Physiology of the renal system

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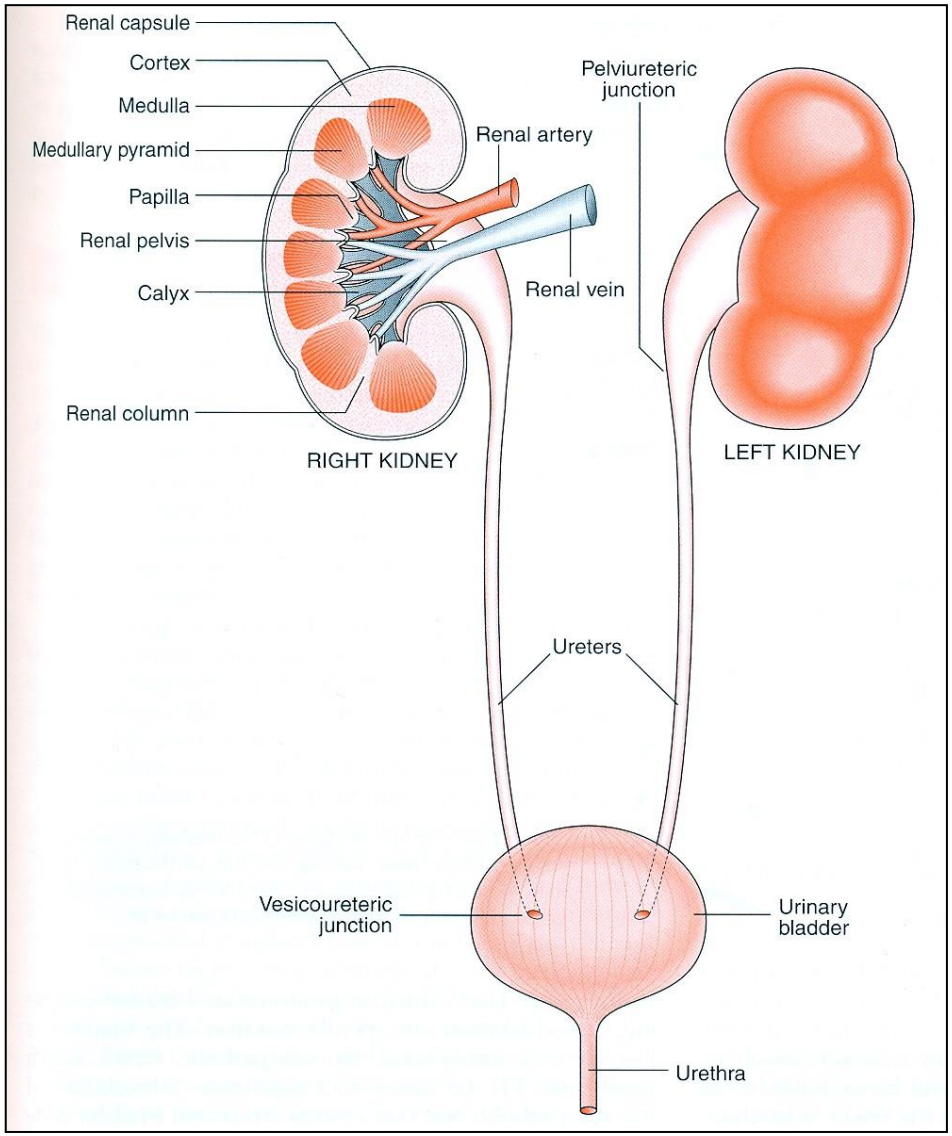


Anatomy of renal system:

kidneys – uretes – urinary bladder - urethra

Anatomy of kidneys

cortex-medulla

Medullary pyramids

Calyx - pelvis

Renal artery – renal vein

The functional unit of the kidneys are the nephrons

Kidney function: Homeostasis of body fluids

The maintenance of constant volume and composition of the body fluid compartments and their temperature in warm-blooded animals and humans

Renal functions:

1. regulate volume, composition of body fluids

2. produce and secrete three hormones (renin, calcitriol, erythropoietin)

renin *is an enzyme which helps regulate blood pressure –* ***calcitriol****, a metabolite of vitamin D, is necessary for calcium absorption and bone formation –* ***erythropoeitin*** *stimulates red blood cell formation*

3. excrete end products (urea, uric acid, creatinine), metabolites of hormones and drugs

Patients with chronic kidney disease, may have bone formation abnormalities and anemia.

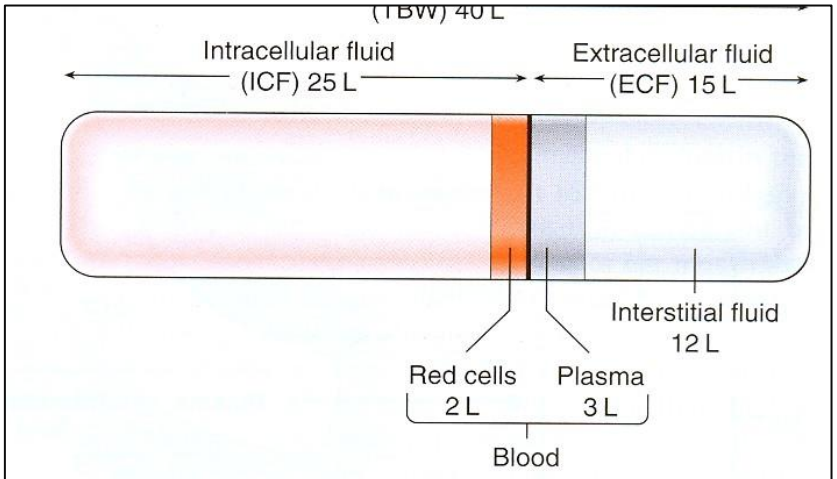


Fig. 2.1 Compartments of distribution of total body water. Approximate volumes (in litres) are shown for an average adult.

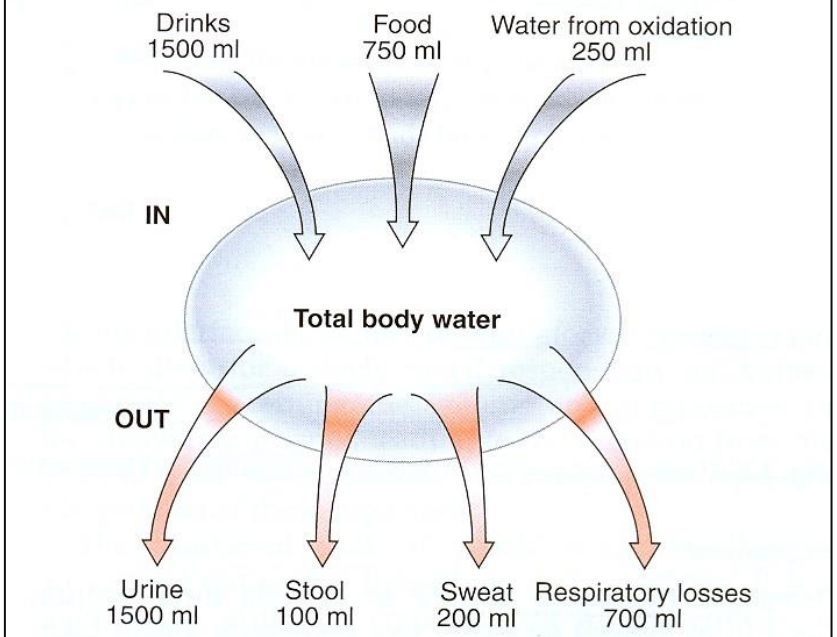


Fig. 2.2 Typical fluxes involved in daily water balance.

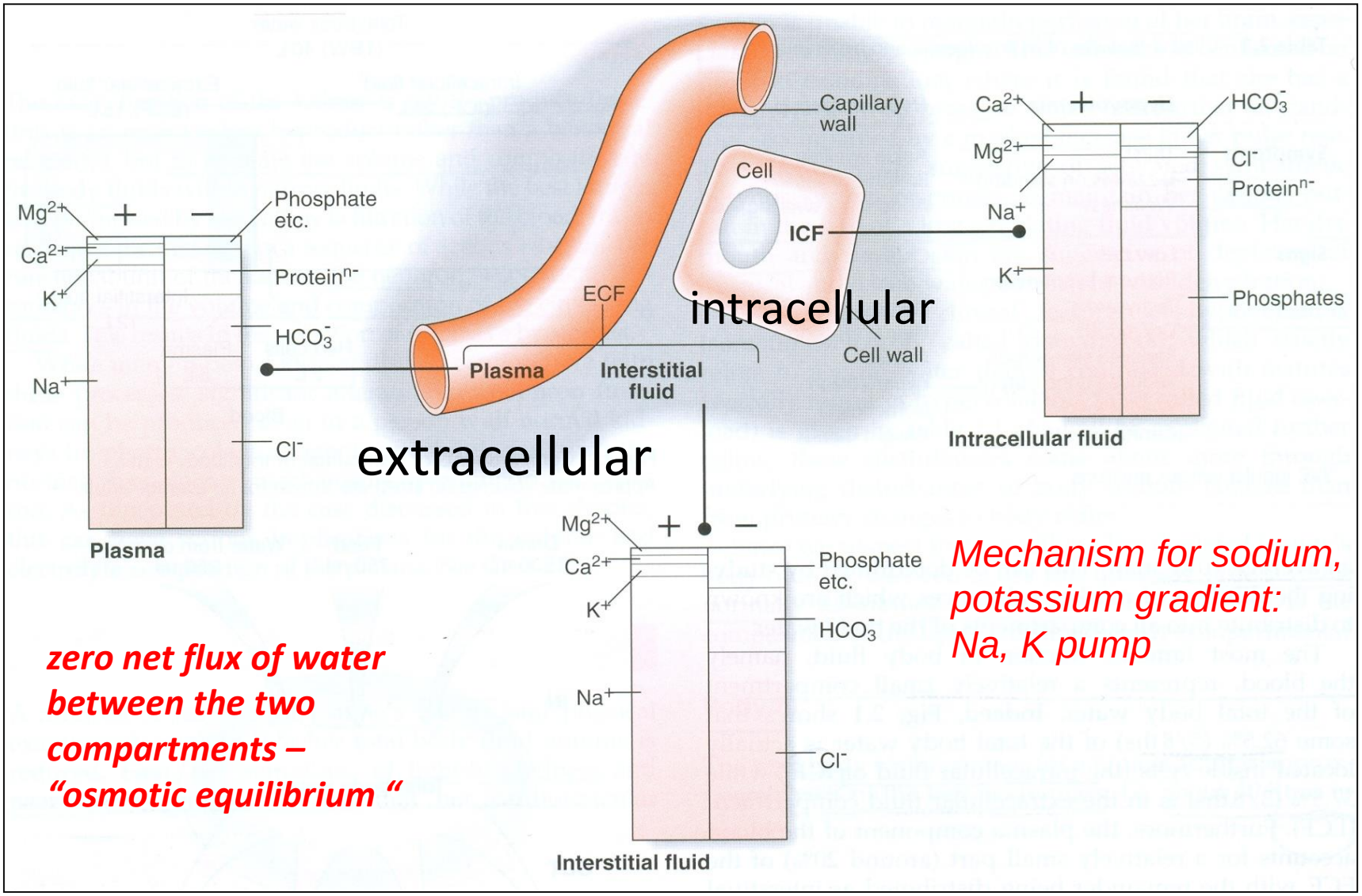
Body fluid compartments

Daily water balance

The kidneys regulate the daily output of urine

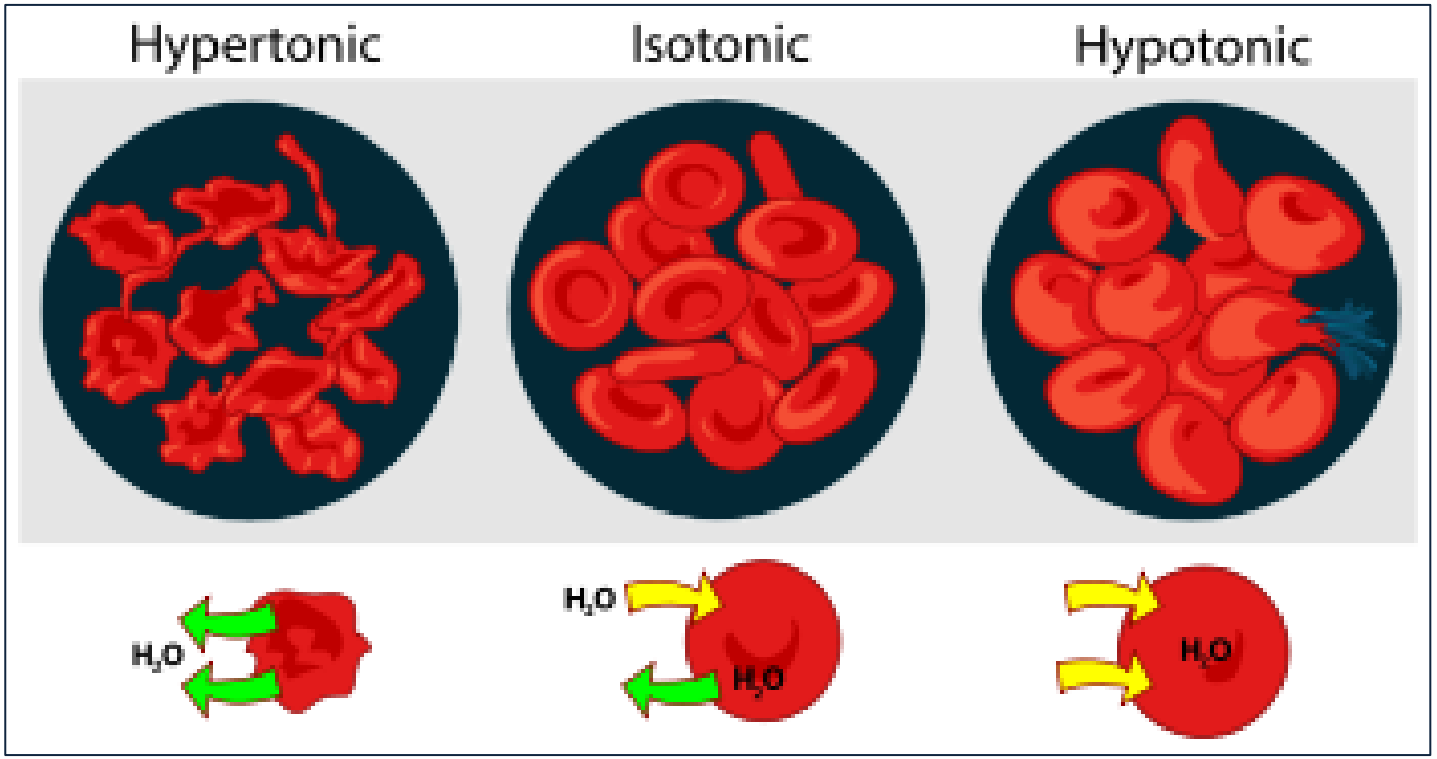
The Renal Physiology – Basic Sciences and Clinical Conditions
Michael Fields, Carol Pollock, David Harris – Elsevier, Second Edition, 2010

Chemical composition of body fluid compartments



zero net flux of water between the two compartments – "osmotic equilibrium "

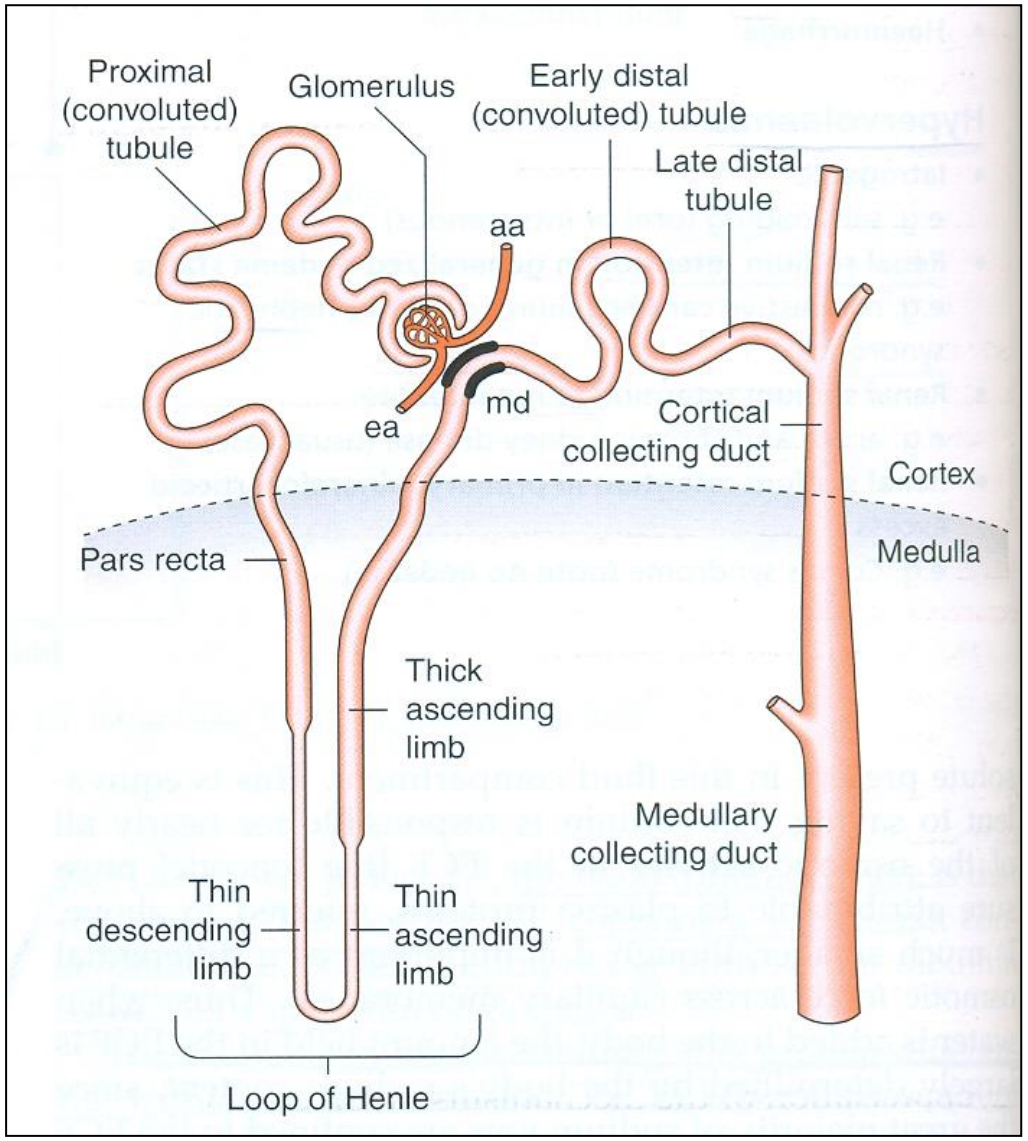
Mechanism for sodium, potassium gradient: Na, K pump



- *A hypertonic extracellular compartment results in shrinkage of cells*
- *A hypotonic extracellular compartment results in swelling of cells*

- *Sodium being the dominant ion in the ECF (95%) is responsible for the osmotic activity in ECF*

Anatomy of the nephron



1.2 million nephrons in each kidney

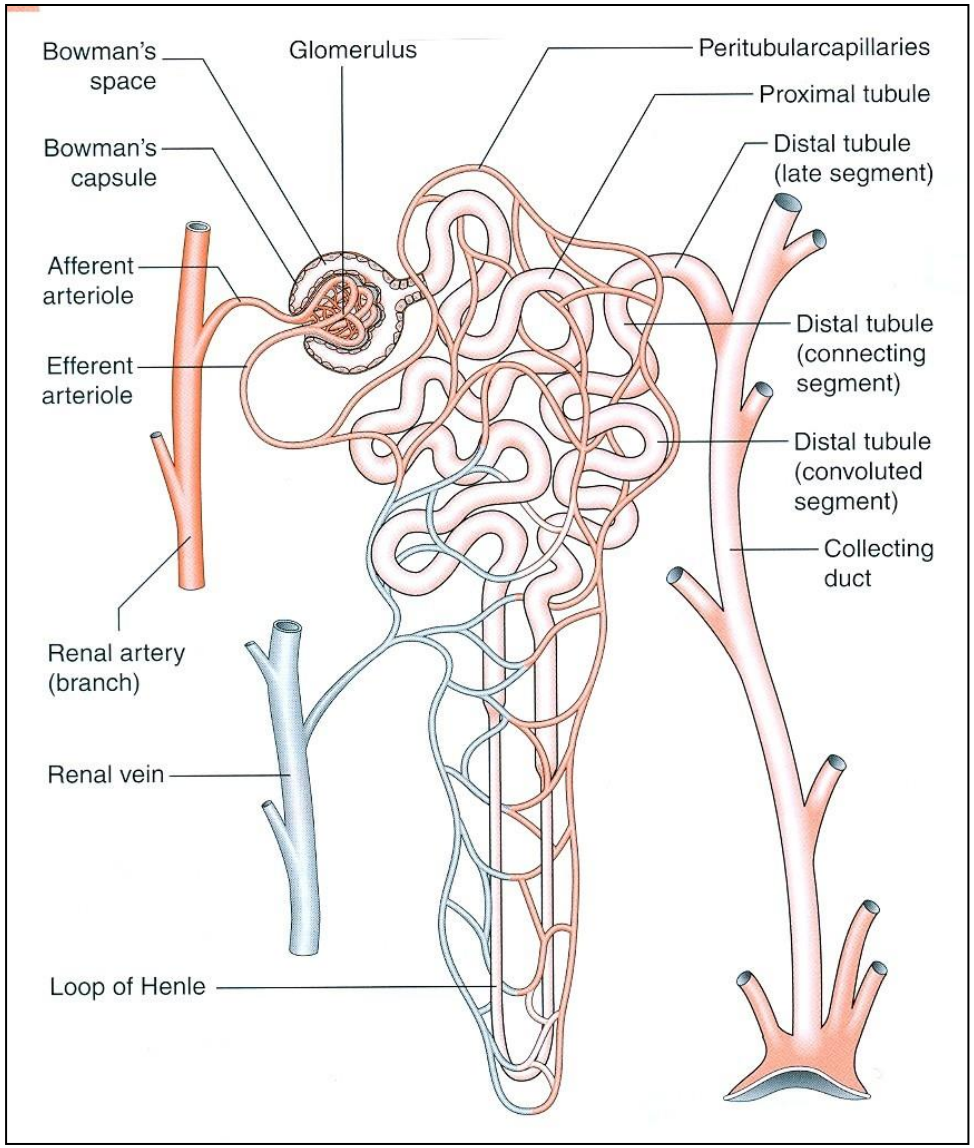
- *Glomerulus (a tuft of specialized capillaries) - afferent – efferent arteriole*

- *Tubule - Bowman's capsule*

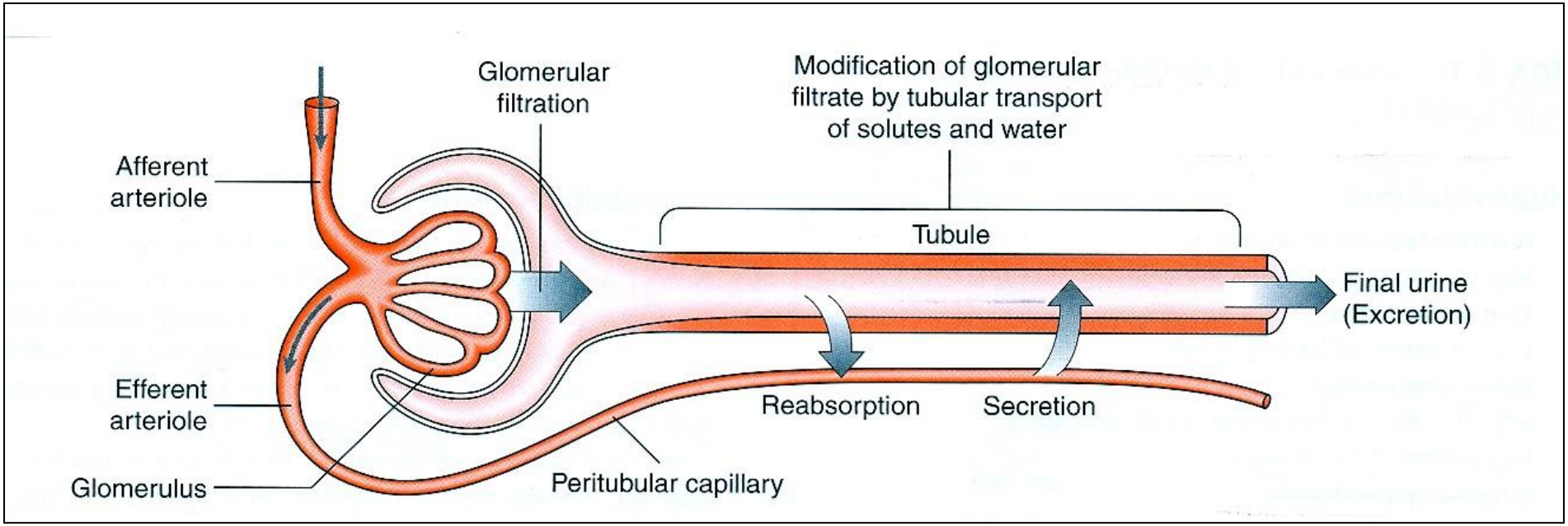
Renal tubule (specialized epithelial cells):

- Proximal
- Loop of Henle (thin descending, thin, thick ascending)
- Distal
- Collecting duct

Anatomy of the nephron showing relationship between vascular and tubular structures

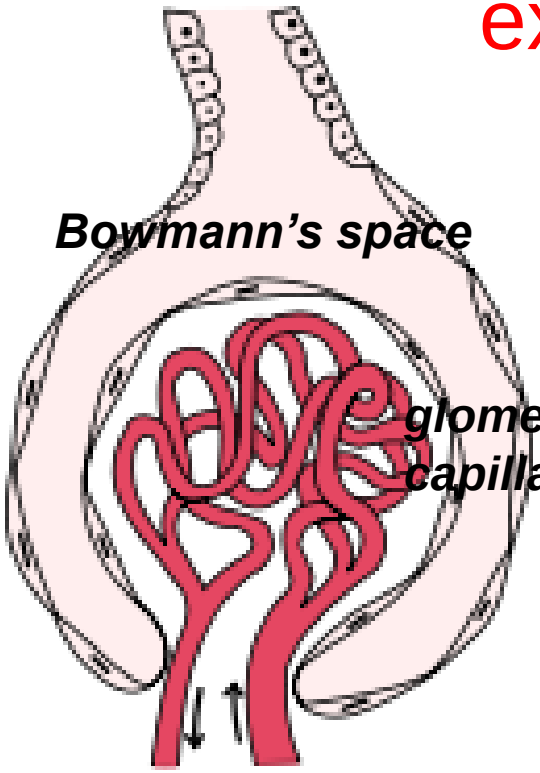


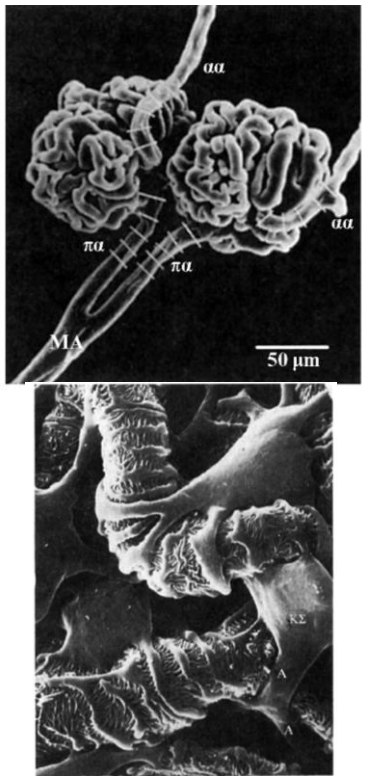
Three processes take place in all nephrons and determine the composition of urine

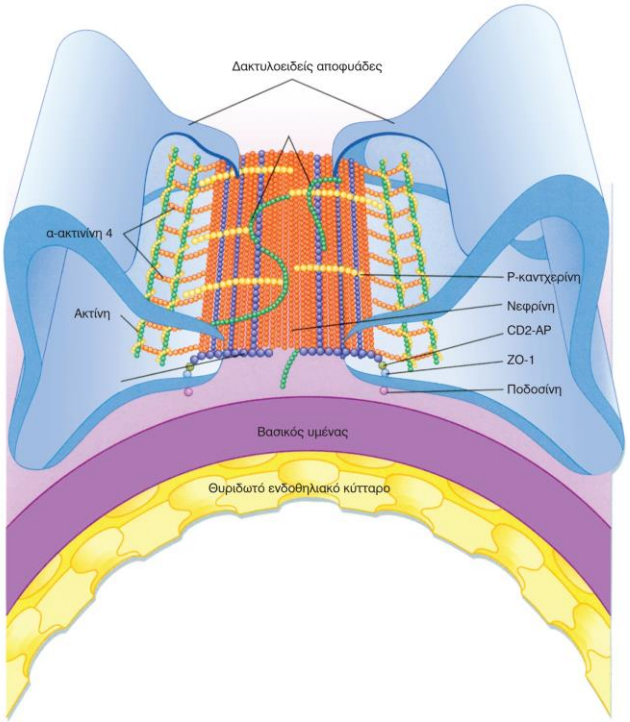


1. Glomerular filtration: passive movement of fluid from glomerulus to Bowman's space - the first step in the formation of urine - a clear fluid (ultrafiltrate) is produced – *blood cells and proteins are excluded*
2. Tubular reabsorption (99%)
3. Tubular secretion

The glomerular filtration barrier excludes blood cells and proteins

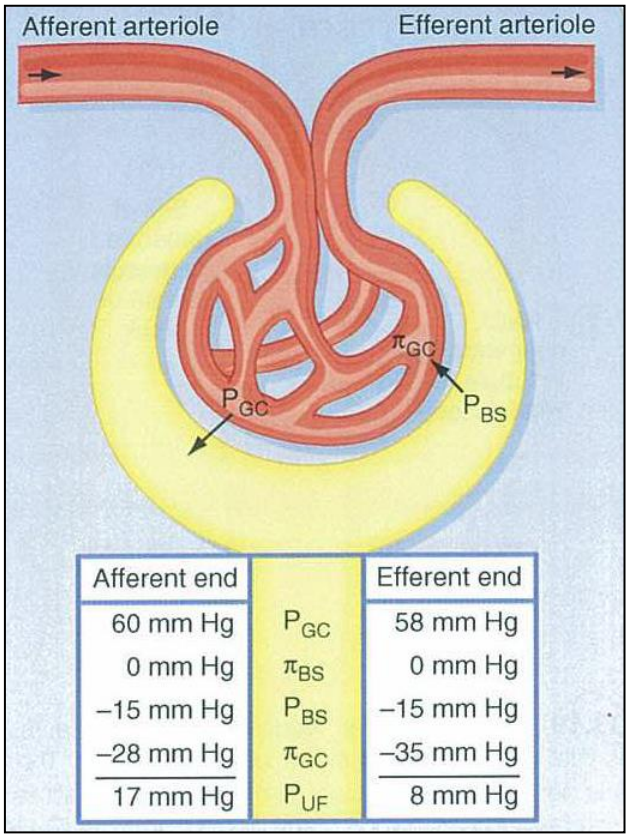






The filtration barrier consists of 1. *capillary endothelial cells*, 2. *epithelial cells (podocytes) of the inner wall of Bowmann's capsule*, 3. *basement membrane (matrix of negatively charged proteins).*

Protein may appear in the urine (proteinuria) when there is failure of the glomerular filtration barrier or when tubular cells are damaged – nephrotic syndrome

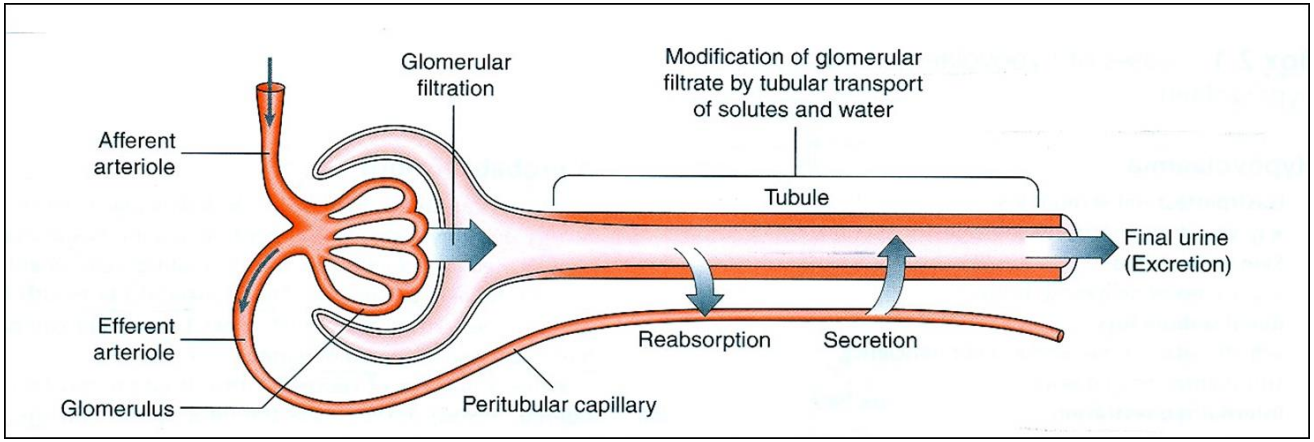


The filtration process is based on passive forces.

Ultrafiltration occurs because the Starling forces (hydrostatic and oncotic pressures) combine to drive fluid from the lumen of glomerular capillaries across the filtration barrier and into the Bowmann's space.

The **hydrostatic pressure in the glomerulus** is the principal driving force, opposed by two pressures, the hydrostatic pressure in Bowmann's space and the oncotic pressure in the glomerulus (due to proteins in the glomerulus).

Glomerular filtration rate – **GFR**
volume of fluids filtered by the kidneys every day

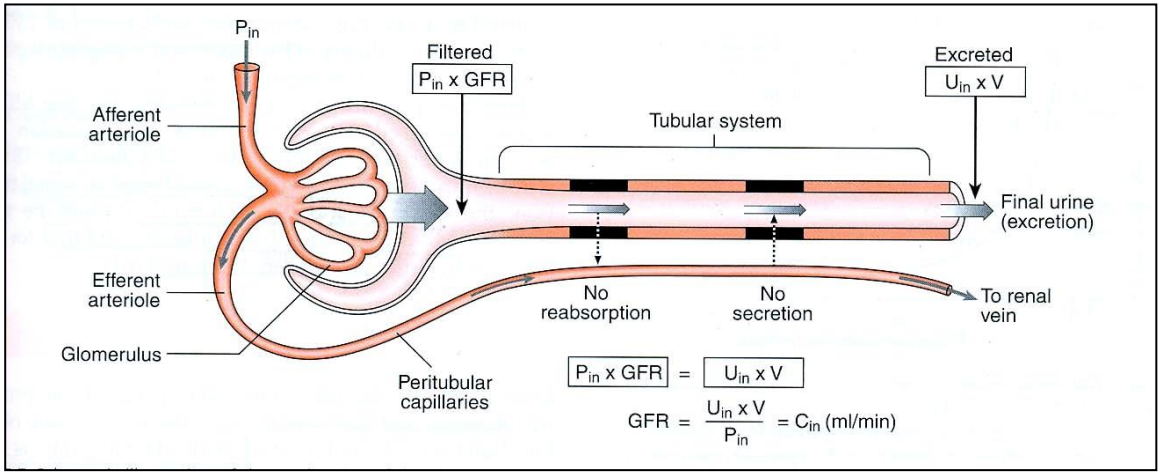


GFR is equal to the sum of the filtration rates of all functioning nephrons. GFR is on average **180 L /day** or **125 ml/min** in a 70kg man.

GFR depends on sex, age, weight (130-200 L /day in man, 115-180 L/day in women)

A fall in GFR means a kidney disease is progressing. End stage renal disease: GFR < 10% of normal, hemodialysis or renal transplantation.

Measuring GFR is important in the clinic



Creatinine is used to estimate GFR.

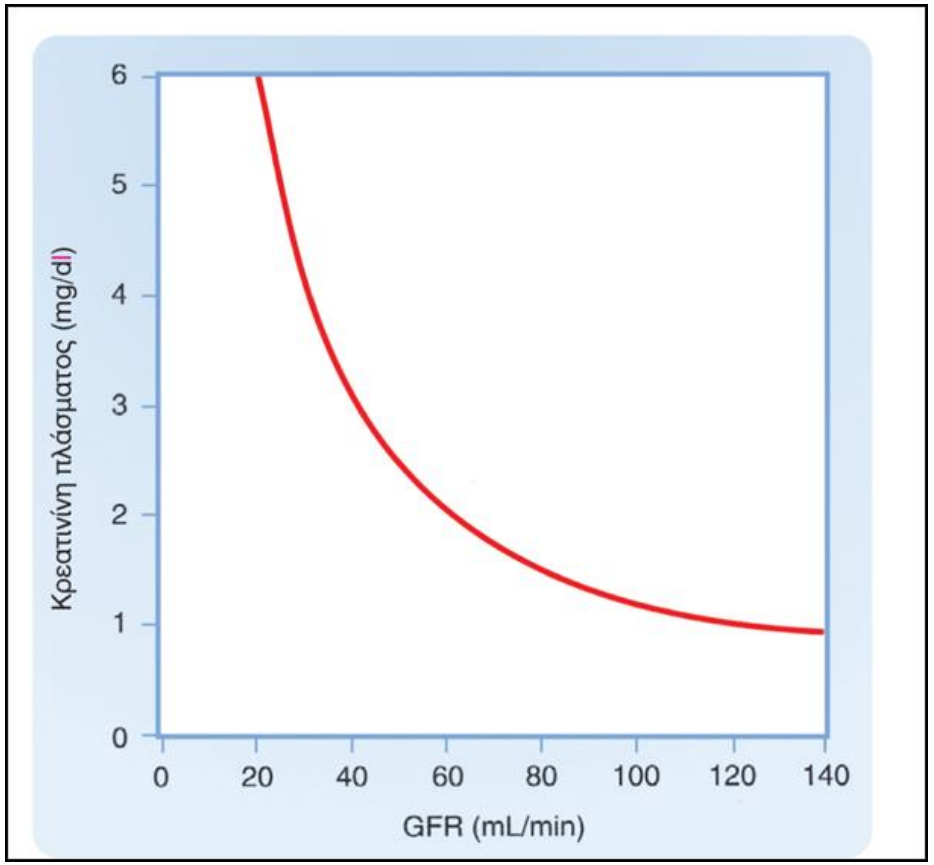
Creatinine is produced at a *constant rate* by the muscle.

It is freely filtered at the glomerulus.

It is *NOT reabsorbed or secreted by the renal tubule*.

The amount excreted equals the amount filtered.

Blood creatinine is used to measure GFR



Curve showing the relationship between plasma creatinine and GFR (ml/min)

An increase in plasma creatinine indicates a substantial decrease in GFR

Estimated GFR includes age, sex, body size and race.

https://www.kidney.org/apps/professionals/egfr-calculator.

Water and solute transport along the tubule

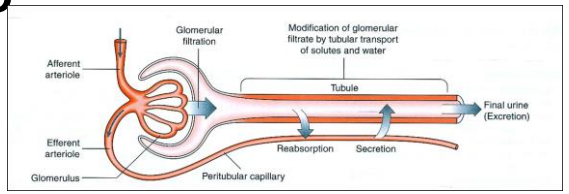


TABLE 34.1 Filtration, Excretion, and Reabsorption of Water, Electrolytes, and Solutes by the Kidneys

Substance	Measure	Filtered[a]	Excreted	Reabsorbed	% Filtered Load Reabsorbed
Water	L/day	180	1.5	178.5	99.2
Na^+	mEq/day	25,200	150	25,050	99.4
K^+	mEq/day	720	100	620	86.1
Ca^{++}	mEq/day	540	10	530	98.2
HCO_3^-	mEq/day	4320	2	4318	99.9+
Cl^-	mEq/day	18,000	150	17,850	99.2
Glucose	mmol/day	800	0	800	100.0
Urea	g/day	56	28	28	50.0

180 liters of fluid is filtered by the human glomeruli.
Less than 1% of filtered water and sodium chloride and variable amounts of other solutes are excreted in the urine.
The processes of reabsorption and secretion determine the volume and composition of the urine.
Transport proteins in cell membranes of epithelial cells of renal tubules.
Reabsorption of NaCl and water are major functions of nephrons.

Sodium (Na^+) transport along the nephron

Daily food intake of Na^+ : 100 mEq

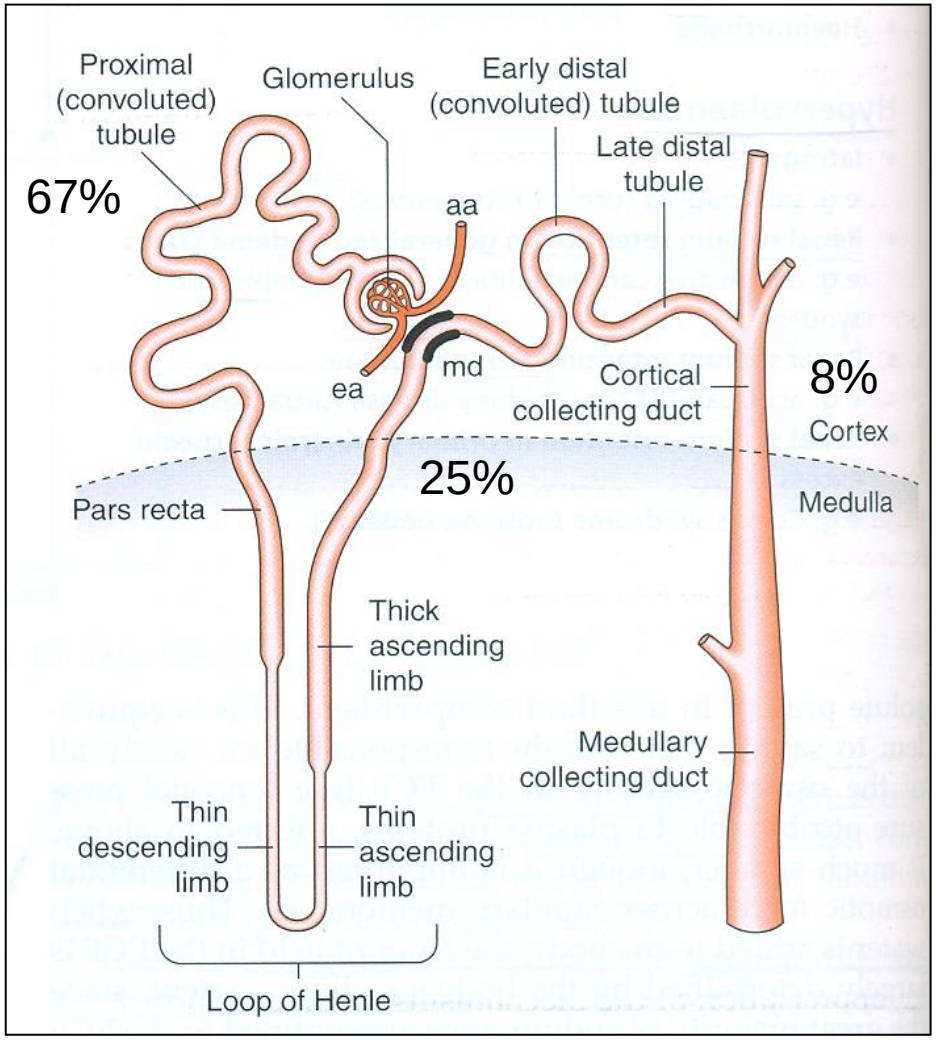
99.5% of filtered Na^+ is reabsorbed by the renal tubule

Na^+ excreted in the urine is 50-130 mEq/day - small amount lost through gut and skin

The amount of Na^+ that enters our body is excreted in the urine.

The kidneys are responsible for sodium homeostasis

Na^+ and water transport along the nephron



Proximal tubule

67% of water, Na^+, Cl, K and other solutes are reabsorbed, virtually all glucose and amino acids are reabsorbed.

Henle's loop

25% of filtered NaCl and
15% of water are reabsorbed

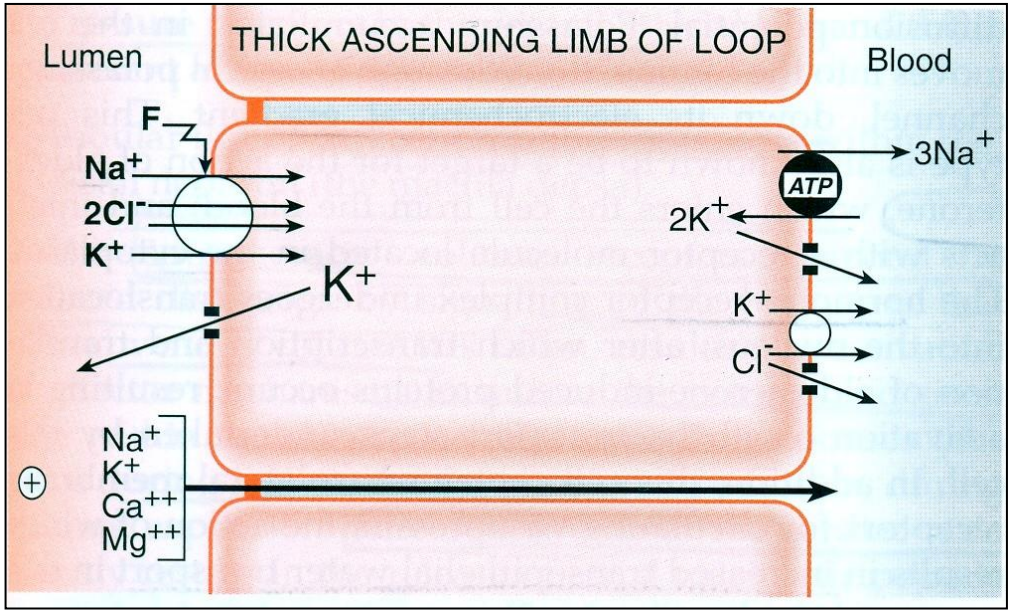
Differences in reabsorption between the two limbs are important for urine concentration.

Distal tubule and collecting duct

8% of NaCl, variable amounts of water (8%-17%) are reabsorbed.

Water is reabsorbed by osmosis through aquaporin water channels (AQP) of epithelial cells or between cells.

The transport mechanisms of Na are different along the nephron - Na^+ reabsorption in ascending limb of loop of Henle



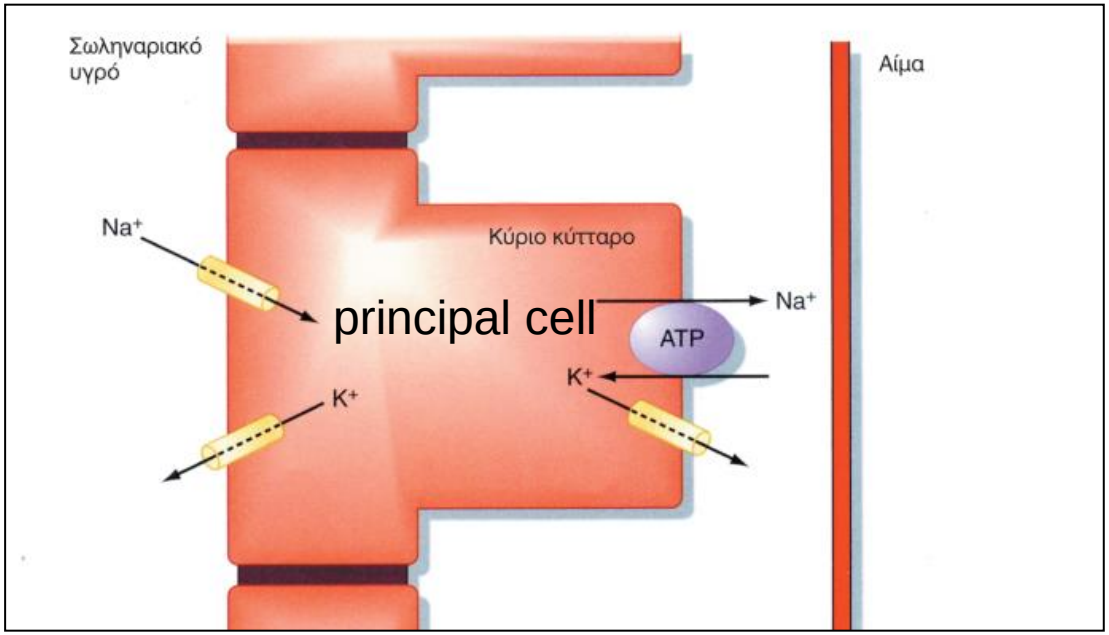
Na^+ enters the cell by a triple co-**transporter** in apical membrane.

Na^+ exits the cell by a Na^+-K^+ pump in basal membrane.

This nephron segment is impermeable to water.

Na^+ transport is inhibited by diuretics (drugs).

Na^+ reabsorption by principal cells of collecting duct (distal nephron)

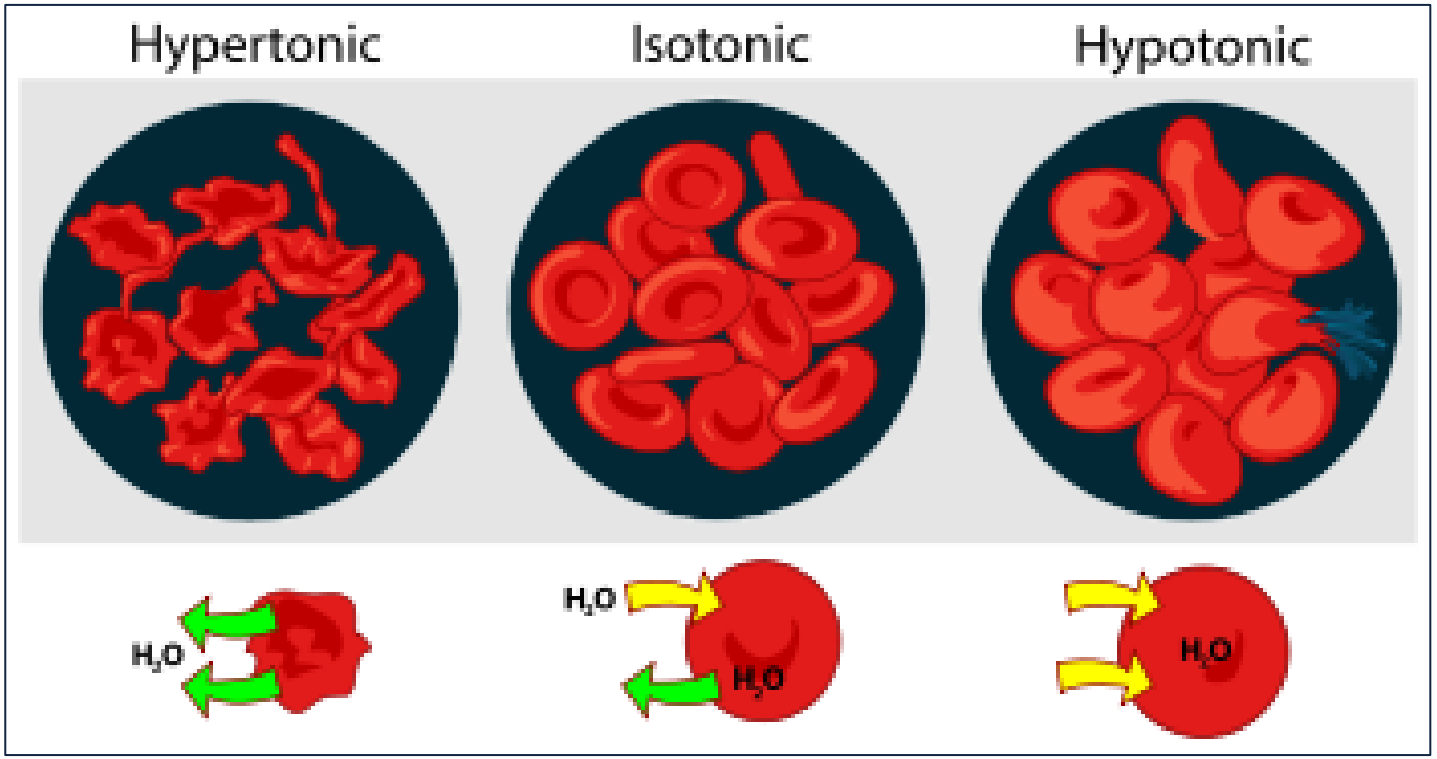


Na^+ enters the cell by Na^+ channels in apical membrane

Na^+ exits the cell by the Na-K pump in basal membrane

The steroid hormone aldosterone stimulates Na^+ reabsorption
The hormone vasopressin stimulates water permeability

Control of body fluid osmolality: urine concentration and dilution



- *A hypertonic extracellular compartment results in shrinkage of cells*
- *A hypotonic extracellular compartment results in swelling of cells*

- *Sodium being the dominant ion in the ECF (95%) is responsible for the osmotic activity in ECF*

Control of body fluid osmolality: urine concentration and dilution

Water constitutes 60% of adult human body divided in two compartments (ICF, ECF).

ICF and ECF are in osmotic equilibrium because of high permeability of most cells to water.

Water intake occurs orally.

The kidneys are responsible for regulating water balance – the major route for water elimination from our body.

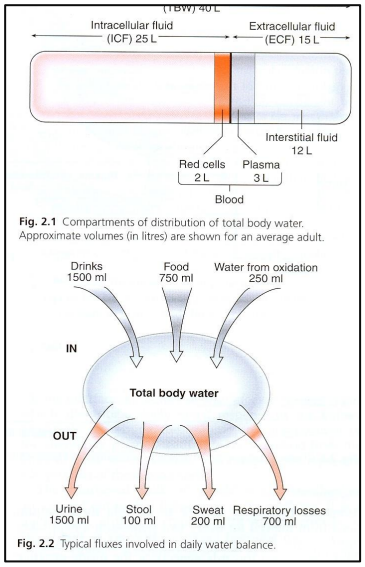
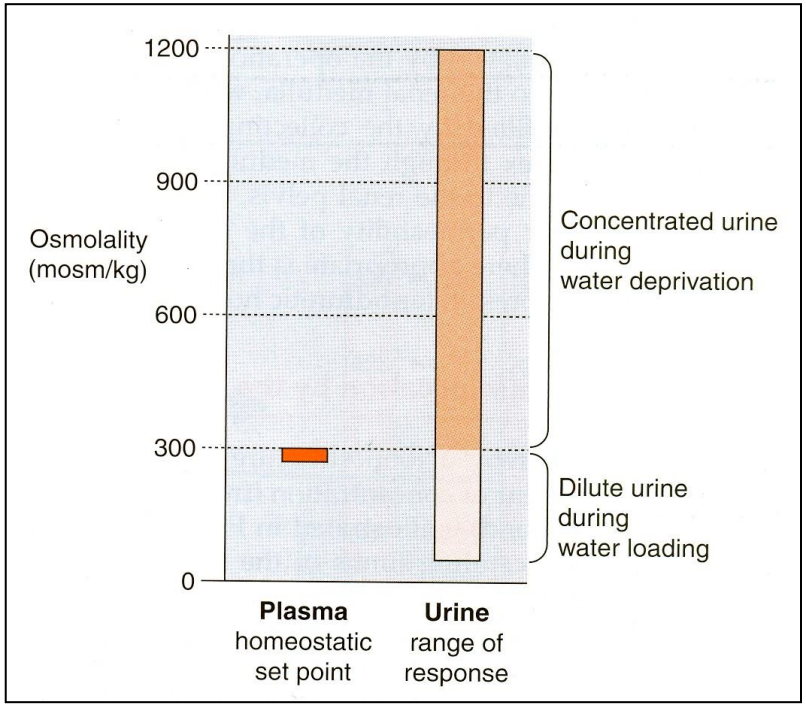


Fig. 2.1 Compartments of distribution of total body water. Approximate volumes (in litres) are shown for an average adult.

Fig. 2.2 Typical fluxes involved in daily water balance.



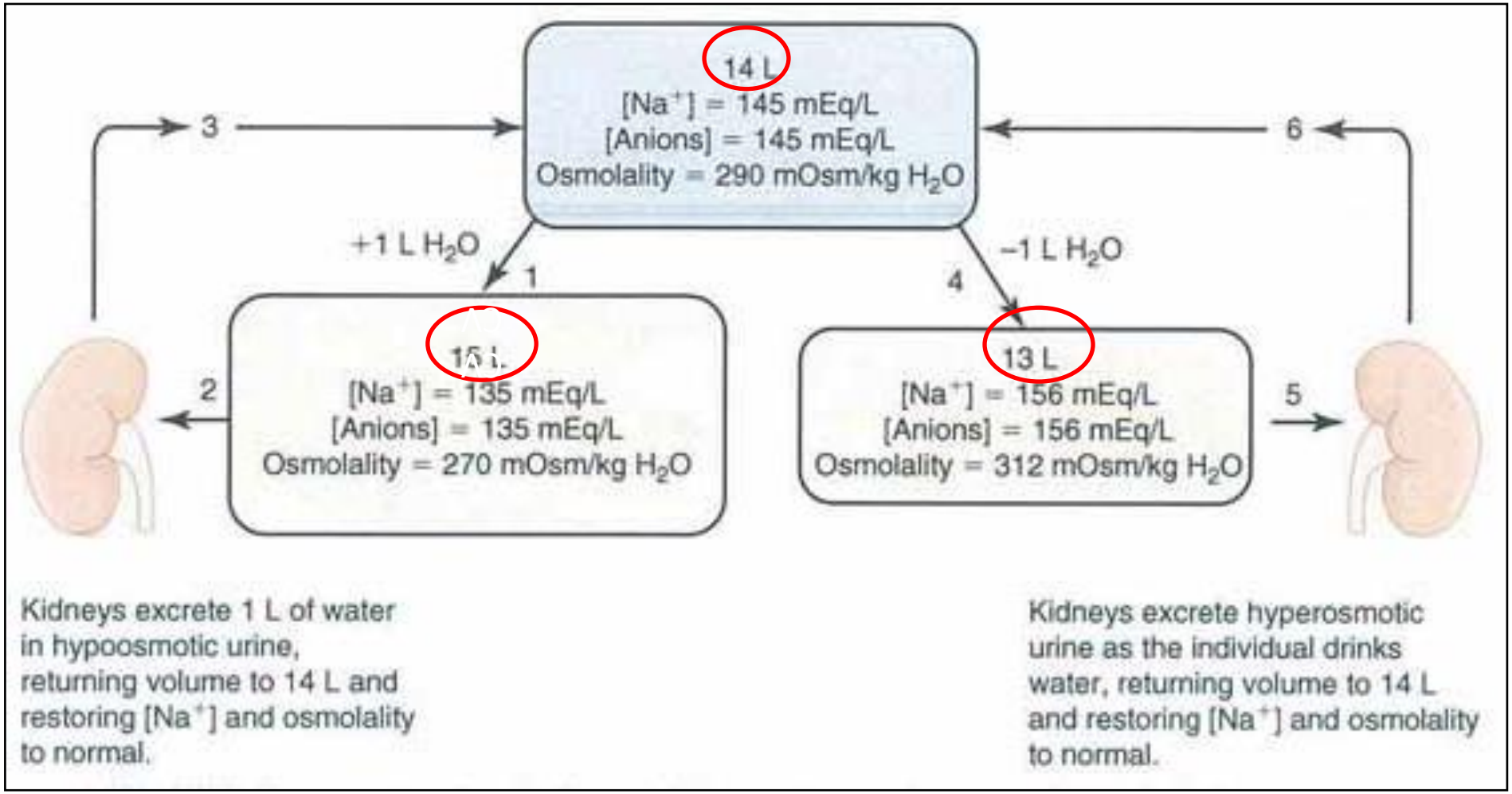
Normal range of plasma osmolality*:
285-295 mOsm/kg water.

The kidneys maintain the osmolality of body fluids within a narrow range by regulating the excretion of water.

Urine osmolality varies from 50 to 1200 mOsm/Kg. The kidneys produce hypoosmotic (dilute) or hyperosmotic (concentrated) urine.

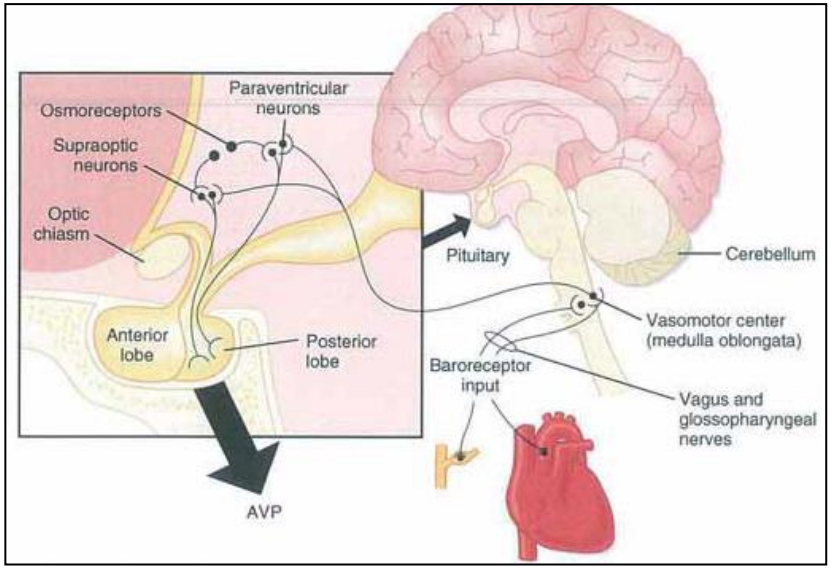
*refers to the osmotic pressure generated by the number of molecules dissolved in 1 kg of solvent

Kidney response to changes in water balance



What are the mechanisms that restore plasma osmolality?

Hormone AVP and thirst

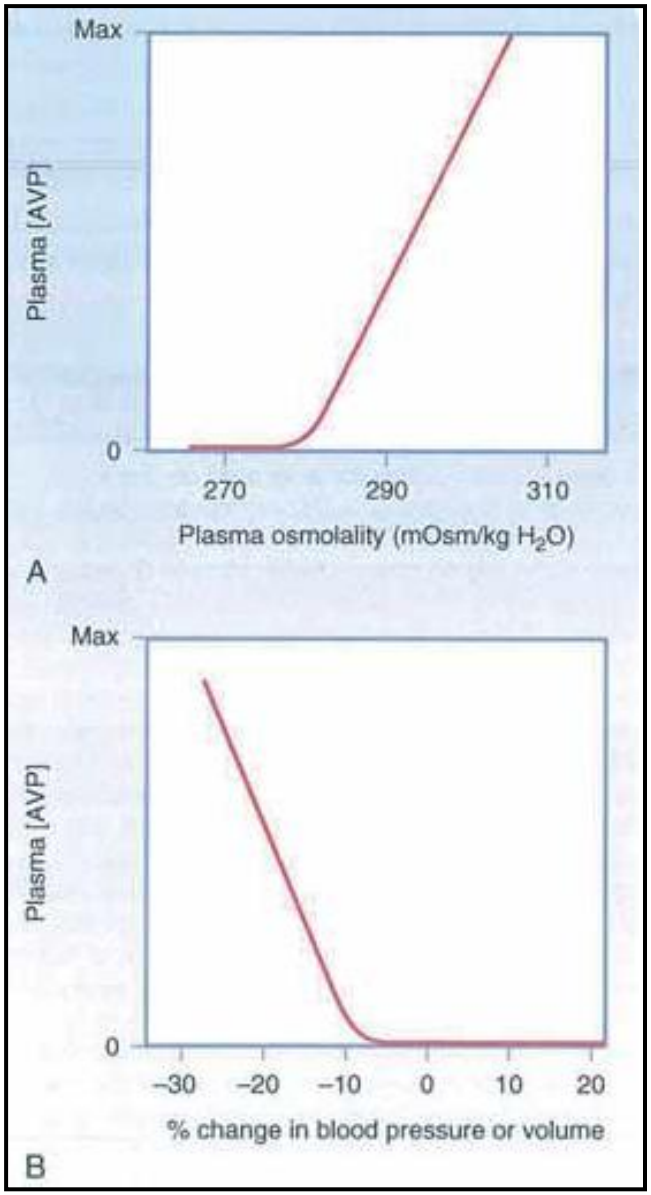


Osmotic and nonosmotic control of AVP secretion

- Hormone vasopressin, AVP (or arginine-vasopressin or antidiuretic hormone) secreted by the brain.

Osmoreceptors in hypothalamus monitor changes in osmolality - the osmoreceptors send signals to AVP synthesizing neurons in hypothalamus – AVP is secreted by the pituitary gland.

Relationship between plasma osmolality, blood pressure and AVP



Osmotic control of AVP secretion:

AVP is secreted when plasma osmolality increases above a set point.

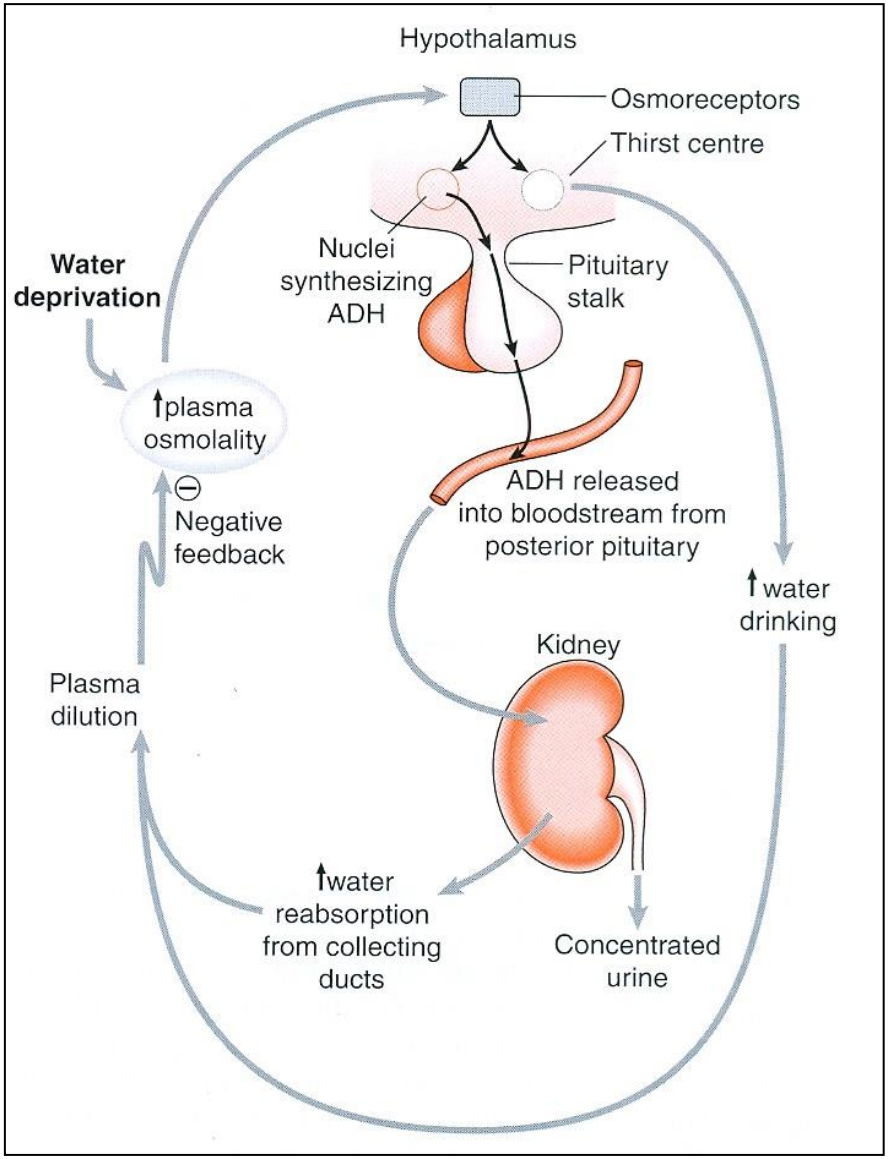
The set point ranges from 275 to 290 mOsm/Kg and varies among individuals.

Steep linear rise in AVP as osmolality passes above set point.

Nonosmotic control of AVP secretion:

A decrease in blood volume also stimulates AVP secretion.

Feedback control mechanism of plasma osmolality

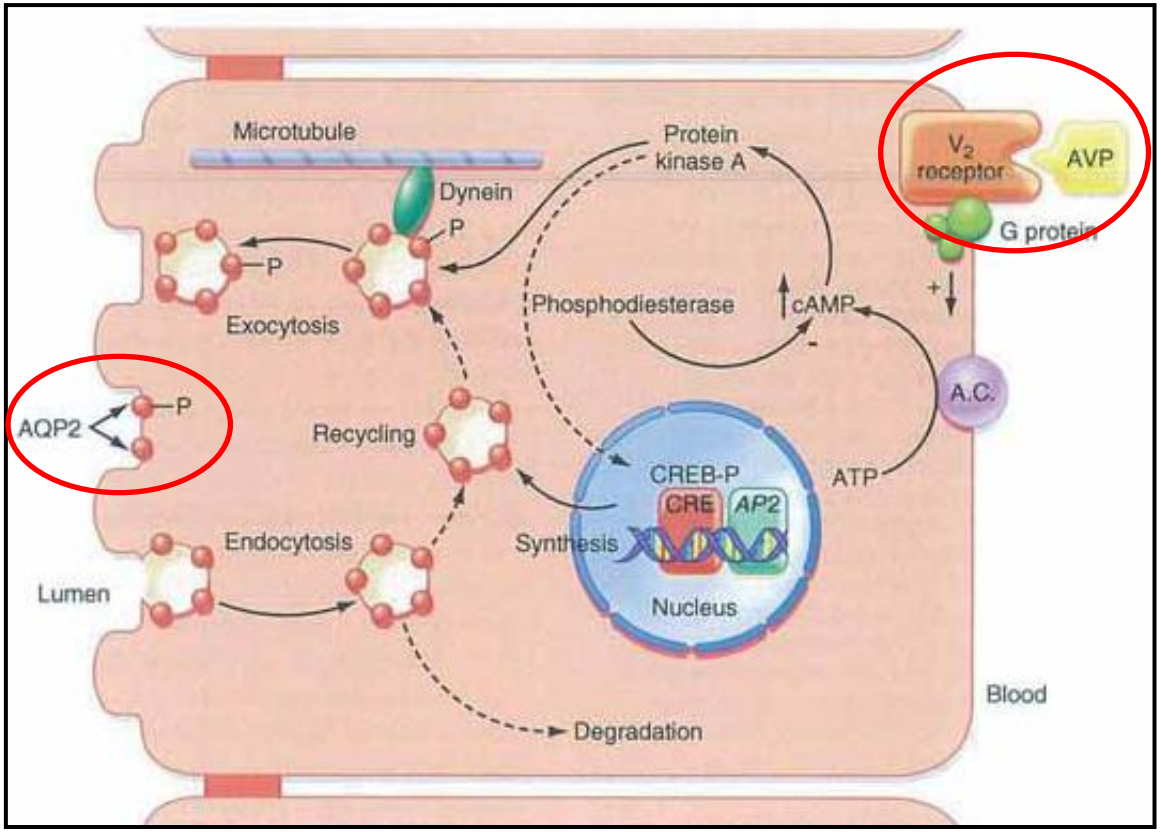


Water deprivation increases plasma osmolality - osmoreceptors sense changes in osmolality and signal synthesis and release of AVP (ADH) by pituitary gland.

AVP increases water permeability of collecting ducts of nephrons by adding aquaporins (water channels) on apical membrane of collecting duct cells.

Changes in plasma osmolality and blood volume or pressure leads to thirst – thirst center in hypothalamus

Water reabsorption from kidneys and water drinking restores plasma osmolality to normal (negative feedback)

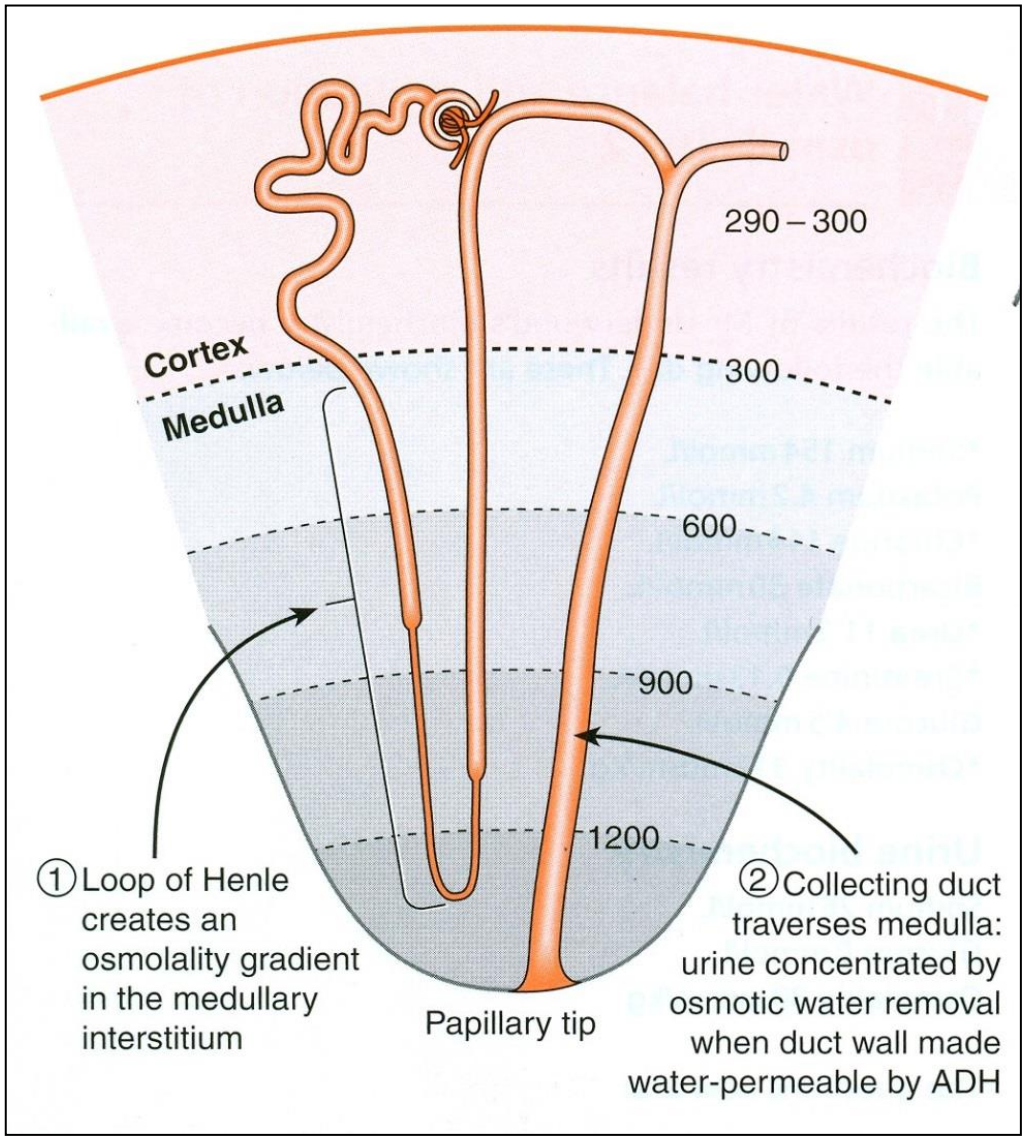


When AVP binds to its receptor aquaporin water channels (AQP) insert in the apical membrane, allowing water to enter the cell from the tubule lumen.

In the presence of AVP distal nephron is highly permeable to water and a concentrated urine is excreted by the kidneys.

In the absence of AVP the distal nephron is impermeable to water.

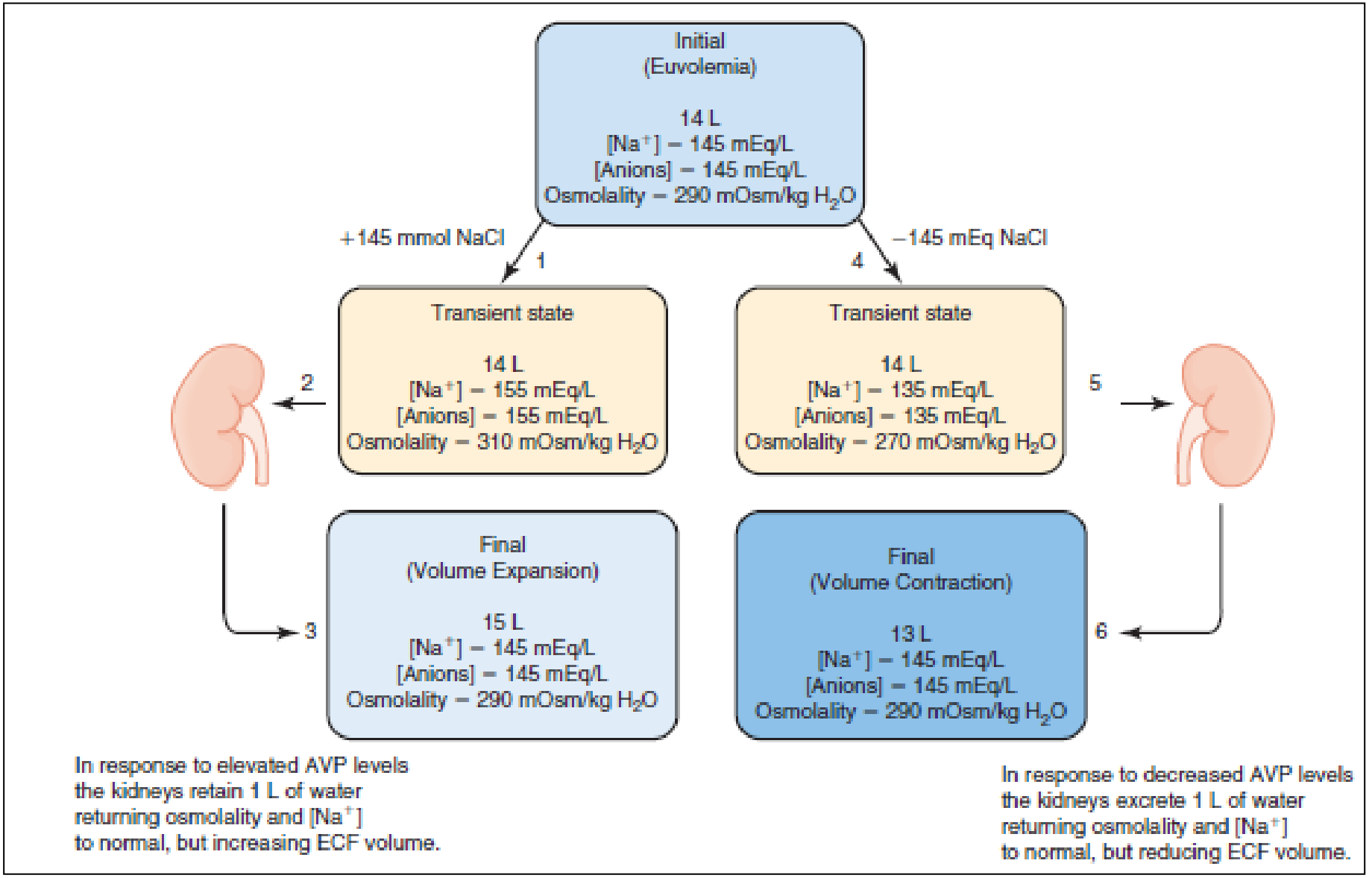
Renal mechanism for urine dilution and concentration

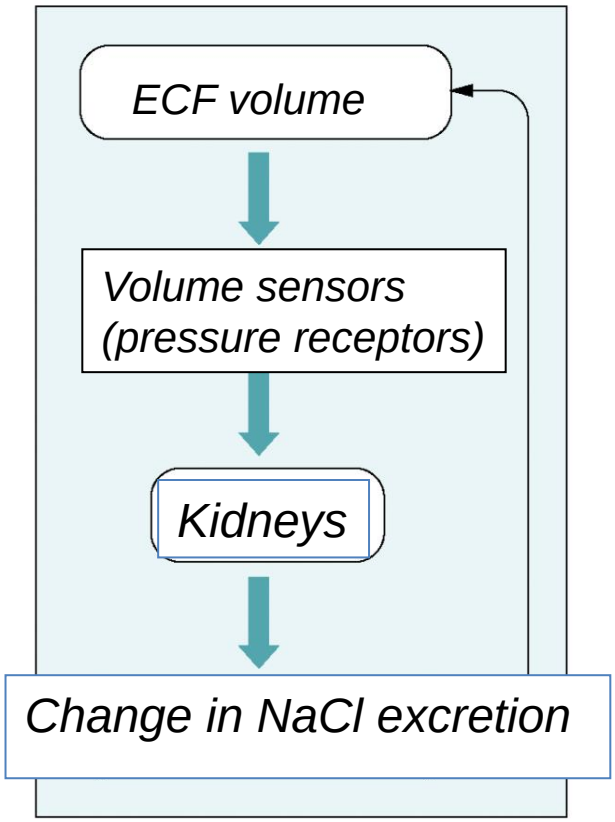


Loop of Henle creates hyperosmotic medullary interstitium - osmolality gradient is necessary for removing water from the tubular fluid

- high levels of AVP – urine is concentrated
- low levels of AVP – urine is diluted

Control of extracellular fluid volume (ECF) and regulation of renal NaCl excretion


Initial
(Euvolemia)
14 L
[Na+] = 145 mEq/L
[Anions] = 145 mEq/L
Osmolality = 290 mOsm/kg H2O
+145 mmol NaCl
1
−145 mEq NaCl
4
Transient state
14 L
[Na+] = 155 mEq/L
[Anions] = 155 mEq/L
Osmolality = 310 mOsm/kg H2O
Transient state
14 L
[Na+] = 135 mEq/L
[Anions] = 135 mEq/L
Osmolality = 270 mOsm/kg H2O
2
5
3
6
Final
(Volume Expansion)
15 L
[Na+] = 145 mEq/L
[Anions] = 145 mEq/L
Osmolality = 290 mOsm/kg H2O
Final
(Volume Contraction)
13 L
[Na+] = 145 mEq/L
[Anions] = 145 mEq/L
Osmolality = 290 mOsm/kg H2O
In response to elevated AVP levels
the kidneys retain 1 L of water
returning osmolality and [Na+]
to normal, but increasing ECF volume.
In response to decreased AVP levels
the kidneys excrete 1 L of water
returning osmolality and [Na+]
to normal, but reducing ECF volume.

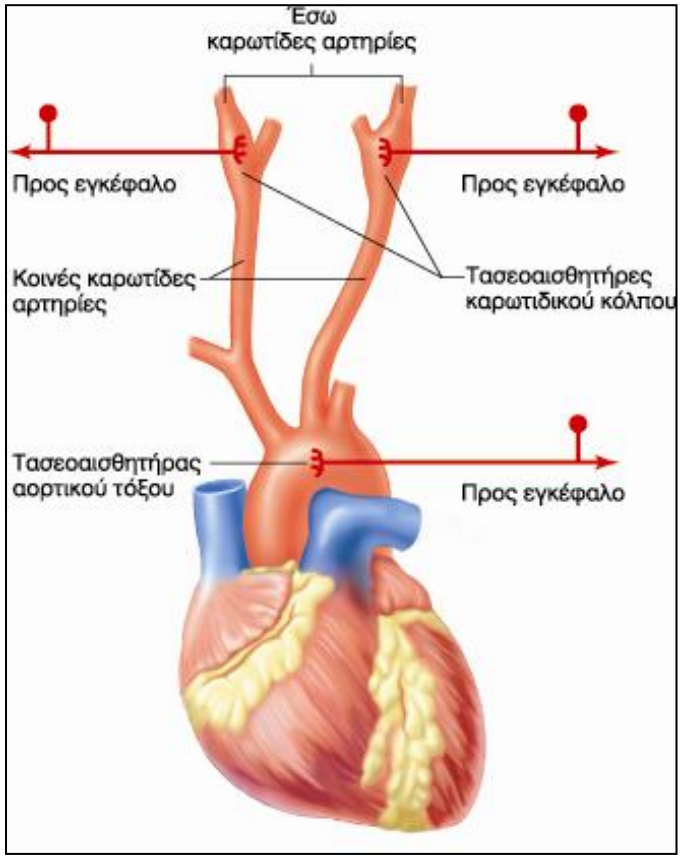


To maintain ECF volume, the body monitors the volume of this compartment and, in response to changes, signals the kidneys to make appropriate adjustments in NaCl excretion.

The major solutes in ECF are salts of Na. Changes in sodium content of our body are associated with ECF volume:

- adding NaCl to ECF increases ECF volume
- removing NaCl from ECF lowers ECF volume

Pressure receptors in central arterial tree (baroreceptors)

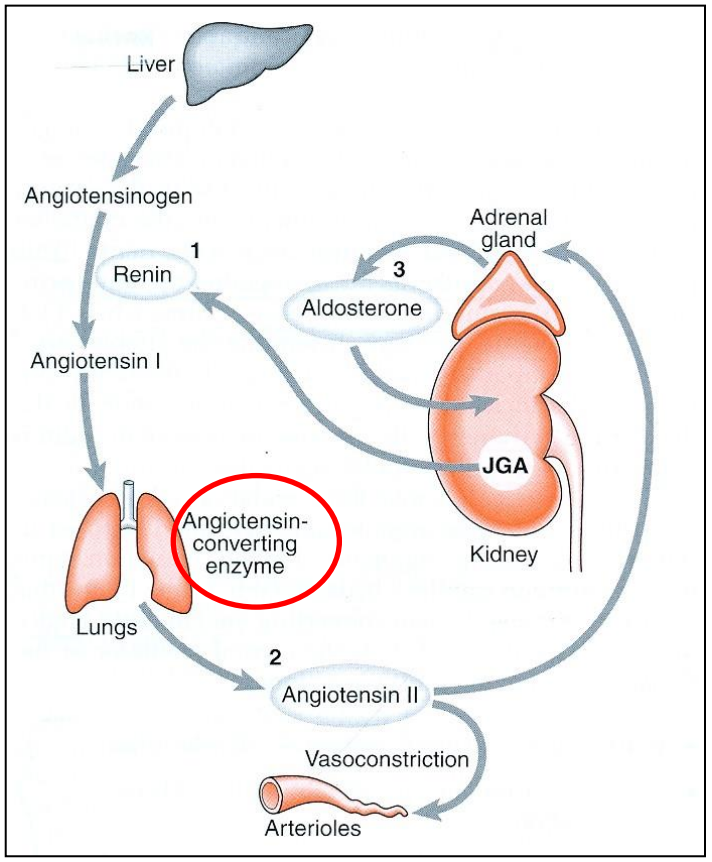


Several sensing mechanisms detect changes in ECF volume and blood pressure: heart, intrathoracic veins, central arterial tree and kidneys (pressure receptors in the afferent arteriole).

Signals - both neural and hormonal- couple volume sensors to the kidneys.

The kidneys adjust renal NaCl and water excretion.

The most important effector system in adjusting renal sodium excretion is the RAAS system

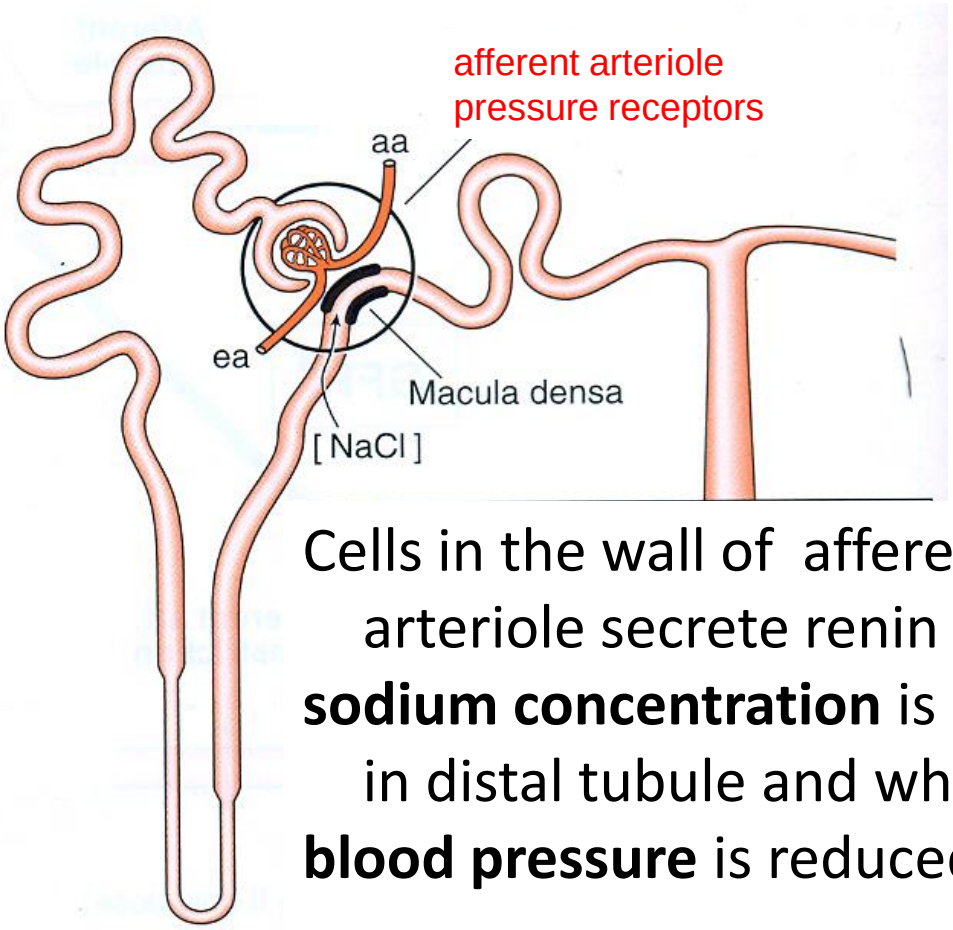


A sequence of steps leads to the release of aldosterone by adrenal gland:

- Renin, an enzyme secreted by the kidneys, converts angiotensinogen to angiotensin I
- ACE enzyme of the lungs converts angiotensin I to angiotensin II
- Angiotensin II stimulates the secretion of aldosterone by the adrenal glands
- Aldosterone acts to stimulate sodium reabsorption – reducing sodium and water excretion from the kidneys

- *Aldosterone regulates sodium homeostasis*
- The *renin-angiotensin-aldosterone system (RAAS)* is activated when blood pressure falls and ECF volume is reduced

When is renin released by the kidneys?



Cells in the wall of afferent arteriole secrete renin when:

sodium concentration is reduced in distal tubule and when

blood pressure is reduced

The kidneys regulate the volume of body fluids and participate in the long-term regulation of arterial blood pressure by regulating sodium transport in the nephron.

Diuretics (block Na^+ transport) and inhibitors of angiotensin-converting enzyme are drugs for hypertension.

Role of the kidney in the regulation of acid-base balance - pH homeostasis

Normally the pH of ECF is maintained between 7.35 and 7.45.

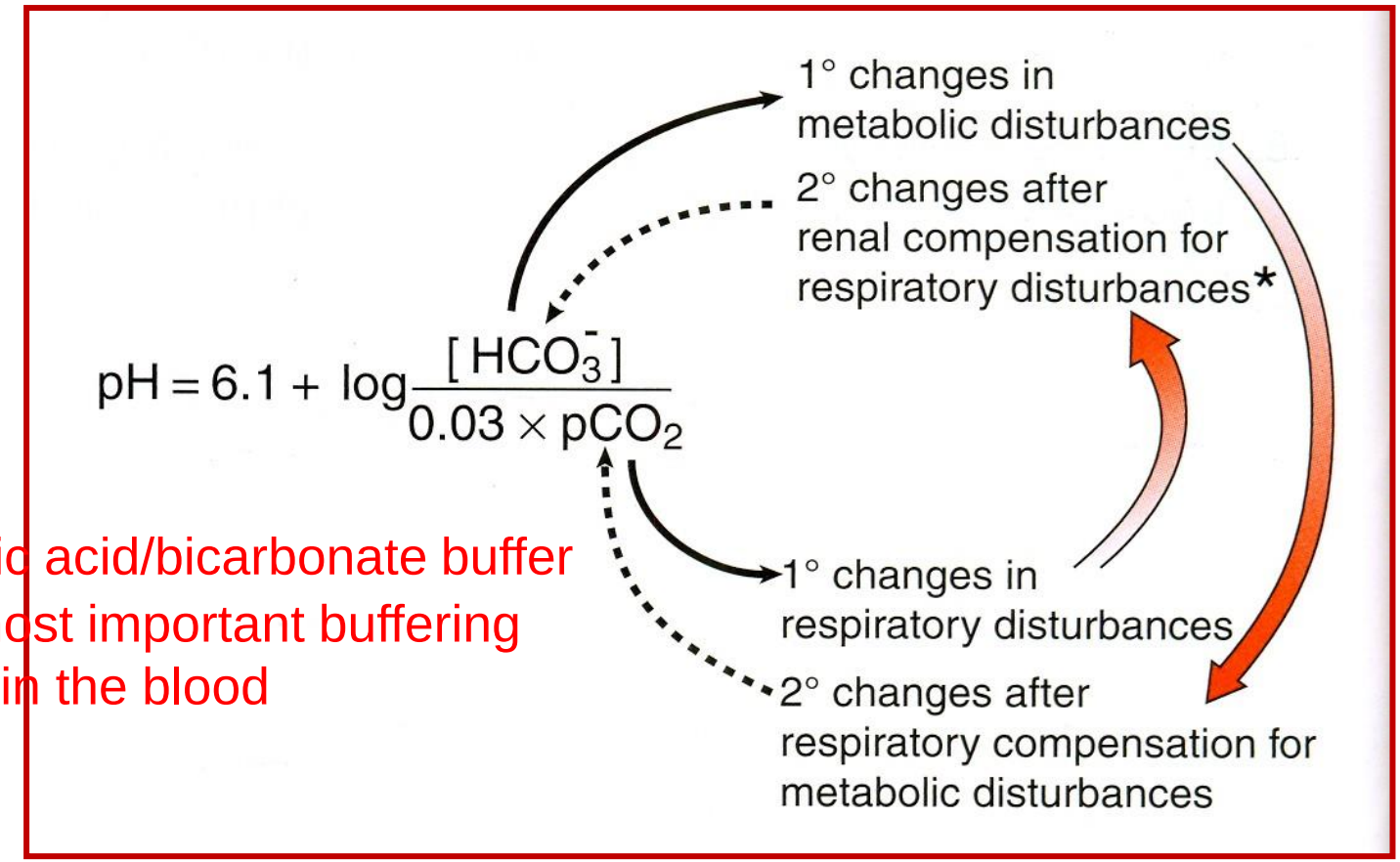
Life cannot exist outside of a range of extracellular pH from 6.8 to 7.8.

The kidneys, lungs and liver are responsible for the maintenance of normal pH.

The diet of humans contains constituents that are either acid or alkali. Cellular metabolism produces acid and alkali. Alkali is normally lost in feces.

For acid-base balance to be maintained, acid must be excreted from the body at a rate equivalent to its addition.

The concentration of H+ is expressed as pH



Carbonic acid/bicarbonate buffer is the most important buffering system in the blood

Concentration of H^+ in ECF is 40mmol/L, pH=7.4

Normal range of plasma pH is **7.35 – 7.45**

Acidosis <7.35, alkalosis >7.45

Carbonic acid/bicarbonate buffer is the most important mechanism of preventing pH changes

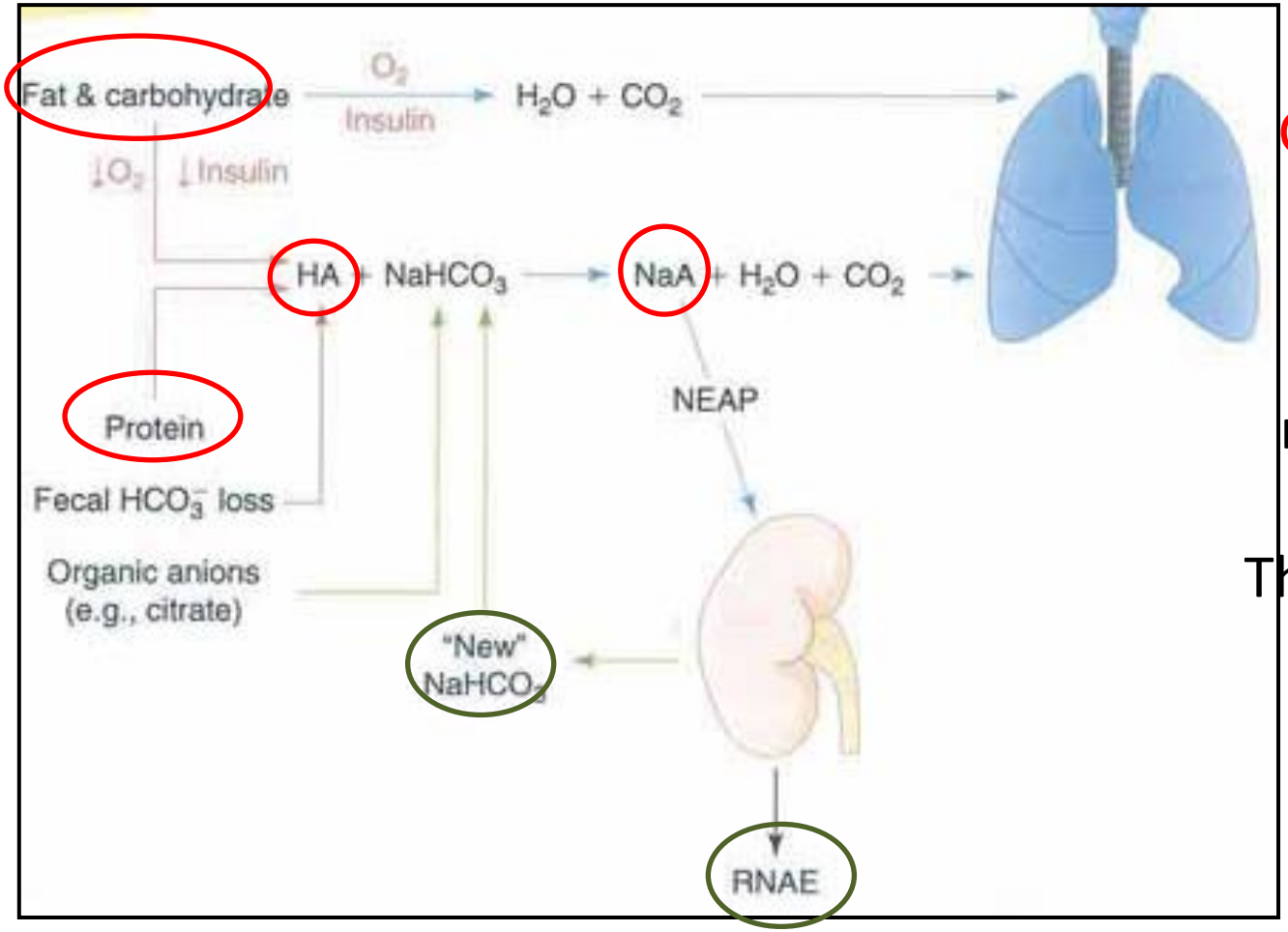
1. The CO_2 of the blood is under the physiological control of the lungs

   Adjustments of CO_2 pressure by changes in respiratory rate by the **lungs**

2. Bicarbonate of the blood is under the physiological control of the **kidneys**

   The kidneys reabsorb all the filtered bicarbonate

   The kidneys secrete acid to the tubular fluid



Overview of acid-base balance

Lungs and kidneys work together to maintain acid-base balance.

The lungs excrete CO_2 and the kidneys excrete acid.

Carbohydrates and fats are metabolized to CO_2 which is eliminated from the body by the lungs. The metabolism of proteins yields on average nonvolatile acids (not CO_2).

In an individual ingesting a meat containing diet there is a net endogenous acid production (NEAP). This results in an equivalent loss of HCO_3 from the body that must be replaced.

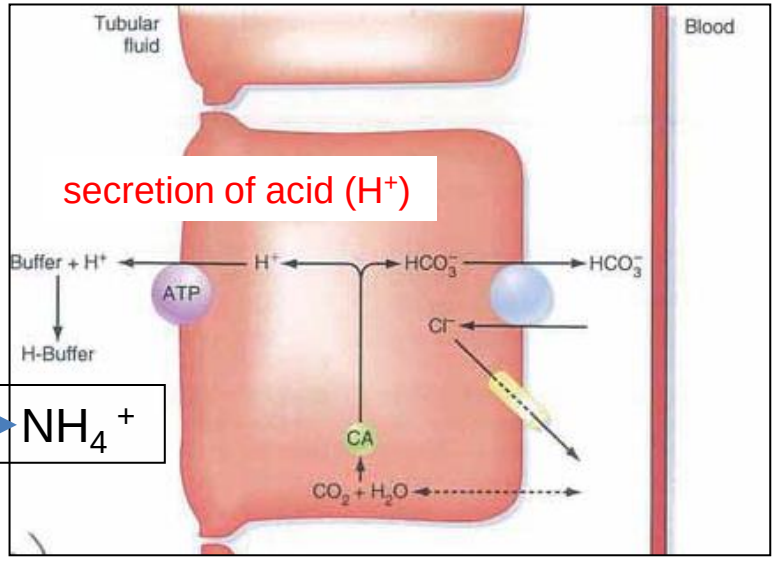
Role of kidneys in pH homeostasis is achieved through the production of acidic urine (pH=5,5-6,5)

The kidneys reabsorb all filtered bicarbonate (cells in proximal tubule) and produce “new” bicarbonate
The kidneys add acid (secrete) to the tubular fluid (by cells in collecting duct)

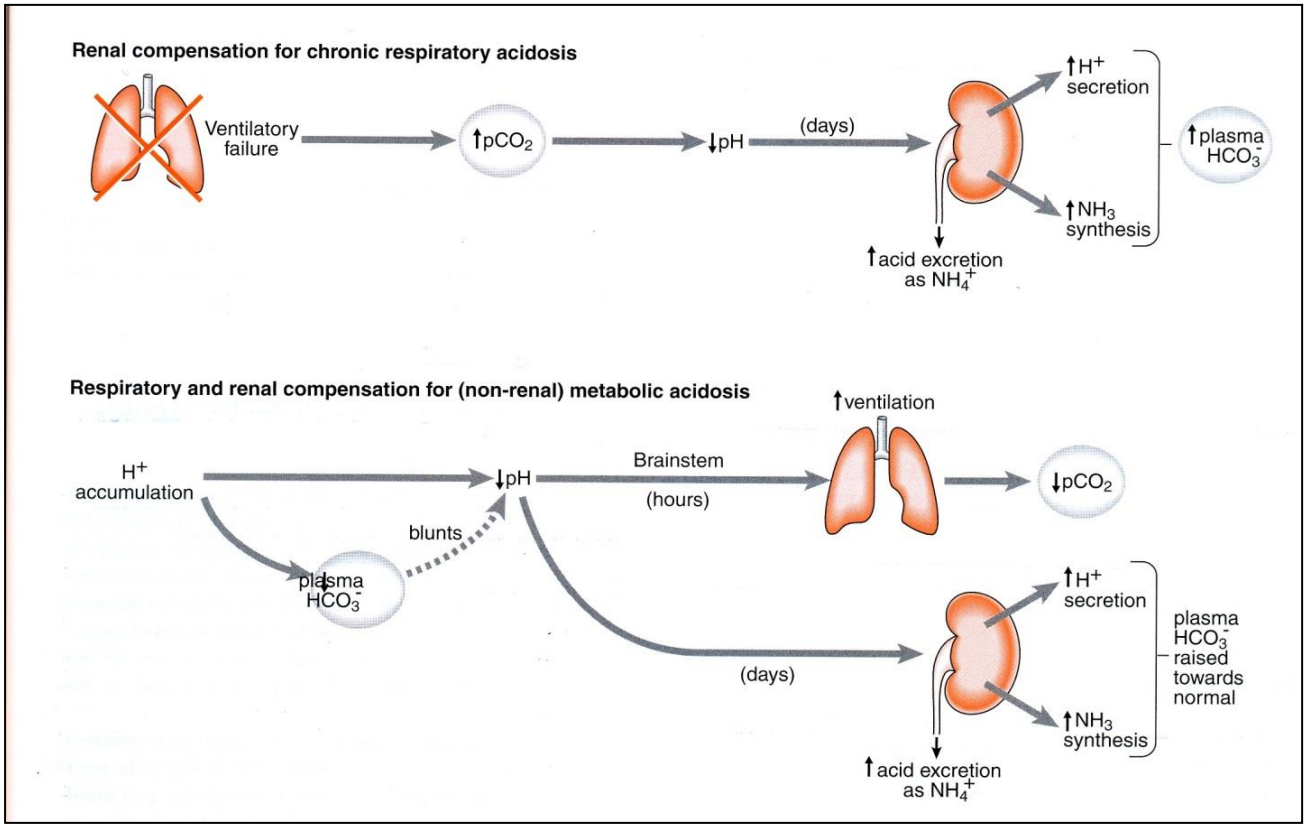
Tubular cells synthesize ammonia

Kidneys excrete acid as ammonium in the urine

$NH_3^+ + H^+ \rightarrow NH_4^+$



Response of kidneys to acid-base disturbances: renal and respiratory compensation to acidosis



Kidney response to acidosis (pH<7,4):

- reabsorption of all filtered bicarbonate
- H^+ secretion by collecting duct cells
- synthesis of ammonia NH_3 by tubular cells
- excretion of acid in urine as ammonium ions