YU - Medicine Passion Academic Team

The Urogenital System

Sheet# 6 - Physiology

Lec. Title : Acid Base Balance

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table 5.7 Summary of Hormones That Act on the Kidney

Hormone	Stimulus for Secretion	Time Course	Mechanism of Action	Actions on the Kidneys
PTH	↓ plasma [Ca^{2+}]	Fast	Basolateral receptor Adenylate cyclase cAMP→urine	↓ Phosphate reabsorption (proximal tubule) ↑ Ca^{2+} reabsorption (distal tubule) Stimulates 1α-hydroxylase (proximal tubule)
ADH	↑ plasma osmolarity ↓ blood volume	Fast	Basolateral V_2 receptor Adenylate cyclase cAMP (Note: V_1 receptors are on blood vessels; mechanism is Ca^{2+}–IP_3)	↑ H_2O permeability (late distal tubule and collecting duct principal cells)
Aldosterone	↓ blood volume (via renin–angiotensin II) ↑ plasma [K^+]	Slow	New protein synthesis	↑ Na^+ reabsorption (ENaC, distal tubule principal cells) ↑ K^+ secretion (distal tubule principal cells) ↑ H^+ secretion (distal tubule α-intercalated cells)
ANP	↑ atrial pressure	Fast	Guanylate cyclase cGMP	↑ GFR ↓ Na^+ reabsorption
Angiotensin II	↓ blood volume (via renin)	Fast		↑ Na^+–H^+ exchange and HCO_3^- reabsorption (proximal tubule)

ADH = antidiuretic hormone; ANP = atrial natriuretic peptide; cAMP = cyclic adenosine monophosphate; cGMP = cyclic guanosine monophosphate; GFR = glomerular filtration rate; PTH = parathyroid hormone; EnaC = epithelial Na^+ channel.

Acid-base balance

بنعتذر عن التأخير ، المحاضرة طويلة وهي عبارة عن تشابتر كامل بالكتاب لهيك فرغنا كلام الدكتورة فقط

رابط الكتاب :

https://drive.google.com/file/d/1hEIQEnk8b_ZNqsHtybavkwCNMJL2prZr/view?usp=drivesdk

رقم التشابتر بالكتاب 7، بيبدأ من صفحة 311

دعواتكم لأهلنا في فلسطين، كل الحُبّ...

pH of body fluids

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

- The **normal range of arterial pH is 7.37–7.42.**
- When arterial pH is less than 7.37, it is called **acidemia.**
- When arterial pH is greater than 7.42, it is called **alkalemia.**
- The pH range compatible with life is 6.8–8.0.

pH of body fluids

- **Intracellular** pH is approximately 7.2.
- Transporters in cell membranes regulate intracellular pH:

1. **Na^+-H^+ exchangers** extrude H^+ from cells, which tends to alkalinize intracellular fluid (ICF).
2. **Cl^--$HCO3^-$ exchangers** extrude $HCO3^-$ from cells, which tends to acidify ICF.

pH of body fluids

- The mechanisms that contribute to maintaining pH in the normal range include:
  1. buffering of H^+ in both ECF and ICF, fast
  2. respiratory compensation, fast
  3. Renal compensation, slow , needs hours To dayd

- The mechanisms for buffering and respiratory compensation occur rapidly, within minutes to hours.
- The mechanisms for renal compensation are slower, requiring hours to days.

Acid production in the body

- Two types of acid are produced in the body:

1. Volatile
2. Nonvolatile

1. Volatile acid

- Is CO_2
- Is produced from the aerobic metabolism of cells.
- CO_2 combines with H_2O to form weak acid H_2CO_3, which dissociates into H^+ and $HCO3^-$ by the following reactions:

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

- Carbonic anhydrase, which is present in most cells, catalyzes the reversible reaction between CO_2 and H_2O.

2. Nonvolatile acids

- Also called **fixed acids. They produced as a product of the protein and phospholibid catabolism a process**
- Include **sulfuric acid** (a product of protein catabolism) **and phosphoric acid** (a product of phospholipid catabolism).
- Are normally produced at a rate of **40 to 60 mmoles/day.**
- **Use acids are different from CO2 because they cannot be removed by expiration they need to be removed by the renal compensation**
- Other fixed acids that may be overproduced in disease or may be ingested include **ketoacids,** (β-hydroxybutyric acid and acetoacetic acid), **lactic acid, and salicylic acid.**

Buffers

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

- It prevents changes in pH when H^+ ions are added to or removed from a solution.

Using the Henderson-Hasselbalch equation to calculate pH

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

where:

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

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

$[A^-]$ = concentration of base form of buffer (mM)

$[HA]$ = concentration of acid form of buffer (mM)

- A^-, the base form of the buffer, is the H^+ acceptor.
- HA, the acid form of the buffer, is the H^+ donor.
- When the concentrations of A^- and HA are equal, the pH of the solution equals the pK of the buffer.
- pK is higher in weak acids and lower in strong acids
- pK must be between 6 To 8 or 6.4 to 7.1

Titration curves

- Are graphic representations of the Henderson-Hasselbalch equation.
  - They describe how the pH of a buffered solution changes as H^+ ions are added to it or removed from it.
- As H^+ ions are added to the solution, the HA form is produced; as H^+ ions are removed, the A^- form is produced.
- A buffer is **most effective within 1.0 pH unit of the pK of the buffer** (in the linear portion of the titration curve), where the addition or removal of H^+ causes little change in pH.

• According to the Henderson-Hasselbalch equation, when the pH of the solution equals the pK, the concentrations of HA and A^- are equal.

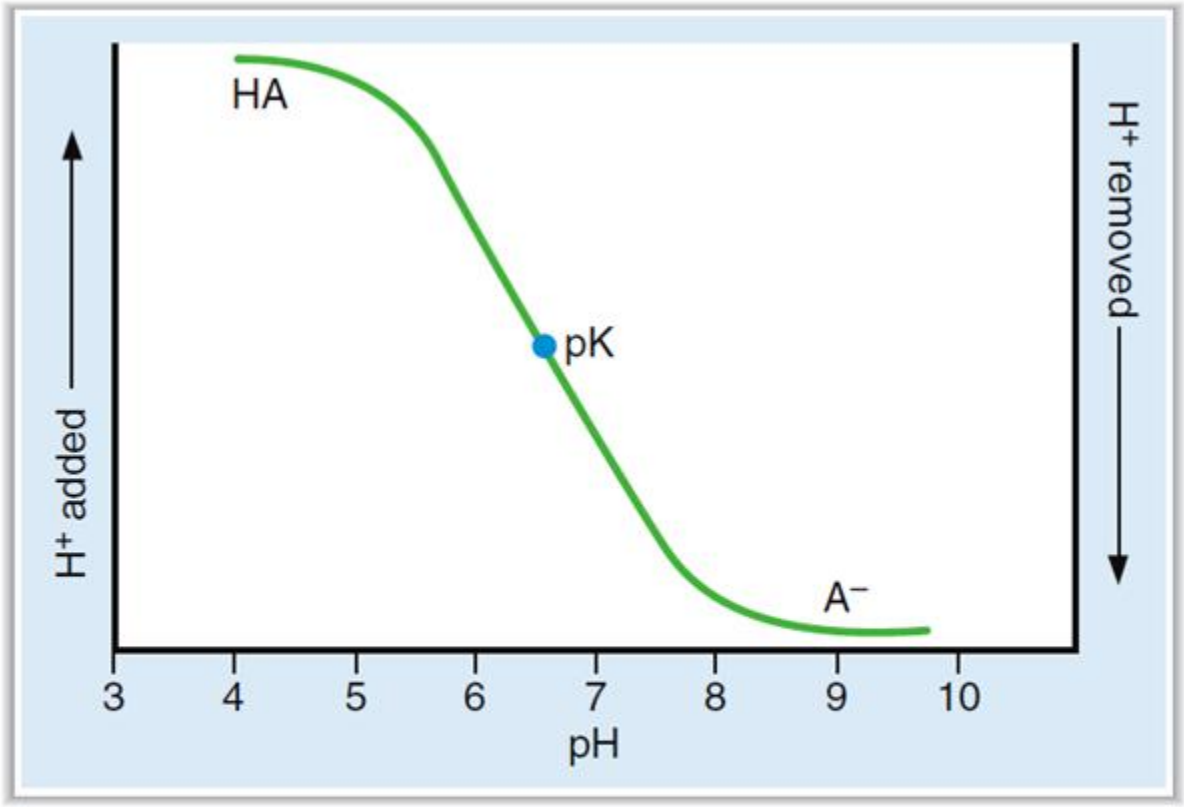


FIGURE 5.20 Titration curve for a weak acid (HA) and its conjugate base (A^-).

Extracellular buffers

- The major extracellular buffer is bicarbonate (**$HCO3^-$**) (**A^-**) which is produced from CO_2 (HA) and H_2O.
  - The **pK** of the CO_2/HCO_3^- buffer pair is 6.1.
  - When HCl is added to ECF, H+ combines with some of the HCO_3^- to form H_2CO_3. Thus a strong acid (HCl) is converted to a weak acid (H_2CO_3). H_2CO_3 then dissociates into CO_2 and H_2O, both of which are expired by the lungs.

Extracellular buffers

- **Phosphate** is a minor extracellular buffer.
  - The **pK** of the H_2PO4^-(HA)/HPO_4^{-2} (A^-)buffer pair is 6.8.
  - Phosphate is most important as a **urinary buffer;** excretion of H^+ as $H_2PO_4^-$ is called **titratable acid.**

Intracellular buffers

- الصوت ما كان واضح هون، شوفوا دقيقة 17:12

- **Organic phosphates**

(e.g., AMP, ADP, ATP, 2,3-diphosphoglycerate [DPG]).

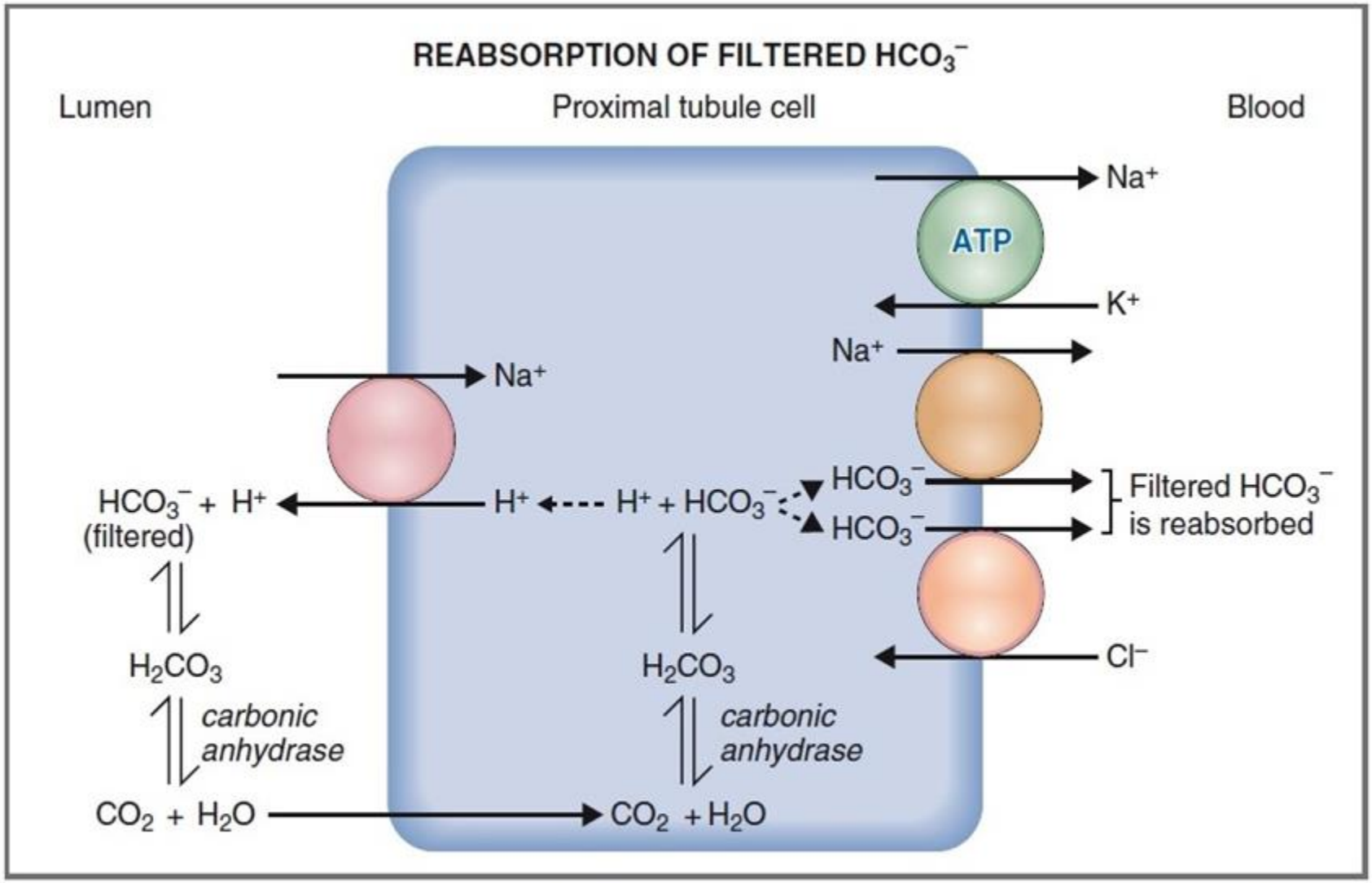
- **Proteins**
  - Imidazole and α-amino groups on proteins have pKs that are within the physiologic pH range.
  - **Hemoglobin** is a major intracellular buffer.
  - In the physiologic pH range, **deoxyhemoglobin is a better buffer than oxyhemoglobin.**

Intracellular buffers

- When buffering hydrogen ions using a proteins the calcium is significantly affected. Why? You too calcium homeostasis. She said to find out and check with her via email 
- Deoxyhemoglobin is better than oxyhemoglobin because oxy hemoglobin carries oxygen and it's BK is 6.7 while the oxyhemoglobin is 7.9. also, deoxyhemoglobin carries CO2 and helps in the production of bicarbonate buffer which is very important

Renal mechanisms in acid-base balance

1. Reabsorption of filtered HCO3- Read the book,page 318



Mechanism for reabsorption of filtered HCO_3^- in a cell of the proximal tubule.
ATP, Adenosine triphosphate.

Reabsorption of filtered HCO_3^-

- Occurs primarily in the **proximal tubule.**

1. H^+ and HCO_3^- are produced in the proximal tubule cells from CO_2 and H_2O.
2. CO_2 and H_2O combine to form H_2CO_3, catalyzed by **intracellular carbonic anhydrase**
3. H_2CO_3 dissociates into H^+ and HCO_3^-
4. H^+ is secreted into the lumen via the *Na^+-H^+ exchange mechanism* in the luminal membrane.
5. The $HCO3^-$ **is reabsorbed** (by Na+-$HCO3^-$ cotransport and Cl^--$HCO3^-$ exchange).

Reabsorption of filtered $HCO3^-$

6. In the lumen, the secreted H^+ combines with filtered HCO_3^- to form H_2CO_3, which dissociates into CO_2 and H_2O, catalyzed by **brush border carbonic anhydrase.** CO_2 and H_2O diffuse into the cell to start the cycle again.

- The process results in **net reabsorption of filtered Na^+ and HCO_3^-.** However, **it *does not result in* net secretion of H^+** → produces little change in tubular fluid pH.

Regulation of reabsorption of filtered $HCO3^-$

1) Filtered load

- Increases in the filtered load of HCO_3^- result in increased rates of HCO_3^- reabsorption.

- However, if the plasma HCO_3^- concentration becomes very high (e.g., metabolic alkalosis), the filtered load will exceed the reabsorptive capacity, and HCO_3^- will be excreted in the urine.

2) P_{CO2}

- **Increases in P_{CO2}** result in increased rates of HCO_3^- reabsorption because the supply of intracellular H^+ for secretion is increased.
  - This mechanism is the basis for the renal compensation for respiratory acidosis.

- **Decreases in P_{CO2}** result in decreased rates of HCO_3^- reabsorption because the supply of intracellular H^+ for secretion is decreased.
  - This mechanism is the basis for the renal compensation for respiratory alkalosis.

3) ECF volume

- HCO_3^- is a part of isosmotic reabsorption in the proximal tubule → changes in ECF volume alter isosmotic reabsorption via changes in the Starling forces in the peritubular capillaries.
  - ECF volume **expansion** results in decreased HCO_3^- reabsorption.
  - ECF volume **contraction** results in increased HCO_3^- reabsorption → *contraction alkalosis.*

4) Angiotensin II

- ↓ ECF volume → **Angiotensin II** stimulates Na^+-H^+ exchange in the proximal tubule → stimulates $HCO3^-$ reabsorption → increases the blood $HCO3^-$ concentration

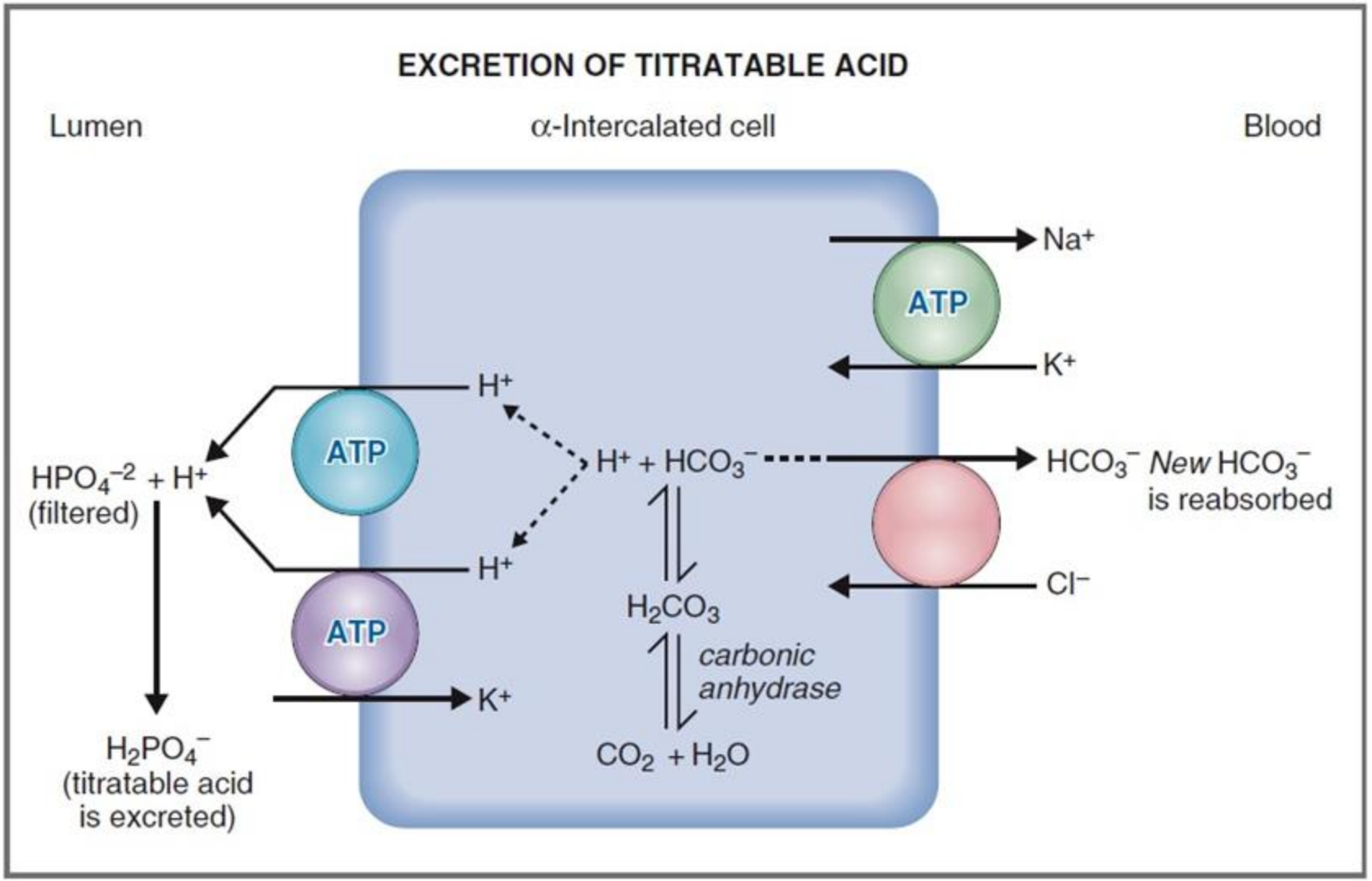
  ➢ contributes to the *contraction alkalosis* that occurs secondary to ECF volume contraction.

2. Excretion of fixed H^+

- Titratable acid is H^+ excreted with urinary buffers.

- Fixed H^+ produced from the catabolism of protein and phospholipid is excreted by two mechanisms, **titratable acid** and **NH_4^+**.

Excretion of H^+ as titratable acid (H2PO4-) Read the book, page 320



Mechanism for excretion of H^+ as titratable acid. *ATP,* Adenosine triphosphate.

Excretion of H^+ as titratable acid ($H_2PO_4^-$)

- H^+ and HCO_3^- are produced in the intercalated cells from CO_2 and H_2O.
- H^+ is secreted into the lumen by H^+-ATPase and H^+-K^+ ATPase , and the HCO_3^- is reabsorbed into the blood ("new" $HCO3^-$).
- In the urine, the secreted H^+ combines with filtered HPO_4^{-2} to form $H_2PO_4^-$, which is excreted as **titratable acid.**

  The H^+-ATPase is stimulated by **aldosterone.**

Excretion of H^+ as titratable acid ($H_2PO_4^-$)

- This process results in **net secretion of H^+ and net reabsorption of newly synthesized HCO_3^-.**

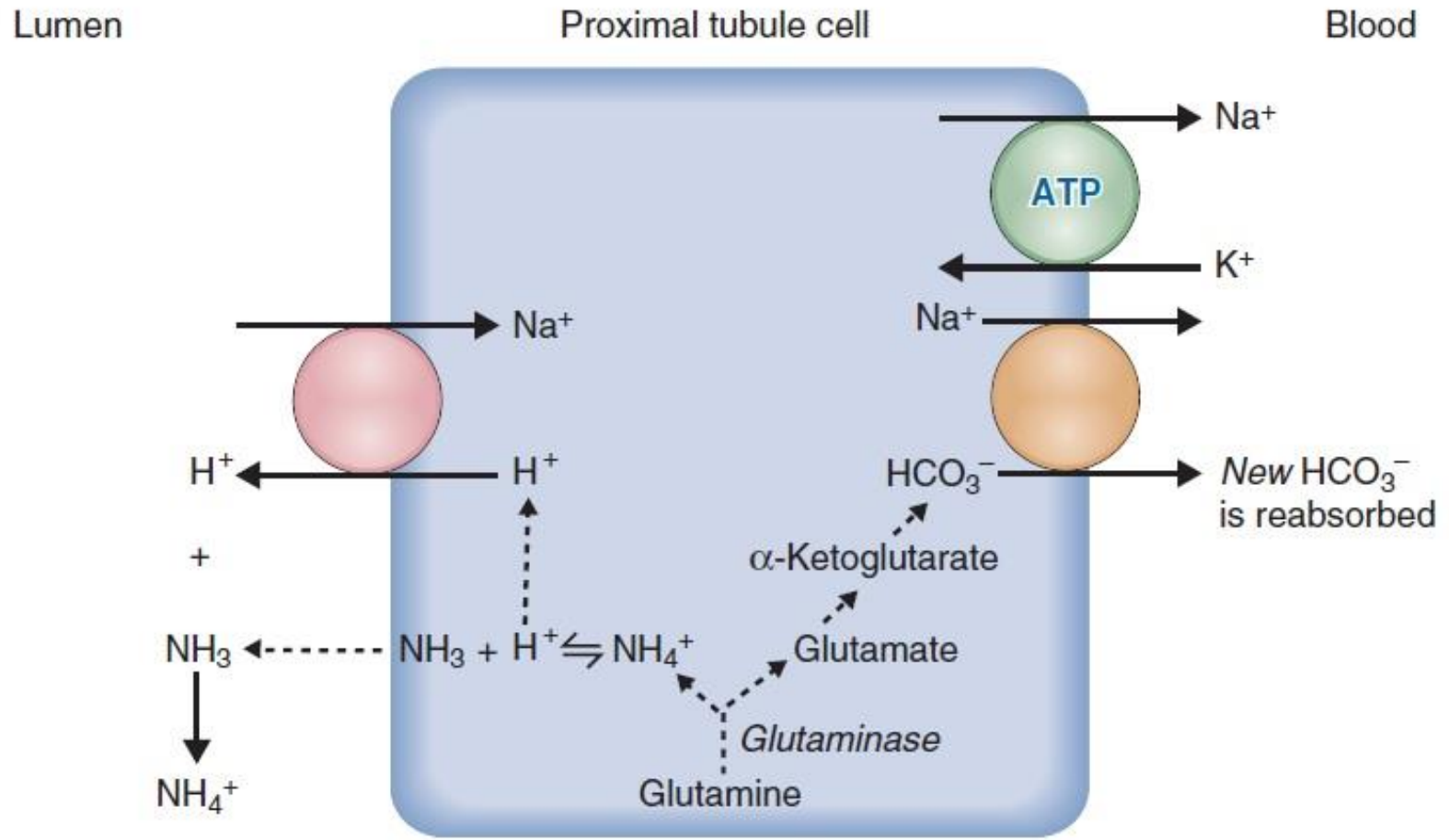
- As a result of H^+ secretion, the pH of urine becomes progressively lower. **The minimum urinary pH is 4.4.**

- The amount of H^+ excreted as titratable is determined by the **amount of urinary buffer** (usually HPO_4^{-2}) **and the pK of the buffer.**

Excretion of H^+ as NH_4^+

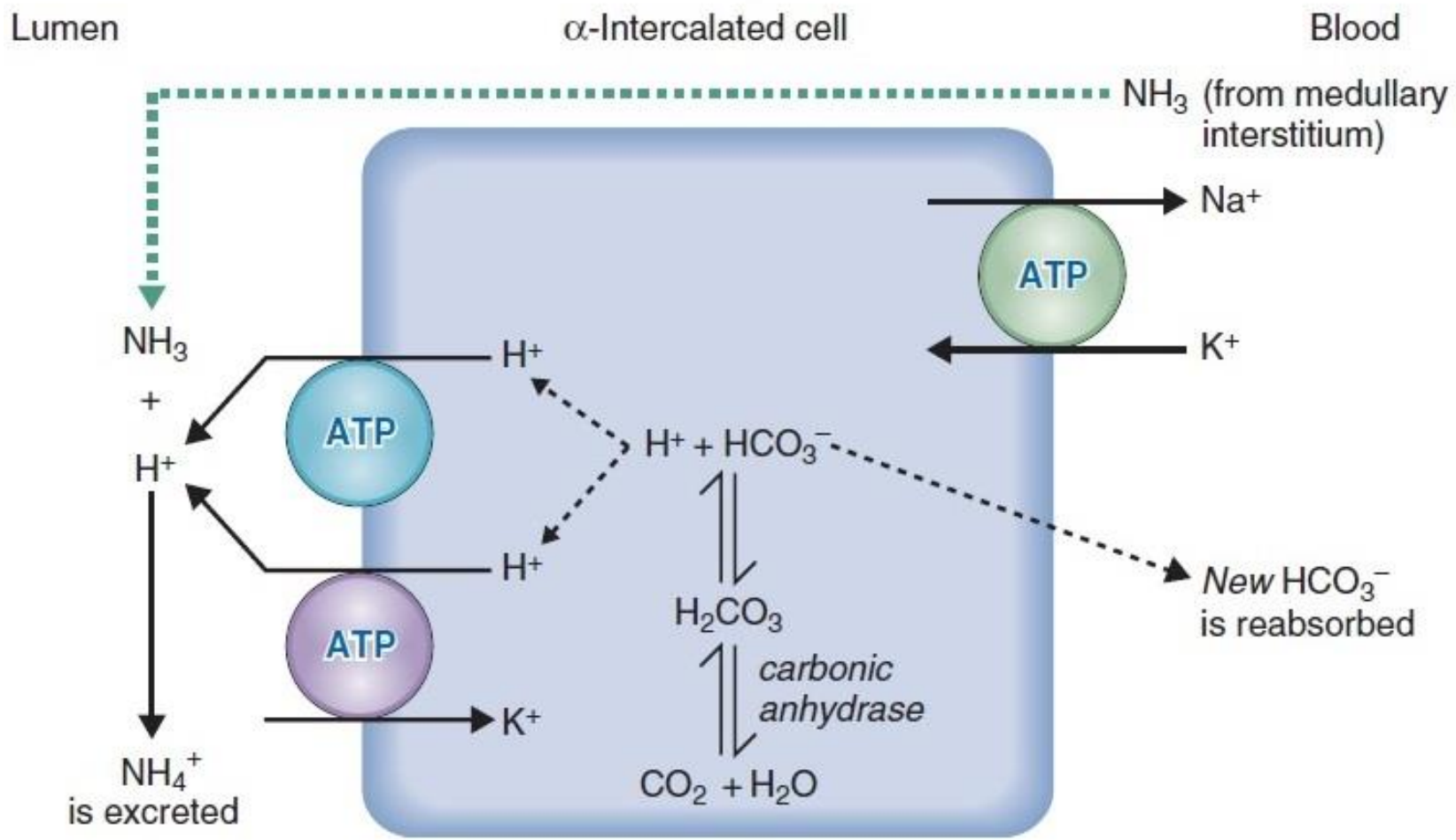
Read the book, page 322

I)



Excretion of H^+ as NH_4^+

2)



Excretion of H^+ as NH_4^+

1. **In the proximal tubule,** NH_3 is produced in renal cells from glutamine. It then diffuses down its concentration gradient from the cells into the lumen. It combines with $H^+ \rightarrow NH_4^+$ is produced.

2. **In the thick ascending limb** of the loop of Henle, NH_4^+ is reabsorbed by Na^+-K^+-$2Cl^-$ cotransporter and deposited in the medullary interstitial fluid.

3. **In the intercalated cells**, NH_3 diffuses from the medullary interstitium into the lumen.

   H^+ and HCO_3^- are produced from CO_2 and H_2O.

   H^+ is secreted into the lumen via H^+-ATPase and H^+-K^+ ATPase and combines with NH_3 to form NH_4^+, which is excreted.

   - This process is termed **diffusion trapping** because the *water-soluble* form of the buffer (NH_4^+) is *trapped* and excreted.

   The HCO_3^- is reabsorbed into the blood ("new" HCO_3^-).

- The amount of H^+ excreted as NH_4^+ depends on both the **amount of NH_3** synthesized by renal cells and the **urine pH.**
  - The lower the pH of the tubular fluid, the greater the excretion of H^+ as NH_4^+; at low urine pH, there is more NH_4^+ relative to NH_3 in the urine, thus increasing the gradient for NH_3 diffusion.

- In acidosis, an adaptive increase in NH_3 synthesis occurs and aids in the excretion of excess H^+.

- **Hyperkalemia inhibits NH_3 synthesis,** which produces a decrease in H^+ excretion as NH_4^+ **(type 4 renal tubular acidosis [RTA]).**
  - For example, **hypoaldosteronism** causes hyperkalemia and thus also causes type 4 RTA.

- Conversely, **hypokalemia** stimulates NH_3 synthesis, which produces an increase in H^+ excretion.

Acid-base disorders

- The minimum urinary pH is 4.4 if the value of dips under 4.4 the net secretion of hydrogen ions well cease. The excretion of h+ as a tritrtable acid removes 20 mmol of the fixed acid. the rest of the acid (13 to 14 mmol) will be excreted as NH3. This is why we need more than one way to remove the fixed acid
- Hyperkalemia means more potassium ions will be secreted in exchange of hydrogen ions which means inhibits ammonia synthesis due to less secretion of hydrogen as ammonia

1. Metabolic acidosis

- Overproduction or ingestion of fixed acid or loss of base produces a **decrease in arterial [$HCO3^-$].** This decrease is the primary disturbance in metabolic acidosis.

- Decreased HCO_3^- concentration causes a **decrease in blood pH (acidemia).**

- Acidemia causes **hyperventilation (Kussmaul breathing),** which is **the respiratory compensation** for metabolic acidosis.

- Correction of metabolic acidosis consists of increased excretion of the excess fixed H^+ as titratable acid and NH_4^+, and increased reabsorption of "new" HCO_3^-, which replenishes the blood HCO_3^- concentration.

- In chronic metabolic acidosis, an **adaptive increase in NH_3 synthesis** aids in the excretion of excess H^+.

- **Serum anion gap =** $[Na^+]–([Cl^-] + [HCO_3^-])$

- The serum anion gap represents **unmeasured anions** in serum**.** These unmeasured anions include phosphate, citrate, sulfate, and protein.

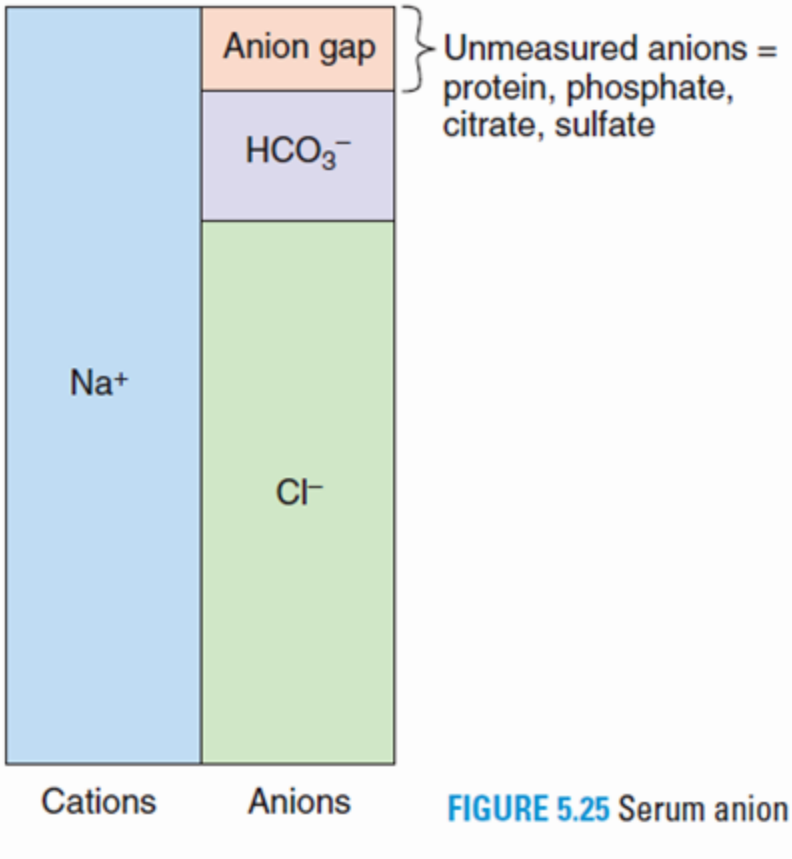


FIGURE 5.25 Serum anion gap.

- The normal value of the serum anion gap is **12 mEq/L** (range, 8 to 16 mEq/L).

- In metabolic acidosis, the serum [HCO_3^-] decreases. For electroneutrality, the concentration of another anion must increase to replace HCO_3^-. That anion can be Cl^- or it can be an unmeasured anion.

- **The serum anion gap is increased** if the concentration of an unmeasured anion (e.g., phosphate, lactate, β-hydroxybutyrate, and formate) is increased to replace HCO_3^-.

- **The serum anion gap is normal** if the concentration of Cl^- is increased to replace HCO_3^- **(hyperchloremic metabolic acidosis).**

2. Metabolic alkalosis

- **Loss of fixed H^+ or gain of base produces an increase in arterial [HCO_3^-].** This increase is the primary disturbance in metabolic alkalosis.
  - For example, in **vomiting,** H^+ is lost from the stomach, HCO_3^- remains behind in the blood, and the [HCO_3^-] increases.

- Increased HCO_3^- concentration causes an **increase in blood pH** (alkalemia).
- Alkalemia causes **hypoventilation,** which is the **respiratory compensation** for metabolic alkalosis.

- Correction of metabolic alkalosis consists of increased excretion of HCO_3^- because the filtered load of HCO_3^- exceeds the ability of the renal tubule to reabsorb it.

- If metabolic alkalosis is accompanied by **ECF volume contraction** (e.g., vomiting), the reabsorption of HCO_3^- increases (secondary to ECF volume contraction and activation of the renin–angiotensin II–aldosterone system), worsening the metabolic alkalosis (i.e., **contraction alkalosis).**

3. Respiratory acidosis

- **Is caused by decreased alveolar ventilation and retention of CO_2.**

- Increased arterial P_{CO2}, which is the primary disturbance, causes an **increase in $[H^+]$ and $[HCO3^-]$** by mass action**.**

- There is **no respiratory compensation** for respiratory acidosis.

- **Renal compensation consists of increased excretion of H^+ as titratable acid and NH_4^+** and increased reabsorption of "new" HCO_3^-.

  This process is aided by the increased P_{co2}, which supplies more H^+ to the renal cells for secretion. The resulting increase in serum [HCO_3^-] helps to normalize the pH.

- In **acute respiratory acidosis,** renal compensation has not yet occurred.
- In **chronic respiratory acidosis,** renal compensation (increased HCO_3^- reabsorption) has occurred. Thus, arterial pH is increased toward normal (i.e., a compensation).

4. Respiratory alkalosis

- Is **caused by increased alveolar ventilation** and **loss of CO_2.**

- Decreased arterial P_{CO2}, which is the primary disturbance, causes a **decrease in $[H^+]$ and $[HCO_3^-]$** by mass action.

- There is **no respiratory compensation** for respiratory alkalosis.

- **Renal compensation** consists of decreased excretion of H+ as titratable acid and NH_4^+ and decreased reabsorption of "new" HCO_3^-. This process is aided by the decreased P_{CO2}, which causes a deficit of H^+ in the renal cells for secretion. The resulting decrease in serum [HCO_3^-] helps to normalize the pH.

- In **acute respiratory alkalosis, renal compensation has not yet occurred.**

- In **chronic respiratory alkalosis,** renal compensation (decreased HCO_3^- reabsorption) has occurred. Thus, arterial pH is decreased toward normal (i.e., a compensation).

table 5.8 Summary of Acid–Base Disorders

Disorder	$CO_2 + H_2O$	↔	H^+	HCO_3^-	Respiratory Compensation	Renal Compensation
Metabolic acidosis	↓ (respiratory compensation)		↑	**↓**	Hyperventilation	
Metabolic alkalosis	↑ (respiratory compensation)		↓	**↑**	Hypoventilation	
Respiratory acidosis	**↑**		↑	↑	None	↑ H^+ excretion ↑ HCO_3^- reabsorption
Respiratory alkalosis	**↓**		↓	↓	None	↓ H^+ excretion ↓ HCO_3^- reabsorption

Heavy arrows indicate *primary* disturbance.

table 5.10 Calculating Compensatory Responses to Simple Acid–Base Disorders

Acid–base Disturbance	Primary Disturbance	Compensation	Predicted Compensatory Response
Metabolic acidosis	↓ $[HCO_3^-]$	↓ Pco_2	1 mEq/L decrease in HCO_3^- → 1.3 mm Hg decrease in Pco_2
Metabolic alkalosis	↑ $[HCO_3^-]$	↑ Pco_2	1 mEq/L increase in HCO_3^- → 0.7 mm Hg increase in Pco_2
Respiratory acidosis			
Acute	↑ Pco_2	↑ $[HCO_3^-]$	1 mm Hg increase in Pco_2 → 0.1 mEq/L increase in HCO_3^-
Chronic	↑ Pco_2	↑ $[HCO_3^-]$	1 mm Hg increase in Pco_2 → 0.4 mEq/L increase in HCO_3^-
Respiratory alkalosis			
Acute	↓ Pco_2	↓ $[HCO_3^-]$	1 mm Hg decrease in Pco_2 → 0.2 mEq/L decrease in HCO_3^-
Chronic	↓ Pco_2	↓ $[HCO_3^-]$	1 mm Hg decrease in Pco_2 → 0.4 mEq/L decrease in HCO_3^-

Table 7–4 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

Table 7–4 Causes of Metabolic Acidosis

Cause	Examples	Comments
Loss of $HCO3^-$	Diarrhea	Gastrointestinal loss of $HCO3^-$ Normal anion gap Hyperchloremia
	Type 2 renal tubular acidosis (type 2 RTA)	Renal loss of $HCO3^-$ (failure to reabsorb filtered $HCO3^-$) Normal anion gap Hyperchloremia
Inability to excrete fixed H^+	Chronic renal failure	↓ Excretion of H^+ as $NH4^+$ ↑ Anion gap
	Type 1 renal tubular acidosis (type 1 RTA)	↓ Excretion of H^+ as titratable acid and $NH4^+$ ↓ Ability to acidify urine Normal anion gap
	Type 4 renal tubular acidosis (type 4 RTA)	Hypoaldosteronism ↓ Excretion of $NH4^+$ Hyperkalemia inhibits $NH3$ synthesis Normal anion gap

Table 7–5 Causes of Metabolic Alkalosis

Cause	Examples	Comments
Loss of H^+	Vomiting	Loss of gastric H^+ $HCO3^-$ remains in the blood Maintained by volume contraction Hypokalemia
	Hyperaldosteronism	Increased H^+ secretion by intercalated cells Hypokalemia
Gain of $HCO3^-$	Ingestion of NaHCO3 Milk-alkali syndrome	Ingestion of large amounts of $HCO3^-$ in conjunction with renal failure
Volume contraction alkalosis	Loop or thiazide diuretics	↑ $HCO3^-$ reabsorption due to ↑ angiotensin II and aldosterone