ACID-BASE HOMEOSTASIS IN HUMAN

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Introduction

Organism can be defined as a physical-chemical system that exists in the environment in a steady state. It is this ability of living systems to maintain steady state in an ever-changing environment that determines their survival. To ensure a steady state in all organisms – from morphologically most simple to the most complex – to elaborate a variety of anatomical, physiological and behavioural adaptations that serve one purpose – the preservation of the constancy of internal environment. This relative constancy of the dynamic internal environment (blood, lymph, tissue fluid) and the stability of the basic physiological functions (circulation, respiration, thermoregulation, metabolism, etc.) of the human and animal is called homeostasis.

What is pH?

Many chemical reactions are affected by the acidity of the solution in which they occur. In order for a particular reaction to occur or to occur at an appropriate rate, the pH of the reaction medium must be controlled. The term pH represents the negative logarithm of the hydrogen ion (H^+) concentration, and reflects acidity and alkalinity. The "p" stands for potential and "H" stands for Hydrogen-the potential of the solution to attract hydrogen ions. Body pH refers to the pH of the fluids inside and outside of the cells. Since most of the body is water-based, the pH level has profound effects on all body chemistry, health and disease. All biochemical reactions are influenced by the pH of their fluid environment as all functional proteins (enzymes, hemoglobin, cytochromes and others) because of their abundant hydrogen bonds are influenced by H^+ concentration. The normal pH of arterial blood is 7.4, that of venous blood and interstitial fluid (IF) is 7.35, and that of intracellular fluid (ICF) averages 7.0. The lower pH in cells and venous blood reflects their greater amounts of acidic metabolites and CO_2, which combines with water to form H_2CO_3. Whenever the pH of the arterial blood rises above 7.45, a person is said to have alkalosis or alkalemia. A drop in arterial pH to below 7.35 results in acidosis or acidemia. Because pH 7.0 is neutral, chemically speaking 7.35 is not acidic. However, it is a higher-than-optimal H^+ concentration for most cells, so any

arterial pH between 7.35 and 7.0 is called physiological acidosis.

Sources of Hydrogen Ions in the Body

Ingested foods carry small amounts of acidic substances into the body but most hydrogen ions originate as metabolic by-products or end-products. For example, (a) breakdown of phosphorous containing proteins releases phosphoric acid into the extracellular fluid (ECF), (b) anaerobic respiration of glucose produces lactic acid, (c) fat metabolism yields other organic acids, such as fatty acids and ketone bodies, and (d) the loading and transport of CO_2 in the blood as HCO_3^- liberates hydrogen ions (H^+). In the stomach, the HCl produced is a source of H^+ that must be buffered if digestion is to occur normally in the small intestine.

Defenses Against Changes in H^+ Concentration

In a healthy person, several mechanisms help maintain the pH of systemic arterial blood between 7.35 and 7.45. Because metabolic reactions often produce a huge excess of H^+, the lack of any mechanism for the disposal of H^+ would cause H^+ level in the body fluids to rise quickly to a lethal level. Homeostasis of H^+ concentration within a narrow range is thus essential to survival. There are three primary systems that regulate sequentially the H^+ concentration in the body fluids to prevent acidosis or alkalosis:

1. ***Buffer systems***: Chemical buffers act within a fraction of a second which immediately combine with acid or base to prevent excessive changes in H^+ concentration and are the first line of defense.
2. ***The respiratory centre***: By increasing the rate and depth of breathing, more CO_2 can be exhaled. Within minutes this reduces the level of H_2CO_3 in blood, which raises the blood pH (reduces blood H^+ level). This forms the second line of defense.
3. ***Renal mechanism***: The kidneys are the third line of defense, which can excrete either acidic or alkaline urine, thereby readjusting the extracellular fluid H^+ concentration toward normal during acidosis.

A. Buffer systems of acid-base homeostasis

Acids are molecules containing hydrogen atoms that can release H^+ in solutions i.e., acids are proton donors. A strong acid is one that rapidly dissociates and releases especially large amounts of H^+ in solution (eg. HCl). Weak acids have fewer tendencies to dissociate their ions and, therefore, release H^+ with less vigour (eg. H_2CO_3).

A ***base*** is an ion or molecule that can accept an H^+ i.e., proton acceptors. A strong base is one that reacts rapidly and strongly with H^+ and therefore, quickly removes these from a solution. Conversely, weak bases are slower to accept protons.

A ***buffer*** is any substance that can reversibly bind H^+. Most buffer systems in the body consist of a weak acid and the salt of that acid, which function as a weak base. Buffers prevent rapid, drastic changes in the pH of body fluids by converting strong acids and bases into weak acids and weak bases within fraction of a second. They do this by binding to H^+ whenever the pH drops and releasing them when pH rises. The principal

buffer systems of the body fluids are the bicarbonate buffer system, phosphate buffer system and protein buffer system.

Bicarbonate Buffer System

It works in the blood, lymph, tissue fluids, and kidneys. Bicarbonate ions are generated in the red blood cells from carbon dioxide (CO_2) and diffuse into the plasma to act as an alkaline reserve against hydrogen ions. The carbonic acid-bicarbonate buffer system is a mixture of carbonic acid (H_2CO_3) and its salt, sodium bicarbonate ($NaHCO_3$) in the same solution. H_2CO_3 act as a weak acid is formed in the body by the reaction of CO_2 with H_2O.

$$Co_2 + H_2o \xrightleftharpoons{\text{Carbonic anhydrase}} H_2Co_3$$

H_2CO_3 ionizes weakly to form small amounts of H^+ and HCO_3^-.

$$H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$

The second component of the system, bicarbonate salt, act as a weak base, occurs predominantly as $NaHCO_3$ in the ECF. $NaHCO_3$ ionizes almost completely to form HCO_3^- and Na^+, as follows:

$$NaHCO_3 \rightleftharpoons Na^+ + HCO_3^-$$

Carbonic acid, a weak acid, does not dissociate to any great extent in neutral or acidic solutions. When a strong acid such as HCl is added to the bicarbonate buffer system, most of the existing carbonic acid remains intact. However, the bicarbonate ions of the salt act as weak bases to tie up the H^+ released by stronger acid (HCl), forming more H_2CO_3:

$$\underset{\text{Strong acid}}{HCL} + \underset{\text{Weak base}}{NaHCO_3} \longrightarrow \underset{\text{Weak acid}}{H_2CO_3} + \underset{\text{Salt}}{Nacl}$$

As HCl is converted to the weak acid H_2CO_3, it lowers the pH of the solution only slightly.

When a strong base, such as sodium hydroxide (NaOH), is added to the bicarbonate buffer solution, a weak base such as $NaHCO_3$ does not dissociate under the alkaline conditions and so does not contribute to the rise in pH. However, the added base forces the carbonic acid to dissociate further donating more H^+ to tie up the OH^- released by a strong base:

$$\underset{\text{Strong base}}{NaOH} + \underset{\text{Weak acid}}{H_2CO_3} \longrightarrow \underset{\text{Weak base}}{NaHCO_3} + \underset{\text{Water}}{H_2O}$$

Thus, the strong base (NaOH) is replaced by a weak base ($NaHCO_3$), so the pH of the solution rises very little.

At a pH 7.4 HCO_3^- concentrations is about 24 mEq/liter and H_2CO_3 concentration is about 1.2 mmol/liter, so bicarbonate ions out number carbonic acid molecules by 20 to 1. Because CO_2 and H_2O combine to form H_2CO_3, this buffer system cannot protect against pH changes due to respiratory problems in which there is an excess or shortage of CO_2.

Phosphate Buffer System

The phosphate buffer system acts via a mechanism similar to the one for the carbonic acid-bicarbonate buffer system. The components of the phosphate system are the sodium salts of dihydrogen phosphate ($H_2PO_4^-$) and mono-hydrogen 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.

When a strong acid such as HCl is added to a mixture of these two substances, the hydrogen is accepted by the base HPO_4^{2-} and converted to H_2PO_4 .

$$\underset{\text{Strong acid}}{HCL} + \underset{\text{Weak base}}{Na_2HPO_4} \longrightarrow \underset{\text{Weak acid}}{NaH_2PO_4} + \underset{\text{Salt}}{NACL}$$

The result of this reaction is that the strong acid, HCl is replaced by an additional amount of a weak acid, NaH_2PO_4 and the decrease in pH is minimised.

When a strong base, such as NaOH, is added to this buffer system, the OH^- is buffered by the $H_2PO_4^-$ to form additional amount of HPO_4^{2-}.

$$\underset{\text{Strong base}}{NAOH} + \underset{\text{Weak acid}}{NaH_2PO_4} \longrightarrow \underset{\text{Weak base}}{Na_2HPO_4} + \underset{\text{Water}}{H_2O}$$

In this case, a strong base, NaOH is converted to a weak base, Na_2HPO_4, causing only a slight increase in pH.

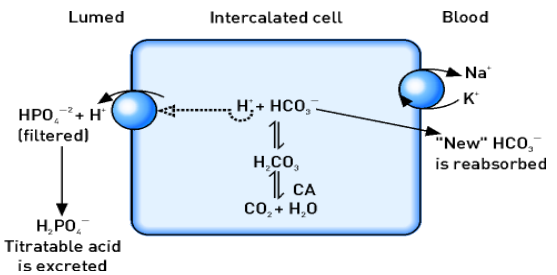
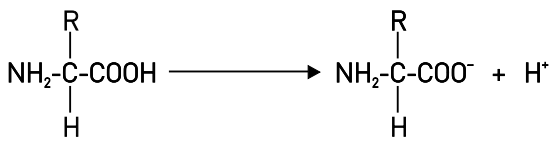


Fig. 1 Action of phosphate buffers in the elimination f H^+.

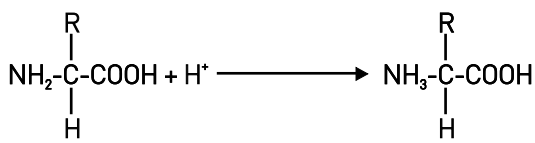
The concentration of the phosphate buffer system in the ECF is low in comparison to carbonic acid-bicarbonate buffer system. Therefore, the total buffering power of the phosphate system in ECF is much less than that of the carbonic acid-bicarbonate buffering system. However, the concentration of the phosphates is highest in ICF, the phosphate buffer system is an important regulator of pH in the cytosol. The phosphate buffer is especially important in the tubular fluids of the kidneys.

Protein Buffer System

The protein buffer system is the most abundant buffer in ECF and blood plasma. Proteins are polymers of amino acids, that contain at least one carboxyl group (-COOH) and at least one amino group ($-NH_2$), these groups are the functional components of the protein buffer system. The free carboxyl group at one end of a protein functions like an acid which dissociates to release H^+ when the pH begins to rise:



The H^+ released is then able to react with any excess OH^- in the solution to form water. The free amino group at the other end of a protein can act as a base by combining with H^+ when pH falls, as follows:



Because this removes free H+ from the solution, it prevents the solution from becoming too acidic. Consequently, a single protein molecule can function reversibly as either an acid or a base depending on the pH of its environment. Molecules with this ability are called **amphoteric molecules.**

Hemoglobin (Hb) is an excellent example of a protein that act as a intracellular buffer in RBCs. CO_2 passes from tissue cells into the plasma of blood and then into RBCs, where it combines with water to form carbonic acid. H_2CO_3 dissociates

into H^+ and HCO_3^-. Meanwhile, Hb is unloading O_2 to tissue cells becoming reduced Hb, which carries a negative charge. The reduced Hb (deoxyhemoglobin) picks most of the H^+, minimising the pH change.

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

$$\underset{\text{Oxyhemoglobin}}{Hb\text{-}O_2} + \underset{\text{(From carbonic acid)}}{H^+} \longrightarrow \underset{\text{Reduced Hb}}{Hb\text{-}H} + \underset{\text{(Released to tissue cells)}}{O_2}$$

In this case, H_2CO_3, a weak acid is buffered by even weaker acid, hemoglobin.

B. Respiratory regulation of acid-base homeostasis

Respiratory system regulation of acid-base balance provides a physiological buffering system. CO_2 is formed continually in the body by intracellular metabolic processes. After it is formed, it diffuses from the cells into the interstitial fluids of blood, and the blood transport it to the lungs, where it diffuses into the alveoli and is transferred to the atmosphere by pulmonary ventilation. An increase in the CO_2 concentration in the ECF increases H^+ concentration and thus lowers the pH making it more acidic. Conversely, a decrease in the CO_2 concentration of ECF raises the pH making it more alkaline.

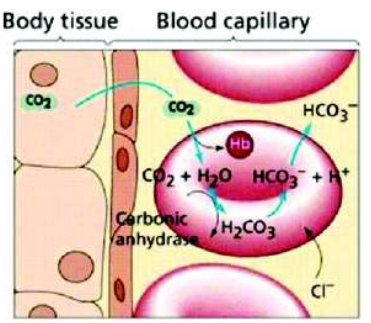


Fig. 2 *Carbon dioxide transport*

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

The rate and depth of breathing (ventilation) can alter the pH of body fluids. With increased ventilation, more CO_2 is exhaled. Thus, during CO_2 unloading, the above reaction is pushed to the left, reducing the H^+ concentration and blood pH increases. If the rate of ventilation decreases below normal, less CO_2 is exhaled. This result in accumulation of CO_2 in ECF, the reaction is driven to the right, the H^+ concentration increases, the blood pH decreases.

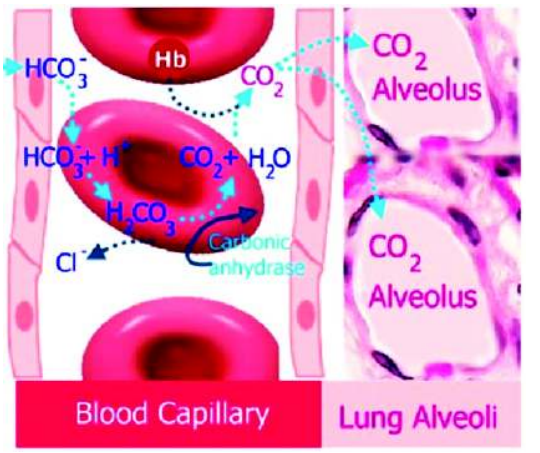


Fig. 3 *Carbon dioxide exchange in lungs.*

Renal Mechanism of Acid-base Homeostasis

Chemical buffers can bind excess acids or bases temporarily, but they cannot eliminate them from the body. The kidneys control acid-base balance by excreting either acidic or basic urine. Amount of acid in ECF is reduced by excreting acidic urine, whereas base is reduced by excreting basic urine. Each day body produces about 80 milliequivalents of nonvolatile acids, mainly from the metabolism of proteins. These acids are called nonvolatile because they are not H_2CO_3 and therefore, cannot be excreted by the lungs. The primary mechanism for removal of these acids from the body is renal excretion.

The most important renal mechanisms for regulating acid-base balance of the blood involve H^+ secretion and bicarbonate reabsorption. Each day the kidneys filter about 4320 milliequivalents of bicarbonate; under normal conditions, almost all this is reabsorbed from the tubules thereby conserving the primary buffer system of the ECF. About 80 to 90 per cent of the bicarbonate reabsorption (and H^+ secretion) occurs in the proximal convoluted tubule (PCT) of nephrons, so that only a small amount of bicarbonate flows into the distal convoluted tubules (DCT) and collecting ducts (CD). In the thick ascending loop of Henle, another 10 per cent of the filtered bicarbonate is reabsorbed, and the remainder of the reabsorption takes place in the DCT and CD.

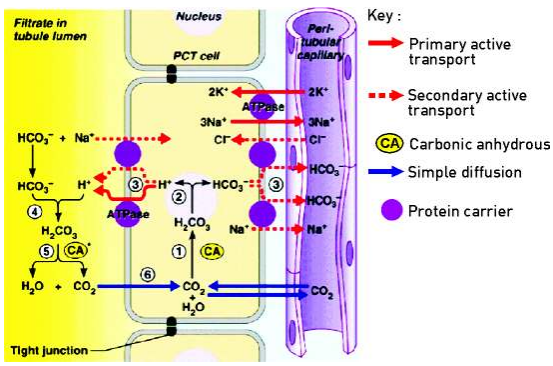


Fig. 4 Reabsorption of HCO_3^- and secretion of H^+ in the renal tubular cells.

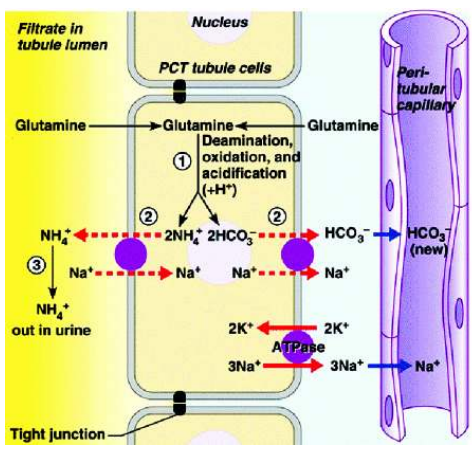


Fig. 5 Excretion of H^+ in the form of NH_4^+

Reabsorption of Bicarbonate and Secretion of H^+

The epithelial cells of the PCT, thick segment of ascending limb of loop of Henle and initial part of DCT secrete H^+ into the tubular fluid by secondary active transport process with the help of Na^+/H^+ antiporters. These antiporters carry filtered Na^+ down its concentration gradient from tubular fluid into cells as H^+ is secreted from the cytosol into the tubular lumen. The epithelial cells produce H^+ in the following way. CO_2 diffuses from peritubular blood or tubular fluid or is produced by metabolic reactions within the cells. In the cytosol of cells, the enzyme carbonic anhydrase catalyses the reaction of CO_2 with water to form H_2CO_3, which then dissociates into H^+ and HCO_3^-:

$$CO_2 + H_2O \xrightarrow{\text{carbonic anhydrase}} H_2CO_3 \longrightarrow H^+ + HCO_3^-$$

After H^+ is secreted into the tubular fluid within the lumen, it reacts with filtered HCO_3^- to form H_2CO_3, which readily dissociates into CO_2 and H_2O. CO_2 then diffuses into the tubule cells and join with H_2O to form H_2CO_3, which dissociates into H^+ and HCO_3^-. As the level of HCO_3^- rises in the cytosol, it exits via facilitated diffusion transporters in the basolateral membrane and diffuses into the blood. Thus, for every H^+ secreted into the tubular fluid, one HCO_3^- is reabsorbed (one Na^+ also reabsorbed).

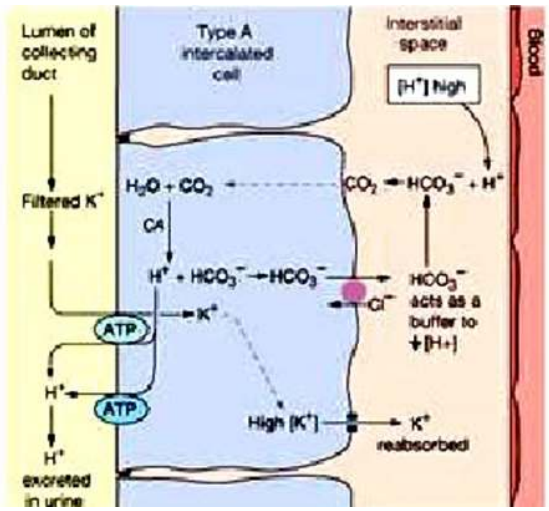


Fig. 6 Type A intercalated cell function in acidosis. H^+ is excreted, HCO_3^- and K^+ reabsorbed

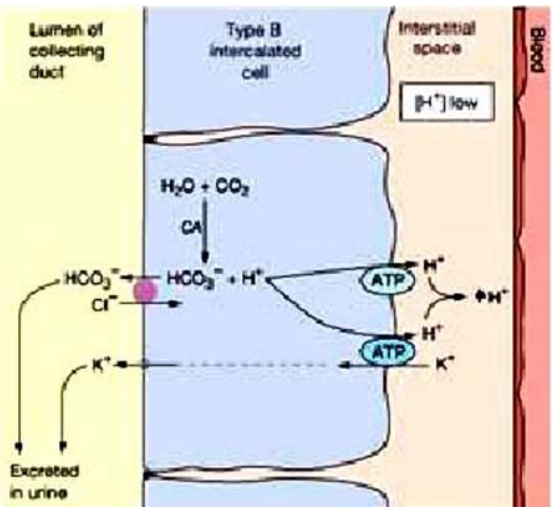


Fig. 7 Type B intercalated cell function in alkalosis. H^+ is reabsorbed, HCO_3^- and K^+ excreted

The apical membranes of intercalated cells (type A) present in the last part of DCT and CD contains proton pumps (H^+ pumps) that secrete H^+ into the tubular fluid. The HCO_3^- produced in the cytosol of intercalated cells by dissociation of H_2CO_3 crosses the basolateral membrane into the interstitial fluid by means of Cl^-/HCO_3^- antiporters and then diffuses into blood. Although the secretion of H^+ in the last part of DCT and CD account for only about 5 per cent of the total H^+ secreted, this mechanism is important in forming a maximally acidic urine.

When the body is in alkalosis, a second type of intercalated cells (type B) present in CD has H^+ proton pumps in its basolateral membrane and Cl^-/HCO_3^- antiporters in its apical membrane play an important role in acid-base balance. These intercalated cells secrete HCO_3^- and reabsorbs H^+. Thus, the two types of intercalated cells help maintain pH of body fluids in two ways: by excreting excess H+ when pH of body fluids is too low and by excreting excess HCO_3^- when pH is too high.

Some H^+ secreted into tubular fluid of the CD are buffered, but not by HCO_3^-, most of which has been filtered and reabsorbed. Two other buffers combine with H^+ in the CD. The most plentiful buffer in the tubular fluid of the CD is HPO_4^- (monohydrogen phosphate ion). In addition, a small amount of NH_3 (ammonia) also is present. H^+ combines with HPO_4^- to form $H_2PO_4^-$ (dihydrogen phosphate ion) and with NH_3 to form NH_4^+ (ammonium ion). Because these ions cannot diffuse back into tubule cells, they are excreted in the urine.

Acid-base Disorders

A change in blood pH leads to acidosis or alkalosis which can be classed according to cause as respiratory or metabolic.

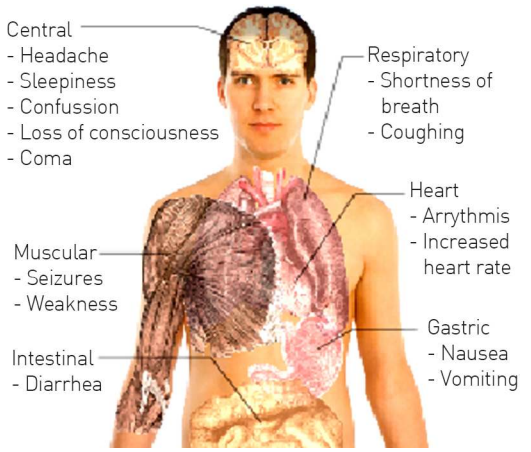


Fig. 8 Symptoms of acidosis.

A. Respiratory acidosis and alkalosis

Respiratory pH imbalances results from some failure of the respiratory system to perform its normal pH balancing role. Both respiratory acidosis and alkalosis are disorders resulting from changes in the Pco_2 in the systemic arterial blood (normal range is 35-45 mm of Hg).

Respiratory acidosis is caused by a buildup of carbon dioxide in the blood. This is a result of decreased lung function, which can be caused by emphysema or chronic bronchitis, neurological and neuromuscular diseases that affect the muscles of the chest, as well as drug or alcohol overdose. Respiratory acidosis causes headaches and drowsiness, which can quickly lead to stupor and coma.

Respiratory alkalosis occurs when the body hyperventilates (breaths too quickly), and expels too much carbon dioxide from the blood. This can occur in cases of extreme anxiety, pain, fever and aspirin overdose. Respiratory alkalosis can cause dizziness; however, it usually corrects itself with the return of normal breathing.

B. Metabolic acidosis and alkalosis

Metabolic pH imbalances are disorders resulting from changes in HCO_3^- concentration (normal range is 22-26 mEq/liter in systemic arterial blood).

Metabolic acidosis occurs when the body produces an excessive amount of organic acids, when an acid is ingested or when the kidneys are not functioning correctly. Metabolic acidosis causes nausea, vomiting and fatigue. People with mild metabolic acidosis may also have changes in respiration, breathing faster and deeper. These symptoms will progressively worsen and eventually lead to shock, coma and death.

Metabolic alkalosis occurs when the body loses too much acid, such as stomach acid lost during vomiting, or has too much bicarbonate in the blood. Kidney problems can also lead to metabolic alkalosis. Metabolic alkalosis causes irritability, muscle cramps and spasms and muscle twitching.

Effects of Acidosis and Alkalosis

When blood pH falls below 7.0, the CNS is so depressed that the person goes into coma and death soon follows. When blood pH rises above 7.8, the nervous system is over excited and causes muscle tetany, extreme nervousness, and convulsions.

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