Acid-Base Balance

- Estrogens:
  - Enhance NaCl reabsorption by renal tubules
  - May cause water retention during menstrual cycles
  - Are responsible for edema during pregnancy
- Progesterone:
  - Decreases sodium reabsorption
  - Acts as a diuretic, promoting sodium and water loss
- Glucocorticoids – enhance reabsorption of sodium and promote edema

Regulation of Potassium Balance

- Relative ICF-ECF potassium ion concentration affects a cell’s resting membrane potential
  - Excessive ECF potassium decreases membrane potential
  - Too little $K^+$ causes hyperpolarization and nonresponsiveness

Regulatory Site: Cortical Collecting Ducts

- Less than 15% of filtered $K^+$ is lost to urine regardless of need
- $K^+$ balance is controlled in the cortical collecting ducts by changing the amount of potassium secreted into filtrate
- Excessive $K^+$ is excreted over basal levels by cortical collecting ducts
- When $K^+$ levels are low, the amount of secretion and excretion is kept to a minimum
- Type A intercalated cells can reabsorb some $K^+$ left in the filtrate

Influence of Other Hormones on Sodium Balance

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Influence of Plasma Potassium Concentration

- High $K^+$ content of ECF favors principal cells to secrete $K^+$
- Low $K^+$ or accelerated $K^+$ loss depresses its secretion by the collecting ducts
**Influence of Aldosterone**
- Aldosterone stimulates potassium ion secretion by principal cells
- In cortical collecting ducts, for each Na\(^+\) reabsorbed, a K\(^+\) is secreted
- Increased K\(^+\) in the ECF around the adrenal cortex causes:
  - Release of aldosterone
  - Potassium secretion
- Potassium controls its own ECF concentration via feedback regulation of aldosterone release

**Regulation of Calcium**
- Ionic calcium in ECF is important for:
  - Blood clotting
  - Cell membrane permeability
  - Secretory behavior
- Hypocalcemia:
  - Increases excitability
  - Causes muscle tetany

**Regulation of Calcium**
- Hypercalcemia:
  - Inhibits neurons and muscle cells
  - May cause heart arrhythmias
- Calcium balance is controlled by parathyroid hormone (PTH) and calcitonin

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**Regulation of Calcium and Phosphate**
- PTH promotes increase in calcium levels by targeting:
  - Bones – PTH activates osteoclasts to break down bone matrix
  - Small intestine – PTH enhances intestinal absorption of calcium
  - Kidneys – PTH enhances calcium reabsorption and decreases phosphate reabsorption
- Calcium reabsorption and phosphate excretion go hand in hand

**Regulation of Calcium and Phosphate**
- Filtered phosphate is actively reabsorbed in the proximal tubules
- In the absence of PTH, phosphate reabsorption is regulated by its transport maximum and excesses are excreted in urine
- High or normal ECF calcium levels inhibit PTH secretion
  - Release of calcium from bone is inhibited
  - Larger amounts of calcium are lost in feces and urine
  - More phosphate is retained

**Influence of Calcitonin**
- Released in response to rising blood calcium levels
- Calcitonin is a PTH antagonist, but its contribution to calcium and phosphate homeostasis is minor to negligible
Regulation of Magnesium Balance
- Magnesium is the second most abundant intracellular cation
- Activates coenzymes needed for carbohydrate and protein metabolism
- Plays an essential role in neurotransmission, cardiac function, and neuromuscular activity
- There is a renal transport maximum for magnesium
- Control mechanisms are poorly understood

Regulation of Anions
- Chloride is the major anion accompanying sodium in the ECF
- 99% of chloride is reabsorbed under normal pH conditions
- When acidosis occurs, fewer chloride ions are reabsorbed
- Other anions have transport maximums and excesses are excreted in urine

Acid-Base Balance
- Normal pH of body fluids
  - Arterial blood is 7.4
  - Venous blood and interstitial fluid is 7.35
  - Intracellular fluid is 7.0
- Alkalosis or alkalemia – arterial blood pH rises above 7.45
- Acidosis or acidemia – arterial pH drops below 7.35 (physiological acidosis)

Sources of Hydrogen Ions
- Most hydrogen ions originate from cellular metabolism
  - Breakdown of phosphorus-containing proteins releases phosphoric acid into the ECF
  - Anaerobic respiration of glucose produces lactic acid
  - Fat metabolism yields organic acids and ketone bodies
  - Transporting carbon dioxide as bicarbonate releases hydrogen ions

Hydrogen Ion Regulation
- Concentration of hydrogen ions is regulated sequentially by:
  - Chemical buffer systems – act within seconds
  - The respiratory center in the brain stem – acts within 1–3 minutes
  - Renal mechanisms – require hours to days to effect pH changes

Chemical Buffer Systems
- Strong acids – all their H⁺ is dissociated completely in water
- Weak acids – dissociate partially in water and are efficient at preventing pH changes
- Strong bases – dissociate easily in water and quickly tie up H⁺
- Weak bases – accept H⁺ more slowly (e.g., HCO₃⁻ and NH₃)
Chemical Buffer Systems
• One or two molecules that act to resist pH changes when strong acid or base is added
• Three major chemical buffer systems
  – Bicarbonate buffer system
  – Phosphate buffer system
  – Protein buffer system
• Any drifts in pH are resisted by the entire chemical buffering system

Bicarbonate Buffer System
• A mixture of carbonic acid ($H_2CO_3$) and its salt, sodium bicarbonate ($NaHCO_3$) (potassium or magnesium bicarbonates work as well)
• If strong acid is added:
  – Hydrogen ions released combine with the bicarbonate ions and form carbonic acid (a weak acid)
  – The pH of the solution decreases only slightly

Bicarbonate Buffer System
• If strong base is added:
  – It reacts with the carbonic acid to form sodium bicarbonate (a weak base)
  – The pH of the solution rises only slightly
• This system is the only important ECF buffer

Phosphate Buffer System
• Nearly identical to the bicarbonate system
• Its components are:
  – Sodium salts of dihydrogen phosphate ($H_2PO_4^-$), a weak acid
  – Monohydrogen phosphate ($HPO_4^{2-}$), a weak base
• This system is an effective buffer in urine and intracellular fluid

Protein Buffer System
• Plasma and intracellular proteins are the body's most plentiful and powerful buffers
• Some amino acids of proteins have:
  – Free organic acid groups (weak acids)
  – Groups that act as weak bases (e.g., amino groups)
• Amphoteric molecules are protein molecules that can function as both a weak acid and a weak base

Physiological Buffer Systems
• The respiratory system regulation of acid-base balance is a physiological buffering system
• There is a reversible equilibrium between:
  – Dissolved carbon dioxide and water
  – Carbonic acid and the hydrogen and bicarbonate ions

\[ CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^- \]
Physiological Buffer Systems

- During carbon dioxide unloading, hydrogen ions are incorporated into water
- When hypercapnia or rising plasma H\(^+\) occurs:
  - Deeper and more rapid breathing expels more carbon dioxide
  - Hydrogen ion concentration is reduced
- Alkalosis causes slower, more shallow breathing, causing H\(^+\) to increase
- Respiratory system impairment causes acid-base imbalance (respiratory acidosis or respiratory alkalosis)

Renal Mechanisms of Acid–Base Balance

- Chemical buffers can tie up excess acids or bases, but they cannot eliminate them from the body
- The lungs can eliminate carbonic acid by eliminating carbon dioxide
- Only the kidneys can rid the body of metabolic acids (phosphoric, uric, and lactic acids and ketones) and prevent metabolic acidosis
- The ultimate acid-base regulatory organs are the kidneys

Renal Mechanisms of Acid–Base Balance

- The most important renal mechanisms for regulating acid-base balance are:
  - Conserving (reabsorbing) or generating new bicarbonate ions
  - Excreting bicarbonate ions
- Losing a bicarbonate ion is the same as gaining a hydrogen ion; reabsorbing a bicarbonate ion is the same as losing a hydrogen ion

Reabsorption of Bicarbonate

- Carbon dioxide combines with water in tubule cells, forming carbonic acid
- Carbonic acid splits into hydrogen ions and bicarbonate ions
- For each hydrogen ion secreted, a sodium ion and a bicarbonate ion are reabsorbed by the PCT cells
- Secreted hydrogen ions form carbonic acid; thus, bicarbonate disappears from filtrate at the same rate that it enters the peritubular capillary blood

Reabsorption of Bicarbonate

- Carbonic acid formed in filtrate dissociates to release carbon dioxide and water
- Carbon dioxide then diffuses into tubule cells, where it acts to trigger further hydrogen ion secretion
Generating New Bicarbonate Ions

• Two mechanisms carried out by type A intercalated cells generate new bicarbonate ions
• Both involve renal excretion of acid via secretion and excretion of hydrogen ions or ammonium ions (NH₄⁺)

Generating New Bicarbonate Ions Using Hydrogen Ion Excretion

• Dietary hydrogen ions must be counteracted by generating new bicarbonate
• The excreted hydrogen ions must bind to buffers in the urine (phosphate buffer system)
• Intercalated cells actively secrete hydrogen ions into urine, which is buffered and excreted
• Bicarbonate generated is:
  – Moved into the interstitial space via a cotransport system
  – Passively moved into the peritubular capillary blood

Figure 25.13 Generating New Bicarbonate Ions Using Hydrogen Ion Excretion

• In response to acidosis:
  – Kidneys generate bicarbonate ions and add them to the blood
  – An equal amount of hydrogen ions are added to the urine

Generating New Bicarbonate Ions Using Ammonium Ion Excretion

• This method uses ammonium ions produced by the metabolism of glutamine in PCT cells
• Each glutamine metabolized produces two ammonium ions and two bicarbonate ions
• Bicarbonate moves to the blood and ammonium ions are excreted in urine

Figure 25.14 Generating New Bicarbonate Ions Using Ammonium Ion Excretion

Bicarbonate Ion Secretion

• When the body is in alkalosis, type B intercalated cells:
  – Exhibit bicarbonate ion secretion
  – Reclaim hydrogen ions and acidify the blood
• The mechanism is the opposite of type A intercalated cells and the bicarbonate ion reabsorption process
• Even during alkalosis, the nephrons and collecting ducts excrete fewer bicarbonate ions than they conserve
Respiratory Acidosis and Alkalosis

- Result from failure of the respiratory system to balance pH
- $P_{CO_2}$ is the single most important indicator of respiratory inadequacy
- Normal $P_{CO_2}$
  - Fluctuates between 35 and 45 mm Hg
  - Values above 45 mm Hg signal respiratory acidosis
  - Values below 35 mm Hg indicate respiratory alkalosis

Respiratory Acidosis and Alkalosis

- Respiratory acidosis is the most common cause of acid-base imbalance
  - Occurs when a person breathes shallowly, or gas exchange is hampered by diseases such as pneumonia, cystic fibrosis, or emphysema
- Respiratory alkalosis is a common result of hyperventilation

Metabolic Acidosis

- All pH imbalances except those caused by abnormal blood carbon dioxide levels
- Metabolic acid-base imbalance – bicarbonate ion levels above or below normal (22–26 mEq/L)
- Metabolic acidosis is the second most common cause of acid-base imbalance
  - Typical causes are ingestion of too much alcohol and excessive loss of bicarbonate ions
  - Other causes include accumulation of lactic acid, shock, ketosis in diabetic crisis, starvation, and kidney failure

Metabolic Alkalosis

- Rising blood pH and bicarbonate levels indicate metabolic alkalosis
- Typical causes are:
  - Vomiting of the acid contents of the stomach
  - Intake of excess base (e.g., from antacids)
  - Constipation, in which excessive bicarbonate is reabsorbed

Respiratory Compensation

- In metabolic acidosis:
  - The rate and depth of breathing are elevated
  - Blood pH is below 7.35 and bicarbonate level is low
  - As carbon dioxide is eliminated by the respiratory system, $P_{CO_2}$ falls below normal
- In respiratory acidosis, the respiratory rate is often depressed and is the immediate cause of the acidosis

Respiratory and Renal Compensations

- Acid-base imbalance due to the inadequacy of a physiological buffer system is compensated for by the other system
  - The respiratory system will attempt to correct metabolic acid-base imbalances
  - The kidneys will work to correct imbalances caused by respiratory disease
Respiratory Compensation

• In metabolic alkalosis:
  – Compensation exhibits slow, shallow breathing, allowing carbon dioxide to accumulate in the blood
• Correction is revealed by:
  – High pH (over 7.45) and elevated bicarbonate ion levels
  – Rising $P_{CO_2}$

Renal Compensation

• To correct respiratory acid-base imbalance, renal mechanisms are stepped up
• In acidosis
  – High $P_{CO_2}$ and high bicarbonate levels
    • The high $P_{CO_2}$ is the cause of acidosis
    • The high bicarbonate levels indicate the kidneys are retaining bicarbonate to offset the acidosis
• In alkalosis
  – Low $P_{CO_2}$ and high pH
    • The kidneys eliminate bicarbonate from the body by failing to reclaim it or by actively secreting it

Assessing Acid-Base Balance Using Blood Values

• Note the pH: this indicates if the person is in acidosis (pH<7.35) or alkalosis (pH>7.45), but it does not tell the cause
• Check the $P_{CO_2}$: excessively high or low $P_{CO_2}$ indicate
  – Whether the condition is caused by the respiratory system
  – Whether the respiratory system is compensating
• Check the bicarbonate level: if the respiratory system is not the cause, it is a metabolic condition