Chapter 15 腎臟生理

15-1 腎臟的構造及功能

15-2 尿液的形成

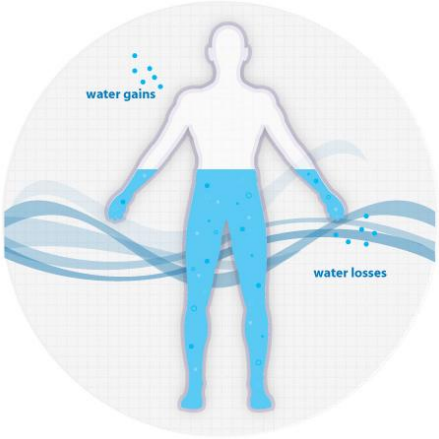
15-3 腎血漿清除率

15-4 排尿作用

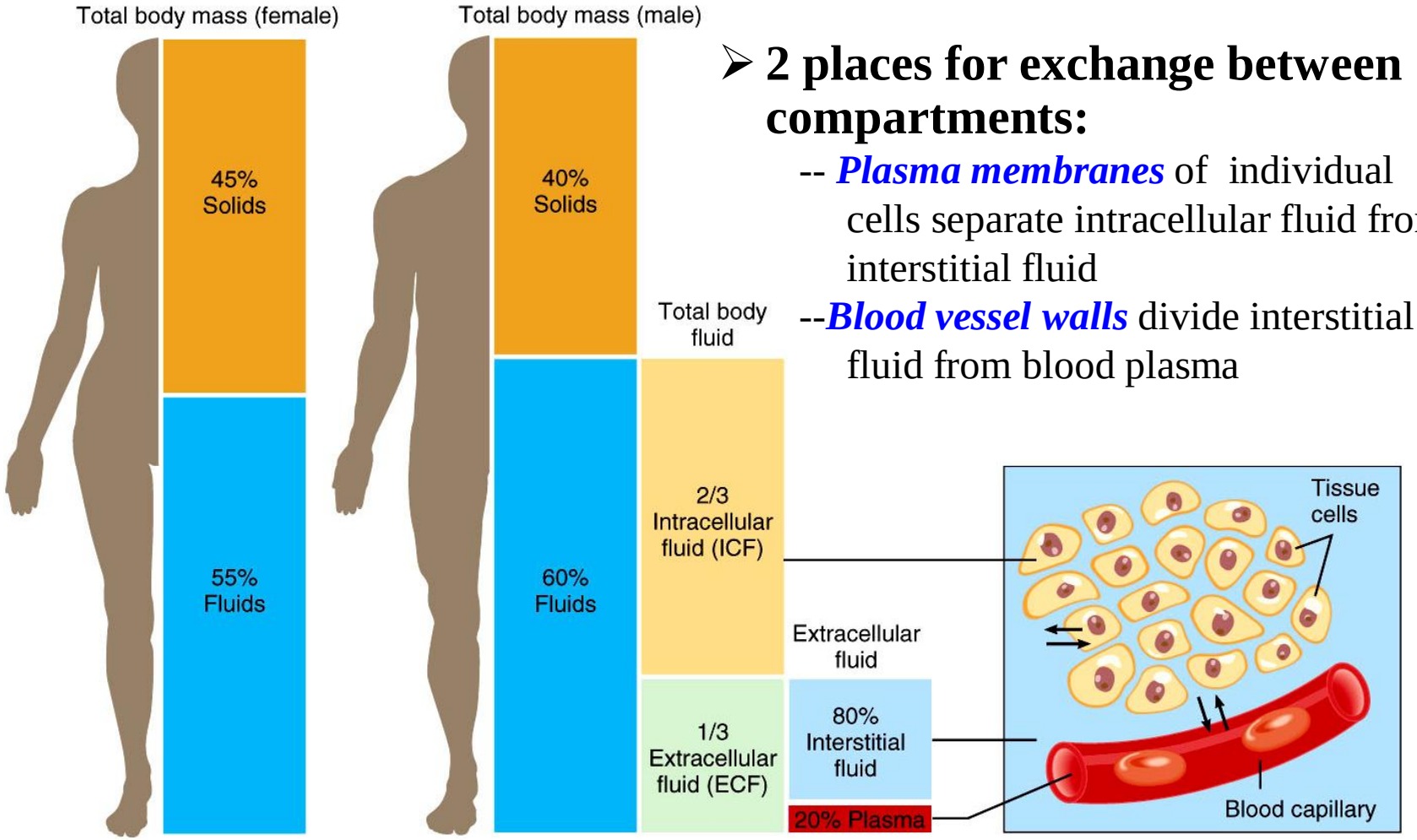
✓ 15-5 電解質及酸鹼平衡的調節

The Concept of Balance

- To ***maintain homeostasis***, what comes in the body must eventually be used or excreted
- Balance → ***Input + production = utilization + output***
- **Kidneys** regulating fluid and electrolyte balance, and acid-base balance
- In lean adults, body fluids constitute **55%** of **female** and **60%** of **male** total body mass
- **Body fluid** =all the **water** and **dissolved solutes** in the body's fluid compartments
- Mechanisms regulate
  - ***--Total volume***
  - ***--Distribution***
  - ***--Concentration of solutes and pH***



Normal Body Fluid Compartments

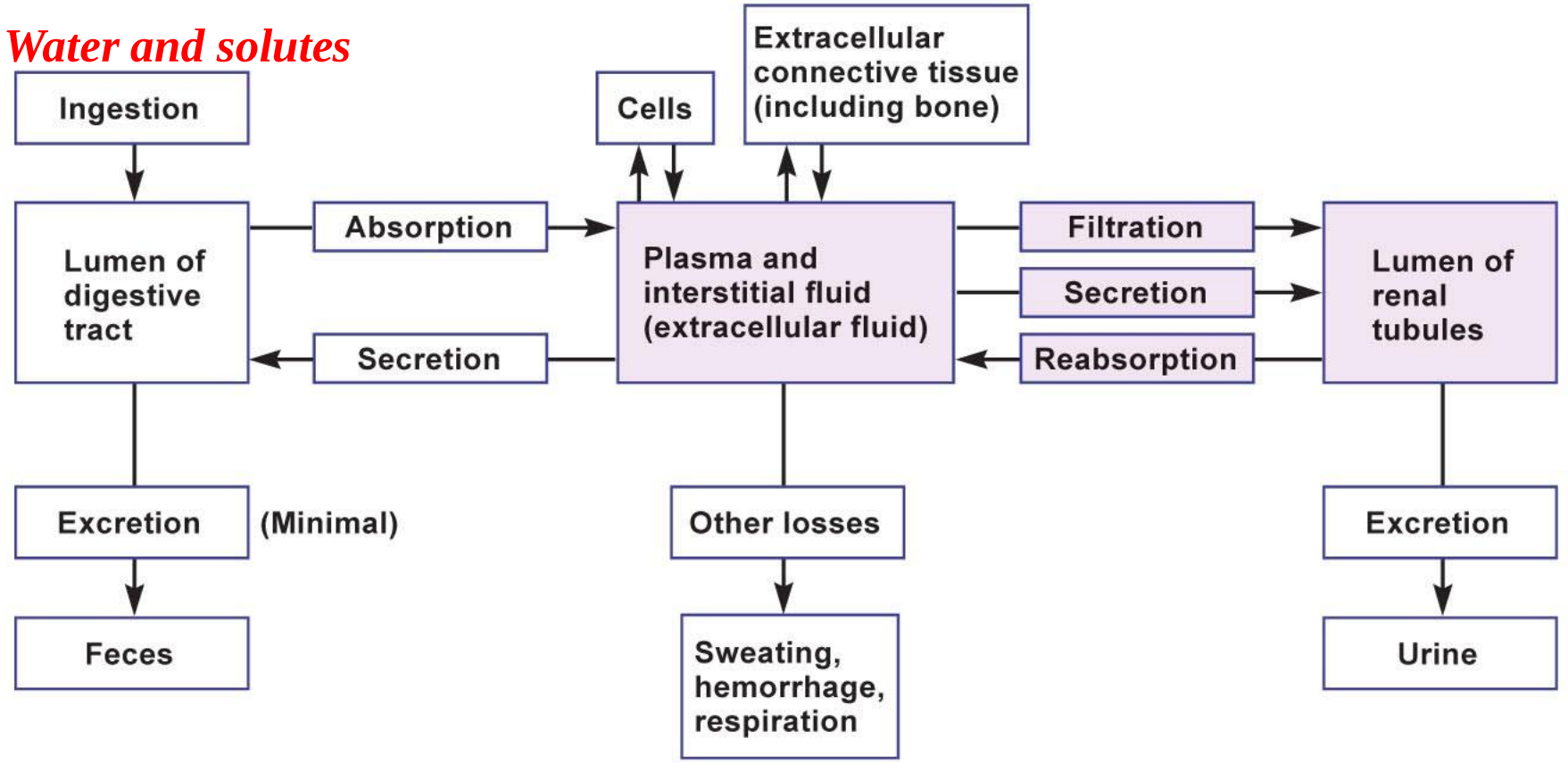


(a) Distribution of body solids and fluids in an average lean, adult female and male

(b) Exchange of water among body fluid compartments

- **2 places for exchange between compartments:**
  - -- ***Plasma membranes*** of individual cells separate intracellular fluid from interstitial fluid
  - --***Blood vessel walls*** divide interstitial fluid from blood plasma

Material Exchanges Affecting Plasma Content

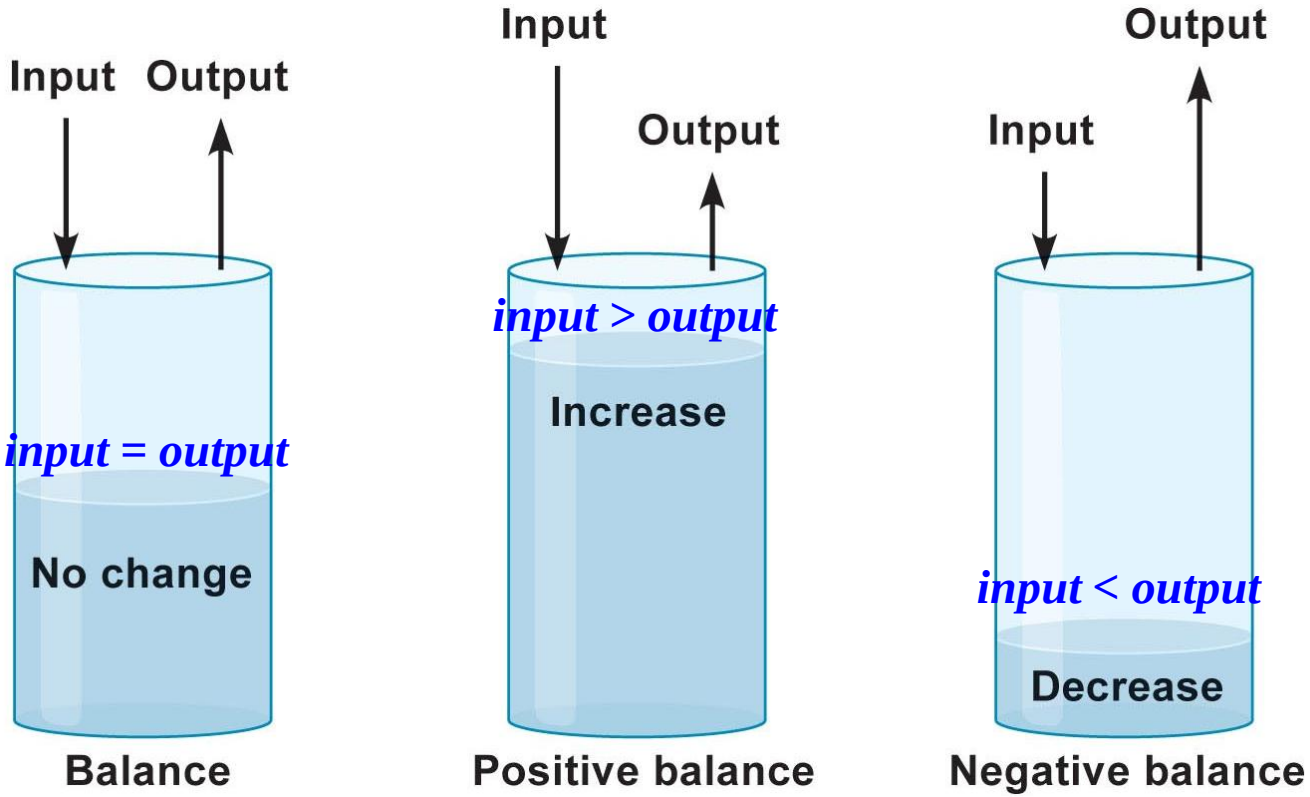


- *Kidneys regulate solute and water content, which also determines volume*
- *Composition also affected by exchange between different compartments of body*

Water and Solute Balance

- ***Fluid balance*** means that the various body compartments contain the required amount of water, proportioned according to their needs
  - --Fluid balance = ***water balance***, but also implies ***electrolyte balance***; the two are inseparable
- ***Osmosis*** is the primary way in which **water** moves in and out of body compartments
  - --The ***concentrations of solutes*** in the fluids is therefore a major determinant of fluid balance
- Most solutes in body fluids are ***electrolytes***, compounds that dissociate into ions

Water and Solute Balance

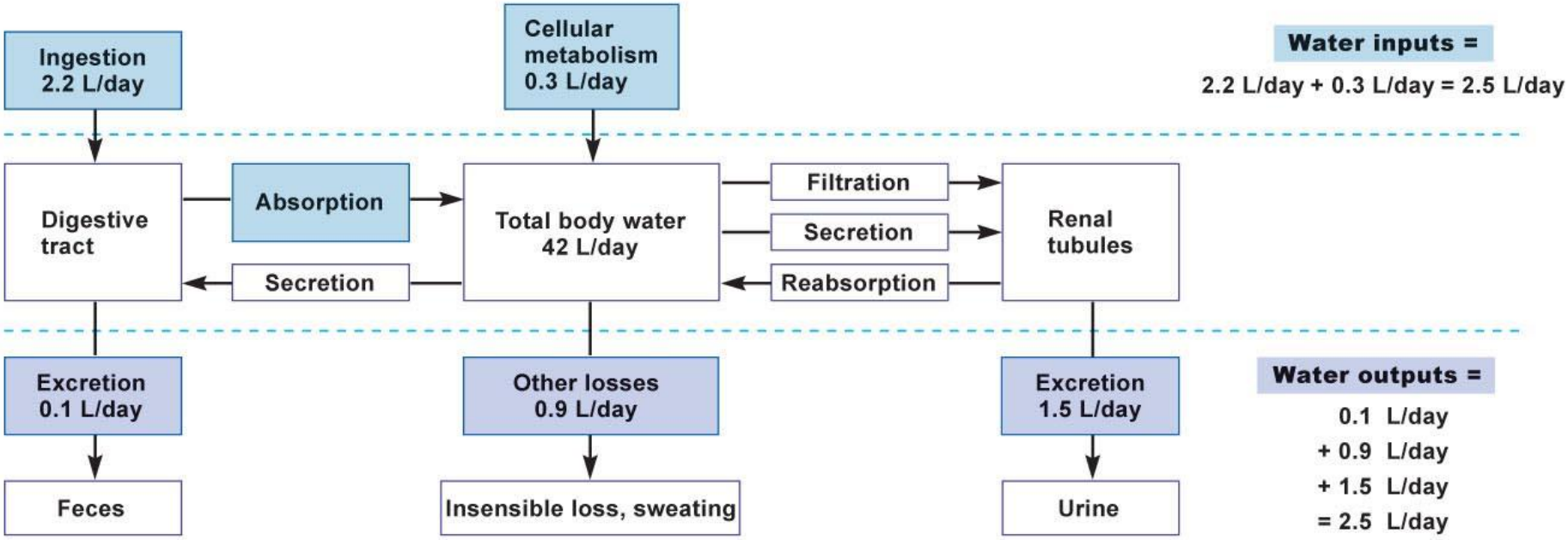


- ***Regulation of renal excretion occurs primarily in late distal tubule and collecting duct***
  - --***Principal cells:*** ***Water and electrolytes balance*** by hormonal actions
  - --***Intercalated cell:*** ***Acid-base balance*** by different processes

Factors Affecting Water Balance

Water Balance

Water input = Water output



- ***Water intake + metabolically produced = water output + water used***
  = ***Normovolemia*** = normal blood volume
- ***Hypervolemia*** = high blood volume due to **positive water balance**
- ***Hypovolemia*** = low blood volume due to **negative water balance**

Movement of Water Between Compartments

- Normally, cells neither shrink or swell because intracellular and interstitial fluids have the **same osmolarity**
  - --***Increasing* osmolarity** of interstitial fluid draws ***water out*** of cells and cells ***shrink***
  - --***Decreasing* osmolarity** of interstitial fluid causes cells to ***swell***
- Water reabsorption **passive (**based on **osmotic gradient)**
- Changes in osmolarity most often result from ***changes in Na^+ concentration***
- **Water intoxication –** drinking water faster than the kidneys can excrete it (lead to convulsions, coma or death)

Clinical Application: Water intoxication

Dilutional Hyponatremia

Excessive blood loss, sweating, vomiting, or diarrhea coupled with intake of plain water

↓

Decreased Na^+ concentration of interstitial fluid and plasma (hyponatremia)

↓

Decreased osmolarity of interstitial fluid and plasma

↓

Osmosis of water from interstitial fluid into intracellular fluid

↓

Water intoxication (cells swell)

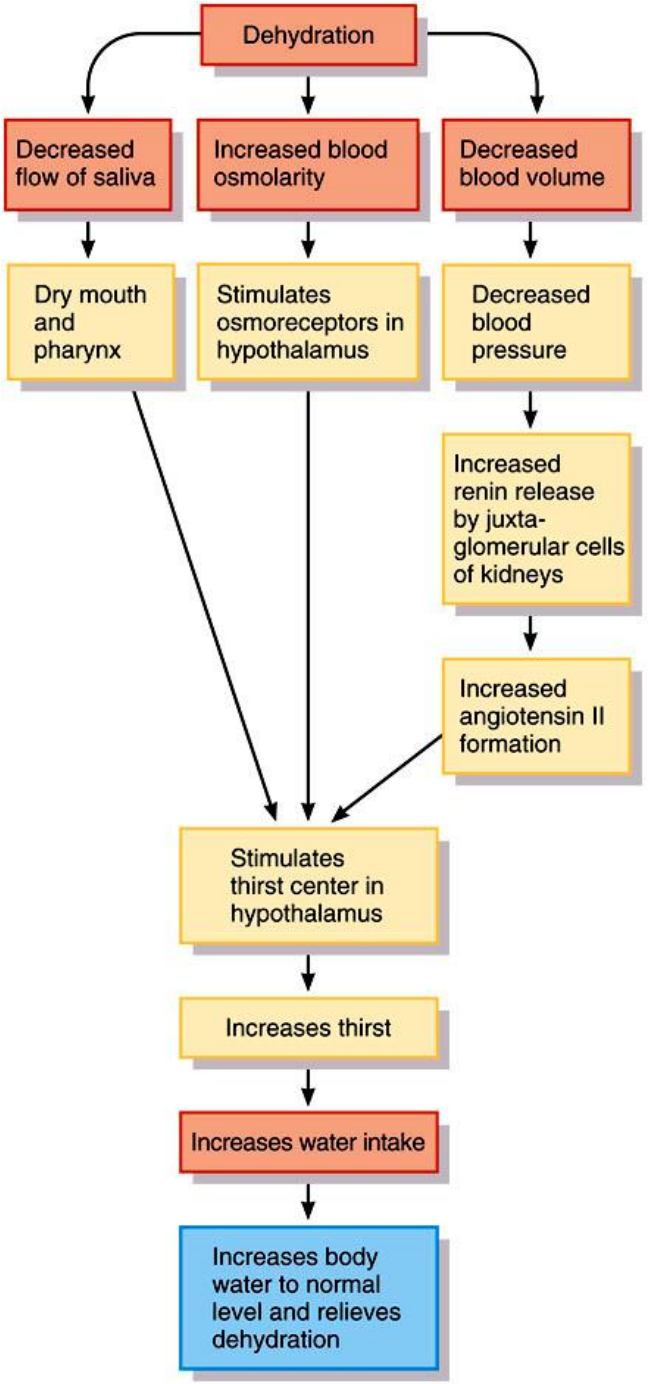
Swollen brain ↓ ***ICP ↑***

Convulsions, coma, and possible death

Clinical Application:
Dehydration

- Mainly by volume of water intake/ how much you drink

- **Dehydration** – when water loss is greater than gain
  - --Decrease in volume, increase in osmolarity of body fluids
  - --Stimulates ***thirst center in hypothalamus***



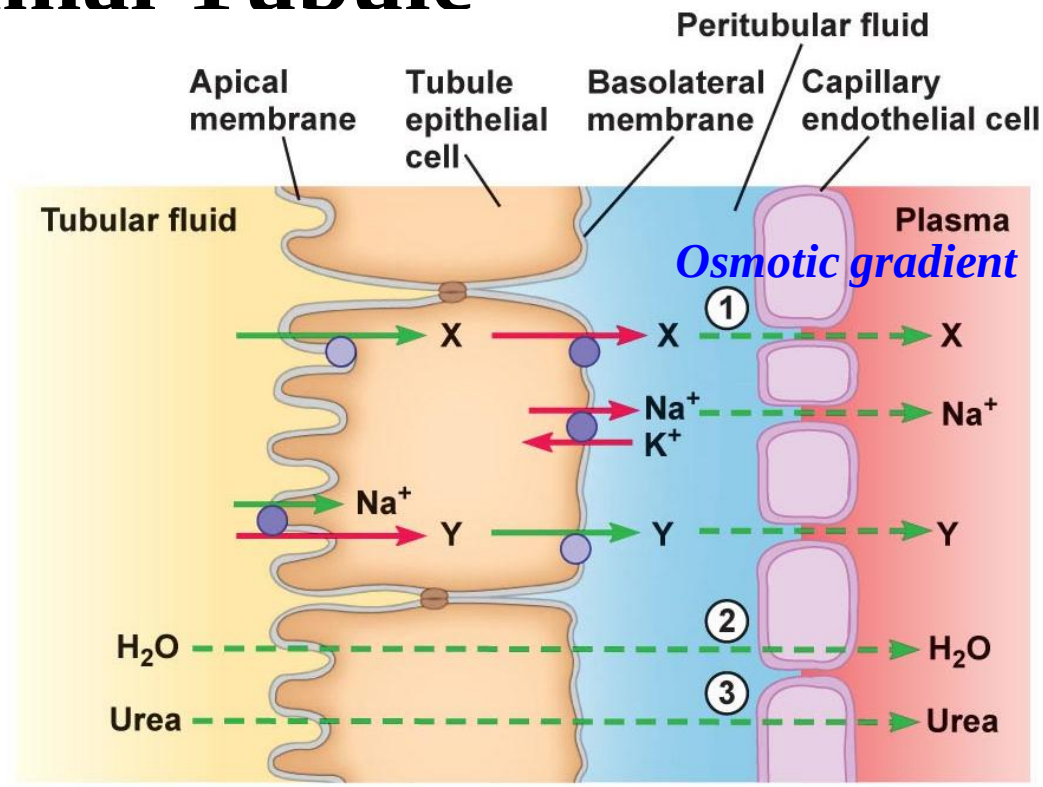
Factors Affecting Body Water Balance

- Under normal conditions, fluid output (loss) is adjusted by
  - --***Antidiuretic hormone (ADH)***
  - --***Atrial natriuretic peptide (ANP)***
  - --***Aldosterone***
- All of which regulate urine production

Factor	Mechanism	Effect
Thirst center in hypothalamus	Stimulates desire to drink fluids.	Water gain if thirst is quenched.
Angiotensin II	Stimulates secretion of aldosterone.	Reduces loss of water in urine.
Aldosterone	By promoting urinary reabsorption of Na^+ and Cl^-, increases water reabsorption via osmosis.	Reduces loss of water in urine.
Atrial natriuretic peptide (ANP)	Promotes natriuresis, elevated urinary excretion of Na^+ (and Cl^-), accompanied by water.	Increases loss of water in urine.
Antidiuretic hormone (ADH), also known as vasopressin	Promotes insertion of water-channel proteins (aquaporin-2) into the apical membranes of principal cells in the collecting ducts of the kidneys. As a result, the water permeability of these cells increases and more water is reabsorbed.	Reduces loss of water in urine.

Water Reabsorption in the Proximal Tubule

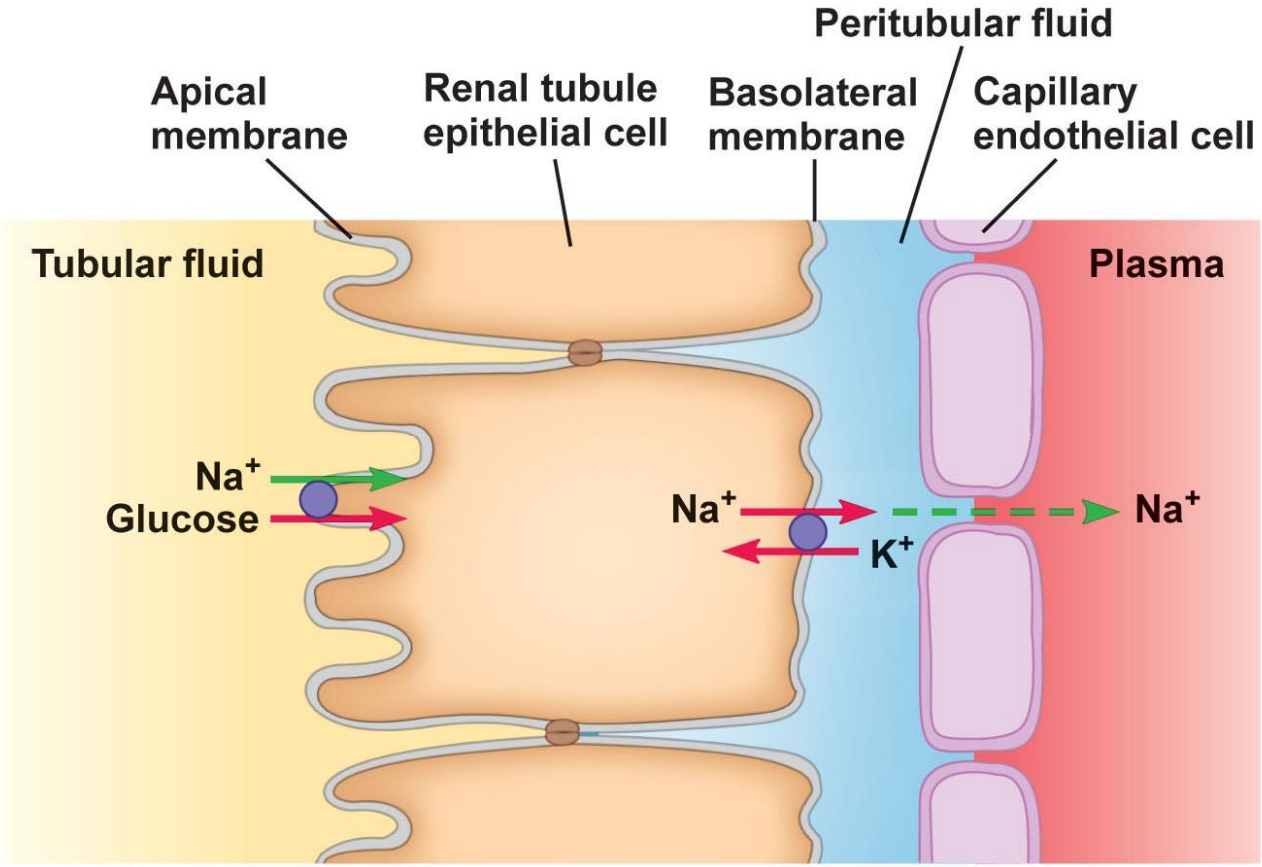
- **Proximal tubules**
  - --70% filtered water is reabsorbed
  - --Not regulated
- **Distal tubules and collecting ducts**
  - --Most remaining water is reabsorbed
  - --Regulated by ***ADH***
- Water reabsorption follows solute reabsorption
- Primary solute = ***sodium***



Steps for water and urea reabsorption:

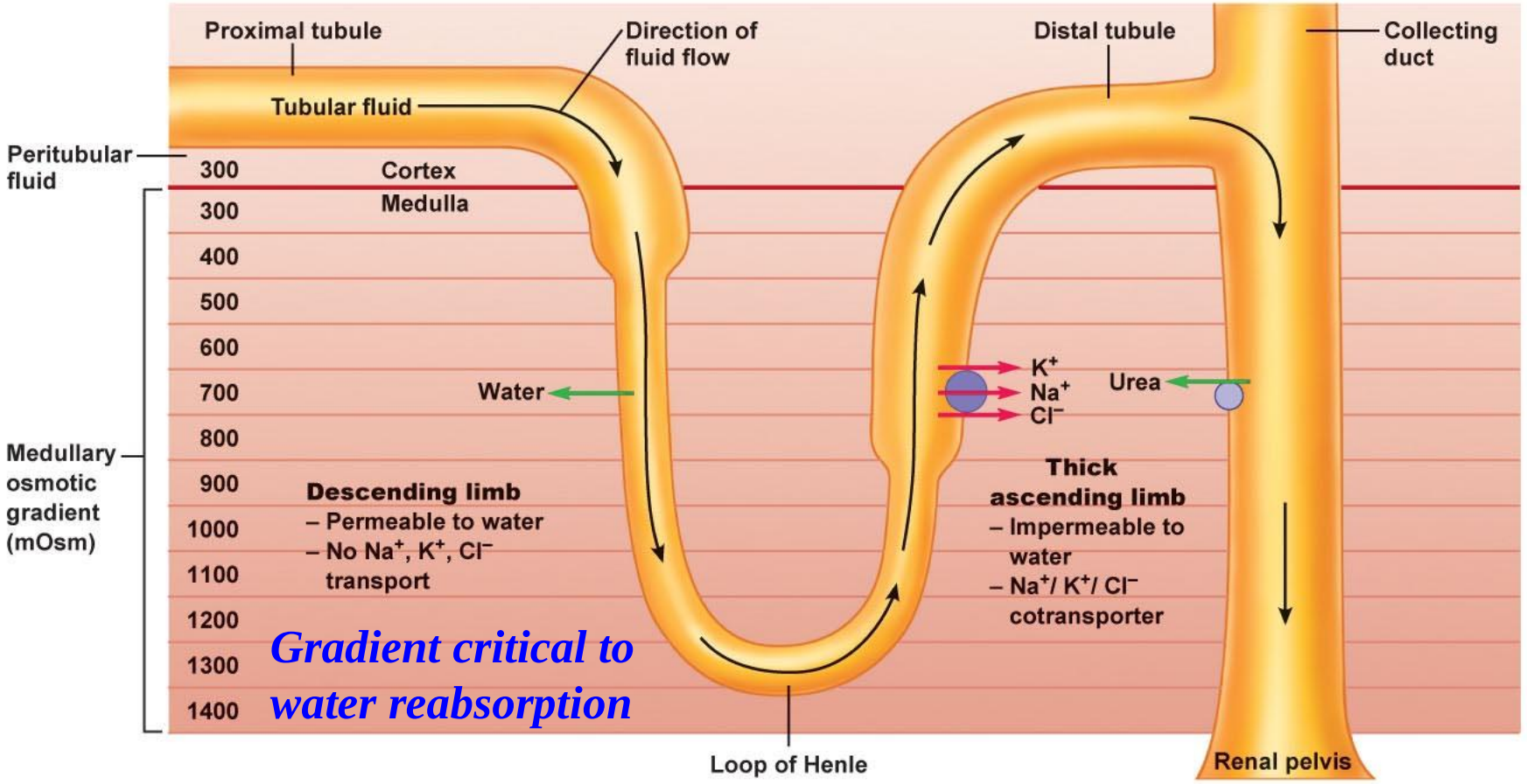
1. Solutes (Na^+, X, Y) are actively reabsorbed, increasing the osmolarity of peritubular fluid and plasma.
2. Water is reabsorbed by osmosis.
3. Urea (permeating solute) is reabsorbed passively.

Na Reabsorption in the Proximal Tubule



- *Na^+ is actively transported across basolateral membrane; this establishes an osmotic gradient for water reabsorption*

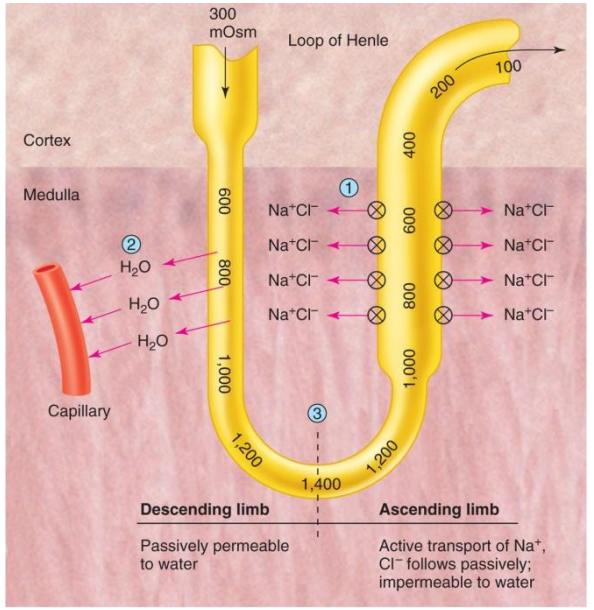
Medullary Osmotic Gradient for Water Reabsorption



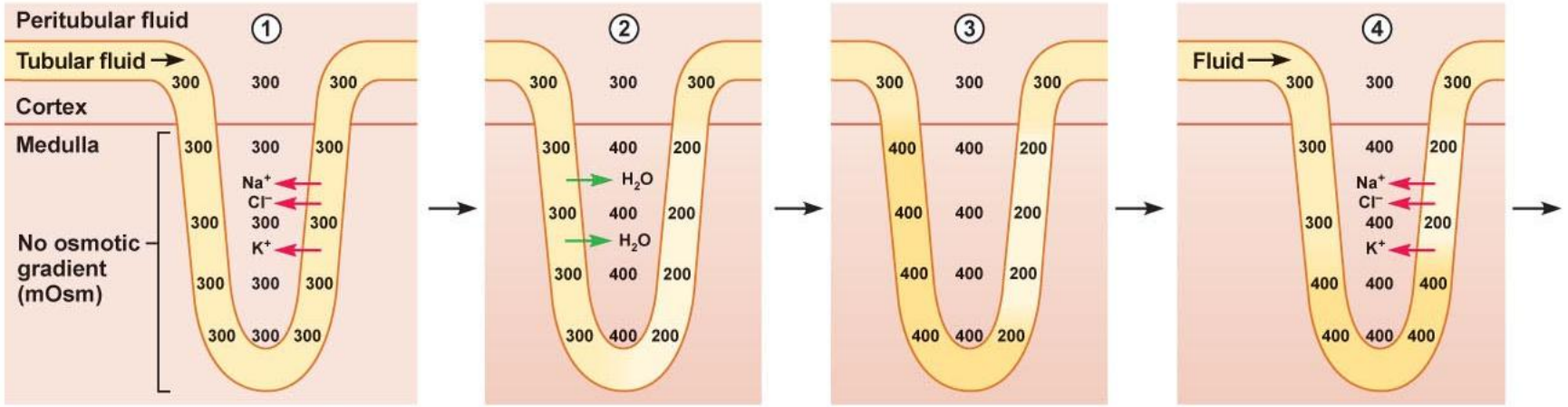
- Osmolarity of interstitial fluid of renal medulla varies with depth
  - --*Lower osmolarity near cortex*
  - --*Greater osmolarity near renal pelvis*

Counter-Current Multiplier in the Loop of Henle

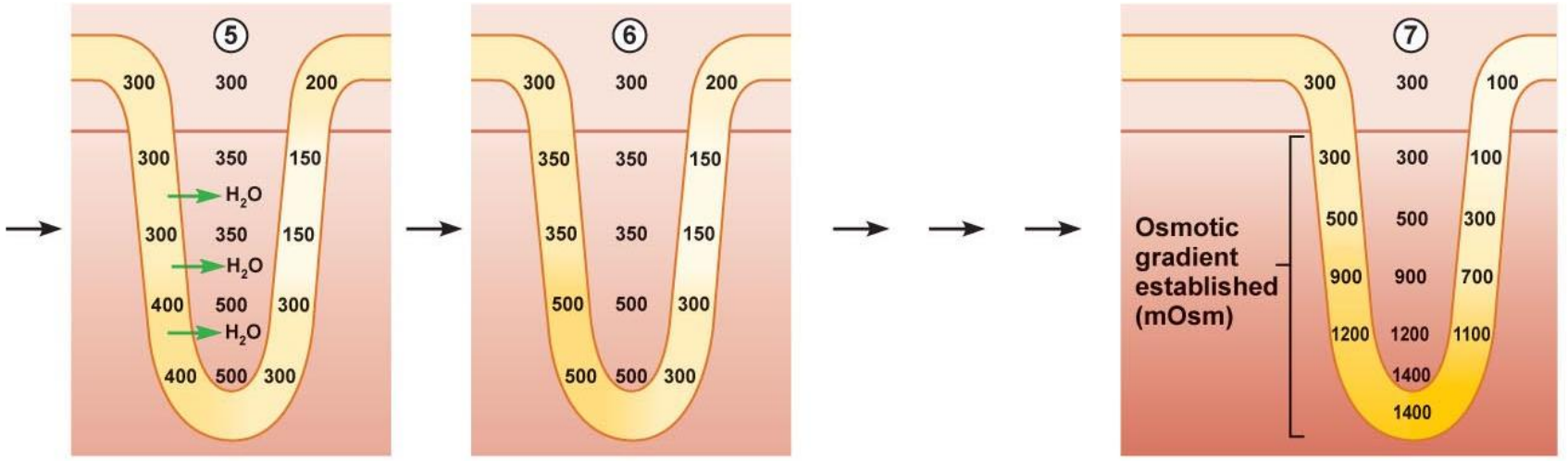
- Process by which a progressively increasing **osmotic gradient (urine concentration)** established by ***counter-current multiplier system (逆流放大系統)***
- Dependent on **loop of Henle** of juxtamedullary nephrons (function as countercurrent multiplier)
- **Ascending limb**
  - ***--Impermeable to water***
  - ***--Active transport of Na^+, Cl^-, and K^+***
- **Descending limb**
  - ***--Permeable to water***
  - ***--No transport of Na^+, Cl^-, or K^+***



Counter-Current Multiplier



Fluid enters tubule → Active transport of Na^+, Cl^-, K^+ ions into medullary interstitial fluid increases osmolarity → Water moves out of descending limb by osmosis → Iso-osmotic state in descending limb; osmotic difference between descending and ascending limbs → More fluid enters tubule, pushing fluid through by bulk flow → Active transport of Na^+, Cl^-, K^+ ions into medullary interstitial fluid increases osmolarity



→ Water moves out of descending limb by osmosis → Iso-osmotic state in descending limb; osmotic difference between descending and ascending limbs → More water enters tubule and process continues → System is in steady state

Result of Counter-Current Multiplier

- Fluid in **proximal tubule = 300 mOsm**
- Fluid in **descending limb**—osmolarity ***increases as it descends***

  --Osmolarity = interstitial fluid

  --Osmolarity > descending limb
- Fluid in **ascending limb**—osmolarity ***decreases as it ascends***

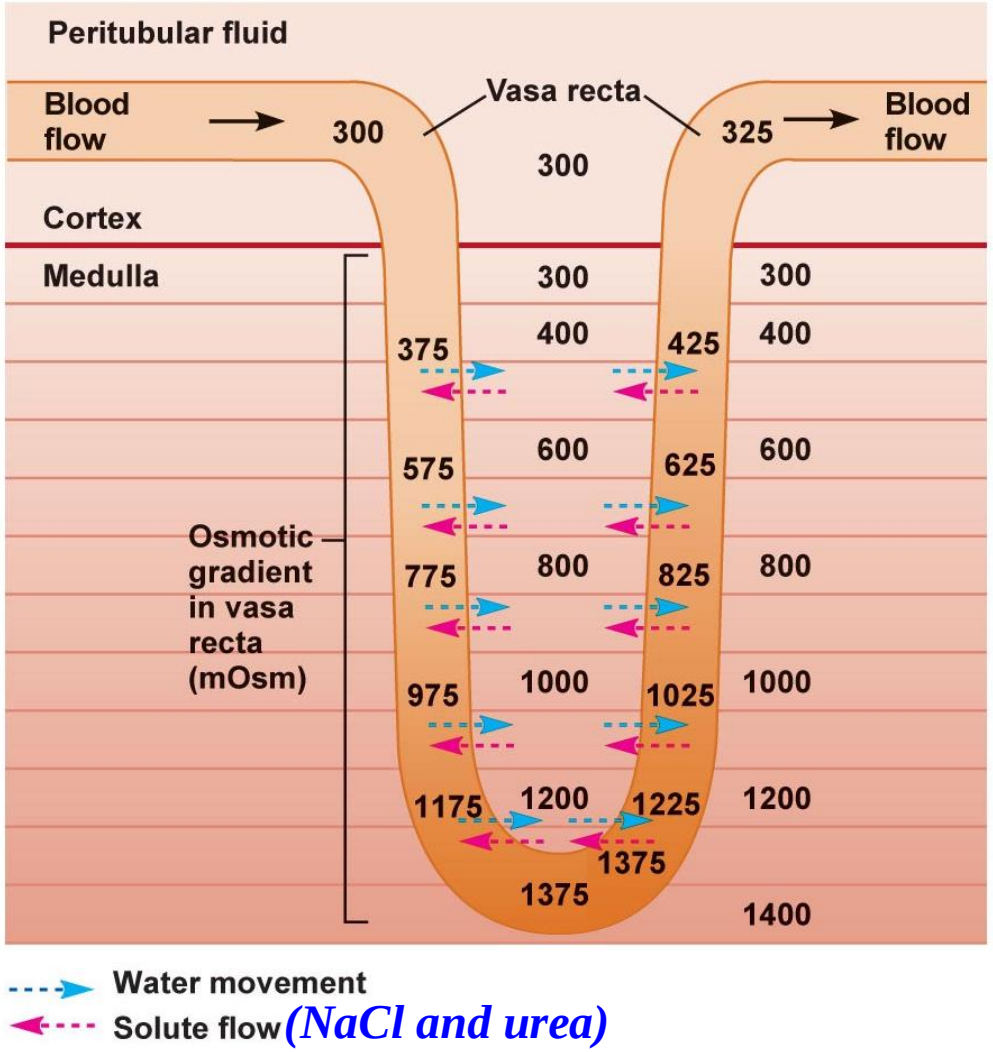
  --Osmolarity < interstitial fluid, descending limb
- Fluid in **distal tubule = 100 mOsm**
- **Cortical interstitial fluid = 300 mOsm**
- **Medullary interstitial fluid**

  --Increases from cortex to renal pelvis

Vasa Recta: Counter-Current Exchanger

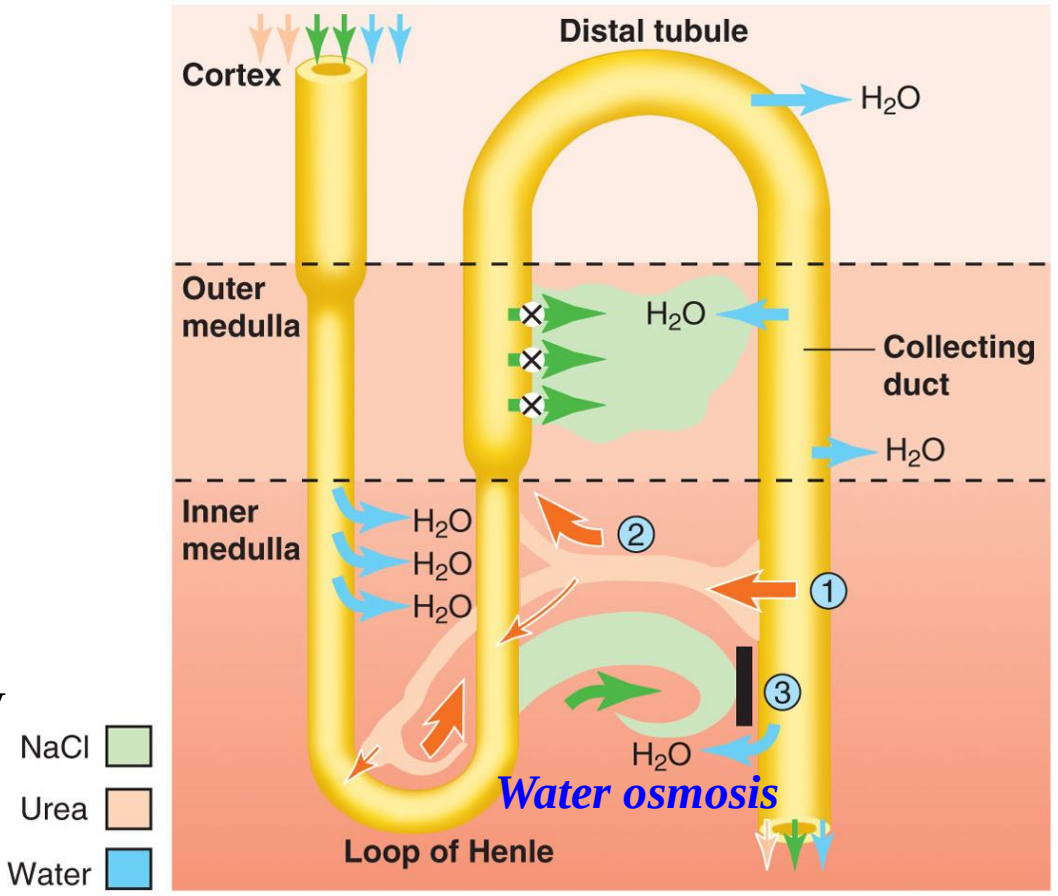
- Process by which ***solutes and water*** are passively exchanged **between blood of the vasa recta** and **interstitial fluid of the renal medulla** as a result of **countercurrent flow**

- Vasa recta **maintains medullary osmotic gradient** by countercurrent exchange
  - --Plasma water losses and solute gains on the way ***into*** the medulla (descending region)
  - --Plasma water gains and solute losses on the way ***out*** of the medulla (ascending region)



Urea Recycling

- A waste product of **protein metabolism**
- Contributes to **countercurrent system**
  - (1)Transported out of ***collecting duct*** and into interstitial fluid
  - (2)Diffuses back into ***ascending limb (thin)*** and cycles around continuously
- Helps set up **solute concentration gradients**



Formation of Concentrated Urine

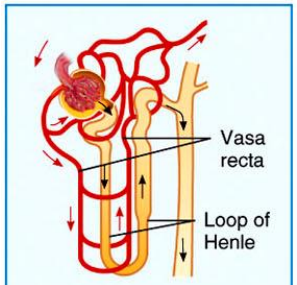
- Urine can be up to ***4 times*** more concentrated than blood plasma
- Ability of **ADH** depends on presence of osmotic gradient in interstitial fluid of renal medulla
- **3 major solutes contribute – Na^+, Cl^-, and urea**
  - --***$Na^+/K^+/Cl^-$ symporters*** reabsorb Na^+ and Cl^- from tubular fluid to create osmotic gradient in the renal medulla
  - --***Urea recycling*** contributes to the medullary osmotic gradient
- **2 main factors build and maintain gradient**
  - --**Differences in solute and water permeability** in different sections of ***loop of Henle and collecting ducts (ADH)***
  - --**Countercurrent flow** of fluid (**positive feedback**) though descending and ascending ***loop of Henle*** and blood through ascending and descending limbs of ***vasa recta***

Water, Na and Urea Transport in Renal Tubules

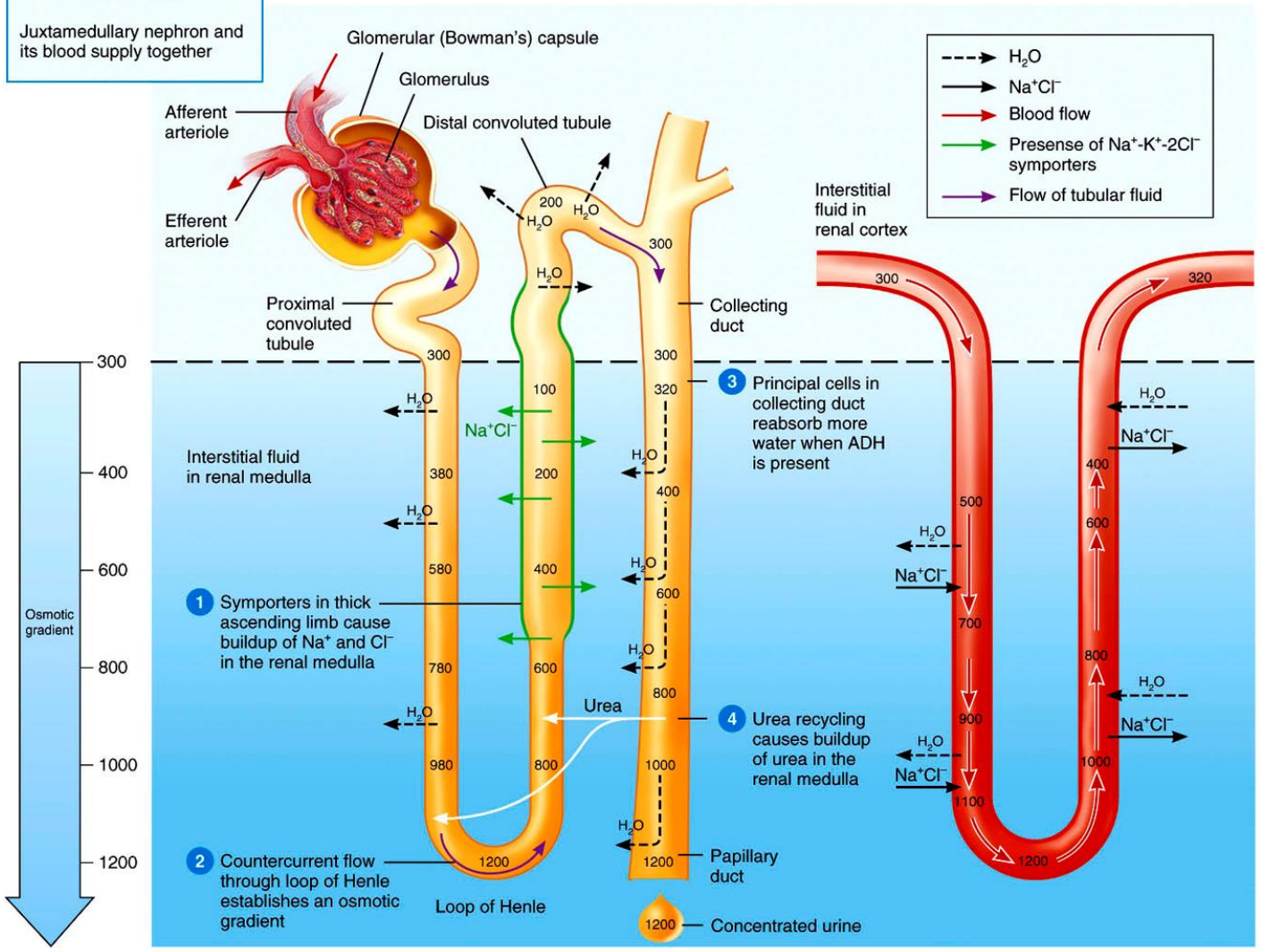
Nephron Segment	Active Transport	Passive Transport		
		Salt	Water	Urea
Proximal tubule	Na^+	Cl^-	Yes	Yes
Descending limb of Henle's loop	None	Maybe	Yes	No
Thin segment of ascending limb	None	NaCl	No	Yes
Thick segment of ascending limb	Na^+	Cl^-	No	No
Distal tubule	Na^+	Cl^-	No**	No
Collecting duct*	Slight Na^+	No	Yes (ADH) or slight (no ADH)	Yes

*The permeability of the collecting duct to water depends on the presence of ADH.
**The last part of the distal tubule, however, is permeable to water.

Mechanism of Urine Concentration in Long-loop Juxtamedullary Nephrons



Juxtamedullary nephron and its blood supply together



(a) Reabsorption of Na^+, Cl^- and water in a long-loop juxtamedullary nephron

(b) Recycling of salts and urea in the vasa recta

Obligatory Water Loss

- **Minimum volume of water that must be excreted in the urine per day**
- **Max osmolarity urine = 1400 mOsm**
- **Some solute must be excreted**
- **Minimum water loss = 440 mL/day**

  --Necessary to eliminate non-reabsorbed solutes

➢ ***Length*** **of the loop of Henle** determines the **maximum concentration of urine (larger medullary osmolarity gradient)**

➢**Camels** (max osmolarity urine = **2800 mOsm)**

➢**Australian hopping mice** = **9800 mOsm)**

Water Reabsorption in Distal Tubules and Collecting Ducts

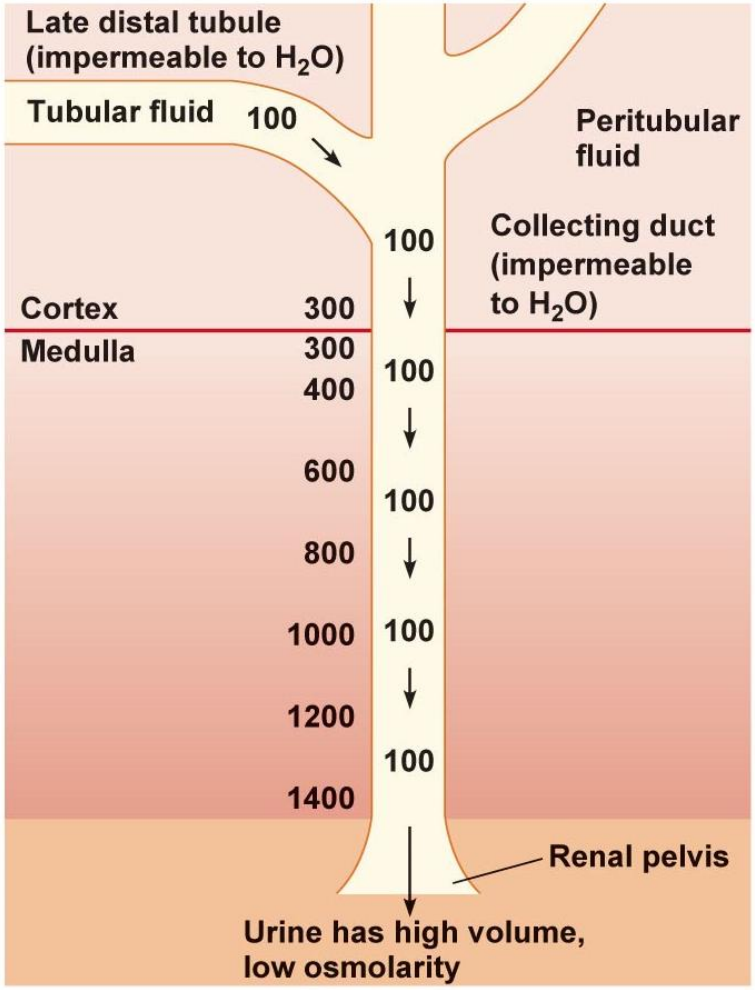
- Dependent on **osmotic gradient** established by counter-current multiplier
- Dependent on **epithelium permeability** to water
- **Water permeability** dependent on ***water channels***

  --***Aquaporin-3***: present in **basolateral membrane of principal cells** always

  --***Aquaporin-2***: present in **apical membrane of principal cells** only when ***ADH*** present in blood

Water Reabsorption in Late DCT and CD

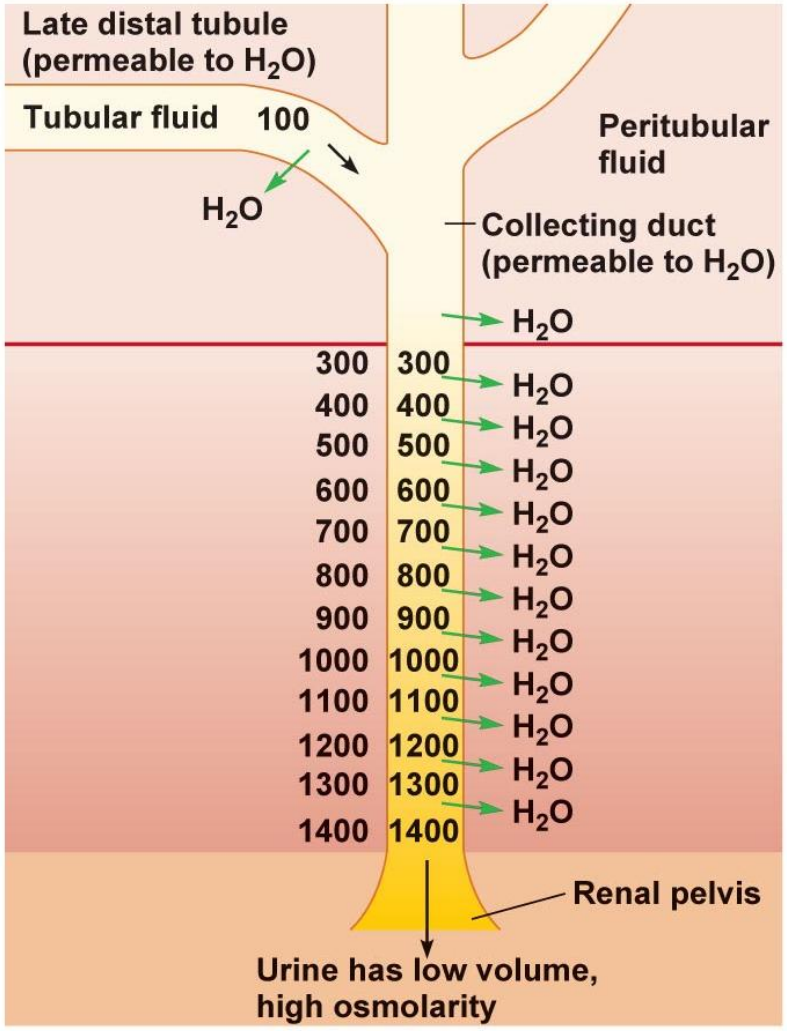
- **When membrane of late DCT and CD is impermeable to water**
  - --Water cannot leave the tubules
  - --No water reabsorption
  - --More water is excreted in urine



(a) Late distal tubule and collecting duct impermeable to water

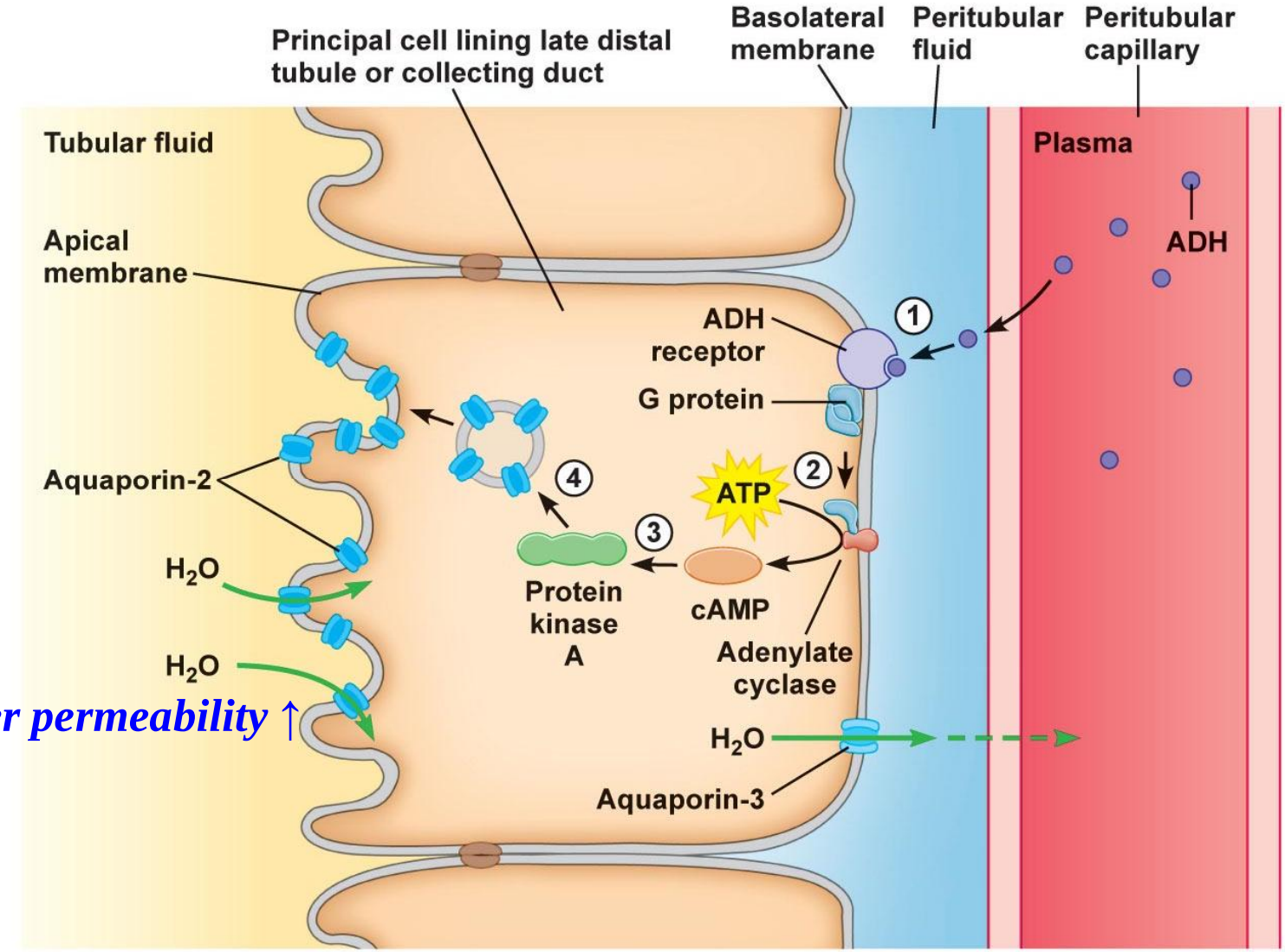
Water Reabsorption in Late DCT and CD

- **ADH** stimulates the insertion of water channels ***(aquaporin-2)*** into apical membrane
  - --Water is reabsorpbed by ***osmosis***
  - --Maximum urine concentration is ***1400 mOsm***



(b) Late distal tubule and collecting duct permeable to water

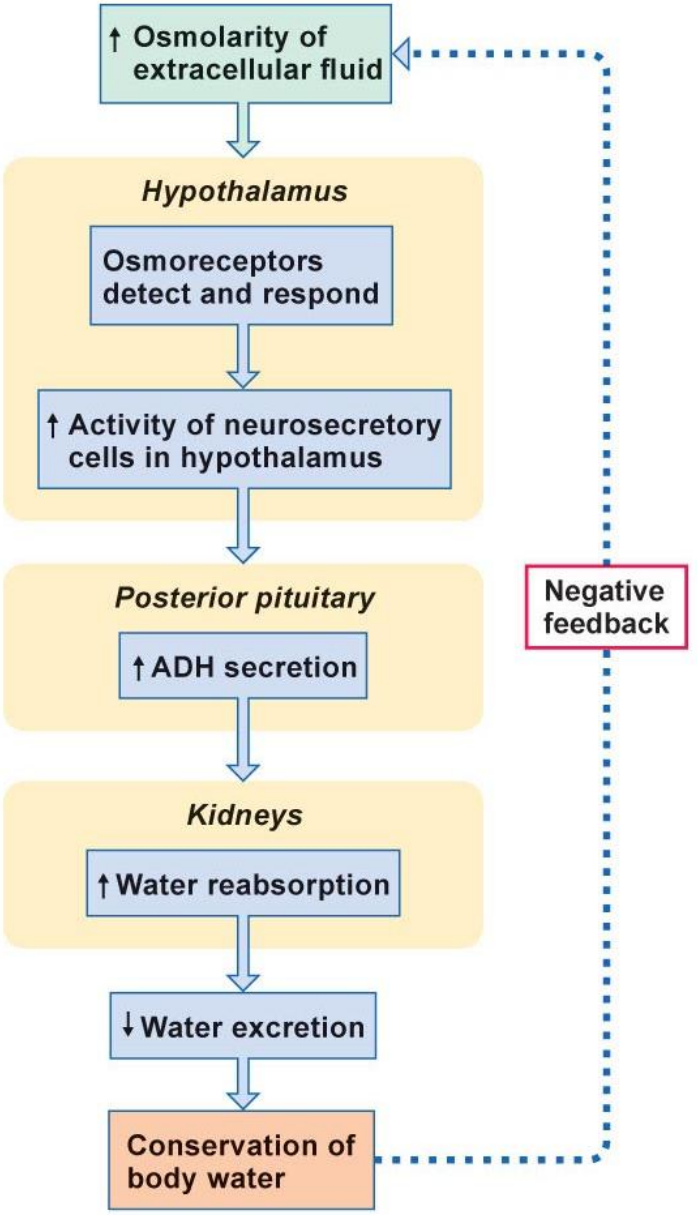
Effects of ADH on Principal Cells

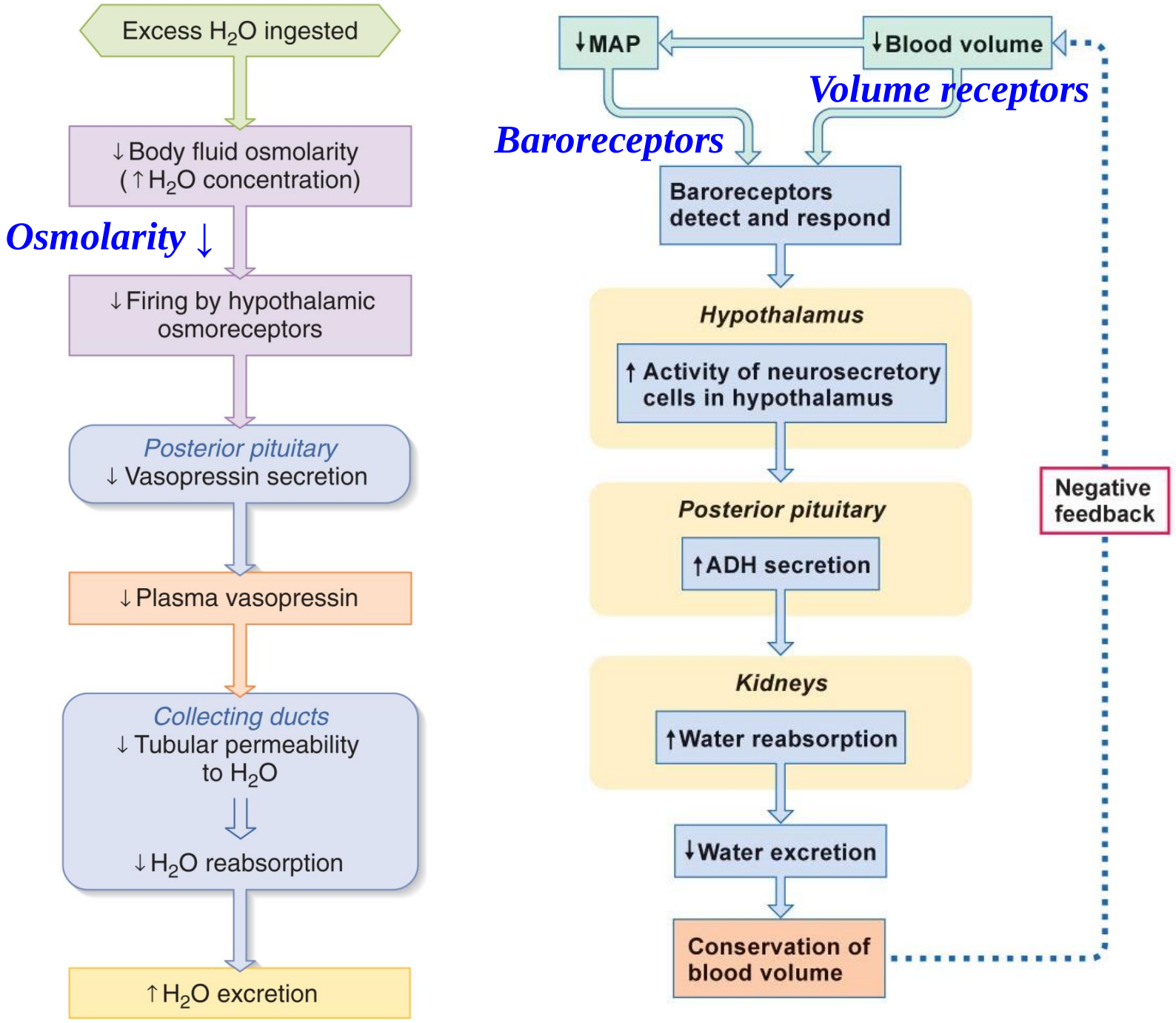


Water permeability ↑

Regulation of ADH Release

- ADH = **posterior pituitary hormone**
- Released from neurosecretory cells originating in **hypothalamus (SON and PVN)**
- Primary stimulus for release
  - --***Increased osmolarity (osmoreceptors)***
- Secretion is increased
  - --***Decreased blood pressure (baroreceptors)***
  - --***Decreased blood volume (volume receptors)***




Excess H_2O ingested
↓Body fluid osmolarity (↑H_2O concentration)
Osmolarity ↓
↓Firing by hypothalamic osmoreceptors
Posterior pituitary
↓ Vasopressin secretion
↓Plasma vasopressin
Collecting ducts
↓ Tubular permeability to H_2O
↓H_2O reabsorption
↑H_2O excretion
↓MAP
↓Blood volume
Volume receptors
Baroreceptors
Baroreceptors detect and respond
Hypothalamus
↑ Activity of neurosecretory cells in hypothalamus
Posterior pituitary
↑ADH secretion
Kidneys
↑Water reabsorption
↓Water excretion
Conservation of blood volume
Negative feedback

ADH Secretion and Action

Stimulus	Receptors	Secretion of ADH	Effects on Urine Volume	Effects on Blood
↑Osmolality (dehydration)	Osmoreceptors in hypothalamus	Increased	Decreased	Increased water retention; decreased blood osmolality
↓Osmolality	Osmoreceptors in hypothalamus	Decreased	Increased	Water loss increases blood osmolality
↑Blood volume	Stretch receptors in left atrium	Decreased	Increased	Decreased blood volume
↓Blood volume	Stretch receptors in left atrium	Increased	Decreased	Increased blood volume

Clinical Application: Diabetes Insipidus

- The word ***diabetes*** is derived from the Greek word for "**siphon**" =large volume of urine
- Symptoms: ***polyuria*** (20 L/day), ***hypernatremia***, ***plasma osmolarity***↑, ***polydipsia***
- A deficiency in ADH actions
  - **--Central diabetes insipidus:** ADH levels low (head injury, inflammation of hypothalamus, tumors etc.)
  - **--Nephrogenic diabetes insipidus:** lack of response to ADH (renal disease and hereditary: ADH receptor mutation—X chromosome)

GFR and Water Excretion

- **GFR normally autoregulated**
- **Decreases in blood pressure < 80 mm Hg**
  - ***--Decrease GFR***
  - ***--Decrease water filtered***
  - ***--Decrease water excretion***
- **Increases in blood pressure > 180 mm Hg**
  - ***--Increase GFR***
  - ***--Increase water filtered***
  - ***--Increase water excretion***

Electrolytes in Body Fluids

- ***Electrolytes*** **serve four general functions in the body**
  - --***Control the osmosis of water*** between body compartments
  - --***Maintain the acid-base balance***
  - --***Carry electrical current***, which allows production of action potentials and graded potentials and controls secretion of some hormones and neurotransmitters. Electrical currents are also important during development
  - --***Cofactors*** needed for optimal activity of enzymes
- **Concentration of ions typically expressed in *mEq/liter***
  - --Na^+ or Cl^- number of mEq/liter = ***mmol/liter***
  - --Ca^{2+} or HPO_4^{2-} number of mEq/liter = ***2 x mmol/liter***
- Chief difference between plasma and interstitial fluid (ECF) is ***plasma contains many more protein anions***
  - --Largely responsible for ***blood colloid osmotic pressure***

Solutes (Major Electrolytes)

➢ ***Control of Na^+ levels is important in blood pressure and blood volume***

➢ ***Control of K^+ levels is important in healthy skeletal and cardiac muscle activity***

ELECTROLYTE	CHARACTERISTICS
Sodium	• Major extracellular fluid (ECF) cation • Maintains tonicity of ECF • Regulates acid-base balance by renal reabsorption of sodium ion (base) and excretion of hydrogen ion (acid) • Facilitates nerve conduction and neuromuscular function • Facilitates glandular secretion • Maintains water balance
Potassium	• Major intracellular fluid (ICF) cation • Maintains cell electrical neutrality • Facilitates cardiac muscle contraction and electrical conductivity • Facilitates neuromuscular transmission of nerve impulses • Maintains acid-base balance
Chloride	• Mainly an ECF anion • Accounts for two-thirds of all serum anions • Secreted by the stomach mucosa as hydrochloric acid, providing an acid medium for digestion and enzyme activation • Helps maintain acid-base and water balances • Influences tonicity of ECF • Facilitates exchange of oxygen and carbon dioxide in red blood cells • Helps activate salivary amylase, which triggers the digestive process
Calcium	• Indispensable to cell permeability, bone and teeth formation, blood coagulation, nerve impulse transmission, and normal muscle contraction • *Hypo*calcemia can cause tetany and seizures • *Hyper*calcemia can cause cardiac arrhythmias and coma
Magnesium	• Present in small quantities, but physiologically as significant as the other major electrolytes • Enhances neuromuscular communication • Stimulates parathyroid hormone secretion, which regulates intracellular calcium • Activates many enzymes in carbohydrate and protein metabolism • Facilitates cell metabolism • Facilitates sodium, potassium, and calcium transport across cell membranes • Facilitates protein transport
Phosphate	• Involved in cellular metabolism as well as neuromuscular regulation and hematologic function • Phosphate reabsorption in the renal tubules inversely related to calcium levels: an increase in urinary phosphorous triggers calcium reabsorption and vice versa

Sodium Na^+

- Most abundant ion in **ECF**
- 90% of extracellular cations
- Plays pivotal role in **fluid and electrolyte balance, and osmotic pressure and function of excitable cells**
  because it account for almost 50% osmolarity of ECF
  - ***--Excess Na^+ in the body → edema and hypertension***
  - ***--Excess loss of Na^+ → excessive loss of water → hypovolemia***
- Level in blood controlled by
  - ***--Aldosternone*** – increases renal reabsorption
  - ***--ADH*** – if sodium too low, ADH release stops
  - ***--Atrial natriuretic peptide*** – increases renal excretion

Chloride Cl^-

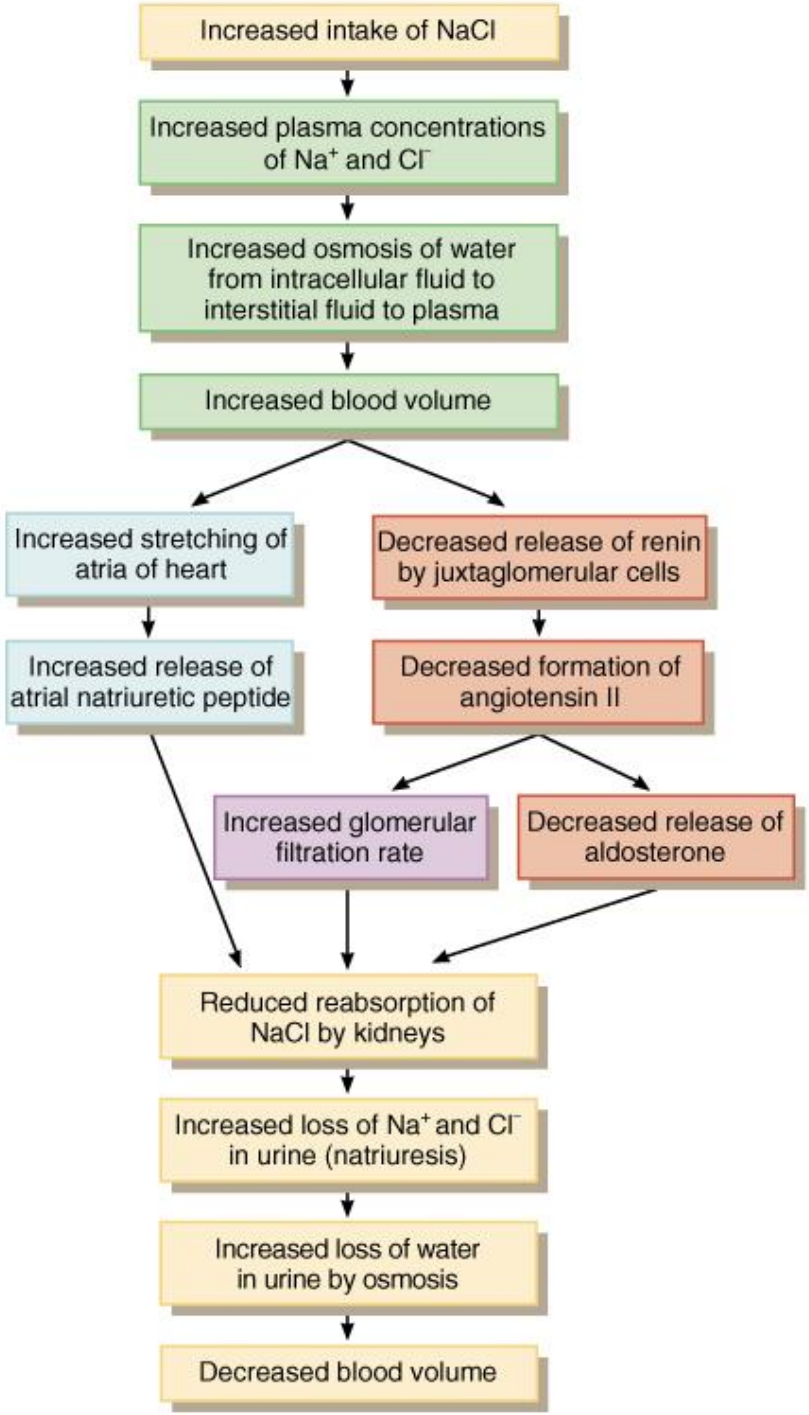
- Most prevalent anions in **ECF**
- Moves relatively easily between ECF and ICF because most plasma membranes contain **Cl^- leakage channels and antiporters**
- It plays a role in forming **HCl** in the stomach
- Can help **balance levels of anions** in different fluids
  --***Chloride shift in RBCs*** with buffer movement
- Regulated by
  --**Passively** follows Na^+ so it is regulated indirectly by ***aldosterone levels***
  --***ADH*** helps regulate Cl^- in body fluids because it controls water loss in urine

Regulation of Na^+ and Cl^-

- Extent of **urinary salt (NaCl) loss** is the main factor that determines ***body fluid volume***
- Main factor that determines ***body fluid osmolarity*** is extent of **urinary water loss**
- **3 hormones** regulate renal **Na^+ and Cl^-** reabsorption (or not)
  - --**Angiotensin II** and **aldosterone** promote urinary Na^+ and Cl^- reabsorption of (and water by osmosis) when ***dehydrated***
  - --**Atrial natriuretic peptide (ANP)** promotes excretion of Na^+ and Cl^- followed by water excretion to decrease blood volume

Hormonal Regulation of Na^+ and Cl^-

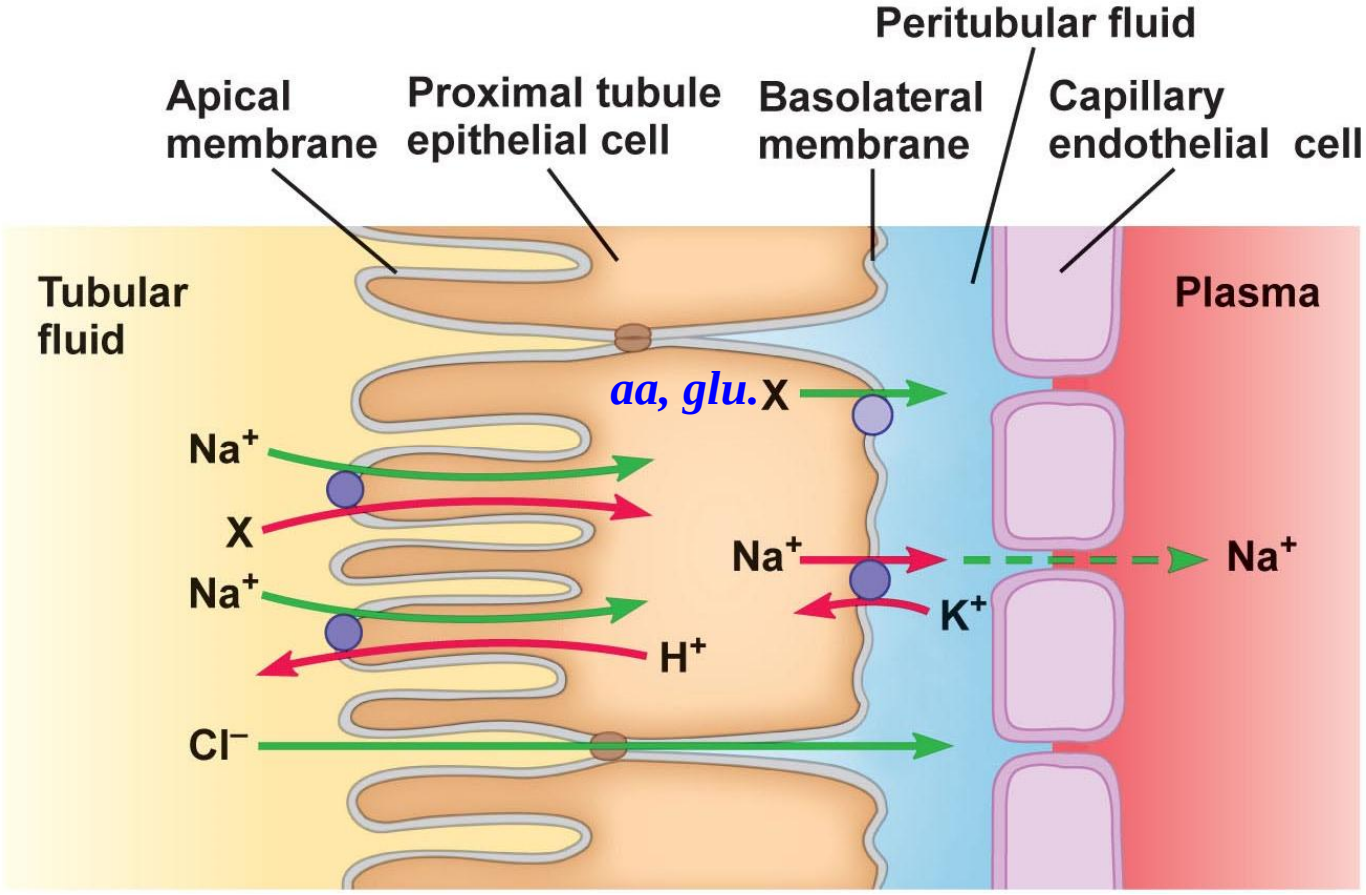
- Elimination of excess water or solutes occurs through urination
- Consumption of **very salty meal** demonstrates function of three hormones (**AII, aldosterone and ANP**)
- Demonstrates how
  - ***--"Water follows salt"***
  - ***--Excrete Na+ and water will follow and decrease blood volume***



Renal Handling of Sodium

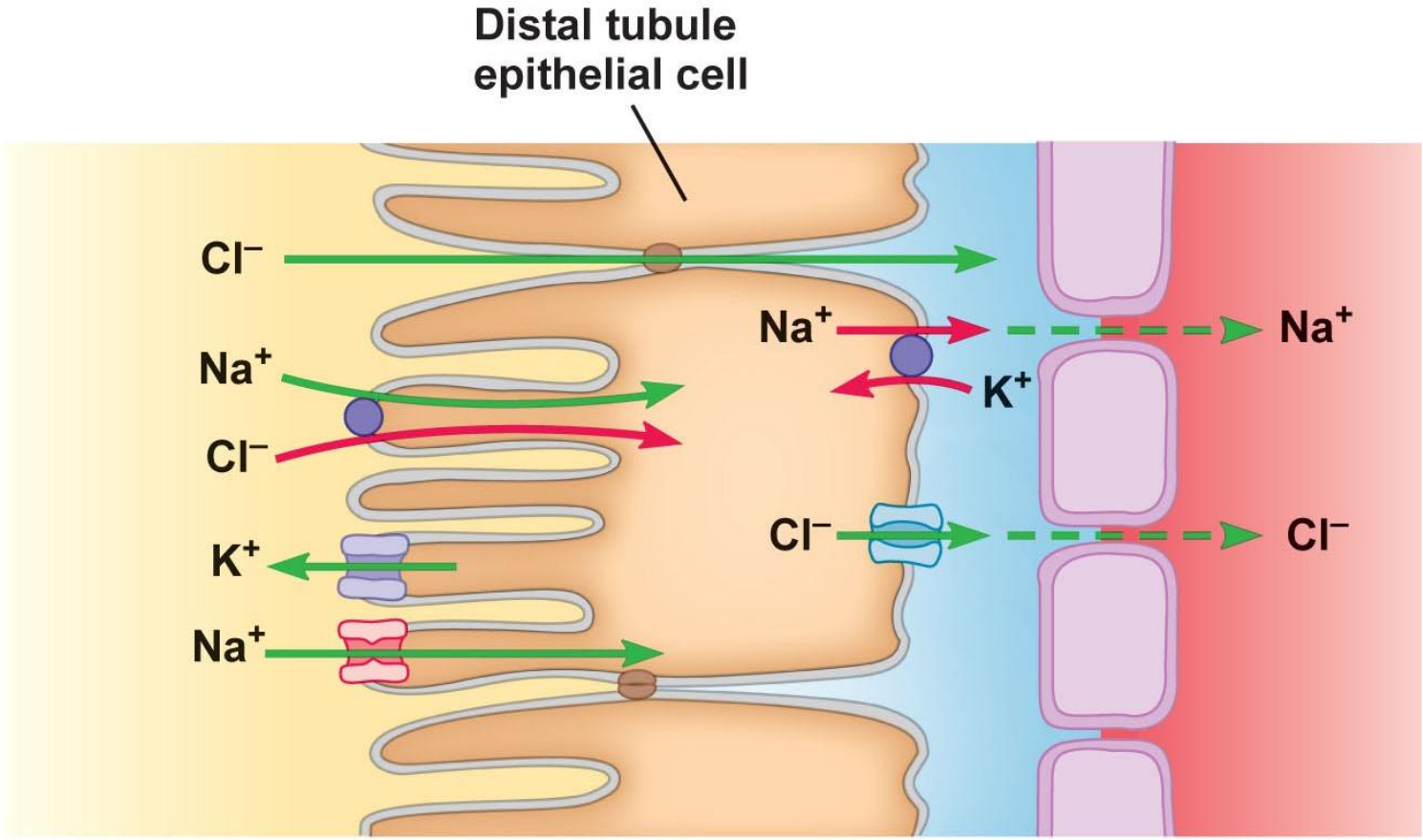
- Freely filtered and No secretion
- Reabsorbed in ***proximal tubule, distal tubule, and collecting duct***
- Sodium reabsorbed in ***proximal tubule (70%)*** and in ***distal tubule and collecting ducts***
- Reabsorption regulated by ***aldosterone and ANP***
- Reabsorption regulated at ***principal cells of distal tubule and collecting duct***
- **Active** reabsorption
- **Na^+/K^+ pump** on ***basolateral membrane*** drives reabsorption

Proximal Tubule Sodium Reabsorption



- *Active reabsorption (cotransport: Na-aa, Na-glu; countertransport: Na-H)*
- *Na^+/K^+ pump on basolateral membrane drives reabsorption*
- *Coupled to the reabsorption of other solutes*

Distal Tubule Sodium Reabsorption

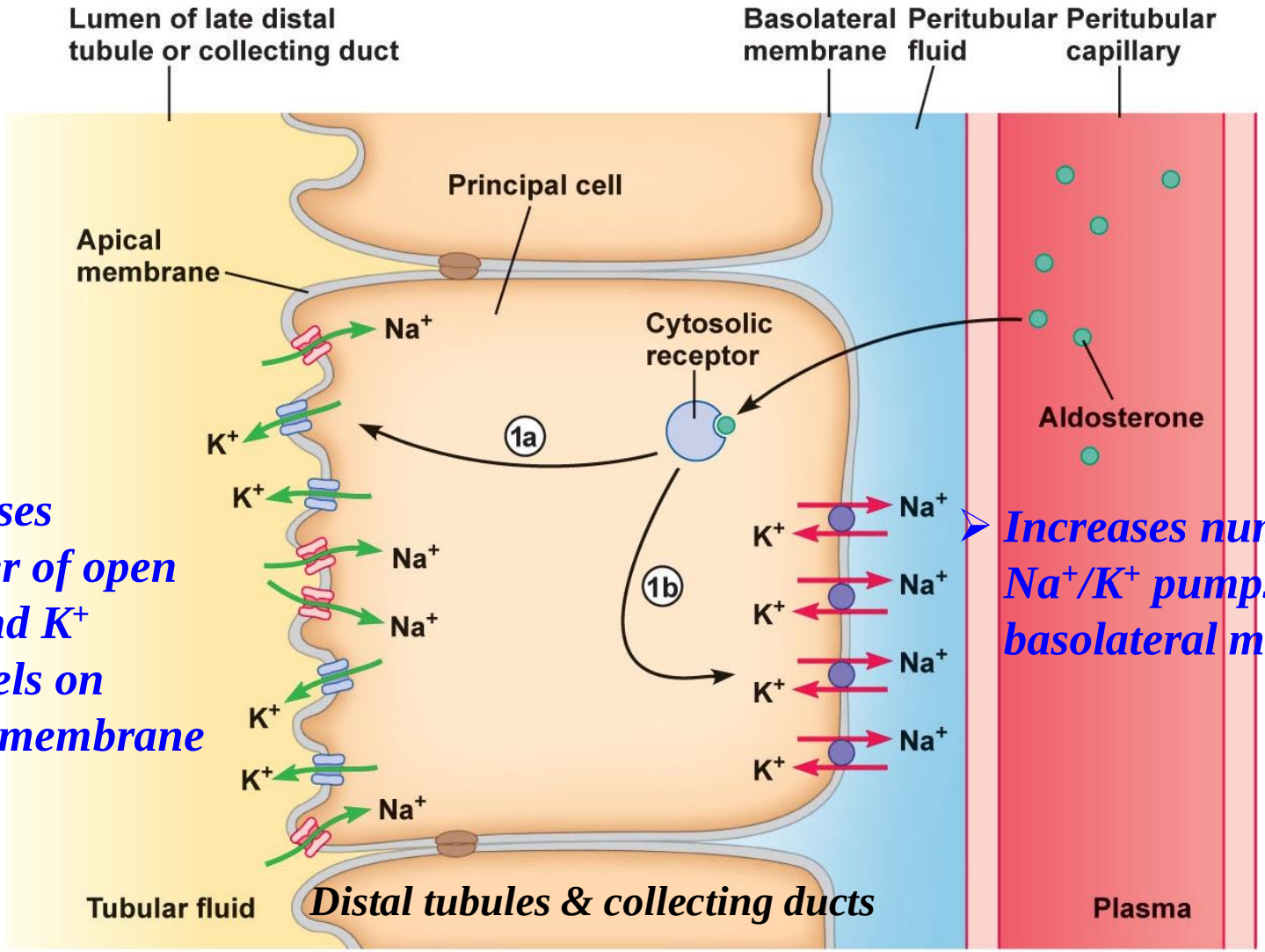


- ***Active reabsorption (cotransport: Na-Cl) or diffusion (Na channel)***
- ***Na^+/K^+ pump on basolateral membrane drives reabsorption***
- ***Coupled to the secretion of K^+ and H^+***

Effects of Aldosterone on Sodium Reabsorption

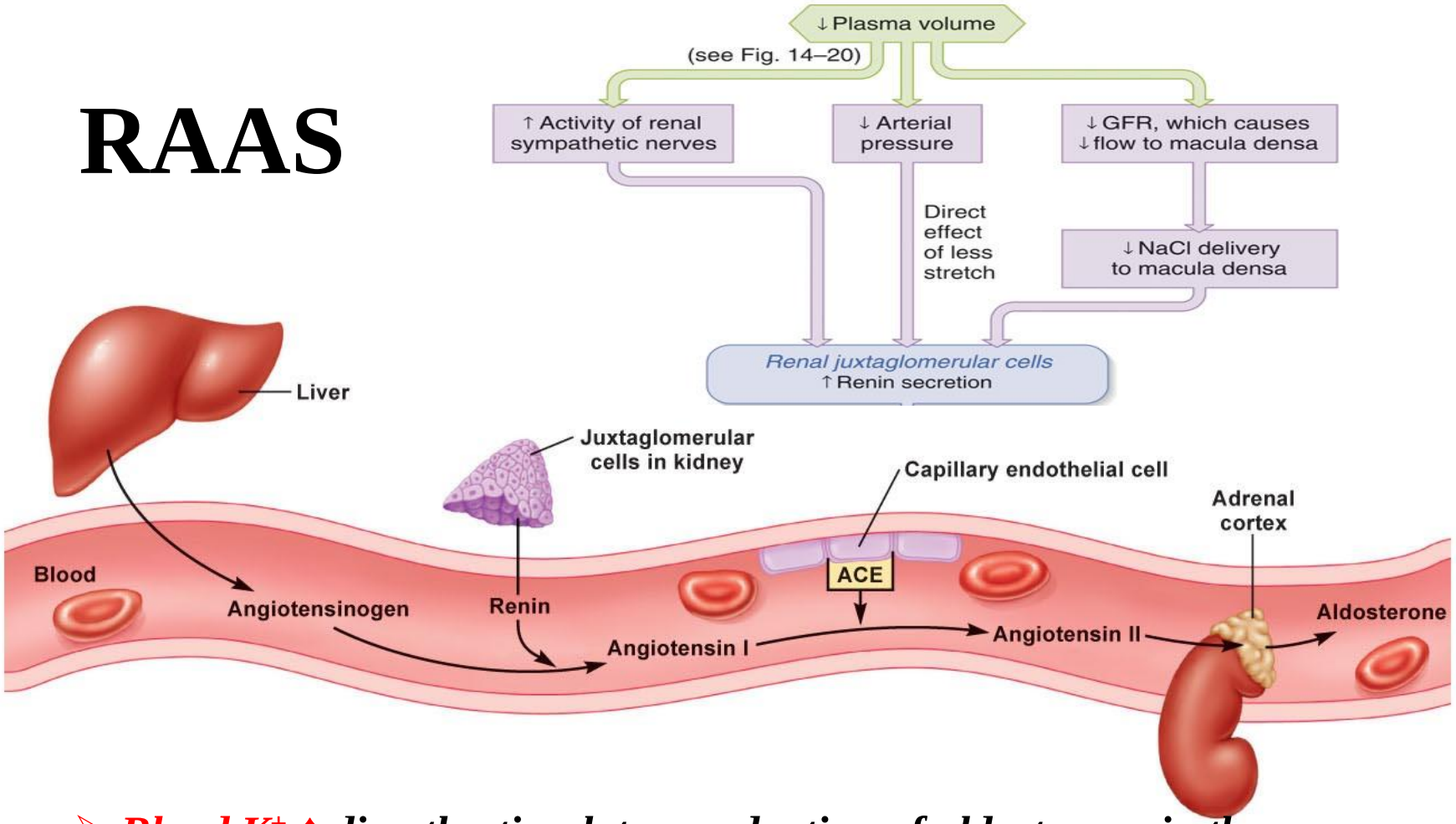
- Aldosterone ***increases Na^+ (Cl^- and water) reabsorption*** and ***K^+(H^+) secretion***
- **Steroid hormone** and secreted from **adrenal cortex**
- Acts on ***principal cells*** ***of distal tubules and collecting ducts***
  - --Increases number of ***Na^+/K^+ pumps*** ***on basolateral membrane***
  - --Increases number of ***open Na^+ and K^+ channels*** ***on apical membrane***
- ***Renin-angiotensin-aldosterone system (RAAS)*** control aldosterone release

Effects of Aldosterone



- *Increases number of open Na^+ and K^+ channels on apical membrane*
- *Increases number of Na^+/K^+ pumps on basolateral membrane*

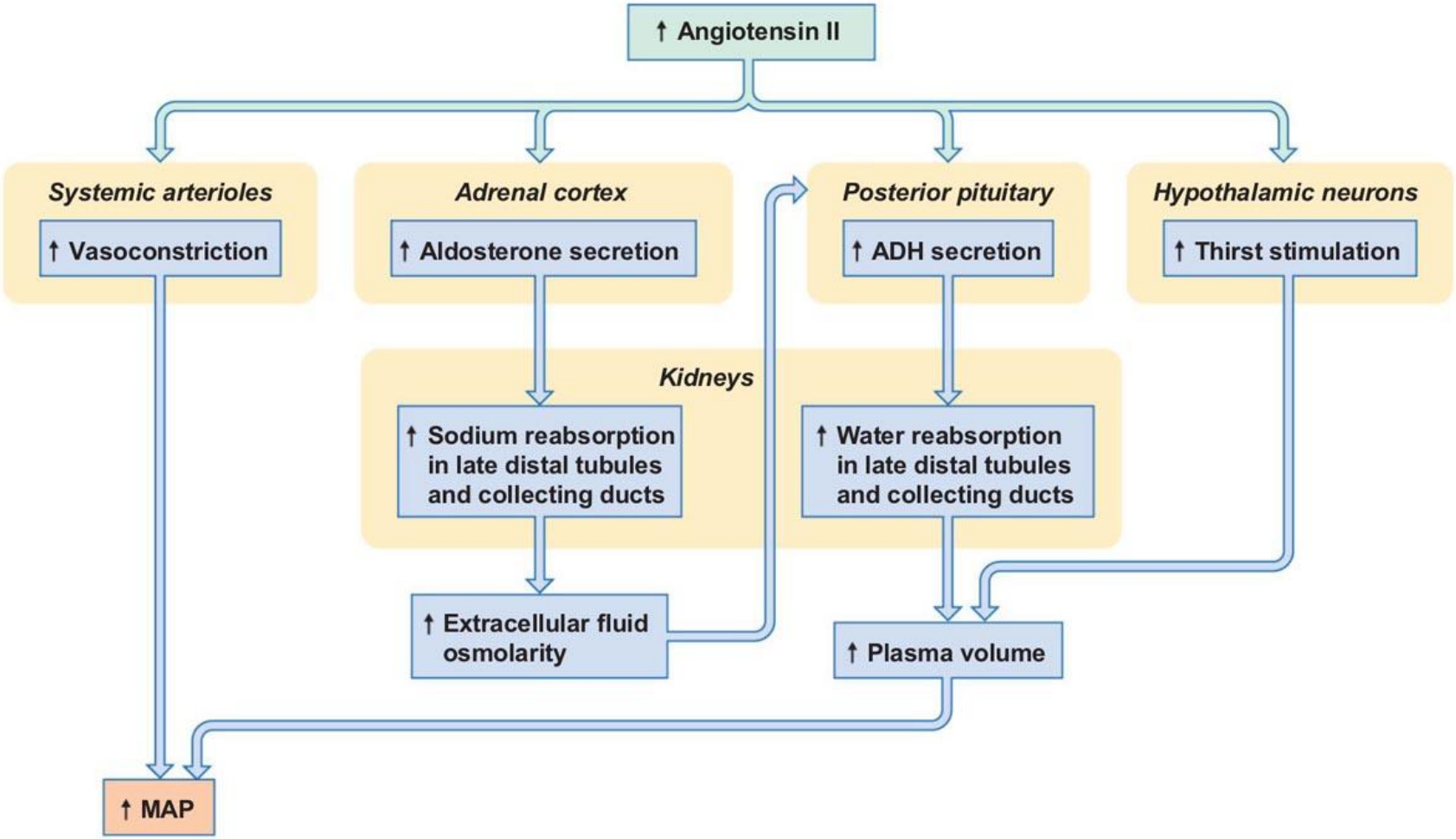
RAAS



- ***Blood K^+ ↑ directly stimulates production of aldosterone in the adrenal cortex***
- ***Blood Na^+ ↓ indirectly stimulates production of aldosterone via the renin- angiotensin-aldosterone system***

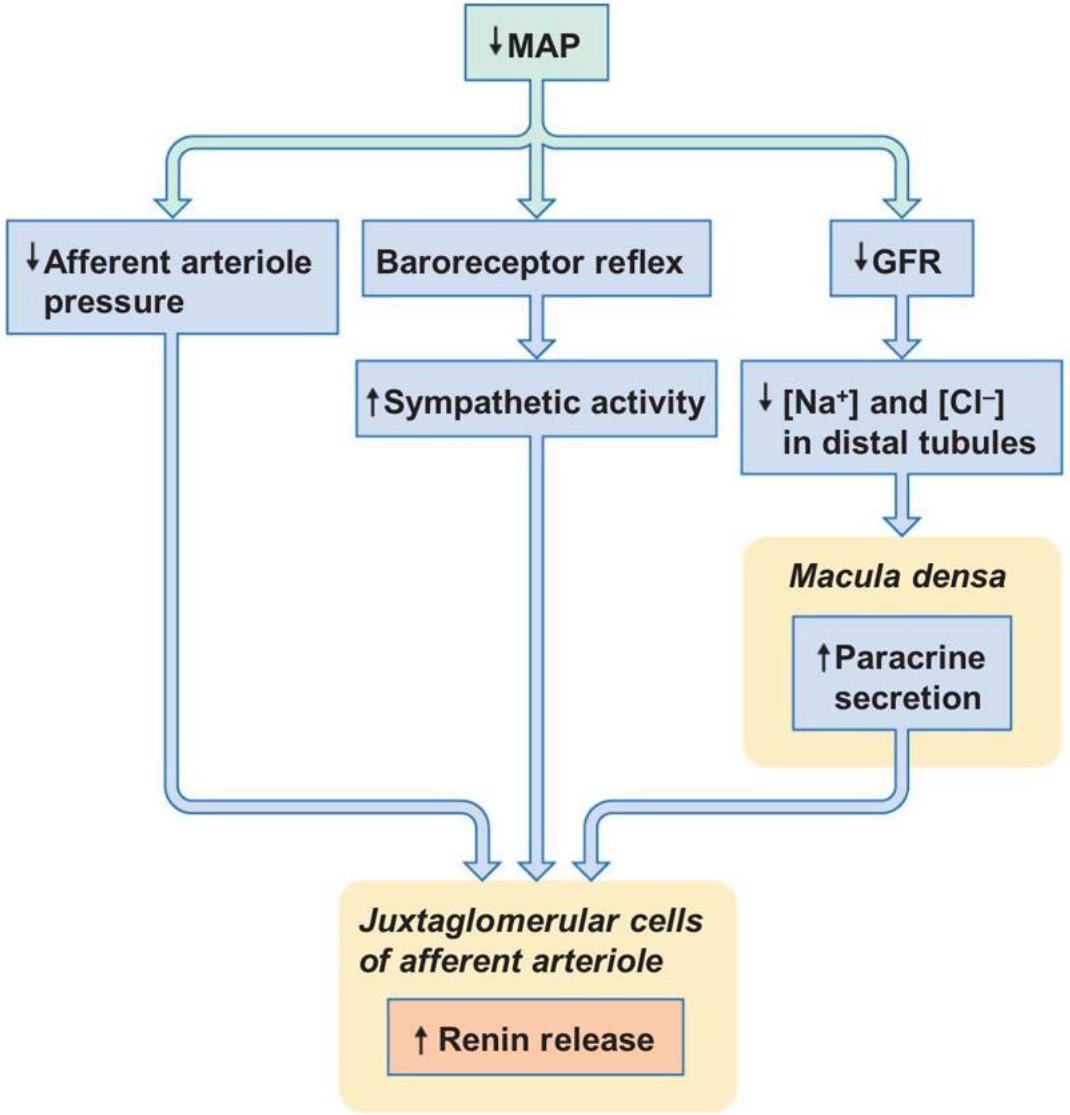
Angiotensin-converting enzyme (ACE)

Actions of Angiotensin II



Renin

- Renin = ***proteolytic enzyme***
- Secreted by ***juxtaglomerular cells***
- Stimuli for renin release
  - --↓ ***Pressure in afferent arteriole***
  - --↑***Renal sympathetic nerve activity***
  - --↓ ***Na^+ and Cl^- in distal tubule filtrate***

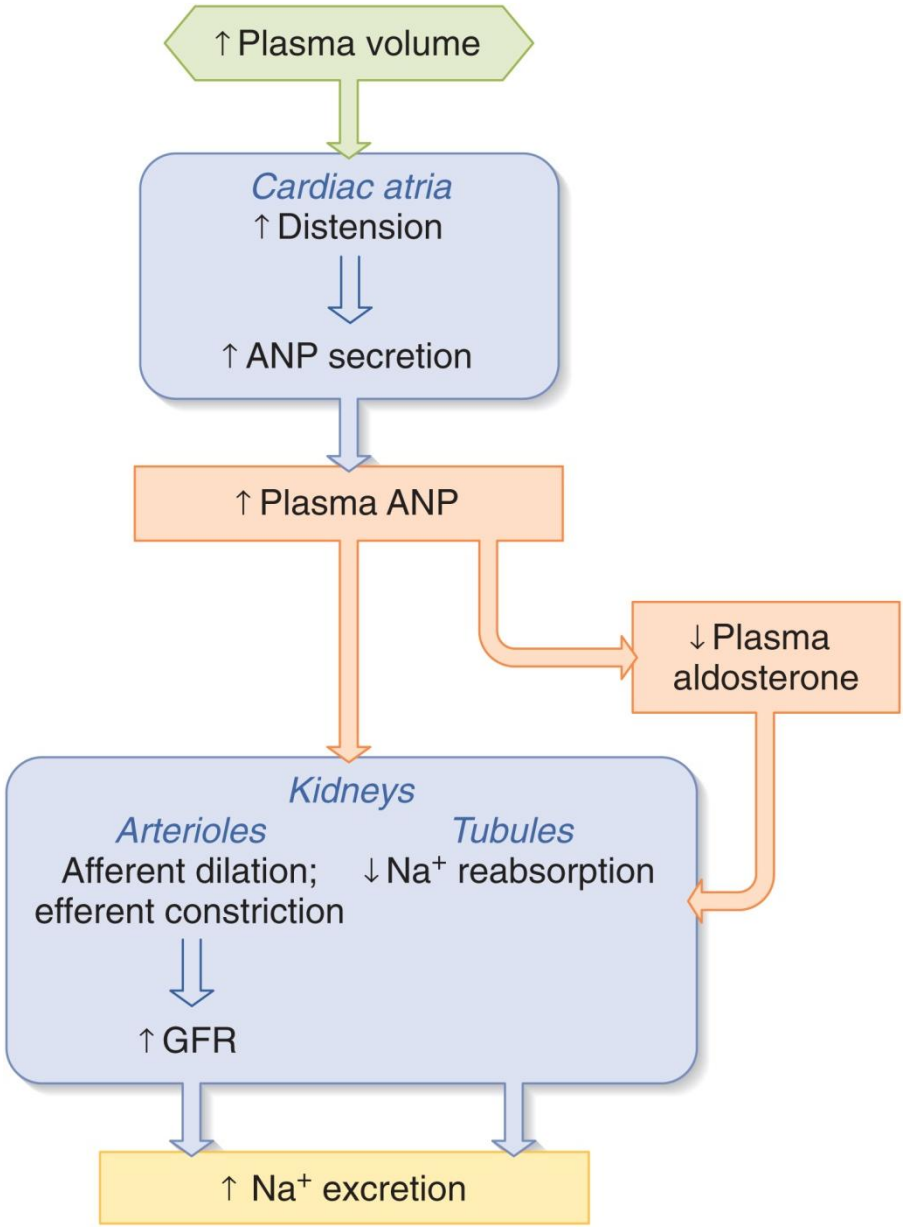


Regulation of Renin and Aldosterone Secretion

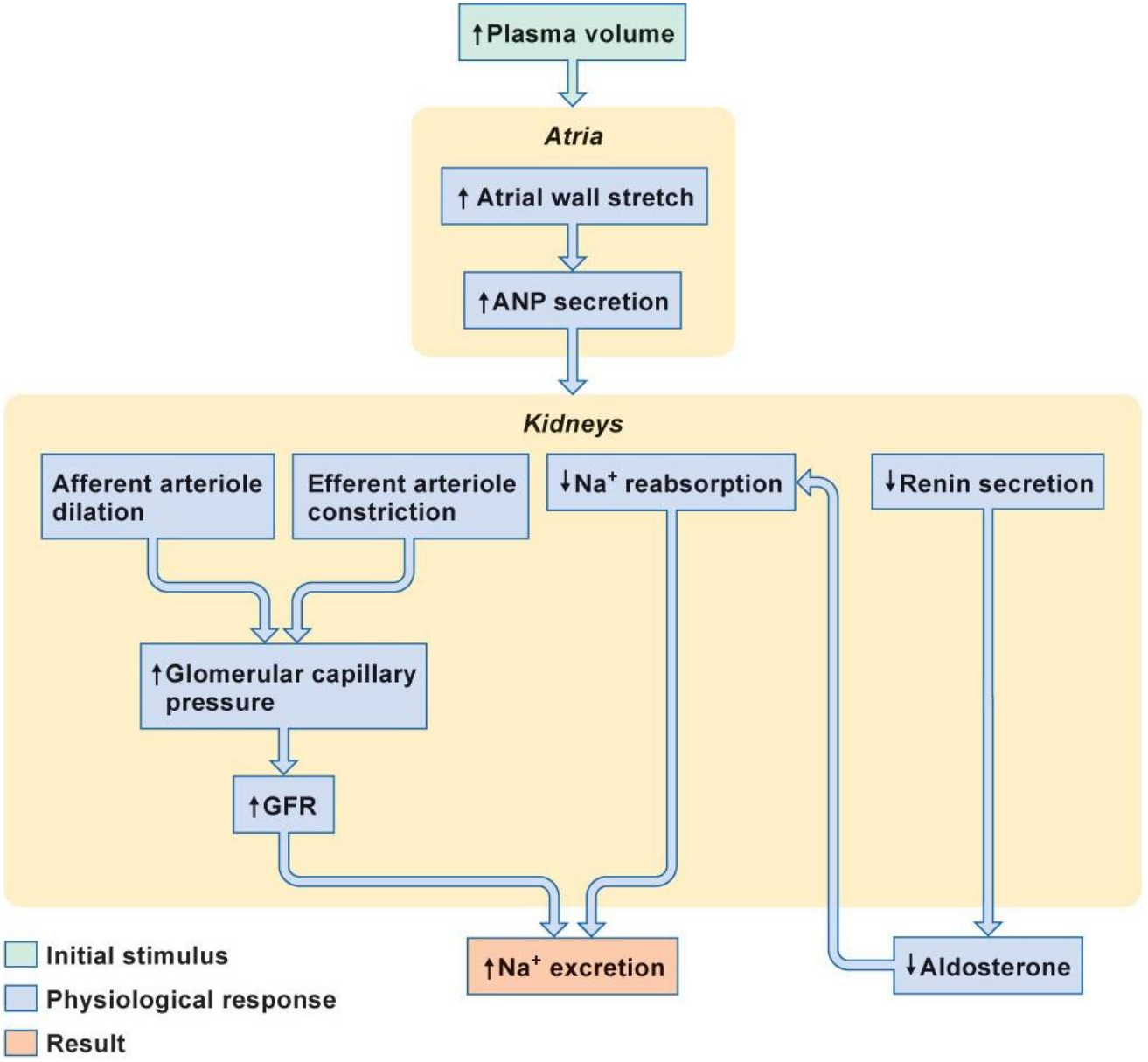
Stimulus	Effect on Renin Secretion	Angiotensin II Production	Aldosterone Secretion	Mechanisms
↓Blood volume	Increased	Increased	Increased	Low blood volume stimulates renal baroreceptors; granular cells release renin.
↑Blood volume	Decreased	Decreased	Decreased	Increased blood volume inhibits baroreceptors; increased Na^+ in distal tubule acts via macula densa to inhibit release of renin from granular cells.
↑ K^+	None	Not changed	Increased	Direct stimulation of adrenal cortex
↑Sympathetic nerve activity	Increased	Increased	Increased	α-adrenergic effect stimulates constriction of afferent arterioles; β-adrenergic effect stimulates renin secretion directly.

ANP and Sodium Excretion

- Secreted by ***atrial cells*** in response to distension of atrial wall
- **Increases GFR**
  - ***--Dilation of afferent arteriole***
  - ***--Constriction of efferent arteriole***
- **Decreases sodium reabsorption** by closing sodium channels in apical membrane
- Overall effect**:** ***increased sodium excretion***



ANP and Sodium Excretion



Clinical Application: Sweating

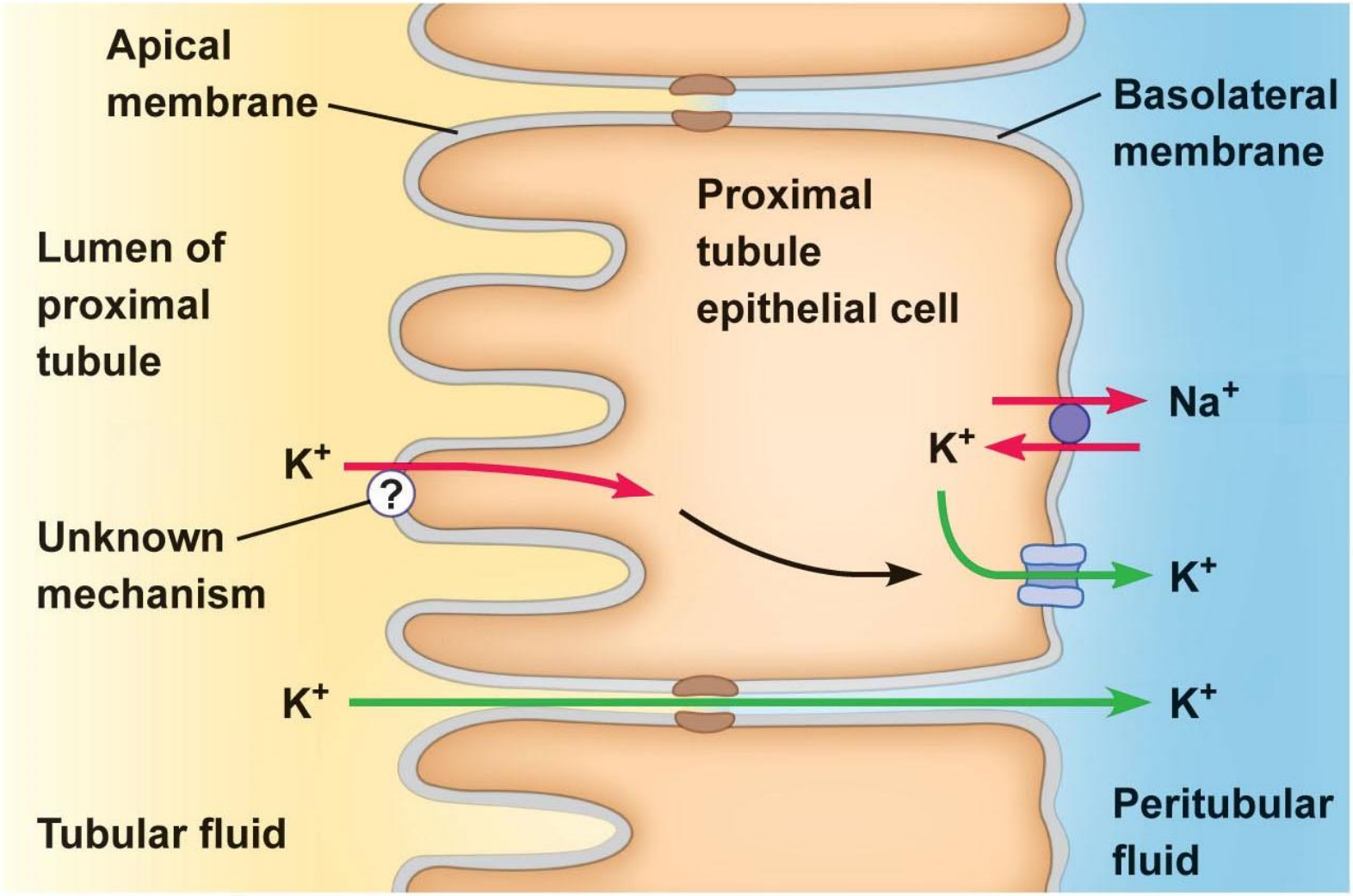
Potassium K^+

- Most abundant cations in **ICF**
- Helps ***establish resting membrane potential*** & ***repolarize nerve & muscle tissue***
- Also helps ***maintain normal ICF fluid volume***
- Helps ***regulate pH*** of body fluids when exchanged for H^+
- Control is mainly by ***aldosterone*** ***(mineralocorticoids)*** – stimulates principal cells in renal collecting ducts to **secrete excess K^+**
- Helps ***establish resting membrane potential*** & ***repolarize*** nerve & muscle tissue
- Abnormal plasma K^+ levels adversely affect **cardiac and neuromuscular function**

Renal Handling of Potassium

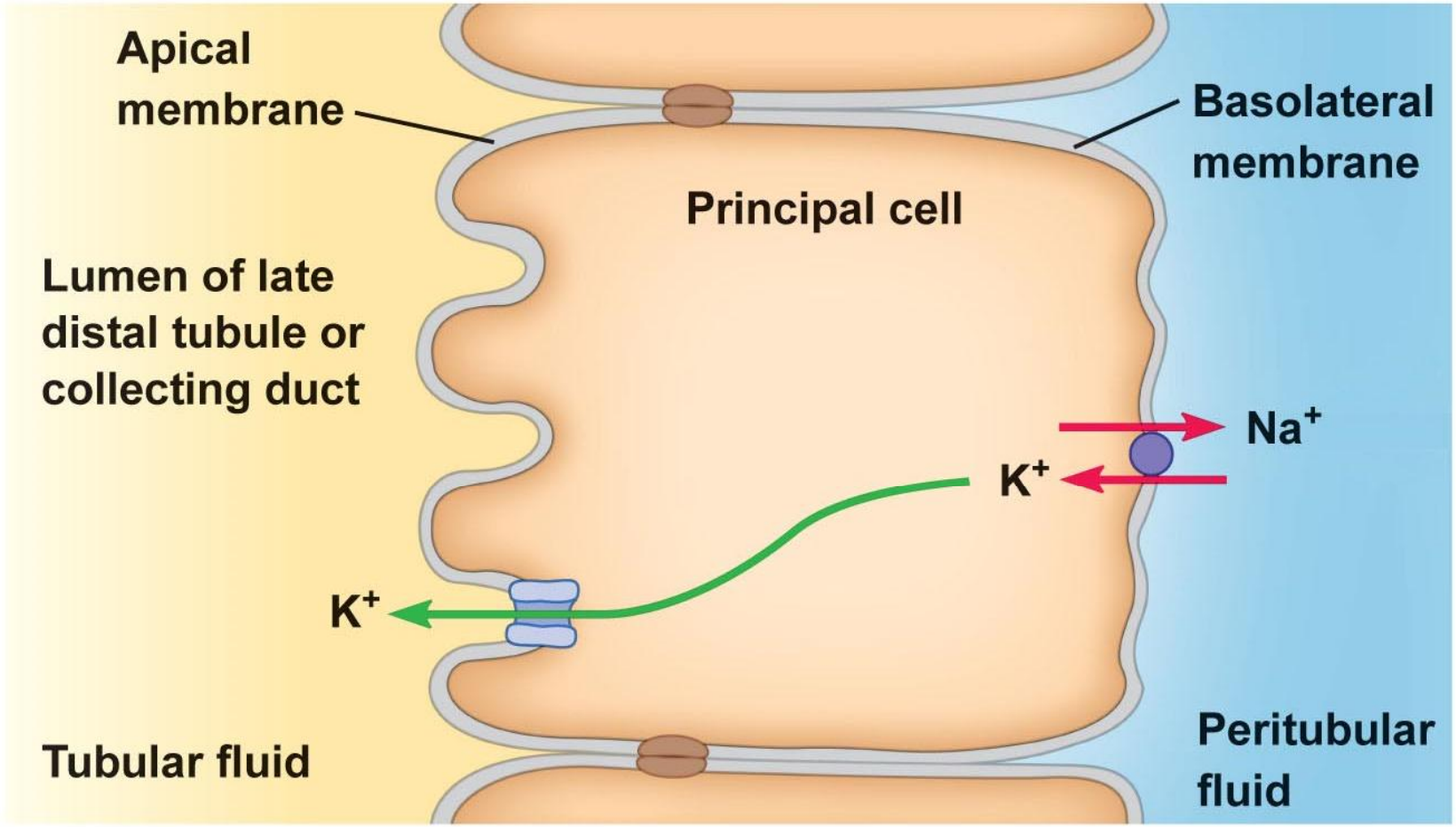
- Glomerulus—freely filtered
- **Proximal tubules**—reabsorbed
- **Distal tubules and collecting ducts**—reabsorbed and secreted
- Potassium secretion in distal tubules and collecting ducts ***is regulated*** (**aldosterone** regulates principal cells)
- Regulation of aldosterone release
  - --***Renin-angiotensin-aldosterone system***
  - --***Plasma [K^+]*** directly stimulates aldosterone release
    - ✓As K^+ increases, more aldosterone released

Proximal Tubule K Reabsorption



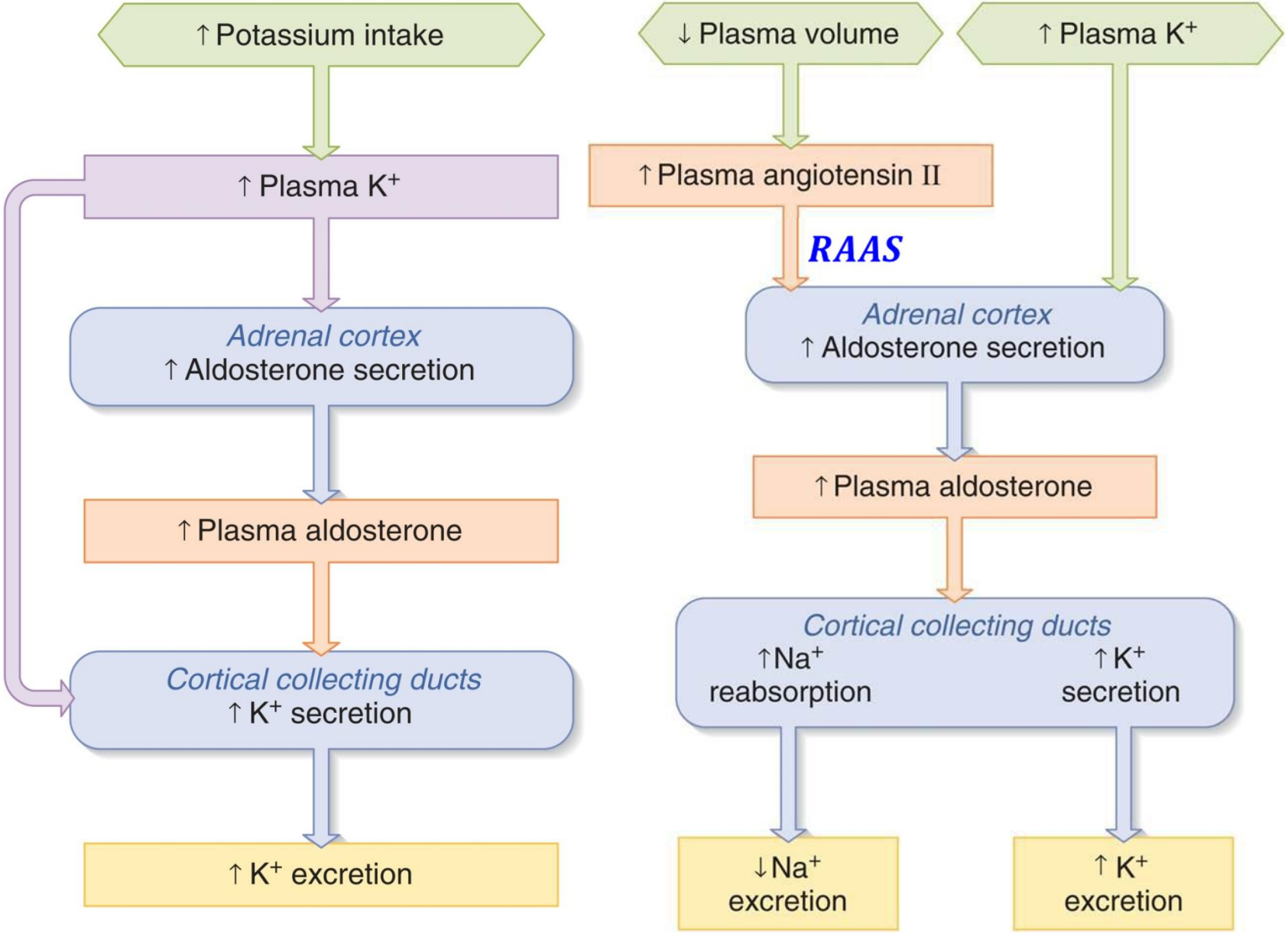
(a) Potassium reabsorption in the proximal tubule

Proximal Tubule K Secretion



(b) Potassium secretion in the principal cells of the late distal tubule and collecting duct

Regulation of Aldosterone Release



Clinical Application:
Abnormal Plasma K^+ Levels

Organ System	Hypokalemia	Hyperkalemia
Cardiovascular	Dysrhythmias Electrocardiogram changes Cardiac arrest Weak irregular pulse Postural hypotension	Dysrhythmias Bradycardia Heart block Cardiac arrest
Nervous	Lethargy Fatigue Confusion Paresthesias	Anxiety Tingling Numbness
Gastrointestinal	Nausea and vomiting Decreased motility Distention Decreased bowel sounds Ileus	Nausea and vomiting Diarrhea Colicky pain
Kidney	Water loss Thirst Inability to concentrate urine Kidney damage	Oliguria Kidney damage
Skeletal muscle	Weakness Flaccid paralysis Respiratory arrest	Early: hyperactive muscles Late: weakness and flaccid paralysis

Causes of Hypokalemia

- Hypokalemia is not commonly caused by poor dietary intake
- **Excessive loss** is the most common reason that potassium levels are low. Loss of potassium may occur from both the **GI tract** and from the **kidney**
- Potassium loss from the **intestines** may be caused by:

  --***Vomiting, diarrhea, laxative use, villous adenoma*** (a type of colon polyp that can cause the colon to leak potassium), etc.

- Causes of potassium loss from the **kidney**:

  --***Diuretic medications*** like furosemide (Lasix)

  --***Elevated corticosteroid levels*** **(**medication like prednisolone or from **Cushing's Syndrome)**

  --***Elevated levels of aldosterone*** (**renal artery stenosis** or **adrenal tumors)**

  --***Renal tubular acidosis*** **and** ***Low body magnesium levels***

Causes of Hyperkalemia

1. **Acute or chronic renal insufficiency**: Due to a decrease in distal solute (NaCl) delivery and a decrease in overall renal mass
2. **Impaired Na^+reabsorption** (common): **Aldosterone deficit** results in decreased K^+ excretion

   --Resistance to aldosterone: Drugs (e.g., potassium-sparing diuretics, trimethoprim, pentamidine)

   --Secondary hypoaldosteronism: Drugs (e.g., ACE inhibitors, NSAIDs, heparin), hyporeninemia, AIDS

   --Renal tubular acidosis, type 4

   --Primary hypoaldosteronemia

3. Increased K release from cells (Hyperkalemia)

- **Pseudohyperkalemia**

  --**Prolonged use of a tourniquet** with or without repeated fist clenching

  --**Hemolysis** after blood is drawn

  --**Marked leukocytosis and thrombocytosis**: Cells release K^+ into the serum in the process of clotting

- **Tissue breakdown**: Intravascular hemolysis, tumor lysis syndrome, excessive exercise, trauma, and rhabdomyolysis
- **Metabolic acidosis**: $K^+$is shifted out of cells to buffer the increased H^+
- **Hyperosmolar states** (e.g., hyperglycemia): K^+ diffuses out of cells along with water
- **Insulin deficiency and Medications** (α-adrenergic agonists and β_2 antagonists etc.)

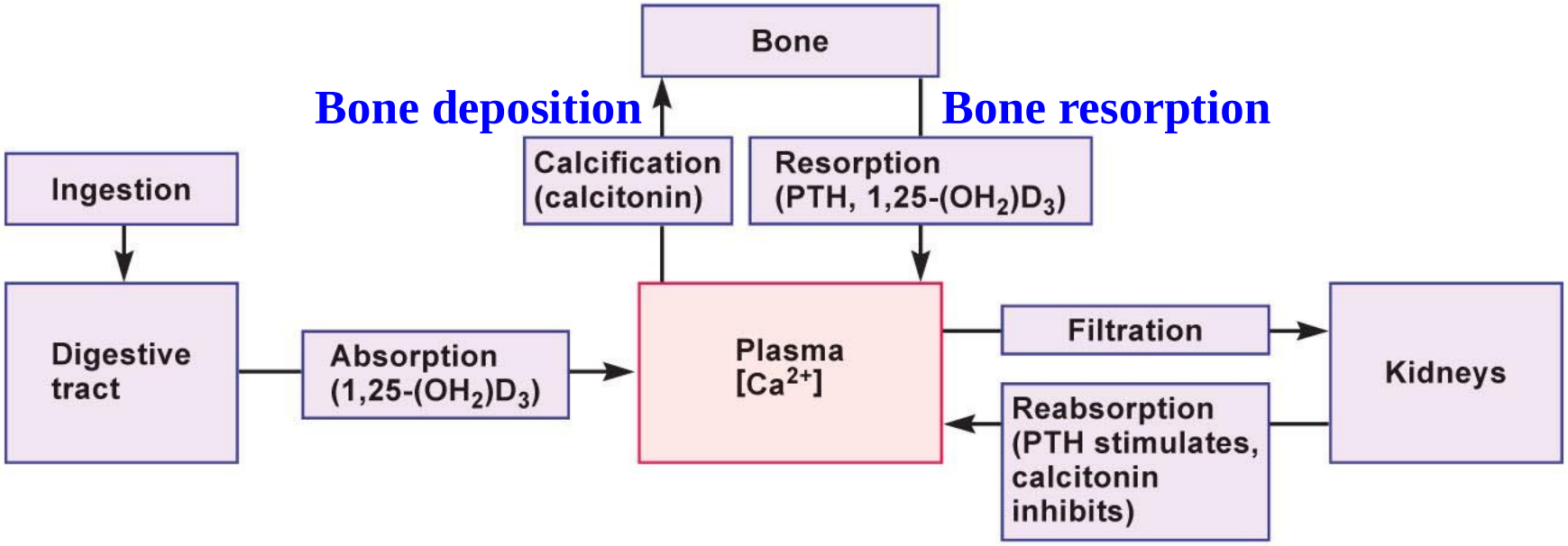
Calcium Ca^{2+}

- **Most abundant mineral** in body
- **99%** of calcium in adults in ***skeleton and teeth***
- In body fluids mainly an **extracellular cation**
- Contributes to **hardness** of teeth and bones
- Plays important roles in ***blood clotting, neurotransmitter release, muscle tone, and excitability of nervous and muscle tissue***
- Regulated by ***parathyroid hormone (↑blood Ca levels)***
  - **--Bone:** Stimulates osteoclasts to release calcium from bone (***bone resorption***)
  - **--Kidney:** enhances ***reabsorption*** from glomerular filtrate
  - **--GI tract:** Increases production of ***calcitrol*** to increase absorption for GI tract
- ***Calcitonin*** lowers blood calcium levels

Renal Handling of Calcium

- **Blood calcium**
  - --Bound to carrier proteins
  - --Free in plasma
  - --Ca^{2+} + Protein ←→ Ca-Protein
  - --Free calcium—freely filtered at glomerulus
- **70%** reabsorbed in ***proximal tubules***
- **19–20%** reabsorbed in ***thick ascending limbs of the loops of Henle***
- **9–10%** reabsorbed in ***distal tubules***
- Reabsorption in loops of Henle and distal tubules ***is regulated***

Routes of Calcium Exchange



- **Organs**
  - *--Kidneys*
  - *--Digestive tract*
  - *--Bone*
  - *--Skin*
- **Hormones**
  - *--Parathyroid hormone (PTH)*
  - *--Calcitriol (Vitamin D_3)*
  - *--Calcitonin (CT)*

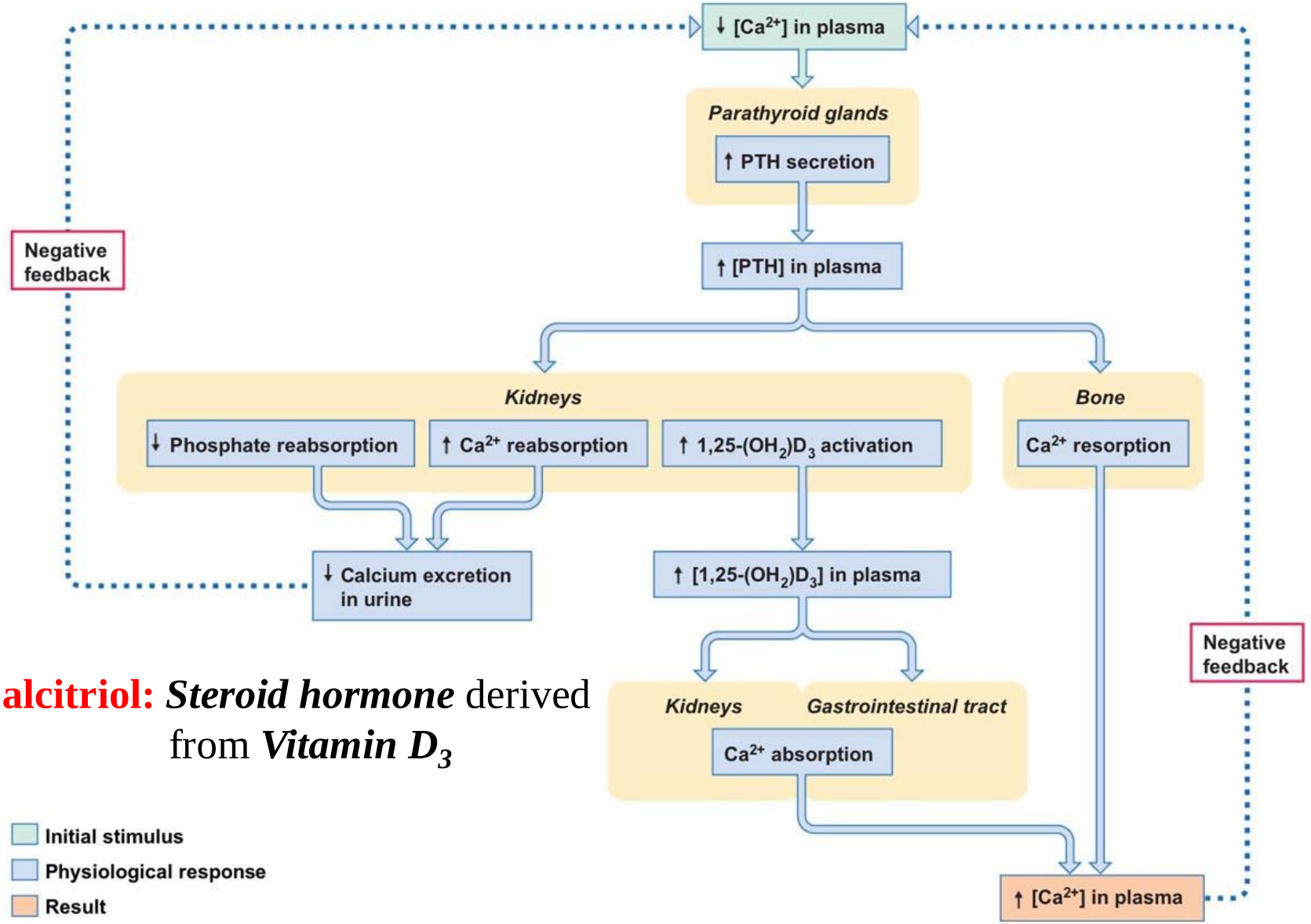
Parathyroid Hormone
Increases Plasma Calcium

- PTH released from parathyroid glands
- Stimulus = ***decrease Ca^{2+} in plasma***
- Actions:

1. Increase Ca^{2+} reabsorption by **kidneys**
2. Stimulates **activation of calcitriol** in kidneys (**calcitriol --**increase in calcium absorption from **digestive tract**)
3. Stimulates resorption of **bone**
4. Stimulates small increase in calcium absorption from **digestive tract**

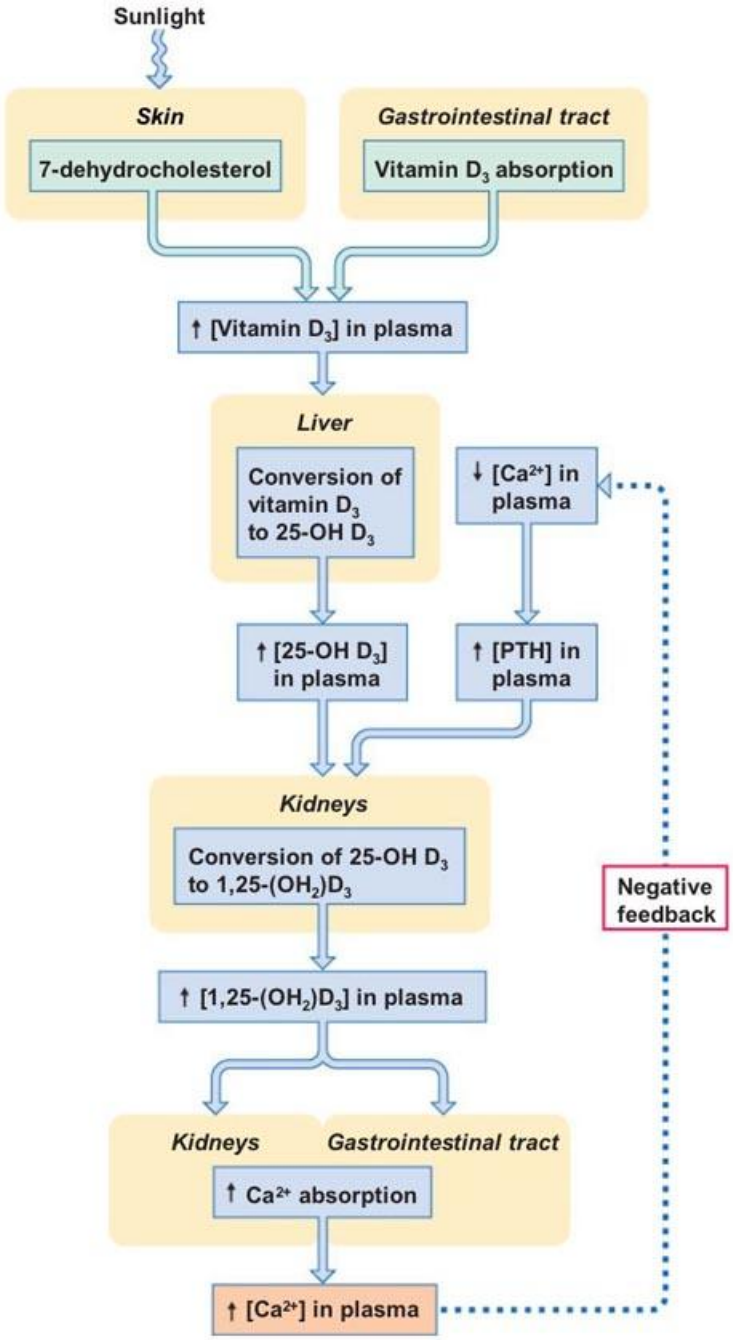
--Overall effect: ***increase blood calcium***

Regulation of PTH in Ca Balance



Calcitriol: ***Steroid hormone*** derived from ***Vitamin D_3***

Activation of Calcitriol =1,25-(OH_2)D_3



Bicarbonate HCO_3^-

- Second most prevalent **extracellular anion**
- Concentration increases in blood passing through systemic capillaries picking up ***carbon dioxide***
  - --Carbon dioxide combines with water to form ***carbonic acid*** which dissociates
  - --Drops in ***pulmonary capillaries*** when carbon dioxide exhaled
- **Chloride shift** helps maintain correct balance of anions in ECF and ICF
- **Kidneys** are main regulators of blood HCO_3^-
  - --Can form and release HCO_3^- when low or excrete excess

Phosphate

- About **85%** in adults present as ***calcium phosphate*** salts in bone and teeth, and in phospholipids, ATP, DNA and RNA
- Remaining **15% ionized** – $H_2PO_4^-$, HPO_4^{2-}, and PO_4^{3-} are important ***intracellular anions***
- **HPO_4^{2-}** important buffer of H^+ in body fluids and urine
- Same hormones governing calcium homeostasis also regulate HPO_4^{2-} in blood
  - --***Parathyroid hormone*** – stimulates resorption of bone by osteoclasts releasing calcium and phosphate but inhibits reabsorption of phosphate ions in kidneys
  - --***Calcitrol*** promotes absorption of phosphates and calcium from GI tract

Magnesium

- In adults, about **54%** of total body magnesium is part of bone as ***magnesium salts***
- Remaining **46%** as Mg^{2+} in ***ICF (45%)*** or ECF (1%)
- Second most common ***intracellular cation***
- **Cofactor** for certain enzymes and sodium-potassium pump
- Essential for ***normal neuromuscular activity*****,** ***synaptic transmission*****, and** ***myocardial function***
- **Secretion of PTH** depends on Mg^{2+}
- Regulated in blood plasma by varying rate ***excreted in urine***

Electrolytes Imbalances

	Deficiency		Excess	
Electrolyte*	**Name and Causes**	**Signs and Symptoms**	**Name and Causes**	**Signs and Symptoms**
Calcium (Ca^{2+}) Total 5 9–10.5 mg/dL; ionized = 4.5–5.5 mEq/liter	**Hypocalcemia** (hī-pō-kal-SĒ-mē-a) may be due to increased calcium loss, reduced calcium intake, elevated levels of phosphate, or hypoparathyroidism.	Numbness and tingling of the fingers; hyperactive reflexes, muscle cramps, tetany, and convulsions; bone fractures; spasms of laryngeal muscles that can cause death by asphyxiation.	**Hypercalcemia** may result from hyperparathyroidism, some cancers, excessive intake of vitamin D, and Paget's disease of bone.	Lethargy, weakness, anorexia, nausea, vomiting, polyuria, itching, bone pain, depression, confusion, paresthesia, stupor, and coma.
Phosphate (HPO_4^{2-}) 1.7–2.6 mEq/liter	**Hypophosphatemia** (hī-pō-fos′-fa-TĒ-mē-a) may occur through increased urinary losses, decreased intestinal absorption, or increased utilization.	Confusion, seizures, coma, chest and muscle pain, numbness and tingling of the fingers, decreased coordination, memory loss, and lethargy.	**Hyperphosphatemia** occurs when the kidneys fail to excrete excess phosphate, as happens in renal failure; can also result from increased intake of phosphates or destruction of body cells, which releases phosphates into the blood.	Anorexia, nausea, vomiting, muscular weakness, hyperactive reflexes, tetany, and tachycardia.
Magnesium (Mg^{2+}) 1.3–2.1 mEq/liter	**Hypomagnesemia** (hī′-pō-mag′-ne-SĒ-mē-a) may be due to inadequate intake or excessive loss in urine or feces; also occurs in alcoholism, malnutrition, diabetes mellitus, and diuretic therapy.	Weakness, irritability, tetany, delirium, convulsions, confusion, anorexia, nausea, vomiting, paresthesia, and cardiac arrhythmias.	**Hypermagnesemia** occurs in renal failure or due to increased intake of Mg^{2+}, such as Mg^{2+}-containing antacids; also occurs in aldosterone deficiency and hypothyroidism.	Hypotension, muscular weakness or paralysis, nausea, vomiting, and altered mental functioning.

Electrolytes Imbalances

	Deficiency		Excess	
Electrolyte*	**Name and Causes**	**Signs and Symptoms**	**Name and Causes**	**Signs and Symptoms**
Sodium (Na^+) 136–148 mEq/liter	**Hyponatremia** (hī-pō-na-TRĒ-mē-a) may be due to decreased sodium intake; increased sodium loss through vomiting, diarrhea, aldosterone deficiency, or taking certain diuretics; and excessive water intake.	Muscular weakness; dizziness, headache, and hypotension; tachycardia and shock; mental confusion, stupor, and coma.	**Hypernatremia** may occur with dehydration, water deprivation, or excessive sodium in diet or intravenous fluids; causes hypertonicity of ECF, which pulls water out of body cells into ECF, causing cellular dehydration.	Intense thirst, hypertension, edema, agitation, and convulsions.
Chloride (Cl^-) 95–105 mEq/liter	**Hypochloremia** (hī-pō-klō-RĒ-mē-a) may be due to excessive vomiting, overhydration, aldosterone deficiency, congestive heart failure, and therapy with certain diuretics such as furosemide (Lasix®).	Muscle spasms, metabolic alkalosis, shallow respirations, hypotension, and tetany.	**Hyperchloremia** may result from dehydration due to water loss or water deprivation; excessive chloride intake; or severe renal failure, hyperaldosteronism, certain types of acidosis, and some drugs.	Lethargy, weakness, metabolic acidosis, and rapid, deep breathing.
Potassium (K^+) 3.5–5.0 mEq/liter	**Hypokalemia** (hī-pō-ka-LĒ-mē-a) may result from excessive loss due to vomiting or diarrhea, decreased potassium intake, hyperaldosteronism, kidney disease, and therapy with some diuretics.	Muscle fatigue, flaccid paralysis, mental confusion, increased urine output, shallow respirations, and changes in the electrocardiogram, including flattening of the T wave.	**Hyperkalemia** may be due to excessive intake, renal failure, aldosterone deficiency, crushing injuries to body tissues, or transfusion of hemolyzed blood.	Irritability, nausea, vomiting, diarrhea, muscular weakness; can cause death by inducing ventricular fibrillation.

Acid-Base Balance

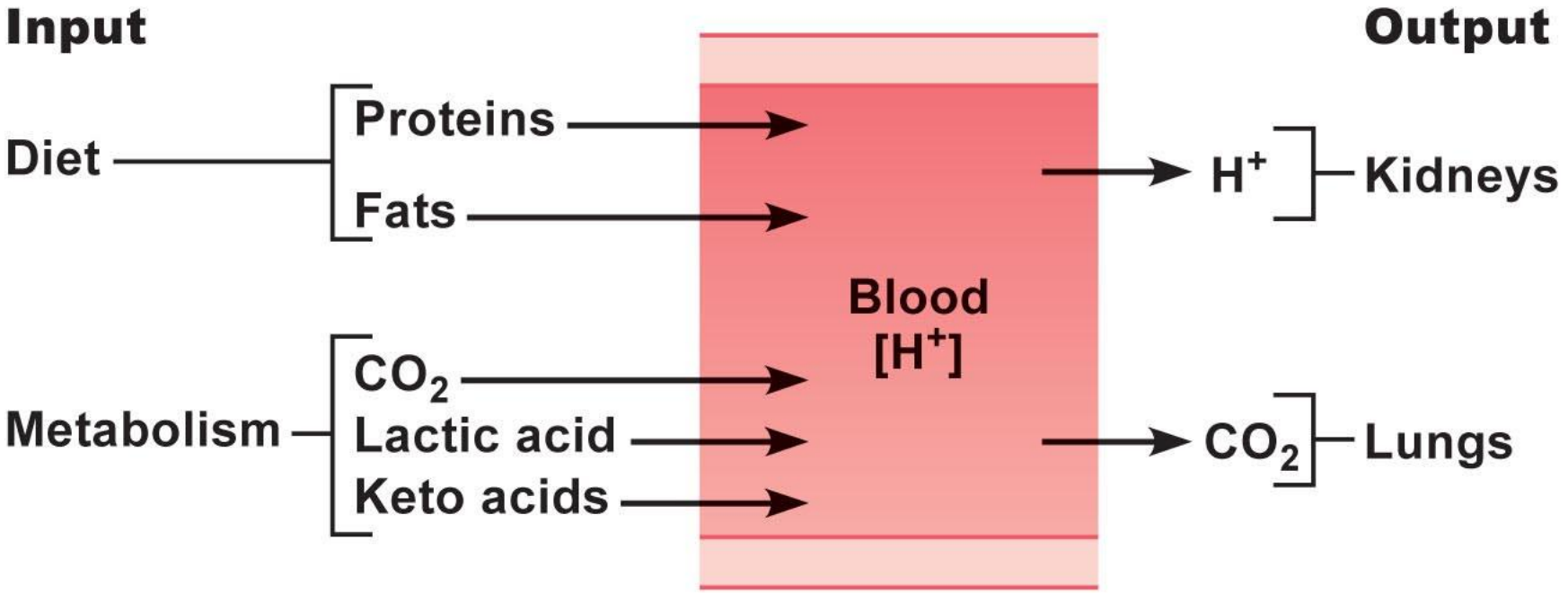
- Normal pH of arterial blood = **7.35–7.45**
- Regulated by the combined actions of the ***lungs and kidneys***
  - --pH < 7.35 = ***acidosis***
  - --pH > 7.45 = ***alkalosis***
- **Complications** with acid-base disturbance
  - --Conformation change in ***protein structure***
  - --Changes in ***excitability of neurons***
  - --Changes in ***potassium balance***
    (acidosis→hyperkalemia; alkalosis →hypokalemia)
  - --***Cardiac arrhythmias (acidosis)***
  - --***Vasodilation (acidosis)***

Acid-Base Balance

- The overall acid-base balance of the body is maintained by controlling the **H^+ concentration (pH)** of body fluids, especially **extracellular fluid**
- Homeostasis of H+ concentration ***is vital***
  - --***Proteins 3-D structure*** sensitive to pH changes
  - --Normal plasma pH ***must be maintained*** (7.35-7.45)
  - --Diet ***high in proteins*** tends to ***acidify*** the blood
- **3 major mechanisms** to regulate pH
  - --***Buffer system***
  - --***Exhalation of CO_2 (respiratory system)***
  - --***Kidney excretion of H+ (urinary system)***

Source of Acid-Base Disturbances

Input of acids > Output of acids = Acidosis
Input of acids < Output of acids = Alkalosis



Respiratory Disturbances

Carbon dioxide is a source of acid

Carbonic anhydrase (CA)

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow HCO_3^- + H^+$$

--Normal P_{CO_2} arterial blood = **40 mm Hg**

--Sources of CO_2: **metabolism**

--Output of CO_2: through **respiratory system**

--Increases in plasma [CO_2] → ***Respiratory acidosis***

--Decreases in plasma [CO_2] → ***Respiratory alkalosis***

Metabolic Acidosis

- **Decrease pH** through something other than carbon dioxide

1. ***High-protein diet***
2. ***High-fat diet***
3. ***Heavy exercise***
4. ***Severe diarrhea***

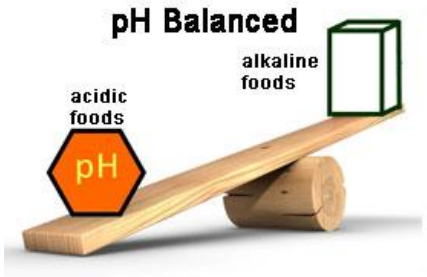
   (loss of bicarbonate)
5. ***Renal dysfunction***

Metabolic Alkalosis

- **Increase pH** through something other than carbon dioxide

1. ***Excessive vomiting***

   (loss of hydrogen ions)
2. ***Consumption of alkaline products (baking soda)***
3. ***Renal dysfunction***



Categories of Acid-Base Disturbances

	Bicarbonate (mEq/L)*		
P_{CO_2} (mmHg)	*Less than 21*	*21–26*	*More than 26*
More than 45	Combined metabolic and respiratory acidosis	Respiratory acidosis	Metabolic alkalosis and respiratory acidosis
35–45	Metabolic acidosis	Normal	Metabolic alkalosis
Less than 35	Metabolic acidosis and respiratory alkalosis	Respiratory alkalosis	Combined metabolic and respiratory alkalosis

*mEq/L = milliequivalents per liter. This is the millimolar concentration of HCO_3^- multiplied by its valence (× 1).

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow HCO_3^- + H^+$$

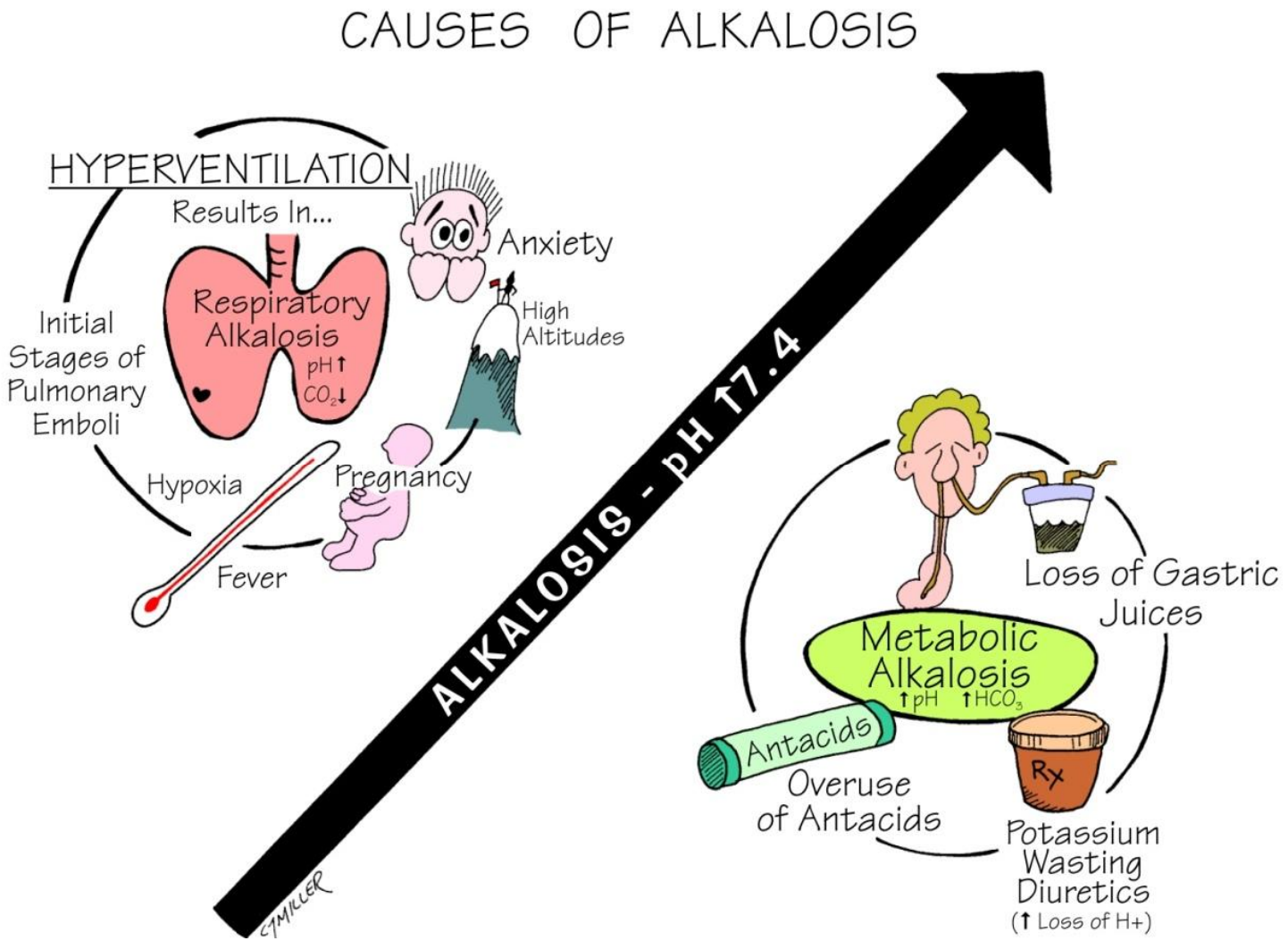
--Increases in plasma [CO_2] → ***Respiratory acidosis***

--Decreases in plasma [CO_2] → ***Respiratory alkalosis***

--Increases in plasma [HCO_3^-] → ***Metabolic alkalosis***

--Decreases in plasma [HCO_3^-] → ***Metabolic acidosis***

Causes of Alkalosis



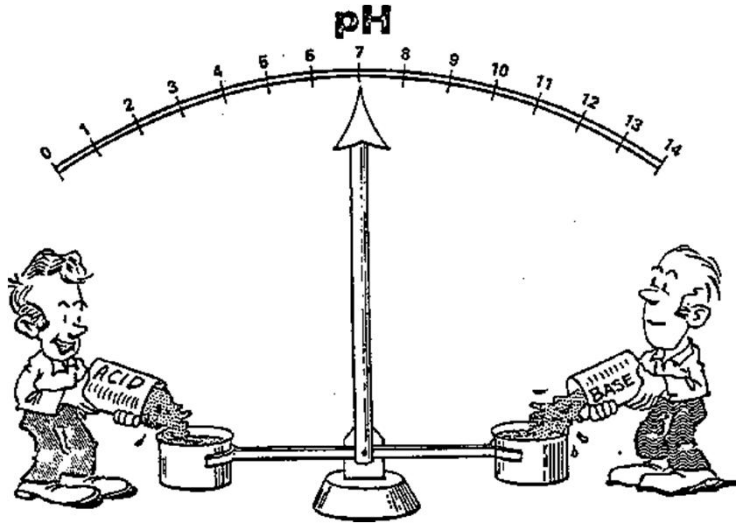
Causes of pH Imbalance

Acidosis (pH <7.2)	Alkalosis (pH >7.6)
Carbon dioxide gain Respiratory failure Obstructive airways disease Respiratory depression (inc. drugs)	**Carbon dioxide loss** Hyperventilation (panic attacks)
Bicarbonate loss Diarrhoea Carbonic anhydrase inhibitors Renal tubular acidosis Aldosterone deficiency Hyperkalaemia Hyperchloraemia	**Bicarbonate gain** Antacid overuse (Sodium bicarbonate) 'Milk alkali syndrome' Potassium citrate mixture Aldosteronism Hypokalaemia Hypochloraemia Diuretics
Acid gain Renal failure Ketoacidosis • starvation • diabetes mellitus Lactic acidosis • exercise • shock • hypoxia • biguanides • fructose/sorbitol IV Salicylate poisoning Reye's syndrome Ammonium chloride overuse	**Acid loss** Vomiting, pyloric stenosis Aldosteronism Hypokalaemia

Defense Mechanisms Against Acid-Base Disturbances

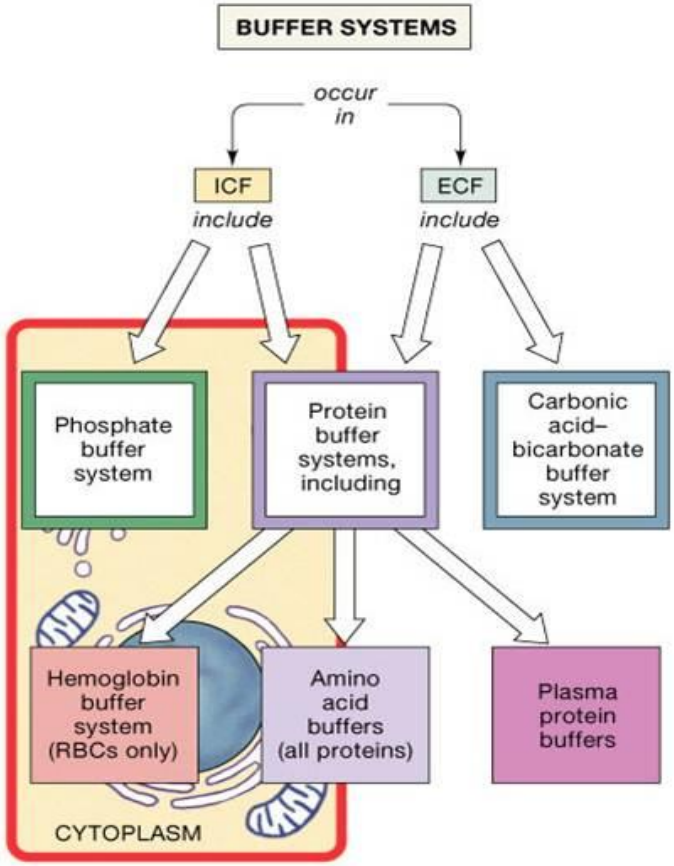
- **Three major mechanisms of defense**

  1. ***Buffer system (Buffering of hydrogen ions)***
  2. ***Respiratory compensation (Exhalation of CO_2)***
  3. ***Renal compensation (H^+ excretion of Kidney)***



1. Buffer Systems

- **Quickest** defense against changes in pH (act to quickly temporarily ***bind H^+***)
- **3 principal buffer systems**
  - --***Bicarbonate buffer system***
  - --***Protein buffer system***
  - --***Phosphate buffer system***
- Most important ***ECF buffer = bicarbonate***
  - --$HCO_3^- + H^+ \leftrightarrow H_2CO_3$
- **ICF buffers**
  - --**Proteins**: $Protein^- + H^+ \leftrightarrow H{\bullet}Protein$
  - --**Phosphates**: $HPO_4^{2-} + H^+ \leftrightarrow H_2PO_4^-$
- Raise pH but **do not remove H^+**
- Most consist of weak acid and salt of that acid functioning as weak base



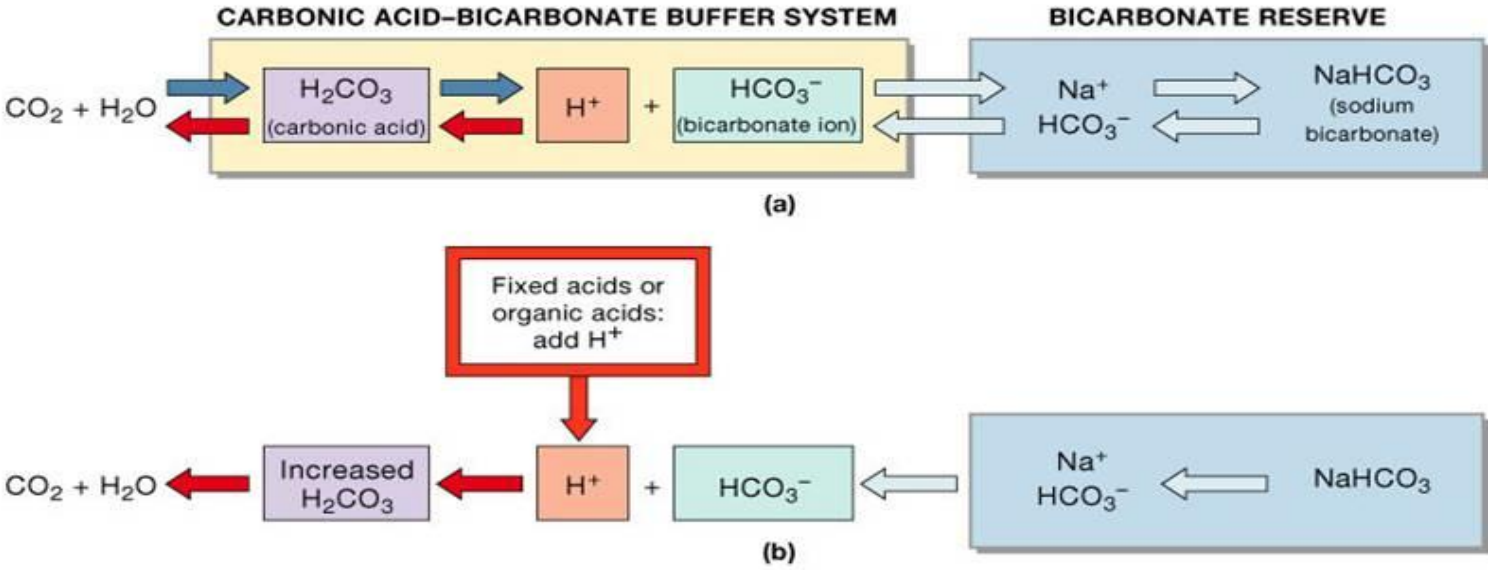
1. Buffer Systems

- **Carbonic acid- bicarbonate buffer system**

--Based on **bicarbonate ion (HCO_3^-)** acting as ***weak base (holds excess H^+)*** and carbonic acid (H_2CO_3) acting as ***weak acid (dissociates into H^+ ions)***

--At a pH of 7.4, bicarbonate ion concentration is **about 20 times** that of carbonic acid

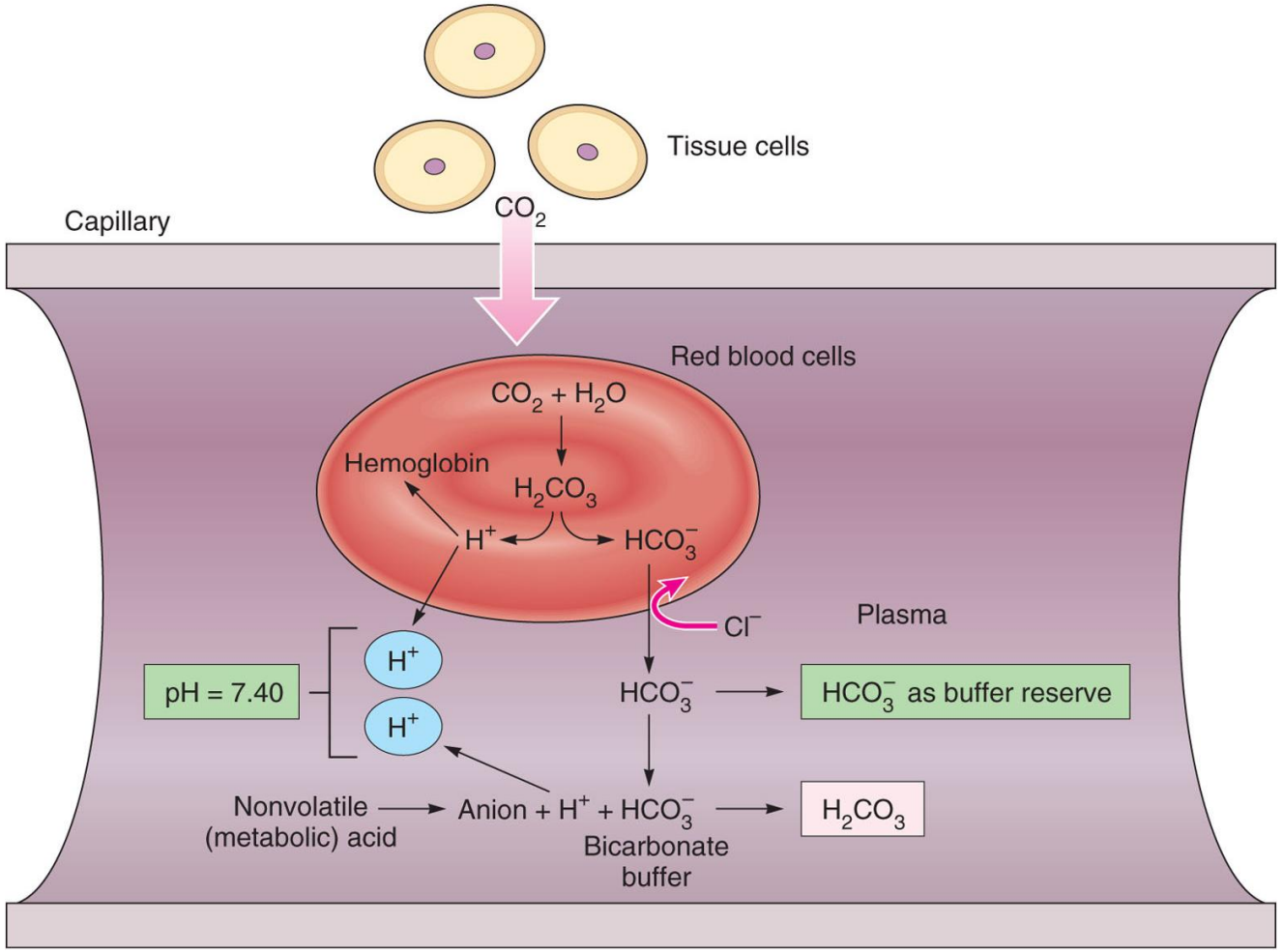
--Cannot protect against pH changes due to ***respiratory problems*** in which there is an excess or shortage of CO_2



1. Buffer Systems

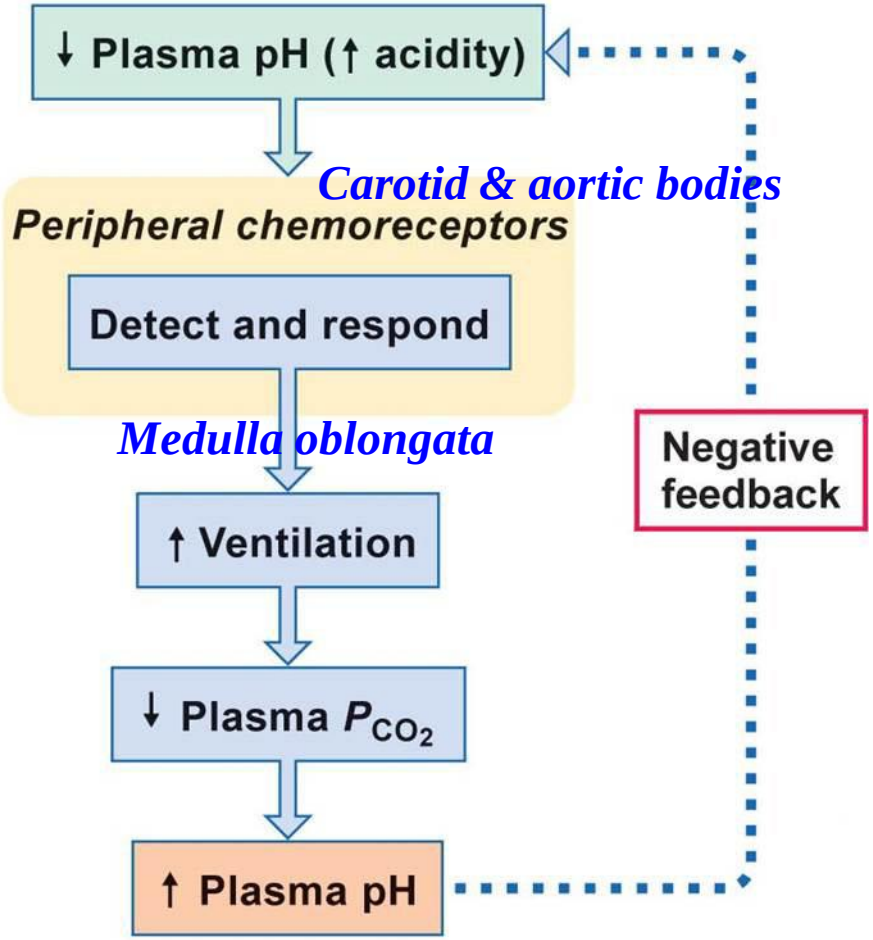
- **Protein buffer system**
  - --Most abundant buffer in **ICF and blood plasma**
  - --**Hemoglobin** very good at buffering H^+ in RBCs
  - --**Albumin** is main plasma protein buffer
  - --**Free carboxyl group** acts like an acid by ***releasing H^+***
  - --**Free amino group** acts as a base to ***combine with H^+***
  - --**Side chain groups** on ***7 of 20 amino acids*** also can buffer H^+
- **Phosphate buffer system**
  - --Dihydrogen phosphate **($H_2PO_4^-$), a weak acid** and monohydrogen phosphate **(HPO_4^{2-}), a weak base**
  - --**Phosphates** are major anions in **ICF** and minor ones in ECF
  - --Important regulator of pH in **cytosol**

Buffer System:
Hemoglobin (HCO_3^-)



2. Respiratory Compensation (Exhalation of CO_2)

- **Second line of defense**
  - --Takes ***minutes*** (1-3 min) to have effect
- **Regulates pH by varying ventilation**
  - --***Increase ventilation → decreases CO_2***
  - --***Decrease ventilation → increases CO_2***



2. Respiratory Compensation (Exhalation of CO_2)

Effect of Lung function on Blood Acid-Base Balance

Condition	pH	P_{CO_2}	Ventilation	Cause or Compensation
Normal	7.35–7.45	39–41 mmHg	Normal	Not applicable
Respiratory acidosis	Low	High	Hypoventilation	Cause of the acidosis
Respiratory alkalosis	High	Low	Hyperventilation	Cause of the alkalosis
Metabolic acidosis	Low	Low	Hyperventilation	Compensation for acidosis
Metabolic alkalosis	High	High	Hypoventilation	Compensation for alkalosis

呼吸暫停 (apnea)	呼吸中止
呼吸困難 (dyspnea)	不適的、主觀上覺得困難或費力的呼吸
呼吸正常 (eupnea)	在休息時正常、舒服的呼吸
換氣過度 (hyperventilation)	肺泡的換氣超過代謝率；造成肺泡 CO_2 不正常偏低
換氣不足 (hypoventilation)	肺泡的換氣低於代謝率；造成 CO_2 不正常偏高

3. Renal Compensation

- **Third line** of defense (Takes ***hours to days***), maintain blood pH by ***reabsorbing bicarbonate and secreting H^+*** in urine (urine is thus **acidic pH 4.5**)
- ***Losing a bicarbonate ion*** is the same as ***gaining a hydrogen ion***; ***reabsorbing a bicarbonate ion*** is the same as ***losing a hydrogen ion***
- Metabolic reactions produce nonvolatile acid (phosphoric, uric, and lactic acids and ketones) = ***Metabolic acidosis***
- **Excretion of H^+ in the urine** is only way to eliminate huge excess
- **Renal failure** can cause **death rapidly** due to its role in pH balance

3. Renal Compensation

- **Increase in acidity causes**

  --Increased secretion of hydrogen ions

  - In the **proximal convoluted tubule**, ***Na^+ /H^+ antiporters*** secrete H^+ as they reabsorb Na^+
  - **Intercalated cells of collecting duct** include ***proton pumps*** that secrete H^+ into tubule fluid
  - Urine can be up to **1000 times more acidic** than blood

  --Increased reabsorption of bicarbonate

  - Bicarbonate reabsorption coupled to hydrogen ion secretion in **proximal convoluted tubule**

  --Increased synthesis of new bicarbonate

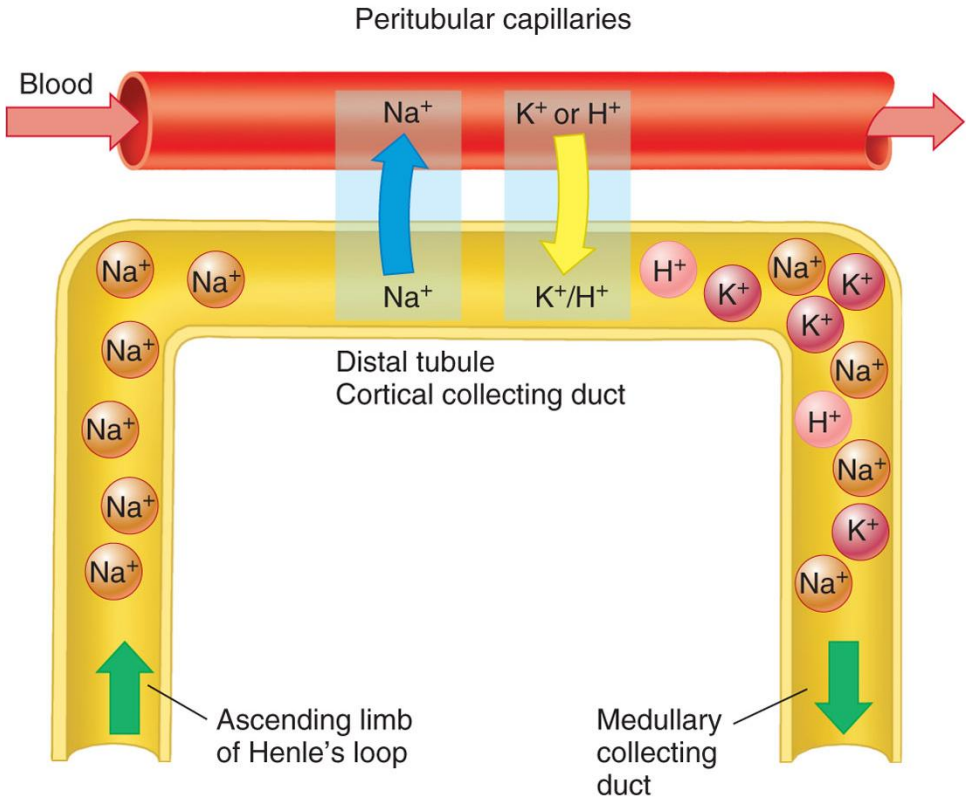
  - Secretion of hydrogen ions coupled to synthesis of new bicarbonate ions in the **intercalated cells of late distal tubule and collecting duct**

3. Renal Compensation

- **Reabsorption of Na^+** stimulates the secretion of other positive ions

  --**K^+ and H^+** compete

- **Acidosis** stimulates the secretion of H^+ and inhibits the secretion of K^+ (***hyperkalemia***)
- **Alkalosis** stimulates the secretion and excretion of more K^+(***hypokalemia***)



➢ ***Primary aldosteronism (Conn's syndrome)*** → ***hypokalemia & metabolic alkalosis***

➢ ***Addison's disease*** → ***hyperkalemia & metabolic acidosis***

3. Renal Compensation

- **Proximal tubule uses *Na^+/H^+ pumps* to exchange Na^+ out and H^+ in**

  --Some of the H^+ brought in is used for the reabsorption of bicarbonate (***bicarbonate reabsorption coupled to hydrogen ion secretion***)

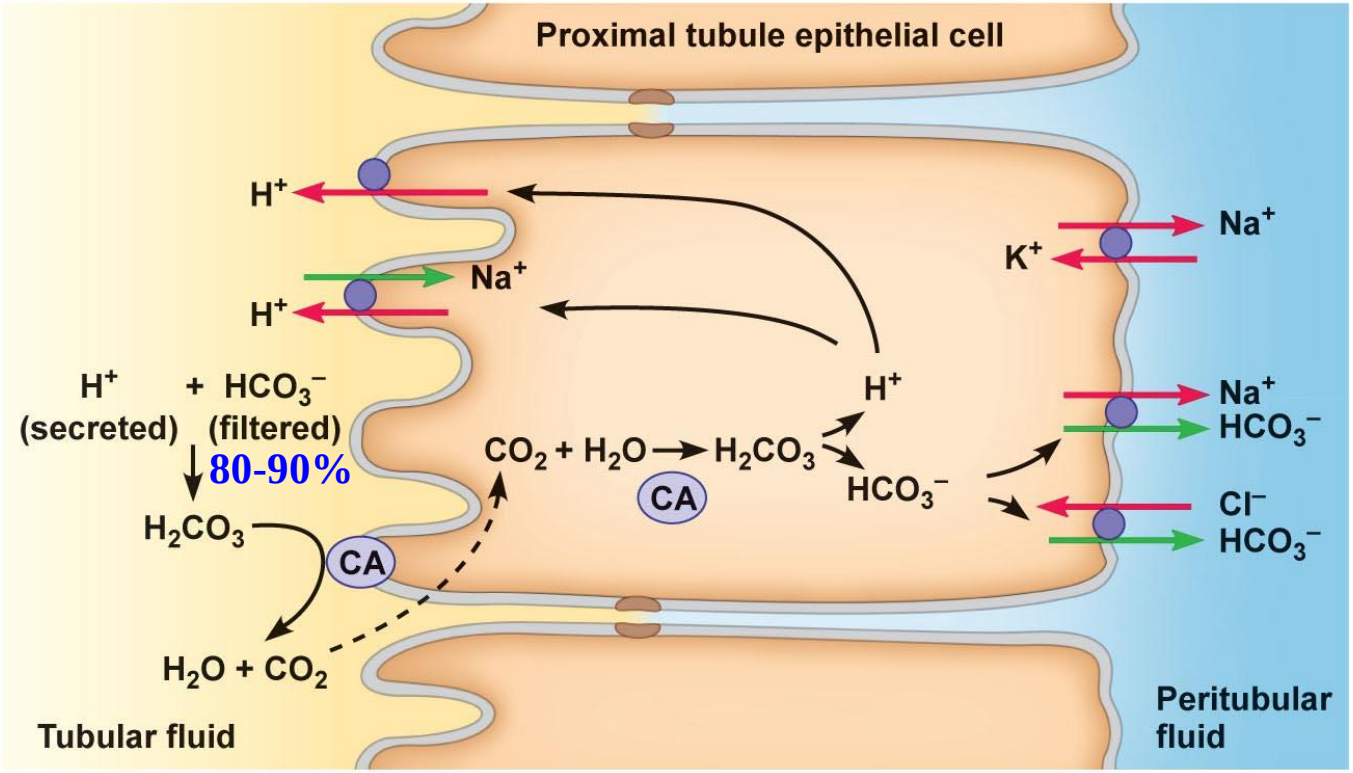
  --**Bicarbonate cannot** cross the inner tubule membrane so must be converted to CO_2 and H_2O using ***carbonic anhydrase (CA)***

  $$HCO_3^- + H^+ \xleftarrow{CA} H_2CO_3 \leftrightarrow H_2O + CO_2$$

  --CO_2 can cross into tubule cells, where the reaction reverses and bicarbonate is made again

  --This diffuses into the interstitial space (***bicarbonate reabsorption***)

Renal Handling of H^+ and HCO_3^- in the Proximal Tubule

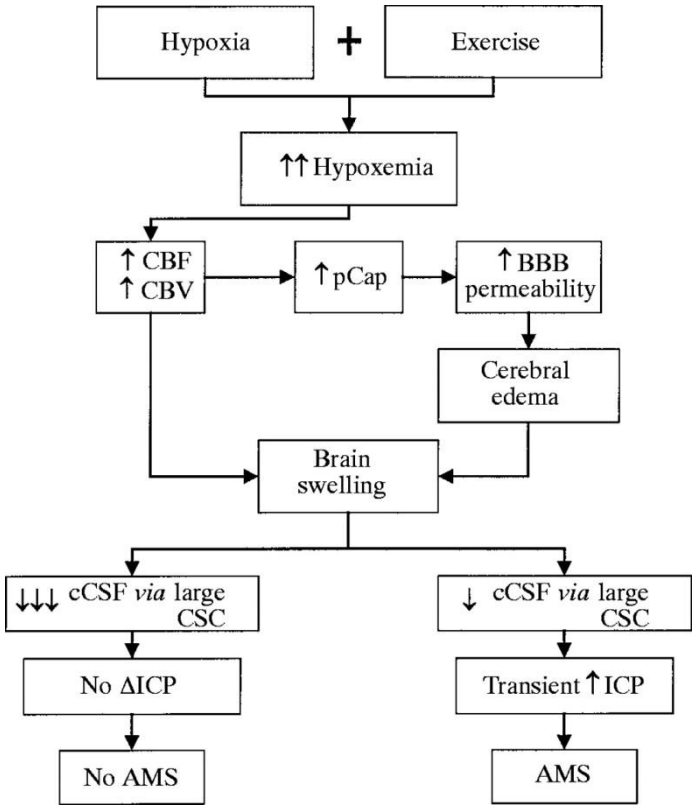


- ***Increased secretion of hydrogen ions***
  1. ***Na^+/H^+ antiporter (reabsorb Na^+)***
  2. ***Proton pumps***
- ***Increased reabsorption of bicarbonate***
  1. ***Na^+/K^+ pumps (reabsorb Na^+)***
  2. ***Na^+/HCO_3^- symporter***
  3. ***HCO_3^-/Cl^- antiporter***

- ***CA inhibitor:*** **acetazolamide (treatment of acute mountain sickness)**

Clinical Application: Acute Mountain Sickness (AMS)

High-altitude→Hyperventilation→Pco_2↓→Respiratory alkalosis →Renal bicarbonate diuresis



➢ ***CSC, cerebrospinal compliance; pCap, cerebral capillary perfusion pressure; CBV, cerebral blood volume; CBF, cerebral blood flow***

Mild AMS[2-4]

Definition: Mild headache, nausea, decreased appetite, fatigue, poor sleep

- Oxygen 1 to 2 L / minute for 12 to 24 hour
- Descent is not required but the individual should hold further ascent for one to two
- Symptomatic therapy as needed
- Consider
  - Acetazolamide to speed acclimatization (250 to 500 mg PO bid)
  - Descend 500 m

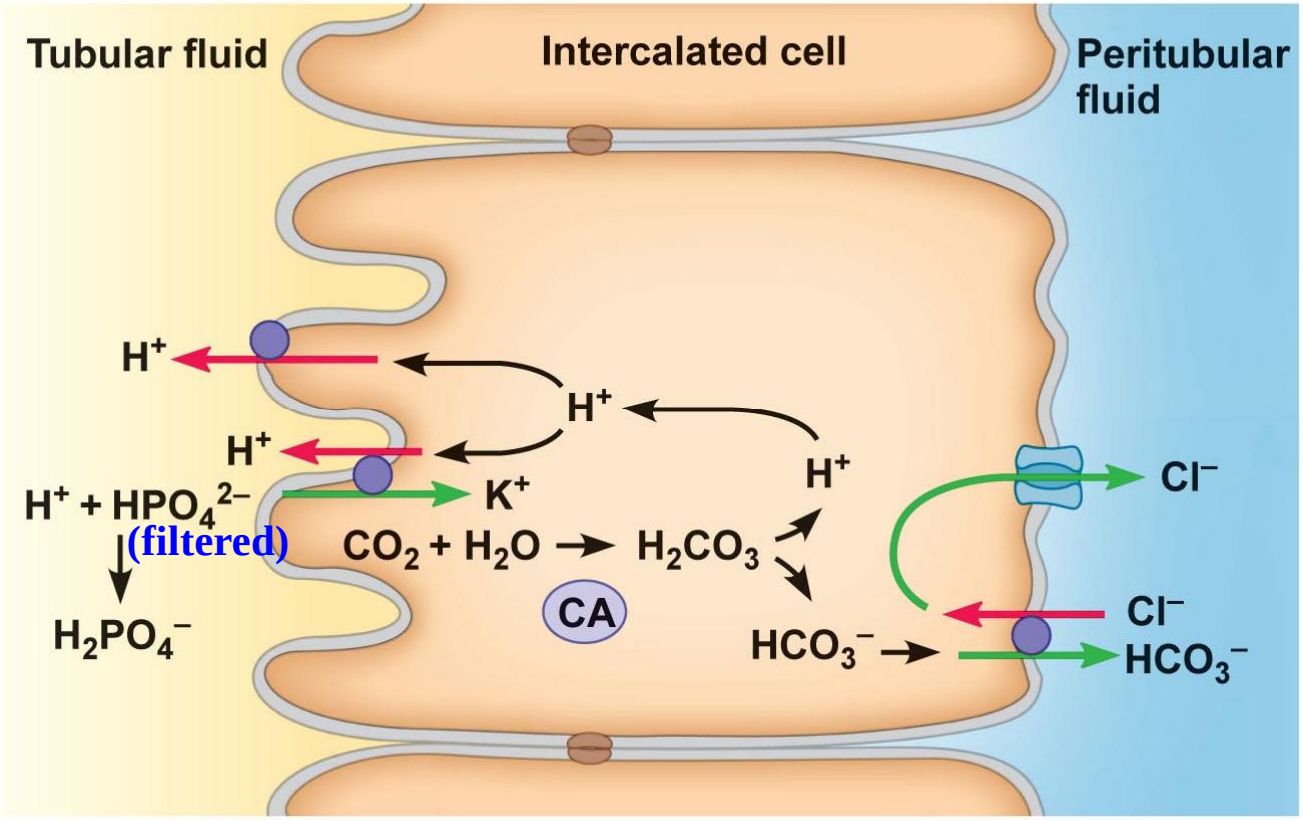
Moderate AMS[2-4]

Definition: Protracted or worsening headache, nausea, vomiting, dizziness, fatigue

- Oxygen 1 to 2 L / minute continuously until symptoms resolve
- Descend 500 m or provide acetazolamide 250 mg
- Consider dexamethasone 4 mg PO every six hours

- **CA inhibitor acetazolamide: prevention and treatment of AMS**
- Causes a ***metabolic acidosis*** **(decreased secretion of hydrogen ions)** through ***renal bicarbonate diuresis*** **(decreased reabsorption of bicarbonate)**
- **Decrease in CSF volume and pressure**

Renal Handling of H^+ and HCO_3^- in the Late Distal Tubule and Collecting Duct

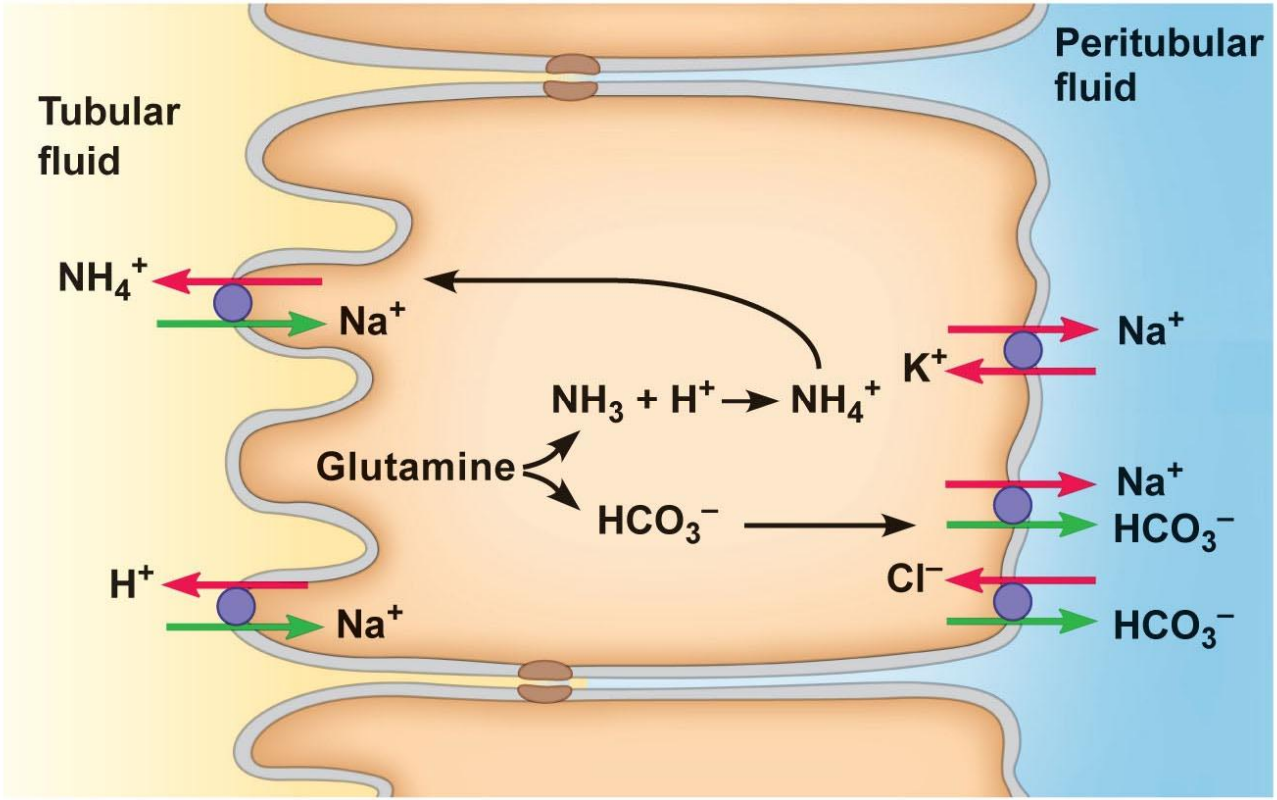


- ***Increased secretion of hydrogen ions***
  1. ***K^+/H^+ antiporter***
  2. ***Proton pumps***
  3. ***Form of $H_2PO_4^-$ (buffer H^+)***

- ***Increased synthesis of new bicarbonate***
  1. ***HCO_3^-/Cl^- antiporter***
  2. ***Cl^- channels***

Renal Handling of H^+ and HCO_3^- by Glutamine Metabolism in the Proximal Tubule

➢ ***Severe acidosis:*** Glutamine metabolism to produce **new bicarbonate** and **ammonia**



➢ ***Increased secretion of hydrogen ions***

1. ***Na^+/NH_4^+ antiporter (form of ammonium)***
2. ***Na^+/H^+ antiporter***

➢ ***Increased synthesis of new bicarbonate***

1. ***HCO_3^-/Cl^- antiporter***
2. ***Na^+/HCO_3^- symporter***

Defense Mechanisms Against Acid-Base Disturbances

MECHANISM	COMMENTS
Buffer systems	Most consist of a weak acid and the salt of that acid, which functions as a weak base. They prevent drastic changes in body fluid pH.
Proteins	The most abundant buffers in body cells and blood. Hemoglobin inside red blood cells is a good buffer.
Carbonic acid–bicarbonate	Important regulator of blood pH. The most abundant buffers in extracellular fluid (ECF).
Phosphates	Important buffers in intracellular fluid and in urine.
Exhalation of CO_2	With increased exhalation of CO_2, pH rises (fewer H^+). With decreased exhalation of CO_2, pH falls (more H^+).
Kidneys	Renal tubules secrete H^+ into the urine and reabsorb HCO_3^- so it is not lost in the urine.

Acid-Base Disturbances

Terms Used of Acid-Base Disturbances

Term	Definition
Acidosis, respiratory	Increased CO_2 retention (due to hypoventilation), which can result in the accumulation of carbonic acid and thus a fall in blood pH to below normal
Acidosis, metabolic	Increased production of "nonvolatile" acids, such as lactic acid, fatty acids, and ketone bodies, or loss of blood bicarbonate (such as by diarrhea), resulting in a fall in blood pH to below normal
Alkalosis, respiratory	A rise in blood pH due to loss of CO_2 and carbonic acid (through hyperventilation)
Alkalosis, metabolic	A rise in blood pH produced by loss of nonvolatile acids (such as excessive vomiting) or by excessive accumulation of bicarbonate base
Compensated acidosis or alkalosis	Metabolic acidosis or alkalosis are partially compensated for by opposite changes in blood carbonic acid levels (through changes in ventilation) Respiratory acidosis or alkalosis are partially compensated for by increased retention or excretion of bicarbonate in the urine.

Classification of Metabolic and Respiratory Components of Acid-Base Disturbances

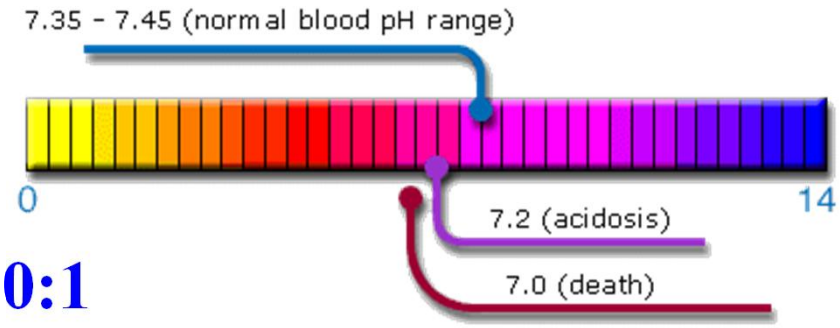
Plasma CO_2	Plasma HCO_3^-	Condition	Causes
Normal	Low	Metabolic acidosis	Increased production of "nonvolatile" acids (lactic acids, ketone bodies, and others), or loss of HCO_3^- in diarrhea
Normal	High	Metabolic alkalosis	Vomiting of gastric acid; hypokalemia; excessive steroid administration
Low	Low	Respiratory alkalosis	Hyperventilation
High	High	Respiratory acidosis	Hypoventilation

Compensation for Acid-Base Disturbances

Henderson-Hasselbalch equation

$$pH = 6.1 + \log[HCO_3^-]/[CO_2]$$

- **For pH = 7.4, $[HCO_3^-]/[CO_2]$ = 20:1**
- **Respiratory and renal systems work together to control this ratio**
  - ***--Kidneys regulate $[HCO_3^-]$***
  - ***--Lungs regulate $[CO_2]$***
- **Acidosis:** $[HCO_3^-]/[CO_2]$ **< 20:1**
- **Alkalosis:** $[HCO_3^-]/[CO_2]$ **> 20:1**



Compensation for Acid-Base Disturbances

Respiratory Acidosis

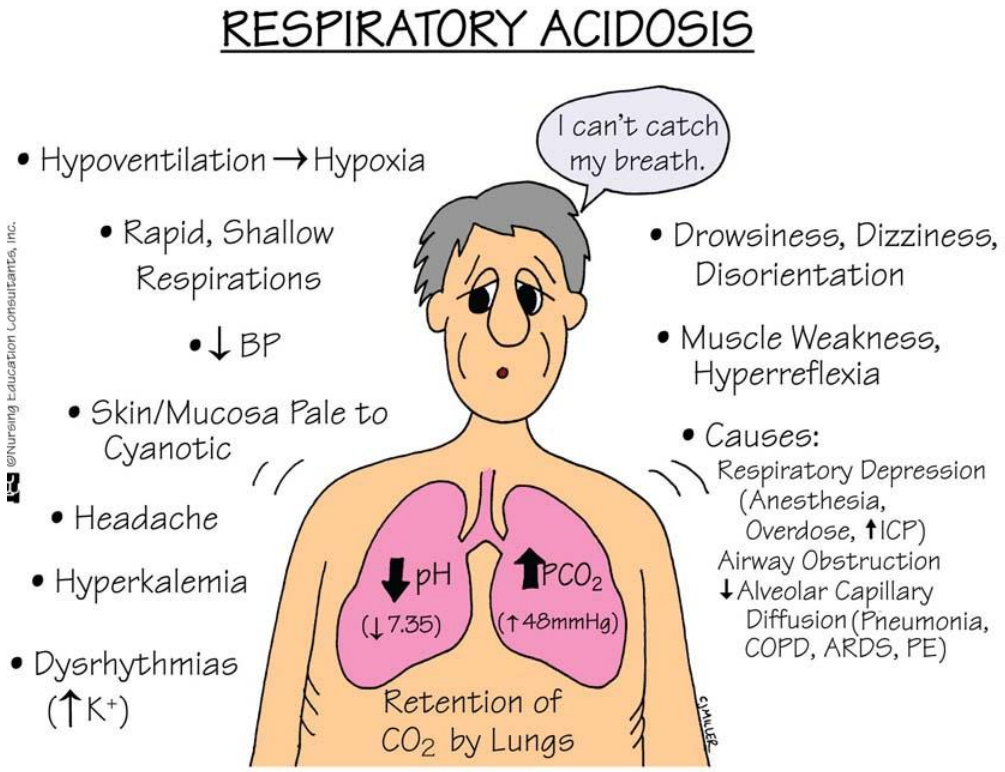
--Cause: ***hypoventilation***

--Increased CO_2 →

increased H^+

--Compensation: ***renal***

- ✓***Increase H^+ secretion***
- ✓***Increase HCO_3^- reabsorption***



Compensation for Acid-Base Disturbances

Respiratory Alkalosis

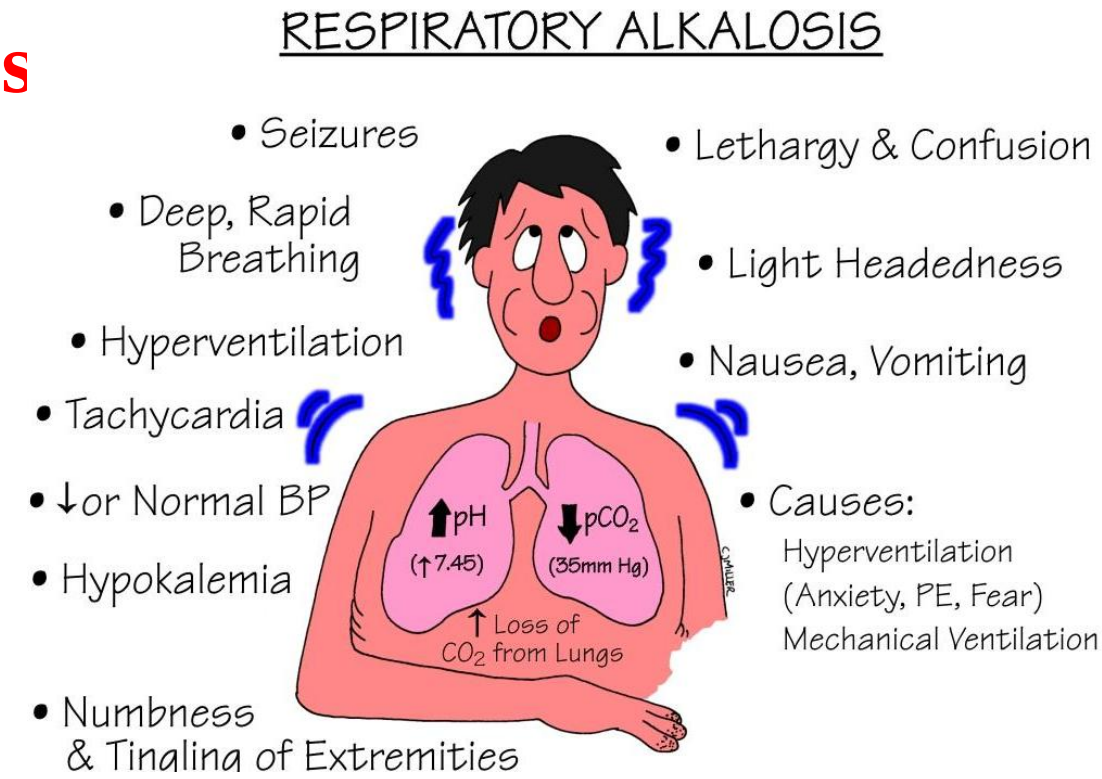
--Cause: ***hyperventilation***

--Decreased CO_2 →

decreased H^+

--Compensation: ***renal***

- ✓***Decrease H^+ secretion***
- ✓***Decrease HCO_3^- reabsorption***



Compensation for Acid-Base Disturbances

Metabolic Acidosis

--Cause: **increased** H^+ ***independent of CO_2 (diarrhea, DM, strenuous exercise etc.)***

--Compensation: ***respiratory and renal*** (unless renal problem)

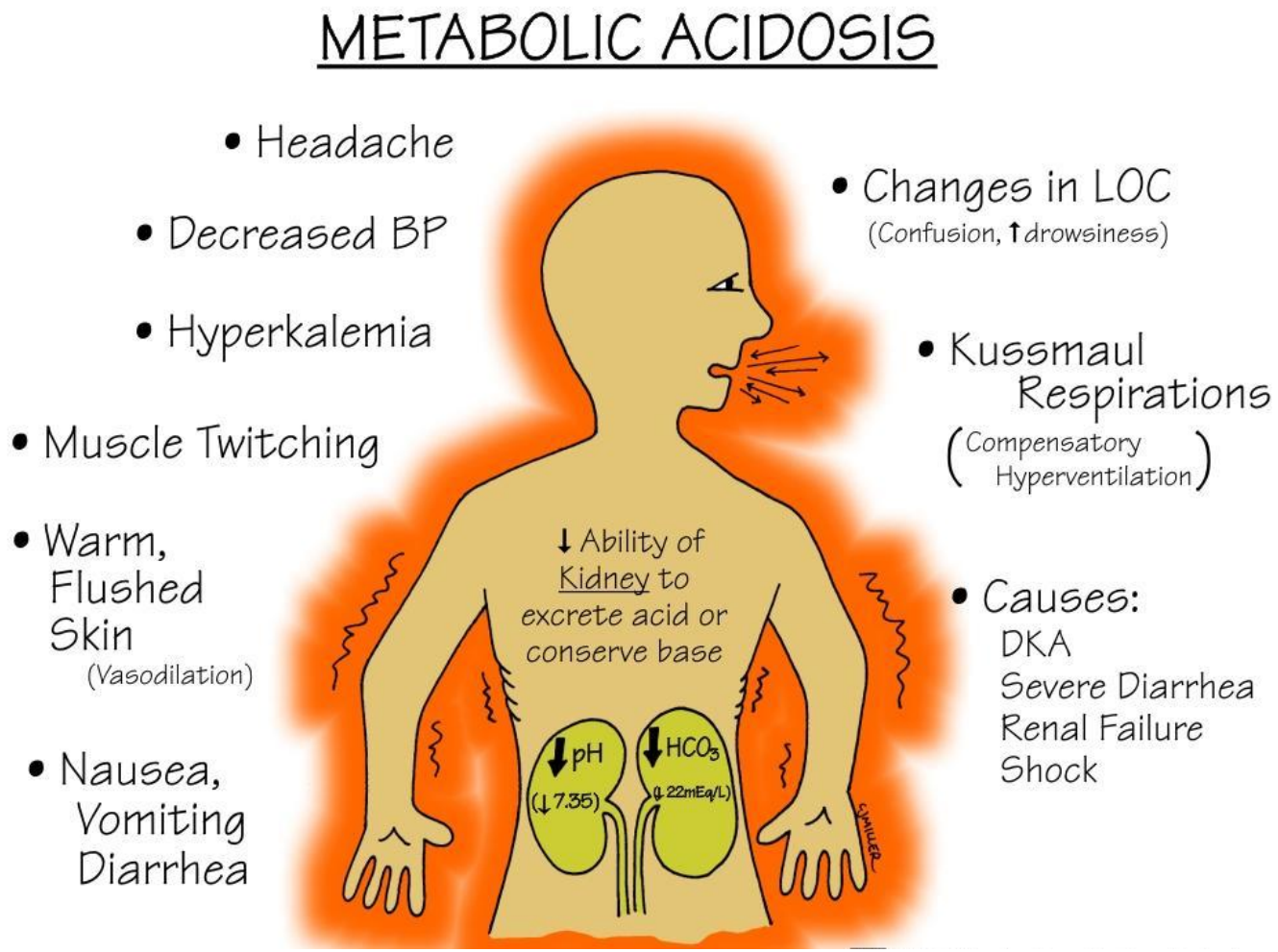
--Respiratory compensation

- ✓***Increase ventilation → decrease CO_2***

--Renal compensation

- ✓***Increase H^+ secretion***
- ✓***Increase HCO_3^- reabsorption***
- ✓***Increase synthesis of new bicarbonate***

Metabolic Acidosis



Compensation for Acid-Base Disturbances

Metabolic Alkalosis

--Cause: **decreased** H^+ ***independent of CO_2 (Vomiting, alkaline drugs, antacids etc.)***

--Compensation: ***respiratory and renal*** (unless renal problem)

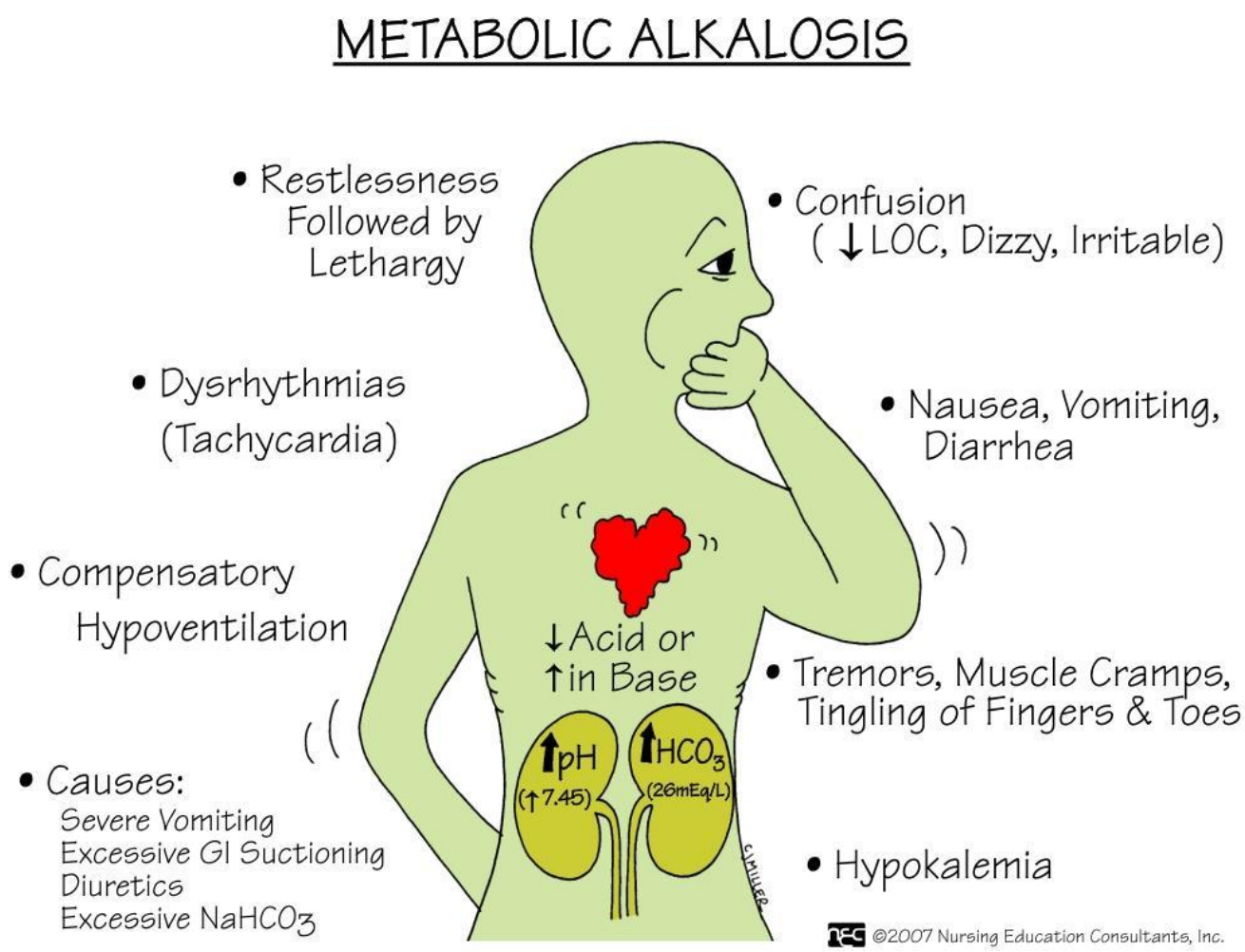
--Respiratory compensation

- ✓***Decrease ventilation → increase CO_2***

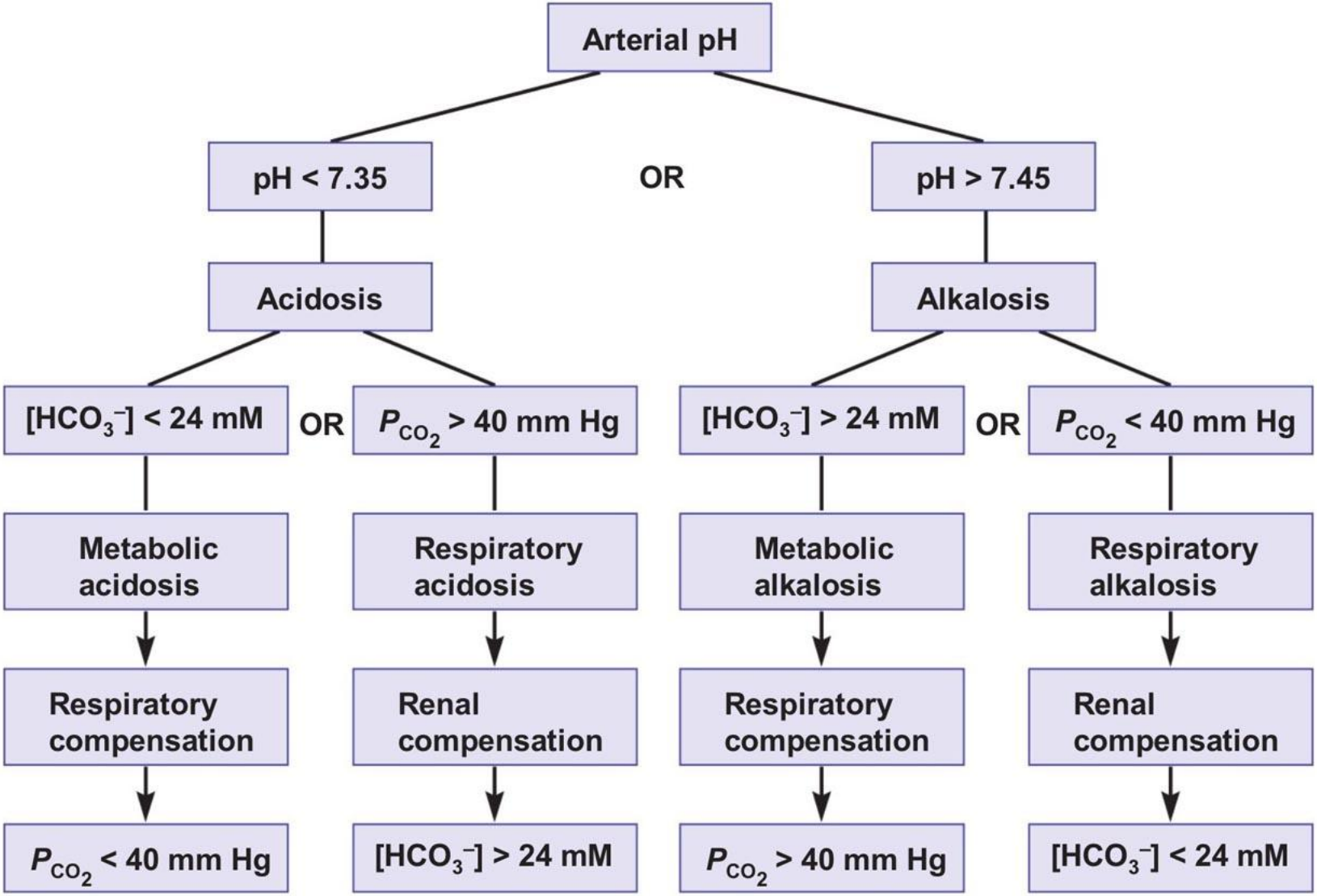
--Renal compensation

- ✓***Decrease H^+ secretion***
- ✓***Decrease HCO_3^- reabsorption***
- ✓***Decrease synthesis of new bicarbonate***

Metabolic Alkalosis



Compensation for Acid-Base Disturbances



Compensation for Acid-Base Disturbances

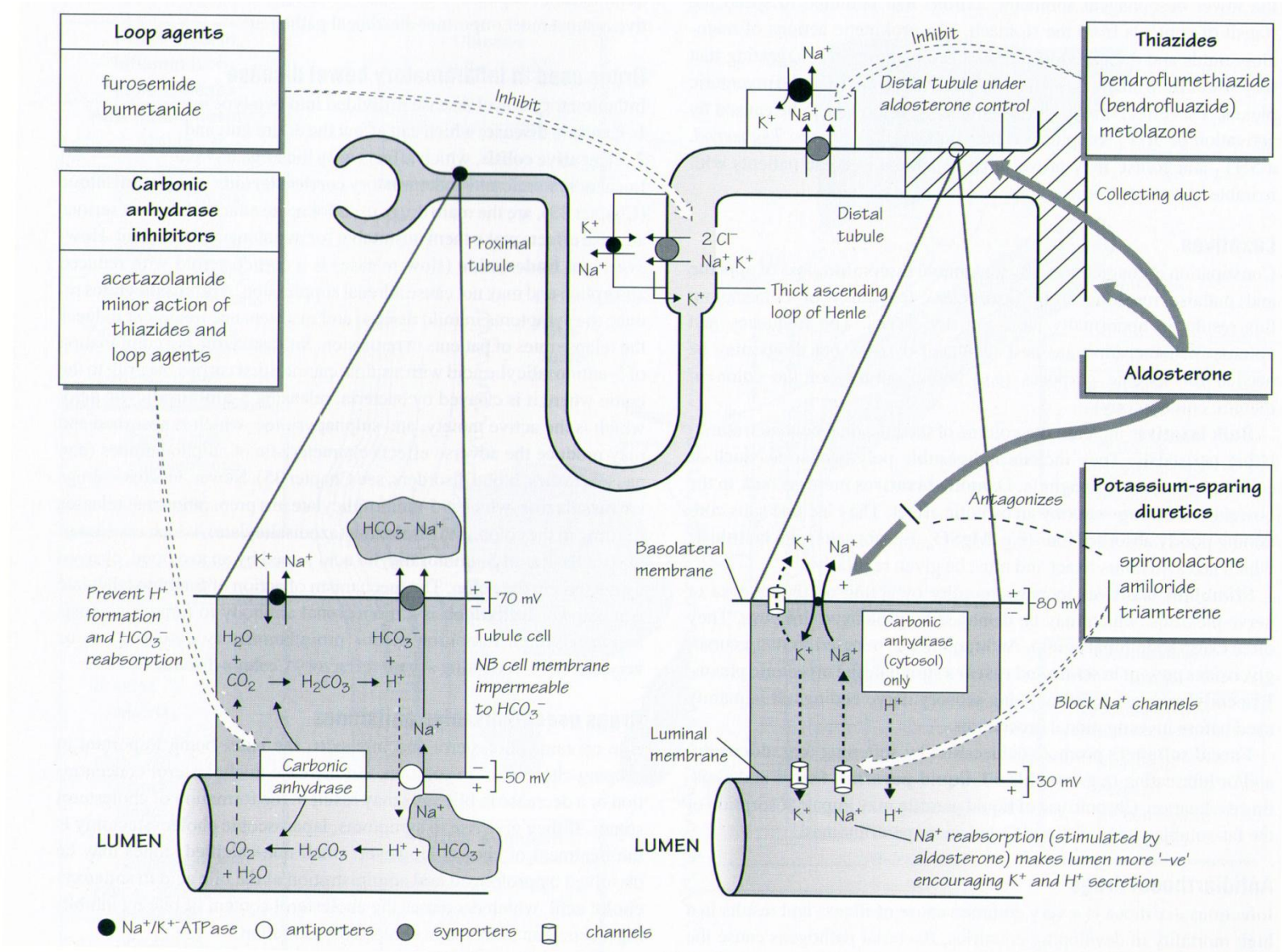
CONDITION	DEFINITION	COMMON CAUSES	COMPENSATORY MECHANISM
Respiratory acidosis	Increased P_{CO_2} (above 45 mmHg) and decreased pH (below 7.35) if there is no compensation.	Hypoventilation due to emphysema, pulmonary edema, trauma to respiratory center, airway obstructions, or dysfunction of muscles of respiration.	Renal: increased excretion of H^+; increased reabsorption of HCO_3^-. If compensation is complete, pH will be within the normal range but P_{CO_2} will be high.
Respiratory alkalosis	Decreased P_{CO_2} (below 35 mmHg) and increased pH (above 7.45) if there is no compensation.	Hyperventilation due to oxygen deficiency, pulmonary disease, cerebrovascular accident (CVA), or severe anxiety.	Renal: decreased excretion of H^+; decreased reabsorption of HCO_3^-. If compensation is complete, pH will be within the normal range but P_{CO_2} will be low.
Metabolic acidosis	Decreased HCO_3^- (below 22 mEq/liter) and decreased pH (below 7.35) if there is no compensation.	Loss of bicarbonate ions due to diarrhea, accumulation of acid (ketosis), renal dysfunction.	Respiratory: hyperventilation, which increases loss of CO_2. If compensation is complete, pH will be within the normal range but HCO_3^- will be low.
Metabolic alkalosis	Increased HCO_3^- (above 26 mEq/liter) and increased pH (above 7.45) if there is no compensation.	Loss of acid due to vomiting, gastric suctioning, or use of certain diuretics; excessive intake of alkaline drugs.	Respiratory: hypoventilation, which slows loss of CO_2. If compensation is complete, pH will be within the normal range but HCO_3^- will be high.

Clinical Applications: Diuretics

利尿劑 (diuretics) 是一類直接作用於腎臟，抑制腎小管的再吸收功能，增加電解質（特別是 Na^+）和水的排出，使尿液量增加的藥物。在臨床上，利尿劑主要用於以下幾個方面：(1) 各種原因所致的水腫；(2) 作為基礎降壓藥用於各型高血壓；(3) 藥物中毒時，強迫利尿，加速毒物的排泄；(4) 預防急性腎功能衰竭和治療急性腎功能衰竭初期的少尿。

- ***Caffeine* which inhibits Na^+ reabsorption**
- ***Alcohol* which inhibits secretion of ADH**

Major Actions of Diuretics



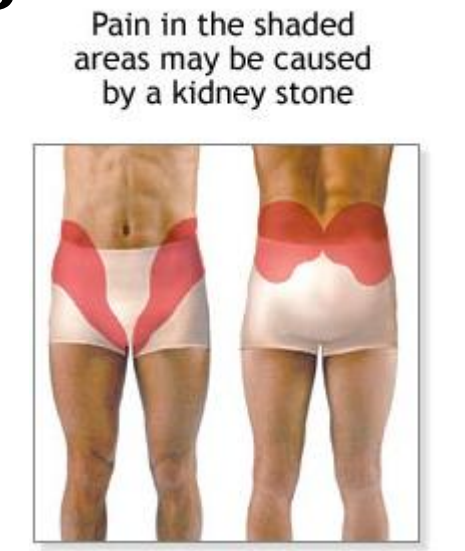
Major Actions of Diuretics

Category of Diuretic	Example	Mechanism of Action	Major Site of Action
Loop diuretics	Furosemide	Inhibits sodium transport	Thick segments of ascending limbs
Thiazides	Hydrochlorothiazide	Inhibits sodium transport	Last part of ascending limb and first part of distal tubule
Carbonic anhydrase inhibitors	Acetazolamide	Inhibits reabsorption of bicarbonate	Proximal tubule
Osmotic diuretics	Mannitol	Reduces osmotic reabsorption of water by reducing osmotic gradient	Last part of distal tubule and cortical collecting duct
Potassium-sparing diuretics	Spironolactone	Inhibits action of aldosterone	Last part of distal tubule and cortical collecting duct
	Triamterene	Inhibits Na^+ reabsorption and K^+ secretion	Last part of distal tubule and cortical collecting duct

Segment	Functions	Water Permeability	Primary Transporters and Drug Targets at Apical Membrane	Diuretic with Major Action
Glomerulus	Formation of glomerular filtrate	Extremely high	None	None
Proximal convoluted tubule (PCT)	Reabsorption of 65% of filtered Na^+/ K^+/ CA^{2+}, and Mg^{2+}; 85% of $NaHCO3$, and nearly 100% of glucose and amino acids. Isosmotic reabsorption of water.	Very high	Na/H^1 (NHE3), carbonic anhydrase	Carbonic anhydrase inhibitors
Proximal tubule, straight segments	Secretion and reabsorption of organic acids and bases, including uric acid and most diuretics	Very high	Acid (eg, uric acid) and base transporters	None
Thin descending limb of Henle's loop	Passive reabsorption of water	High	Aquaporins	None
Thick ascending limb of Henle's loop (TAL)	Active reabsorption of 15–25% of filtered Na^+/ K^+/ Cl^-; secondary reabsorption of Ca^{2+} and Mg^{2+}	Very low	Na/K/2Cl (NKCC2)	Loop diuretics
Distal convoluted tubule (DCT)	Active reabsorption of 4–8% of filtered Na^+ and Cl^-; Ca^{2+} reabsorption under parathyroid hormone control	Very low	Na/Cl (NCC)	Thiazides
Cortical collecting tubule (CCT)	Na^+ reabsorption (2–5%) coupled to K^+ and H^+ secretion	Variable[2]	Na channels (ENaC), K channels,[1] H transporter,[1] aquaporins	K^+-sparing diuretics
Medullary collecting duct	Water reabsorption under vasopressin control	Variable[2]	Aquaporins	Vasopressin antagonist

Clinical Application: Kidney Stones

- **Urinary stones are typically classified**
  --**Location:** kidney (nephrolithiasis), ureter (ureterolithiasis), or bladder (cystolithiasis)
  --**Chemical composition:** calcium-containing, struvite, uric acid, or other compounds
- About 80% of those with kidney stones are **men**
- Dietary factors include ***low fluid intake*** and ***high dietary intake of animal protein, sodium, refined sugars, high fructose corn syrup, and cola drinks***



成功之前

多學習成功之後必須要有的**慈悲**

這樣才能達到成功的位置

才懂得**珍惜與體諒**