Regulation of Body Fluids: $\text{Na}^+$ and Water
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OBJECTIVES:

After studying this lecture, the student should understand:

1. Why body sodium content determines ECF volume and the relationships between sodium content and arterial pressure.
2. The concepts of sodium balance and positive and negative sodium balance.
3. The functions of the major systems that regulate ECF volume, including the RAA, the sympathetic nervous system, natriuretic hormones, and ADH.
4. How to estimate plasma osmolarity.
5. Regulation of ADH secretion, including osmotic and volume stimuli.
6. The major actions of ADH.

Separate (but related) systems control the amount of $\text{Na}^+$ in the body and the amount of water in the body. As you will learn, body $\text{Na}^+$ content is the major determinant of $\text{ECF}$ volume. On the other hand, body water content is the major determinant of body fluid osmolarity.

Note: The purpose of this lecture is to introduce the “players” that regulate $\text{Na}^+$ and $\text{H}_2\text{O}$ balance. To introduce the players, we will need to use a few terms that are not yet familiar. Don’t worry -- these will be explained in detail in subsequent lectures.

1. REGULATION OF $\text{NA}^+$ BALANCE (i.e., regulation of ECF volume)

   A. **Why body $\text{Na}^+$ content determines ECF volume.** This key idea can seem strange at first. The reasoning goes like this. (1) $\text{Na}^+$ and its accompanying anions, $\text{Cl}^-$ and $\text{HCO}_3^-$, are the major solutes of ECF. Furthermore, most of the body $\text{Na}^+$ is in the ECF. (2) You’ve already learned that when solute moves, $\text{H}_2\text{O}$ follows. (There are very few exceptions to this rule, and you will see those few exceptions later in renal physiology. For now, we will ignore the exceptions.) Therefore, the amount of $\text{Na}^+$ in ECF determines the amount of water in ECF, which is the ECF volume.

   B. **Relation between $\text{Na}^+$ content, ECF volume, and arterial pressure ($P_a$).** Recall that plasma volume is part of the ECF volume. Thus, ECF $\text{Na}^+$ content determines ECF volume, which determines plasma volume and blood volume, which determines arterial pressure ($P_a$). An increase in $\text{Na}^+$ content (called **positive $\text{Na}^+$ balance**) causes increased ECF volume, an increase in blood volume and usually an increase in $P_a$. A decrease in $\text{Na}^+$ content (called **negative $\text{Na}^+$ balance**) causes decreased ECF volume, blood volume, and $P_a$. 
C. **Na⁺ balance.** In the steady state, Na⁺ intake equals renal Na⁺ output plus losses by extrarenal routes (e.g., skin). Normally, extrarenal Na⁺ losses are negligible, although in disease, they can be significant (e.g., diarrhea, excessive sweating, burn).

1. Normally, the body maintains Na⁺ balance by renal mechanisms. That is, Na⁺ intake will be matched by urinary Na⁺ output. For example (see figure below), if a person abruptly increases their Na⁺ (and water) intake, initially, Na⁺ intake is greater than Na⁺ excretion by the kidneys; the Na⁺ content of the body increases, and the person is in **positive Na⁺ balance.** During this period of positive Na⁺ balance, the extra Na⁺ was added to the ECF, causing an increase in ECF volume. There is increased body weight due to the increased ECF volume. After several days, the kidneys detect the increased ECF volume and initiate mechanisms that cause excretion of the extra Na⁺; during this compensatory period, the kidneys excrete more Na⁺ than is being ingested, and the person loses weight, reflecting the decrease in ECF volume. If renal compensatory mechanisms are normal, all of the extra Na⁺ originally ingested will be excreted in the urine, and ECF volume and body weight return to normal.

![A Effect of Abrupt Changes in Na⁺ Intake](image)

**Figure 1.**

2. The opposite example (not shown in the figure) is a person who has severe diarrhea for several days. Na⁺ is lost in diarrhea fluid, causing a decrease in Na⁺ content, ECF volume, and body weight. During this period, Na⁺ loss from the body is greater than Na⁺
intake (negative Na\(^+\) balance). After several days, the kidneys detect the decrease in ECF volume and initiate mechanisms that decrease Na\(^+\) excretion by the kidneys until the person is returned to Na\(^-\) balance; during this compensatory period, Na\(^-\) excretion is less than Na\(^+\) intake.

In sum, the body detects changes in Na\(^+\) content (by detecting changes in ECF volume), and then makes appropriate adjustments in Na\(^+\) excretion to bring Na\(^+\) content back to normal.

3. A new concept that we will introduce here is **effective arterial blood volume (EABV)**. EABV cannot be identified anatomically, but it is the “functional” arterial blood volume, which determines tissue perfusion. Usually, changes in EABV parallel changes in ECF volume (since effective arterial blood volume is part of the blood volume, which is part of the ECF volume). However, there are important situations (e.g., congestive heart failure) where ECF volume is drastically increased, but EABV is decreased; the reason for the dissociation is that the excess ECF volume is located in the interstitial fluid (edema), not in the circulation. In this case, the body responds to decreased EABV, causing Na\(^+\) retention, increasing ECF volume further, and worsening the edema – a dangerous vicious cycle.

D. **Mechanisms for regulating ECF volume (i.e., Na\(^+\) balance).** Four systems detect changes in ECF volume (or EABV) and adjust Na\(^+\) excretion. By adjusting Na\(^+\) excretion, they are trying to restore body Na\(^+\) content and ECF volume to normal. These systems, as you will see, have overlapping effects.

1. **Renin-angiotensin II-aldosterone system (hereafter, the “RAA”).** The RAA is the major system for regulating body Na\(^+\) content and ECF volume. You are familiar with it from cardiovascular physiology.
Figure 2. The renin-angiotensin II-aldosterone system. The system is described in terms of the response to a decrease in Pa. TPR, Total peripheral resistance.

Briefly, a decrease in $P_a$ causes a decrease in renal perfusion pressure, which is sensed by renal afferent arterioles. Prorenin is converted to renin in juxtaglomerular cells. Renin is an enzyme that catalyzes conversion of angiotensinogen to angiotensin I. Angiotensin I is converted to angiotensin II, by the action of angiotensin converting enzyme (ACE), primarily in the lung. Angiotensin II has several actions, including: increasing production and secretion of aldosterone in the adrenal cortex, constriction of arterioles, stimulating $Na^+$ reabsorption in the proximal tubule, and stimulating thirst. Aldosterone is the major $Na^+$-regulating hormone; it acts on the principal cells of late distal tubule and collecting duct to induce the synthesis of $Na^+$ channels, thereby increasing $Na^+$ reabsorption, ECF volume, blood volume, and $P_a$. 
The tables below list the major stimulants and inhibitors of renin, angiotensin II, and aldosterone secretion.

### Renin Secretion

<table>
<thead>
<tr>
<th>Stimulation</th>
<th>Inhibition</th>
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<tbody>
<tr>
<td>Decreased perfusion pressure</td>
<td>Increased perfusion pressure</td>
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<tr>
<td>Increased sympathetic</td>
<td>Decreased sympathetic</td>
</tr>
<tr>
<td>Decreased distal delivery of Na(^+)</td>
<td>Increased distal delivery of Na(^+)</td>
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<tr>
<td>Prostaglandins</td>
<td>ANP</td>
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### Angiotensin II secretion

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<tr>
<th>Stimulation</th>
<th>Inhibition</th>
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<tbody>
<tr>
<td>Increased renin</td>
<td>ACE inhibitors</td>
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### Aldosterone secretion

<table>
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<tr>
<th>Stimulation</th>
<th>Inhibition</th>
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<tr>
<td>Increased angiotensin II</td>
<td>Decreased angiotensin II</td>
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<tr>
<td>Decreased P(_a) (via RAA)</td>
<td>Increased P(_a) (via RAA)</td>
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<tr>
<td>Hyperkalemia</td>
<td>Hypokalemia</td>
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2. **Sympathetic nervous system.** You have already learned the major effects of the sympathetic nervous system on the organ systems. It also participates in Na\(^+\) balance as follows. When there is decreased body Na\(^+\) content, ECF volume, and P\(_a\), the decrease in P\(_a\) is detected by the carotid sinus baroreceptors. This leads to activation of the sympathetic nervous system (which will attempt to restore P\(_a\) back to normal). In the kidney, sympathetic activation has two effects: (1) constriction of afferent arterioles (thus decreasing GFR) and (2) stimulation of Na\(^+\) reabsorption in proximal tubule. You will learn that these two effects cause decreased Na\(^+\) excretion and help restore body Na\(^+\) content, ECF volume, and P\(_a\) back toward normal.

The opposite occurs when there is increased body Na\(^+\) content, ECF volume, and P\(_a\). There is inhibition of the sympathetics, leading to dilation of afferent arterioles (increasing GFR) and decreased Na\(^+\) reabsorption, leading to increased Na\(^+\) excretion,
thus decreasing body Na\(^+\) content, ECF volume, and Pa back toward normal.

3. **Natriuretic hormones (e.g., atrial natriuretic peptide, ANP).** ANP is released from the **atria** in response to stretch. When there is increased blood volume, there is increased volume in the veins and the atria and increased atrial pressure, which causes secretion of ANP; these stretch receptors are called “low-pressure” sensors, because they respond to changes in blood volume and pressure on the *venous* (low pressure) side of the circulation (in contrast to “high-pressure” sensors for Pa on the arterial side that are used in the RAA and sympathetic nervous system). ANP then has several actions on the kidneys that lead to increased Na\(^+\) excretion: (1) dilation of afferent arterioles and constriction of efferent arterioles, which leads to increased GFR and (2) inhibition of Na\(^+\) reabsorption in late distal tubule and collecting ducts. The result, “natriuresis,” tries to decrease ECF Na\(^+\) content, ECF volume, and blood volume back to normal.

<table>
<thead>
<tr>
<th>ANP Secretion</th>
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<tbody>
<tr>
<td><strong>Stimulation</strong></td>
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<tr>
<td>Increased ECF Volume</td>
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<td>Increased atrial pressure</td>
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**Brain natriuretic peptide (BNP)** is structurally related to ANP. First discovered in brain, BNP is secreted by the **ventricles** in response to increased pressure. Its actions are the same as ANP’s, but even stronger. Recombinant BNP (nesiritide) has been used clinically to produce a large increase Na\(^+\) excretion in order to reduce ECF volume (e.g., in heart failure).

**Urodilatin** is also structurally related to ANP. It is secreted by the **distal nephron** and causes a local inhibition of Na\(^+\) reabsorption, leading to increased Na\(^+\) excretion. It is secreted by and then acts in the distal nephron.

4. **Pressure natriuresis** is the phenomenon whereby an increase in arterial pressure *per se* (i.e., independent of hormonal effects) causes increased Na\(^+\) excretion. The mechanisms underlying pressure natriuresis are not fully understood, but include “washout” of factors that normally promote Na\(^+\) reabsorption; when “washed out,” Na\(^+\) reabsorption is inhibited, and Na\(^+\) excretion is increased.
5. **Antidiuretic hormone (ADH)** is primarily important for water balance and regulation of body fluid osmolarity. However, ADH is also involved in regulating ECF volume and blood volume as follows. You will learn that one stimulus for secretion of ADH is a decrease in blood volume (hypovolemia). In turn, the major action of ADH is to increase water reabsorption. Therefore, decreased blood volume turns on both the RAA and ADH secretion. The activated RAA leads to increased Na\(^+\) reabsorption and increased ECF Na\(^+\) content. The increased ADH leads to increased water reabsorption and increased body water. For example, following hemorrhage, the RAA and ADH systems are co-activated and work in complimentary fashion to increase ECF volume and blood volume back toward normal. More on ADH in the next section.

II. **REGULATION OF WATER BALANCE (i.e., regulation of body fluid osmolarity).**

Body fluid osmolarity (osmolar concentration) is normally held within a very tight range, that is approximately 290 mOsm/L. (Recall that, in the steady state, osmolarity of all body fluid compartments is the same.)

We will digress slightly here so that you can learn how to estimate the value of **plasma osmolarity**, as it is done clinically. You learned earlier that plasma osmolarity is approximately 2 x [Na\(^+\)], since Na\(^+\) (and the associated anions) represent most of the solute in ECF and plasma. To be more precise, though, we include glucose and urea in the estimate as follows:

\[
\text{Plasma osmolarity} = 2 \times [\text{Na}^+] + \frac{\text{glucose}}{18} + \frac{\text{BUN}}{2.8}
\]

where:

- plasma osmolarity = total osmolar concentration (in mOsm/L)
- Na\(^+\) = plasma Na\(^+\) concentration (in mmol/L)
- glucose = plasma glucose concentration in mg/dL
- BUN = blood urea nitrogen concentration in mg/dL

The Na\(^+\) is multiplied by 2 because Na\(^+\) must be balanced by an equal concentration of anions (in plasma, these are Cl\(^-\) and HCO\(_3^−\)). Glucose concentration in mg/dL is converted to mOsm/L when it is divided by 18. The BUN in mg/dL is converted to mOsm/L when it is divided by 2.8.

The value of body fluid osmolarity is kept constant by adjusting body water content, rather than by adjusting body solute content. What does that mean? Note that the units of osmolarity are mosmol/L. The body keeps osmolarity constant by adjusting volume in the denominator. Two systems are involved in regulating water balance: thirst and ADH.
A. **Thirst.** When body fluid osmolarity rises by as little as 1%, there is immediate stimulation of thirst and drinking behavior. Osmoreceptors in the hypothalamus detect the increase in osmolarity, trigger drinking behavior, which brings water into the body and decreases body fluid osmolarity back to normal. Incidentally, these osmoreceptors for thirst are nearby, but distinct from, the osmoreceptors involved in ADH secretion (see below).

B. **ADH** (also called vasopressin) is the major regulator of body fluid osmolarity (by altering water reabsorption in late distal tubule and collecting ducts).

1. **Synthesis of ADH.** Briefly, ADH is a peptide hormone that is synthesized in hypothalamic neurons, packaged in vesicles, and transported down the axons of those neurons to the posterior pituitary, where it is stored until there is a stimulus for its release.

2. **Regulation of ADH secretion.** The major, physiologic stimulus for ADH secretion from the posterior pituitary is an increase in plasma osmolarity. As little as a 1% increase in plasma osmolarity is sufficient to trigger ADH secretion. Osmoreceptive neurons in the hypothalamus (nearby the ADH-synthesizing neurons) are sensitive to changes in plasma osmolarity. When plasma osmolarity increases, water shifts out of these neurons, they shrink, and then depolarize; depolarization leads to action potentials, which project to and activate the ADH-secreting neurons.

There are other (non-osmotic) stimuli for ADH secretion. The most important is a decrease in blood volume (hypovolemia). If blood volume decreases by 10%, ADH secretion is stimulated. Decreased blood volume is associated with decreased venous blood volume; decreased venous volume causes decreased venous and atrial pressure, which is detected by low-pressure sensors. These low-pressure sensors send information via the vagus to the ADH-secreting hypothalamic neurons.

Note that the response of ADH to hypovolemia is less sensitive than the response to increased osmolarity; that is, to stimulate ADH secretion, it takes a larger decrease in blood volume (10%) than an increase in osmolarity (1%). However, when evoked, the hypovolemic stimulus is more powerful and will “override” osmotic stimuli, as shown in the figure. Thus, hypovolemia (volume contraction) stimulates ADH secretion, even when plasma osmolarity is lower than normal. Conversely, hypervolemia (volume expansion) inhibits ADH secretion, even when plasma osmolarity is higher than normal.
Other stimuli for ADH secretion are pain, nausea, angiotensin II, hypoglycemia, nicotine, and opiates. Other inhibitors of ADH secretion are ethanol and ANP.

<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Increased plasma osmolarity</td>
<td>Decreased plasma osmolarity</td>
</tr>
<tr>
<td>Hypovolemia (volume contraction)</td>
<td>Hypervolemia</td>
</tr>
<tr>
<td>Pain</td>
<td>ANP</td>
</tr>
<tr>
<td>Nausea</td>
<td>Ethanol</td>
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<tr>
<td>Angiotensin II</td>
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<td>Hypoglycemia</td>
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<td>Nicotine</td>
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<td>Opiates</td>
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3. **ADH actions.** ADH has two major actions:

a. **Increased water permeability** in *principle cells* of late distal tubule and collecting ducts, via insertion of water channels (*aquaporin 2, AQP2*) in the luminal membrane. The receptor on the principal cells is a $V_2$ receptor, that acts via the adenylyl cyclase (*cyclic AMP*) mechanism and utilizes a Gs protein. The increase in water permeability leads to increased water reabsorption.

b. **Contraction of vascular smooth muscle**, or vasoconstriction. The receptor on *blood vessels* is a $V_1$ receptor, that acts via the phospholipase C (*IP_3/Ca^{2+}* ) mechanism. Vasoconstriction
of arterioles leads to increased TPR and $P_a$.

c. Other actions of ADH include increasing the $\text{Na}^+ - \text{K}^+ - 2\text{Cl}^-$ transporter of thick ascending limb and increasing urea permeability of inner medullary collecting ducts. These actions will be discussed in the lectures on concentration of the urine.

III. PRACTICE QUESTIONS

1. Over a two-day period, a man ate 4 g of $\text{Na}^+$. During the two-day period, his total urine volume was 2.5 L, and the urinary $\text{Na}^+$ concentration was 100 mg/100 ml. Ignoring extrarenal losses of $\text{Na}^+$, is the man in normal, positive, or negative $\text{Na}^+$ balance?

2. A person with hypertension has left renal artery stenosis and an elevated renin in blood from the left kidney. What change would you expect in the blood level of the following?

   Angiotensin II
   Aldosterone
   Renin in blood from the right kidney

3. A person with an aldosterone-secreting tumor has hypertension. What change would you expect in each the following?

   Aldosterone level
   Renin level
   Angiotensin II level
   $\text{Na}^+$ balance

4. Estimate the plasma osmolarity in a person with a plasma $\text{Na}^+$ concentration of 140 mEq/L, plasma glucose concentration of 100 mg/dL, and BUN of 8 mg/dL.

5. Which of the following would be expected to have increased ADH secretion? (Indicate all that are correct)

   Person with serum osmolarity of 275 mOsm/L
   Person with diarrhea for three days that caused a 20% loss of ECF volume
   Person who drank 1 liter of beer
   Person with severe nausea
   Person with volume expansion
ANSWERS

1. Positive Na\(^+\) balance. Intake = 4 g. Urinary excretion = 2.5 L x 100 mg/100 ml = 2500 mg = 2.5 g. Intake > excretion.

2. Angiotensin II – increased
   Aldosterone – increased
   Renin in blood from the right kidney – decreased (because increased P\(_a\) is sensed by right kidney)

3. Aldosterone level – increased
   Renin level – decreased (due to increased P\(_a\))
   Angiotensin II level – decreased (due to decreased renin)
   Na\(^+\) balance – increased (due to increased aldosterone)

4. 
   \[
   \text{Plasma osmolarity} = 2 \times 140 + \frac{100}{18} + \frac{8}{2.8} = 288.4 \text{ mOsm/L}
   \]

5. Person with serum osmolarity of 275 mOsm/L – no
   Person with diarrhea for three days that caused a 20% loss of ECF volume – yes
   Person who drank 1 liter of beer – no
   Person with severe nausea – yes
   Person with volume expansion – no