كلية المستقبل الجامعة الاهلية
قسم الصيدلة

Lecture: 3 of Pharmaceutical Chemistry

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Acid-Base Balance

Balance between acid and base is essential for many metabolic processes. Reaction of any solution depends on free hydrogen ions concentration [H^+]. The term used to indicate [H^+] is pH. pH is negative logarithm of hydrogen ions concentration:

$$pH = - \log [H^+]$$

The Henderson–Hasselbalch equation expresses the relation between pH and a buffer pair that is, a weak acid and its conjugate base. The pH being dependent on the ratio of the concentration of base to acid.

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

pH depends on balance between bicarbonate ion concentration [HCO_3^-] and carbonic acid concentration [H_2CO_3]. Bicarbonate ion is a base, metabolized mainly in kidneys. Carbonic acid is the main acid component of blood and it is not possible to measure the carbonic acid concentration directly; however, it is in equilibrium with dissolved CO_2, of which the partial pressure (PCO_2) can be estimated and CO_2 is regulated by lungs. The concentration of H_2CO_3 is derived by multiplying of PCO_2value by the solubility constant (S) for CO_2. Thus:

$$pH = pK_a + \log \frac{[HCO_3^-]}{P_{CO_2} \times S}$$

The PCO_2 is 40 mmHg, S = 0.03 and [HCO_3^-] is 24 mmol/L. The overall pKa of the bicarbonate system is 6.1, then: Therefore:

$$pH = 6.1 + \log \frac{24}{40 \times 0.03}$$

$$pH = 6.1 + 1.3 \longrightarrow pH = 7.4$$

In different cases of acid-base disturbances when acid content increases, it lead to acidosis will develop, if base increases, it lead to alkalosis. The constancy of pH is maintained by several mechanisms. They are sensitive enough to minimal changes in pH, and allow keeping pH in normal range for a long time (normal pH = 7.35-7.45).

Regulation of Acid-Base Balance

The regulation of acid-base balance done by:

1. Physiological buffers
2. The role of organs in regulation of acid-base
   - A. Respiratory systems
   - B. Renal mechanisms
   - C. Erythrocytes mechanisms
   - D. Gastrointestinal tract mechanisms

1. Physiological buffers

Buffer solution: is defined as a solution will resist changes in pH upon the addition of small amounts of either acid or base. Buffer solutions, or buffers, are found in all body fluids and are responsible for helping maintain the proper pH of those fluids. The normal range of the blood is 7.35 to 7.45. A buffer system consists of weak acid and its salt or weak base and its salt.

The main buffer systems are the following:

A. Bicarbonate buffer: the most important extracellular buffer, produced by kidneys, has the largest buffering capacity (53%).

B. Hemoglobin buffer: main intracellular buffer of the blood. Buffering capacity (35%).

C. Protein buffer: is an extracellular buffer together with bicarbonate buffer, represented by plasma proteins. Buffering capacity (7%).

D. Phosphate buffer: takes part in hydrogen ions excretion in renal tubules, is not of great importance in blood. Buffering capacity (5%).

2. The role of organs in regulation of acid-base

A. Respiratory system

Lungs are responsible for CO_2 elimination. CO_2 content in plasma depends on alveolar ventilation. Changes in pH lead to stimulation of chemoreceptors in the brain stem, causing a compensatory mechanism; therefore changing the respiratory rate.

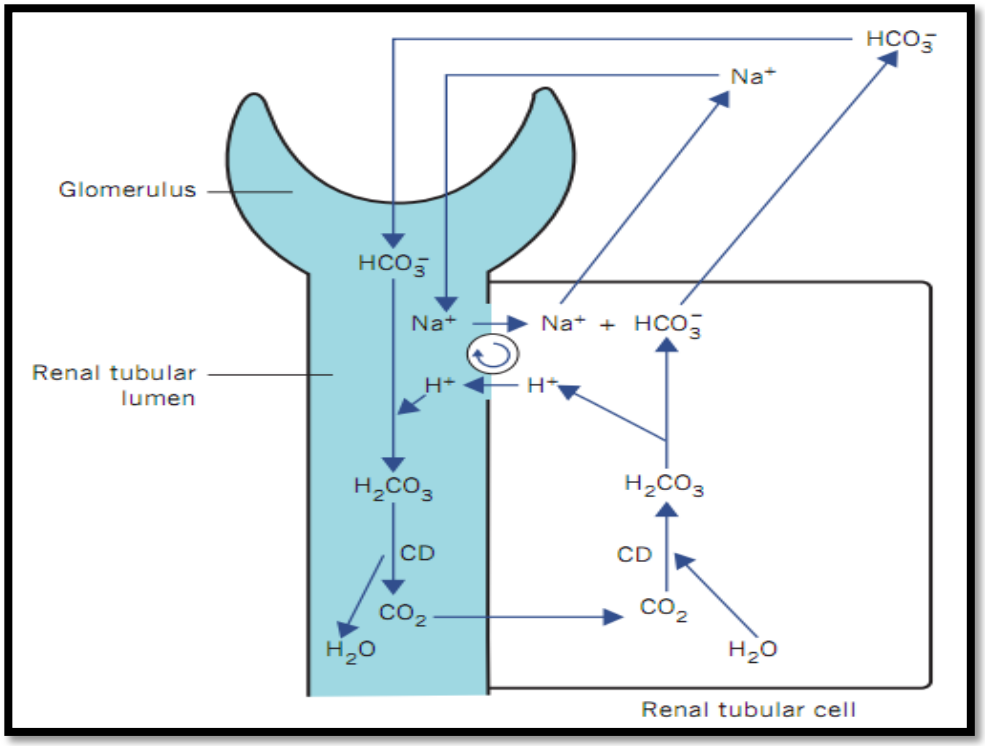
In acidosis (decreases in pH) lead to stimulation of chemoreceptors in the brain stem, causing a increases in alveolar ventilation (hyperventilation) for expelling the CO_2, then, the PCO_2 decreases and pH increase (i.e. return to normal).

In alkalosis (increase in pH) lead to inhibition of chemoreceptors in the brain stem, causing a decrease in alveolar ventilation (hypoventilation) for trapping the CO_2, then, rising in PCO_2 that leads to fall in pH (i.e. return to normal).

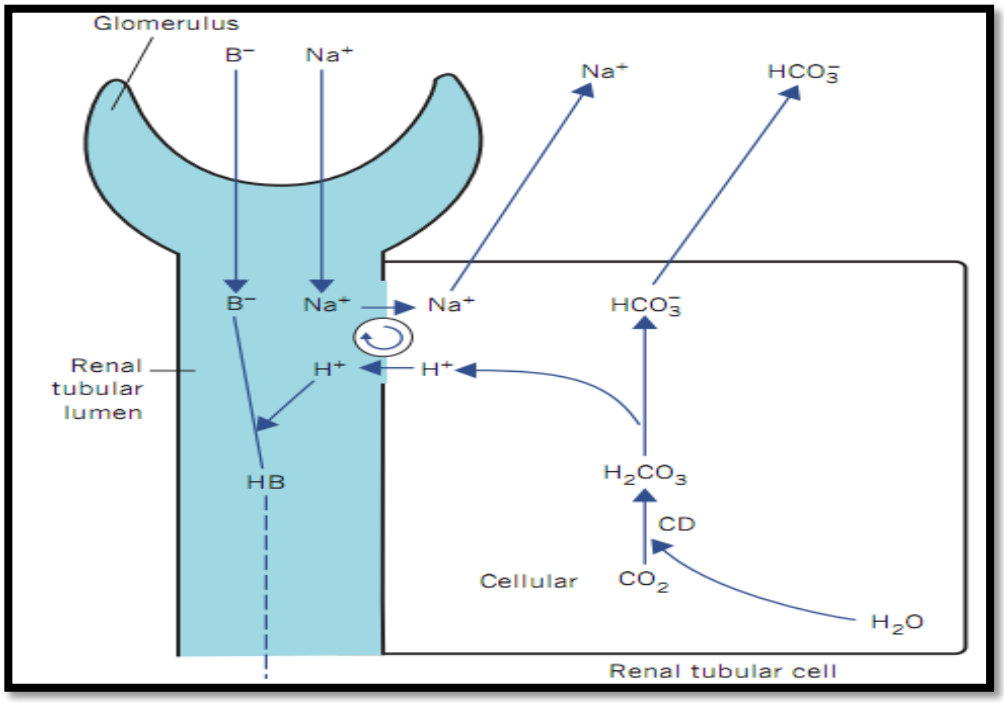
B. Renal mechanisms

Renal mechanisms are the most complex and effective. Renal compensation occurs by three main mechanisms:

1. Bicarbonate ions reabsorption in proximal tubules.
2. Bicarbonate ions generation in distal tubules.
3. Hydrogen ions excretion.



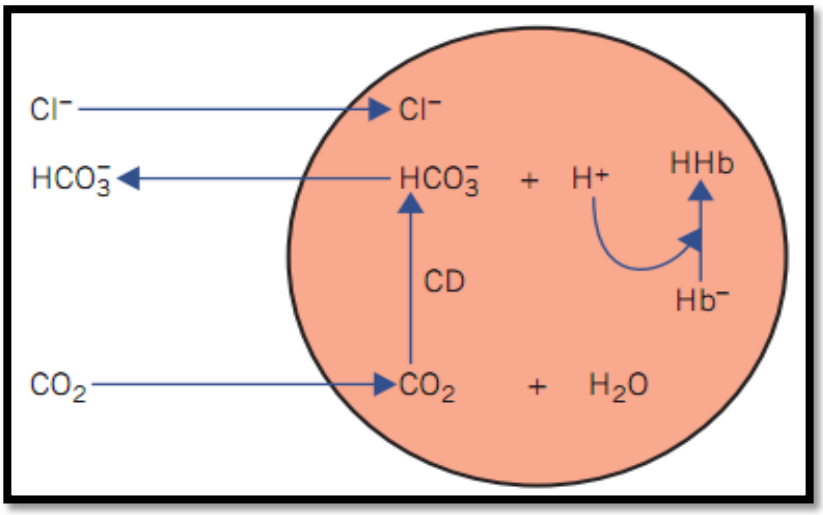
Bicarbonate ions reabsorption from the renal tubules



Bicarbonate ions generation and hydrogen ions excretion by renal tubules

C. Erythrocytes mechanism

Haemoglobin is an important blood buffer. Erythrocytes produce little CO_2 as they lack aerobic pathways. Plasma CO_2 diffuses along a concentration gradient into erythrocytes, where CD catalyzes its reaction with water to form carbonic acid (H_2CO_3), which then dissociates. Much of the H^+ is buffered by Hb, and the HCO_3^- diffuses out into the extracellular fluid along a concentration gradient. Electrochemical neutrality is maintained by diffusion of Cl^- in the opposite direction into cells. This movement of ions is known as the 'chloride shift'.



Generation of bicarbonate by erythrocytes

D. Gastrointestinal tract mechanisms

1. Acid secretion by the stomach

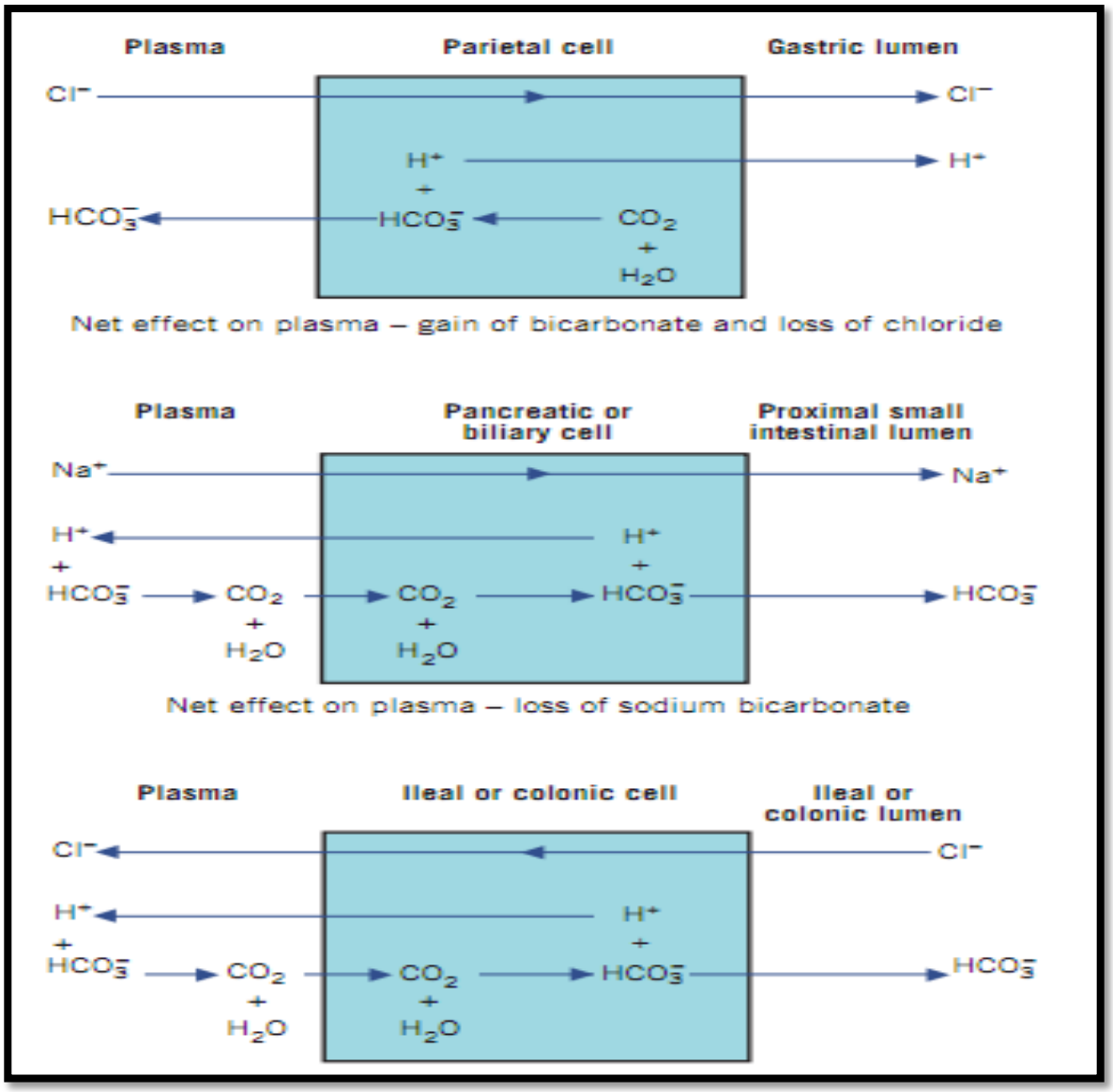
The parietal cells of the stomach secrete H^+ into the lumen together with Cl^-. As H^+Cl^- enters the gastric lumen, HCO_3^- diffuses into the ECF, thus accounting for the post-prandial 'alkaline tide'. In the healthy subject this is rapidly corrected by HCO_3^- secretion, mainly by the pancreas, as food passes down the intestinal tract. This mechanism explains the metabolic alkalosis that occurs in pyloric stenosis.

2. Sodium bicarbonate secretion by pancreatic and biliary cells

Sodium bicarbonate secretion by the pancreatic and biliary cells in response to stimulation by secretin accounts for the alkalization of the duodenal fluid and occurs by the reverse process of $NaHCO_3$ reabsorption in renal tubular cells. Loss of large amounts of duodenal fluid may cause HCO_3^- depletion.

C. Bicarbonate secretion and chloride reabsorption by intestinal cells

As fluid passes down the intestinal tract, HCO_3^- enters and Cl^- leaves the lumen by a reversal of the gastric mucosal mechanism.



Acid–base balance in intestinal cells

Acid-base balance disturbances

1. Acidosis

Acidosis (decrease pH less than 7.35) occurs if there is a fall in the ratio of $[HCO_3^-]$ to PCO_2 in the ECF. It may be due to:

A. Metabolic acidosis, the which the primary abnormality is a reduction in $[HCO_3^-]$.

B. Respiratory acidosis, the which the primary abnormality is a rise in PCO_2.

2. Alkalosis

Alkalosis (increase pH more than 7.45) occurs if there is a rise in the ratio of $[HCO_3^-]$ to PCO_2in the ECF. It may be due to:

A. Metabolic alkalosis, the primary abnormality is a rise in $[HCO_3^-]$.

B. Respiratory alkalosis, the primary abnormality is a fall in the PCO_2.

Acid-base balance disturbances and compensation

Type of disturbance	$[H^+]$	pH	Primary disturbance	Compensation
Metabolic acidosis	↑	↓	↓$[HCO_3^-]$	↓pCO_2
Metabolic alkalosis	↓	↑	↑$[HCO_3^-]$	↑pCO_2
Respiratory acidosis	↑	↓	↑pCO_2	↑$[HCO_3^-]$
Respiratory alkalosis	↓	↑	↓pCO_2	↓$[HCO_3^-]$

1. Metabolic Acidosis

Metabolic acidosis is defined as a reduction in a bicarbonate level with a resulting in a fall in blood pH (pH of less than 7.35).

Causes of metabolic acidosis

1. Kidney dysfunction, that results in retention of nonvolatile acids, decrease of the renal tubules ability to generate bicarbonate ions and increase renal losses of bicarbonate.

2. Increased endogenous organic acids production:

- Ketoacidosis due to insulin deficiency (diabetic ketoacidosis) or due to starvation.
- Lactic acidosis due to tissue hypoxia.

3. Intake of exogenous acids, their precursors, or substances, that block certain metabolic pathways, that leads to acids accumulation in the body (poisoning by salicylate, ammonium chloride, methanol, ethanol, ethylene glycol).

4. Gastrointestinal bicarbonate loss: diarrhea and GIT drainage.

Compensatory mechanism of metabolic acidosis:

In metabolic acidosis, the decrease pH stimulate the chemoreceptor in the brain stem. This stimulation lead to increase the respiratory rate (hyperventilation) that increase CO_2 elimination and pH tends to return to normal.

2. Metabolic Alkalosis

Metabolic alkalosis is defined as an increase in a bicarbonate level with a resulting in a increase in blood pH (pH of more than 7.45).

Causes of Metabolic Alkalosis

1. Bicarbonate administration, such as the ingestion of large amounts of HCO_3^- to treat indigestion (milk–alkali syndrome, which is rare) or during intravenous HCO_3^- infusion.

2. Severe K^+ depletion (hypokalemia) with the generation of HCO_3^- by the kidney. This is one of the most common causes.

3. Loss of H^+: if a H^+ is excreted, a HCO_3^- is gained in the extracellular space. The most likely loss of H^+ is through either the kidneys or the gastrointestinal tract. In the case of the renal losses occur when the [Na^+] reabsorption increases and H^+ or K^+ secretion into the lumen in the presence of excessive aldosterone. In the case of the gastrointestinal tract, vomiting causes loss of gastric secretions, which are rich in hydrochloric acid (pyloric stenosis).

Compensatory mechanism of metabolic alkalosis

In metabolic alkalosis, the increase pH inhibit the chemoreceptors in the brain stem. This lead to decrease the respiratory rate (hypoventilation) that decrease CO_2 elimination and pH tends to return to normal.

3. Respiratory Acidosis

Respiratory acidosis is defined as an increase in a PCO_2 level with a resulting in a fall in blood pH (pH of less than 7.35).

Causes of respiratory acidosis

Any condition that results in hypoventilation can cause respiratory acidosis.

1. Respiratory center depression: A central nervous system depression related to head injury, infection, stroke, medications such as narcotics, tranquilizes, sedatives, barbiturates, or anesthetics.

2. Neuromuscular diseases: Impaired respiratory muscle function related to spinal cord injury, or neuromuscular blocking drugs.

3. Pulmonary disorders: It includes pneumonia, bronchitis, asthma, pulmonary oedema, emphysema, or bronchial obstruction

Compensatory mechanism of respiratory acidosis

In respiratory acidosis, the decrease pH stimulate the renal reabsorption of bicarbonate ion. This lead to increase the bicarbonate level and pH tends to return to normal.

4. Respiratory Alkalosis

Respiratory alkalosis is defined as a reduction in a $PaCO_2$ level with a resulting in an increase in blood pH (pH of more than 7.45).

Causes of respiratory alkalosis

Any condition that results in hyperventilation can cause respiratory alkalosis. These conditions include:

1. Increased metabolic demands such as thyrotoxicosis
2. Central nervous system lesions and cerebral hemorrhage
3. Hysterical over breathing
4. Motion sickness
5. Excessive artificial respiration

Compensatory mechanism of respiratory alkalosis

In respiratory alkalosis, the increase pH inhibit the renal reabsorption and generation of bicarbonate ion. This lead to decrease the bicarbonate level and pH tends to return to normal.