not water. As a result, NaCl becomes concentrated in the medullary interstitium (interstitium surrounding the ascending limb and the collecting duct*); i.e. it becomes hyperosmolar. This is called ***the single effect***. The single effect means that you reabsorb NaCl without water. Usually water follows NaCl but in this segment only NaCl is reabsorbed without water.

So we end up with hyperosmolar interstitium in the medulla:
The osmolarity of the interstitium = 700 mOsm (due to NaCl) + 500 mOsm (due to urea)
= **1200 mOsm/L**

| The osmolarity of the interstitium in the rest of the body is 300 mOsm/L |
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The osmolarity of the interstitium in the medulla is hyperosmolar which is unique to this area. When ascending toward the cortex, the osmolarity of the interstitium decreases gradually until we reach the cortex (**osmotic gradient**). The osmolarity of the interstitium in the entire cortex equals 300mOsm/L.

It is true that $Na^+$ reabsorption is mostly in the proximal tubule, but it is much more important in the ascending tubule because we have active transporters that pump NaCl into the interstitium (the surrounding of the collecting duct*). So, the interstitium surrounding the collecting duct is hyperosmolar.
The collecting duct is the final step in tubular modification; after the collecting duct we can't modify the tubular fluid anymore and it is now called urine.

The cortex receives high blood flow (95% of renal blood flow) and as a result, it has the same osmolarity as the plasma (300 mOsm). However, the blood flow in the medulla is sluggish; only 5% of the total renal blood flow goes to the medulla. If blood flow in the medulla was high, the reabsorbed NaCl would be washed out very quickly and the interstitium cannot be hyperosmolar. That's why it is necessary to have very little blood flow (through vasa recta) in the medulla, just enough to remove some particles to a certain limit.

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*Remember: the proximal tubules, distal tubules and the first part of the collecting ducts are located in the cortex of the kidneys, while the descending and ascending loops of Henle and the second part of the collecting ducts are located in the medulla.

The blood coming to the medulla via vasa recta has an osmolarity of 300mOsm/L and leaves with an osmolarity of 350 mOsm/L; we didn't remove much of NaCl. If blood flow was high, it will wash out NaCl and blood leaving through vasa recta will have a much higher osmolarity and the interstitium will not become hyperosmolar because we didn't allow for NaCl and urea (which also contributes to the osmolarity) to be accumulated.

This was only discovered less than 100 years ago when the micro-puncture technique* was invented. They inserted the micropipette from the renal pelvis and discovered a very strange finding; the osmolarity of the interstitium in the medulla is 1200mOsm/L even though it equals 300 in the rest of the body!

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There are water channels in the collecting duct. These channels are either open or close and ADH is what opens them. When ADH is secreted from the posterior pituitary it will insert water channels in the collecting duct. Now the intra-tubular fluid will equilibrate with the interstitium. So, the osmolarity of it will increase as we go down the collecting duct until reaching 1200mOsm/L (**osmotic gradient**).

The presence of this gradient through the medulla is weird; it is like there are 1200 colors in a water bowl but didn't mix.

When we try to study this, there will be a problem. When I want to study how the nephron works, I have to put it in an environment that is similar to its normal environment. With any other cell it would be easy; we can put it in plasma. But with the collecting duct the case is different.

10:00-20:00

I can isolate the nephron easily, but this is not the actual normal surrounding of a nephron and any conclusion here is questionable (can be right or wrong). So I need to study the collecting duct while inside the working kidney. When working with live rats, this mission is so hard because their kidneys are small and it is pushed with the diaphragm during breathing. So it is very hard to reach the collecting duct (you can't be sure if you reached it or not).

*It is a technique by which a micropipette (25 µm) is inserted in different parts of the nephron

Since reabsorption of water from the collecting ducts is controlled by ADH, it is this segment of the lobules which determines the osmolarity of the urine.

So **in the presence of ADH**, the osmolarity of tubular fluid will be the same as the interstitium. Meaning that urine osmolarity can reach 1200mOsm/L.

**In the absence of ADH**, water channels in the collecting duct will close. So, the osmolarity of the tubular fluid will not be related to that of the interstitium; it can be different (it could be 300, 400, 50 etc.). This is because I can always remove $Na^+$ actively but there is no active transport of water (water only moves passively by osmosis).

## Urea reabsorption:

We mentioned previously that urea also contributes to the hyperosmolarity of the medullary interstitium. But how?

Our bodies don't reabsorb waste products but it reabsorbs urea even though it is a waste product.

Urea has a small molecular weight so it is freely filtered. The medullary collecting ducts facilitate reabsorption of urea which is found in high concentrations in these ducts. The reabsorption of urea into the interstitium is **passive** and accounts for about 500 of the 1200 mOsm/L. This is even more activated in the presence of **ADH**. So, ADH does not only facilitate water reabsorption but it also facilitates urea reabsorption.

Urea reabsorbed from the medullary collecting ducts is secreted again into the ascending loop of Henle. This is called ***urea cycle***.

The aim of this cycle is to keep the interstitium hyperosmolar.

*Note* that 50% of the filtered load of urea is reabsorbed by the proximal epithelial cells and the medullary collecting ducts because they are permeable to urea. This helps to raise the osmolarity in the interstitium surrounding these ducts.
But in the ascending loop of Henle, the distal tubules and the cortical collecting tubules, little urea is reabsorbed because these segments are impermeable to urea.

***Recap:***

The high osmolarity (1200mOsm/L) of the medullary interstitial fluid is maintained by three complex mechanisms:

1. **Reabsorption of NaCl** which accounts for 700 mOsm:
   The thick ascending loop of Henle continuously pumps Na+ into the surrounding interstitium without permeating water to be reabsorbed by osmosis (even in the presence of large amounts of ADH).
2. **Reabsorption of urea** which accounts for 500 mOsm:
   The medullary collecting ducts facilitate passive reabsorption of urea which is more activated in the presence of ADH.
3. **The blood vessels** which supply medullary cells (vasa recta) carry only 5% of the renal blood flow. This prevents the loss of the hypertonicity of the medullary interstitial fluid, though does not add to the osmolarity of the interstitial fluid.

## The importance of the high osmolarity (1200mOsm/L) of the medullary interstitium

The high osmolarity of the medullary interstitium is very important, its importance can be understood in the following two scenarios:

Case1: When someone is bleeding, he will have hypovolemia, hypotension and may have hyperosmolar plasma. In the hypothalamus there are volume receptors, pressure receptors and osmo-receptors. Osmo-receptors are the most important. When these receptors sense hypovolemia, hypotension and hyperosmolarity of plasma they stimulate ADH secretion from the posterior pituitary. ADH reaches the collecting duct through circulation. ADH will insert water channels in the collecting duct allowing for the reabsorption of water. As a result, the amount of urine will be less and it will be very concentrated.

The ability of the kidney to make concentrated urine = conservation of water. Reabsorption of water cannot be done if the osmolarity of the medullary interstitium wasn't high.

Case2: When you drink too much water, you will have hypervolemia and hypo-osmolar plasma. This leads to suppression of ADH secretion.

No ADH secretion → no water channels inserted in the collecting duct → no reabsorption of water → amount of urine will be high and it will be very diluted (hypo-osmolar). I got rid of the waste products AND the extra water.

The ascending limp of Henle being permeable to NaCl but not to water is a gift; it is what mostly accounts for the high osmolarity of the medullary interstitium. Otherwise, the medullary interstitium will never have high osmolarity.

If the osmolarity of the medullary interstitium was 300mOsm (like everywhere else) tubular osmolarity can maximally reach 300 mOsm/L when water channels are open. If urine output is 1.5L/day you can maximally excrete 450mOsm/day (300 X 1.5). But because your body makes 1000mOsm/day, you need ≈3L of urine to excrete 1000mOsm. Imagine you excrete 3L of urine every day! You will end up with dehydration.

Because the medullary interstitium is hyperosmolar I can excrete a small amount of urine when I need to by secreting ADH. Urine amount will be small but it will be concentrated and have all the waste products in it.

*Remember*:
Our bodies must remove 1000mOsm/day in the urine (which equals production).

## Measuring water reabsorption

$Na^+$ is first reabsorbed in the proximal tubule.
We can find $Na^+$ concentration in the different parts of the nephron using the micropuncture technique.

If $Na^+$ concentration at the beginning and at the end of the proximal tubule was 140 mEq/L, what does this mean?

There are 2 possibilities: There was no $Na^+$ reabsorption OR there was reabsorption of $Na^+$ and water in the same fraction.

20:00-30:00

Let's assume we still don't know if the proximal tubule is permeable to water or not. What can we do to know which possibility is true (if there is water reabsorption or not)?

We inject inulin*. If inulin concentration at the beginning of the proximal tubule was 1 mEq/L and at the end it became 3mEq/L we conclude that there *is* water reabsorption in the proximal tubule.

*Remember: inulin is freely filtered but not reabsorbed or secreted. So it can be used to determine where and how much water is reabsorbed in different parts of the nephron by observing inulin dilution as it passes through these parts.

If inulin concentration was doubled then 50% of water would have been reabsorbed. But in our example, 2/3 (≈66%) of water was reabsorbed because inulin concentration has tripled.

So, I knew that 66% of water was reabsorbed in the proximal tubule by using inulin. From this information, I can know that 66% of $Na^+$ was also reabsorbed because its concentration stayed the same.

If $Na^+$ concentration increased, its reabsorption would be less than that of water. If it decreased, its reabsorption will be more than that of water like glucose for example. The concentration of glucose at the beginning of the proximal tubule is 100 and it becomes 0 at the end (completely reabsorbed).

But what if inulin concentration didn't change? This means that water is not reabsorbed as it passes through, like in the ascending loop of Henle.

With water reabsorption in different parts of the nephron known, this method can be used to estimate the reabsorption of other substances like $Na^+$.
This method is also used to test how drugs, or even endogenous hormones, affect reabsorption of water (e.g. ADH had no effect on water reabsorption from the loop of Henle.)

## Segmental Clearance

To study reabsorption of any substance (Na+ for example), I calculate what is called ***segmental clearance***. Let's take the proximal tubule as an example:

A is the beginning of the proximal tubule
B is the end of the proximal tubule

**Clearance of $Na^+$ across the proximal tubule:**

$$C\ (Na^+) = \frac{Na^+\ concentration\ in\ B}{Na^+\ concentration\ in\ A} X\ flow\ rate = \frac{TF(Na^+)}{P(Na^+)}\ X\ V$$

**Clearance of inulin across the proximal tubule:**

$$C\ (inulin) = \frac{inulin\ concentration\ in\ B}{inulin\ concentration\ in\ A} X\ flow\ rate = \frac{TF(inulin)}{P(inulin)}\ X\ V$$

*Key:*
- Concentration of $Na^+$ at A = concentration of $Na^+$ in plasma =$P(Na^+)$
- TF ($Na^+$): concentration of $Na^+$ in the tubular fluid
- V is the flow rate in this particular segment

$$\frac{C_{Na}}{C_{in}} = \frac{\frac{T_{Na} \times V}{P_{Na}}}{\frac{T_{in} \times V}{P_{in}}}$$

Since the flow rate is the same:

$$\frac{C_{Na}}{C_{in}} = \frac{\frac{T_{Na}}{P_{Na}}}{\frac{T_{in}}{P_{in}}}$$

If $C_X/C_{inulin}$ :

- =1 → this means that X, like inulin, is neither reabsorbed nor secreted i.e. whatever is filtered at A reached point B. However, this is not necessarily true; X might have been reabsorbed and secreted again through this segment. Because of this, short segments give more accurate conclusions.
- >1 → there is secretion of X at this segment
- <1 → there was reabsorption

Back to our example: $\frac{C\ (Na^+)}{\mathrm{C(inulin)}} = \frac{^{140}/_{140}}{^{3}/_{1}} = \frac{1}{3}$ [in the proximal tubule]

What does this result tell us?

It means that 1/3 of the filtered Na+ reached point B and 2/3 was reabsorbed. If it was 1/4 it means that 1/4 was reached point B and 3/4 was reabsorbed and so on.

How can we study each segment by itself in the lab?
We inject a dye. If the dye returned back from the medulla to the cortex we know that we are inside the nephron. Second, we inject a drop of oil, wait a bit and then inject another drop of oil. So now I have 1 segment that is isolated between the 2 drops of oil which I can work on. Using this technique we divided the nephron into segments: early proximal, late proximal, descending, thin and thick ascending, early and late distal, cortical and medullary collecting ducts.

30:00-40:00

## Na+ Reabsorption from the proximal tubules

We know by now that almost 65% of the filtered $Na^+$ and the filtered water are reabsorbed from the proximal tubules.

$Na^+$ can either pass through or between cells of the proximal tubule; transcellular or paracellular, respectively. It can pass between cells because tight junctions between them are not that tight ($Na^+$ leakage). That's why $Na^+$ concentration here is not dependent on Tmax.

In the distal tubule, however, they are tight so $Na^+$ cannot pass between cells. Here, there is Tmax for $Na^+$ transport ($Na^+$ reabsorption is Tmax dependent).

**In early proximal:** $Na^+$ is either co-transported with glucose and amino acids, or counter-transported with $H^+$, as discussed later. When $Na^+$ is reabsorbed in the early proximal, water is reabsorbed with it but $Cl^-$ is left (wasn't reabsorbed). So, as water is reabsorbed along the proximal tubule, $Cl^-$ concentration increases from 105mEq/L (in the first part of proximal) to 150mEq/L in the second part. This causes its reabsorption in the late proximal.

**In late proximal:** In the second half of the proximal tubule most organic solutes are reabsorbed. Here, $Cl^-$ is reabsorbed, so it leaves a positive charge in the lumen. This positive charge is another force that helps in $Na^+$ reabsorption. Thus, in this half, $Na^+$ is mainly coupled with $Cl^-$ reabsorption.

*****Conclusion***: $Na^+$ reabsorption in the proximal tubule is NOT Tmax dependent; it is time-gradient dependent. If flow is slow, there will be more time for Na+ reabsorption. If concentration of $Na^+$ in the proximal tubule is high there will be more reabsorption.

## Regulation of Na+ and Water Reabsorption

$Na^+$ and water reabsorption is under the influence of 4 factors:

1. **GRF**

   Too much $Na^+$ in plasma → ↑ECF volume and blood pressure, ↓capillary oncotic pressure → ↑GFR → ↑$Na^+$ and water excretion
   This effect of increased blood pressure on Na+ and water excretion is called ***pressure natriuresis and diuresis***, respectively.

2. **Aldosterone**

   Aldosterone increases Na+ reabsorption and at the same time increases K+ secretion.

3. **ANP (atrial natriuretic peptide, factor or hormone)**

   ANP is the only hormone that increases excretion of $Na^+$ (by ↓reabsorption). It is secreted from the cardiac atrial cells in response to stretch (i.e. increased plasma volume). It directly decreases $Na^+$ reabsorption at the distal tubules and inhibits aldosterone secretion. Also, it dilates the afferent arterioles to increase GFR and $Na^+$ excretion.

   40:00-46:20

4. **ADH**

   - ADH is synthesized in the hypothalamus and is stored in the posterior pituitary.
   - Its release is stimulated by:
     - Osmoreceptors in the hypothalamus: an increase by 1% in the osmolarity of plasma increases ADH release.
     - Volume receptors: a decrease by 10% in ECF volume increases ADH release.
     - Pressure receptors: decreased blood pressure (as in bleeding) also leads to ADH release.
   - ADH binds to specific V2 receptors in the late distal tubules, collecting tubules, and collecting ducts. The stimulation of this receptor eventually increases the density of water channels (aquaporin) at the luminal and basolateral sides of the cells membranes.

THE END

GOOD LUCK