Renal Physiology For Medical students

Part-2

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HUCMHS, 2017

Outlines

- **Concentration and dilution of Urine**
- **ECF Osmolarity regulation**
- **[Na+] Regulation and renal handling**
- **[K+] Regulation and Renal Handling**
- **[Ca+] Regulation and renal handling**
- **Micturition reflex**

Formation of Concentrated and Diluted Urine

Dilution and Concentration of Urine

- Kidneys have a capability to vary the relative **proportions of solutes and water** in the urine in response to challenges.

1. When there is excess water in the body and body fluid osmolality is reduced:
   - ❖Kidney excrete urine with an osmolarity as low as **50 mOsm/l**,
2. In a deficient of water and ECF osmolarity is high:
   - ❖ the kidney excrete urine with a concentration of
     - about **1200 mOsm/liter**.

- Kidney has the ability to regulate water excretion **independently of solute excretion.**
- Osmolality of urine depends upon two factors:
  1. Water content in the body
  2. Antidiuretic hormone (ADH

Dilution and Concentration of Urine…,

- **The basic requirements for formation of concentrated or diluted urine;**
  1. **Controlled secretion of (ADH)**
  2. **High osmolality of the renal medullary interstitial fluid.**
  - **ADH** controls whether dilute urine or concentrated urine is formed.
  - In the absence of ADH, urine is very dilute.
  - However, a high level of ADH stimulates Reabsorption of more water into blood, producing a concentrated urine.

Renal Mechanism Of Urine Dilution

A. Controlled secretion of ADH

- **Excess water in our body** ; kidney can excrete 20L urine/day.
  - Dilution is achieved by **reabsorbing solutes to a greater extent than water**

I. Tubular fluid remains isosmotic in the proximal tubule

II. As fluid passes down the **descending loop of Henle**, it will be hyperosmolar.

III. Tubular fluid is diluted in the **ascending loop of henle**

- Especially in the t**hick segment**, sodium, potassium, and chloride are avidly reabsorbed.
- This portion is impermeable to water.

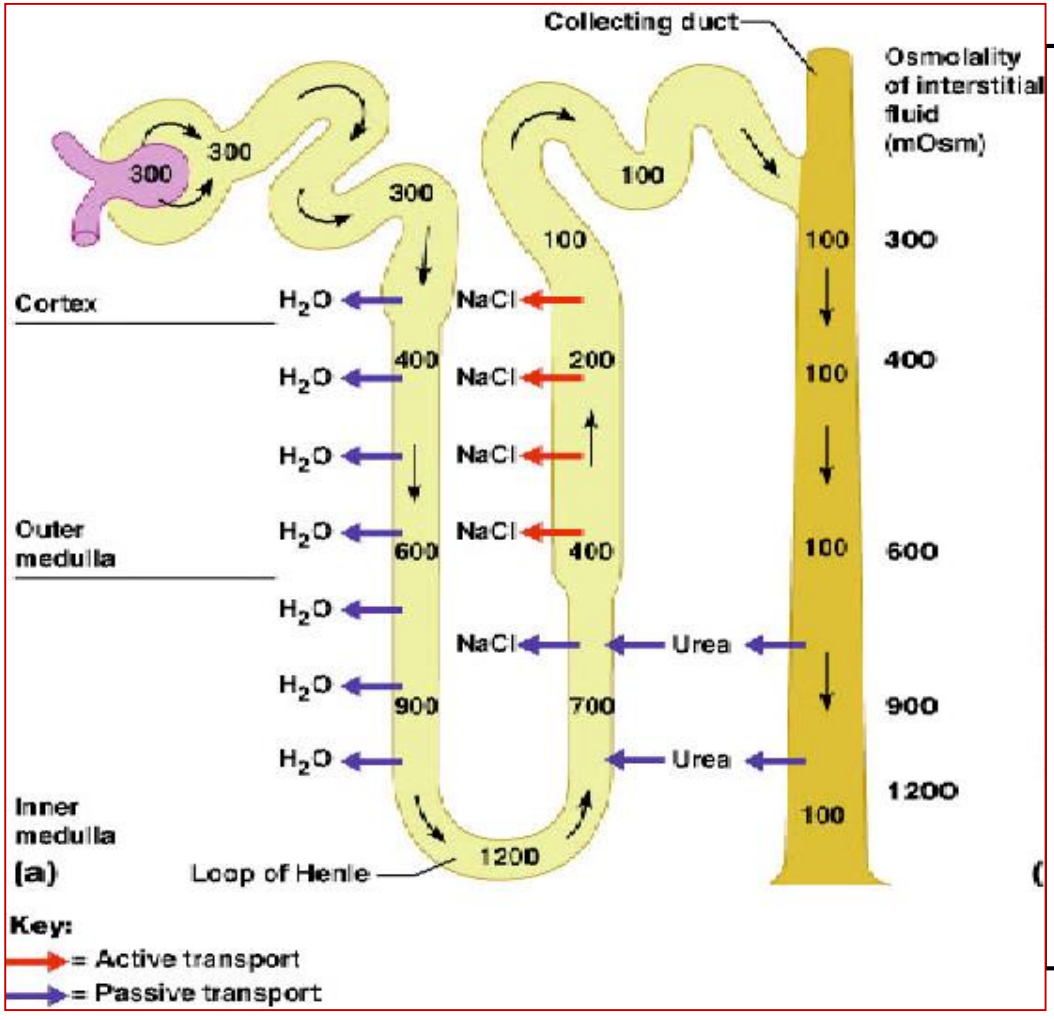
Renal mechanisms of diluting urine...,

IV. Tubular fluid in distal and collecting tubules is further diluted in the absence of ADH.

V. In late DT and CD there is additional reabsorption of NaCl

- **Forming dilute urin**e is
  - To continue reabsorbing solutes from the distal segments of the tubular system while failing to reabsorb ***water***.
  - Additional reabsorption of solutes causes the tubular fluid to become even more dilute,
  - decreasing its osmolality to as low as 50 mOsm/L.

Mechanism of formation of diluted urine



When there is excess H2O in the body

↓

↑ECF vlume, ↓Osmolality

↓

↑Aldosterone secretion

↓ADH secretion

↓

↑NaCl reabsorption in the DT & CD

↓

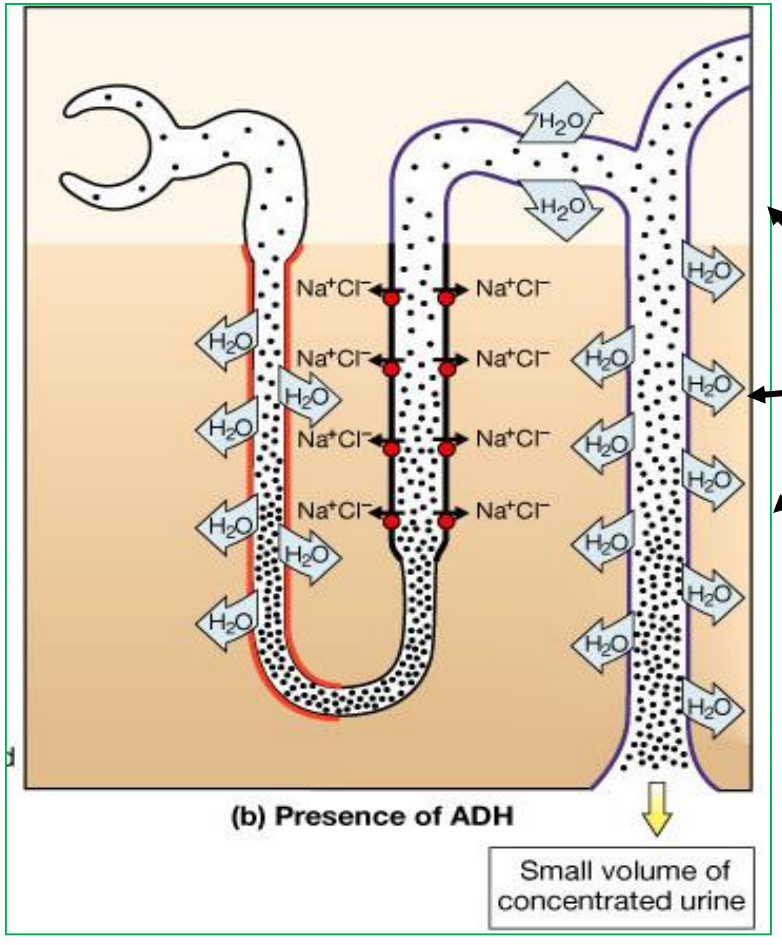
↑H2O excretion

Diluted urine (50-100 mosm/l)

Formation of Concentrated Urine

- When water intake is low or water loss is high; The kidneys conserve water while still eliminating wastes and excess ions.
- Under the influence of ADH, the kidneys produce a small volume of highly concentrated urine.
- Urine can be **four times more concentrated** (up to 1200 mOsm/liter).
- **Requirements for excreting a concentrated urine**
  1. **High ADH levels** and
     - increases the permeability of the DT and CD for water
  2. **Hyperosmotic renal medulla**
     - provides the osmotic gradient for water reabsorption in the presence of high ADH
     - The water reabsorbed in to the interstitium it is carried away by the vasa recta back into the blood.

Mechanism of formation of concentrated urine



ADH

When there is a shortage of H_2O in the body

↓

↓ECF volume, ↑Osmolality

↓

Stimulates osmoreceptors in the HT

↓

↑ADH secretion

↓

↑ H_2O reabsorption in the DT & CD

↓

↑Excrition of solutes

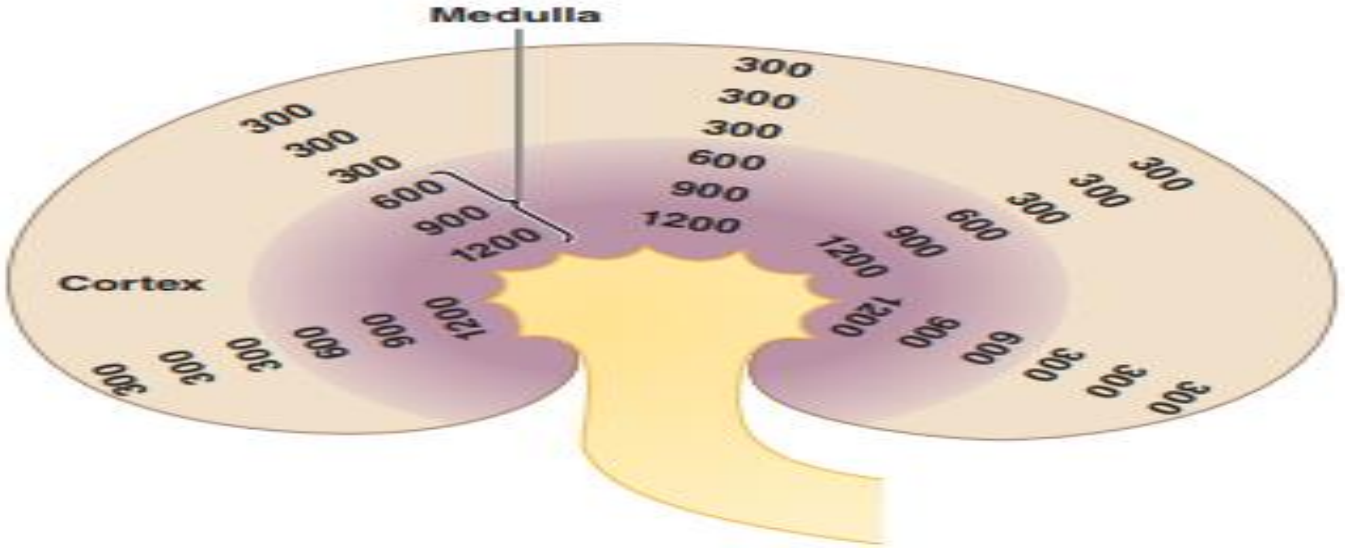
↓

Concentrated (1200 mosm/l), in small volume of urine is produced

Urine Concentration...,

B. Renal medullary interstitial hyperosmolarity

- Countercurrent Multiplier
- Countercurrent exchanger
- Role Of Urea



Medullary Hyperosmolarity …,

- Osmolarity of medullary interstitial fluid near the cortex is also 300 mOsm/L.
- proceeding towards the inner part of medulla, the osmolarity increases & reaches the maximum.
- The interstitial fluid is **hypertonic** with osmolarity of **1,200 mOsm/L** plays an important **role in the concentration of urine**.
- The osmotic pressure of the interstitial fluid provides the driving force for reabsorbing water from the **descending thin loop** of Henle and the **collecting duct.**
- The **principal solutes** of the medullary interstitial fluid are **NaCl and urea.**
- A **vertical osmotic gradient** is uniquely maintained in the medullary interstitial fluid of each kidney.

Countercurrent system

- A system of **U-shaped tubules.**
- The **flow of fluid is in opposite direction** .

- Unique anatomy and functional interactions among nephron components in medulla establish vertical osmotic gradient.
- The **juxtamedullary nephrons loop** plunges through depth of the medulla.
- **The vasa recta** of juxtamedullary nephrons follow the same deep hairpin loop as the long loop of Henle.
- Flow in both the **long loops of Henle and the vasa recta** is considered ***countercurrent.***

Countercurrent system….,

- Immediately after the filtrate is formed, uncontrolled osmotic reabsorption of filtered H2O occurs in the **proximal tubule** secondary to active Na+ reabsorption.
- By the end of the proximal tubule, about 65% reabsorbed, but the 35% remaining in the tubular lumen still **iso-osmolar**.
- **Juxtamedullary nephrons'** long loops of Henle *establish* the vertical osmotic gradient by means of **countercurrent multiplication**.
- **The vasa recta** *preserve* this gradient while providing blood to the renal medulla by means of **countercurrent exchange**.
- The collecting ducts of all nephrons *use* the gradient, in conjunction with the hormone **ADH** to produce **urine of varying concentrations**.

Countercurrent mechanism

- **Components and their functions**
  - Proximal convoluted tubules (continuous supply)
  - **Loop of Henle (countercurrent multiplier)**
  - **Vasa recta (countercurrent exchanger)**
  - Collecting duct (final urine osmotic adjustment)
  - Interstitium (osmotic equilibrating device)
- Osmotic stratification in medulla
- Formation of dilute and concentrated urine
  - Absence or presence of ADH

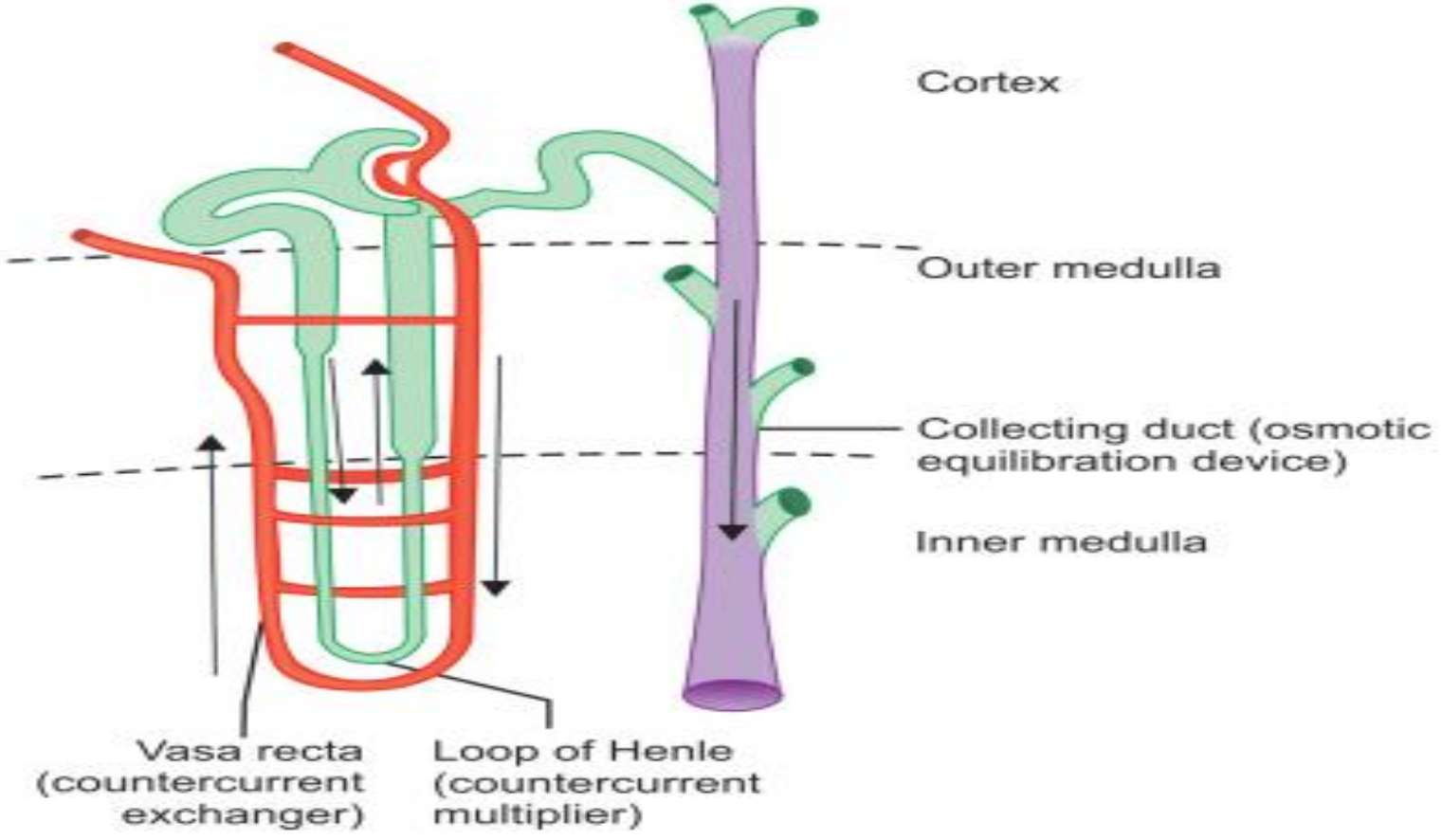


Fig. Components of counter-current mechanism in kidney for concentration of urine. Note that the flow is in opposite direction in descending and ascending limbs of loop of Henle (as indicated by arrows inside), and vasa recta (as indicated by arrows outside vasa recta). This close proximity of descending and ascending limbs in a parallel arrangement and the opposite direction of flow in limbs are essential components of a counter-current mechanism to be effectively operative. Also, note the direction of flow in collecting duct (as indicated by arrow within the collecting duct).

Countercurrent system…,

Properties of the Descending and Ascending Limbs of a Long Henle's Loop

- The descending limb of loop of Henle carries fluid from the PCT to depths of medulla.
- It is highly permeable to H2O via abundant, AQP-1.
- Does not actively extrude Na+ that is.
- It is the only segment of tubule that does not do so.

- The ascending limb carries fluid up and out of medulla into DCT.
- Actively transports Na Cl out of the tubular lumen into ISF.
- Always impermeable to H2O.
- Salt leaves the tubular fluid without H2O.

1. Countercurrent Multiplier

- The close proximity and countercurrent flow of the two limbs allow important interactions between them.
- Before the vertical osmotic gradient is established, the medullary interstitial fluid concentration is 300 mOsm/L.

1. The **active salt pump in the ascending limb** can transport NaCl out of the lumen until the surrounding **interstitial fluid** is 200 mOsm/L more concentrated than the tubular.

2. When the ascending limb pump starts actively extruding NaCl, the **medullary interstitial fluid becomes hypertonic**.

Countercurrent Multiplier…,

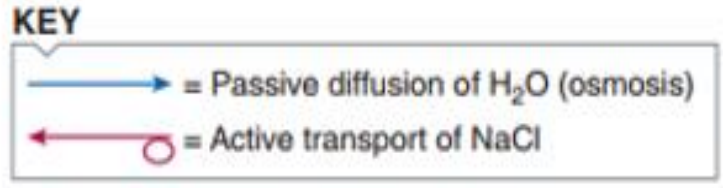
3. This decreases the osmolality in the tubular fluid and raises the osmolality of the interstitium at this point.
4. The increased osmolality of the interstitium then causes water to be reabsorbed from the descending limb of Henle's loop.

❑ This increasing the tubular fluid osmolality in this segment.

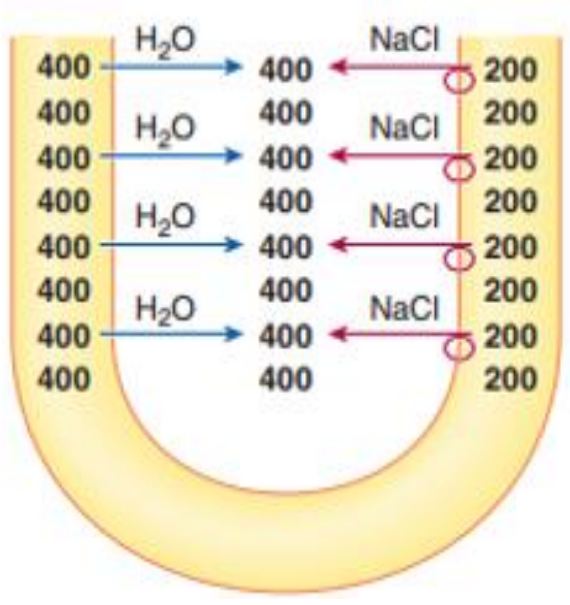
- The ascending limb has an osmolality less than descending limb (**single effect)**.
- Because of the countercurrent flow of tubular fluid, this single effect could be multiplied.
- Resulting in an osmotic gradient within the medullary interstitium, where the **tip of the papilla has an osmolality of 1200 mOsm/kg H2O**.

Countercurrent Multiplier...,

- The tubular fluid entering the loop of Henle immediately become concentrated as it loses H2O.

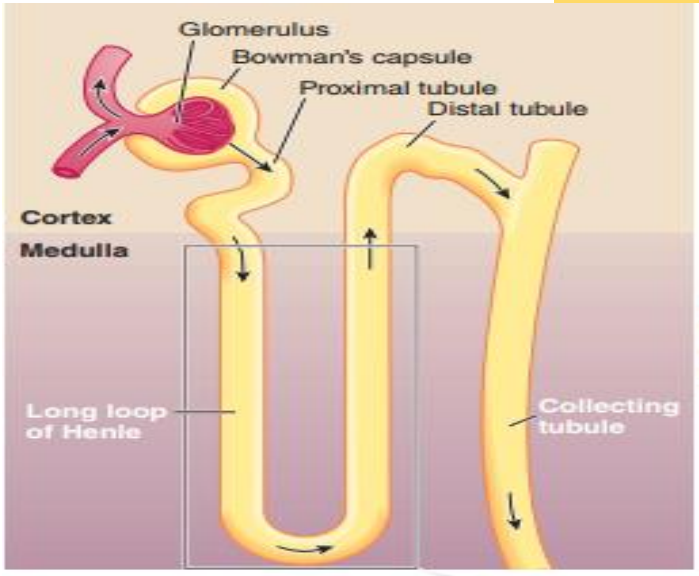


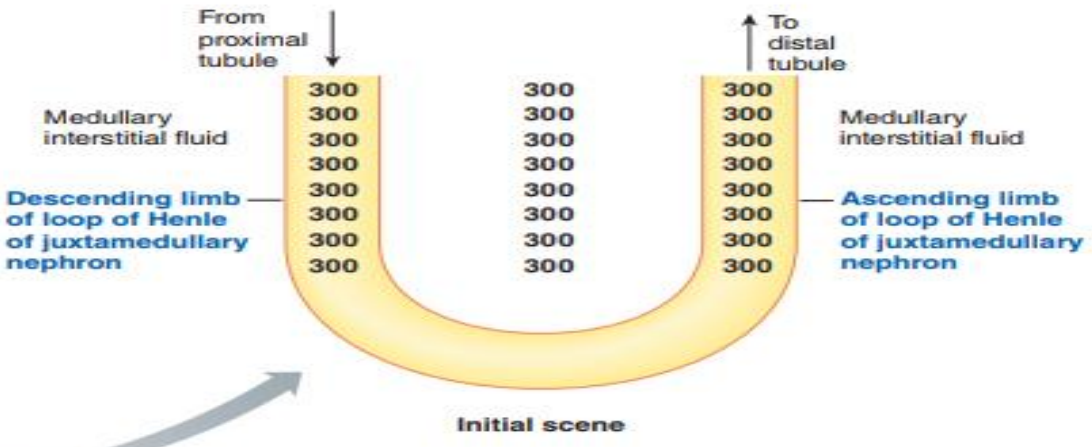
- At equilibrium, the osmolarity of the ascending limb fluid is 200 mOsm/L and the osmolarities of the interstitial fluid and descending limb fluid are equal at 400 mOsm/L.

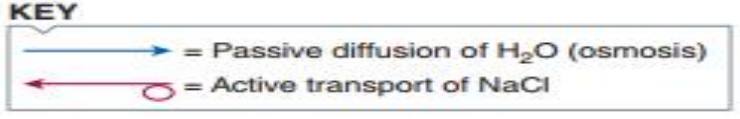


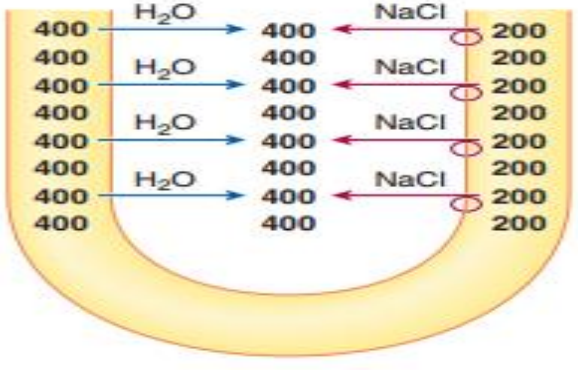
- **<u>Note,</u> the concentration of tubular fluid** is progressively increasing in the descending limb and progressively decreasing in the ascending limb.

Countercurrent Multiplier

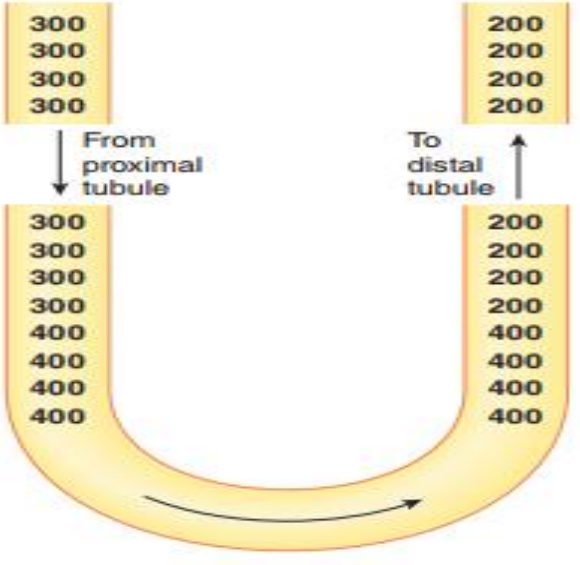






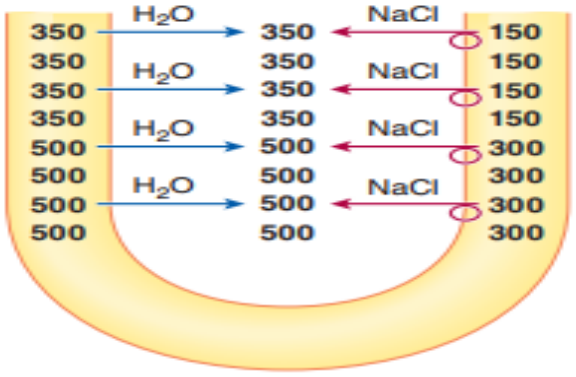


1 The active salt pump in the ascending limb establishes a 200 mOsm/L gradient at each horizontal level.

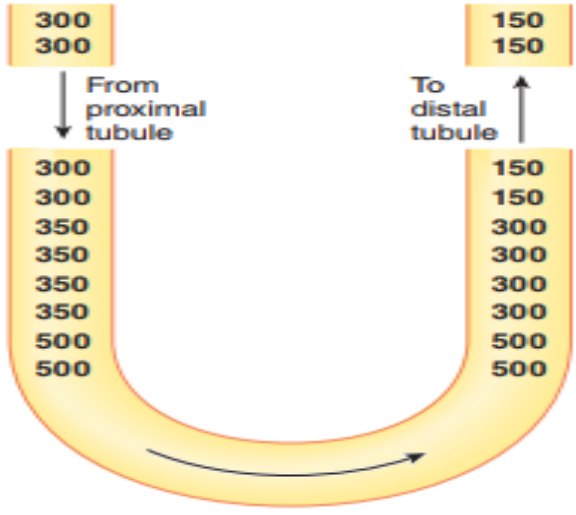


2 As the fluid flows forward several "frames," a mass of 200 mOsm/L fluid exits into the distal tubule and a new mass of 300 mOsm/L fluid enters from the proximal tubule.

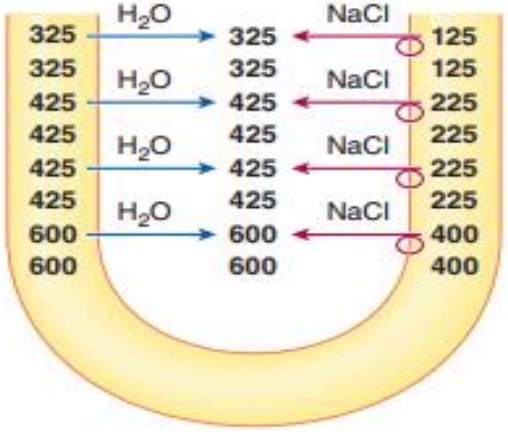
Countercurrent Multiplier...,



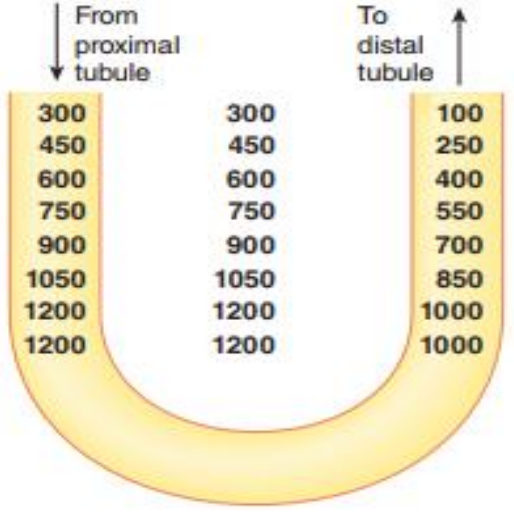
3 The ascending limb pump and descending limb passive fluxes reestablish the 200 mOsm/L gradient at each horizontal level.



4 Once again, the fluid flows forward several "frames."



5 The 200 mOsm/L gradient at each horizontal level is established once again.



6 The final vertical osmotic gradient is established and maintained by the ongoing countercurrent multiplication of the long loops of Henle.

2. Countercurrent Exchanger

- The **vasa recta,** the capillary networks that supply blood to the medulla, are highly permeable to solute and water.

- Vasa recta runs parallel to loop of Henle.
- **This passive exchange of *solutes* and *H2O between* the two limbs of the vasa recta and the interstitial fluid is known as *countercurrent exchange.***

- ***Vassa Recta has also slow blood flow that contributes hyperosmolar interstitium and it preserves the gradient.***
- It is responsible for the maintenance of medullary gradient

2. Countercurrent Exchanger...,

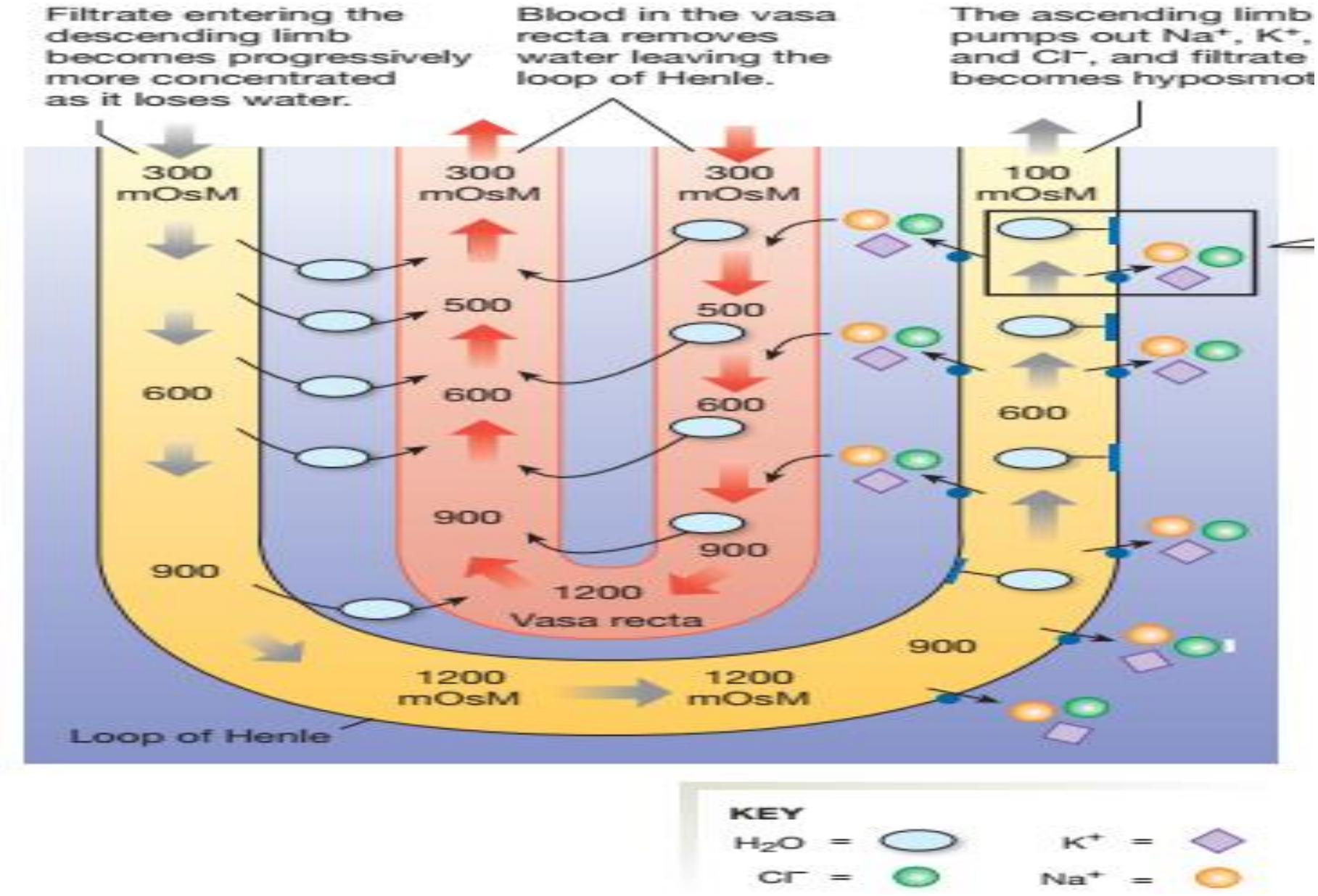
- **Events during maintenance of medullary gradient by countercurrent exchanger**

1. **Sodium chloride reabsorbed from ascending limb of Henle's loop** enters the medullary interstitium. From here it enters the **descending limb of vasa recta.**
2. Simultaneously **water diffuses from descending limb of vasa recta** into **medullary interstitium.**
3. Blood flows very slowly through vasa recta. So, a **large quantity of sodium chloride accumulates in descending limb** of vasa recta and flows slowly towards ascending limb.

2. Countercurrent Exchanger…,

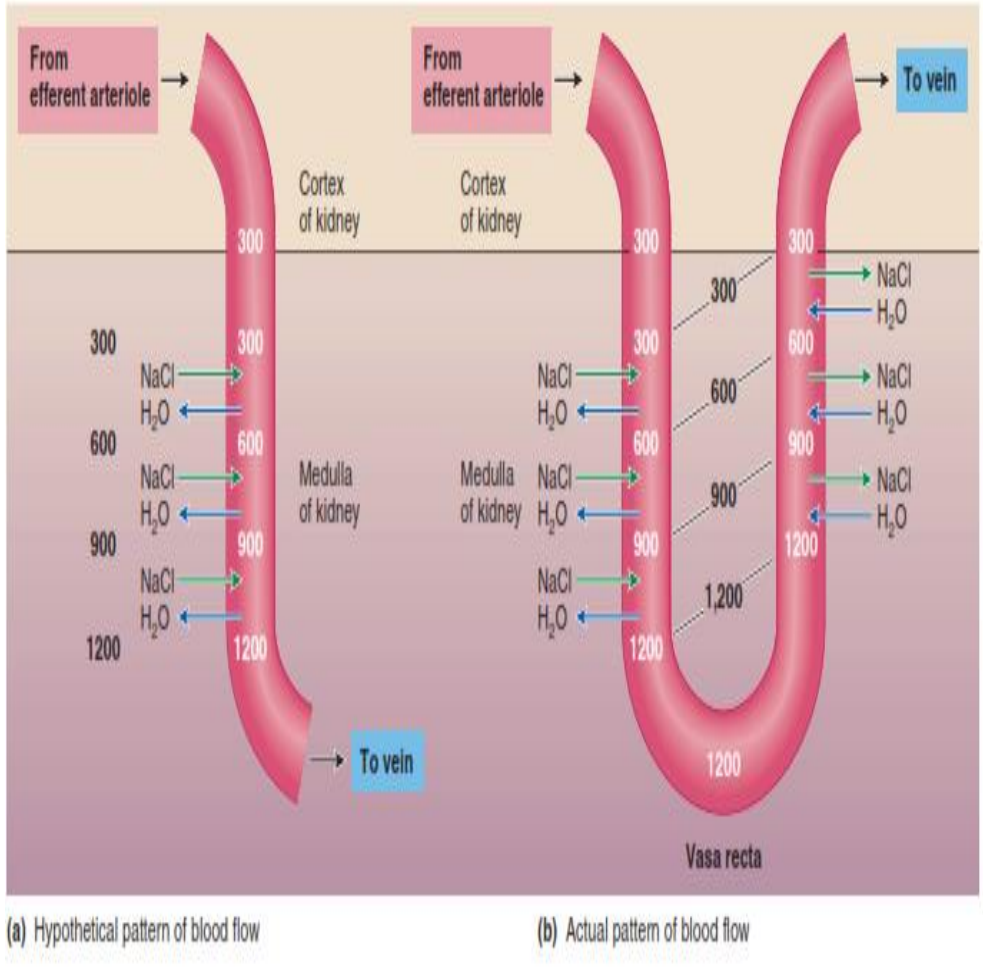
4. By the time the blood reaches the **ascending limb of vasa recta**, the concentration of sodium chloride increases very much.
5. This causes **diffusion of sodium chloride** into the medullary interstitium.
6. **Water** from medullary interstitium **enters the ascending limb of vasa recta**. And the cycle is repeated.

2. Countercurrent Exchanger...,



2. Countercurrent exchange…,

- **Preserves hyperosmolarity of the renal medulla**
- As blood passes down the **descending limb of the vasa recta**
  - it picks up salt and loses H2O until it is very hypertonic by the bottom of the loop.
- Then, as blood flows up the ascending limb,
  - salt diffuses back out into the interstitium, and
  - H2O reenters the vasa recta as progressively decreasing concentrations are encountered in the surrounding interstitial fluid.



3. Role of UREA

- Urea contributes to hyperosmotic renal medullary interstitium and formation of concentrated urine
- In addition to NaCl, urea contributes about 40 to 50 % of the osmolarity (500 to 600 mOsm/L) of medullary interstitium.
- In ascending loop of henle and Cortical collecting tubule little absorption of urea b/s this site is impermeable to urea.
- In the presence of high ADH water is reabsorbed from cortical CT so urea get concentrated.
- It is passively reabsorbed from the **medullary collecting duct** by **UT-A1 and UT-A3, in the presence of ADH.**

Role of UREA…

- **Recirculation of urea** from the collecting duct to the loop of henle
  - Contributes to hyperosmotic renal medulla.

- **The passive** secretion of urea into the thin loops of Henle
  - is facilitated by the urea transporter UT-A2.

- Low ADH level in the blood decreases the permeability of the inner medullary collecting ducts to both **water** and **urea.**

Role of Urea..,

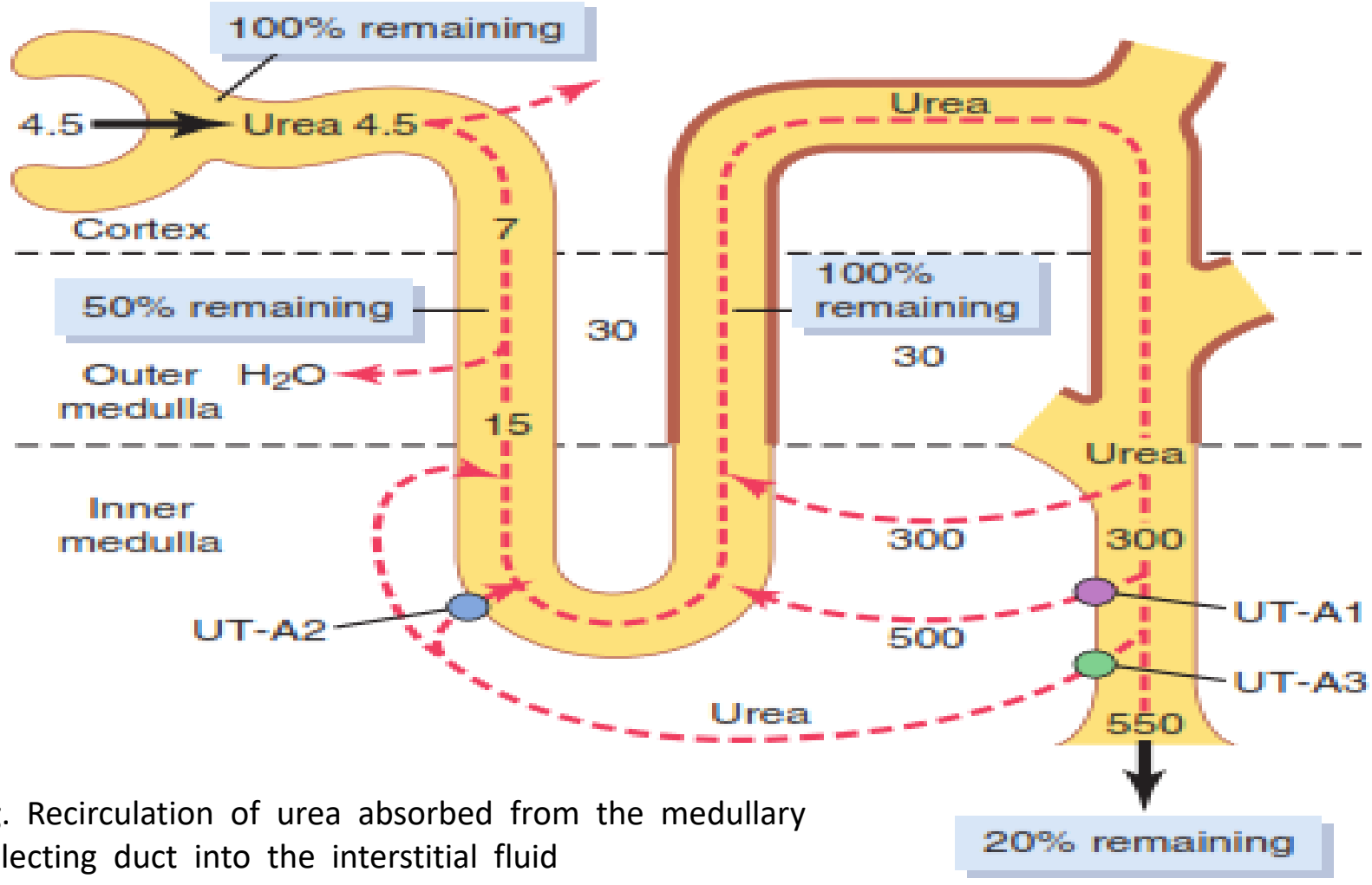


Fig. Recirculation of urea absorbed from the medullary collecting duct into the interstitial fluid

Summary of Urine dilution and concentration

1. Fluid entering the descending thin limb of the loop of Henle from the proximal tubule is isosmotic. Solute and water(Aqu-1) reabsorption in the proximal tubule.

2. **Water is reabsorbed from descending LH**. Most of this water is reabsorbed in the **outer medulla (Aqu-1)** making tubular fluid hypertonic.

3. The inner medulla the terminal portion of the descending limb and all of the thin ascending limb is **impermeable to water.**

➢These nephron segments has **Cl- reabsorption, with Na+** following via the par acellular pathway.

Summary Urine Concentration &Dilution…

4. The thick ascending limb of the loop of Henle is also **impermeable to water** and actively **reabsorbs NaCl** from the tubular fluid. (Diluting Segment).

5. The distal tubule and cortical portion of the collecting duct actively reabsorb NaCl. In the absence of AVP these segments are **not permeable to water.**

6. The medullary collecting duct **actively reabsorbs NaCl.**
7. The urine has an osmolality as low as **50 mOsm/kg H2O** and contains low NaCl.

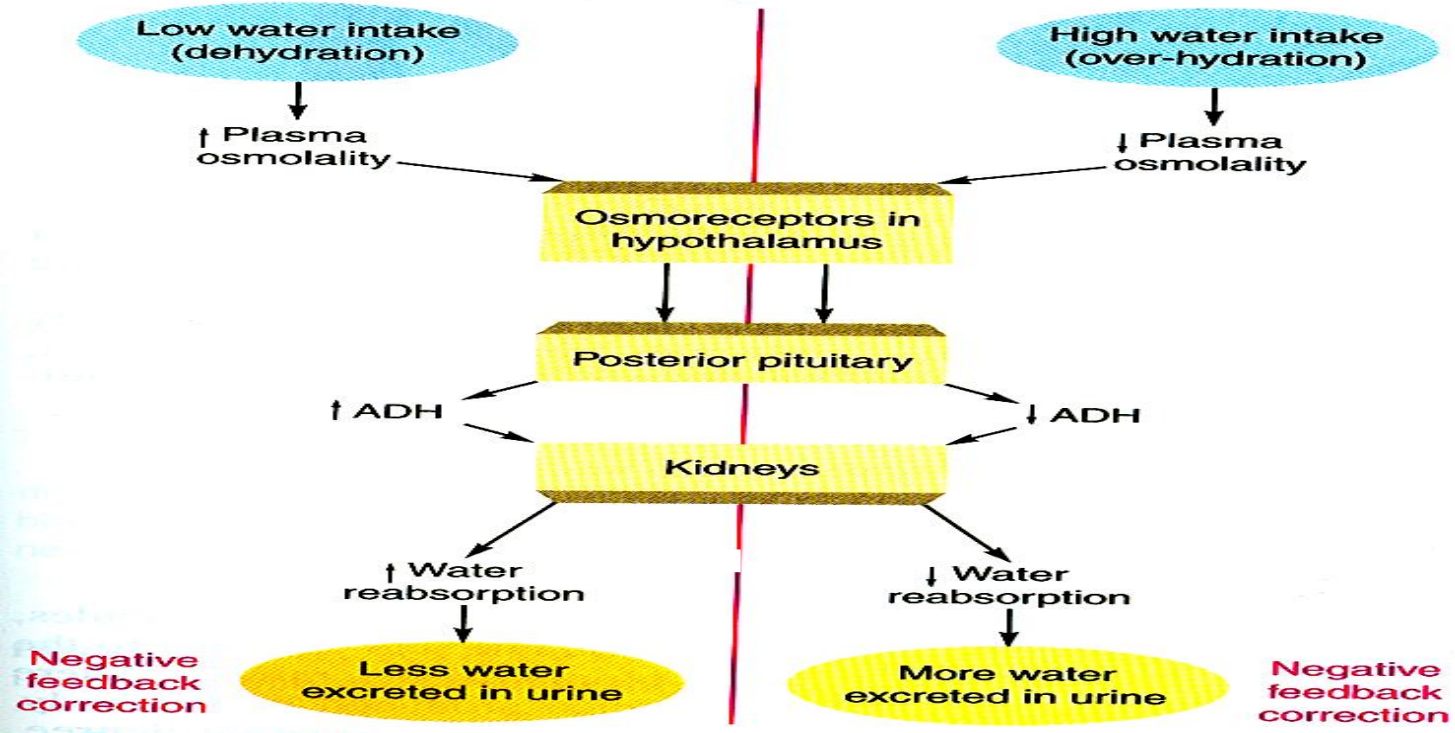
✓The volume of urine excreted can be as much as 18 L/day, or approximately **10% of (GFR**).

Summary Urine concentration..,

1. **In the presence of AVP**, which increases the water permeability of the latter portion of the distal tubule and the collecting duct by causing **insertion of AQP2 into the luminal membrane.**
2. Water diffuses and the **tubule fluid osmolality increases**.
3. As the tubular fluid descends deeper into the medulla, water **reabsorbed from the collecting duct**, increasing **osmolality to 1200 mOsm/ kg H2o.**
4. The urine produced **when AVP is high** has an osmolality of 1200 mOsm/kg H2O and contains high concentrations of urea and other solutes.
5. Urine volume under this condition can be as **low as 0.5 L/day.**

Table 17.3 Antidiuretic Hormone Secretion

Stimulus	Receptors	Secretion
↑Osmolality (dehydration)	Osmoreceptors in hypothalamus	Increased
↓Osmolality	Osmoreceptors in hypothalamus	Decreased
↑Blood volume	Stretch receptors in left atrium	Decreased
↓Blood volume	Stretch receptors in left atrium	Increased



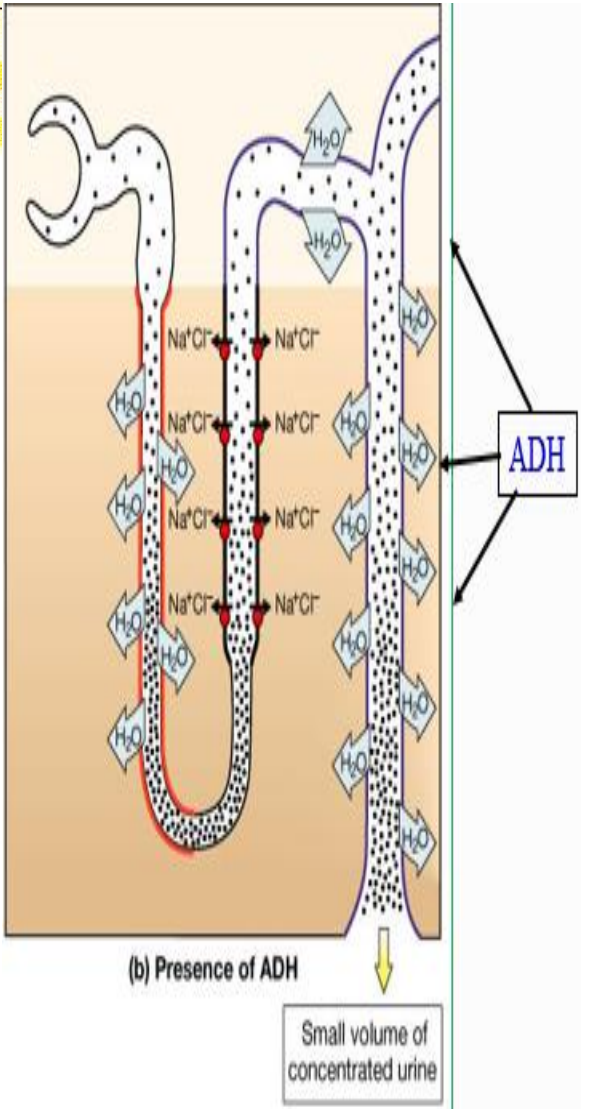


Figure 17.20 **Homeostasis of plasma concentration is maintained by ADH.** In dehydration (left side of figure), a rise in ADH secretion results in a reduction in the excretion of water in the urine. In overhydration (right side of figure), the excess water is eliminated through a decrease in ADH secretion. These changes provide negative feedback correction, maintaining homeostasis of plasma osmolality and, indirectly, blood volume.

Characteristics of Normal Urine

CHARACTERISTIC	DESCRIPTION
Volume	One to two liters in 24 hours; varies considerably.
Color	Yellow or amber; varies with urine concentration and diet. Color due to urochrome (pigment produced from breakdown of bile) and urobilin (from breakdown of hemoglobin). Concentrated urine is darker in color. Color affected by diet (reddish from beets), medications, and certain diseases. Kidney stones may produce blood in urine.
Turbidity	Transparent when freshly voided; becomes turbid (cloudy) on standing.
Odor	Mildly aromatic; becomes ammonia-like on standing. Some people inherit ability to form methylmercaptan from digested asparagus, which gives characteristic odor. Urine of diabetics has fruity odor due to presence of ketone bodies.
pH	Ranges between 4.6 and 8.0; average 6.0; varies considerably with diet. High-protein diets increase acidity; vegetarian diets increase alkalinity.
Specific gravity (density)	Specific gravity (density) is ratio of weight of volume of substance to weight of equal volume of distilled water. In urine, 1.001–1.035. The higher the concentration of solutes, the higher the specific gravity.

Role of kidney in regulating ECF Osmolality

- **ECF composition and Osmolality**
- **Renal mechanism of regulation osmolality**
- **Overview of renal electrolyte regulation**
- **Na+ Homeostasis**
- **Renal Handling of Na+**

Concepts of ECF osmolality regulation

- Water constitutes 60% of human body; 2 compartments ICF and ECF.
- The major solutes of ECF are the salts of Na+, Of these, NaCl is the most abundant.
- Osmolarity is the concentration of osmoles in a volume of solution (mOsm/ **L of solution** .)
- Normal serum osmolality ranges from 275-295 mOsmol/L

Calculated osmolarity = 2 (Na+) + Glucose + Urea (all in mmol/L),

- Electrolyte concentrations are expressed in terms **of(mEq/L):**

TABLE Major Body Fluid Compartments

Compartment	Volume of Fluid (in Liters)	Percentage of Body Fluid	Percentage of Body Weight
Total body fluid	42	100	60
Intracellular fluid (ICF)	28	67	40
Extracellular fluid (ECF)	14	33	20
Plasma	2.8	6.6 (20% of ECF)	4
Interstitial fluid	11.2	26.4 (80% of ECF)	16

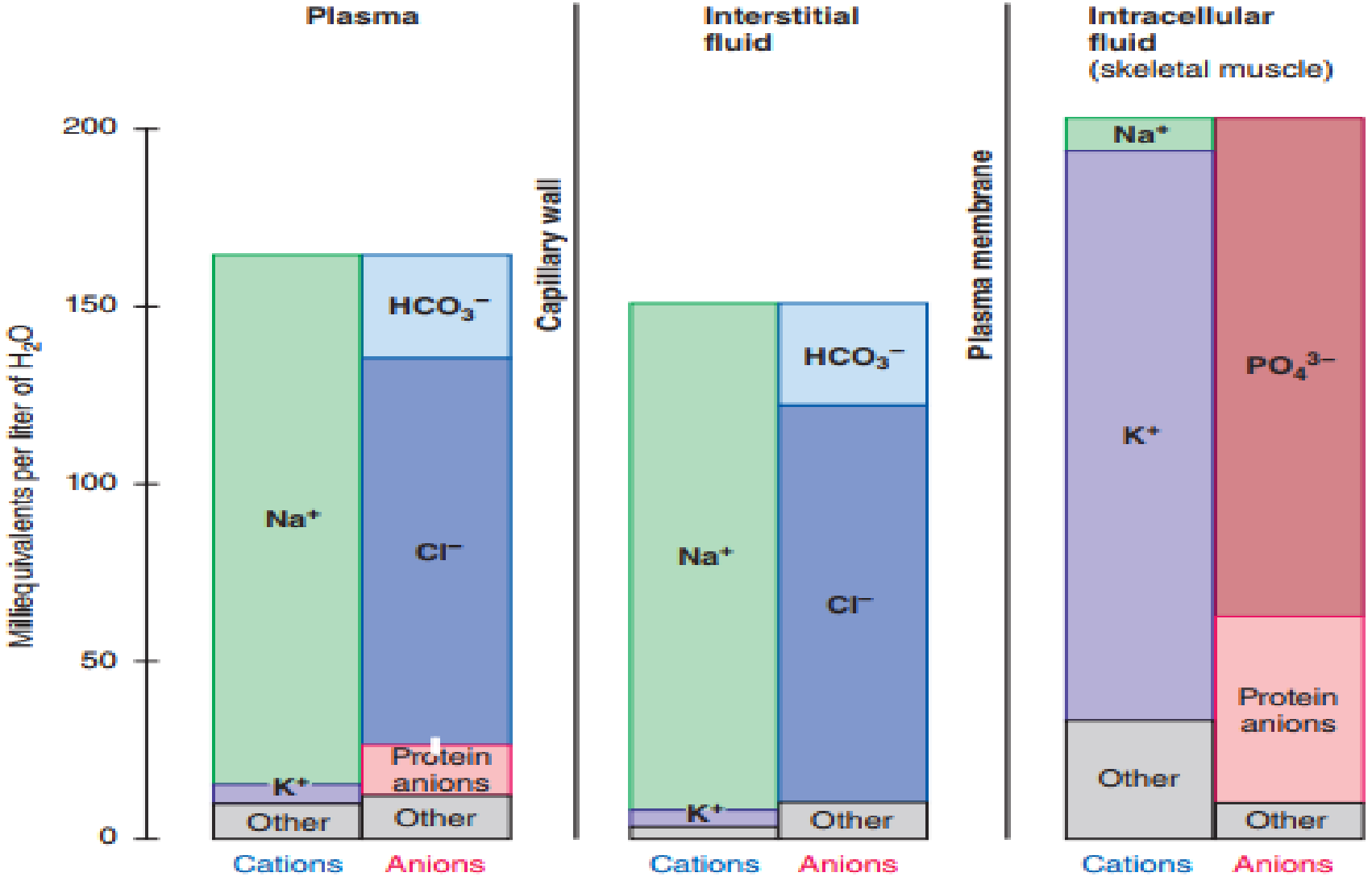


Figure Ionic composition of the major body-fluid compartments.

Concepts of ECF osmolality regulation…,

- Cells to function properly, they must be surrounded in ECF that is relatively constant in osmolality.
- The **kidneys regulate the volume and osmolality** of the extracellular fluid by **altering the amount of sodium and water excreted.**
- The regulation of body fluid osmolarity is divided as
  - The body's response to **hyper osmolality**
  - The body's response to **hypo- osmolality**

Concepts of body fluid osmolality and its regulation …

1.Increased osmolality >295mOsm/Kg

Causes : increase sodium

- ❖Iv hypertonic solution
- ❖Hperaldosteronnism
- ❖Ingestion of sea water

Water deficit

- ❖Increase Insensible loss
- ❖Inadequate water intake
- ❖Diabetes insipidus

Stimulate ADH synthesis and thirst

Concepts of ECF osmolality regulation

- **Fluid balance is maintained by regulating ECF volume and osmolarity**
- Osmolarity must be precisely regulated to prevent the cells from shrinking or swelling.
- Osmolarity determined by the **amount of solute** (mainly Nacl) divided by the volume of ECF.
- Thus, ECF osmolarity and Nacl concentration are regulated by the amount of water.
- The total body water is controlled by;

1. Fluid intake, which is regulated by factors that determine thirst, and
2. Renal water excretion, which is controlled by multiple factors that influence GFR and TR.

Concepts of ECF osmolality regulation…,

- The body regulates plasma osmolality and sodium concentration by altering renal excretion of water.
- kidneys can conserve water by producing a small volume hyperosmotic urine and hypo-osmotic urine according to body need.
- Urine osmolality can vary from 50 to 1200 mOsm, and volume can vary 18 to 0.5 L/day.
- Two primary systems are especially involved in regulating the concentration of sodium and osmolarity of ECF:

1. The osmoreceptor ADH system and

2. The thirst mechanism

Osmoreceptor-ADH feedback system

1. An increase in ECF osmolarity causes the special nerve cells called *osmoreceptor cells* in **OVLT anterior HT.**

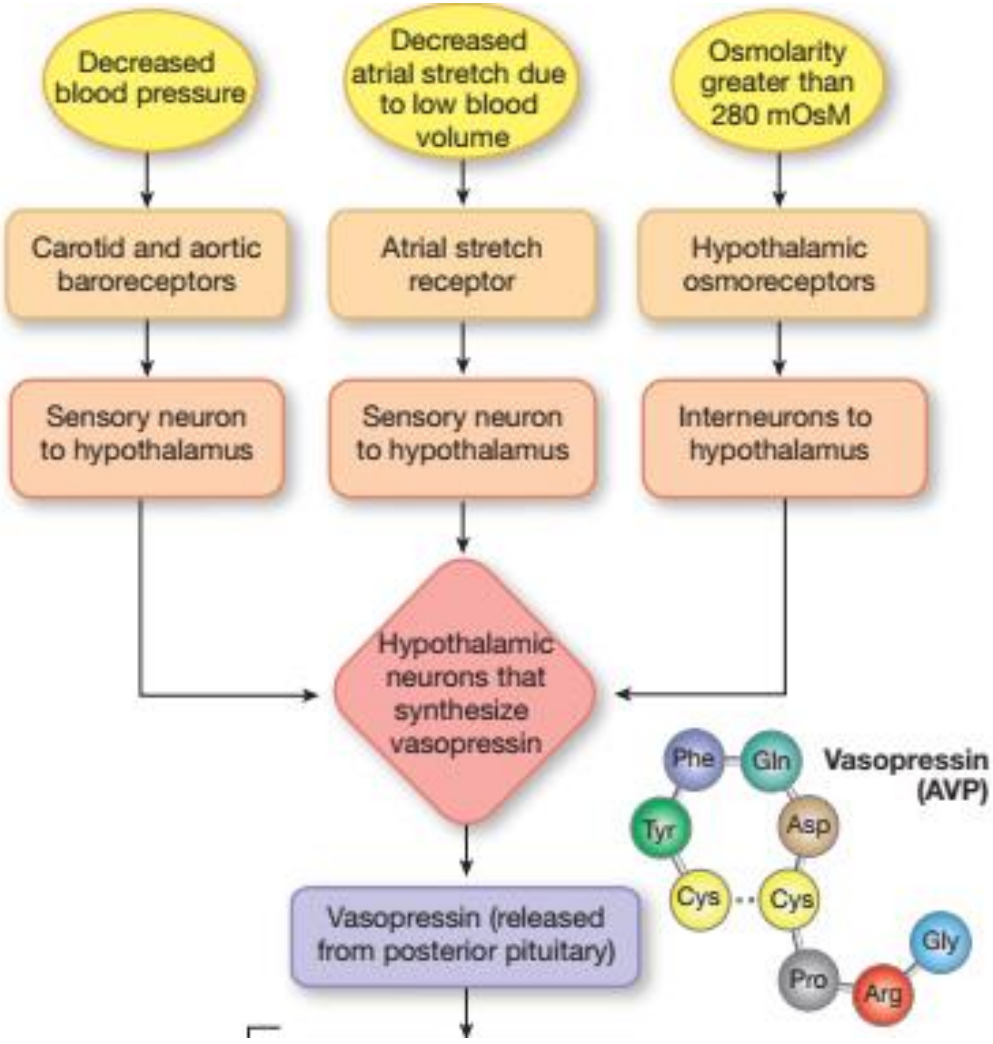
2. Shrinkage of the osmoreceptor cells causes them to fire, sending nerve signals to additional nerve cells in the **supraoptic nuclei (SON)**&PVN

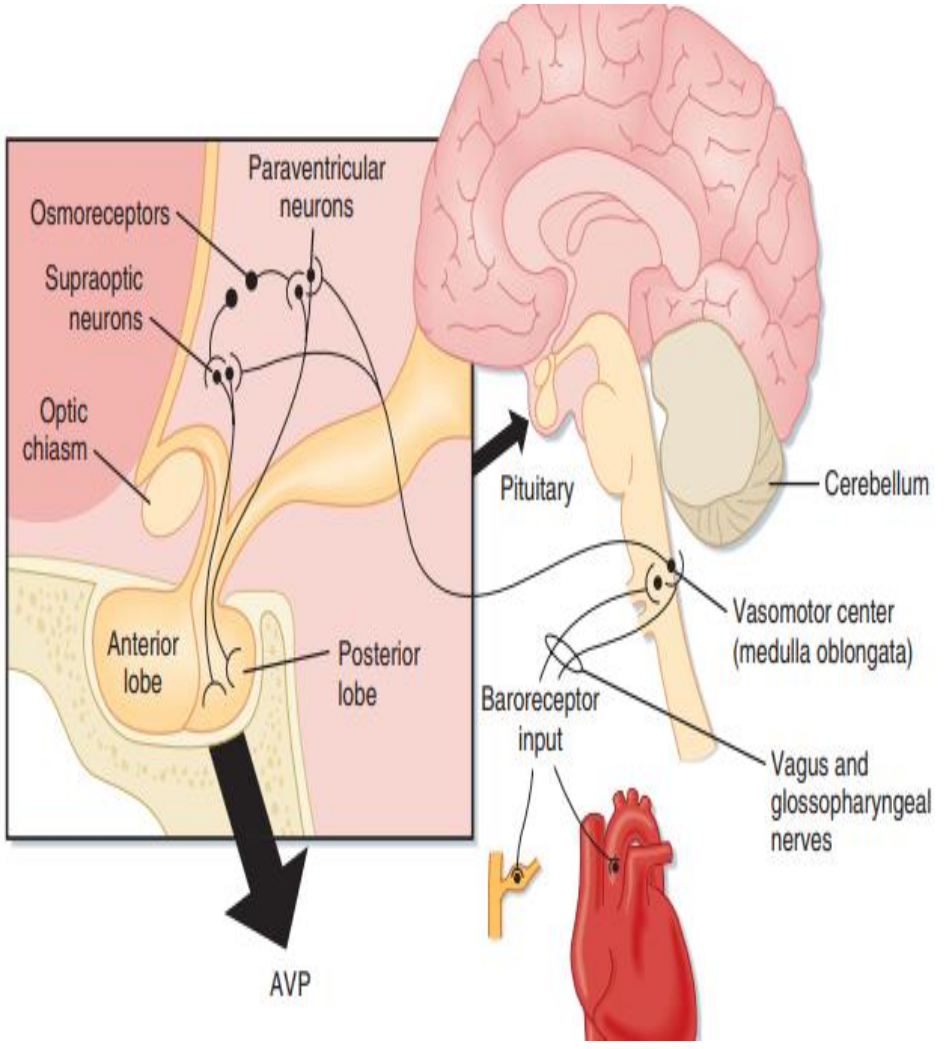
3. These Signal conducted to the **posterior pituitary** stimulate the release of ADH.

4. ADH transported to the kidneys, where it increases the water permeability of the late distal tubules, cortical collecting tubules.

5. The increased water permeability in the distal nephron segments causes increased water reabsorption and excretion of a small volume of concentrated urine.

ADH system…,


Decreased blood pressure
Decreased atrial stretch due to low blood volume
Osmolarity greater than 280 mOsM
Carotid and aortic baroreceptors
Atrial stretch receptor
Hypothalamic osmoreceptors
Sensory neuron to hypothalamus
Sensory neuron to hypothalamus
Interneurons to hypothalamus
Hypothalamic neurons that synthesize vasopressin
Vasopressin (released from posterior pituitary)
Vasopressin (AVP)
Phe
Gln
Tyr
Asp
Cys
Cys
Gly
Pro
Arg


Osmoreceptors
Paraventricular neurons
Supraoptic neurons
Optic chiasm
Pituitary
Cerebellum
Vasomotor center (medulla oblongata)
Anterior lobe
Posterior lobe
Baroreceptor input
Vagus and glossopharyngeal nerves
AVP

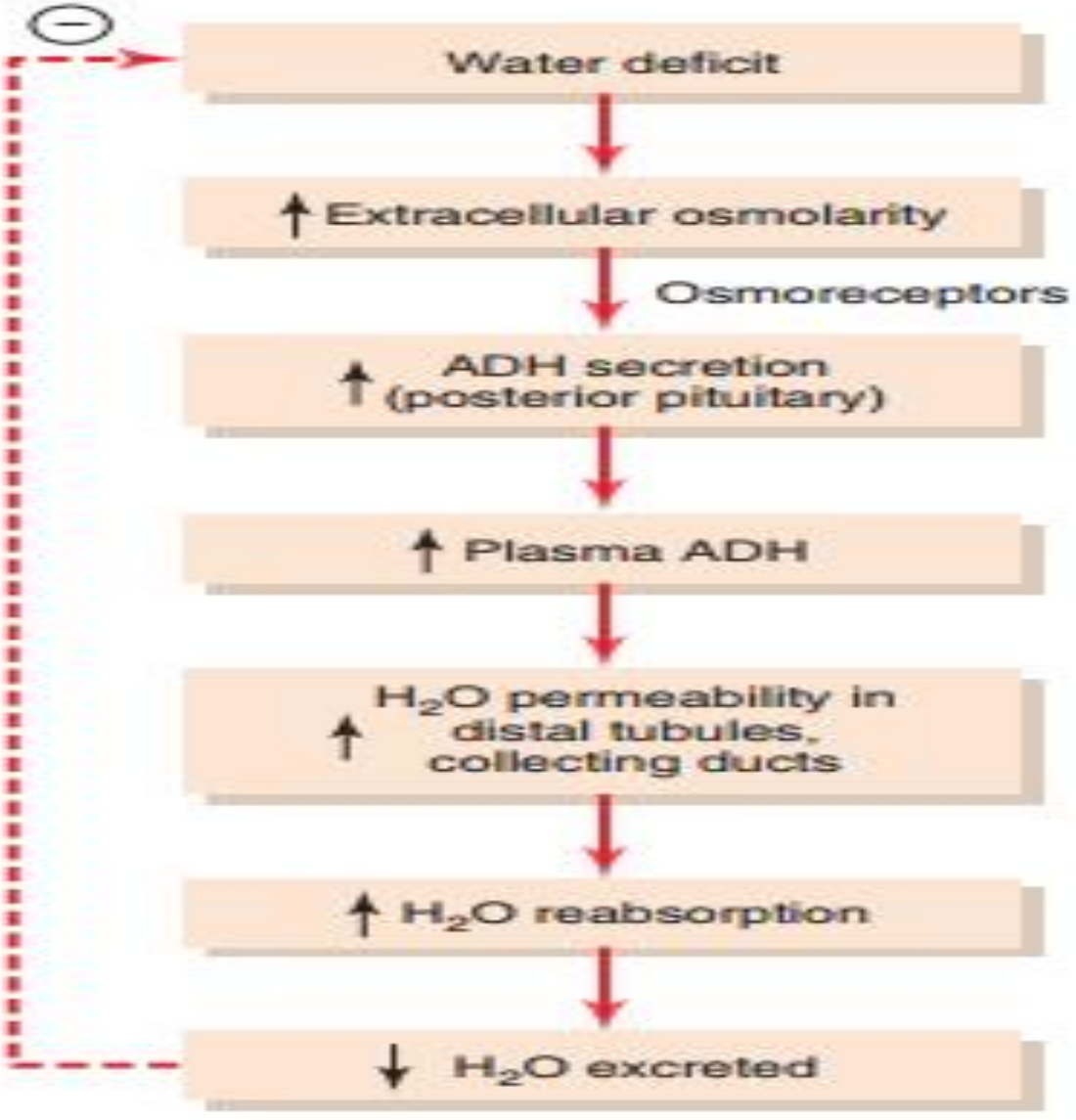


Figure Osmoreceptor-antidiuretic hormone *(ADH)* feedback mechanism for regulating extracellular fluid osmolarity in response to a water deficit.

Secretion Of ADH...,

- ADH synthesis in SON and PVN of the HT and release from the posterior pituitary.
- **Secretion of ADH by the posterior pituitary can be influenced by several factors.**
- The primary physiological regulators of AVP secretion are;
    1. The osmolality of body fluids (**osmotic**).
    2. The volume and pressure of the vascular system (**nonosmotic).**
    3. **Other factors**; nausea (stimulates), ANP (inhibits), and angiotensin II (stimulates)

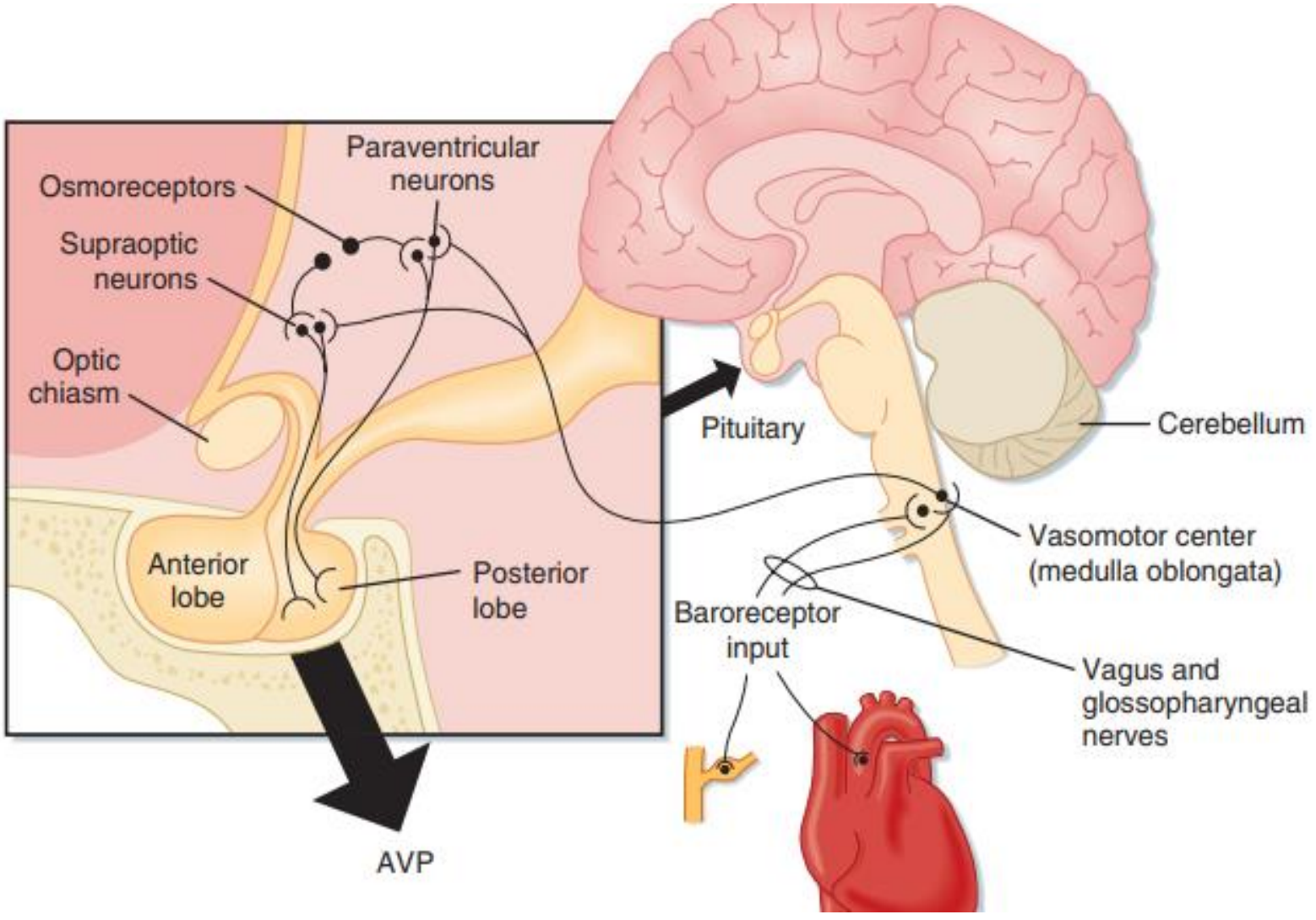
NB: ADH is considerably more sensitive to small changes in osmolarity than to blood volume. only 1 % v 10 %.

Secretion Of ADH…,

- In addition to increased osmolarity, **Decreased arterial pressure** and **Decreased blood volume** increase ADH secretion:
- It is controlled by cardiovascular reflexes, (1) the ***arterial baroreceptor reflexes*** and (2) *the cardiopulmonary reflexes.*

1. Reflex pathways originate in **high pressure regions** of the circulation, such as the **aortic arch and carotid sinus**, and in the **low pressure regions**, especially in the **cardiac atria.**
2. Vagus and glossopharyngeal nerves with synapses in the nuclei of the **tractus solitaries (BS).**
3. Projections from these nuclei relay signals to the hypothalamic nuclei that control ADH synthesis and secretion.

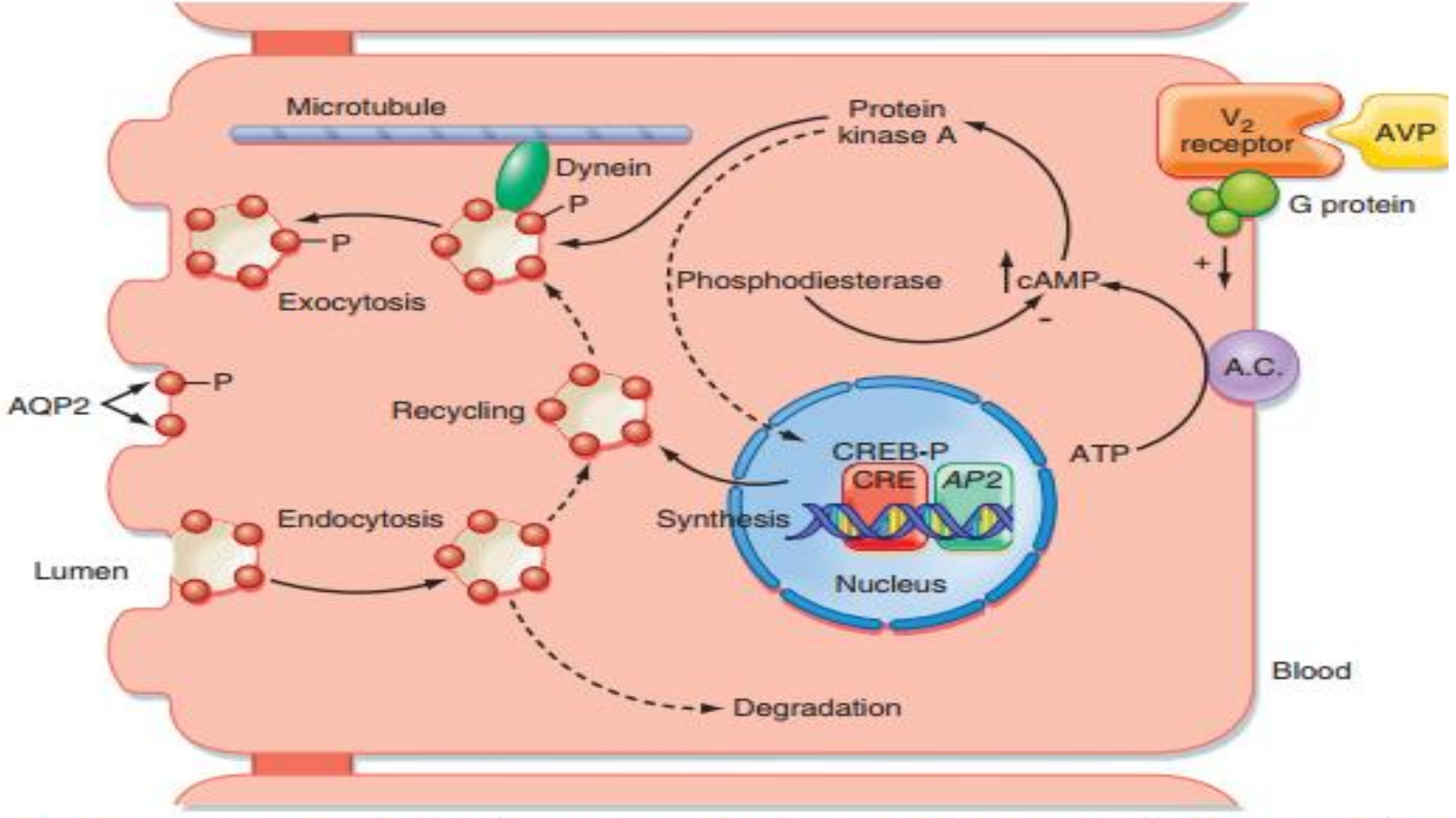
ADH secretion...,



ADH Actions on the Kidney

- Primary action of AVP on the kidneys is to enhance absorption of **water.**
- **Increases water permeability** of the latter portion of the **distal tubule and collecting** duct by regulating long-term expression of **AQP2**.
- In the absence of AVP the apical membrane of these cells contains few water channels (aquaporins).
- AVP also increases the permeability of the terminal portion of the inner medullary **collecting duct to urea.**

ADH Actions...,



• **Fig.** Action of AVP via the V_2 receptor on the principal cell of the late distal tubule and collecting duct. See text for details. AC, adenylcyclase; cAMP, cyclic adenosine monophosphate;

2. Thirst mechanism

- **Fluid intake** is regulated by the thirst mechanism
- Together with the **osmoreceptor-ADH mechanism**, maintains ECF osmolarity and [Na+].

- The **thirst threshold is higher than** the threshold for AVP secretion.
- The neural centers **(the thirst center**) are located in the same region of the hypothalamus involved with regulating AVP secretion.

- Factors that stimulate ADH secretion also **increase thirst**,

Increase Thirst	Decrease Thirst
↑ Plasma osmolarity	↓ Plasma osmolarity
↓ Blood volume	↑ Blood volume
↓ Blood pressure	↑ Blood pressure
↑ Angiotensin II	↓ Angiotensin II
Dry mouth	Gastric distention

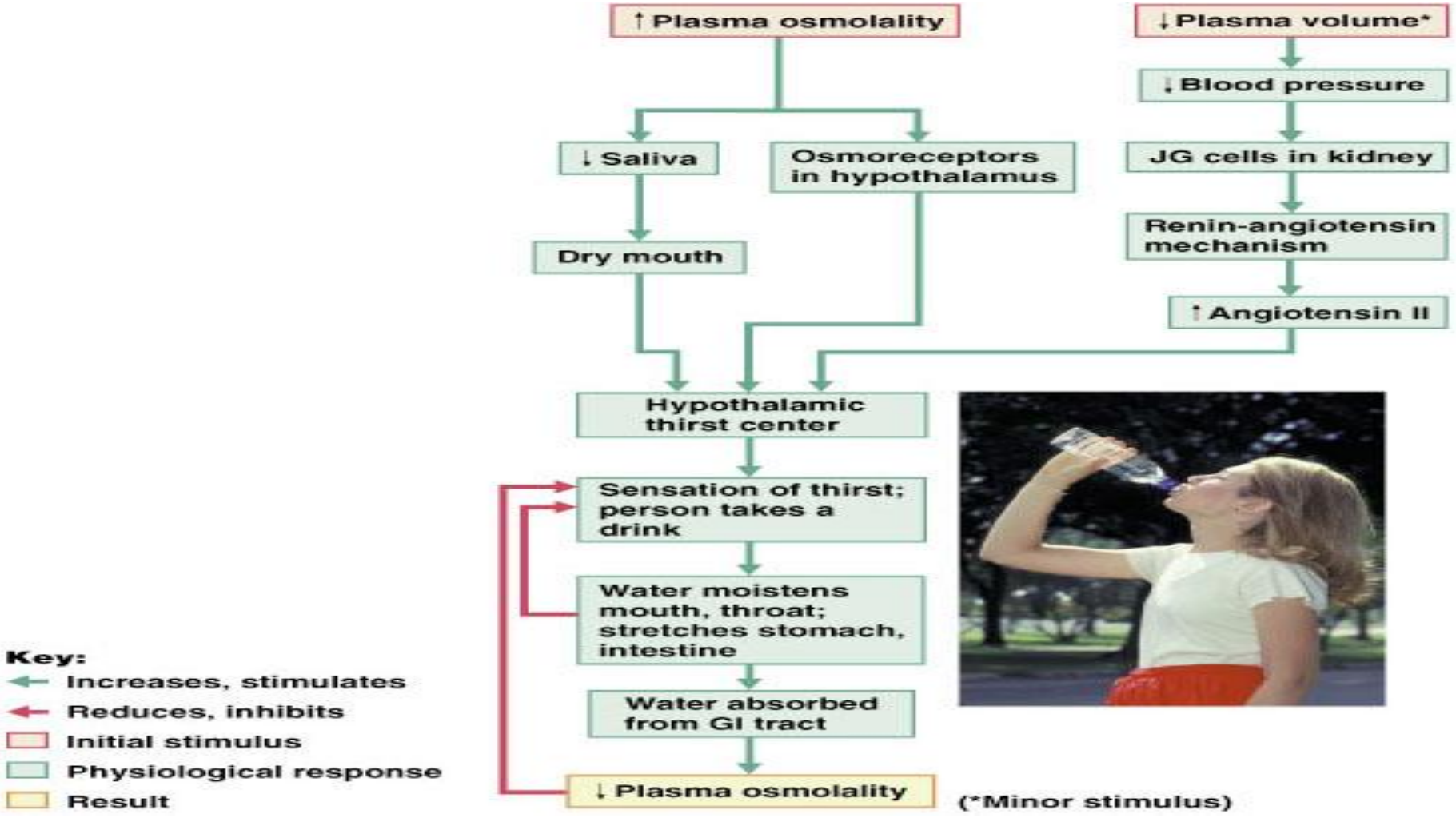
Thirst, ECF osmolarity and Na+ concentration

- When the [Na+] increases only about 2 mEq/L above normal, the thirst mechanism is activated (the *threshold for drinking*).
  1. Increased ECF osmolarity, which causes intracellular dehydration in the thirst centers.
  2. Decreases in ECF volume and arterial pressure.
  3. Angiotensin II
  4. Others, Dryness of the mouth and mucous membranes of the esophagus, Gastrointestinal and pharyngeal stimuli.

Thirst mechanism…,

- The sensation of thirst is satisfied by the act of drinking, even before sufficient water is absorbed.
- Cold water is more effective in reducing the thirst sensation.
- Oropharyngeal and upper gastrointestinal receptors appear to be involved in this response.
- However, relief of the thirst sensation via these receptors is short lived.
- Thirst is only completely satisfied when the plasma osmolality or blood volume or pressure is corrected.

Thirst Mechanism…,



Concepts of body fluid osmolality and its regulation …

2.Reduced osmolarity

- ✓**The decrease in plasma osmolality**
  - ✓**inhibits osmoreceptors in the anterior hypothalamus**.
  - ✓**inhibits secretion of ADH** from the posterior pituitary gland.
  - ✓No ADH is delivered to the kidney
  - ✓**Decreased H2O reabsorption** by DT &CD
  - ✓It also decreases thirst.
- ❑Normalize osmolality
  - ❑ Plasma osmolality increases back toward the normal value.

Renal regulation of osmolality and Na+

- The body regulates ECF volume by adjusting the total-body content of NaCl.
- The body regulates ECF osmolality by adjusting total-body water content.
- The kidneys help to regulate the concentrations of plasma electrolytes, by matching excretion to intake.
- Special regulatory mechanisms maintain the levels of certain specific ions in the ECF.

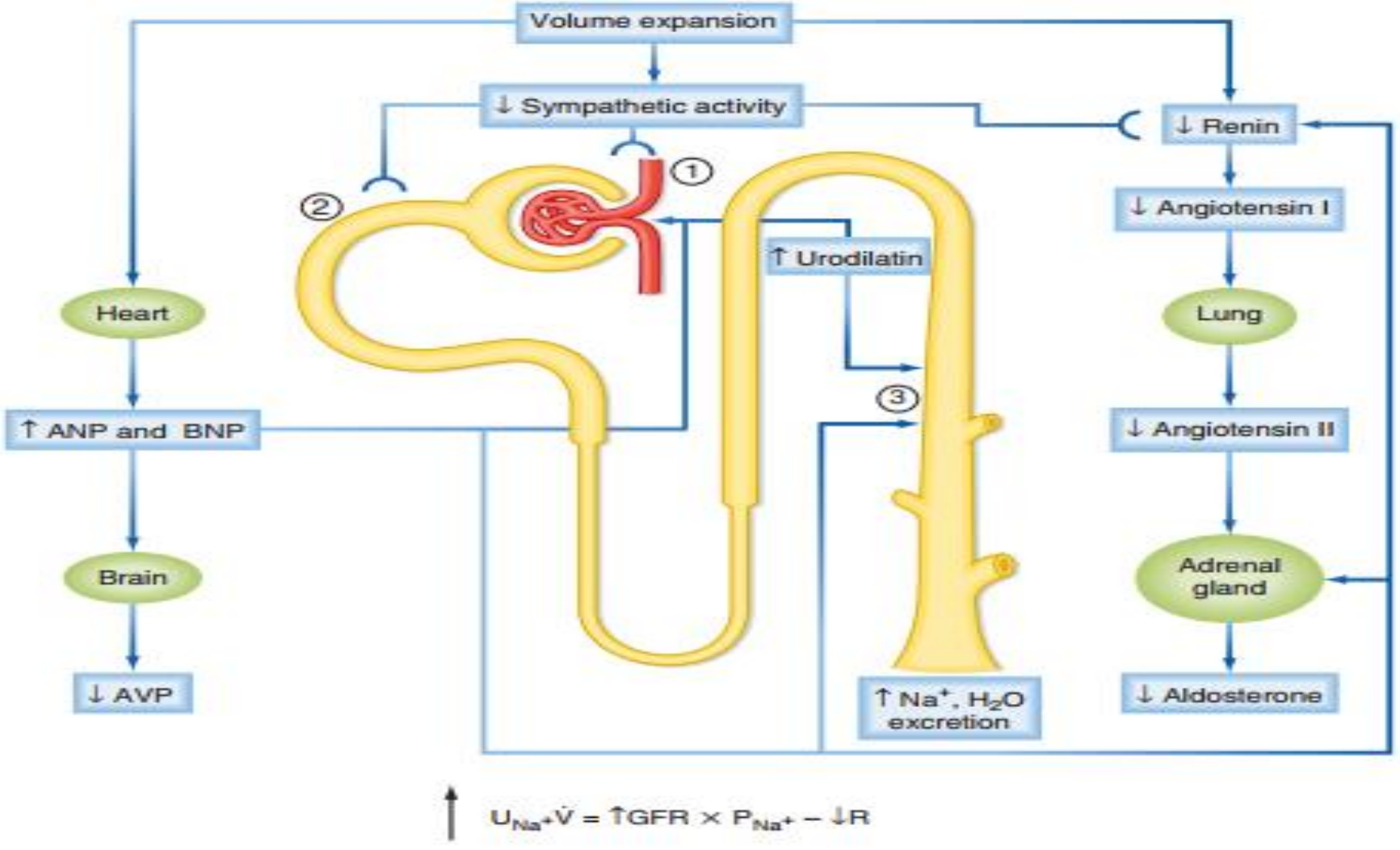
Signals Involved in Control of Renal NaCl and Water Excretion

- **Renal Sympathetic Nerves (↑Activity:↓NaCl Excretion)**
  - ✓↓GFR
  - ✓↑Renin secretion
  - ✓↑Na+ reabsorption along the nephron
- **Renin-Angiotensin-Aldosterone** (↑Secretion: ↓NaCl Excretion)
  - ↑Angiotensin II stimulates Na+ reabsorption along the nephron
  - ↑Aldosterone stimulates Na+ reabsorption in the distal tubule and collecting duct and to a lesser degree in the thick ascending limb of Henle's loop
  - ↑Angiotensin II stimulates AVP secretion

Signals Involved in Control of Renal NaCl and Water Excretion

- **Natriuretic Peptides:** **ANP, BNP** (↑Secretion: ↑NaCl Excretion)
  - ↑GFR
  - ↓Renin secretion
  - ↓Aldosterone secretion (indirect via ↓angiotensin II and direct on adrenal gland)
  - ↓NaCl and water reabsorption by the collecting duct
  - ↓AVP secretion
- **AVP (↑Secretion: ↓H2O Excretion)**
  ↑H2O reabsorption by the distal tubule and collecting duct

Signals Involved in Control of Renal NaCl and Water Excretion



Water Reabsorption

Types of Water Reabsorption

- Water reabsorption in renal tubules is of two types.

Obligatory Reabsorption

- The water reabsorption that occurs secondary to reabsorption of solutes.
- This accounts for about **85% of the total water reabsorption**
- most part of it occurs in proximal tubule.

Facultative Reabsorption

- The water reabsorption occurs secondary to the effects of hormone.
- ***ADH and aldosterone***.
- This accounts for about **15% of total water reabsorption** from kidney.
- Occurs mostly in distal parts of nephron (i**n collecting duct and DCT**).

Aquaporin

- **Thirteen aquaporins** have been identified till date.
- In human beings, **four types of aquaporins** have been characterized.
- These are **aquaporin1, aquaporin2, aquaporin5, and aquaporin9**.
- **Aquaporins1 and 2** are mainly involved in water reabsorption from kidney.

Mechanism of Water Reabsorption

- **Proximal Tubule**
- Normally, **65% of the filtered water** is reabsorbed in the proximal tubule.
- The driving force for water reabsorption is the **transcellular osmotic gradient**.
- Permeability of epithelium of proximal tubule to water is extremely high, due to the presence of **aquaporin1**.
- **In LOH**
- The loop of Henle reabsorbs approximately **15% of the filtered water**.
  1. Water reabsorption **occurs mainly in the descending limb**.
- 2. The water reabsorption in descending limb of LOH **is a passive process** that occurs secondary to higher osmolality of medullary interstitium.

Water absorption…,

In DCT

- DCT is **relatively impermeable to water**. Inspite of osmotic gradient across the tubular epithelium, water reabsorption is poor.
- Only about **5% of the filtered water** is removed in DCT, which is influenced by aldosterone and ADH.

In Collecting Duct

- Collecting duct (CD) has two parts: cortical and medullary.
- Reabsorption of solute and water from the collecting duct mainly depends on the concentration of **ADH acting on it.**
- About 12–15% of water is reabsorbed in collecting duct.

Sodium Homeostasis

- The typical diet contains approximately 140 mEq/ day of Na+ (8-10 gm of NaCl).
- Normal value 135-145 mEq/L in ECF
- Control is through kidneys involving Renin-Angiotensin-Aldosterone system.
- Losses are through the kidneys, GIT and skin

Importance of sodium

- Regulating extracellular volume
- With its attendant ions it regulate osmolarity.
- With its attendant ion it regulates ph.
- Current carrying ion in the body.
- Control of excitability of cells.

Renal sodium handling…,

- Na+ is freely filtered across the glomerular capillaries.
- Na+ is reabsorbed along the entire nephron, and <1% is excreted.
- Approximately 90% of the filtered Na+ reabsorbed in the early part of the nephron.
- PCT reabsorption is constant rate and is not subject to hormonal regulation.
- The final concentration of Na+ urine is determined by processes that occur in the late DCT and CD.
- The reabsorption of Na+ in the distal tubules and collecting ducts of the kidney is regulated by **aldosterone**:

Renal regulation of Na+

The signals acting on the kidneys include:

- Activity of the renal sympathetic nerves
- Release of ANP and BNP from the heart
- **AVP secretion** from the posterior pituitary and AVP action on the collecting duct.
- **Renin secretion** and thus production of angiotensin II.
- **Aldosterone secretion**, which is a consequence of reduced angiotensin II levels, and elevated natriuretic peptide levels.

Renal Na+ Handling…

- **Aldosterone secretion**

What controls physiological aldosterone secretion from the adrenal cortex?

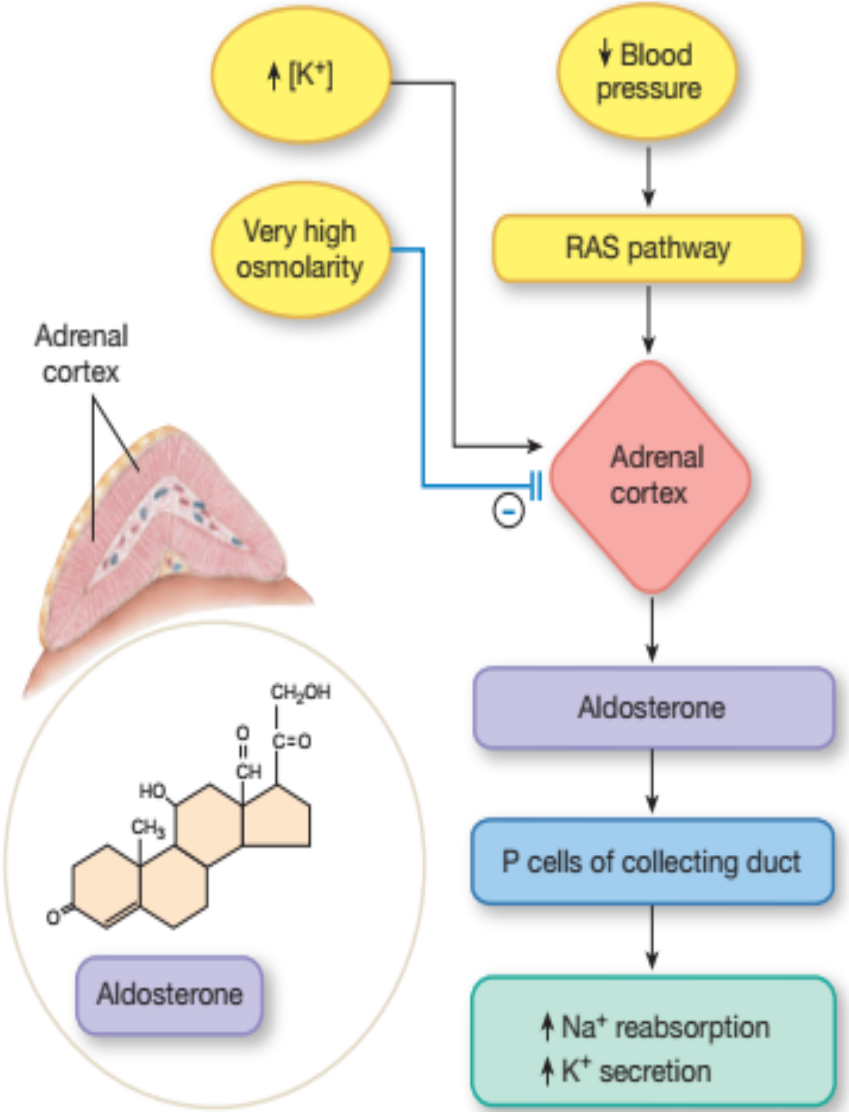
- **Two primary stimuli;**

  1. Increased ECF K+ concentration -Direct

  2. Decreased blood pressure – RAAS

- The primary site of **aldosterone action** is the last third of the distal tubule and the *cortical collecting duct*.
- The primary target of aldosterone is **principal cells (P cells**.
- Principal cells, the apical membranes contain ENaC, and for K+ (called ROMK, BK).

The primary action of aldosterone is renal sodium reabsorption.



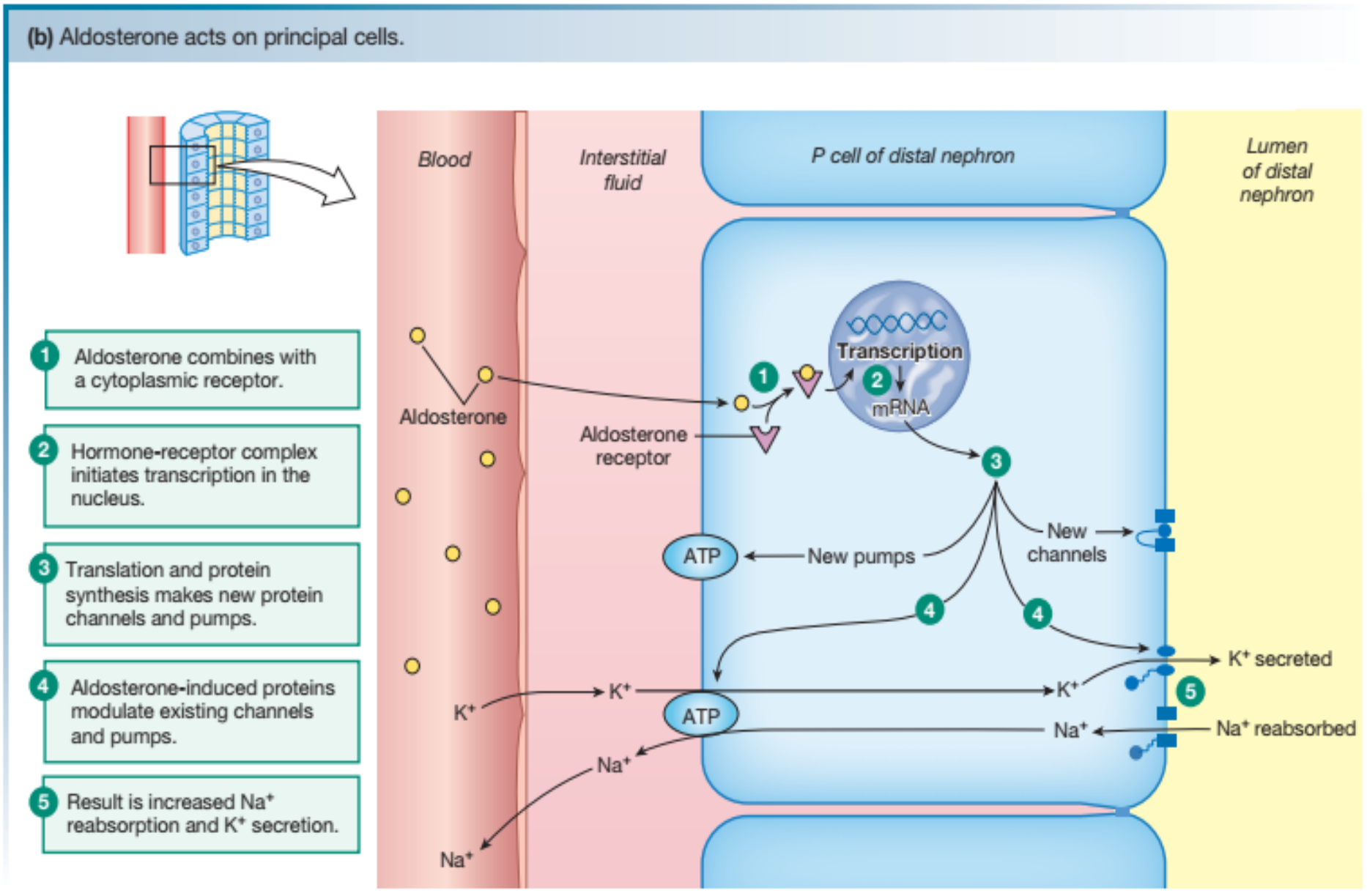
ALDOSTERONE	
Origin	Adrenal cortex
Chemical Nature	Steroid
Biosynthesis	Made on demand
Transport in the Circulation	50–70% bound to plasma protein
Half-Life	15 min
Factors Affecting Release	↓ Blood pressure (via renin) ↑ K^+ (hyperkalemia) Natriuretic peptides inhibit release
Target Cells or Tissues	Renal collecting duct—principal cells
Receptor	Cytosolic mineralocorticoid (MR) receptor
Tissue Action	Increases Na^+ reabsorption and K^+ secretion
Action at Cellular-Molecular Level	Synthesis of new ion channels (ENaC and ROMK) and pumps (Na^+-K^+-ATPase); increased activity of existing channels and pumps.

Effect of Aldosterone

- **Aldosterone** levels enhance Na+ absorption across principal cells in the late DCT and CD.

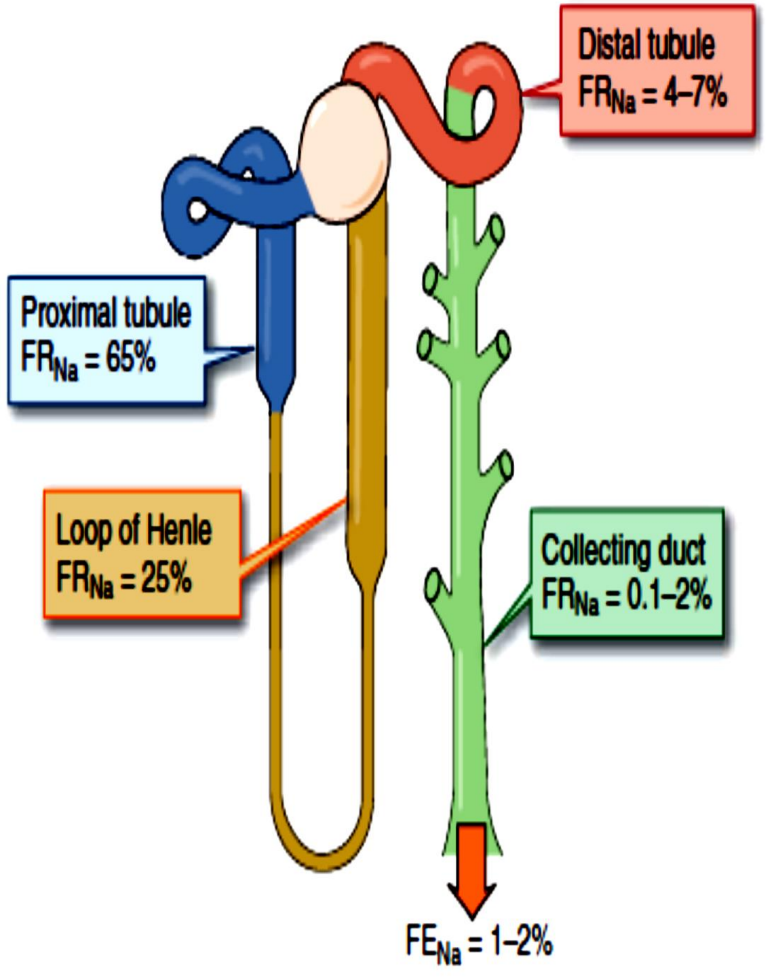
1. Increasing Na+,K+-ATPase in the basolateral membrane;
2. Increasing expression of (ENaC) in the apical cell membrane;
3. Elevating ***g***lucocorticoid-stimulated ***k*inase levels**, which also increases expression of **ENaC** in the apical membrane.
4. Stimulating CAP1 (***c***hannel ***a***ctivating ***p***rotease), which directly activates ENaC;
5. Increases the permeability of the apical membrane to K+ by **increasing the number of K+ channels** in the membrane.

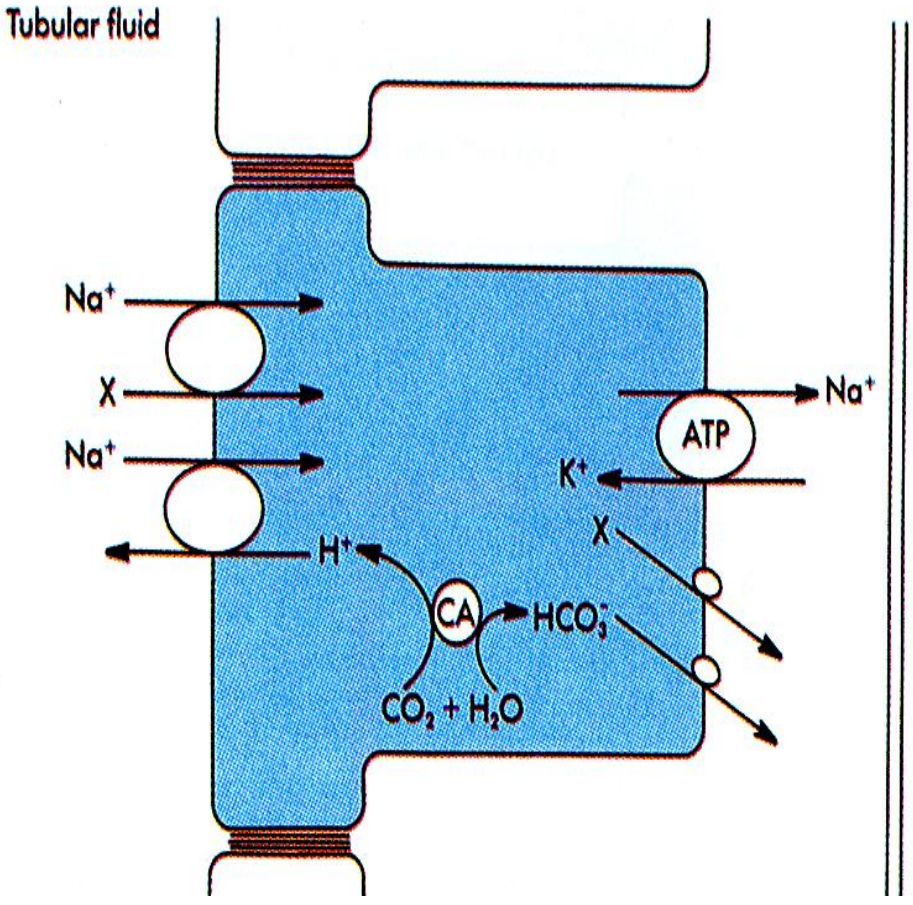
Aldosterone action

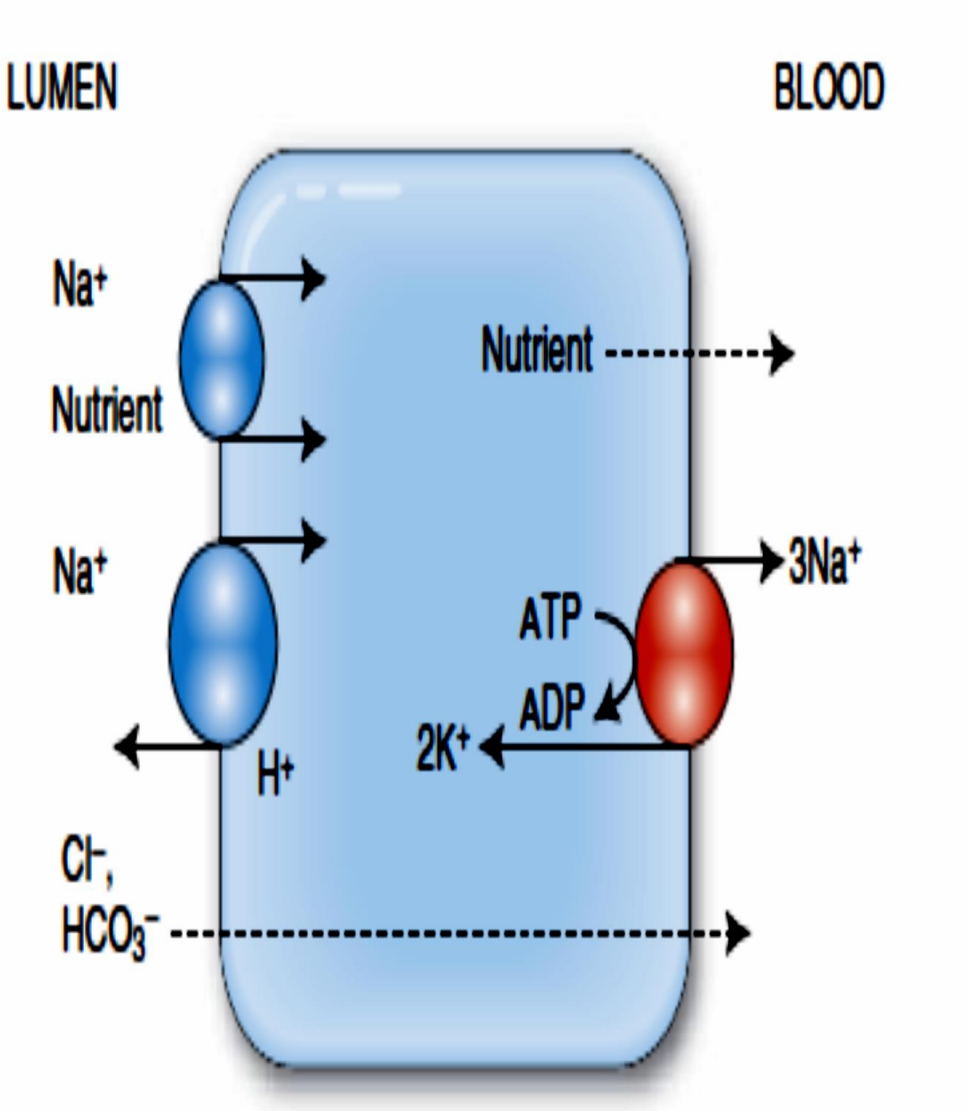


Na^+ Reabsorption…,

- **Filtered load = 600 gm**
- **60 gm/d reach DCT →**
- 70% Obligatory reabsorption in **PCT**
- Proximal convoluted tubule (60-70%)
- **Basolateral mem**. → by Na^+-K^+-ATPase, Na^+-HCO_3^- symporter.
- **Apical Mem**. SGLUT1&2, Na-organic m. symporters, ENC
- 10% aldosterone dependent reabsorption in **DCT**
- *25 mg-15 gm =10 gm/d appear in urine*







Nutrient (X)

- Glucose
- Aminoacids
- Lactate
- Phosphate

Sodium handling by PCT

- ↑GFR= ↑ filtered load, ↑reabsorption rate and ↑excretion rate
- Hypernatremia- ↑tubular load, back Na diffusion, ↑sodium loss
- Alkalosis: Increases sodium loss
- ANP: Increases sodium loss
  - **Relax mesangial cells**
  - **Antagonize aldosterone**
  - **↓ADH**
- Aldosterone: Decrease sodium loss

- Thin ascending limb: *Minor passive reabsorption*
- *Thick ascending limb (20%):* *Na^+-K^+-$2Cl^-$ transport*

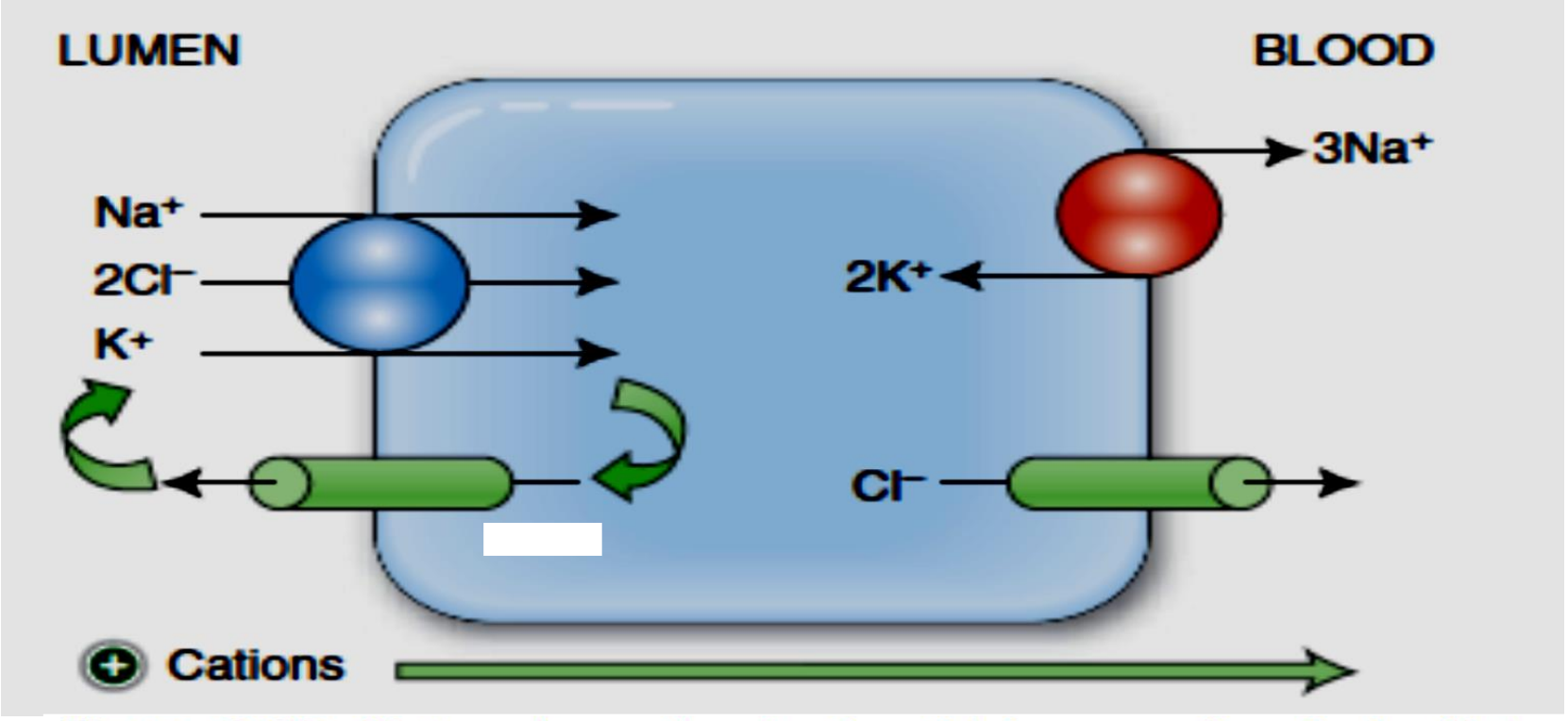
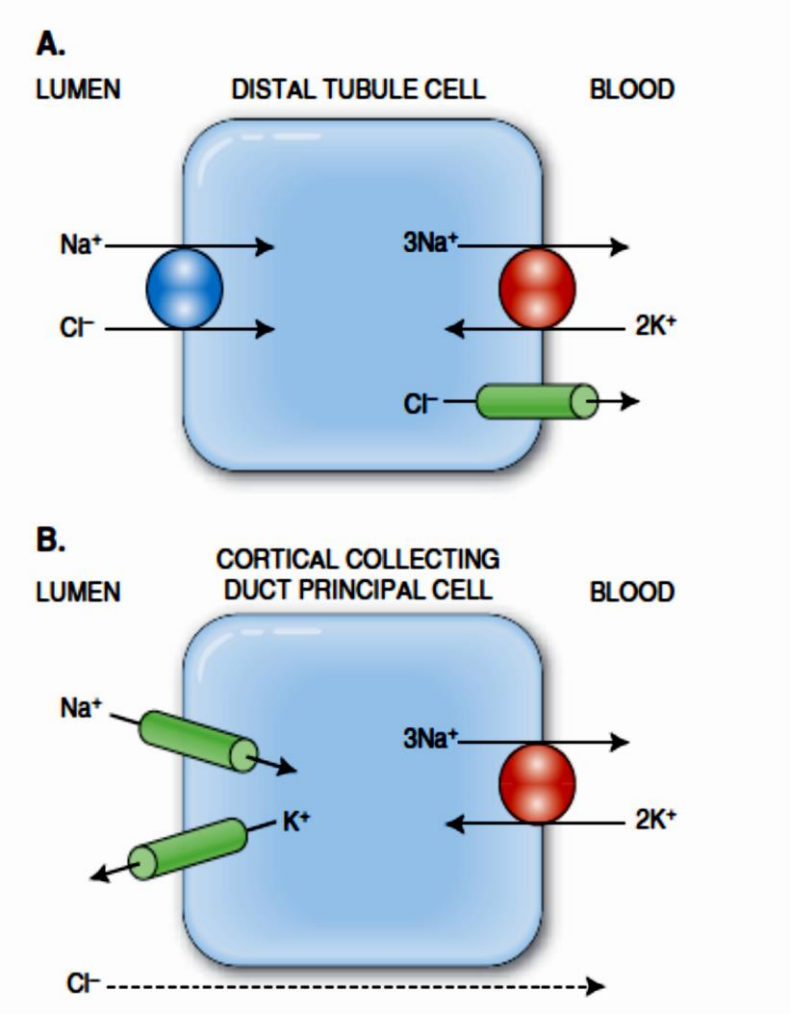


Figure 6-20: Na^+ reabsorption in the thick ascending limb. Na^+ uptake occurs via the $Na^+/K^+/2Cl^-$ cotransport. The combination of luminal K^+ channels and basolateral Cl^- channels creates a lumen-positive transepithelial potential difference, which drives paracellular cation reabsorption.

Sodium reabsorption in DCT/CD

- *Na^+-H^+ exchange: Aldosterone dependent*
- *Na^+-K^+ Atpase: Aldosterone dependent*
- Aldosterone $\rightarrow\uparrow Na^+$-K^+-ATPase synthesis
- $\rightarrow \uparrow$metabolic reactions for ATP synthesis
- $\rightarrow \uparrow$membrane permeability to Na^+ and K^+



Regulation of [Na^+] and osmolality

↑[Na+] and **↑Osmolality**

↓

Stimulates osmoreceptors in the **SON** of **HT**

↓

↑ADH secretion

↓

↑H2O reabsorption in the DT and CD

↓

↓[Na+] and **↓Osmolality** back to normal

↓[Na+] or **↓Osmolality** & ↑[K+]

↓

Stimulates **adrenal cortex**

↓

↑Aldosterone secretion

↓

↑Na+ reabsorption

↑K+ excretion in DT and CD

↓

↑[Na+] &**↑Osmolality** **↓[K+]** back to normal

Renal [K+] regulation

- Total body K+ is 50 mmo1/kg of body weight.
- A total of 98% of the K+ is within cells, where its average [K+] is 150 mEq/L.
- Only 2% of K+ is in the ECF, where its normal concentration is approximately 4 mEq /L.
- [K+] in the ECF that exceeds 5.0 mEq/L **hyperkalemia** or
- Less than 3.5 mEq/L constitutes **hypokalemia.**

K_+ Homeostasis….,

K+ is critical for many cell functions, including;

- **Cell volume regulation,**
- **Intracellular pH regulation,**
- **DNA and protein synthesis,**
- **Growth, enzyme function,**
- **RMP, and cardiac and neuromuscular activity**.

K_+ Homeostasis…,

Several factors can alter the plasma [K+] altering the movement of K+ between the ICF and ECF.

1. **Acid-Base Disturbance;** The increased [H+] promotes the movement of H+ into cells and the reciprocal **movement of K+ out of cells** to maintain electro neutrality. **Acidosis inhibits the transporters** that accumulate K+ inside cells,

2. **Plasma Osmolality;** The alterations in plasma [K+] associated with changes in osmolality are related to **changes in cell volume**.

3. **Cell Lysis;** Cell lysis causes hyperkalemia, which results from the addition of intracellular K+ to the ECF

4. **Exercise ;** More K+ is released from skeletal muscle cells during exercise than during rest. (Sympathetic, & cell volume, Muscle contraction).

K_+ Homeostasis.,

The only plasma electrolyte that is reabsorbed and secreted.

- Urinary K+ excretion is about 15% of the amount filtered.
- **Two sets of regulatory mechanisms maintain K+ homeostasis**.

1. **Regulate [K+] in the ECF, like hormones.**
2. **Adjusting renal K+ excretion to match dietary K+ intake**

K_+ Homeostasis…,

- Excretion of K+ by the kidneys after a meal is slow, uptake of K+ by cells is essential to prevent life-threatening hyperkalemia.
- **Maintaining total body [K+] constant requires that all the K+ absorbed by the GI tract eventually be excreted by the kidneys.**
- Normally, K+ reabsorption is less than filtration, resulting in excretion of 10 -20% of the filtered load of K+ .
- If plasma K+ fall, more K+ is reabsorbed and excretion can be as little as 2% of the filtered load.
- If K+ excess , K+ can be excreted above filtration load.

K_+ Homeostasis...,

Hormones, including **epinephrine, insulin, and aldosterone,** increase uptake of K+ into;

- skeletal muscle, liver, bone, and red blood cells

- By stimulating Na+, K+-ATPase, 1Na+/1K+/2Cl-, and Na+/Cl-.

➢The rise in plasma [K+] that follows K+ absorption by the GI tract stimulates;

➢ Secretion of insulin from the pancreas,

➢Release of aldosterone from the adrenal cortex, and

➢Secretion of epinephrine from the adrenal medulla.

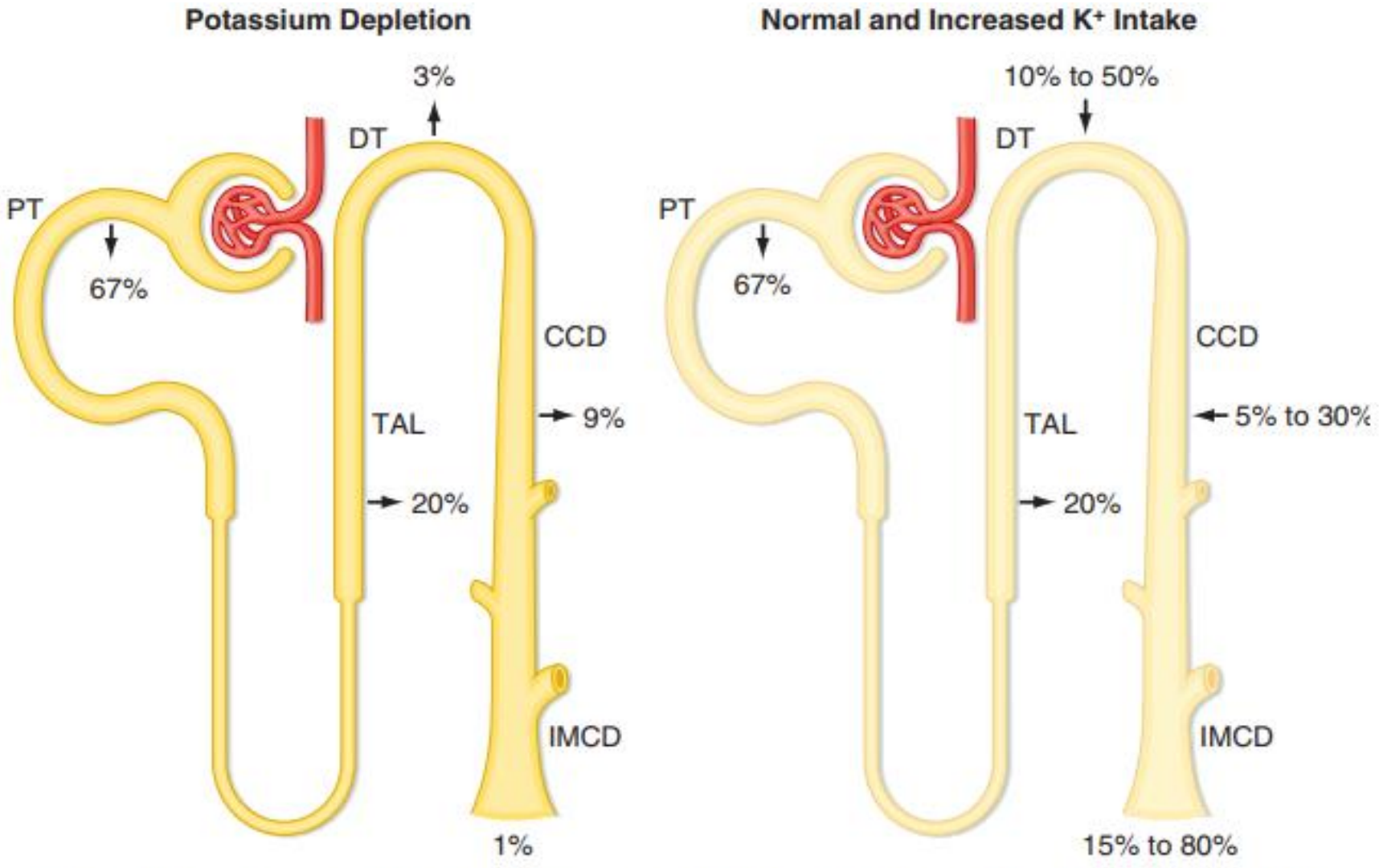
Renal regulation of K+…,

1. **Epinephrine; affect** the distribution of K+ across cell membranes by adrenergic receptors. The stimulation of β2-adrenceptors promotes K+ uptake by cells.
2. **Insulin;** Insulin is **the most important** hormone that shifts K+ into cells after the ingestion of K+ in a meal.
3. **Aldosterone;** Aldosterone, also promotes K+ uptake into cells.

- **Thus aldosterone** alters the plasma [K+] by acting on K+ uptake into cells and by altering urinary K+ excretion

Renal regulation of K+

- **The proximal tubule** reabsorbs about 67% of the filtered K+ under most conditions.
- **Thick ascending loop of Henle ;** ~20% of the filtered K+ is reabsorbed by the **loop of Henle**. Na-K-2Cl-
- In contrast to these nephron segments, which can only reabsorb K+, the **distal tubule and collecting duct** are able to reabsorb or secrete K+.
- **Type-A intercalated cells in DCT & CD** (
    - K-H counter transport)

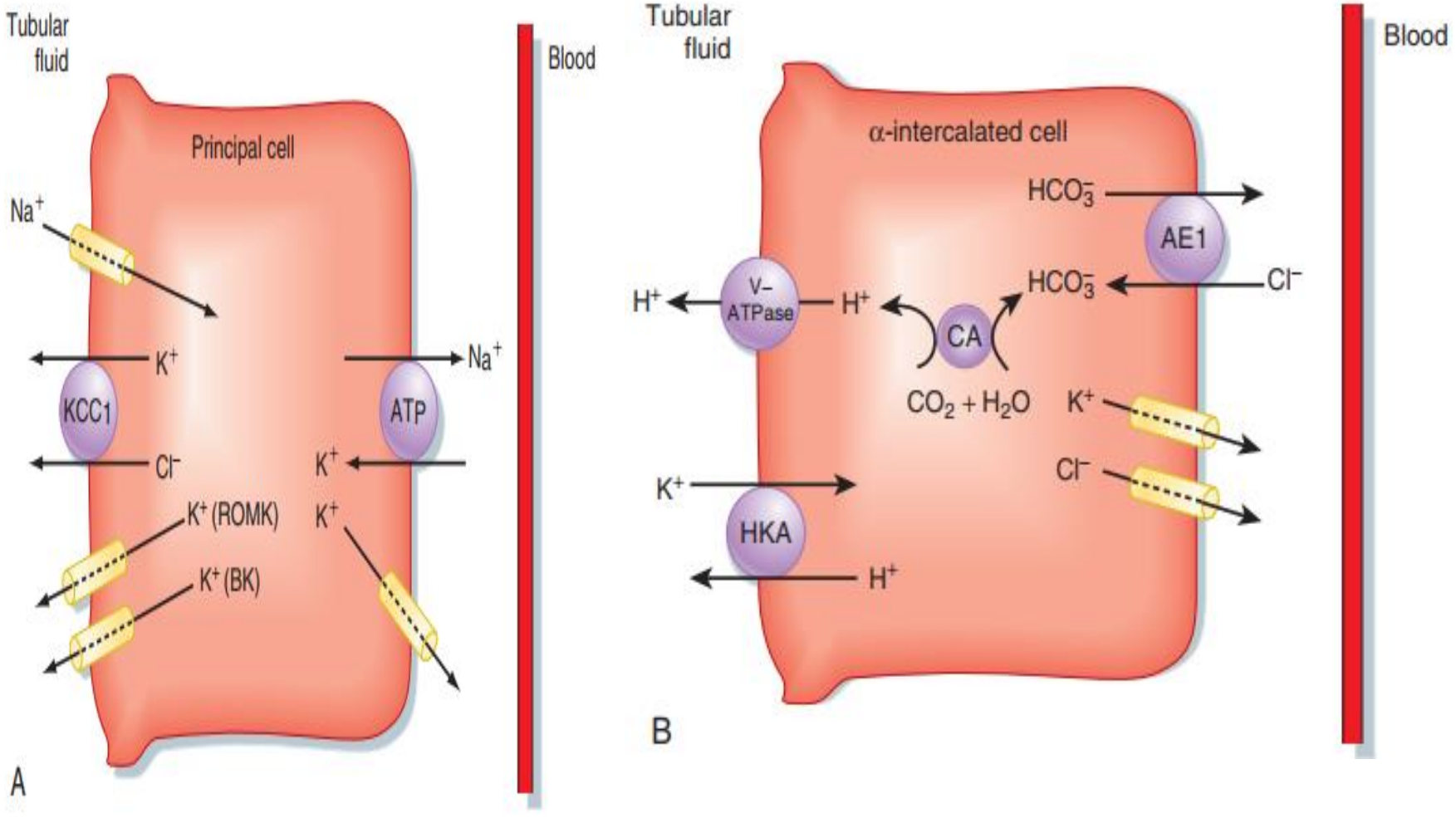


• **Fig. 36.4** K^+ transport along the nephron. Excretion of K^+ depends on the rate and direction of K^+ transport by the late segment of the distal tubule and collecting duct. Percentages refer to the amount of filtered K^+ reabsorbed or secreted by each nephron segment. Arrows indicate direction of transport.

K+ Excretion by the Kidneys

- **K+ secretion** from the distal tubule and collecting duct system is the **key factor**.
- **Plasma [K+]** is an important determinant of K+ secretion.
  - Hyperkalemia stimulates Na+, K+-ATPase and K+ uptake across the basolateral membrane. This raises intracellular [K+] and increases the electrochemical force for exit of K+ to apical membrane.
  - Hyperkalemia also increases the permeability of the apical membrane to K+.
  - Hyperkalemia stimulates secretion of aldosterone by the adrenal cortex,

Cellular Mechanism

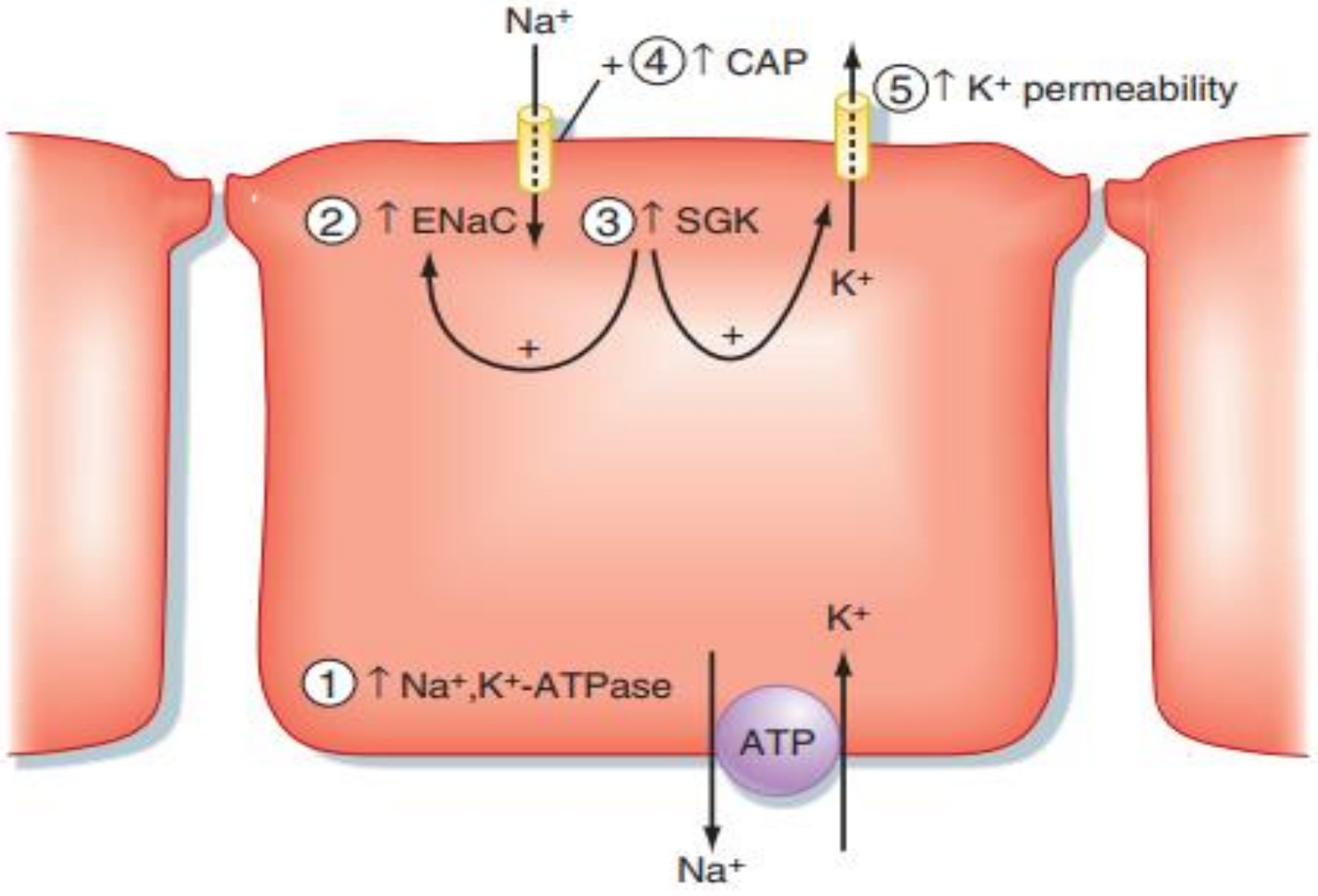


Effect of Aldosterone on K+

- **Aldosterone** levels enhance secretion of K+ in the DCT&CD

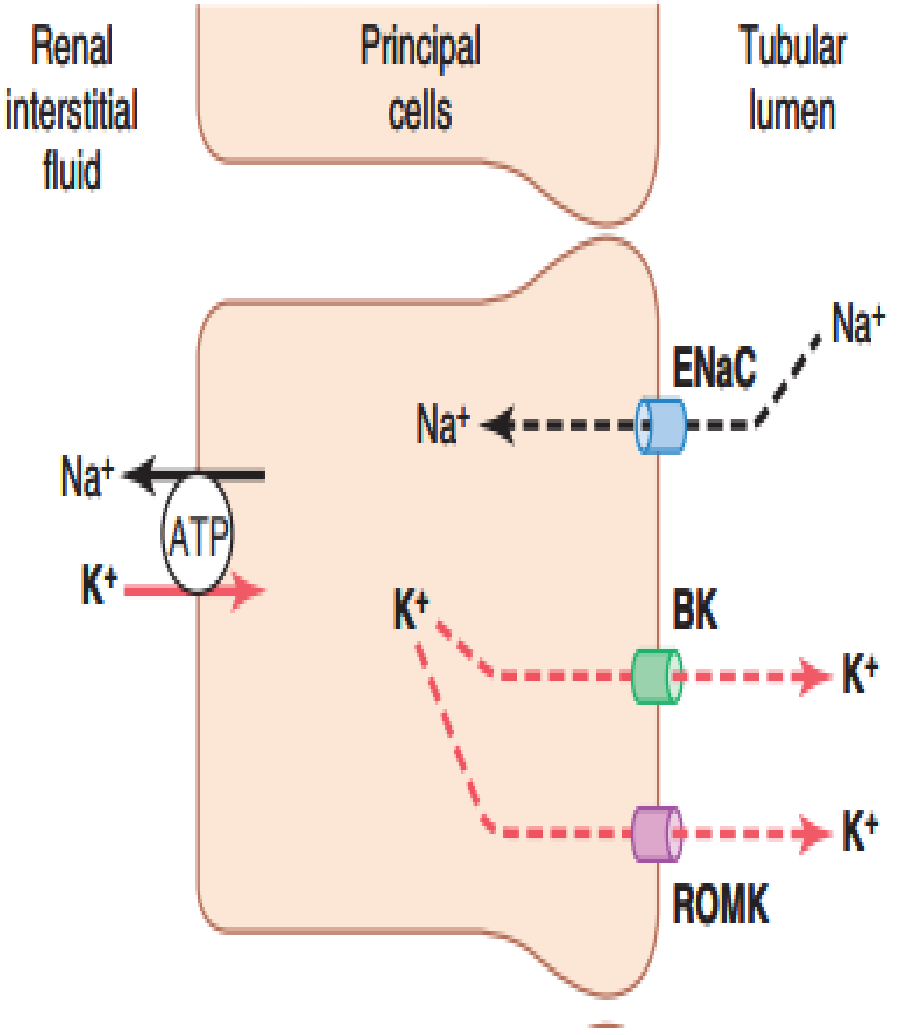
1. Increasing the amount of Na+,K+-ATPase in the basolateral membrane;
2. Increasing expression of the epithelial sodium channel (ENaC) in the apical cell membrane;
3. Elevating ***g***lucocorticoid-stimulated ***k*inase levels**, which also increases expression of **ENaC** in the apical membrane and activates K+ channels;
4. Stimulating CAP1 (***c***hannel ***a***ctivating ***p***rotease), which directly activates ENaC;
5. Increases the permeability of the apical membrane to K+ by **increasing the number of K+ channels** in the membrane.

Aldosterone effect on DCT and CD



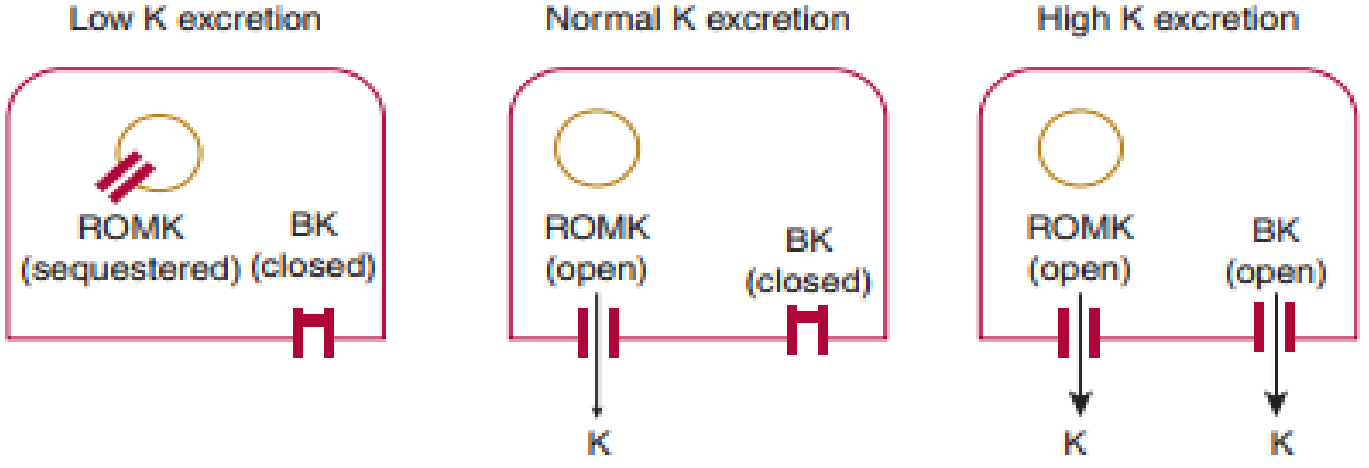
K^+ secretion

- Active process in the DT which is **aldosterone** dependent.
- Basolateral active K-Na exchanger to build up K inside principal cells.
- Electrochemical gradient from ICF to the lumen of the tubules.
- Apical K+ channel permeability into the lumen & K secretion by **P- cells of DCT and CD.**



K^+ secretion…,

- Under modest potassium loads (**normal conditions**), ROMK channels secrete K+, while BK channels closed.
- When the body is **conserving potassium**, ROMK channels sequestered in intracellular vesicles and BK channels are closed;
- When potassium **excretion is very high**, ROMK channel activity is maximized and BK channels are open, allowing substantial secretion.



Activity of ROMK and BK potassium channels in principal cells under different conditions.

Calcium Homeostasis

- **Calcium distribution**
  - 99% is found in the bones, 0.7% located in ECF
  - **0.1%-0.3% in side the cells**
- **Extracellular calcium exists in three forms**
  - Protein bound (40%)
  - Complexed with citrate, phosphate, sulfate (10%)
  - Ionized (50%)

Functions of calcium

- Neuronal excitability
- Muscle contractions
- Releases of hormones, NT
- Blood clotting
- Enzymatic reactions
- Bone formation
- Second messengers

Calcium Homeostasis…,

- Calcium homeostasis depends on
  - Total amount of Ca^{2+} in the body
  - Distribution of Ca^{2+} between ECF and ICF
- Total Ca^{2+} in the body depends on
  - Amount absorbed from GIT
  - Amount excreted
- Amount absorbed from GIT depends on
  - Calcitriol which $\uparrow Ca^{2+}$ absorption
- Amount excreted by the kidney parallels amount absorbed by the GI.

Calcium Homeostasis…,

- The total Ca++] in plasma is 10 mg/dL (2.5 mmol/L, or 5 mEq/L)
- **Ca^{2+} absorption in PCT and TALH**
  - 60% reabsorption in PCT
  - 37% reabsorption in TALH, DCT and CD
  - **Passive** (calcium channels,)
  - Paracellular
  - Driven by elecrochemical forces created by Na

Calcium Homeostasis…,

- **Ca^{2+} absorption in DCT&CD** is
  - Active
  - Transcellular
  - Site of homeostatic control of Ca^{2+} absorption
  - Increasing dietary Ca^{2+} does not increase much its renal excretion because most will not be reabsorbed.
  - **PTH increase** its reabsorption in DCT.

Ca++ Reabsorption

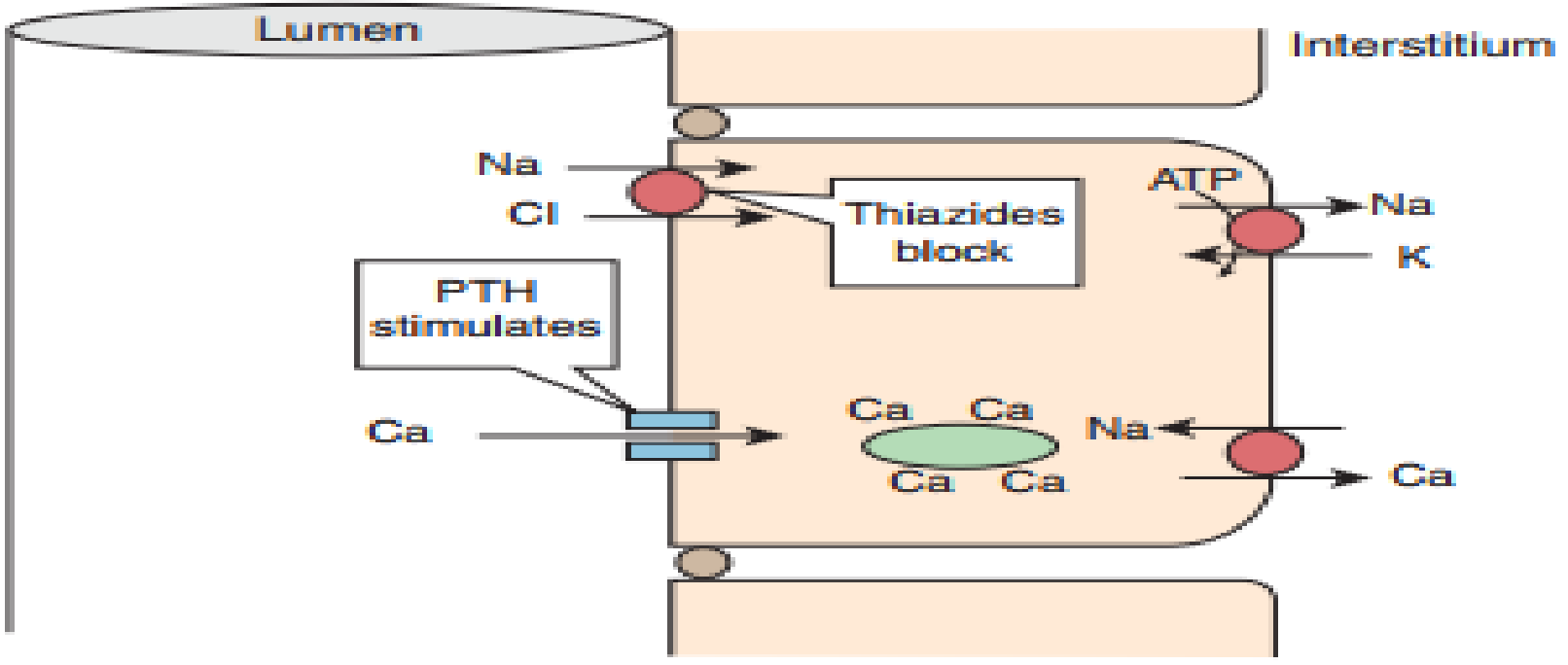
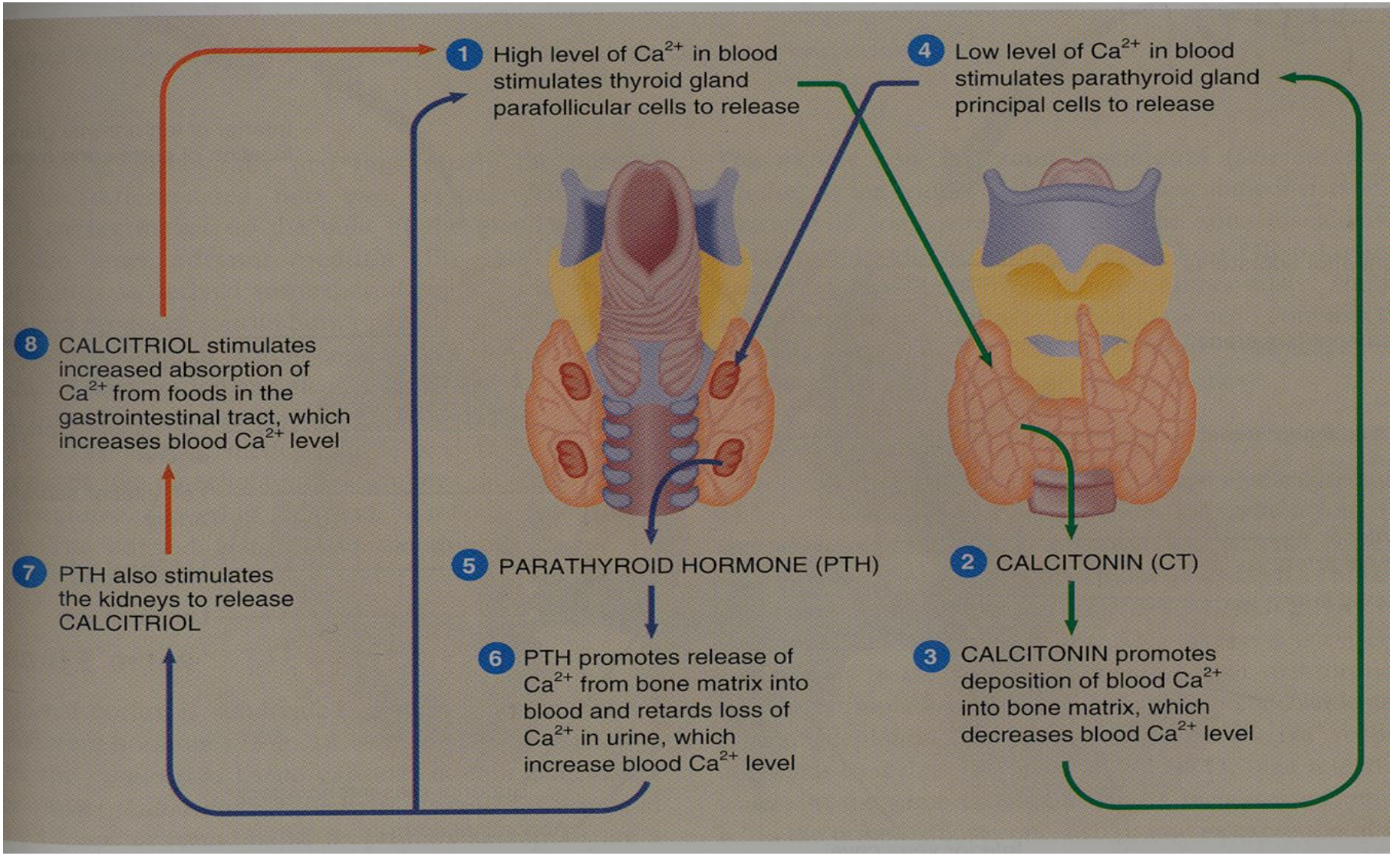


FIGURE **Mechanism of calcium reabsorption in the distal convoluted tubule, which is the major site for regulated reabsorption.** Ca enters via apical Ca channels, under the control of PTH, and is actively transported across the basolateral membrane via Na–Ca antiport and via a Ca-ATPase.

- **Blood calcium level is regulated mainly by three hormones**
  - **PTH, calcitriol,Calcitonin.)**



Control of calcium excretion

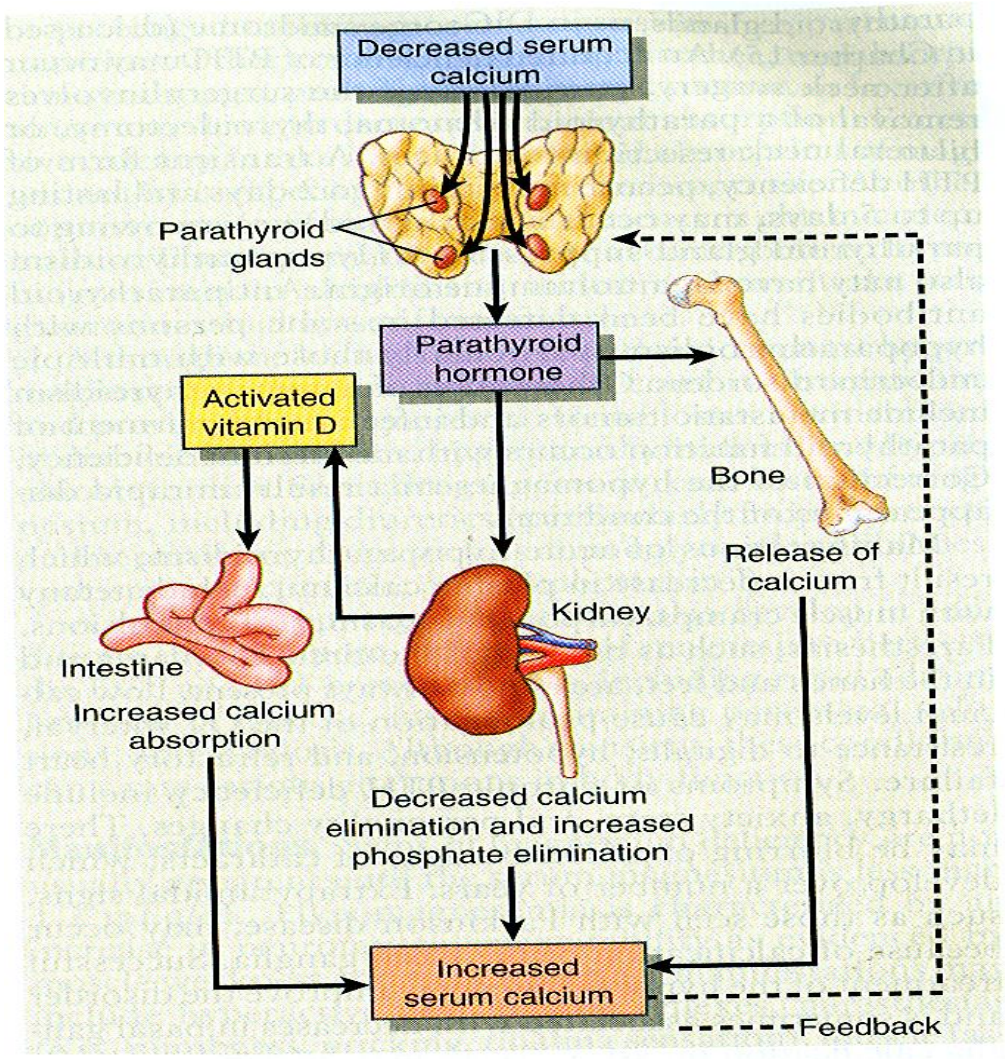
- **The CaSR** expressed in the plasma membrane of cells involved in regulating Ca++ homeostasis.
- Ca++ binds to CaSR receptors in PTH secreting cells of the parathyroid gland and calcitriol-producing cells of the proximal tubule.
- Activation of the receptor by an increase in plasma [Ca++] results in inhibition of PTH secretion and the production of calcitriol.

Effect of PTH

- PTH regulates plasma calcium concentration through **Four main effects:**

1. Stimulating bone resorption(enhance osteclast activity)
2. Stimulating **activation of vitamin D,** which then increases intestinal reabsorption of calcium; and
3. Directly increasing **renal tubular calcium reabsorption**
4. *Reduces* the proximal tubular reabsorption of phosphate, thereby decreasing extracellular phosphate concentration.

Calcium Homeostasis…,



Regulation of serum calcium concentration by parathyroid hormone.

Effect of PTH on renal tubules

- **↑reabsorption of ca^{2+} in DCT& CD**
- **decrease ca2+ excretion by the kidney**
- **↑1, 25 $(oh)_2$ d_3 formation at proximal cells**

Role of V-D

- **Roles of 1, 25 $(OH)_2$ D_3**
  - ↑Release of Ca^{2+} from bone
  - ↑Absorption of Ca^{2+} in intestine
    - **Calcitriol is involved in the formation of calbindin, Ca^{2+} channels and ca^{2+} ATPase**
  - ↑ Reabsorption of Ca^{2+} in the renal tubules
  - Calcitriol increases **Na^+-phosphate co-transporter gene** expression in proximal tubules facilitating **phosphate reabsorption**

Phosphate homeostasis

- Importance of PO_4
  - Intracellular anion
  - Intermediate in glucose metabolism
  - Structure of high energy system of cells
  - Cofactor (Phosphatidylcholine), DNA, RNA
  - Covalent modifier of many enzymes
  - Major bone constituent
  - Important buffer

Phosphate homeostasis…,

- Normal plasma concentration
  - 2.4 -4.5 mg/dl

- Net absorption of phosphate from GIT is directly related to intake.
- Urinary excretion is the main regulatory mechanism for **phosphate balance**

- Tubular reabsorption varies between 70%-100%, flexibility to compensate for variations.

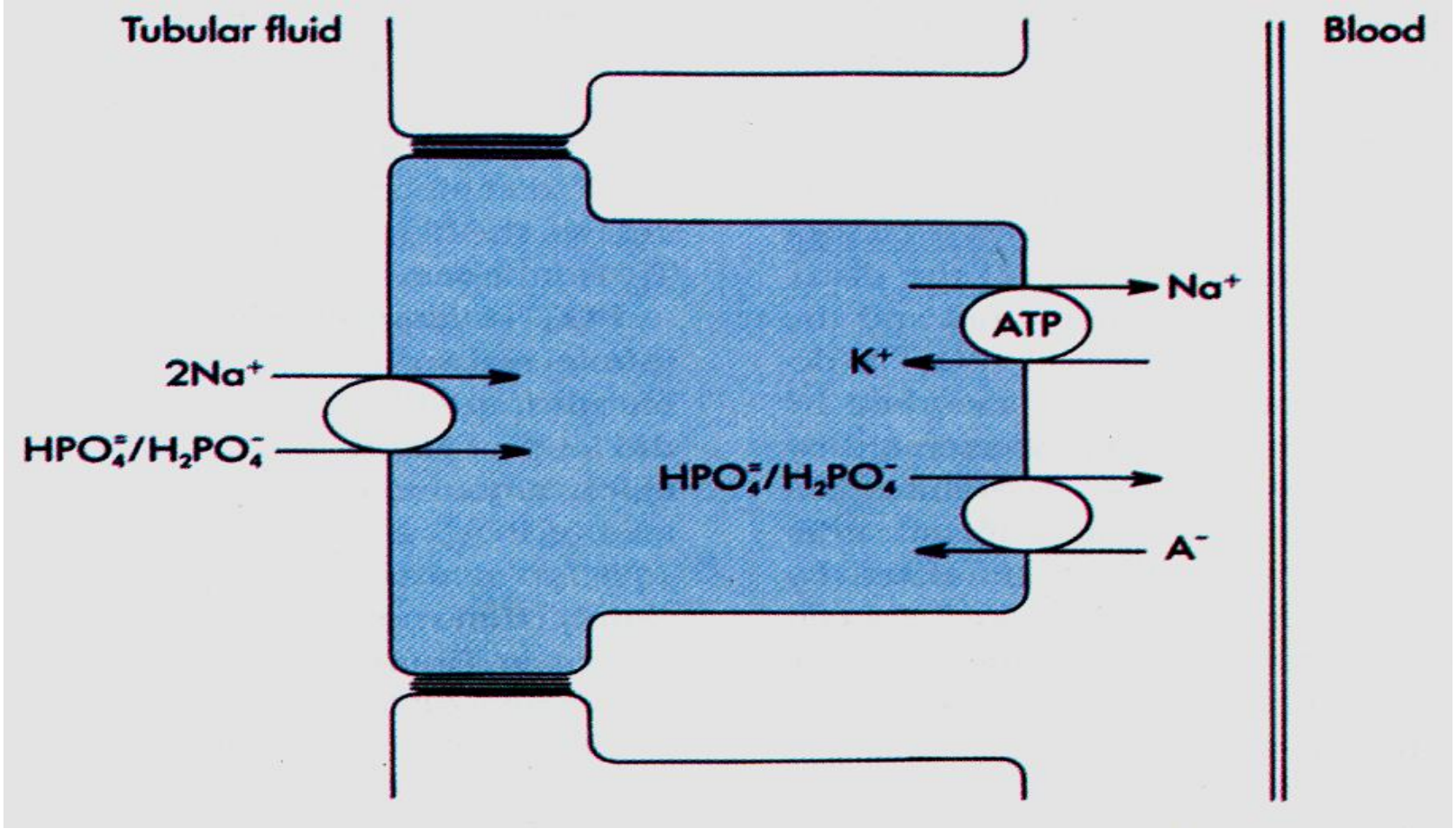
Distribution of PO_4^-

- 85 in bones
- 15% in ICF
- 0.03% in ECF
  - 90% free and filterable
  - 10% protein bound
- 75% of filtered is reabsorbed in PCT actively by co-transport with sodium
- <25% is controlled reabsorption in DCT depending on its GIT absorption

Distribution of PO_4^-

- Phosphate balance involves
  - GIT absorption (calcitriol dependent) which is
    - Active
    - Passive
  - Renal excretion
    - Increase in its intake result in increase of its excretion (PTH) dependent
  - Distribution between ICF and ECF

- Renal reabsorption requires
  - Apical Na-Phosphate cotransport
  - Basal Anion-Phosphate antiport



Micturition

- Process by which the **urinary bladder empties** when it becomes filled
  - First, the **bladder fills progressively** until the tension in its walls rises above a threshold level.
  - This elicits the second step, which is a nervous reflex called **the micturition reflex** that empties the bladder or,
  - It finaly causes a conscious desire to urinate.
- The micturition reflex is an autonomic spinal cord reflex,
- it can also be inhibited or facilitated by centers in the **cerebral cortex or brain stem**

The Micturition Reflex

- Discharge of urine from the urinary bladder, called micturition, is also known as **urination or voiding**.
- Micturition occurs via a combination of **involuntary and voluntary muscle contractions.**
- When the volume of urine in the urinary **bladder exceeds 200–400 mL,** pressure within the bladder increases.
- These impulses propagate to the micturition center in **sacral spinal cord segments S2 and S3 trigger** a spinal reflex called **the micturition reflex.**

Micturition reflex…,

- Micturition is a simple spinal reflex that is subject to both conscious and unconscious control.
- As the bladder fills with urine and its walls expand, **stretch receptors** send signals via sensory neurons to the spinal cord.
- The stimulus of a full bladder excites parasympathetic neurons leading **to the smooth muscle** in the bladder wall.
- The smooth muscle contracts, increasing the pressure on the bladder contents.
- Simultaneously, **somatic motor neurons** leading to the external sphincter are inhibited.

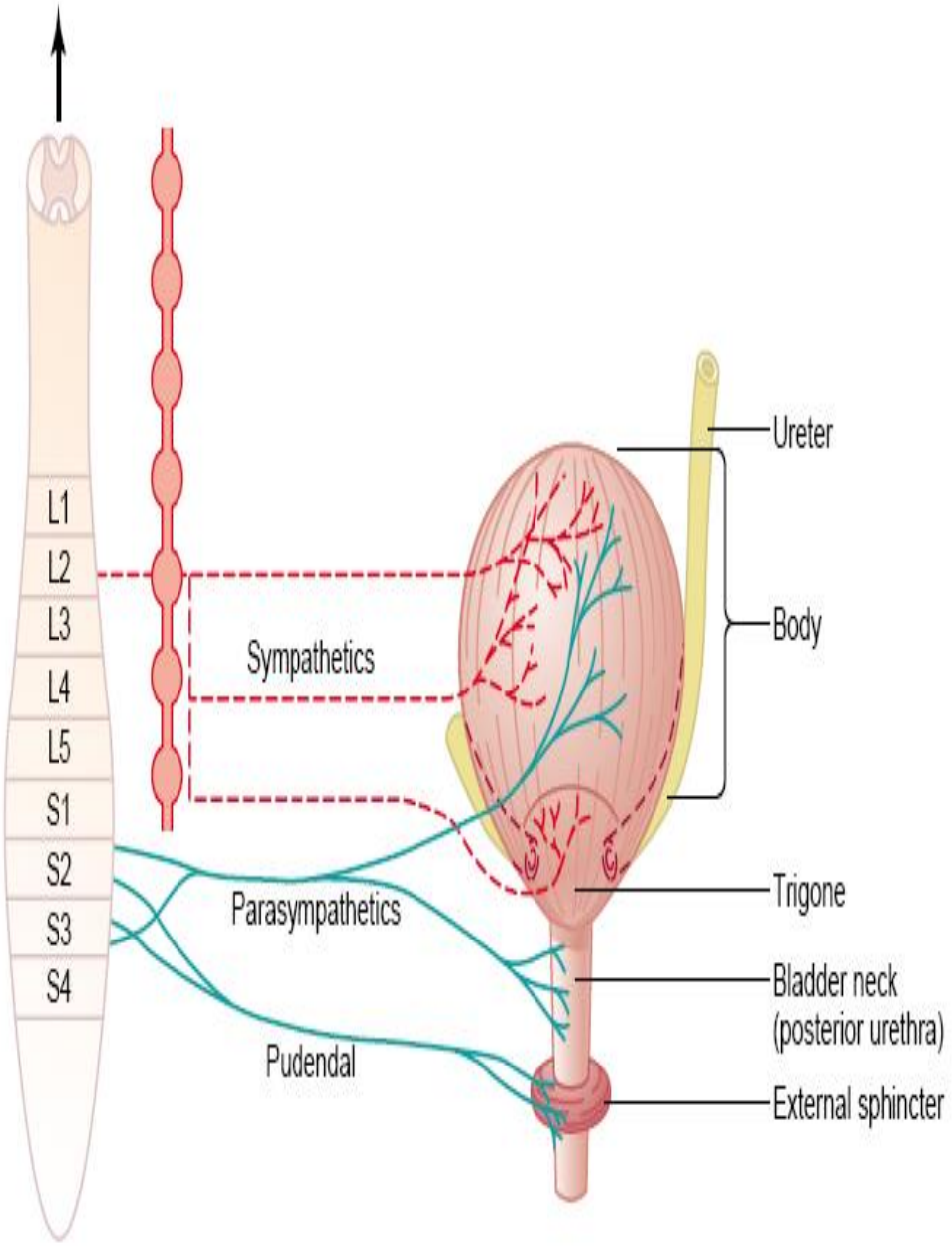
Nerve supply of the bladder

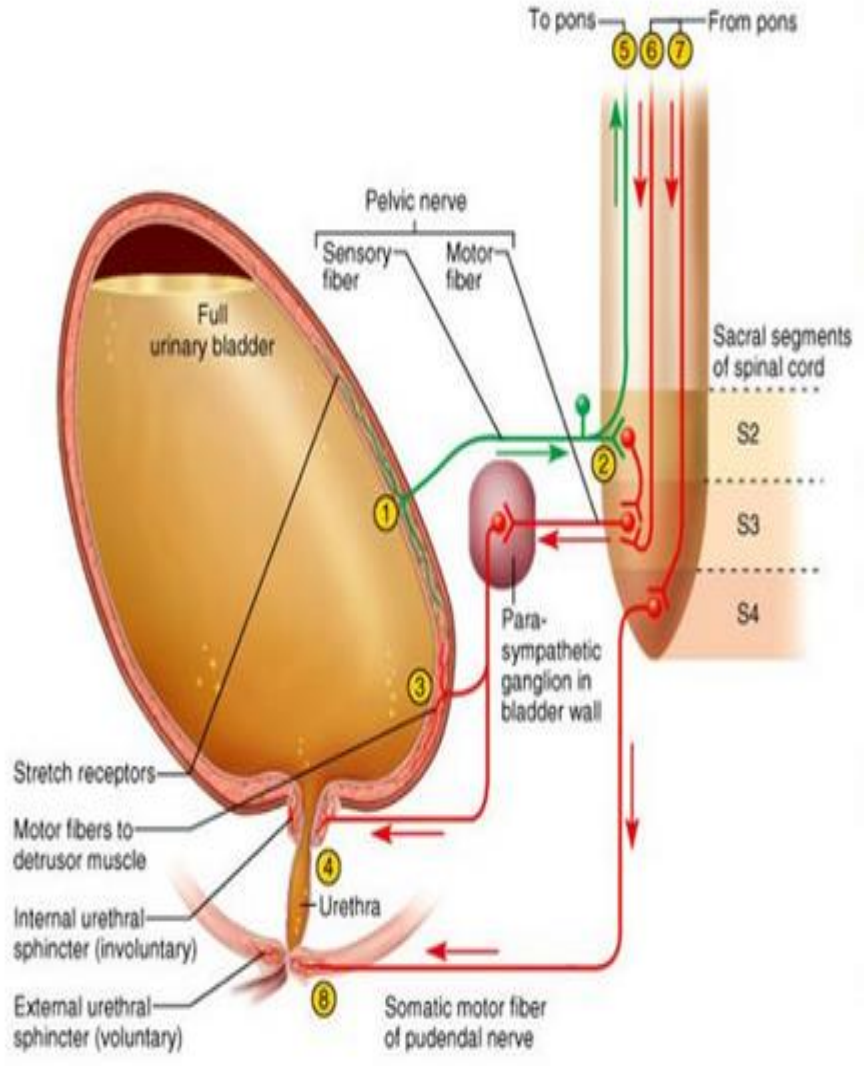
Sympathetic afferent, hypogastric nerves (T11, L2) - pain sensation

Sympathetic efferent, hypogastric nerves (T12, L2)

- Relax bladder
- Contract internal urethral sphincter

- **Parasympathetic afferent** (S2, 3, 4) - sense of fullness, discomfort
- **Parasympathetic efferent** (Pelvic) S2, 3, 4)
  - Motor to Detrusor muscle
  - Inhibitory to IUS
- **Somatic afferent** (S2, 3, 4): Pudendal nerve - sense of flow
- **Somatic efferent** (S2, 3, 4) Pudendal nerve
  - Motor to external urethral sphincter

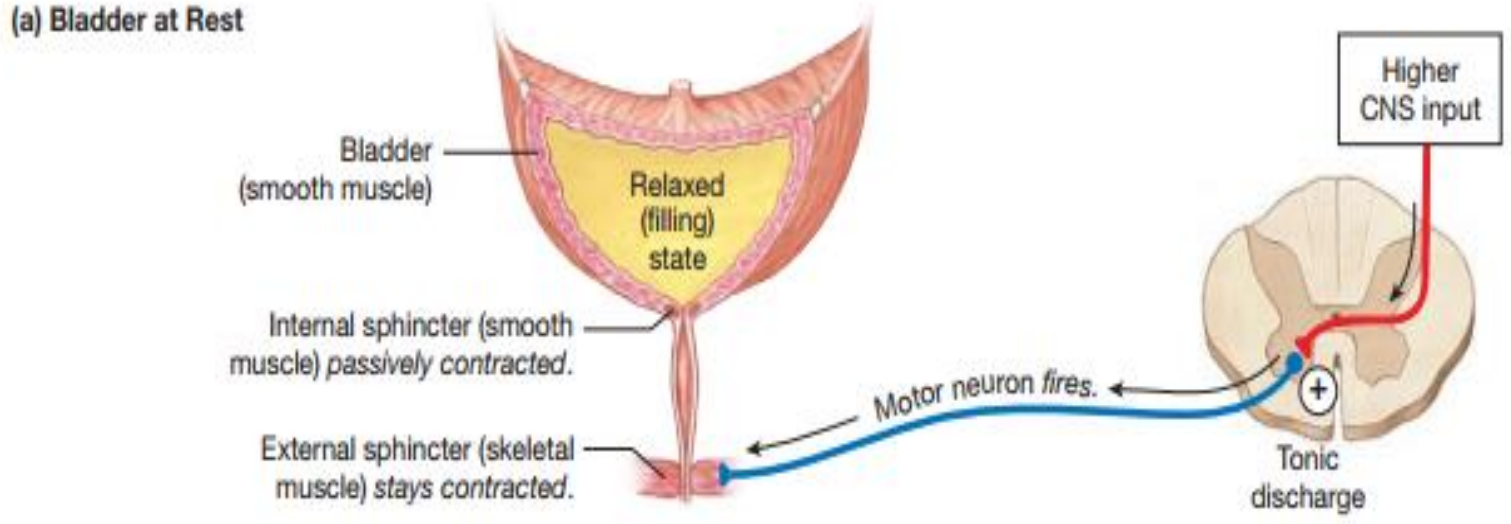

L1
L2
L3
L4
L5
S1
S2
S3
S4
Sympathetics
Parasympathetics
Pudendal
Ureter
Body
Trigone
Bladder neck
(posterior urethra)
External sphincter


To pons
From pons
5
6
7
Pelvic nerve
Sensory fiber
Motor fiber
Full urinary bladder
Sacral segments of spinal cord
S2
S3
S4
1
2
3
Para-sympathetic ganglion in bladder wall
Stretch receptors
Motor fibers to detrusor muscle
4
Urethra
Internal urethral sphincter (involuntary)
External urethral sphincter (voluntary)
8
Somatic motor fiber of pudendal nerve

Micturition…,

Sensation from the bladder

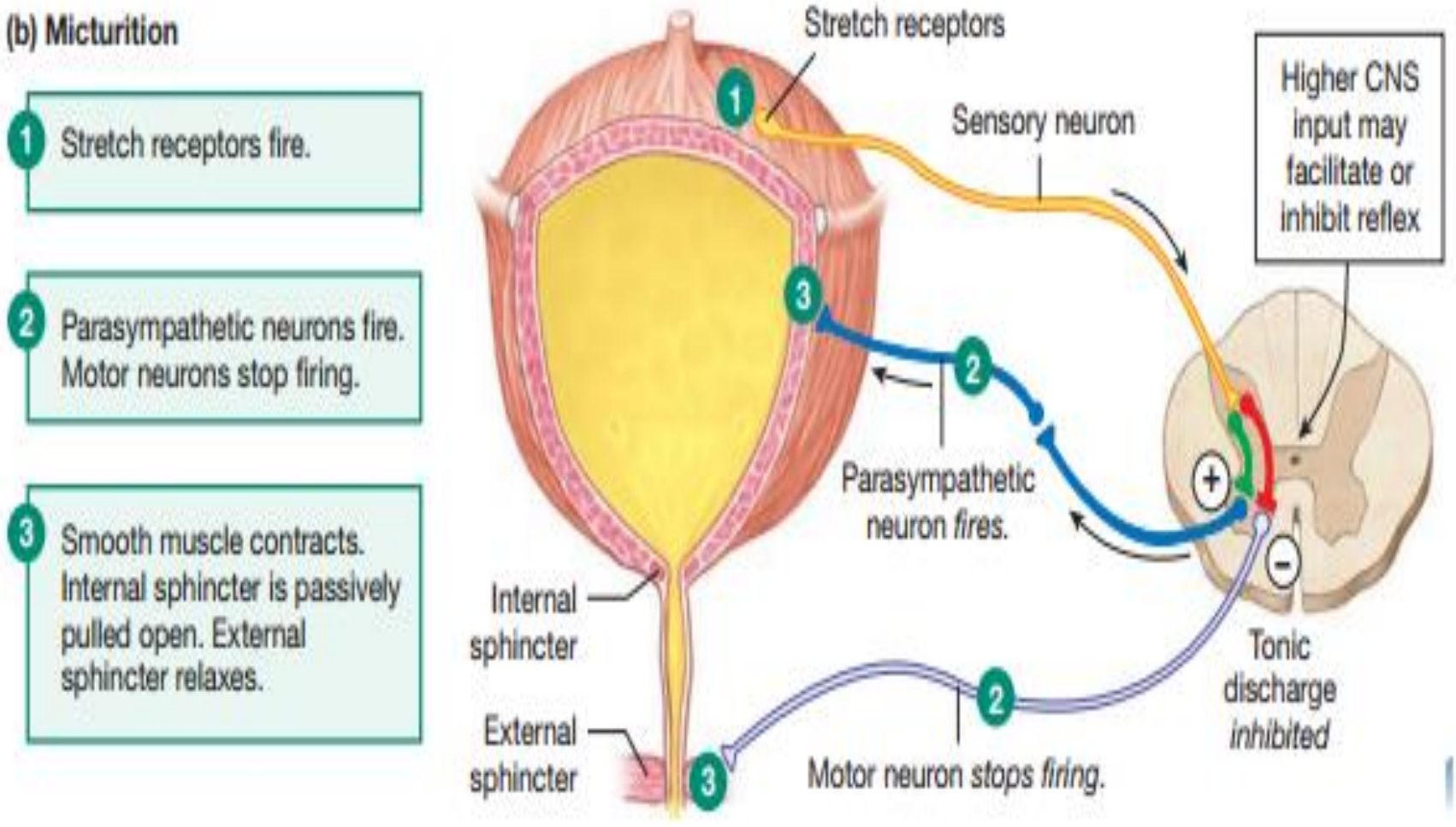
- Urge to void (150-250 ml)
- Sense of fullness (250-350 ml)
- Sense of discomfort (350-600 ml)
- Sense of pain (600-700 ml)
- Break point (>700 ml)



Micturition reflex…,

- Simple micturition reflex occurs primarily in infants who have not yet been toilet trained.
- **Toilet trained person** acquires a learned reflex that keeps the micturition reflex inhibited until she or he consciously desires to urinate.
- The learned reflex involves additional sensory fibers in the bladder that signal the degree of fullness.
- Centers in the **brain stem and cerebral cortex** receive that information and **override the basic micturition reflex**.

Spinal micturition reflex



Micturition Reflex…,

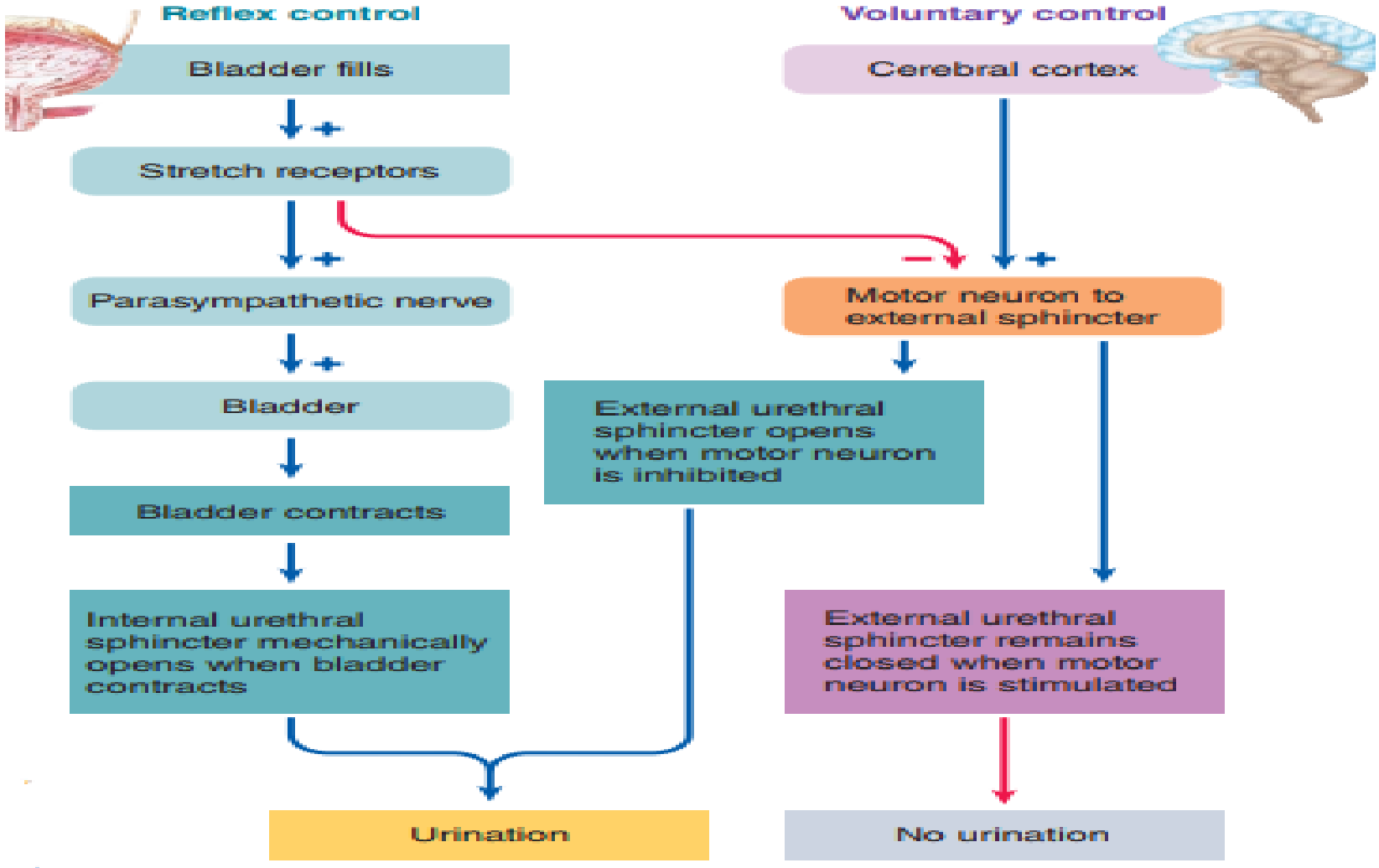
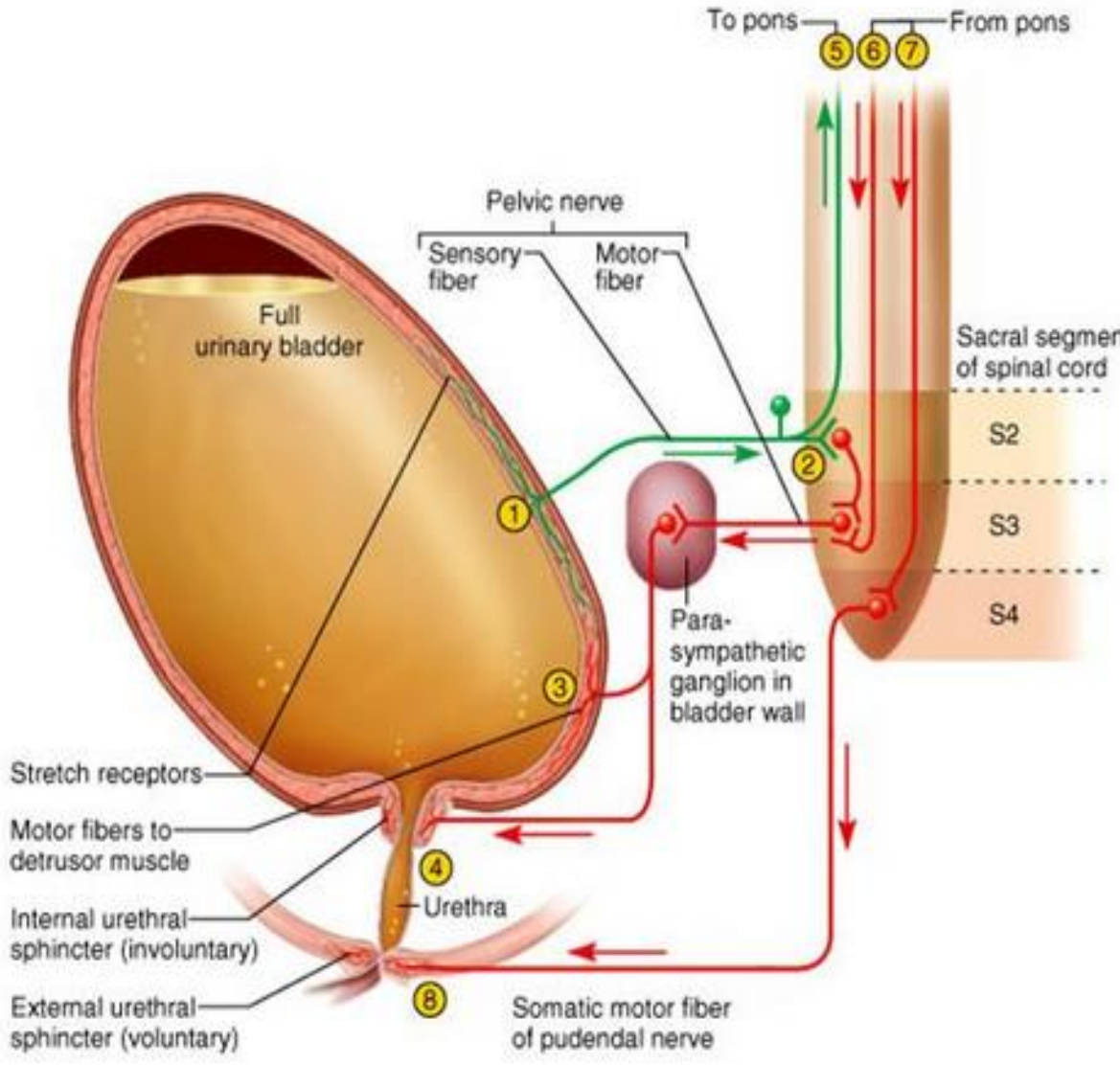


Figure 14-29 Reflex and voluntary control of micturition.



1. Stretch receptors detect filling of bladder, transmit afferent signals to spinal cord.
2. Signals return to bladder from spinal cord segments S2 and S3 via parasympathetic fibers in pelvic nerve.
3. Efferent signals excite detrusor muscle.
4. Efferent signals relax internal urethral sphincter. Urine is involuntarily voided if not inhibited by brain.
5. For voluntary control, micturition center in pons receives signals from stretch receptors.
6. If it is timely to urinate, pons returns signals to spinal interneurons that excite detrusor and relax internal urethral sphincter. Urine is voided.
7. If it is untimely to urinate, signals from pons excite spinal interneurons that keep external urethral sphincter contracted. Urine is retained in bladder.
8. If it is timely to urinate, signals from pons cease and external urethral sphincter relaxes. Urine is voided.

Pontine Micturition center

- **Pontine centers** coordinate **normal micturition reflex**.
- Pons contain facilitatory and inhibitory centers
- The pontine centers are necessary for **coordinated inhibition/ relaxation of EUS.**
- Interruption of pontine inhibitory centers results in **uninhibited bladder** (Neurogenic bladder).
- This is facilitated by **descending input** form **forebrain** and **ascending input** from spinal centers.

Voluntary control of micturition

Initiation of micturition

- Afferent in the pelvic nerve ⇒spinal centers ⇒ ponto-mesensephalic-tegmentum⇒ sensory cortex ⇒ anteromedial part of the frontal cortex (motor region) ⇒
  - Activation of facilitatory pontine centers
  - Inhibition of inhibitory brain stem nuclei
  - Direct cortical projections to spinal centers ⇒ contractions of Detrusor muscle and relaxation of sphincters

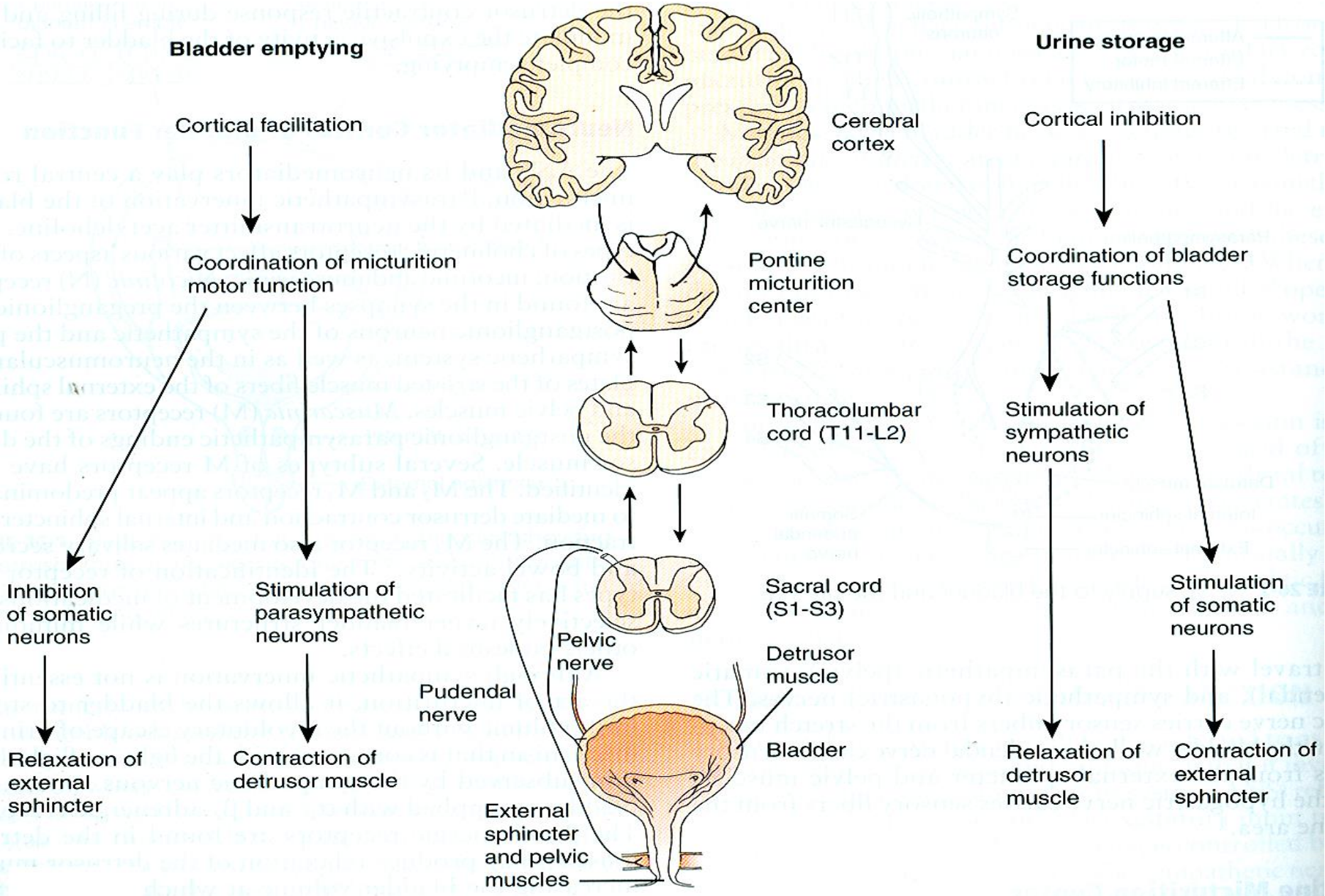
Inhibition of micturition

- Through input from
  - Frontal cortex, limbic regions, amygdaloid nuclei, thalamus hypothalamus, and cerebellum

- The inhibitory brainstem centers (located in pons) continuously inhibit Detrusor muscle and activate sphincters during filling.

Conscious control of bladder functions

- ✓ Normal bladder growth (In child it is small)
- ✓ Myelination of the ascending afferents that signal awareness of bladder filling.
- ✓ Development of cortical control and descending communication with the spinal center.
- ✓ Ability to consciously tighten the external urethral sphincters (2-3 years).



Pathways and central nervous system centers involved in the control of bladder emptying (**left**) and storage (**right**) functions.

Abnormal micturition reflexes

1. Nocturnal Enuresis (bedwetting)

- Relatively small bladder due to maturational failure or failure of modulating nerve.
- Intravesicular pressure rises to much higher level periodically with delayed arousal time.
- Interruption of the neural control at any level from the bladder to cerebral cortex

2. Neurogenic bladder

- Failure to store urine (spastic bladder dysfunction)- due to lesion **above the levels of sacral centers** (uninhibited bladder)
- Failure to empty (flaccid bladder dysfunction)- due to **lesions at the level of sacral centers**

3. Incontinence

A. Stress incontinence

- Involuntary loss of urine during coughing, laughing and sneezing resulting from
  - Pelvic floor muscle weakness secondary to
    - Aging
    - Childbirth
    - Surgical procedure result
  - Poor support of vesicourethral sphincter
    - The posterior viscourethral angle is critical for continence
    - **When the angle is lost,** any downward pressure on the bladder may be sufficient to cause incontinence
  - Congenital sphincter weakness

B. Urge incontinence/Overactive bladder

- Involuntary loss of urine associated with strong desire to void (urgency)
- Overactive bladder describes a clinical syndrome that can include (Sudden contraction of Detrusor without warning)
- The reflex not regulated by higher centers.

- Urgency
- Frequency
- Dysurea
- Nocturea

C. Overflow incontinence

- **Involuntary loss of urine** that occurs when intravescicular pressure exceeds the maximum in the absence of detrusor muscle activity.
- It can occur with **retention of urine** owing to
  - **nervous lesions (pudendal nerve lesions) or**
  - **obstruction of bladder neck** secondary to
  - **prostate gland enlargement** and
  - **large bolus of fecal** matter in the rectum that pushes the urethra.
- **Decreased bladder compliance** (distensibility) resulting from radiation therapy
- This makes bladder hypersensitive to sharp pressure rise following small change in bladder volume.

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THE END