Acid-base balance

Zoo-103, Unit-II

&

Zoo-304 (Allied Elective-CBCS)

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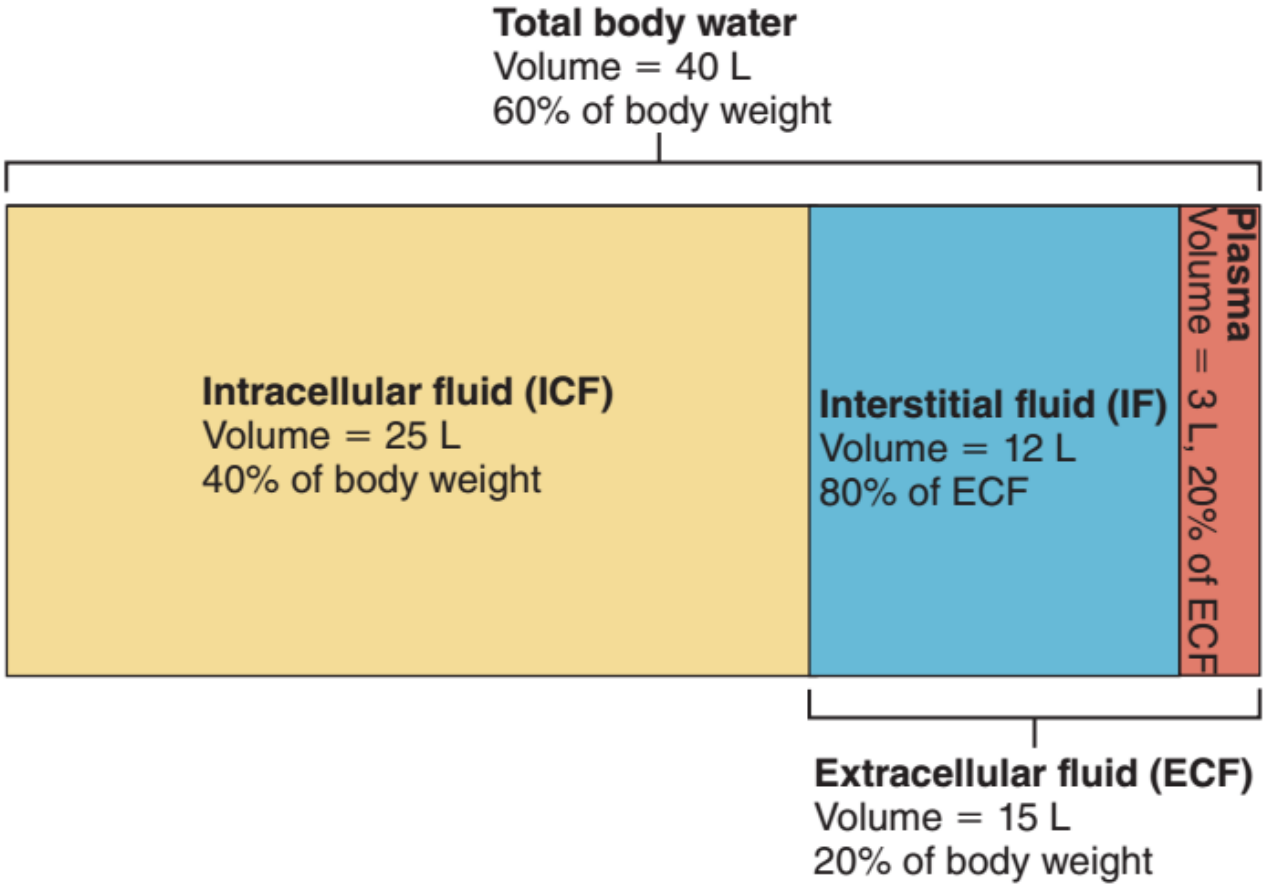
acid-base balance ?

- Refers to the precise regulation of free (that is unbound) hydrogen ion (H^+) concentration in the *body fluids*.

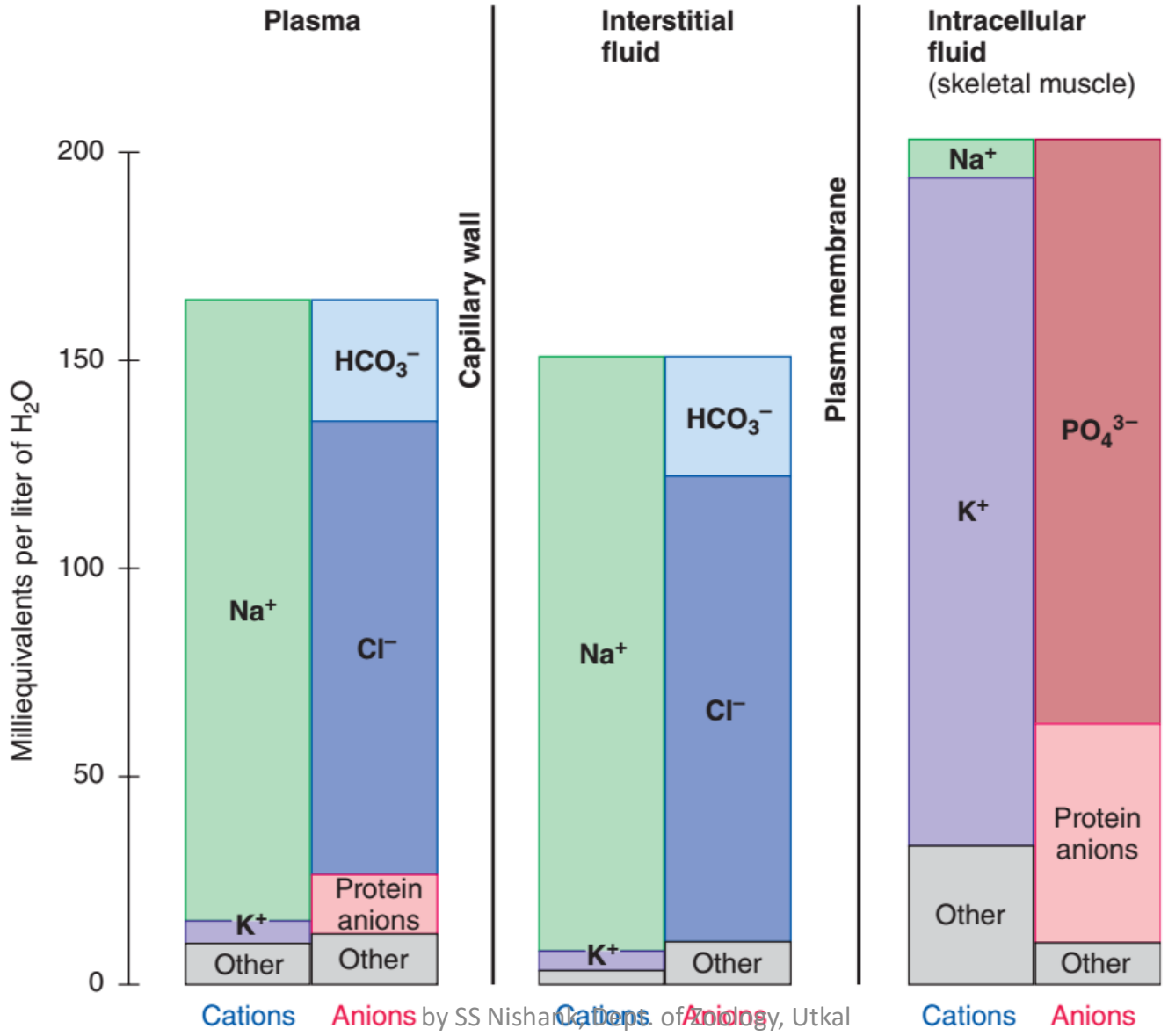
Body fluids consist of water and solutes in three main compartments



The major fluid compartments of the body.

[Values are for a 70-kg (154-lb) male.]

Ionic composition of the major body-fluid compartments.



Homeostasis of body regulated by

- Regulation of water intake & output
- Regulation of Na^+, K^+, Ca^{2+}
- Regulation of pH (acid-base balance regulation)

Why acid base balance is important?

- Changes in excitability of nerve & muscle cells
- Influence on enzyme activity
- Influence on K^+ levels in body (e.g. acidosis causes decreased K^+ secretion whereas alkalosis causes increased K^+ secretion)

Sources of H^+ ion in body

- Carbonic acid formation by metabolic process
- Inorganic acids produced during breakdown of nutrients
- Organic acids from intermediary metabolism

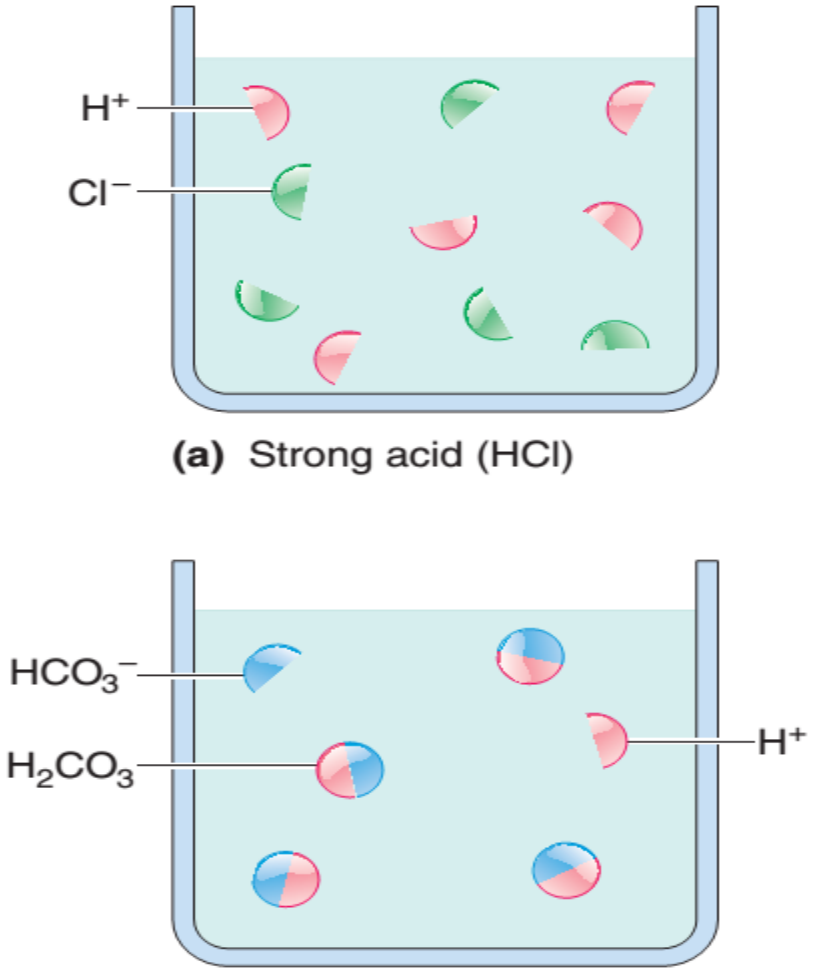
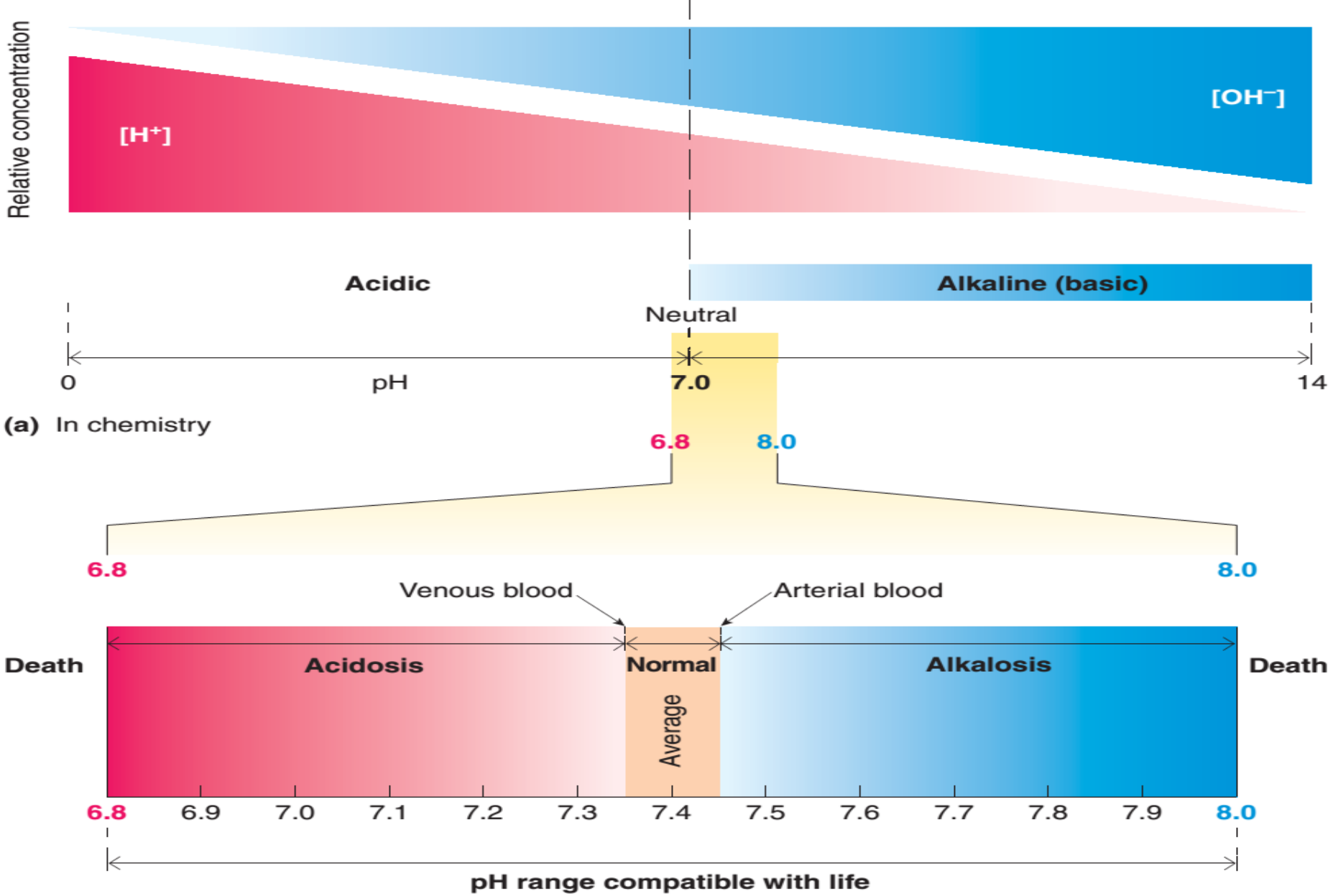


FIGURE 15-5 Comparison of a strong and a weak acid.



pH considerations in chemistry and physiology. (a) Relationship of pH to the relative concentrations of H^+ and base (OH^-) under chemically neutral, acidic, and alkaline conditions. (b) Blood pH range under normal, acidotic, and alkalotic conditions.

Acid dissociation constant shows the strength of an acid.

$$HA \rightleftharpoons H^+ + A^-.$$

Where A^- is a base, / conjugate base

(K_a), which is also called the *ionization constant* or **acid dissociation constant**, is given by the expression

$$K_a = \frac{[H^+] \times [A^-]}{[HA]}$$

$$pK_a = \log_{10}\left(1 / K_a\right) = -\log_{10} K_a$$

$$pH = \log_{10}\left(1/[H^+]\right) = -\log_{10}[H^+]$$

Henderson-Hasselbalch equation

- pH of a solution containing an acid or base can be calculated by Henderson-Hasselbalch equation.
- The Henderson-Hasselbalch equation is used to calculate the pH of a buffered solution.
- This equation is derived from the behavior of weak acids (and bases) in solution, which is described by the kinetics of reversible reactions:

$$HA \underset{K_2}{\overset{K_1}{\rightleftharpoons}} H^+ + A^-$$

$$K_1[HA] = K_2[H^+][A^-]$$

Rearranging,

$$\frac{K_1}{K_2} = \frac{[H^+][A^-]}{[HA]}$$

The ratio of rate constants can be combined into a single constant, **K,** called the **equilibrium constant,** as follows:

$$K = \frac{[H^+][A^-]}{[HA]}$$

Rearranging again to solve for $[H^+]$:

$$[H^+] = K\frac{[HA]}{[A^-]}$$

To express $[H^+]$ as pH, *take the negative* log_{10} of both sides of the previous equation. Then,

$$-\log[H^+] = -\log K - \log\frac{[HA]}{[A^-]}$$

Thus the final form of the **Henderson-Hasselbalch equation** is as follows:

$$pH = pK + \log\frac{[A^-]}{[HA]}$$

where

$pH = -\log_{10}[H^+]$ (pH units)

$pK = -\log_{10} K$ (pH units)

$[A^-]$ = Concentration of base form of buffer (mEq/L)

$[HA]$ = Concentration of acid form of buffer (mEq/L)

$$K_a = \frac{[H^+] \times [A^-]}{[HA]}$$

$$[H^+] = \frac{K_a \times [HA]}{[A^-]}$$

A strong acid has a high K_a and a low pK_a.

A weak acid has a low K_a and a high pK_a.

If we take the negative logarithms of both sides,

$$-\log[H^+] = -\log K_a + \log \frac{[A^-]}{[HA]}$$

Substituting pH for $-\log [H^+]$ and pK_a for $-\log K_a$, we get

$$pH = pK_a + \log \frac{[A^-]}{[HA]}$$ (Henderson-Hasselbalch equation)

Buffer ?

- A buffer is a mixture of a weak acid and its conjugate base or a weak base and its conjugate acid

$$pH = pK_a + \log \frac{[\text{conjugate base}]}{[\text{acid}]}$$

Weak Acid		Conjugate Base	
H_2CO_3 (carbonic acid)	$\rightleftharpoons$	HCO_3^- (bicarbonate) + H^+	(7)
$H_2PO_4^-$ (dihydrogen phosphate)	$\rightleftharpoons$	HPO_4^{2-} (monohydrogen phosphate) + H^+	(8)
NH_4^+ (ammonium ion)	$\rightleftharpoons$	NH_3 (ammonia) + H^+	(9)

Buffering capacity ?

The effectiveness of a buffer—how well it minimizes pH changes when an acid or base is added—depends on its concentration and its pK_a. A good buffer is present in high concentrations and has a pK_a close to the desired pH.

In most cases, pH buffering is effective when the solution pH is within ±1 pH unit of the buffer pKa.

For effective buffering, there is a limit over which the ratio $\frac{[A^-]}{[HA]}$ can be varied; it can only be 10:1 either way, giving a log value ±1. That is, buffers only work ±1 unit on either side of their pK values.

The effectiveness of a buffer—how well it minimizes pH changes when an acid or base is added—depends on its concentration and its pK_a. A good buffer is present in high concentrations and has a pK_a close to the desired pH.

K_a and pK_a Values for Some Weak Acids

Formula	Name	K_a	pK_a
H_3PO_4	Phosphoric acid	7.5×10^{-3}	2.12
HCOOH	Formic acid	1.8×10^{-4}	3.75
$CH_3CH(OH)COOH$	Lactic acid	1.4×10^{-4}	3.86
CH_3COOH	Acetic acid	1.8×10^{-5}	4.75
H_2CO_3	Carbonic acid	4.3×10^{-7}	6.37
$H_2PO_4^-$	Dihydrogen phosphate ion	6.2×10^{-8}	7.21
H_3BO_3	Boric acid	7.3×10^{-10}	9.14
NH_4^+	Ammonium ion	5.6×10^{-10}	9.25
HCN	Hydrocyanic acid	4.9×10^{-10}	9.31
C_6H_5OH	Phenol	1.3×10^{-10}	9.89
HCO_3^-	Bicarbonate ion	5.6×10^{-11}	10.25
HPO_4^{2-}	Hydrogen phosphate ion	2.2×10^{-13}	12.66

pH Values of Some Common Materials

Material	pH	Material	pH
Battery acid	0.5	Saliva	6.5–7.5
Gastric juice	1.0–3.0	Pure water	7.0
Lemon juice	2.2–2.4	Blood	7.35–7.45
Vinegar	2.4–3.4	Bile	6.8–7.0
Tomato juice	4.0–4.4	Pancreatic fluid	7.8–8.0
Carbonated beverages	4.0–5.0	Sea water	8.0–9.0
Black coffee	5.0–5.1	Soap	8.0–10.0
Urine	5.5–7.5	Milk of magnesia	10.5
Rain (unpolluted)	6.2	Household ammonia	11.7
Milk	6.3–6.6	Lye (1.0 *M* NaOH)	14.0

Features of an ideal buffer – for biological purposes a buffer would possess the following characteristics:

- impermeability to biological membranes;
- biological stability and lack of interference with metabolic and biological processes;
- lack of significant absorption of ultraviolet or visible light;
- lack of formation of insoluble complexes with cations;
- minimal effect of ionic composition or salt concentration;
- limited pH change in response to temperature.

TRIS buffer is often toxic to biological systems: because of its high lipid solubility it can penetrate membranes, uncoupling electron transport reactions in whole cells and isolated organelles. In addition, it is markedly affected by temperature, with a tenfold increase in H+ concentration from 4 °C to 37 °C.

Application of Henderson-Hesselbalch equation

SAMPLE PROBLEM. The pK of the $HPO_4^{-2}/H_2PO_4^-$ buffer pair is 6.8. Answer two questions about this buffer: *(1) At a blood pH of 7.4, what are the relative concentrations of the acid form and the base form of this buffer pair? (2) At what pH would the concentrations of the acid and base forms be equal?*

Solution of Q.1

$$pH = pK + \log \frac{HPO_4^{-2}}{H_2PO_4^{-}}$$

$$7.4 = 6.8 + \log \frac{HPO_4^{-2}}{H_2PO_4^{-}}$$

$$0.6 = \log \frac{HPO_4^{-2}}{H_2PO_4^{-}}$$

$$3.98 = HPO_4^{-2} / H_2PO_4^{-}$$

Therefore, at pH 7.4, the concentration of the base form (HPO_4^{-2}) is approximately fourfold that of the acid form ($H_2PO_4^{-}$).

Solution Q.2

$$HPO_4^{-2}/H_2PO_4^{-} = 1.0$$

$$pH = pK + \log \frac{HPO_4^{-2}}{H_2PO_4^{-}}$$

$$= 6.8 + \log 1$$

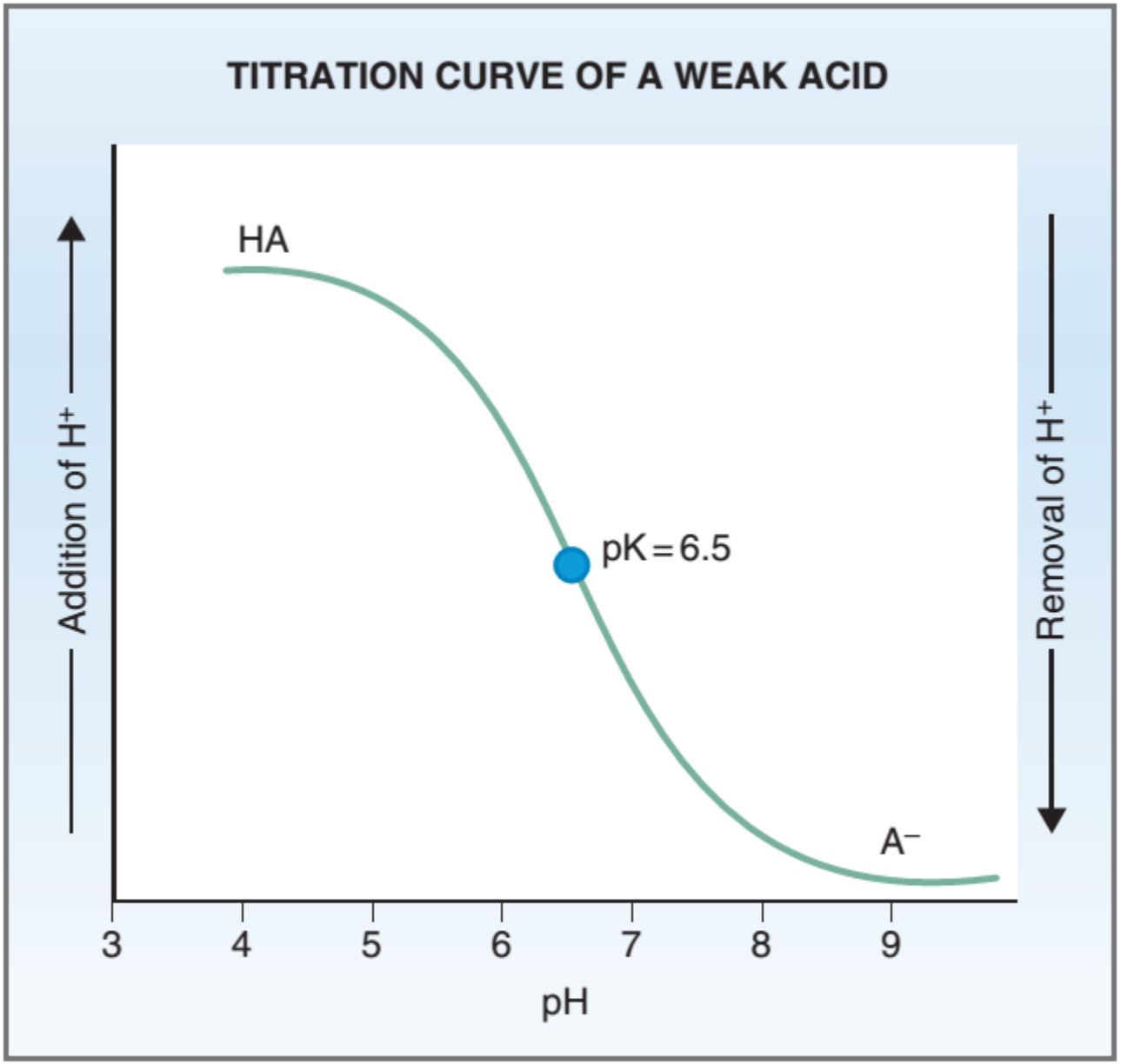
$$= 6.8 + 0$$

$$= 6.8$$

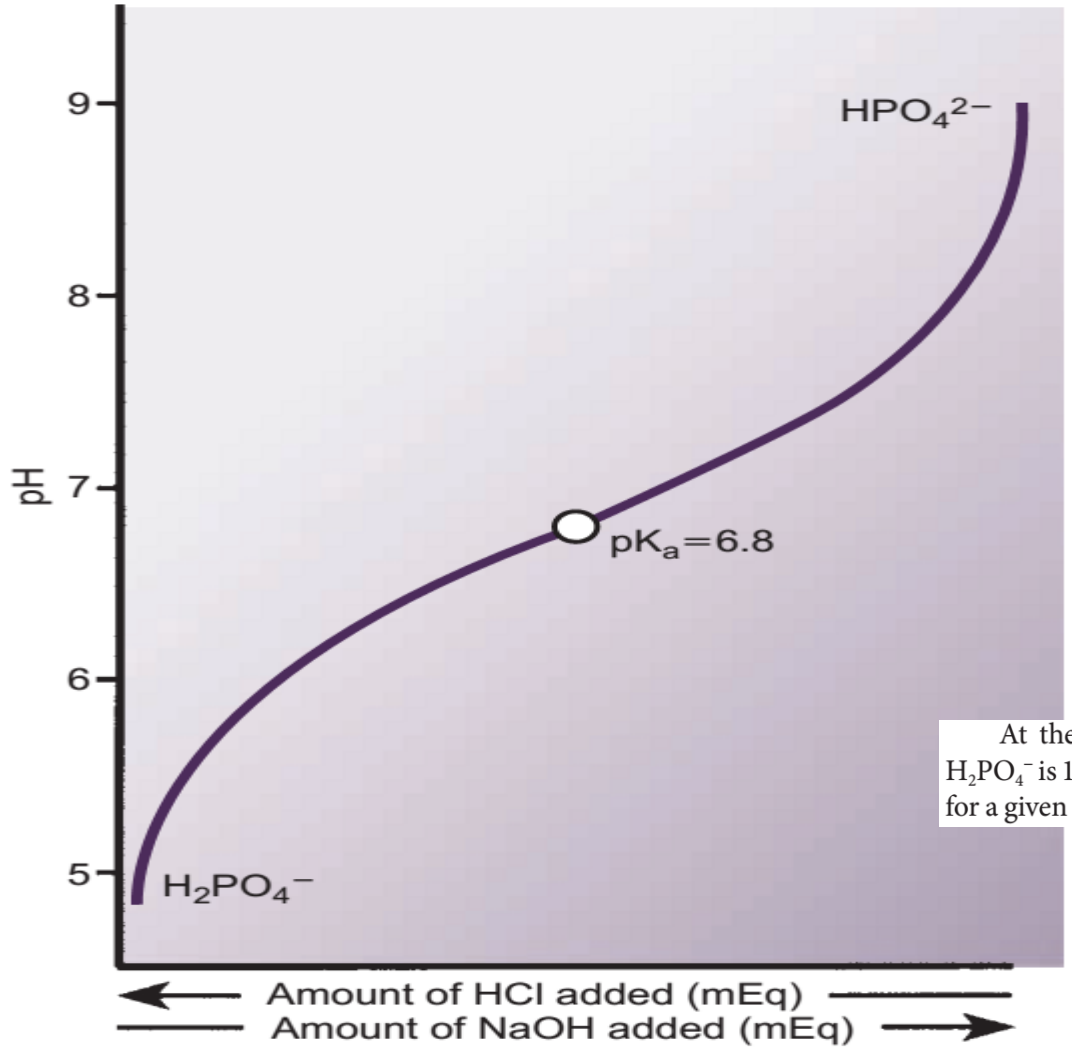
The calculated pH equals the pK of the buffer.

This important calculation demonstrates that *when the pH of a solution equals the pK, the concentrations of the acid and base forms of the buffer are equal.*

A buffer functions best when the pH of the solution is equal (or nearly equal) to the pK of the buffer, precisely because the concentrations of the acid and base forms are equal or nearly equal.



Titration curve of a weak acid (HA) and its conjugate base (A^-). When pH equals pK, there are equal concentrations of HA and A^-.



Titration curve for a phosphate buffer.

The pK_a for $H_2PO_4^-$ is 6.8. A strong acid (HCl) (*right to left*) or strong base (NaOH) (*left to right*) was added and the resulting solution pH recorded (*y* axis). Notice that buffering is best (i.e., the change in pH on the addition of a given amount of acid or base is least) when the solution pH is equal to the pK_a of the buffer.

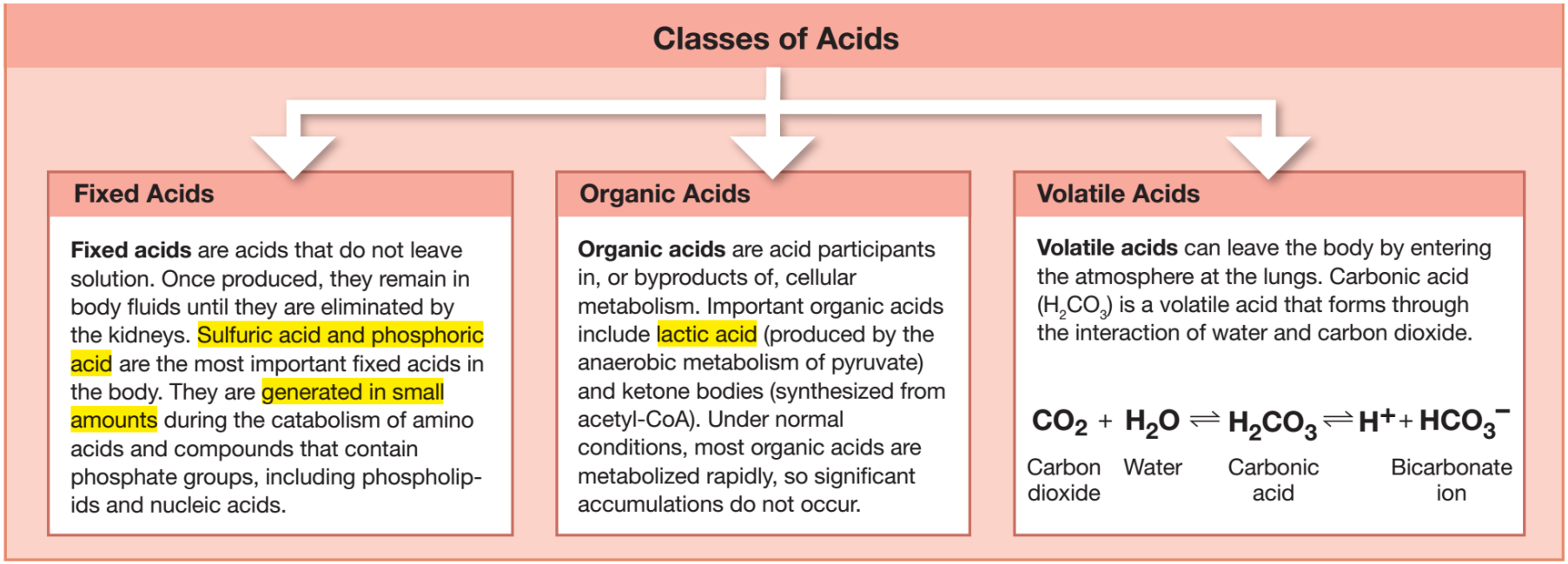
Going from right to left, as strong acid is added, H+ combines with the basic form of phosphate:

$$H^+ + HPO_4^{2-} \rightleftharpoons H_2PO_4^-.$$

Going from left to right, as strong base is added, OH− combines with H+ released from the acid form of the phosphate buffer:

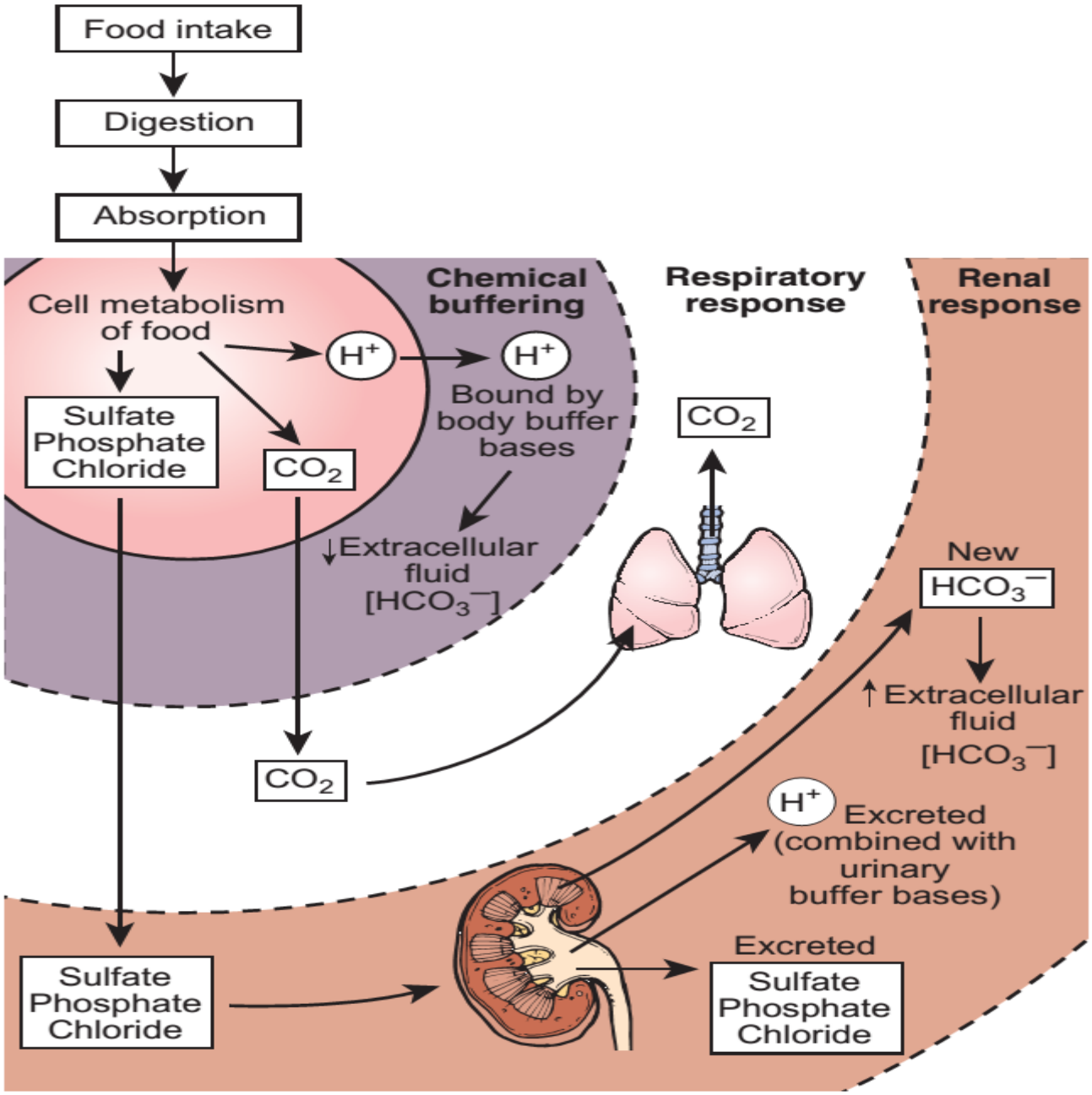
$$OH^- + H_2PO_4^- \rightleftharpoons HPO_4^{2-} + H_2O.$$

At the pK_a of the phosphate buffer, the ratio $HPO_4^{2-}/H_2PO_4^-$ is 1, and the titration curve is flattest (the change in pH for a given amount of an added acid or base is at a minimum).

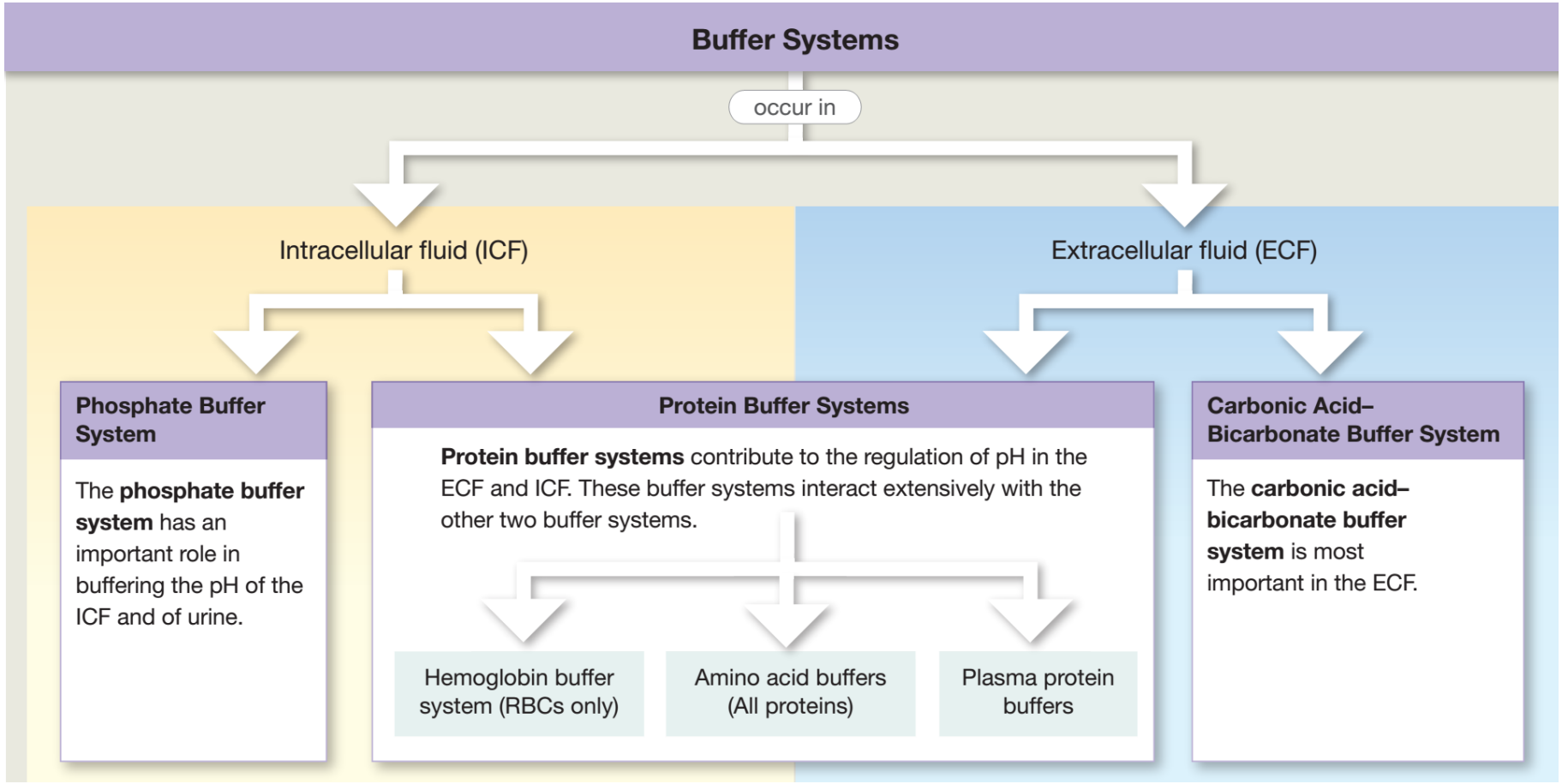

Classes of Acids
Fixed Acids
Fixed acids are acids that do not leave solution. Once produced, they remain in body fluids until they are eliminated by the kidneys. Sulfuric acid and phosphoric acid are the most important fixed acids in the body. They are generated in small amounts during the catabolism of amino acids and compounds that contain phosphate groups, including phospholipids and nucleic acids.
Organic Acids
Organic acids are acid participants in, or byproducts of, cellular metabolism. Important organic acids include lactic acid (produced by the anaerobic metabolism of pyruvate) and ketone bodies (synthesized from acetyl-CoA). Under normal conditions, most organic acids are metabolized rapidly, so significant accumulations do not occur.
Volatile Acids
Volatile acids can leave the body by entering the atmosphere at the lungs. Carbonic acid (H_2CO_3) is a volatile acid that forms through the interaction of water and carbon dioxide.
$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$
Carbon dioxide
Water
Carbonic acid
Bicarbonate ion

pH is regulated by

TYPE	RESPONSE TIME	EXAMPLE
Chemical buffer systems	Immediate	Bicarbonate buffer system Phosphate buffer system Protein buffer system
Physiological buffer systems	Minutes Hours	Respiratory response system Renal response system



The maintenance of normal blood pH by chemical buffers, the respiratory system, and the kidneys.


Buffer Systems
occur in
Intracellular fluid (ICF)
Extracellular fluid (ECF)
Phosphate Buffer System
The phosphate buffer system has an important role in buffering the pH of the ICF and of urine.
Protein Buffer Systems
Protein buffer systems contribute to the regulation of pH in the ECF and ICF. These buffer systems interact extensively with the other two buffer systems.
Hemoglobin buffer system (RBCs only)
Amino acid buffers (All proteins)
Plasma protein buffers
Carbonic Acid–Bicarbonate Buffer System
The carbonic acid–bicarbonate buffer system is most important in the ECF.

Regulation of pH by buffers

Bicarbonate Buffer System

The **bicarbonate buffer system** is a mixture of carbonic acid (H_2CO_3) and its salt, sodium bicarbonate ($NaHCO_3$, a weak base), in the same solution

When a strong acid such as HCl is added to this buffer system

$$HCl + NaHCO_3 \rightarrow H_2CO_3 + NaCl$$

strong acid — weak base — weak acid — salt

When a strong base such as sodium hydroxide (NaOH) is added

$$NaOH + H_2CO_3 \rightarrow NaHCO_3 + H_2O$$

strong base — weak acid — weak base — water

Regulation of pH by buffers

Phosphate Buffer System

The operation of the **phosphate buffer system** is nearly identical to that of the bicarbonate buffer. The components of the phosphate system are the sodium salts of dihydrogen phosphate ($H_2PO_4^-$) and monohydrogen phosphate (HPO_4^{2-}). NaH_2PO_4 acts as a weak acid. Na_2HPO_4, with one less hydrogen atom, acts as a weak base.

Again, H^+ released by strong acids is tied up in weak acids:

$$\underset{\text{strong acid}}{HCl} + \underset{\text{weak base}}{Na_2HPO_4} \rightarrow \underset{\text{weak acid}}{NaH_2PO_4} + \underset{\text{salt}}{NaCl}$$

and strong bases are converted to weak bases:

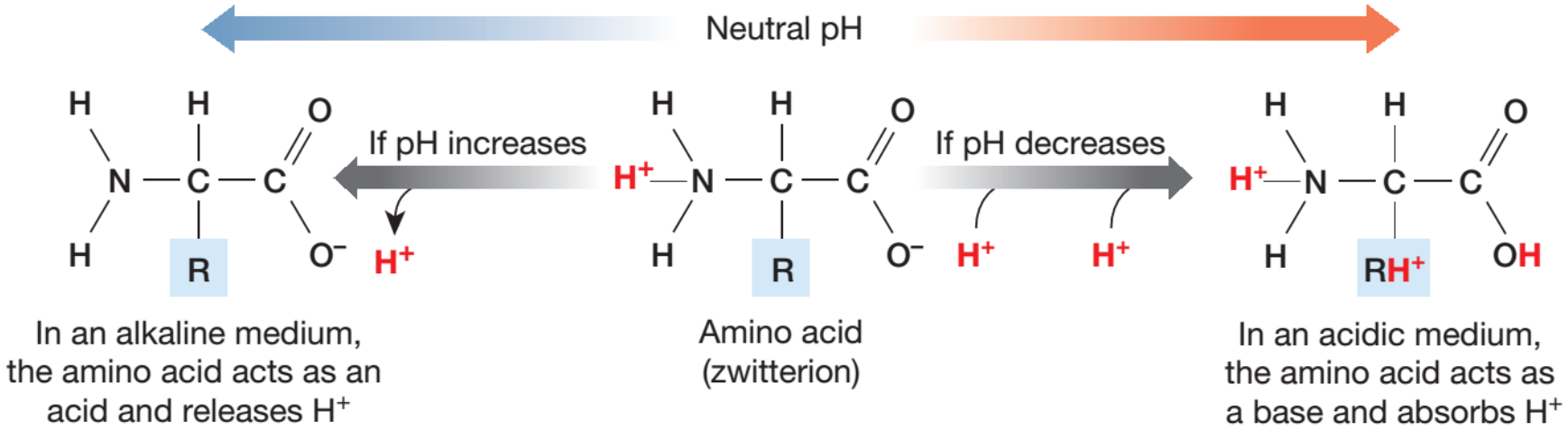
$$\underset{\text{strong base}}{NaOH} + \underset{\text{weak acid}}{NaH_2PO_4} \rightarrow \underset{\text{weak base}}{Na_2HPO_4} + \underset{\text{water}}{H_2O}$$

Regulation of pH by buffers

Protein Buffer System

$$R{-}COOH \rightarrow R{-}COO^- + H^+$$

$$R{-}NH_2 + H^+ \rightarrow R{-}NH_3^+$$



The main buffers in the human body

Buffer	Acid	Conjugate base	Site of main buffering action
Hemoglobin	HHb	Hb^-	Erythrocytes
Proteins	HProt	$Prot^-$	Intracellular fluid
Phosphate buffer	$H_2PO_4^-$	HPO_4^{2-}	Intracellular fluid
Bicarbonate	$CO_2 \rightarrow H_2CO_3$	HCO_3^-	Extracellular fluid

Buffer Pairs Present in Body Fluids

Bicarbonate pairs: $\frac{NaHCO_3}{H_2CO_3}, \frac{KHCO_3}{H_2CO_3}$, etc.

Plasma • protein pair: $\frac{Na \bullet Proteinate}{Proteins\ (weak\ acids)}$

Hemoglobin pairs: $\frac{K \bullet Hb}{Hb}$ and $\frac{K \bullet HbHO_2}{HbO_2}$

(Hb and HbO_2 are weak acids)

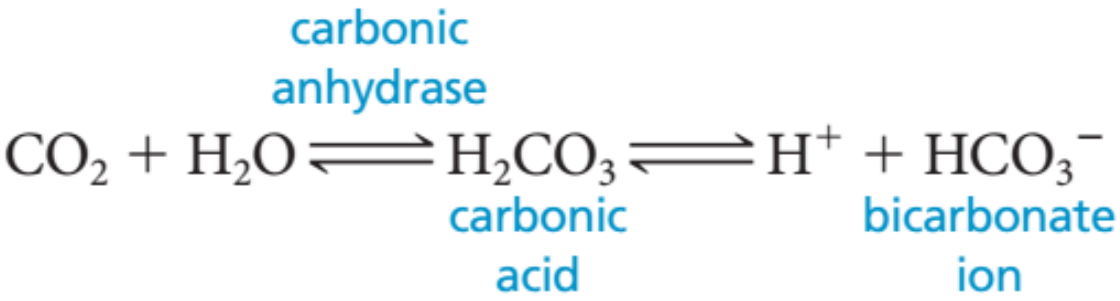
Phosphate buffer pair: $\frac{Na_2HPO_4}{NaH_2PO_4}$ $\frac{(basic\ phosphate)}{(acid\ phosphate)}$

Major Chemical pH Buffers in the Body

Buffer	Reaction
Extracellular fluid	
Bicarbonate/CO_2	$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$
Inorganic phosphate	$H_2PO_4^- \rightleftharpoons H^+ + HPO_4^{2-}$
Plasma proteins (Pr)	$HPr \rightleftharpoons H^+ + Pr^-$
Intracellular fluid	
Cell proteins (e.g., hemoglobin [Hb])	$HHb \rightleftharpoons H^+ + Hb^-$
Organic phosphates	$organic\text{-}HPO_4^- \rightleftharpoons H^+ + organic\text{-}PO_4^{2-}$
Bicarbonate/CO_2	$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$
Bone	
Mineral phosphates	$H_2PO_4^- \rightleftharpoons H^+ + HPO_4^{2-}$
Mineral carbonates	$HCO_3^- \rightleftharpoons H^+ + CO_3^{2-}$

pH regulation by respiration

a rising plasma H+ concentration resulting from any metabolic process excites the respiratory center indirectly (via peripheral chemoreceptors) to stimulate deeper, more rapid respiration. As ventilation increases, more CO_2 is removed from the blood, pushing the reaction to the left and reducing the H+ concentration.



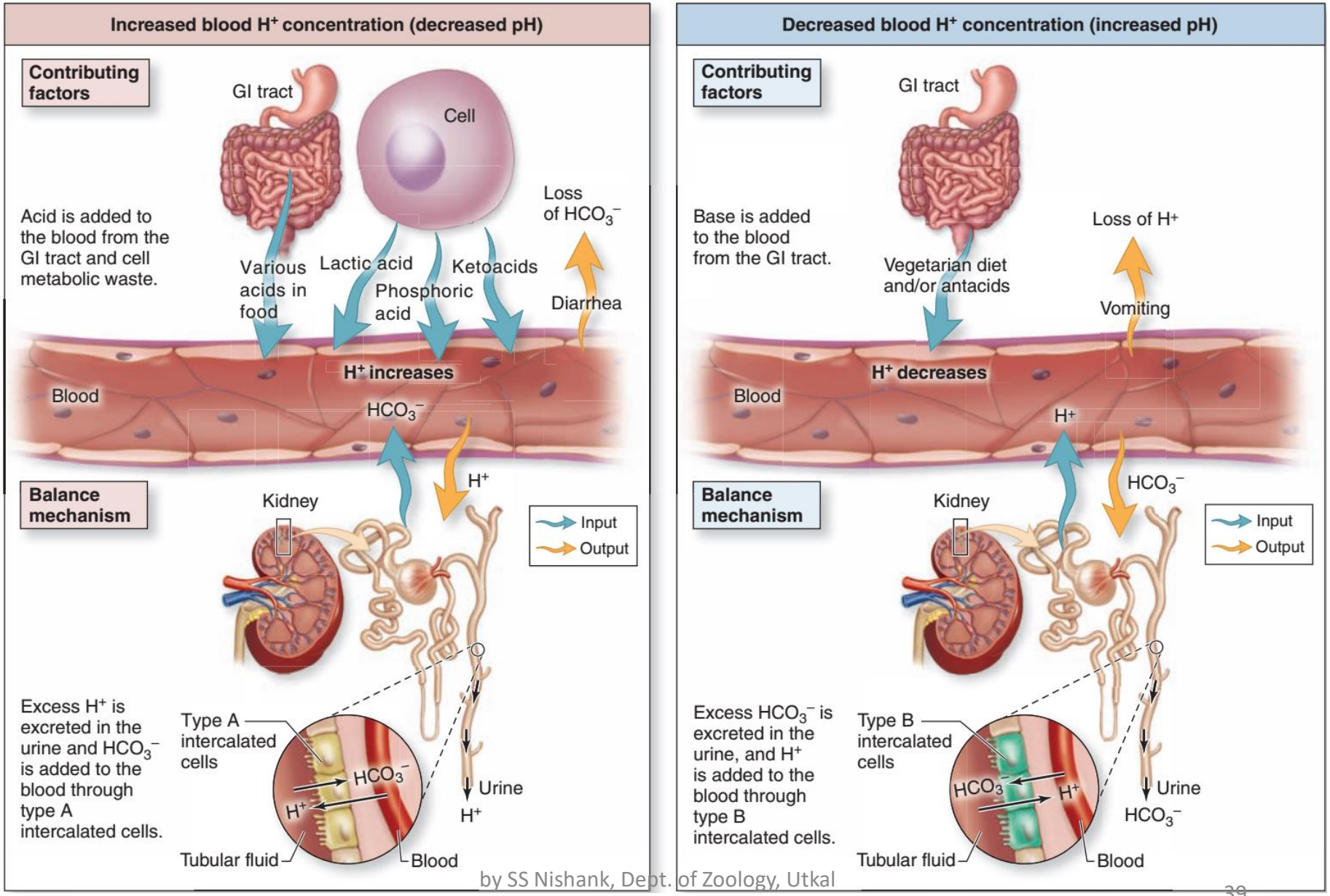
When blood pH rises, the respiratory center is depressed. As respiratory rate drops and respiration becomes shallower, CO2 accumulates, pushing the equilibrium to the right and causing the H+ concentration to increase.

Respiratory Adjustments to Acidosis and Alkalosis Induced by Nonrespiratory Causes

	ACID–BASE STATUS		
Respiratory Compensations	**Normal (pH 7.4)**	**Nonrespiratory (metabolic) Acidosis (pH 7.1)**	**Nonrespiratory (metabolic) Alkalosis (pH 7.7)**
Ventilation	Normal	↑	↓
Rate of CO_2 Removal	Normal	↑	↓
Rate of H_2CO_3 Formation	Normal	↓	↑
Rate of H^+ Generation from CO_2	Normal	↓	↑

Renal mechanism of acid-base balance

Altered Blood H^+ Concentration and Adjustments by the Kidneys.



Renal mechanism for regulation of acid base balance by

- 1. Conservation/ reabsorption of HCO_3^-
- 2. Generation of new HCO_3^- via

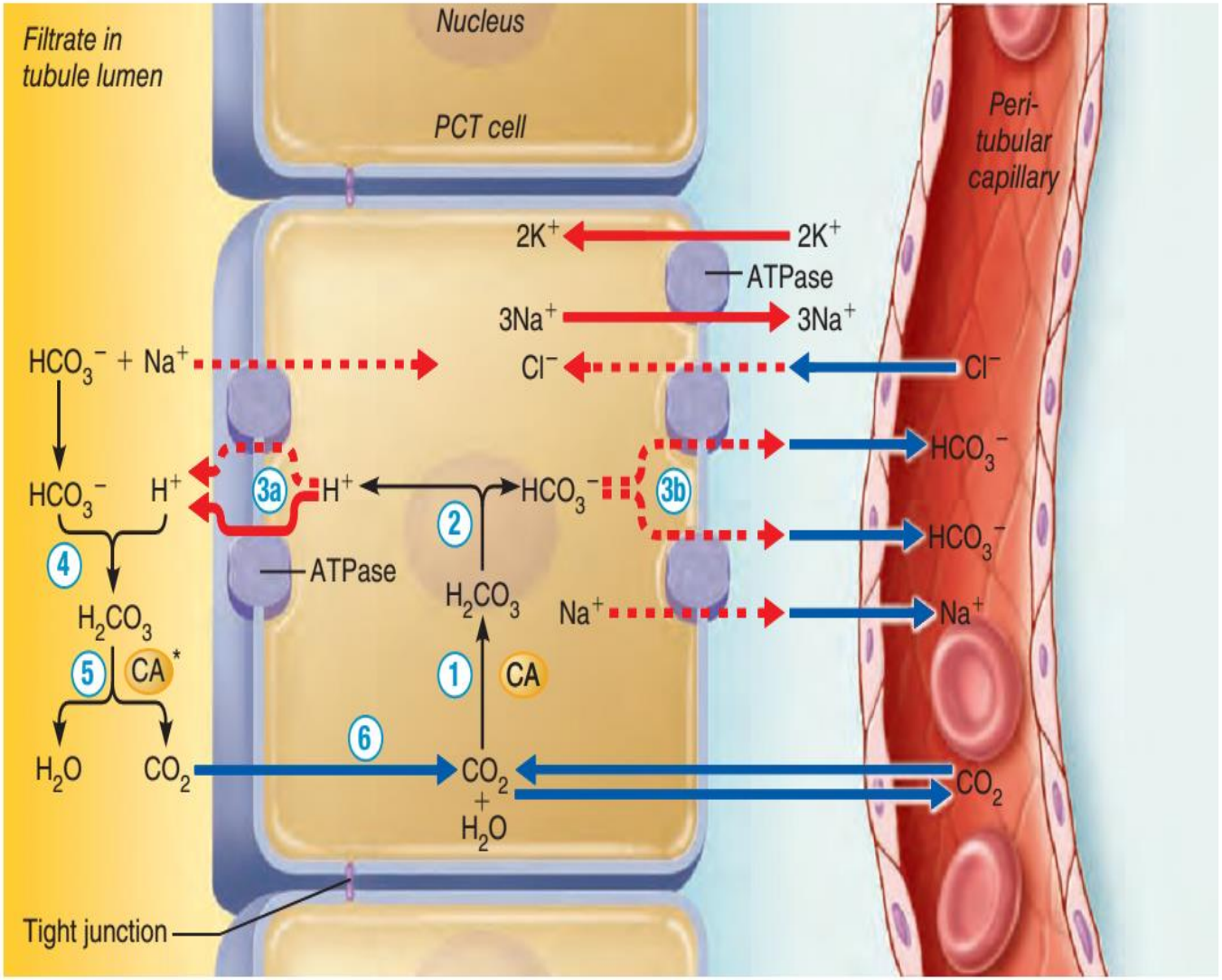
(a) excretion of buffered H^+ / excretion of H+ as titratable acid and

(b) NH^{4+} excretion

- 3. Excretion of HCO_3^-

The rate of H^+ secretion rises and falls with CO_2 levels in the ECF. The more CO_2 in the peritubular capillary blood, the faster the rate of H+ secretion.

Because blood CO_2 levels directly relate to blood pH, this system can respond to both rising and falling H^+ concentrations.

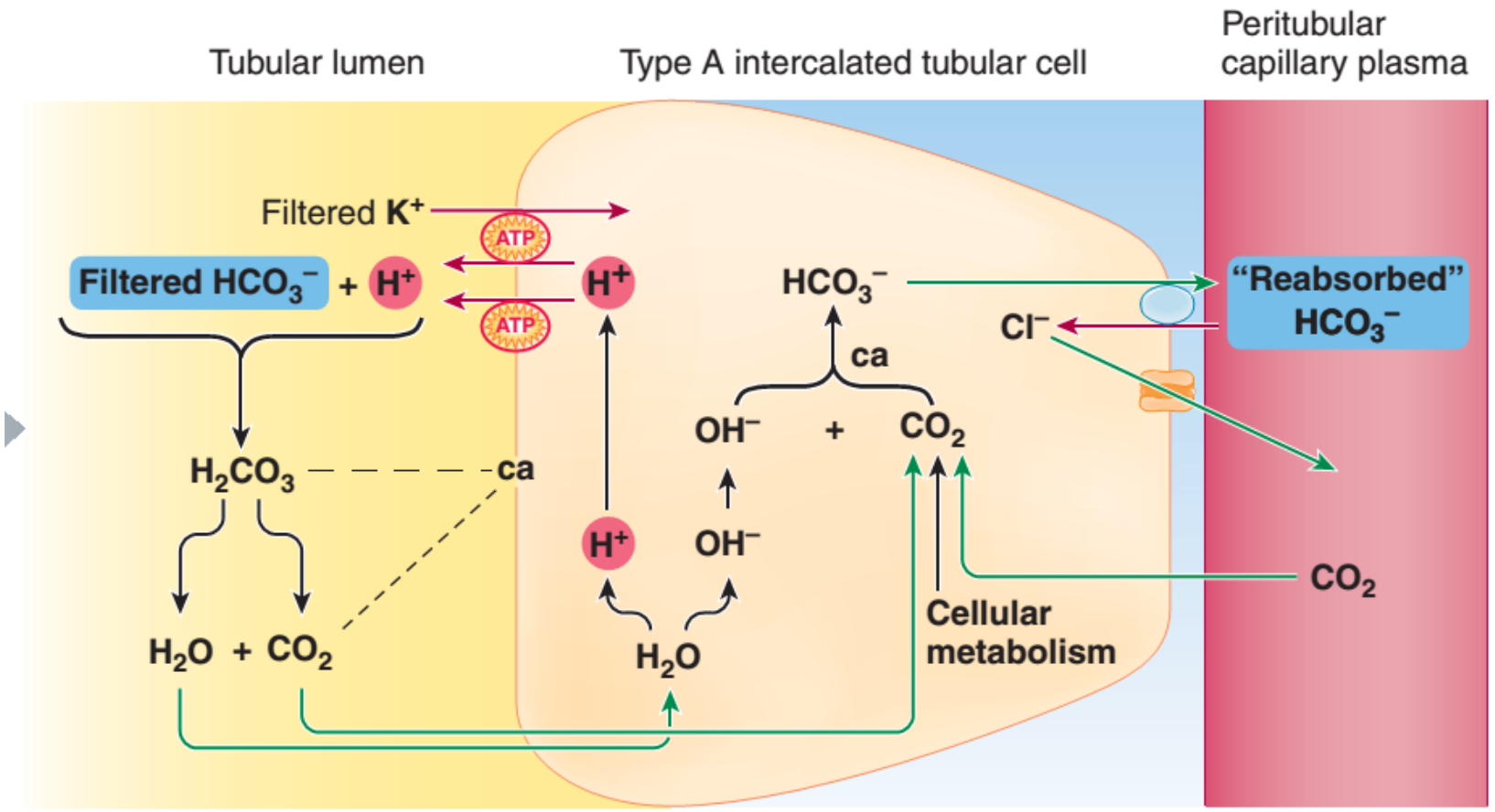


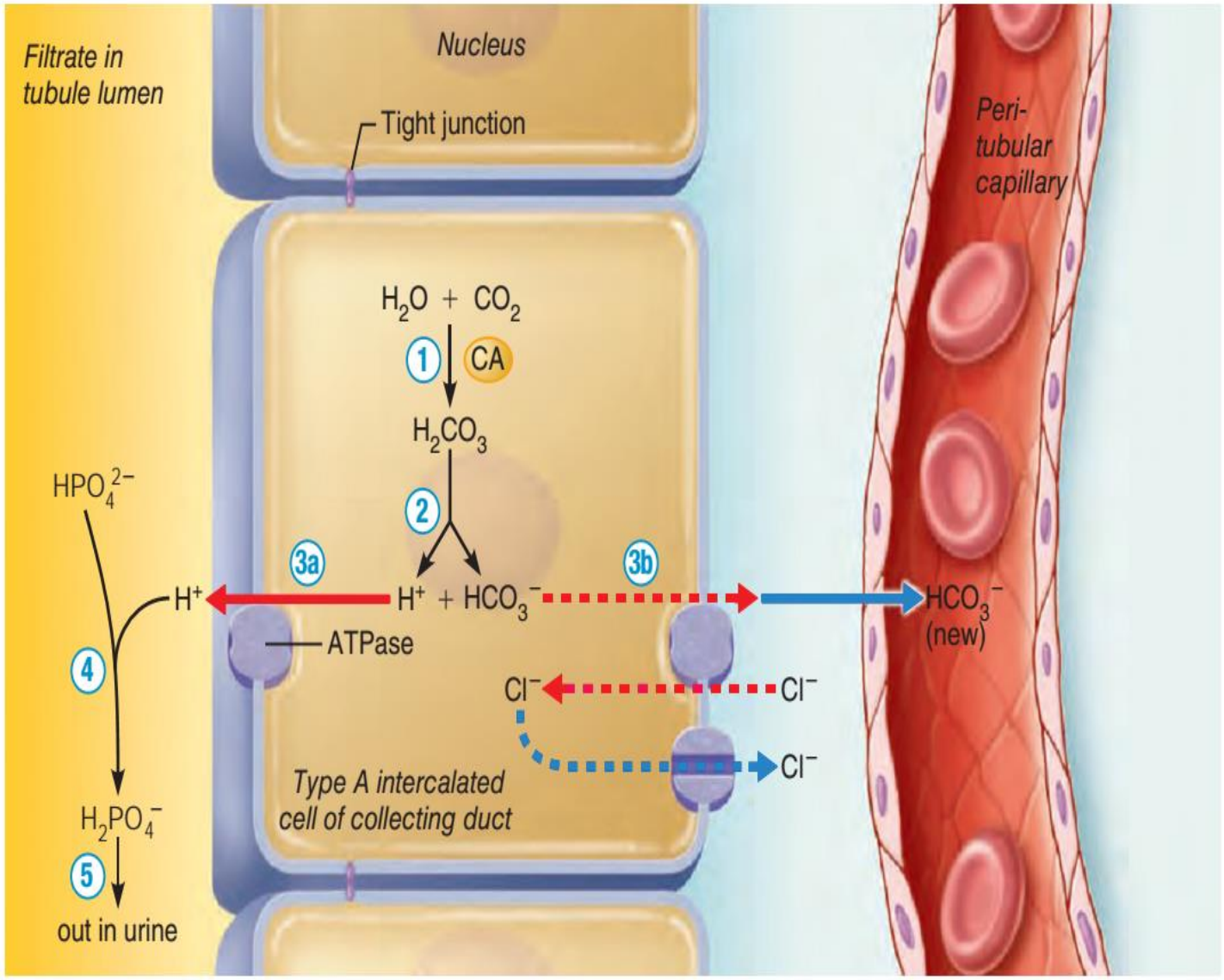
Primary active transport
Secondary active transport
Simple diffusion
Transport protein
CA Carbonic anhydrase

Reabsorption of filtered HCO_3^- is coupled to H^+ secretion.

1. CO_2 combines with water within the tubule cell, forming H_2CO_3.
2. H_2CO_3 is quickly split, forming H^+ and bicarbonate ion (HCO_3^-).
3a. H^+ is secreted into the filtrate.
3b. For each H^+ secreted, a HCO_3^- enters the peritubular capillary blood either via symport with Na^+ or via antiport with Cl^-.
4. Secreted H^+ combines with HCO_3^- in the filtrate, forming carbonic acid (H_2CO_3). HCO_3^- disappears from the filtrate at the same rate that HCO_3^- (formed within the tubule cell) enters the peritubular capillary blood.
5. The H_2CO_3 formed in the filtrate dissociates to release CO_2 and H_2O.
6. CO_2 diffuses into the tubule cell, where it triggers further H^+ secretion.

bicarbonate reabsorption & H^+ ion secretion in distal tubule





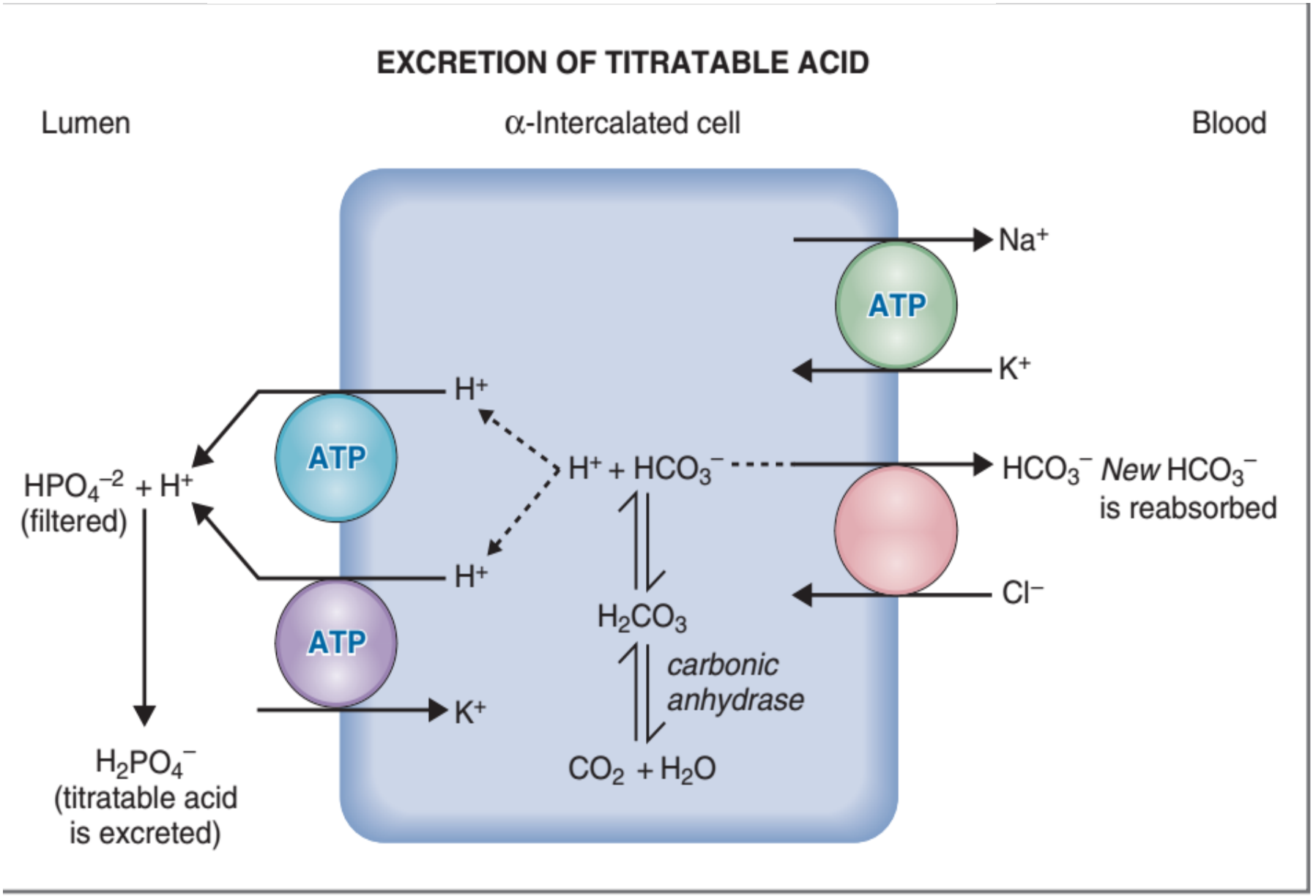
1. CO_2 combines with water within the type A intercalated cell, forming H_2CO_3.
2. H_2CO_3 is quickly split, forming H^+ and bicarbonate ion (HCO_3^-).
3a. H^+ is secreted into the filtrate by a H^+ ATPase pump.
3b. For each H^+ secreted, a HCO_3^- enters the peritubular capillary blood via an antiport carrier in a HCO_3^--Cl^- exchange process.
4. Secreted H^+ combines with HPO_4^{2-} in the tubular filtrate, forming $H_2PO_4^-$.
5. The $H_2PO_4^-$ is excreted in the urine.

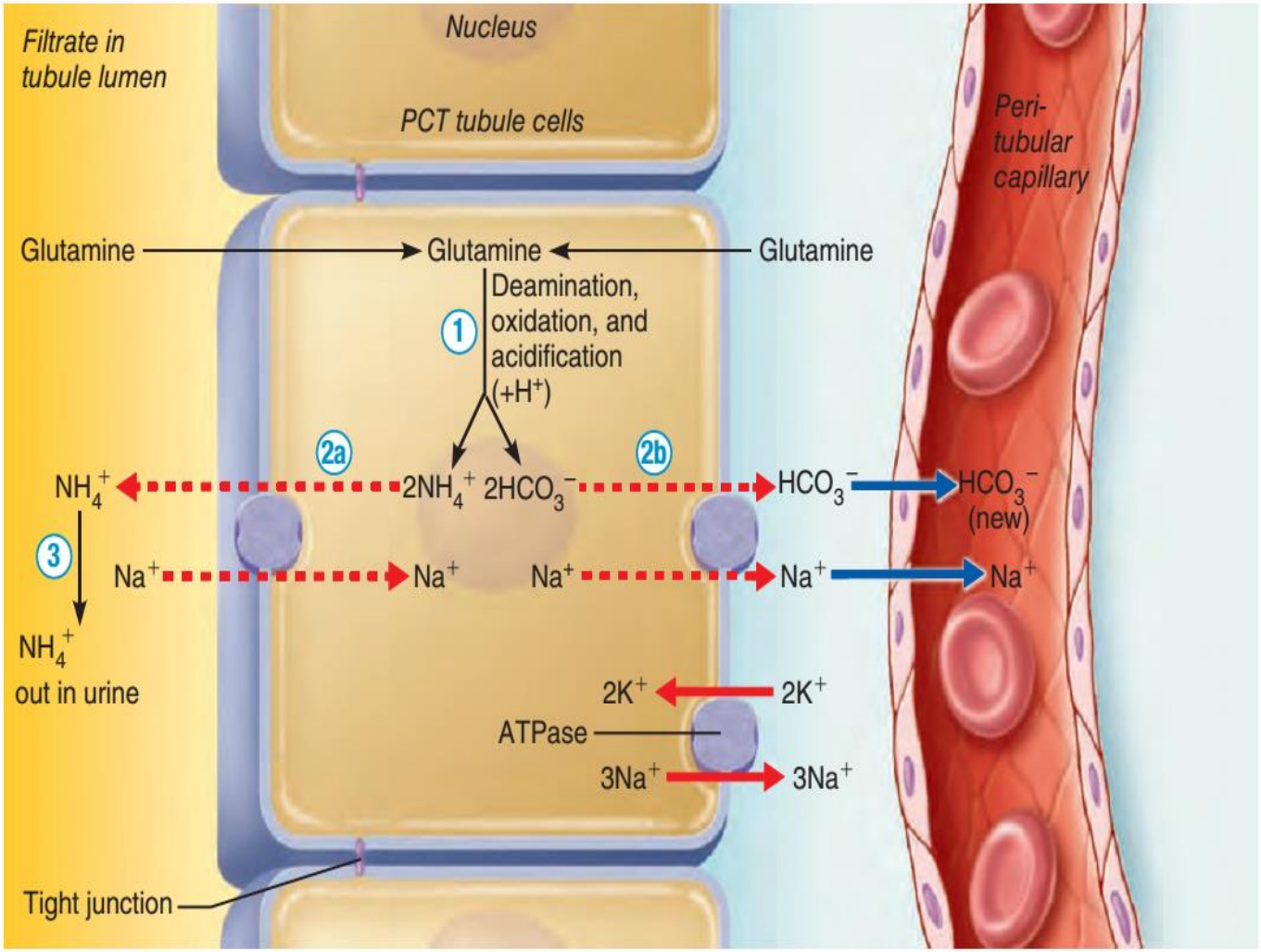
Occurs primarily in α-intercalated cells of late Distal tubule & collecting duct

Primary active transport
Secondary active transport
Simple diffusion
Facilitated diffusion
Transport protein
Ion channel
CA Carbonic anhydrase

Generation of new HCO_3^- via excretion of buffered H+

Mechanism for excretion of H^+ as titratable acid.





1 PCT cells metabolize glutamine to NH_4^+ and HCO_3^-.

2a This weak acid NH_4^+ (ammonium) is secreted into the filtrate, taking the place of H^+ on a Na^+-H^+ antiport carrier.

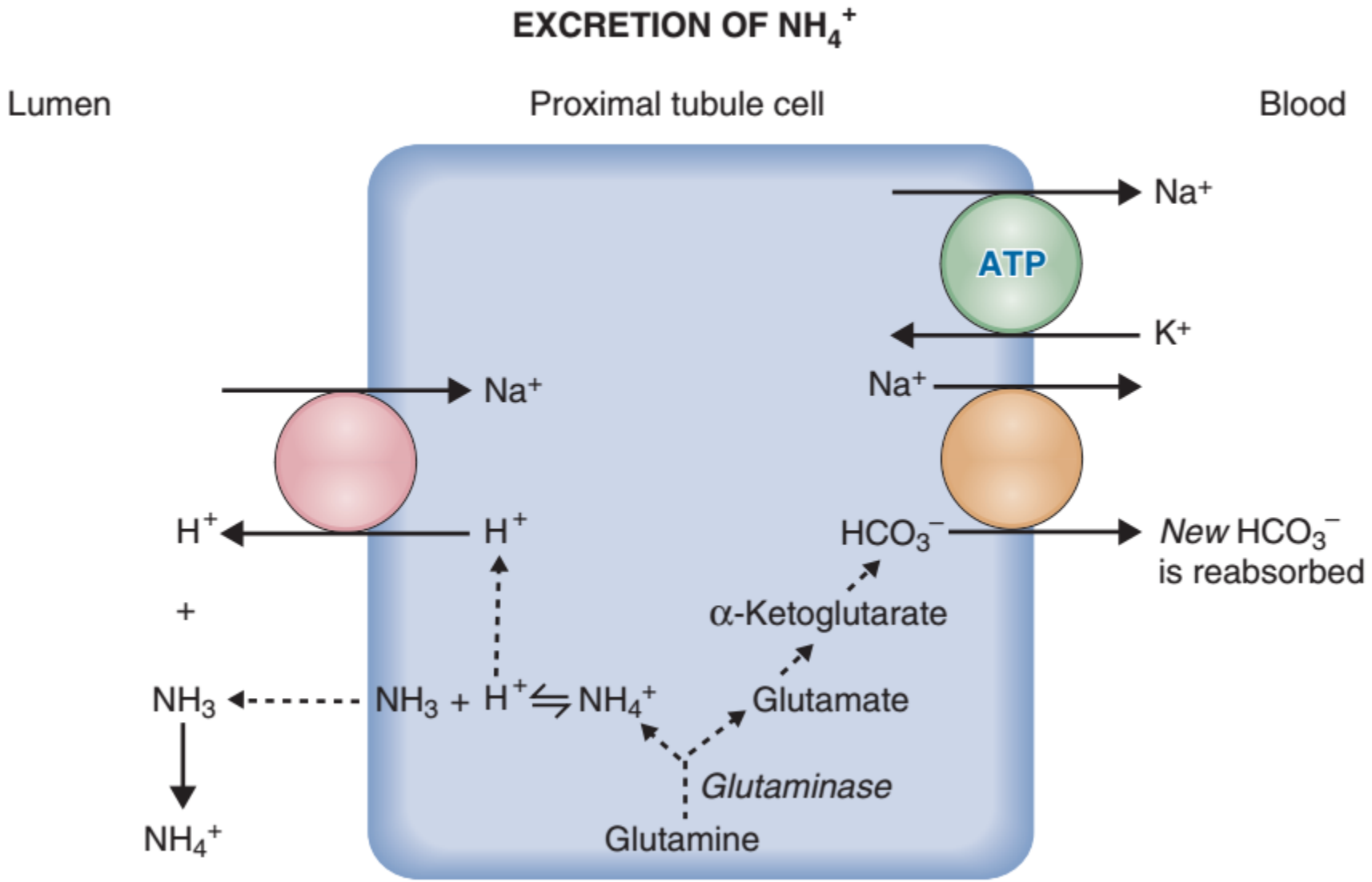
2b For each NH_4^+ secreted, a bicarbonate ion (HCO_3^-) enters the peritubular capillary blood via a symport carrier.

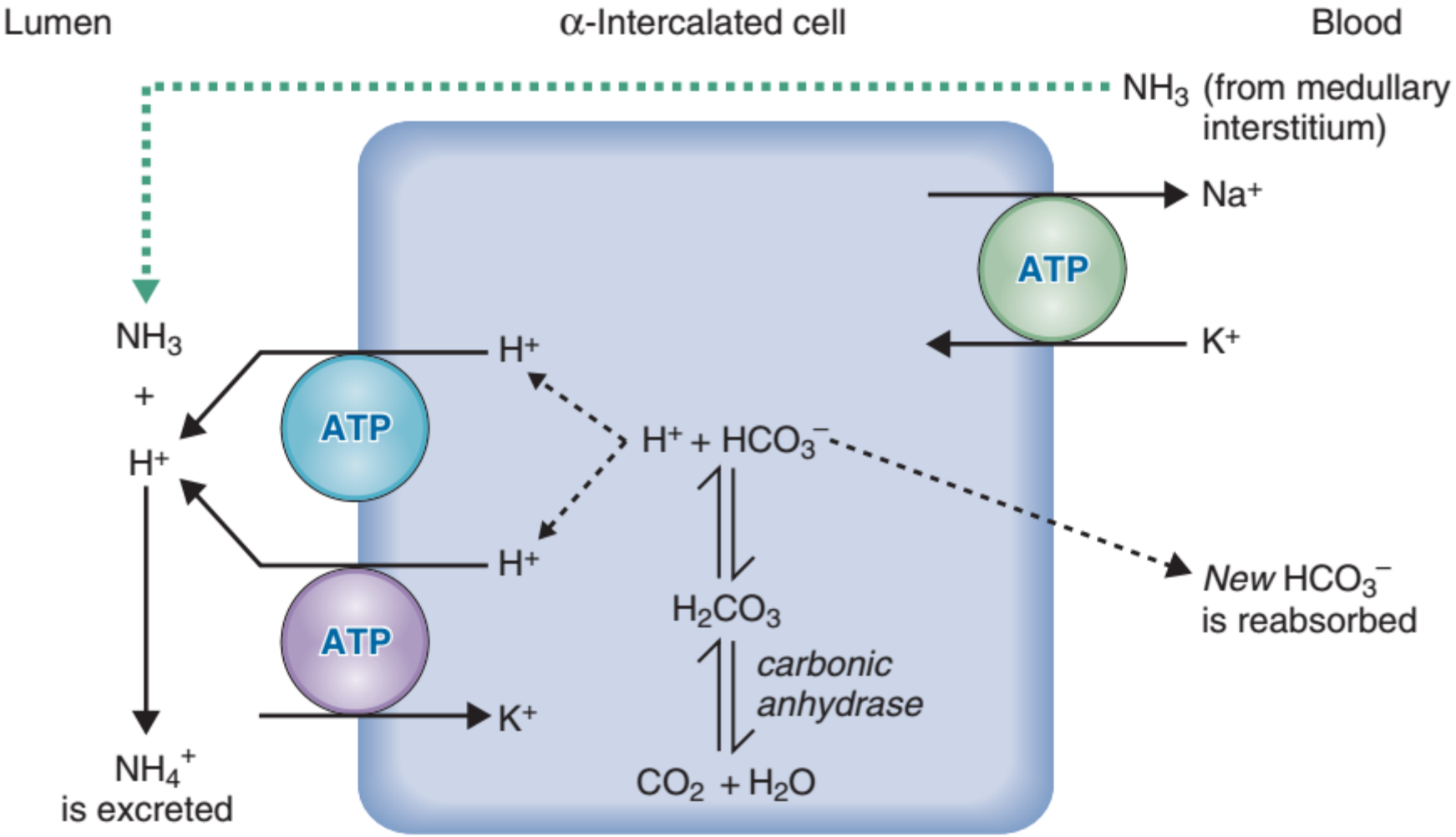
3 The NH_4^+ is excreted in the urine.

Primary active transport
Secondary active transport
Simple diffusion
Transport protein

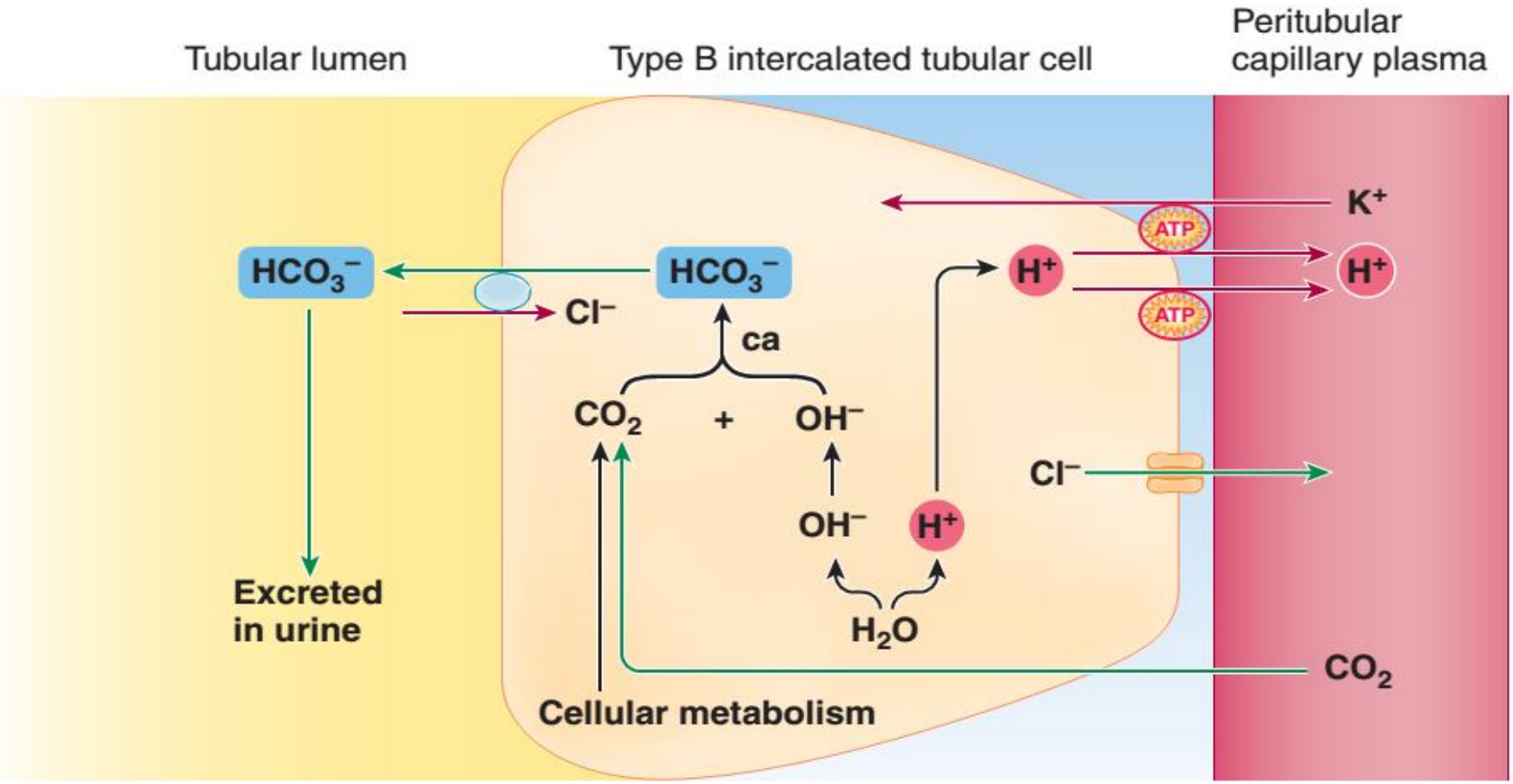
Generation of new HCO_3^- via NH4+ excretion

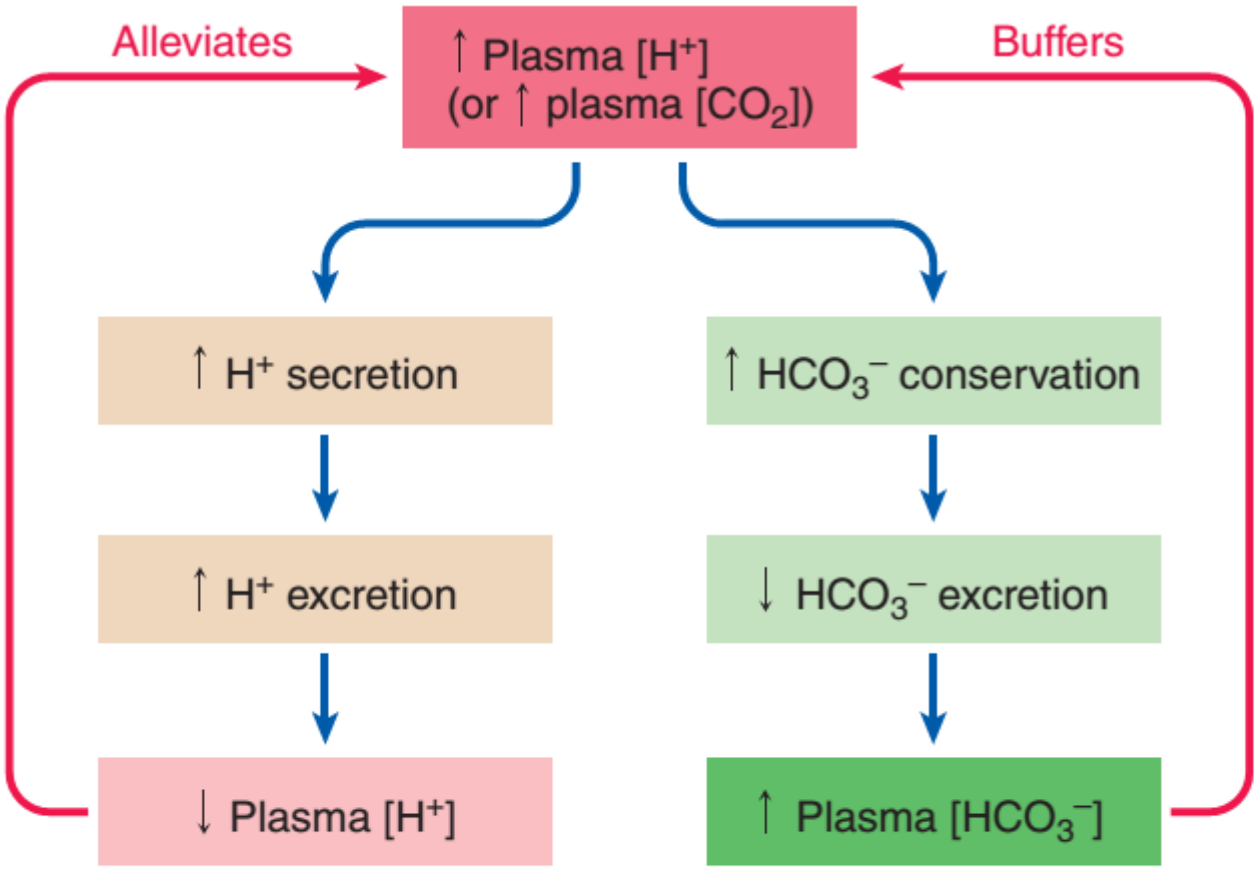
New HCO_3^- is generated via glutamine metabolism and NH_4^+ secretion.

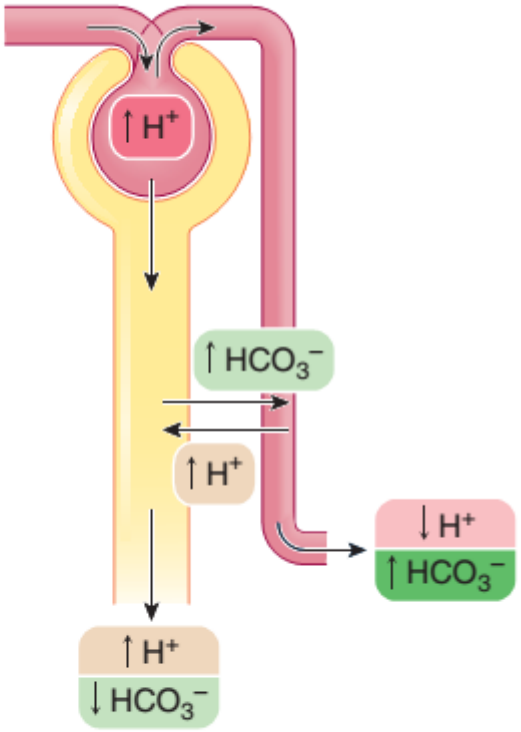

EXCRETION OF NH_4^+
Lumen
Proximal tubule cell
Blood
Na^+
ATP
K^+
Na^+
Na^+
H^+
H^+
HCO_3^-
New HCO_3^- is reabsorbed
+
α-Ketoglutarate
NH_3
$NH_3 + H^+ \rightleftharpoons NH_4^+$
Glutamate
Glutaminase
NH_4^+
Glutamine


Lumen
α-Intercalated cell
Blood
NH3 (from medullary interstitium)
Na+
ATP
K+
NH3
+
H+
ATP
H+
H+ + HCO3−
H+
New HCO3− is reabsorbed
H2CO3
ATP
carbonic anhydrase
K+
NH4+ is excreted
CO2 + H2O

bicarbonate secretion & H^+ ion reabsorption in distal tubule







- **Control of the rate of tubular H^+ secretion and HCO_3^- reabsorption.**

Causes of acid–base disorders

Metabolic acidosis	Respiratory acidosis	Metabolic alkalosis	Respiratory alkalosis
Diabetes mellitus (ketoacidosis)	Chronic obstructive airways disease	Vomiting (loss of hydrogen ion)	Hyperventilation (anxiety, fever)
Lactic acidosis (lactic acid)	Severe asthma	Nasogastric suction (loss of hydrogen ion)	Lung diseases associated with hyperventilation
Renal failure (inorganic acids)	Cardiac arrest	Hypokalemia	Anemia
Severe diarrhea (loss of bicarbonate)	Depression of respiratory center (drugs, e.g. opiates)	Intravenous administration of bicarbonate (e.g. after cardiac arrest)	Salicylate poisoning
Surgical drainage of intestine (loss of bicarbonate)	Failure of respiratory muscles (e.g. poliomyelitis, multiple sclerosis)		
Renal loss of bicarbonate (renal tubular acidosis type 2 – rare)	Chest deformities		
Renal tubular acidosis – rare)	Airway obstruction		

Respiratory acidosis *is common and is caused primarily by diseases of the lung that affect gas exchange.* ***Respiratory alkalosis*** *is rarer and is caused by hyperventilation, which decreases* pCO_2. ***Metabolic acidosis*** *is common and results from either overproduction or retention of nonvolatile acids in the circulation.* ***Metabolic alkalosis*** *is rarer: its most common causes are vomiting and gastric suction, both causing loss of hydrogen ion from the stomach.*

Causes and Consequences of Acid-Base Imbalances

CONDITION AND HALLMARK	POSSIBLE CAUSES; COMMENTS
Respiratory Acidosis (Hypoventilation)	
If uncompensated (uncorrected): P_{CO_2} >45 mm Hg; pH <7.35	**Impaired lung function** (e.g., chronic bronchitis, cystic fibrosis, emphysema): impaired gas exchange or alveolar ventilation
	Impaired ventilatory movement: paralyzed respiratory muscles, chest injury, extreme obesity
	Narcotic or barbiturate overdose or injury to brain stem: depression of respiratory centers, resulting in hypoventilation and respiratory arrest
Respiratory Alkalosis (Hyperventilation)	
If uncompensated: P_{CO_2} <35 mm Hg; pH >7.45	**Strong emotions:** pain, anxiety, fear, panic attack
	Hypoxemia: asthma, pneumonia, high altitude; represents effort to raise P_{O_2} at the expense of excessive CO_2 excretion
	Brain tumor or injury: abnormal respiratory controls

When respiratory function is normal, the PCO2 fluctuates between 35 and 45 mm Hg.

Causes and Consequences of Acid-Base Imbalances

CONDITION AND HALLMARK	POSSIBLE CAUSES; COMMENTS
Metabolic Acidosis	
If uncompensated: HCO_3^- <22 mEq/L; pH <7.35	**Severe diarrhea:** bicarbonate-rich intestinal (and pancreatic) secretions rushed through digestive tract before their solutes can be reabsorbed; bicarbonate ions are replaced by renal mechanisms that generate new bicarbonate ions
	Renal disease: failure of kidneys to rid body of acids formed by normal metabolic processes
	Untreated diabetes mellitus: lack of insulin or inability of tissue cells to respond to insulin, resulting in inability to use glucose; fats are used as primary energy fuel, and ketoacidosis occurs
	Starvation: lack of dietary nutrients for cellular fuels; body proteins and fat reserves are used for energy—both yield acidic metabolites as they are broken down for energy
	Excess alcohol ingestion: results in excess acids in blood

Bicarbonate ion levels below or above the normal range of 22–26 mEq/L indicate a metabolic acid-base imbalance.

The second most common cause of acid-base imbalance, metabolic acidosis, is recognized by low blood pH and $HCO3^-$ levels.

Causes and Consequences of Acid-Base Imbalances

CONDITION AND HALLMARK	POSSIBLE CAUSES; COMMENTS
Metabolic Alkalosis	
If uncompensated: HCO_3^- >26 mEq/L; pH >7.45	**Vomiting or gastric suctioning:** loss of stomach HCl requires that H^+ be withdrawn from blood to replace stomach acid; thus H^+ decreases and HCO_3^- increases proportionately **Selected diuretics:** cause K^+ depletion and H_2O loss. Low K^+ directly stimulates tubule cells to secrete H^+. Reduced blood volume elicits the renin-angiotensin-aldosterone mechanism, which stimulates Na^+ reabsorption and H^+ secretion. **Ingestion of excessive sodium bicarbonate (antacid):** bicarbonate moves easily into ECF, where it enhances natural alkaline reserve **Excess aldosterone** (e.g., adrenal tumors): promotes excessive reabsorption of Na^+, which pulls increased amount of H^+ into urine. Hypovolemia promotes the same relative effect because aldosterone secretion is increased to enhance Na^+ (and H_2O) reabsorption.

Respiratory and metabolic compensation in the acid–base disorders

Acid–base disorder	Primary change	Compensatory change	Timescale of compensatory change
Metabolic acidosis	↓ plasma bicarbonate	↓ pCO_2 (hyperventilation)	Minutes/hours
Metabolic alkalosis	↑ plasma bicarbonate	↑ pCO_2 (hypoventilation)	Minutes/hours
Respiratory acidosis	↑ pCO_2	↑ renal bicarbonate generation: ↑ plasma bicarbonate	Days
Respiratory alkalosis	↓ pCO_2	↓ renal bicarbonate reabsorption: ↓ plasma bicarbonate	Days

Respiratory and metabolic compensation in the acid–base disorders minimizes changes in the blood pH. A change in the respiratory component leads to metabolic compensation, and a change in the metabolic component stimulates respiratory compensation.

Summary of Acid-Base Disorders

Disorder	$CO_2 + H_2O$	↔	H^+	+	HCO_3^-	Respiratory Compensation	Renal Compensation or Correction
Metabolic Acidosis	↓		↑		**↓**	Hyperventilation	↑ HCO_3^- reabsorption (correction)
Metabolic Alkalosis	↑		↓		**↑**	Hypoventilation	↑ HCO_3^- excretion (correction)
Respiratory Acidosis	**↑**		↑		↑	None	↑ HCO_3^- reabsorption (compensation)
Respiratory Alkalosis	**↓**		↓		↓	None	↓ HCO_3^- reabsorption (compensation)

Bold arrows indicate initial disturbance.

Causes of Metabolic Acidosis

Cause	Examples	Comments
Excessive production or ingestion of fixed H^+	Diabetic ketoacidosis	Accumulation of β-OH butyric acid and acetoacetic acid ↑ Anion gap
	Lactic acidosis	Accumulation of lactic acid during hypoxia ↑ Anion gap
	Salicylate poisoning	Also causes respiratory alkalosis ↑ Anion gap
	Methanol/formaldehyde poisoning	Converted to formic acid ↑ Anion gap ↑ Osmolar gap
	Ethylene glycol poisoning	Converted to glycolic and oxalic acids ↑ Anion gap ↑ Osmolar gap
Loss of HCO_3^-	Diarrhea	Gastrointestinal loss of HCO_3^- Normal anion gap Hyperchloremia
	Type 2 renal tubular acidosis (type 2 RTA)	Renal loss of HCO_3^- (failure to reabsorb filtered HCO_3^-) Normal anion gap Hyperchloremia
Inability to excrete fixed H^+	Chronic renal failure	↓ Excretion of H^+ as NH_4^+ ↑ Anion gap
	Type 1 renal tubular acidosis (type 1 RTA)	↓ Excretion of H^+ as titratable acid and NH_4^+ ↓ Ability to acidify urine Normal anion gap
	Type 4 renal tubular acidosis (type 4 RTA)	Hypoaldosteronism ↓ Excretion of NH_4^+ Hyperkalemia inhibits NH_3 synthesis Normal anion gap

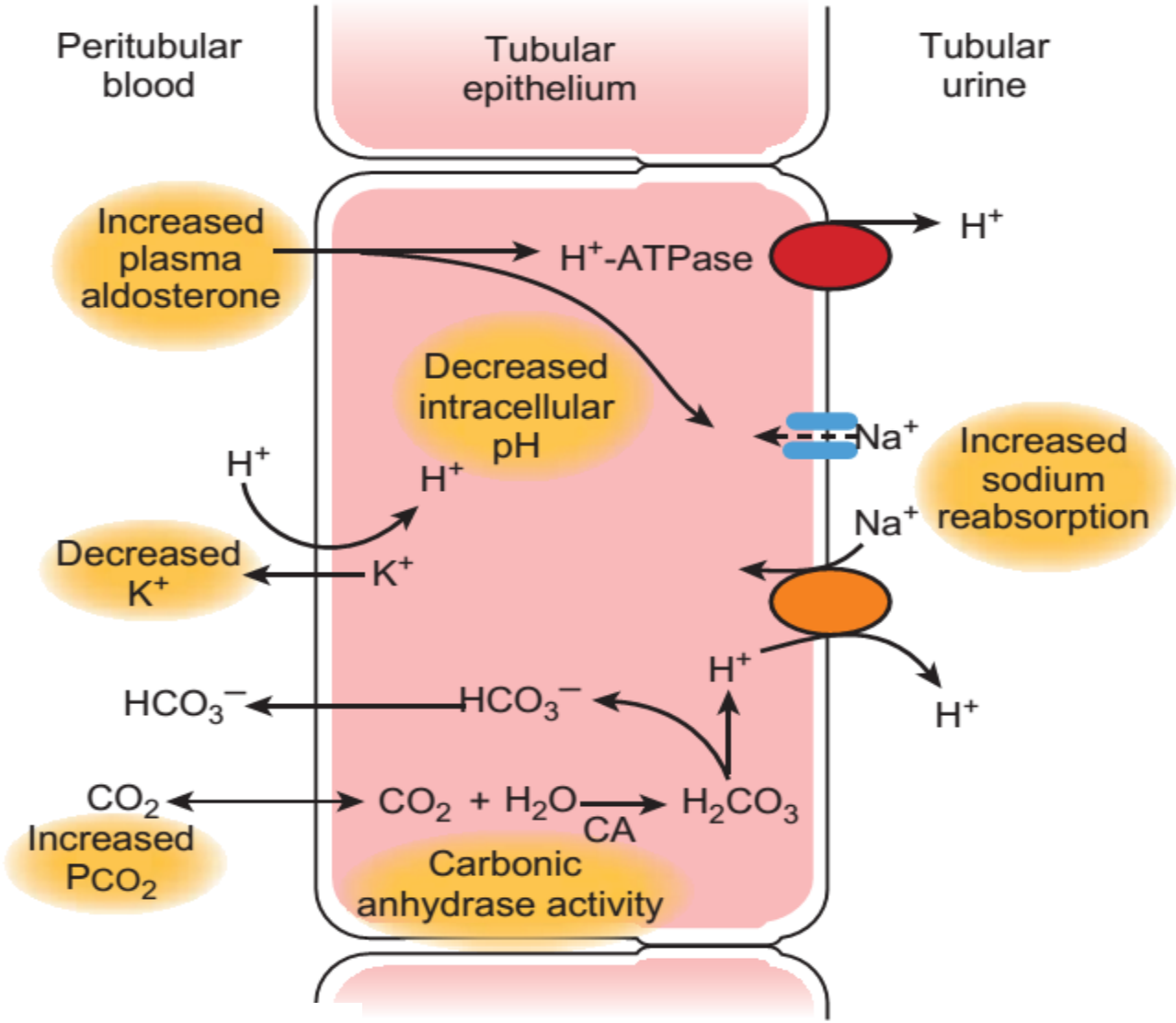
Causes of Metabolic Alkalosis

Cause	Examples	Comments
Loss of H^+	Vomiting	Loss of gastric H^+ HCO_3^- remains in the blood Maintained by volume contraction Hypokalemia
	Hyperaldosteronism	Increased H^+ secretion by intercalated cells Hypokalemia
Gain of HCO_3^-	Ingestion of $NaHCO_3$ Milk-alkali syndrome	Ingestion of large amounts of HCO_3^- in conjunction with renal failure
Volume contraction alkalosis	Loop or thiazide diuretics	↑ HCO_3^- reabsorption due to ↑ angiotensin II and aldosterone

Summary of Renal Responses to Acidosis and Alkalosis

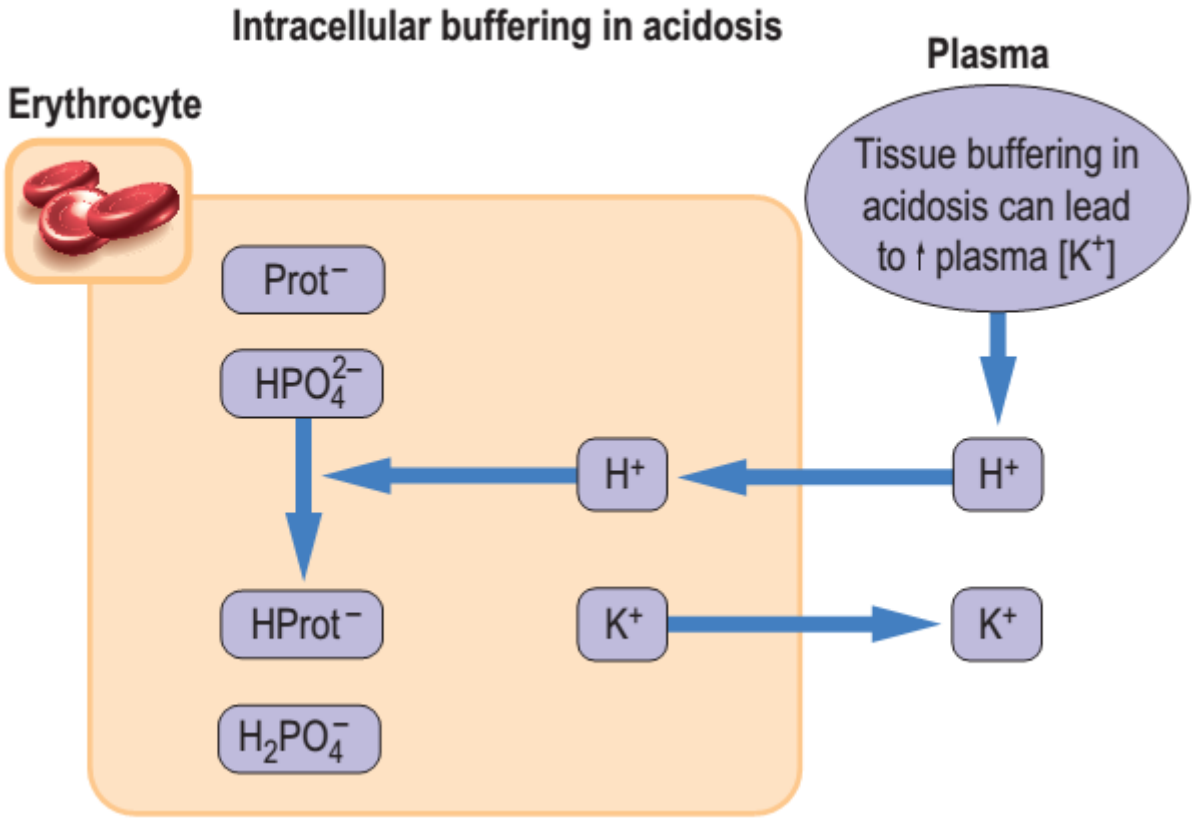
Acid–Base Abnormality	H^+ Secretion	H^+ Excretion	HCO_3^- Reabsorption and Addition of New HCO_3^- to Plasma	HCO_3^- Excretion	pH of Urine	Compensatory Change in Plasma pH
Acidosis	↑	↑	↑	Normal (zero; all filtered is reabsorbed)	Acidic	Alkalinization toward normal
Alkalosis	↓	↓	↓	↑	Alkaline	Acidification toward normal

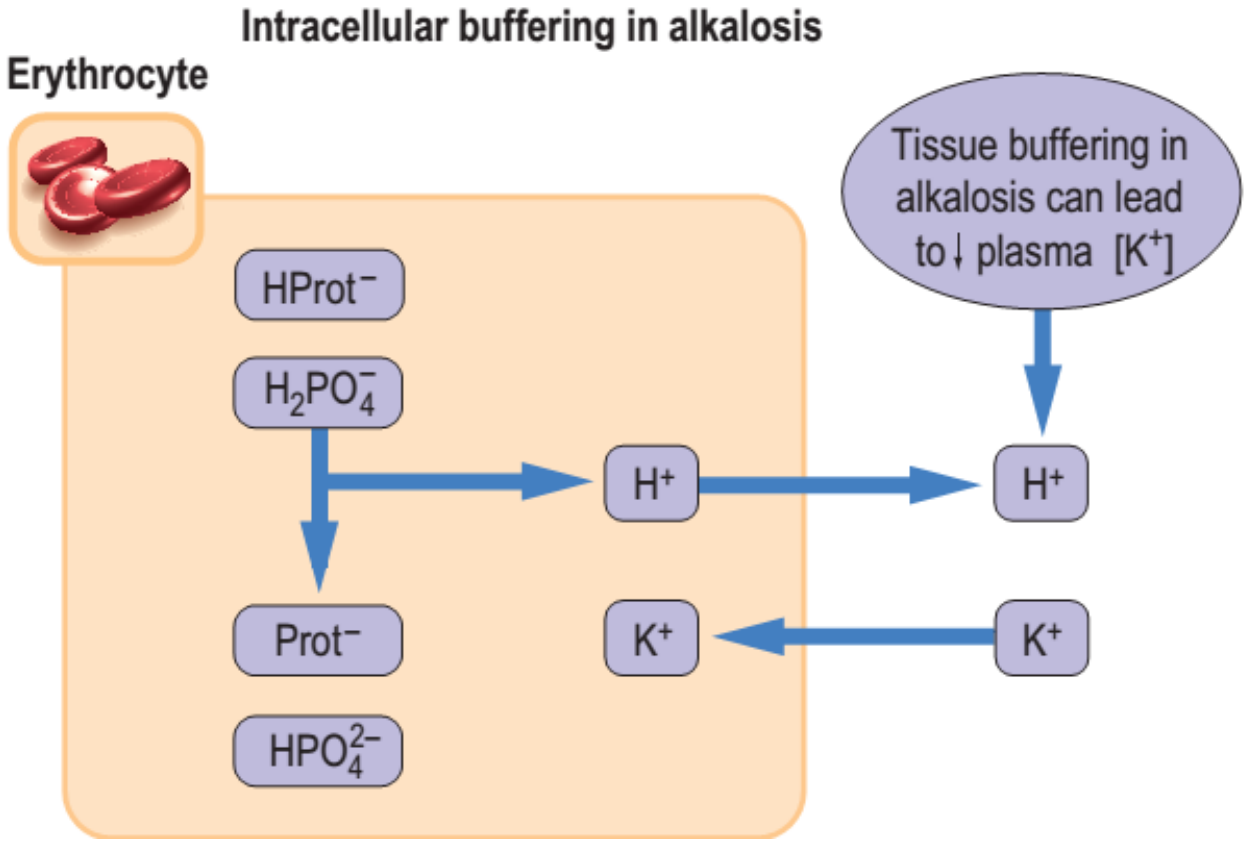
Factors influencing increased H^+ secretion by kidney tubule epithelium



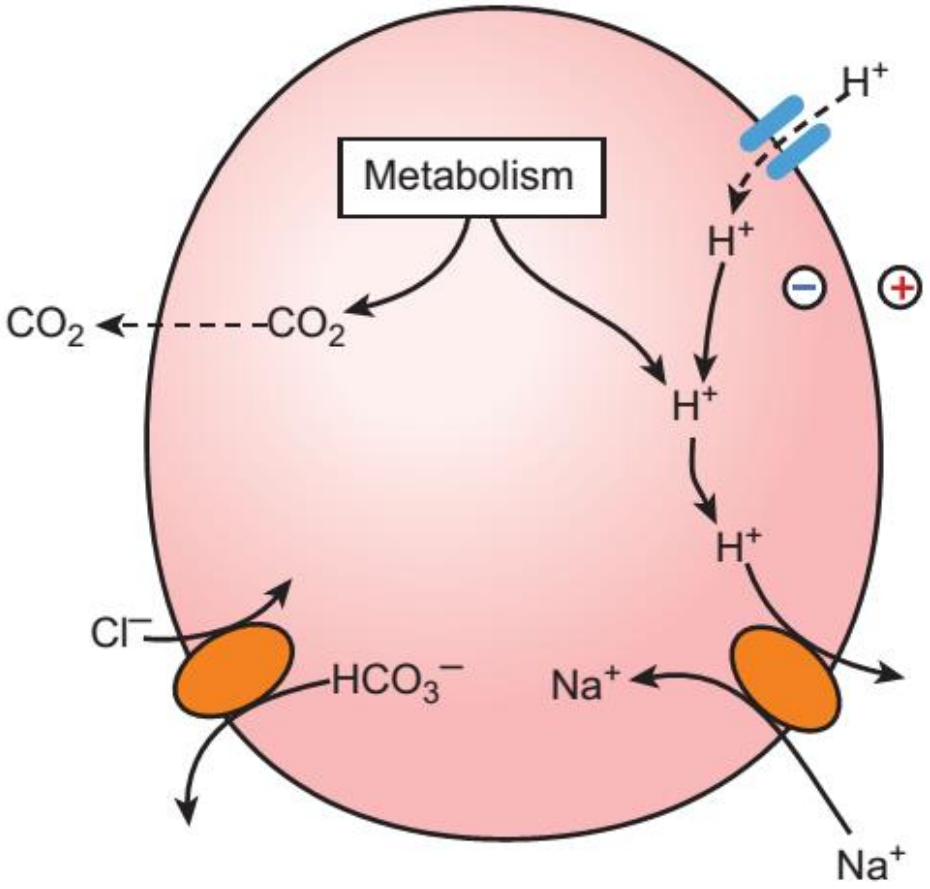
Factors leading to increased H^+ secretion by the kidney tubule epithelium. CA, carbonic anhydrase.

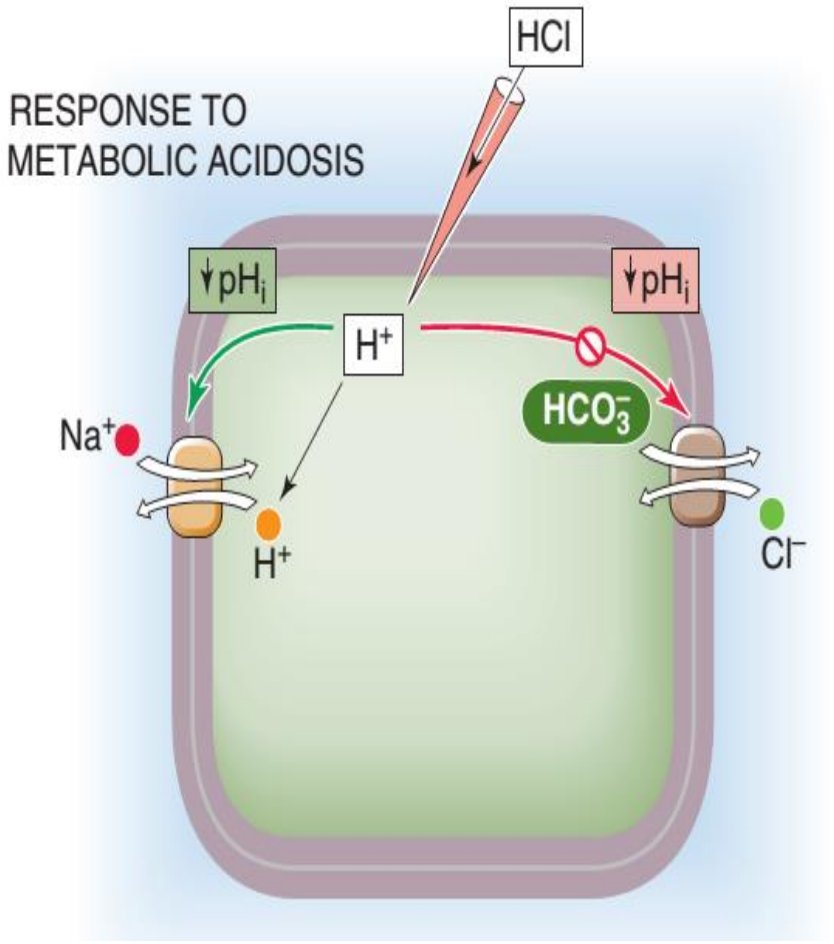
Intracellular pH regulation

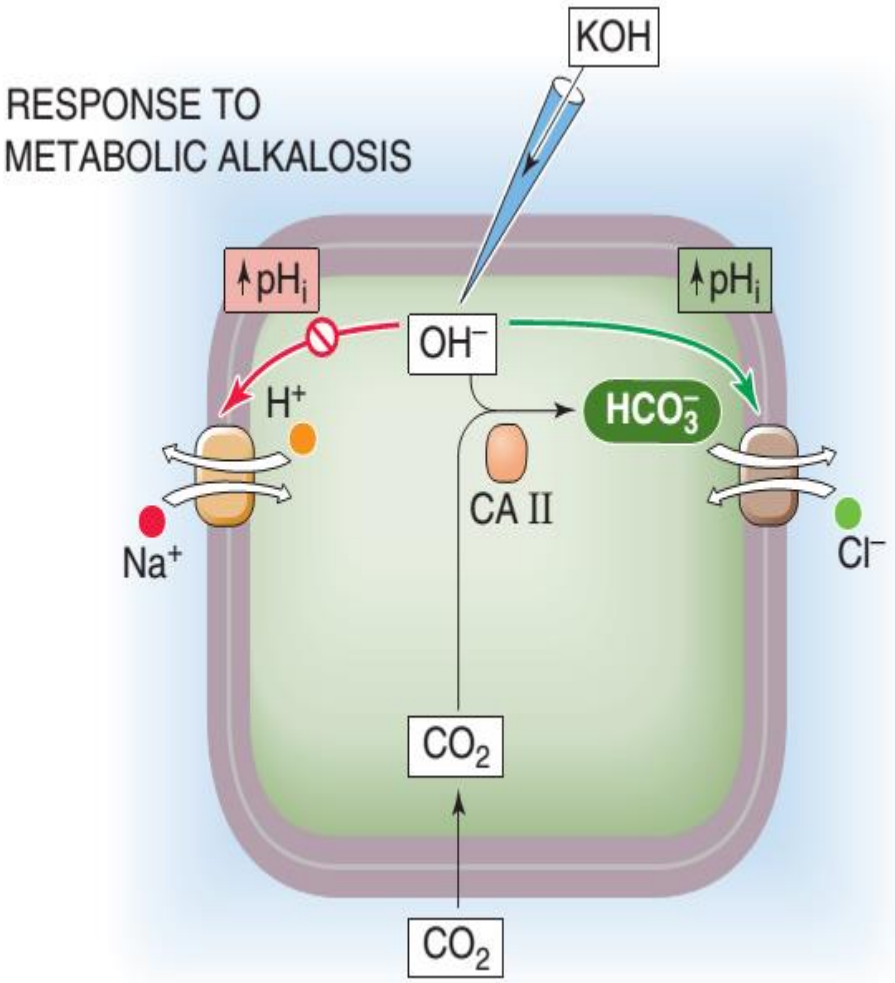

Intracellular buffering in acidosis
Erythrocyte
Plasma
Tissue buffering in acidosis can lead to ↑ plasma [K+]
Prot−
HPO4 2−
H+
H+
HProt−
K+
K+
H2PO4−


Intracellular buffering in alkalosis
Erythrocyte
Tissue buffering in alkalosis can lead to ↓ plasma [K+]
HProt−
H2PO4−
H+
H+
Prot−
K+
K+
HPO4 2−

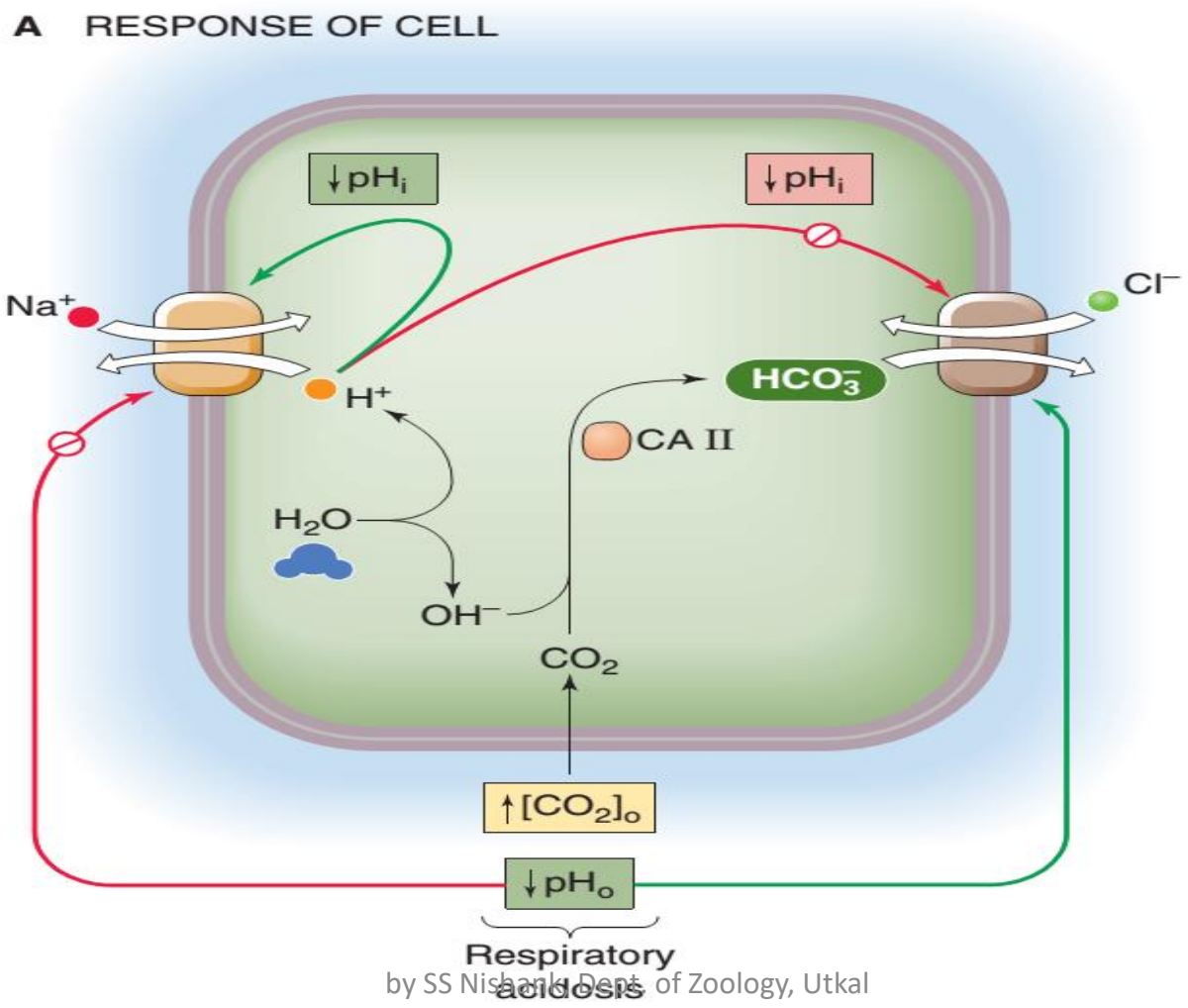
Intra cellular acid-base balance




RESPONSE TO
METABOLIC ACIDOSIS
HCl
↓pH$_i$
↓pH$_i$
H$^+$
HCO$_3^-$
Na$^+$
H$^+$
Cl$^-$


RESPONSE TO
METABOLIC ALKALOSIS
KOH
↑pH$_i$
↑pH$_i$
OH$^-$
H$^+$
HCO$_3^-$
CA II
Na$^+$
Cl$^-$
CO$_2$
CO$_2$

Response of cell to respiratory acidosis



Respiratory & renal compensation

	Normal Range in Plasma		
Acid-Base Disturbance	**pH 7.35–7.45**	**P_{CO_2} 35–45 mm Hg**	**HCO_3^- 22–26 mEq/L**
Respiratory acidosis	↓	↑	↑ if compensating
Respiratory alkalosis	↑	↓	↓ if compensating
Metabolic acidosis	↓	↓ if compensating	↓
Metabolic alkalosis	↑	↑ if compensating	↑