ACID & BASE HOMEOSTASIS

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LEARNING OBJECTIVES FOR ACID & BASE HOMEOSTASIS

1. Describe how the body buffers free H+ that either enter from the diet or are generated by metabolism each day.
2. Explain the role of the lungs and of HCO3-/CO2 buffer pair in maintaining the stability of the pH in the body.
3. Explain the role of the kidney in eliminating filtered H+ and HCO3- to maintain plasma pH.
4. Explain how new bicarbonate is generated when fixed acids and ammonia are eliminated by the body.
5. Explain the classification of the four acid-base disorders. Describe how metabolic acidosis is differentiated from respiratory acidosis.

DETERMINANTS OF ACID-BASE BALANCE

Recall that the acidity of a solution is measured by its hydrogen ion concentration.

***** Acids are substances that can donate hydrogen ions (H+)**.

***** Bases are substances that accept hydrogen ions (protons).**

The amount of an acid (or base) is expressed usually in terms of equivalents (Eq) or milliequivalents (mEq). One Eq of acid will neutralize one Eq of base.

The pH of a solution is a measure of its H+ concentration. A normal arterial plasma sample has an H+ concentration of 40 nEq/L (i.e., 40 X 10^{-9} Eq/L) compared to 140 mEq/L (i.e., 14.0 X 10^{-4} Eq/L) of Na+. Because the H+ concentration is so low, it is expressed on the logarithmic pH scale of 0-14.

At pH 7.0 (i.e., 1 X 10^{-7}M) = neutral.
Below pH 7.0, the H+ concentration is increased = acidic.
Above pH 7.0, the H+ concentration is decreased = basic.
Normal plasma pH 7.4, is slightly basic with 0.00004 mM H+

****** For each change of 1 pH unit there is a 10-fold change in H+ concentration.**

Normally the kidneys and lungs work in concert to maintain the pH of plasma and of intracellular fluid (ICF) between 7.35-7.45. However, there are body fluids such as the luminal contents of the stomach that can have pH as low as 2.0. The pH of urine can vary from 4.5 to 8.5 depending on the body's needs to excrete H+ or HCO_3^-.

REGULATION OF BLOOD pH

Each day acids and bases are added to the body from the diet and by metabolic processes. In addition, base (bicarbonate) is normally lost each day in the feces. To maintain mass balance, the input and output of acids and bases are regulated by the kidney and the lungs. The lungs remove the volatile acid, CO2, but nonvolatile acids such as phosphates and sulfates are removed by the

kidney. The nonvolatile acids added to the body daily usually amount to 1mEq per kg of body weight (i.e., ~ 70 mEq/day for a 70 kg adult). These are eliminated by the kidney as fixed acids and ammonium ion.

The intracellular pH and the pH of the extra cellular fluid (ECF) must be regulated because too low pH and too high pH can affect the conformation of enzymes, receptors, and channels.

In acidosis, **the pH is too low.** The excess protons in the ECF enter the cells. Potassium ions exit the cells to maintain charge balance. In the kidney, the excess protons in the blood are excreted into the filtrate and potassium ions are reabsorbed from the filtrate to enter the blood. Consequently, plasma levels of K+ increase (*hyperkalemia*). This rise in extracellular K+ affects the resting membrane potential (depolarize) of excitable cells. Neurons and muscle depolarize more easily but are more difficult to repolarize leading to CNS depression and muscle weakness.

In alkalosis, the pH is too high. The protons leave the cells to enter the ECF. This causes K+ to enter cells to maintain charge balance. In the kidneys, potassium ions from the blood are excreted into the filtrate and protons are reabsorbed from the filtrate to enter the blood. Consequently, plasma K+ levels fall (*hypokalemia*). This decrease in plasma [K+] alters the resting membrane potential of excitable cells (hyperpolarize) such that a greater stimulus is needed to generate an action potential. This makes skeletal muscle cells less excitable and can lead to weakness and paralysis.

The specific terms used to define the physiological states and the underlying processes are:

> ***Acidemia*** is a state in which the arterial blood pH is lower than 7.35.
> ***Alkalemia*** is a state in which arterial blood pH is greater than 7.45.
>
> ***Acidosis*** is a process that lowers the arterial blood pH to < 7.35.
> ***Alkalosis*** is a process that raises the arterial blood pH to > 7.45.

To maintain blood pH over time, the body uses a complex system of buffers, the lungs, and the kidneys. Each participates as follows:

RAPID BUFFERING (*occurs immediately*). Buffers allow the body to tolerate a small excess (or deficiency) of acid without significant changes in either cellular pH or blood pH.

The major *intracellular* buffers in the body are negatively charged proteins (e.g., hemoglobin).

The major *extracellular* buffer is bicarbonate.

> *** $CO_2 + H_2O = H_2CO_3 = H^+ + HCO_3^-$

The formation of carbonic acid from CO_2 and water occurs in all cells and in the plasma. This reaction is catalyzed by the enzyme **carbonic anhydrase.** This reaction is extremely important because in the lungs, CO_2 is exhaled (removed from the body). By removing the CO_2, the reaction is "pulled" to the left (by mass action) eliminating H+ from the body. **Note that for every H+ removed, one HCO_3^- is lost from the body.**

> **Normal plasma concentration of HCO_3^- is 24 mEq/L**.

VENTILATION BY THE LUNGS (*occurs within minutes*). The lungs can take care of 75% of pH disturbances by eliminating CO_2 from the body and thereby removing carbonic acid. The rate of breathing is controlled by the respiratory center located in the medulla (brain stem) in response to arterial PCO_2 and from input from the peripheral chemoreceptors.

RENAL REGULATION (*occurs within hours to days*). The kidneys can adjust the amount of HCO_3^- and of H+ that are lost in the urine. Both H+ and HCO_3^- are filtered freely by the nephron and under most conditions little or no HCO_3^- is excreted. That means that essentially 99% or more of the **filtered load of HCO_3^-** is reabsorbed by the renal tubule.

Filtered load of substance = $[substance]_{plasma}$ x GFR

For example, filtered load of HCO_3^- = 24 mEq/L x 180 L/day = **4320 mEq/ day**

Specific regions of the renal tubule (see below) can secrete H+. For each H+ lost to the urine, a bicarbonate ion is returned to the blood.

The specific actions of the renal tubules are considered below:
1. The proximal convoluted tubule (PCT) reabsorbs most of the filtered HCO_3^-. Recall that HCO_3^- does not cross the tubule epithelial cell membrane in this region of the tubule. Reabsorption of bicarbonate depends on the carbonic anhydrase reaction and entry of CO_2 and water into these cells (Fig 1). Within the cells, CO_2 and H_2O combine to form H+ and HCO_3^-. The regenerated H+ leaves the epithelial cell via transporters (H+/Na+ antiporter and H+ ATPase) to reenter the tubular lumen; HCO_3 leaves at the basal (blood) side via the HCO_3^-/Cl^- antiporter.

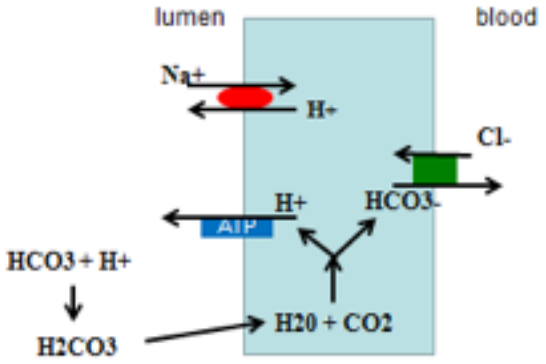

Figure 1. PCT tubules reabsorb most of filtered bicarbonate.

The distal tubule (DCT) and collecting duct (CD) can either reabsorb or excrete the remaining filtered HCO_3 depending on the body's needs. The epithelial cell that is active in this region is called the intercalated cell. There are two types of intercalated cells: A cells and B cells.

In acidosis, the intercalated A cells reabsorb bicarbonate (Fig 2) and return the H+ to the filtrate. Again because the cell is not very permeable to H+, the HCO_3^- and H+ are generated inside the intercalated cells from CO_2 and water in the presence of carbonic anhydrase. The extrusion of H+ is mediated by two proton pumps, H+ ATPase and H+/K+ ATPase, located on the luminal surface. Bicarbonate exits the intercalated A cells via the HCO_3^-/Cl^- antiporter located on the basal lateral surface. [Note: intercalated A cells make Acidic urine].

In alkalosis, the intercalated B cells reabsorb H+ and return HCO3 to the filtrate. The intercalated B cell is built as mirror image of the A cells. Here the proton pumps are located on the basal surface; the HCO_3^-/Cl^- antiporter is at the luminal surface. [Note: B cells make Basic urine].

***** When plasma pH is low, the distal tubule secretes H+ and reabsorbs bicarbonate.**
***** When plasma pH is high, the distal tubule secretes bicarbonate and reabsorbs H+.**

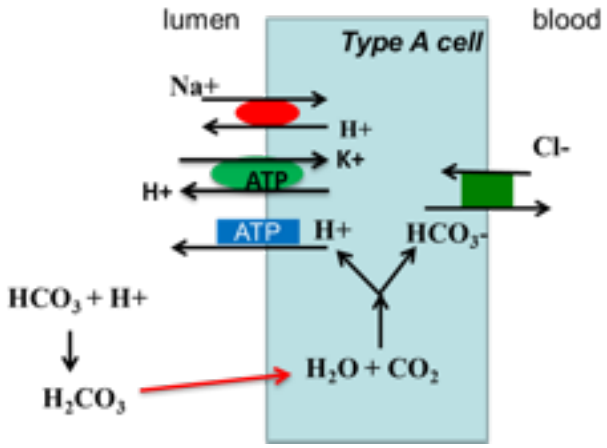

Figure 2. Reabsorption of HCO_3^- by the distal tubule (type A cells) during acidosis. Protons are actively pumped out of the cells by either the H+ ATPase or by the H+/K+ ATPase. Bicarbonate ions leave the cell by the HCO_3^- /Cl^- antiporter on the basal side to enter the blood.

Under normal conditions, H+ secretion predominates in the distal tubules and collecting ducts. Because the luminal surface of the epithelial cells lining the collecting ducts are not very permeable to H+, the **tubular fluid in this region can reach a pH of 4.0 - 4.5, the lowest pH within the nephron.**

GENERATION OF NEW HCO_3^- and EXCRETION OF NH_4+

Bicarbonate reabsorption alone does not replenish the HCO_3^- lost in buffering volatile acids. To maintain pH balance, lost HCO_3^- must be replenished by the kidneys. This involves two mechanisms:

(1) generation of new bicarbonate from glutamine
(2) excretion of nonvolatile acids.

"New" bicarbonate is generated from glutamine (Fig 3). In this process the amino acid glutamine is converted to ammonium ion (NH_4+) and new HCO_3^-. The NH_4+ exits the epithelial cell by the Na+/H+ antiporter substituting NH_4+ for H+ to enter the filtrate and HCO_3^- is added to the blood circulation.

The generation and secretion of NH_4+ occurs in the PCT epithelial cells. En route to the CD, the r NH_4+ is reabsorbed in the TAL to enter the interstitium (IS) of the medulla. Within the IS, NH_4 + is converted to NH_3 which can diffuse across the CD epithelial cells to enter the lumen of the tubule. Once in the filtrate, the NH_3 combines with a H+ to form NH_4+ and is removed from the body in the urine.

The proper functioning of the CD is required for the elimination of the NH_4+. Why is this important? If NH_4+ is not removed by the kidney, then NH_4+ enters the blood circulation of the kidney and is delivered to the liver where it is converted to urea (called BUN or blood urea nitrogen). Conversion of NH_4+ to urea generates H+ which must be buffered by HCO_3^-. This "removes" the newly made HCO_3^- from the circulation and there is no net gain in buffer. **In renal failure, ammonium excretion is insufficient and urea levels (BUN) rise in the blood.**

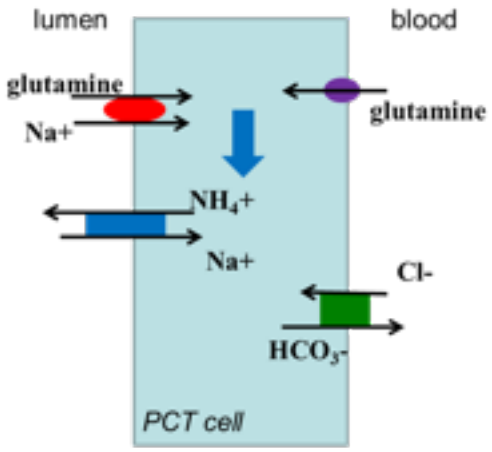

Figure 3. Ammonium ion production, transport, and excretion by the renal tubule. The Na gradient is maintained by the actions of the Na-K ATPase located on the basal surface (facing the IS) of these epithelial cells.

Excretion of nonvolatile fixed (or titratable) acids. Fixed (nonvolatile) acids generated from protein metabolism include sulfuric acid, hydrochloric acid, and phosphoric acid. Others such as lactic acid and ketoic acids are generated from the incomplete metabolism of carbohydrates and fats. In addition, fixed acids can be ingested from the diet. The lungs cannot remove fixed acids, only the kidney. Excretion of fixed acids by the kidney generates new bicarbonate (Fig 4).

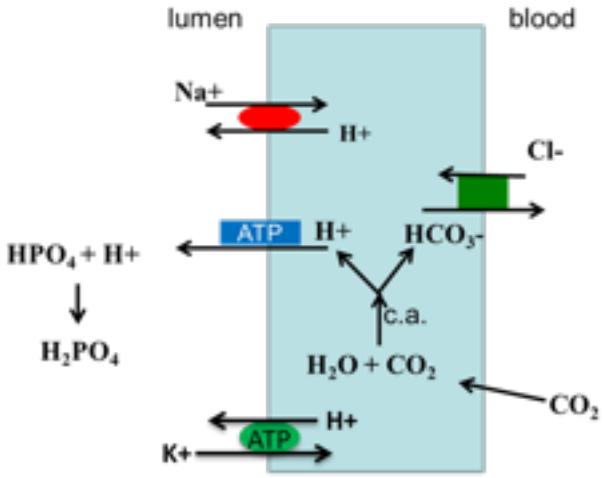

Figure 4. Excretion of fixed acids such as H_2PO_4- adds *new* HCO_3- to the blood.

Typically each day the total acid secretion by the kidney includes:

Fixed acids produced	35 mEq
NH_4+ produced	36 mEq
Acidic urine pH (free H+)	negligible

In response to acidosis, increased production and excretion of NH_4+ is quantitatively more important than increased formation of fixed acids. Usually of the ~70 mEq/L input of acid daily, loss of free H+ in the urine is 40 nEq/L (i.e., pH 7.4).

The **daily net acid excretion** (NAE) is calculated as follows:

NAE = (NH_4+ excreted) + (fixed acid excreted) – (amount of HCO_3^- excreted).

$U_{H+}V = U_{NH4+} V + U_{TA}V – U_{HCO3}-V = 1mEq/L/$ per day

(where U = urinary concentration; V = volume of urine)

INTEGRATED RESPONSE TO ACIDOSIS & ALKALOSIS

Normally, compensatory mechanisms by either the lungs or the kidneys take care of most changes in plasma pH. But under some circumstances those mechanisms fail. In these latter states the pH of the blood moves out of the normal range of 7.35-7.45. A blood pH below 7.00 and above 7.70 can be fatal.

Acid-base problems are classified by the direction of change as follows:

Acidosis is when the pH of blood is in the range of **7.00 -7.34**
Alkalosis is when the pH of blood is in the range of **7.46 -7.70**

Acid-base problems are classified by the underlying cause (metabolic or respiratory) (Table 1).

Primary Disorder	Blood pH	CO_2	Primary Causes of CO_2 Change
Respiratory acidosis	**decrease**	**increase**	**decreased ventilation**
Respiratory alkalosis	increase	decrease	increased ventilation
Metabolic acidosis	**decrease**	**decrease**	**decreased bicarbonate**
Metabolic alkalosis	increase	increase	increased bicarbonate

Table 1. FOUR TYPES OF ACID-BASE DISTURBANCES
Changes in pH due to increased (or decreased) ventilation (CO_2) are *respiratory* disorders.
Changes in pH due to acids (or bases) of non - CO_2 origin, are *metabolic* disorders.

Respiratory acidosis is decreased pH and elevated PaCO2 levels. The most common cause is chronic obstructive pulmonary disease (COPD) such as emphysema. To minimize the change in pH, the kidney excretes H+ and reabsorbs bicarbonate. This is called ***renal compensation,*** a process that can take several hours.

Metabolic acidosis occurs when metabolic input of H+ exceeds H+ excretion. Causes include lactic acid build up from anaerobic exercise and ketosis when there is an excess breakdown of fat. This can occur also if there is a loss of bicarbonate from the body in diarrhea. Under these circumstances, the respiratory system will attempt to compensate by increasing ventilation. Eventually the kidney will excrete H+ and reabsorb bicarbonate but the correction will take several (12-24) hours.

Respiratory alkalosis occurs with increased ventilation that is not matched by metabolism. This is much less common than acidosis but can occur with excessive artificial ventilation.

Metabolic alkalosis has two common causes: excessive vomiting or excessive ingestion of bicarbonate-containing antacids. The respiratory system will compensate by depressing ventilation. Less CO_2 is blown off, raising $PaCO_2$ and thereby creating more H+.

HOW TO ANALYZE ACID-BASE DISORDERS

Ask the following questions of an individual's blood values to determine if a simple acid-base disorder is present.

1. **What is the pH of the arterial blood?** Is the pH state normal, acidemia or alkalemia?
2. **Is it a metabolic or a respiratory disorder and is the process acidosis or alkalosis?** Examine the [HCO_3^-] and $PaCO_2$. Normal values are 24 mEq/L for HCO_3^- and 40 mmHg for $PaCO_2$. Because compensatory mechanisms can not correct an acid-base disorder by themselves, the change in pH indicates the underlying process as acidosis or alkalosis. Consult Table 1 for expected outcomes.
3. **What is the compensatory response?** Metabolic disorders result in changes in ventilation (i.e., $PaCO_2$). Respiratory disorders result in compensatory changes in renal net acid excretion. Again consult Table1 for expected outcomes.

Mixed acid-base disorders can occur in which there is a normal blood pH but the [HCO_3^-] and $PaCO_2$ values are abnormal. We will not consider these circumstances in this course.

KEY CONCEPTS

1. As a result of metabolism, the body has a net production of acids. The kidneys excrete excess H+ combined with urinary buffers such as phosphate (i.e., fixed acids) and ammonia.

2. The kidneys along with the lungs maintain the body's pH by regulating the HCO_3^-/CO_2 buffer pair. The lungs exert an immediate effect by controlling $PaCO_2$; the kidneys exert a slower effect by controlling HCO_3^- and H+ concentration.

3. The kidneys maintain acid-base homeostasis by reabsorbing filtered bicarbonate, forming titratable (fixed) acids and excreting ammonium ions (NH_4).

4. There are four types of acid-base disturbances. They are classified as to the direction of change in pH (acidosis or alkalosis) and by the underlying problem (ventilation or metabolism).

PROBLEMS

1. A person who takes rapid, deep breaths (panting) will exhibit signs of:
   A. respiratory acidosis
   B. respiratory alkalosis
   C. metabolic acidosis
   D. metabolic alkalosis

2. Renal compensation for an acid-base disorder _____ respiratory compensation for an acid-base disorder.
   A. is faster than
   B. is the same as
   C. is slower than

3. In acidosis, the concentration of K+ in the blood:
   A. decreases (hypokalemia)
   B. increases (hyperkalemia)
   C. does not change

ANSWERS

1. B
2. C
3. B