



physiology

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Sheet

Slides

Number

20

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★Molecular basis of physiological actions of the ANS★

★Neurotransmitters

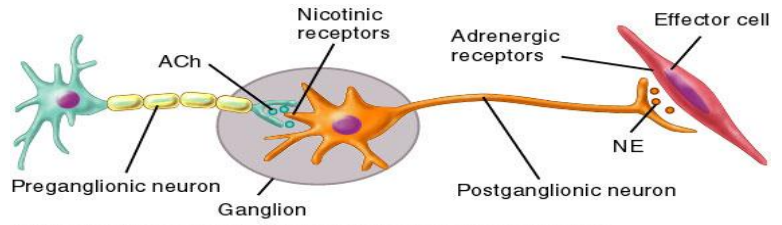
◆ Before we start, let's recall some few basic information about the ANS.

-As you know, the ANS has 2 divisions, these are the sympathetic and the parasympathetic.

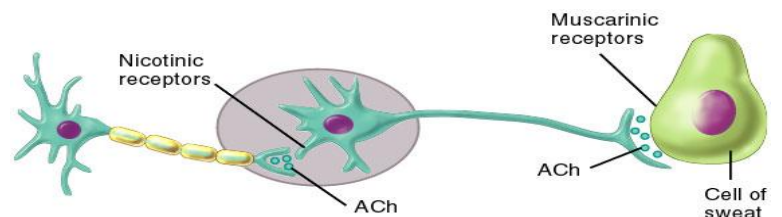
-The parasympathetic division releases the neurotransmitter Acetylcholine from the terminals of both the preganglionic neuron (in the ganglia) and the postganglionic neuron (in the neuro-effector junction).

-In the sympathetic division, the preganglionic neuron also releases Acetylcholine, while the postganglionic releases Norepinephrine.

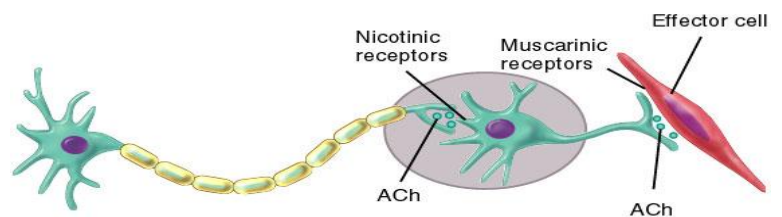
-We have an exception in fibers innervating sweat glands as they also release Acetylcholine although these fibers are part of the sympathetic division.



(a) Sympathetic division—innervation to most effector tissues



(b) Sympathetic division—innervation to most sweat glands



(c) Parasympathetic division

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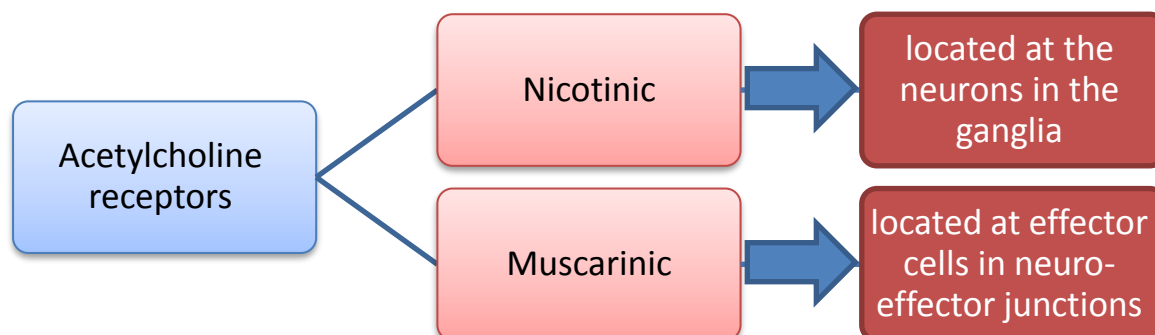
★Receptors and signal transduction mechanisms

◆ These neurotransmitters act over receptors, for example, Acetylcholine acts on receptors on the **postganglionic neuron in the ganglia** and on **organs innervated by the parasympathetic neurons**, in addition to the **sweat glands**. But we have some differences between the receptors located in different places and between the effector cells.

1) Acetylcholine receptors

-At the neurons, receptors for Acetylcholine are called **Nicotinic** receptors, named nicotinic because Nicotine can also stimulate them. While the receptors on the effector cells are called **Muscarinic** receptors, because also Muscarine can stimulate them.

Note Muscarine isn't found in our body, but it can be found in some toxic plants like mushrooms.



◆ Now, what's the signal transduction mechanism between the first and the second neurons? The Nicotinic receptors linked to sodium channels, since the purpose is to generate action potential in the second neuron.

Muscarinic receptors

◆ What about receptors at effector cells? We have many subtypes of muscarinic receptors (M1, M2, M3, M4, and M5), some of these are inhibitory receptors that inhibit effector cells (M2), while some are excitatory receptors that excites them (M1, M3, M5).

1) Inhibitory muscarinic receptors: We can get the inhibitory effect of these receptors by 2 mechanisms:

a) G-protein → potassium (K⁺) channel → Slowing the rate of depolarization

E.g. M2 receptor in the heart.

b) G_i (inhibitory G-protein) → Adenylyl cyclase → Reducing cAMP production

E.g. Other inhibitory receptors and also M2 (as you will see next).

🔗 **How do we get the inhibitory effect in the heart by activating M2 receptor?**

(As mentioned by the doctor), the M2 receptor will induce 2 effects. Firstly, we will have inhibitory G-protein (G_i) which is negatively coupled to adenylyl cyclase, causing a decrease in cAMP which leads to reducing the activity of Na⁺ channels. We will also have the G-proteins increasing the activity of K⁺ channels. All these will decrease the rate of depolarization in the heart, leading in the end to **bradycardia** (slower heart rate).

2) Excitatory muscarinic receptors: They're found in the smooth muscles and glands, they produce their effect as following:

Gq → Phospholipase C (PLC) → Inositol-1,4,5-triphosphate (IP3)

-They're coupled to Gq proteins that transmit the effect by activating PLC, which increases the production of IP3 that releases Ca⁺² from its stores in the ER, this causes the smooth muscle cells to contract.

↳ **What happens if someone ingests muscarine?**

They will generate all parasympathetic activities in general, they will also have more sweat released from their sweat glands. Why? Because muscarine can bind to and activate the muscarinic receptors at these organs.

♦ Muscarine effects on the body:

- Stimulation of secretion: salivation, tearing, sweating, nasal and bronchial secretion.
- Increase gastrointestinal tract motility → vomiting and diarrhea.
- Contraction of urinary bladder → urination.
- Bradycardia.

↳ **How can we block the effect of Muscarine?**

Simply by using **Atropine** (an antagonist) that binds to and blocks the binding sites on muscarinic receptors, thus preventing Muscarine binding to the receptor. This reverses the effects of Muscarine, causing:

- Inhibition of secretion: dry mouth, dry eyes, and dry nasal passages.
- Loss of pupillary light reflex → Mydriasis (dilation of the pupil).
- Loss of ability to focus the lens for near vision.
- Tachycardia.

👉 When you are giving your patient Atropine to block M receptors, you should know when it's enough, how would you know when to stop?

You can follow many changes in their body:

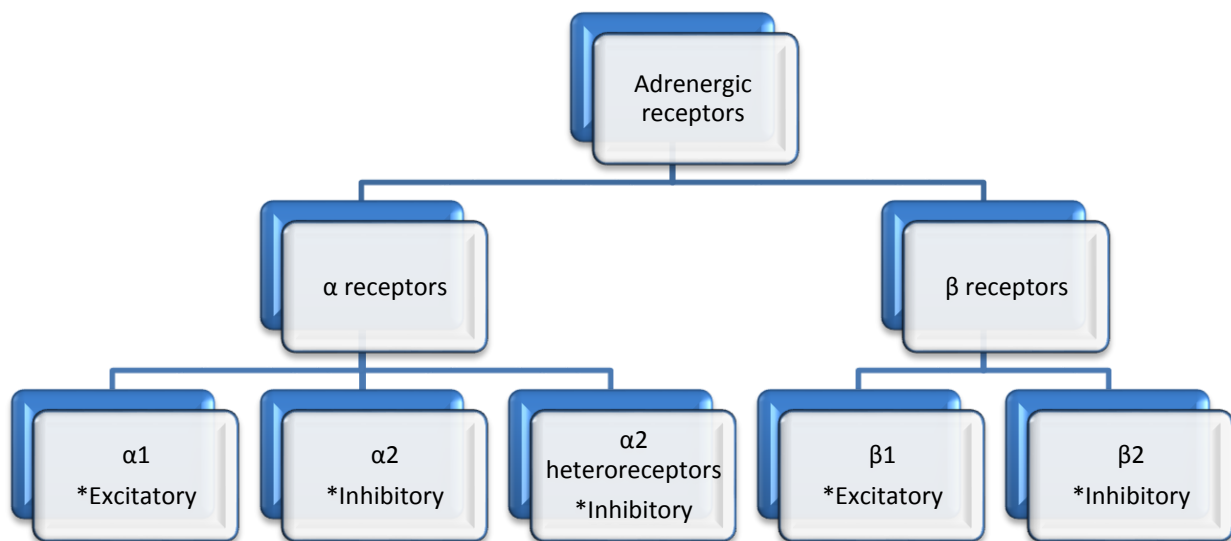
1. The heart rate will start to increase.
2. Their pupil will start to dilate (Mydriasis).
3. They will lose the ability to focus the lens for near vision, means they won't be able to read or write for example.

2) Adrenergic receptors

◆ The sympathetic nervous system releases NE at the neuro-effector junctions, so we must have receptors for this neurotransmitter, those receptors are called **Adrenergic receptors**.

◆ Adrenergic receptors respond to catecholamines (Epinephrine as a hormone & Norepinephrine as a neurotransmitter).

◆ We have 2 main types of adrenergic receptors: α receptor & β receptor.



1) α receptors.

◆ For α receptors, we have many subtypes:

a) α_1 receptors: these receptors are excitatory receptors, they work by the following mechanism:

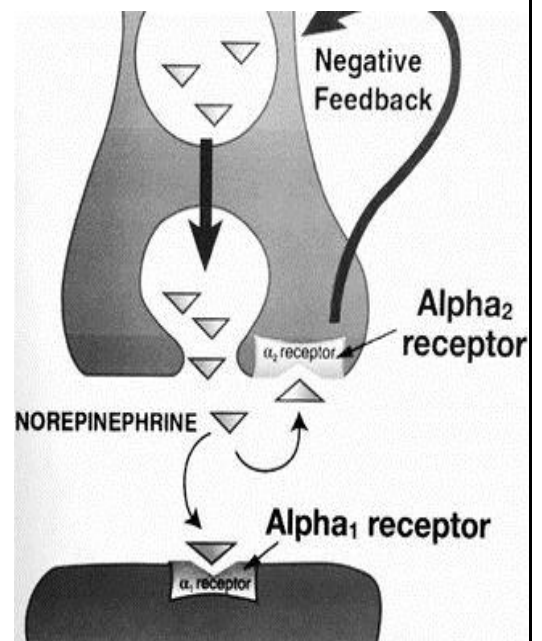
Gq \rightarrow Phospholipase C (PLC) \rightarrow Inositol-1,4,5-triphosphate (IP3)

-They're coupled to Gq proteins that transmit the effect by activating PLC, which increases the production of IP3 that releases Ca^{+2} , this causes the smooth muscle cells to contract.

b) α_2 receptors: these receptors are inhibitory receptors, found at the **terminals of adrenergic neurons** (neurons that release NE), so once NE is released, these receptors can inhibit the release of more NE, so we don't have high amount of NE released at that synapse.

c) α_2 heteroreceptors: these receptors are inhibitory receptors, found at the **terminals of NON-adrenergic neurons** (neurons that don't release NE), they can inhibit the release of Acetylcholine. They work by the following mechanism:

$G_i \rightarrow$ Adenylyl cyclase \rightarrow Reducing cAMP production



Imagine you got an injury, you are having pain of that injury. Now to say somebody is playing football and he got an injury, is he feeling pain during his play?

No, you will only feel a relatively slight pain, because some neurons that are responsible for sensing and transmitting pain sensation to the CNS has the α_2 heteroreceptors. When we're doing exercises, we have a high sympathetic activity, means our sympathetic neurons will release large amount of the neurotransmitter NE which is going to bind to these receptors, inhibiting neurons bearing the α_2 heteroreceptor (slowing the depolarization of the neuron). That's why we will feel less pain.

2) β receptors.

◆ For β receptors, we also have many subtypes:

a) β_1 receptor: these receptors are excitatory receptors and they are found in the **heart**.

b) β_2 receptor: these receptors are inhibitory receptors causing relaxation in smooth muscle cells, found in:

1. Tracheal and bronchial smooth muscle.
2. In the gastrointestinal tract.
3. Smooth muscles of blood vessels supplying skeletal muscles.

β_2 receptor work by the following mechanism:

$G_s \rightarrow$ Adenylyl cyclase \rightarrow increasing cAMP production

Note Both β_1 & β_2 receptors are positively coupled to adenylyl cyclase, so both increase the production of cAMP, but what's the effect of each? In β_1 we get excitatory effect, while in β_2 we get inhibition.

↪ What happens when you give an asthmatic patient β blockers? (asthma is a condition in which the airways narrow, making the patient breath hardly).

Since the patient was given a general β blocker, it will prevent the binding of NE with all types of β receptors. So, the patient will suffer mainly from bronchoconstriction, making them breath even more hardly. So, if an asthmatic patient is having tachycardia and you would like to give them a β blocker, you should give them a β_1 SELECTIVE blocker.

★Body fluids★

★Fluid compartments

◆Most of the human's body weight is water. However, we have higher percentage of water in males (around 60% is water) than we have in females (55%), because females have more fat.

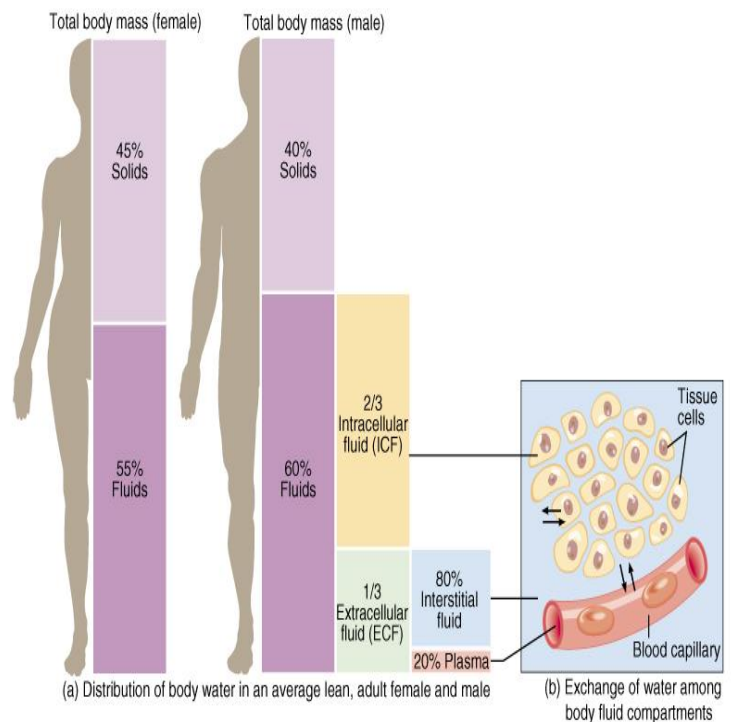
-About $\frac{2}{3}$ of the fluids in our body is found within cells, it's called intracellular fluid.

-The remaining $\frac{1}{3}$ is found outside cells and it's called extracellular fluid.

-The extracellular fluids fall into 2 categories:

A. Interstitial fluid: found in the area between cells, constitute 80% of the extracellular fluid

B. Plasma: found in blood vessels, constitute the remaining 20% of the extracellular fluid.

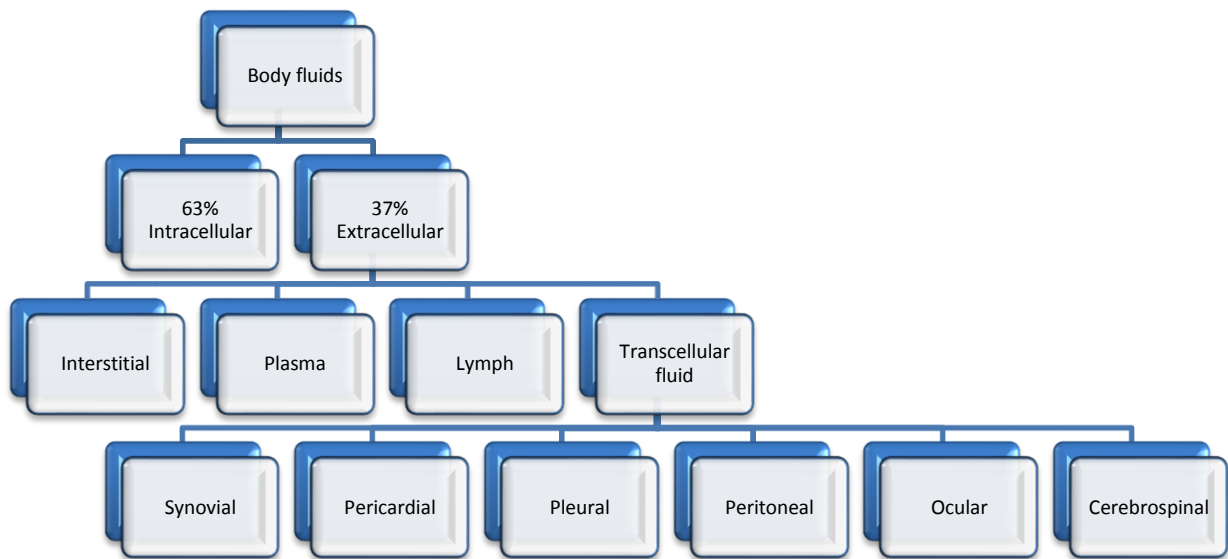


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◆An average adult female is about 52% water, and an average male is about 63% water.
** You don't have to memorize the exact numbers, just to know that we have large amount of water in our body.

★Water distribution

◆As we said, the extracellular fluid is subdivided into many compartments; we already discussed the interstitial fluid that is located between cells separating them from each other, and the plasma that is found in blood vessels. But we also have a small amount of fluid in lymphatic vessels (lymph circulation), as well as a little fluid called transcellular fluid.



◆ Transcellular fluids are found in many places:

- Peritoneal cavity in the abdomen.
- Pericardial cavity in the heart.
- Pleural cavity around the lungs.
- Synovial fluid within synovial joints.
- Ocular fluid in the eye.
- Cerebrospinal fluid around the CNS.

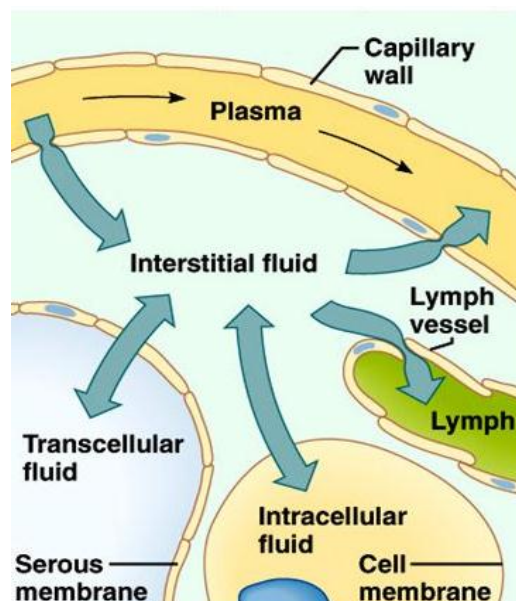
★ Movement of fluids between compartments

◆ Fluids aren't static, there's always an exchange of fluids between different compartments regulated by Osmotic pressure & Hydrostatic pressure.

- Osmotic pressure is the pressure which is created due to the difference in osmolality between these compartments.

- **The doctor didn't talk about any details regarding this figure, only to know that we have continuous movement of water between different compartments.

- The fluids of these compartments are isotonic, they have the same osmolality.



Fluid leaves plasma at arteriolar end of capillaries because outward force of hydrostatic pressure predominates

Fluid returns to plasma at venular ends of capillaries because inward force of colloid osmotic pressure predominates

Hydrostatic pressure within interstitial spaces forces fluid into lymph capillaries

Interstitial fluid is in equilibrium with transcellular and intracellular fluids

◆ Recall that when a solution has higher osmolarity it's called a hypertonic solution. While if it has lower osmolarity we call it a hypotonic solution.

Note Osmolarity is number of osmoles per liter, while Osmolality is number of osmoles per kg.

★Composition of body fluids

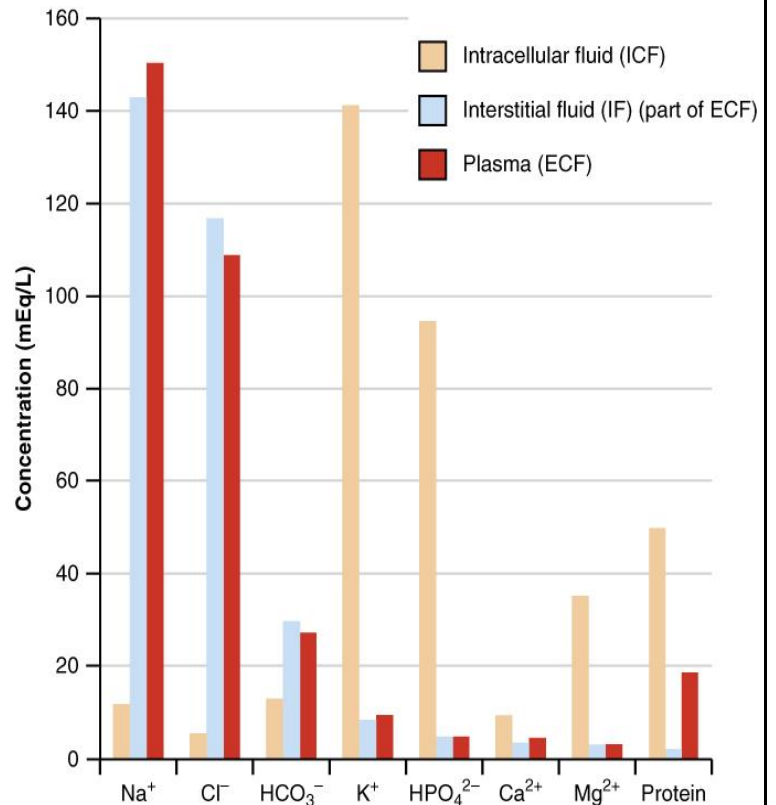
☞ Do we have the same constituents in all fluids of our body?

No, although these fluids are isotonic, constituents of these fluids are different.

-For example, regarding Potassium, we have much higher concentration of K^+ inside the cell than outside. On the other hand, we have much higher concentration of Na^+ within the extracellular compartments.

-There are also some differences between the different extracellular compartments regarding the concentration of substances.

-Also, we have a high amount of proteins inside the cell. But as you can see, the amount of proteins in the plasma are about 10 times more than these in the interstitial fluid. Why? Well, you only need to know that these proteins are important for the exchange between the plasma and the interstitial fluid by creating a pressure called oncotic/colloid pressure.



◆ Oncotic pressure: It's the pressure which is formed by the presence of proteins. Like the osmotic pressure but the main difference is that the osmotic pressure is due to the presence of electrolytes.

◆ Combining the osmotic pressure and the oncotic pressure we have what we call colloid osmotic pressure.

☞ Where do we have a higher colloid osmotic pressure, plasma or interstitial fluid?

In plasma, because of the presence of high amount of proteins compared to the interstitial fluid.

Note You may have 2 isotonic solutions that have different pressures because of the difference in the colloid osmotic pressure, caused by the presence of more proteins in one solution than the other.

★Water balance: Input & Output of water

◆ We have many mechanisms to gain and to lose water from our body, these mechanisms are in balance (homeostasis), thanks to our powerful regulatory system. So, the amount of water that leaves the body per day equals to the amount of water gained.

1. Water input.

◆ The volume of water gained daily varies among individuals, averaging about 2500 mL/day.

-we can gain water from many sources:

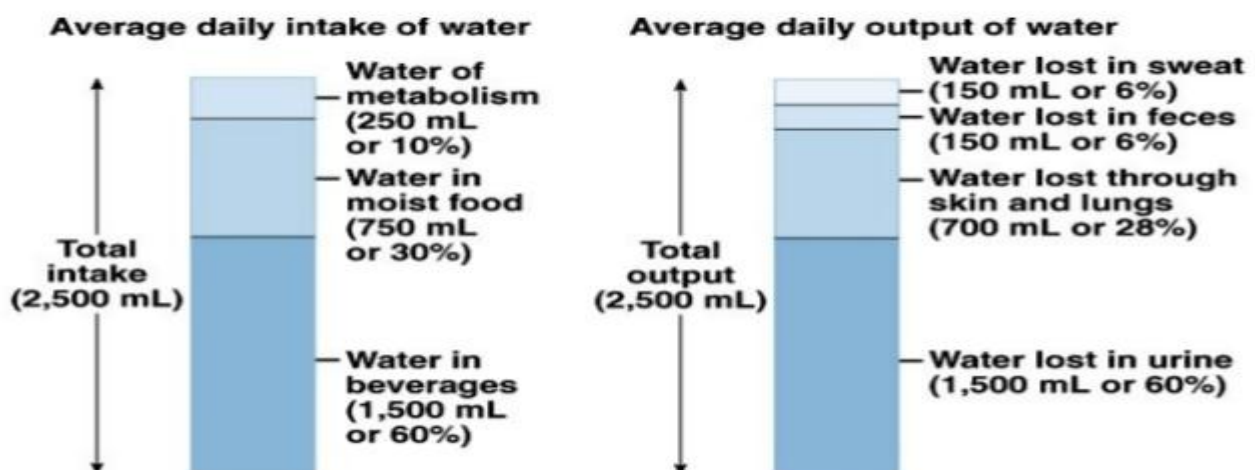
- a. Drinking (60%).
- b. Eating moist food (30%).
- c. As a final product of oxidative metabolism of nutrients (burning glucose for example produces water), we call it water of metabolism (10%).

2. Water output.

◆ Water normally enters the body only through the mouth, but it can be lost by a variety of ways, these include:

- a. Urine (60%).
- b. Feces (6%).
- c. Sweat (sensible loss) (6%).
- d. Evaporation from the skin (insensible loss). →
- e. The lungs during breathing. →

Together, they account for 28% of water lost from the body



Note Water can be lost from the skin by either sweating or evaporation.

-Sweating is a sensible perspiration, simply means that you can sense the loss of water. While evaporation is an insensible perspiration that you can't sense water loss.

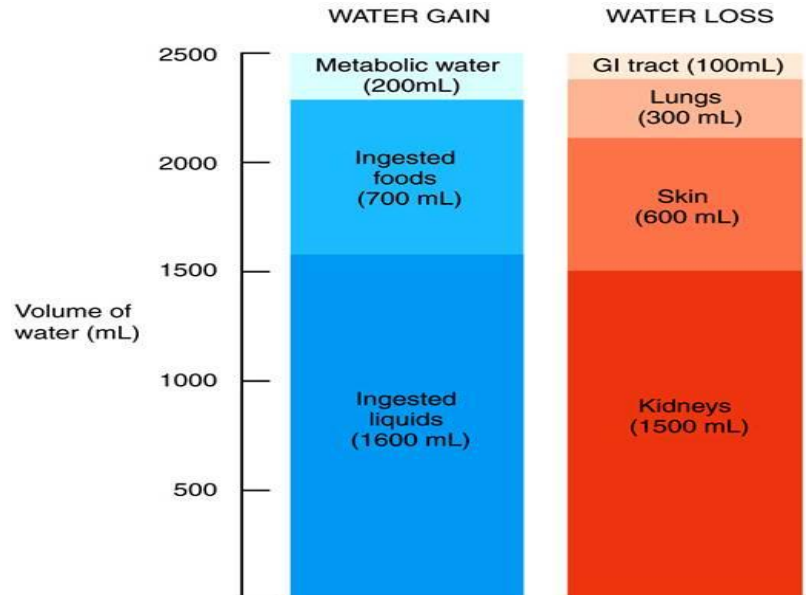


Figure 27.02 Tortora - PAP 12/e
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★Water and electrolytes homeostasis

◆There are many systems that regulate fluids and electrolytes, such as:

1. Kidneys.
2. Cardiovascular system.
3. Endocrine → Hormones of the pituitary, parathyroid, and adrenal glands interfere with water homeostasis.
4. Lungs → They regulate the loss of water.

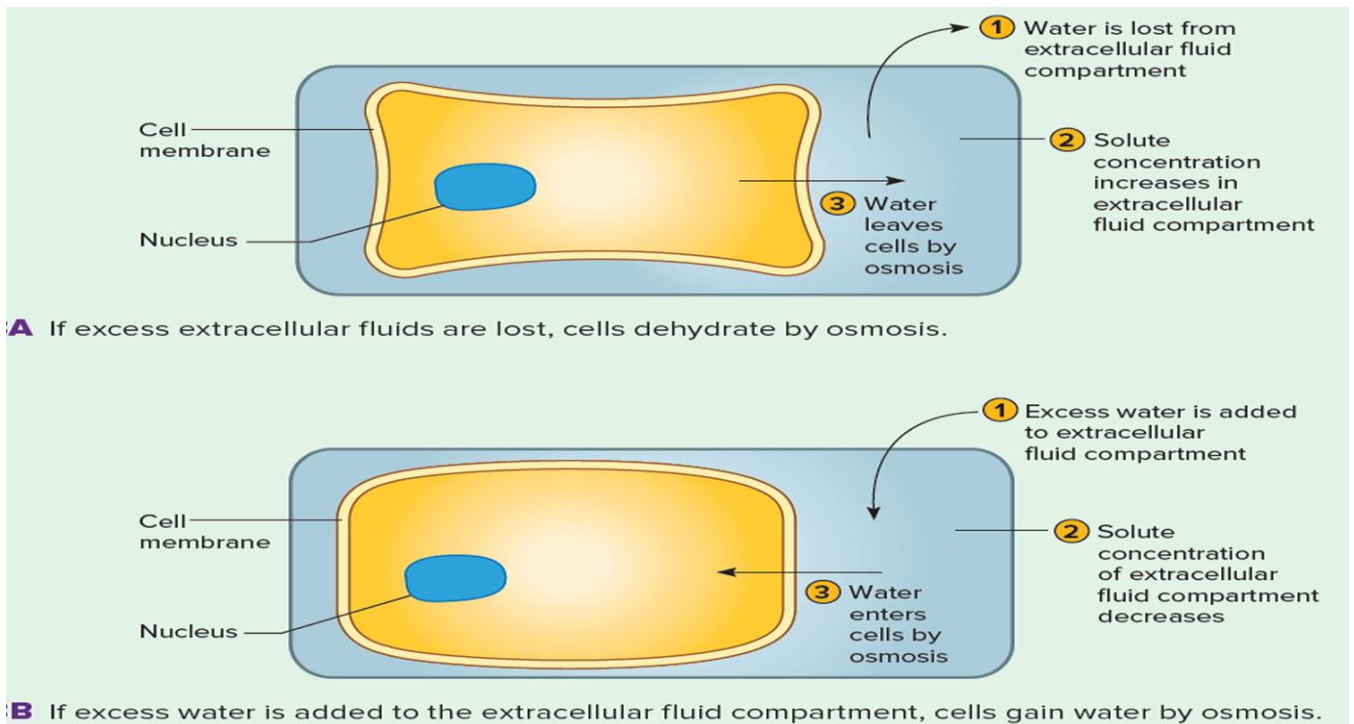
↪ We said that we have exchange of water between different compartments due to different forces (osmotic & hydrostatic pressures), what establishes these forces? (how are we regulating them?)

By the regulation of the volume of the extracellular fluid, also by the regulation of osmolality.

◆Between these 2 regulating methods we have a lot of overlapping, means if we change the volume, we will have interference from the osmolality and vice versa. (see the figure in the next page for details).

★Regulation of electrolytes & water

☛Refer to slide 16 if you are more satisfied with the figure that is in the slides.



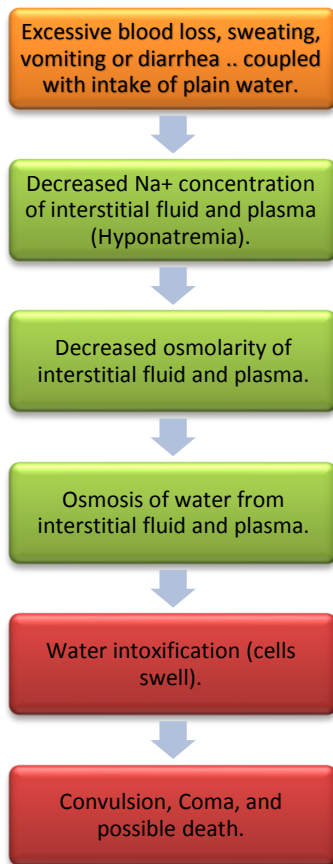
◆ **Consequences of dehydration:** In the first case, let's say we have an excessive loss of hypotonic water (water with only a small concentration of electrolytes) from the extracellular fluid. The extracellular osmotic pressure (concentration of solutes) will increase, becoming hypertonic to intracellular fluid, so water leaves the cell by osmosis causing the cell to shrink.

◆ **Consequences of hypotonic hydration:** In the second one, we add excess hypotonic water to the extracellular fluid (again water with a small concentration of electrolytes) causing its osmotic pressure (concentration of electrolytes) to decrease, becoming hypotonic to the intracellular fluid, so water enters the cell by osmosis causing the cell to swell.

Note -If more water than solutes is lost from the extracellular fluid (hypotonic solution is lost) → cell shrinks.

-If more water than solutes is gained by the extracellular fluid (hypotonic solution is gained) → cell swells.

Note Na⁺ & Cl⁻ are the main determinants of the osmolality in our body.



◆ In some cases, we might have a loss of a lot of water with some electrolytes but have an intake of water with less electrolytes. The extracellular fluid will thus have lower osmotic pressure (lower concentration of solutes) than before, becoming hypotonic to the intracellular fluid. This results in water entering the cells from the extracellular fluid by osmosis, causing cells to swell. In the case of neural cells, this might lead to convulsion, coma, it could even lead to death.

If you have any question, please feel free to ask.

Wishing that happiness, success, and good luck be always with you☆.

لا تنسونا من صالح دعائكم 🌸