

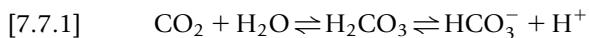
7.7 Renal Component of Acid–Base Balance

Learning Objectives

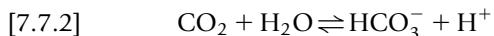
- List the three body systems for regulating plasma pH
- Define titratable acid
- Describe how the kidney can make new HCO_3^- linked to urinary titratable acid and ammonium
- Describe the metabolic origin of urinary ammonium
- Explain why ammonium does not show up as a titratable acid
- Describe the renal response to respiratory acidosis
- Describe the renal response to respiratory alkalosis
- Describe the renal response to metabolic acidosis
- Describe the renal response to metabolic alkalosis

THE KIDNEYS ELIMINATE THE ACID PRODUCED FROM METABOLISM

Addition of CO_2 to blood raises the H^+ concentration of the blood, decreasing its pH. This is caused by the hydration of CO_2 with the formation of carbonic acid (H_2CO_3) and subsequent dissociation of (H_2CO_3) to bicarbonate and H^+ :

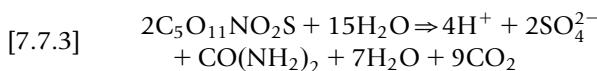


This reaction occurs spontaneously in physiological fluids, but it is slow. The enzyme **carbonic anhydrase** catalyzes the hydration reaction but without the release of H_2CO_3 . Carbonic anhydrase catalyzes the reaction:



The H^+ and HCO_3^- can then combine to form carbonic acid. Because carbonic acid is in equilibrium with the volatile CO_2 , H_2CO_3 is called a **volatile acid**. At rest, the body produces approximately 200 mL of CO_2 per minute (at STPD). This is $200 \text{ mL min}^{-1} \times 1440 \text{ min day}^{-1} / 22.4 \text{ L mol}^{-1} \approx 13 \text{ mol of CO}_2 \text{ per day}$ under resting conditions. The actual production averages about 20 mol of CO_2 per day because activity increases O_2 consumption and CO_2 production. Because the hydration reaction that occurs in the venous blood that collects CO_2 is reversed in the lungs where the CO_2 is eliminated to the atmosphere, there is no net H^+ produced from CO_2 .

In addition to CO_2 , the body produces about 0.3–1 mmol of acid per kilogram of body weight per day or about 20–70 mmol of acid per day. This acid originates from the oxidation of sulfur-containing amino acids as in the oxidation of methionine:



Additional acid originates from oxidation of phospholipids, producing H_3PO_4 , and from partial metabolism of carbohydrates and fats that produce organic acids (lactic acid, acetoacetic acid, and β -hydroxybutyric acid). In rapid muscular activity or hypoxia in which anaerobic metabolism dominates, the production of these nonvolatile acids is markedly enhanced. Thus the normal acid–base situation in blood is the defense of the alkaline blood against a constant assault by acid. The kidneys excrete the excess acid that is produced daily.

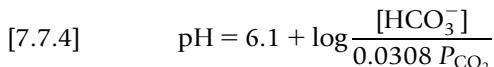
THE BODY USES CHEMICAL BUFFERS, THE RESPIRATORY SYSTEM, AND THE RENAL SYSTEM TO REGULATE pH

THE CHEMICAL BUFFERS RESPOND RAPIDLY AND ARE THE FIRST DEFENSE

The chemical buffers resist change in plasma pH by binding H^+ when it is present in excess and releasing H^+ when there is a deficit. There are a variety of buffers, and their affinity for H^+ is described by their K_A , the acid association constant (see Chapter 6.5). The ability to buffer changes in pH is maximum when the $\text{pH} = \log K_A = -\log K_D = \text{pK}$. All of these buffers are linked by their binding of the H^+ ion (the **isohydric principle**), so that adjustment of any one buffer system adjusts them all through the adjustment of $[\text{H}^+]$. The body adjusts the **bicarbonate buffer system** because CO_2 can be regulated by adjusting CO_2 elimination to the atmosphere.

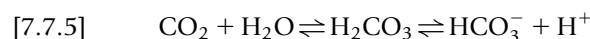
THE RESPIRATORY SYSTEM RESPONDS RAPIDLY BY ADJUSTING P_{aco_2}

Recall the Henderson–Hasselbalch equation for the bicarbonate buffer system that we derived in Chapter 6.5:



Here 6.10 is the pK when $[\text{HCO}_3^-]$ is given in mmol L^{-1} and arterial P_{CO_2} is in mmHg. The log is the logarithm base 10, not the natural logarithm. Increasing P_{CO_2} decreases the argument of the logarithm, which decreases the value of the logarithm, which decreases pH. The alveolar ventilation equation (Eqns 6.3.21 and 6.3.22) shows that the alveolar P_{aco_2} , which equilibrates with the arterial P_{CO_2} , is set by the ratio Q_{CO_2}/Q_A , the rate of CO_2 production divided by the rate of alveolar ventilation. For a given rate of metabolism (Q_{CO_2}), the P_{aco_2} is inversely proportional to the alveolar ventilation, Q_A . Thus increasing the breathing rate and depth increases Q_A and decreases P_{aco_2} . According to Eqn (7.7.3), increasing alveolar ventilation will lower P_{CO_2} , increase the argument of the logarithm, increase its value, and thereby increase plasma pH. Similarly, reducing Q_A raises the plasma P_{CO_2} and lowers pH. Alveolar ventilation is stimulated in part by pH sensors located in the central nervous system (CNS) in the medulla and peripherally in the carotid bodies. Thus acidosis stimulates respiratory drive by stimulating the peripheral chemoreceptors, and this increases Q_A , blowing off CO_2 and raising the pH of the blood back toward normal. The opposite events occur in alkalosis. This response of the respiratory system is rapid but incomplete: it cannot by itself return the blood to a normal pH and P_{CO_2} .

The Henderson–Hasselbalch equation is a different way of representing Eqn (7.7.1), the buffer reaction of carbonic acid. Acid–base balance can also be understood by a straightforward application of Le Chatelier's principle to the bicarbonate buffer reaction (Eqn 7.7.1), except it is more difficult to be quantitative about it. Le Chatelier's principle states that any reaction will respond to a perturbation in its constituents in such a way as to minimize the perturbation. The bicarbonate buffer reaction is as follows:



Thus increasing P_{CO_2} increases $[\text{CO}_2]$, which forces the reaction to the right: the reaction consumes CO_2 to produce H_2CO_3 , HCO_3^- , and H^+ in order to minimize the perturbation of increased CO_2 . In this way, reduction in ventilation increases P_{CO_2} , which subsequently increases $[\text{H}^+]$ and decreases the pH. Similarly, reducing P_{CO_2} forces the reaction in the opposite direction, consuming H^+ and raising the pH.

THE RENAL SYSTEM RESPONDS SLOWLY BUT COMPLETELY BY ADJUSTING $[\text{HCO}_3^-]$

The kidney constitutes the third line of defense against pH disturbances. Although it acts much more slowly than the chemical buffers and the respiratory system, it completely compensates for the addition of acid or base to the blood. It does this either by acidifying the blood by alkalinizing the urine or by alkalinizing the blood by acidifying the urine. The mediator of both of these processes is the bicarbonate ion, HCO_3^- . These relationships can be seen by inspection of the Henderson–Hasselbalch equation or by applying

Le Chatelier's principle to the bicarbonate buffer reaction. In acidosis, $\log ([\text{HCO}_3^-]/0.0308 P_{\text{CO}_2})$ is too low. It can be corrected by lowering P_{CO_2} , which is the respiratory component of compensation, or by raising $[\text{HCO}_3^-]$, which is the renal component of compensation. In the bicarbonate buffer reaction, increased acidity can be corrected by causing the reaction to go to the left, consuming H^+ . This is accomplished by lowering $[\text{CO}_2]$ by hyperventilation, or by raising $[\text{HCO}_3^-]$, which binds the extra H^+ ions. Similar arguments apply to the respiratory and renal components of compensation for alkalosis, with the direction of the reactions reversed compared to acidosis.

ACID EXCRETION BY THE TUBULE ADJUSTS BLOOD pH

Regulation of plasma pH by the kidney is accomplished by secreting more or less acid into the tubule fluid *relative to the filtered load of HCO_3^-* . If the plasma is acidic, secretion of more acid into the tubule fluid than the filtered HCO_3^- acidifies the tubule fluid and alkalinizes the blood. As we shall see, acid secretion is linked to HCO_3^- transfer to the blood. Therefore, acid secretion in excess of the filtered HCO_3^- alkalinizes the blood by increasing its $[\text{HCO}_3^-]$, thereby returning the blood pH toward normal. Similarly, if the blood is too alkaline, less acid is secreted into the tubule than the filtered HCO_3^- , and HCO_3^- is lost in an alkaline urine. The HCO_3^- that is lost originated from the blood by glomerular filtration. Thus less acid secretion is linked to reduction in plasma $[\text{HCO}_3^-]$, which acidifies the blood. The key to this process is the link between acid secretion and HCO_3^- appearance in the plasma.

THE KIDNEY LINKS ACID SECRETION TO HCO_3^- APPEARANCE IN PLASMA

The basic mechanism for the reabsorption of filtered HCO_3^- in proximal tubule cells is shown in Figure 7.7.1. Secretion of acid begins with plasma CO_2 . CO_2 from the plasma can enter the tubule cells where it is hydrated to form HCO_3^- and H^+ . The hydration reaction is catalyzed by carbonic anhydrase. Two mechanisms on the apical membrane pump out the H^+ across the apical membrane into the lumen. These are as follows: (1) an active H^+-ATPase that is a primary active transporter and (2) an Na^+-H^+ exchanger (NHE3) that operates by secondary active transport. In other parts of the nephron, a third secretory mechanism, a $\text{H}^+\text{K}^+-\text{ATPase}$, can pump H^+ from the cell in exchange for K^+ .

In the tubule lumen, carbonic anhydrase IV on the luminal membrane rapidly combines the secreted H^+ with HCO_3^- that was filtered from the plasma. These form CO_2 and H_2O . The CO_2 can then diffuse through the cell and into the plasma. Thus acid secretion results in the disappearance of HCO_3^- from the tubule fluid.

HCO_3^- in the tubule cell is transported across the basolateral membrane into the peritubular fluid by a specific

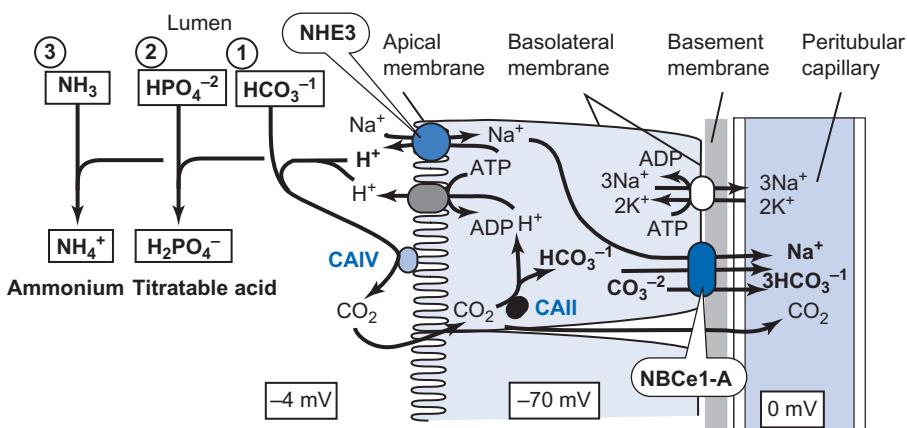


FIGURE 7.7.1 Mechanism of reabsorption of HCO_3^- in proximal tubule cells. H^+ ions within the tubule cell are actively secreted into the lumen across the apical membrane by the operation of primary active transport (H^+-ATPase) or secondary active transport (Na^+-H^+ exchanger). The secreted H^+ combines with HCO_3^- to form carbonic acid, H_2CO_3 . Carbonic anhydrase converts this to CO_2 and H_2O . The H_2O joins the rest of the water in the tubule lumen and may be either reabsorbed or excreted. The CO_2 diffuses into the cell where it may be hydrated to form H_2CO_3 again, catalyzed by cytosolic carbonic anhydrase. The carbonic acid dissociates to form H^+ and HCO_3^- . The H^+ replenishes the cytosolic H^+ initially pumped out of the cell. The HCO_3^- is transported out of the cell into the peritubular fluid by a secondary active transporter, using Na^+ as the cotransported ion. The net result is a disappearance of $\text{Na}^+\text{HCO}_3^-$ from the lumen and appearance of $\text{Na}^+\text{HCO}_3^-$ in the blood. Secreted H^+ ions can also combine with other filtered buffers. The figure shows binding of secreted H^+ with NH_4^+ , which has a $pK = 7.21$. According to the Henderson–Hasselbalch equation, an acid is half neutralized when the $\text{pH} = \text{p}K$, and this is the point of maximal buffering. Addition of strong base will neutralize this acid, and so it forms part of the titratable acid. Its excretion is linked to the formation of new HCO_3^- in plasma. Secreted H^+ ions can also combine with NH_3 , ammonia, to produce NH_4^+ , the ammonium ion. Excretion of NH_4^+ is also linked to the formation of new HCO_3^- in the plasma.

carrier. This $\text{Na}^+-\text{HCO}_3^-$ cotransporter type NBCe1-A appears to transport one HCO_3^- and one CO_3^{2-} for each Na^+ , which is the equivalent of three HCO_3^- for each Na^+ . The NBCe1-A is electrogenic. Since it carries three negative charges for each positive charge, it carries a net current.

In the overall process shown in Figure 7.7.1, a HCO_3^- ion is returned to the blood for every H^+ ion that is secreted. It is important to note that the HCO_3^- that appears in the blood is not the same as that which disappeared from the tubule lumen. The one that disappeared from the tubule lumen became H_2O and CO_2 , whereas the HCO_3^- that is placed in the blood originates from plasma or tubule fluid CO_2 . However, the net effect of the system's operation is the transfer of filtered HCO_3^- to the blood. If H^+ secretion is insufficient to reclaim all of the filtered HCO_3^- , then HCO_3^- will be lost in the urine. If H^+ secretion is sufficiently rapid, all of the filtered HCO_3^- can be reclaimed. If H^+ secretion is more rapid yet, new HCO_3^- can be added to the blood.

SECRETED ACID RECLAIMS HCO_3^- OR COMBINES WITH TITRABLE ACID OR AMMONIUM

Figure 7.7.1 illustrates three possible fates of secreted H^+ . The first is binding to HCO_3^- , which is equivalent to reabsorption of filtered HCO_3^- . Two other fates are possible. Secreted H^+ can bind to ammonia (NH_3) to produce ammonium (NH_4^+), or it can bind to titratable acids. An example of titratable acids is H_2PO_4^- .

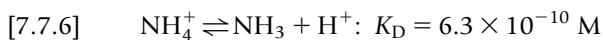
Titratable acid is defined as the amount of strong base needed to titrate the pH of the urine back to

pH 7.4. This is the normal pH of the glomerular ultrafiltrate, so the amount of strong base that is used to titrate the urine back is equal to the amount of titratable acid that was excreted into the tubular fluid to produce the urine. As can be seen in Figure 7.7.1, excretion of titratable acid is linked to the formation of new HCO_3^- ; for every H^+ ion that is secreted into the tubule fluid and combines with a titratable acid, a new HCO_3^- ion is placed into the plasma. Thus the venous blood that drains the kidney can have a net gain in plasma $[\text{HCO}_3^-]$. The increased HCO_3^- binds plasma H^+ , thereby reducing the $[\text{H}^+]$ and raising the pH.

Figure 7.7.1 also shows that the excretion of NH_4^+ is linked to the formation of new HCO_3^- . For every H^+ that is secreted and combines with NH_3 , a new HCO_3^- ion is placed in the plasma. The mechanism is not exactly as shown in Figure 7.7.1 because the binding of H^+ usually occurs within the tubule cell rather than in the lumen, but the net effect is the same: excretion of NH_4^+ increases the plasma $[\text{HCO}_3^-]$.

AMMONIA DOES NOT SHOW UP AS TITRABLE ACID BECAUSE ITS pK IS TOO HIGH

The acid dissociation of NH_4^+ is written as



The pK for this reaction is 9.2. The Henderson–Hasselbalch equation for this reaction is as follows:

$$[7.7.7] \quad \text{pH} = 9.2 + \log \frac{[\text{NH}_3]}{[\text{NH}_4^+]}$$

where NH_4^+ is the acid and NH_3 is the base. What this equation means is that at ordinary pH of 7.4, the equilibrium $[\text{NH}_3]$ will be much smaller than $[\text{NH}_4^+]$. At pH 7.4, in cells and in the tubular fluid, most of the buffer will be present as NH_4^+ . The NH_4^+ will not react with base and be converted to NH_3 until the pH approaches the pK. Thus the titration of the urine to pH 7.4 does not reveal its content of NH_4^+ .

NEW HCO_3^- FORMED IS THE SUM OF TITRATABLE ACID AND NH_4^+ MINUS THE EXCRETED HCO_3^-

For each H^+ excreted as titratable acid, there is one new HCO_3^- transferred to blood. For each H^+ excreted as NH_4^+ , there is also one new HCO_3^- transferred to blood. Urine typically contains some HCO_3^- that has not been

reabsorbed. The net gain of HCO_3^- to the body is the balance of these sources and sinks:

$$\text{Net HCO}_3^- \text{ gain} = \text{titratable acid} + \text{NH}_4^+ - \text{HCO}_3^-$$

[7.7.8]

where the titratable acid, NH_4^+ , and HCO_3^- refer to the amounts present in the urine.

AMMONIUM ORIGINATES FROM AMINO ACIDS IN PROXIMAL TUBULE CELLS

Proximal tubule cells deaminate glutamine to glutamic acid and then form α -ketoglutaric acid, liberating one NH₃ group at each step. These reactions are shown in Figure 7.7.2. Glutamine enters the proximal tubule cell two ways: it is reabsorbed from filtered glutamine

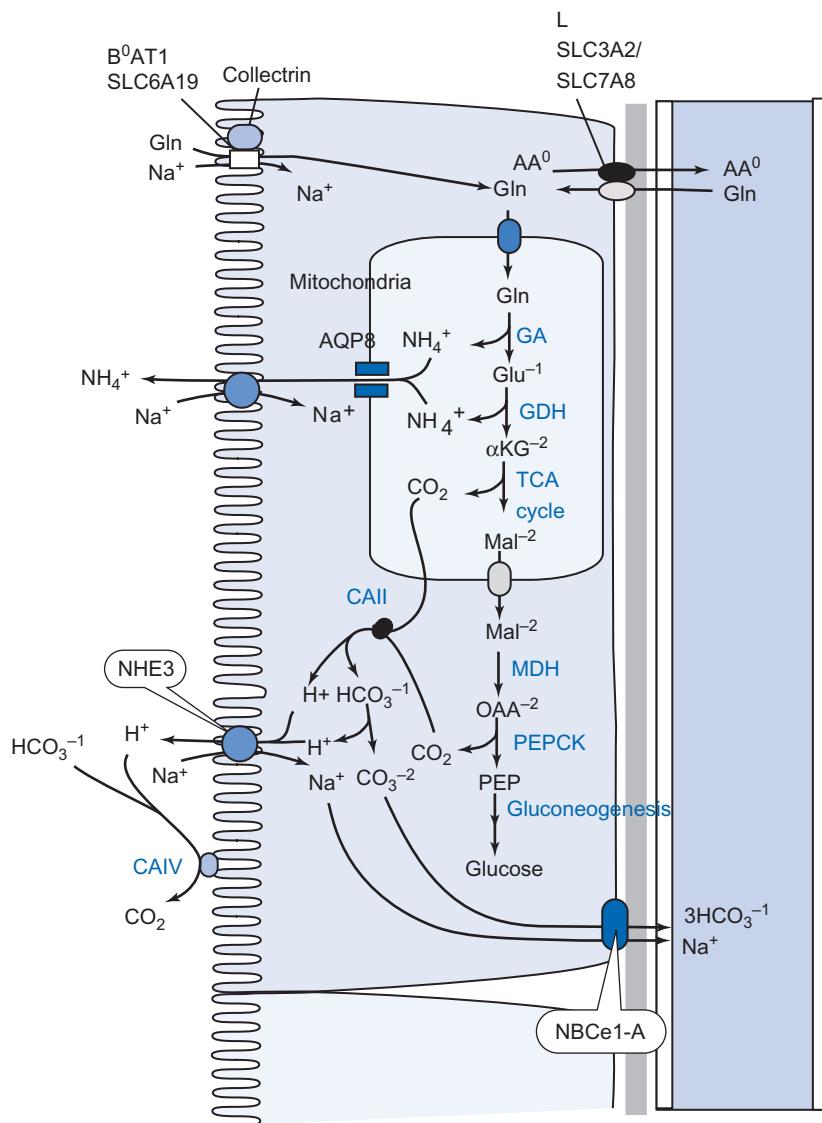


FIGURE 7.7.2 Mechanism of generation of ammonia in proximal tubule cells. Deamination of glutamine occurs in two steps: conversion to glutamic acid and conversion to α -ketoglutaric acid. Ammonia generated in this way quickly is protonated to ammonium, which can be transported across the apical cell membrane by the $\text{Na}^+ - \text{H}^+$ exchanger. Every excreted NH_4^+ is equivalent to the secretion of H^+ that is linked to the formation of a new HCO_3^- that appears in the blood. In this way, the kidney can replenish blood HCO_3^- that has been depleted by acidosis.

through the neutral amino acid transporter, B⁰AT1, or it is taken up from the peritubular capillaries by exchange with neutral amino acids. During normal acid–base balance, filtered glutamine is taken up by these cells and largely returned to the blood. During chronic acidosis, the activity of several enzymes and transporters are increased to increase the rate of deamination of glutamine. The NH₃ liberated from these reactions nearly instantly equilibrates with the cells' [H⁺], with only a small fraction remaining free as NH₃. The NH₄⁺ crosses the apical membrane, probably carried by the Na⁺–H⁺ exchanger. Some free NH₃ may also diffuse across the apical membrane because it is uncharged and lipophilic. In the tubule fluid, NH₃ binds to H⁺ ions secreted by the cells. Once it binds H⁺ to form ammonium, it can no longer easily penetrate the apical membrane. This is called **diffusion trapping** because NH₃ diffuses across the membrane and then becomes trapped in the acid environment as NH₄⁺. For every NH₄⁺ excreted, there is the equivalent

of one H⁺ excreted that is linked to transfer of new HCO₃[−] to the plasma. Other amino acids also can generate ammonium but most of it derives from glutamine.

THE THICK ASCENDING LIMB SECRETES ACID, REABSORBS BICARBONATE AND AMMONIUM

About 80–90% of the filtered HCO₃[−] is reabsorbed in the proximal tubule. Distal tubule fluid has about the same [HCO₃[−]] as the late proximal tubule. Because water is reabsorbed in the loop of Henle, this means that significant HCO₃[−] reabsorption must occur in the loop, about 10–15% of the filtered load. In addition, much of the NH₄⁺ in the proximal tubule does not continue on to the distal tubule; it also must have been reabsorbed. These transport activities occur in the thick ascending limb, through mechanisms outlined in Figure 7.7.3. As in the proximal tubule, the majority of

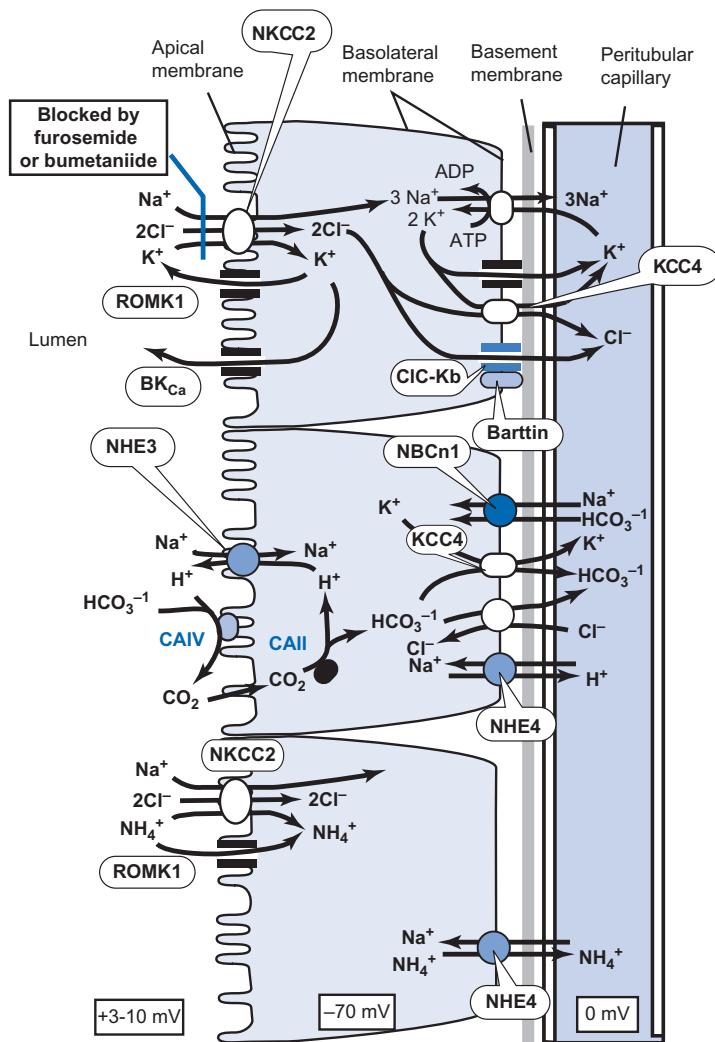


FIGURE 7.7.3 Mechanisms of H⁺ secretion, HCO₃[−] reabsorption, and NH₄⁺ reabsorption in thick ascending limb. Top, mechanisms of Na⁺, K⁺, and Cl[−] transport. Middle, mechanisms of HCO₃[−] reabsorption. Bottom, mechanisms of NH₄⁺ transport. The mechanism of H⁺ secretion is similar to that in the proximal tubule. Most of the H⁺ is secreted through secondary active transport powered by the Na⁺ gradient through an Na⁺–H⁺ exchanger. The thick ascending limb also possesses a H⁺-ATPase. HCO₃[−] in the tubule fluid is neutralized by the secreted H⁺, while a new HCO₃[−] ion made in the cell is transported out of the cell by multiple mechanisms that include Cl[−]–HCO₃[−] exchange, and K⁺–HCO₃[−] cotransport, probably over KCC4. NH₄⁺ in the fluid may enter the cell through the Na:K:2Cl cotransporter or through K⁺ channels. NH₄⁺ exits the cell over the Na⁺–H⁺ exchanger, NHE4.

acid secretion occurs through the $\text{Na}^+ - \text{H}^+$ exchanger (NHE3). The secreted acid combines with HCO_3^- in the lumen to become CO_2 . HCO_3^- exit from the cell is accomplished by multiple mechanisms including a $\text{Cl}^- - \text{HCO}_3^-$ exchange and $\text{K}^+ - \text{HCO}_3^-$ cotransport probably mediated by KCC4. Cells in the thick ascending limb express NBCn1, a $\text{Na}^+ - \text{HCO}_3^-$ cotransporter on the basolateral membranes, but this is thought to mediate an HCO_3^- entry into the cells. NH_4^+ reabsorption is favored by a positive lumen potential. NH_4^+ enters the thick ascending limb cell either through the $\text{Na}: \text{K}: 2\text{Cl}$ transporter or through an apical K^+ channel (ROMK). Most NH_4^+ exits the cells by the NHE4, a $\text{Na}^+ - \text{H}^+$ exchanger that can carry NH_4^+ . The net result of these transport processes is to reabsorb NaHCO_3 and to add $\text{NH}_3/\text{NH}_4^+$ to the kidney interstitium. This sets up another countercurrent multiplier that concentrates $\text{NH}_3/\text{NH}_4^+$ in the medullary interstitium. NH_4^+ is secreted by the proximal tubules, reabsorbed into the interstitium by cells in the thick ascending limb, and then $\text{NH}_3/\text{NH}_4^+$ enters the collecting duct by diffusion trapping driven by the acid pH of the collecting duct fluid.

Increasing $[\text{K}^+]$ in the lumen of the thick ascending limb interferes with NH_4^+ reabsorption, presumably by competition between K^+ and NH_4^+ for transport via NKCC2. Hyperkalemia thus induces an acidosis by preventing the gradient in NH_4^+ between the vasa recta and collecting duct.

DIFFERENT CELL TYPES IN THE DISTAL NEPHRON AND COLLECTING DUCT HANDLE ACID AND BASE DIFFERENTLY

The late distal tubule and collecting duct are heterogeneous structures that contain several cell types. The distal nephron and cortical collecting duct can secrete H^+ or HCO_3^- , depending on the chronic acid–base status of the body. Distinct cell types mediate these functions. Cells called α -intercalated cells secrete acid and β -intercalated cells secrete base. These cells are also called A-intercalated and B-intercalated cells, for acid secreting and base secreting. The mechanisms are shown diagrammatically in Figure 7.7.4. The distal nephron also has other types of cells besides these A-intercalated and B-intercalated types.

The α -intercalated cells secrete H^+ ions across their apical membrane by two primary active transporters: the $\text{H}^+ - \text{ATPase}$ and the $\text{H}^+, \text{K}^+ - \text{ATPase}$. This secretion of H^+ is linked to the formation of new HCO_3^- within the cell, which exits the basolateral membrane over a $\text{Cl}^- - \text{HCO}_3^-$ exchanger, AE1. The $\text{Cl}^- - \text{HCO}_3^-$ exchange is a product of alternate gene splicing of the same gene that produces the $\text{Cl}^- - \text{HCO}_3^-$ exchanger of the red blood cells. HCO_3^- can also exit the cell over a $\text{Cl}^- - \text{HCO}_3^-$ exchanger, SLC26A7.

The ion transport properties of β -intercalated cells look largely like a mirror image of those of the α -intercalated cell. They have $\text{H}^+ - \text{ATPase}$ primary active transport on the basolateral membrane that pumps H^+ into the peritubular fluid rather than into the lumen as in the case

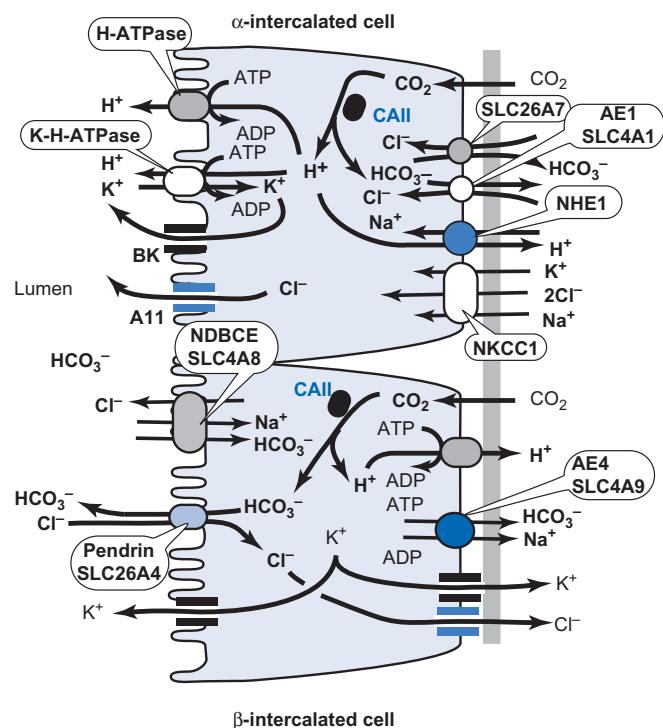


FIGURE 7.7.4 Mechanism of acid and base secretion by α -intercalated cells (top) and β -intercalated cells (bottom) in the distal nephron. The α -intercalated cells secrete acid whereas the β -intercalated cells secrete base. α -intercalated cells secrete H^+ on the apical membrane by primary active transport catalyzed by the H-ATPase and by the K-H-driven ATPase. HCO_3^- linked to this acid secretion is placed into blood by carriers (AE1 and SLC26A7) on the basolateral membrane. In B cells, acid is secreted into the blood and HCO_3^- is secreted into the tubule by Pendrin.

of the α -intercalated cells. Similarly, HCO_3^- generated in the cell exits on an apical membrane $\text{Cl}^- - \text{HCO}_3^-$ exchanger, Pendrin (SLC26A4). HCO_3^- in the lumen can be taken up by a Na-driven bicarbonate exchanger, NDBCE (SLC4A8). This device uses the energy of the Na^+ gradient to drive $\text{Cl}^- - \text{HCO}_3^-$ exchange. HCO_3^- in B-intercalated cells can exit on the basolateral side via AE4, a Na^+ and HCO_3^- cotransporter.

SYNOPSIS OF ACID–BASE HANDLING BY THE NEPHRON

Figures 7.7.1–7.7.4 show a plethora of transport mechanisms that become an unwieldy obstacle to our understanding of acid–base balance. However, it is almost certainly true that all of these transport mechanisms play a role under some conditions. Figure 7.7.5 shows a simplified version of these transport mechanisms, with the identifying names of the transporters.

TUBULAR pH AND CELLULAR PCO_2 REGULATE HCO_3^- REABSORPTION AND H^+ SECRETION

THE LIMITING pH OF THE URINE IS ABOUT 4.4

The active transport pumps present in the apical membrane of acid secreting parts of the nephron can

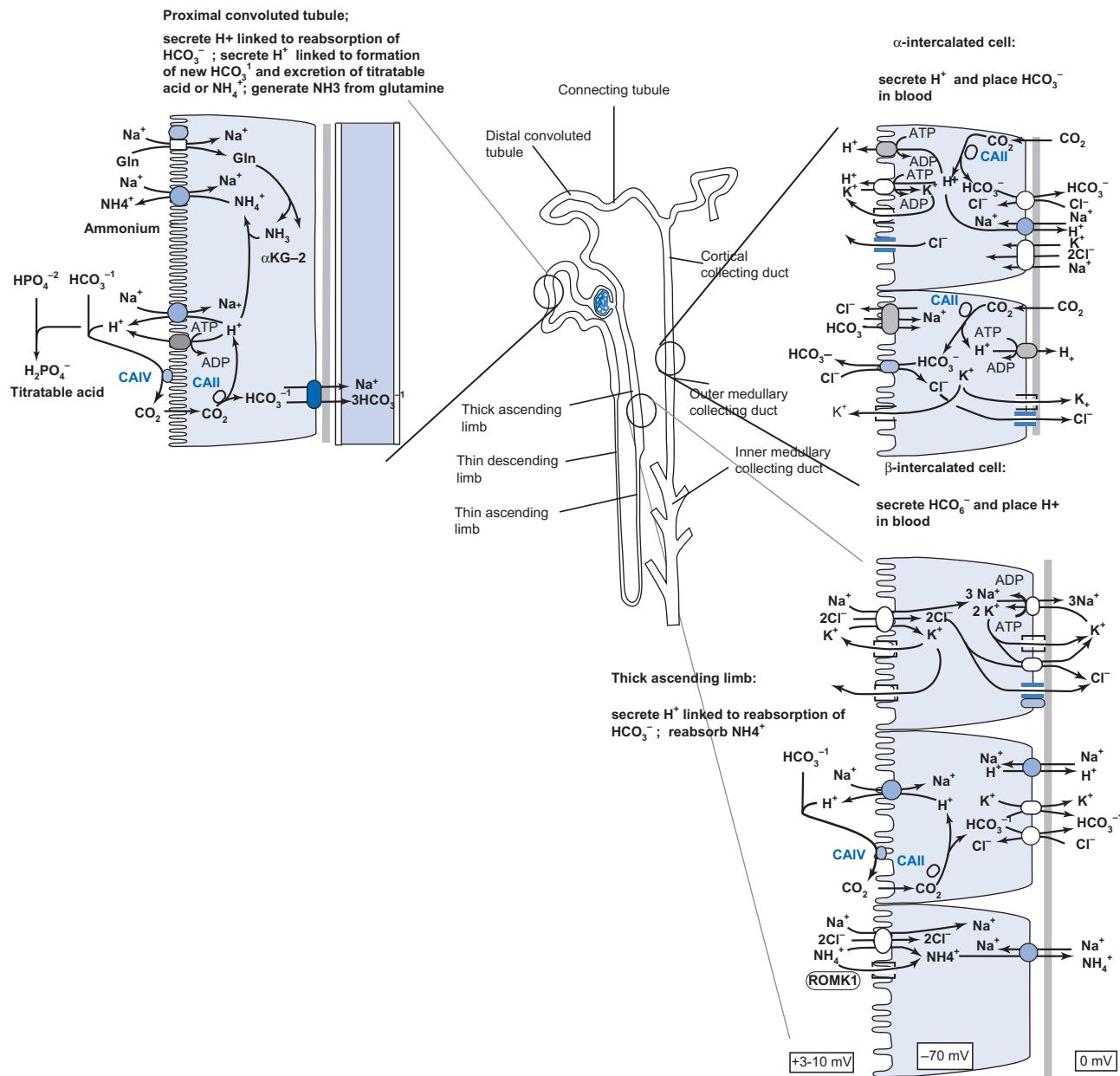


FIGURE 7.7.5 Synopsis of transport mechanisms related to acid–base handling by the nephron. The proximal tubule secretes H^+ by Na^+-H^+ exchange, powered by the basolateral Na,K -ATPase that creates a gradient for Na^+ entry into the cell. The secreted H^+ can combine with filtered HCO_3^- to form CO_2 via a luminal, membrane bound carbonic anhydrase IV. The secreted H^+ can also combine with filtered acids, such as HPO_4^{2-} to form H_2PO_4^- , which is a titratable acid. The third fate of secreted H^+ is to combine with NH_3 produced by the deamination of glutamine. The formation of titratable acid and ammonium is linked to the formation of new HCO_3^- that is placed in the blood. Thus the acidification of the urine by the proximal tubules is accompanied by alkalinization of the blood by addition of HCO_3^- . Cells in the thick ascending limb can also secrete H^+ through the Na^+-H^+ exchanger and reabsorb remaining filtered HCO_3^- . These cells can also reabsorb filtered NH_4^+ by entry across the apical membrane on the NKCC1 transporter, and exit across the basolateral membrane via the NHE4. Cells in the distal nephron are heterogeneous. A-intercalated cells secrete acid and alkalinize the blood by adding HCO_3^- to it. B-intercalated cells secrete base (HCO_3^-) and acidify the blood by secreting H^+ .

produce a limited gradient of $[\text{H}^+]$ because this gradient requires energy. As the gradient gets large, the pump is inhibited. These pumps can maximally concentrate $[\text{H}^+]$ about 1000-fold, from pH 7.4 to about pH 4.4. As the pH of the luminal contents falls, the ability of the pumps to continue secreting H^+ also falls. By binding secreted H^+ , buffers in the tubule fluid enhance H^+ secretion.

HCO_3^- REABSORPTION DISPLAYS GLOMERULOTUBULAR BALANCE

Because HCO_3^- binds H^+ , increased filtered load of HCO_3^- prevents the fall in tubular pH that otherwise would accompany H^+ secretion. This effect allows H^+ secretion to continue, and this H^+ secretion is the first step in the mechanism for HCO_3^- reabsorption.

Thus increased filtered load of HCO_3^- increases the rate of HCO_3^- reabsorption. This constitutes part of glomerulotubular balance, in which increased filtration at the glomerulus increases reabsorption by the tubules.

P_{CO_2} DRIVES ACID SECRETION AND HCO_3^- REABSORPTION

Figure 7.7.1 illustrates how the H^+ ions that drive H^+ secretion from the tubule cells are replenished ultimately from dissolved CO_2 . The dissolved CO_2 , in turn, derives from interstitial fluid CO_2 which derives from arterial CO_2 . Experimental control of P_{aCO_2} levels in the dog reveals increasing HCO_3^- reabsorption (which is approximately equal to acid secretion) with increasing P_{aCO_2} . Thus hypoventilation that increases P_{aCO_2} and causes respiratory acidosis is met with increasing renal H^+ secretion. Figure 7.7.6 illustrates the relationship between P_{aCO_2} and HCO_3^- reabsorption.

RENAL COMPENSATION FOR ACID–BASE DISTURBANCES

Acid–base balance is affected by multiple processes within the body, and dysfunction of the compensatory mechanisms leads to acid–base imbalance. The four major disorders for which the kidneys compensate include:

- respiratory acidosis
- respiratory alkalosis
- metabolic acidosis
- metabolic alkalosis.

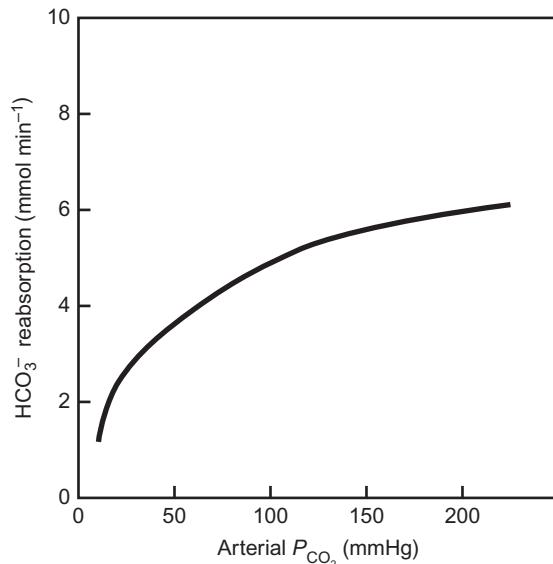


FIGURE 7.7.6 Relationship between arterial P_{CO_2} and the rate of HCO_3^- reabsorption in the dog. Since HCO_3^- reabsorption requires H^+ secretion, this illustrates how H^+ secretion is driven by H^+ supply to the tubule cells through hydration of CO_2 . From F.C. Rector, D.W. Seldin, A.D. Roberts, and J.S. Smith, *The role of plasma CO_2 tension and carbonic anhydrase activity in the renal reabsorption of bicarbonate*, *J. Clin. Invest.* **39**:1706, 1960.

We will consider the renal response to each of these and then consider special circumstances such as K^+ excess or deficit, and volume contraction or expansion.

THE KIDNEYS COMPENSATE FOR RESPIRATORY ACIDOSIS BY INCREASING $[\text{HCO}_3^-]$

In respiratory acidosis, the P_{aCO_2} is increased because either something interferes with ventilation (e.g., CNS depression) or something interferes with gas exchange (e.g., emphysema). The result is increased P_{aCO_2} driving an increased plasma $[\text{H}^+]$ and acidosis. There is also an increased $[\text{HCO}_3^-]$, as is expected from Le Chatelier's principle applied to the bicarbonate buffer system. The increased P_{CO_2} drives acid secretion, so acid secretion is increased. The secreted acid indirectly causes HCO_3^- reabsorption, but there is also more HCO_3^- filtered. Which is increased more, acid secretion by increased P_{CO_2} or filtered load? Here the increased acid secretion is more than the filtered load, so there is reabsorption of most of the filtered HCO_3^- plus formation of additional HCO_3^- linked to the excretion of titratable acid and NH_4^+ . This is what you would expect from the Henderson–Hasselbalch equation, based on teleological arguments: the kidney can restore the acidic plasma pH by raising $[\text{HCO}_3^-]$. This situation is shown in the pH– HCO_3^- diagram (see Figure 7.7.7). Note that the acid–base condition does not return to normal, even if the pH can normalize, because of the continued presence of respiratory acidosis. The normal condition can be attained only by resolving the initial disturbance. Thus plasma pH can be normal even though P_{CO_2} and $[\text{HCO}_3^-]$ is not normal.

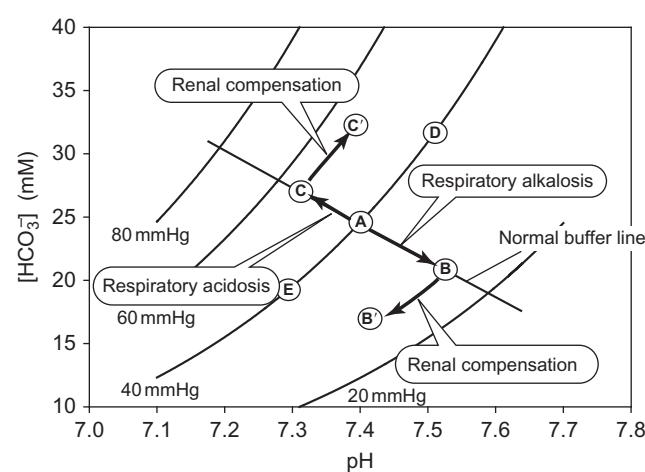


FIGURE 7.7.7 pH– HCO_3^- diagram showing the renal compensation of respiratory acidosis and alkalosis. The normal pH situation is indicated as A. Respiratory acidosis entails an increase in P_{CO_2} and $[\text{HCO}_3^-]$ along the normal buffer line, indicated as point C. Renal compensation is to increase the plasma $[\text{HCO}_3^-]$ along the abnormally high isobar. This can return the pH to normal levels (point C') in the continued presence of the respiratory condition. Respiratory alkalosis involves a decrease in P_{CO_2} and $[\text{HCO}_3^-]$ along the normal buffer line (point B). Renal compensation consists of lowering $[\text{HCO}_3^-]$ by excreting HCO_3^- in an alkaline urine. Compensated respiratory alkalosis is indicated by point B'.

THE KIDNEYS COMPENSATE FOR RESPIRATORY ALKALOSIS BY DECREASING $[HCO_3^-]$

In respiratory alkalosis, everything happens in reverse to respiratory acidosis. The alkalosis is caused by increased, inappropriate ventilation, usually caused by CNS stimulation. The alveolar P_{CO_2} is decreased, and therefore the arterial P_{CO_2} is decreased, and $[HCO_3^-]$ is also decreased due to Le Chatelier's principle. The change in a secondary parameter—one that derives from the primary one—is always less than the change in the primary parameter. The decrease in $[HCO_3^-]$ is less than the decrease in P_{CO_2} . Thus there is insufficient P_{CO_2} to drive acid secretion to reabsorb all of the filtered $[HCO_3^-]$, and HCO_3^- is lost in an alkaline urine. The pH disturbances of respiratory alkalosis and subsequent renal compensation are shown graphically in Figure 7.7.7.

These changes can be predicted by looking carefully at the Henderson–Hasselbalch equation for the bicarbonate buffer system (see Eqn 7.7.4)

$$[7.7.4] \quad pH = 6.1 + \log \frac{[HCO_3^-]}{0.0308 P_{CO_2}}$$

In respiratory acidosis, pH is low because P_{CO_2} is high, making the argument of the log ($= [HCO_3^-]/0.0308 P_{CO_2}$) smaller and therefore the value of log is smaller and the pH is less: it is acidic. Renal compensation consists of raising $[HCO_3^-]$ to increase the argument of the log, thereby increasing its value and increasing the pH. That is, the pH returns towards normal, but the P_{CO_2} and $[HCO_3^-]$ remain abnormal as long as the respiratory problem persists. The rate of new HCO_3^- formation is equal to the rate of titratable acid and ammonium excretion.

Using similar arguments but from the opposite direction, respiratory alkalosis occurs when alveolar ventilation increases and plasma P_{CO_2} decreases. Here the argument of the log is too high because of the reduced P_{CO_2} . Renal compensation consists of lowering plasma $[HCO_3^-]$ so that the argument of the logarithm returns to normal values, though neither numerator nor denominator are normal. The kidneys lower plasma $[HCO_3^-]$ by failing to reabsorb all of the filtered $[HCO_3^-]$, because the P_{CO_2} that drives acid secretion is lowered more than the filtered HCO_3^- .

THE OVERALL RESPONSE TO METABOLIC ACIDOSIS INVOLVES BOTH LUNGS AND KIDNEYS

THE LUNGS RAISE PH BY LOWERING P_{CO_2} BY HYPERVENTILATION

In acidosis, the ratio $[HCO_3^-]/P_{CO_2}$ is lower than normal. Return to normal pH requires either raising $[HCO_3^-]$ or lowering P_{CO_2} . The kidneys raise $[HCO_3^-]$ while the lungs lower P_{CO_2} . Decreased plasma pH by itself excites chemoreceptors in the medulla and carotid body to increase ventilatory drive. Increased ventilation

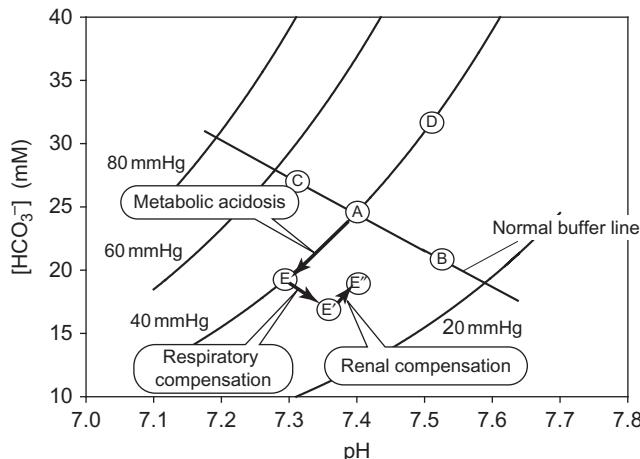


FIGURE 7.7.8 Respiratory and renal compensation of metabolic acidosis. The normal pH status is indicated by point A. Metabolic acidosis is indicated by point E. Acid stimulates ventilation to cause an excursion parallel to the normal buffer line, to point E'. This respiratory compensation occurs rapidly. Renal compensation consists of an excursion parallel to the isobars and results in increasing plasma $[HCO_3^-]$, as indicated in the path from E' to E''. Hyperventilation requires increased stimulatory drive; removal of this stimulation by renal compensation would return the acid–base situation toward the normal isobar.

increases Q_A , which decreases the P_{CO_2} . According to the Henderson–Hasselbalch equation, this raises the pH. The situation is shown graphically in Figure 7.7.8.

THE KIDNEYS RAISE $[HCO_3^-]$ BY EXCRETING AN ACID URINE

In response to acidosis, the kidneys raise plasma $[HCO_3^-]$. Both P_{CO_2} and HCO_3^- are reduced, but P_{CO_2} is reduced less because the HCO_3^- has been removed by combining with plasma H^+ produced by metabolism. Thus there is reabsorption of most of the filtered HCO_3^- and secretion of H^+ by the kidney is linked to formation of new HCO_3^- . The new HCO_3^- is equal to the excretion of titratable acid and ammonia (see Figure 7.7.8).

THE OVERALL RESPONSE TO METABOLIC ALKALOSIS INVOLVES BOTH LUNGS AND KIDNEYS

THE LUNGS LOWER PH BY RAISING P_{CO_2} BY HYPOVENTILATION

In alkalosis, the ratio $[HCO_3^-]/P_{CO_2}$ is elevated. Return to normal pH requires either lowering $[HCO_3^-]$ or raising P_{CO_2} . The kidneys lower $[HCO_3^-]$ while the lungs raise P_{CO_2} . The alkaline pH decreases the respiratory drive tonically provided by the central and peripheral chemoreceptors, reducing Q_A , alveolar ventilation, and raising P_{CO_2} . This lowers the ratio $[HCO_3^-]/P_{CO_2}$, returning the pH toward normal. The lungs cannot return to normal pH because then there would be no reduced ventilatory drive to keep the P_{CO_2} elevated. The result is a partial compensation of alkalosis. The situation is shown graphically in Figure 7.7.9.

THE KIDNEYS LOWER $[HCO_3^-]$ BY EXCRETING AN ALKALINE URINE

Following respiratory compensation for metabolic alkalosis, P_{CO_2} and HCO_3^- are both elevated, but P_{CO_2} is elevated less because the HCO_3^- is increased by more dissociation from H_2CO_3 due to lower $[H^+]$ and more H_2CO_3 made from the increased P_{CO_2} . Thus there is insufficient acid secretion to reabsorb all of the filtered HCO_3^- and HCO_3^- lost in an alkaline urine (see Figure 7.7.9).

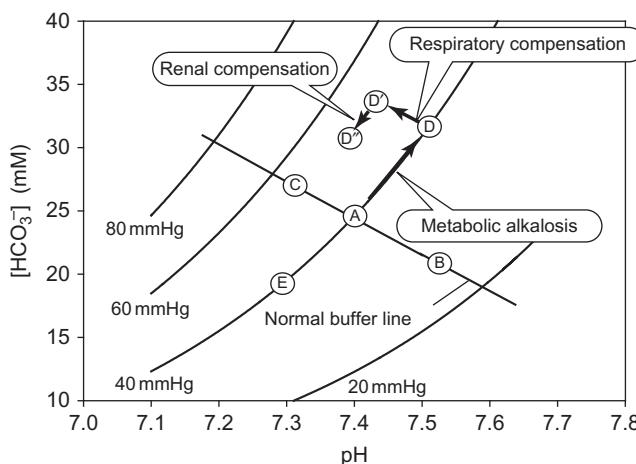


FIGURE 7.7.9 Respiratory and renal compensation of metabolic alkalosis. The normal pH status is indicated by point A. Metabolic alkalosis is indicated by point D. Alkalosis inhibits ventilation to cause an excursion parallel to the normal buffer line, to point D'. This respiratory compensation occurs rapidly. Renal compensation consists of an excursion parallel to the isobars and results in decreasing plasma $[HCO_3^-]$, as indicated in the path from D' to D. Hypoventilation requires decreased stimulatory drive; removal of this inhibition by renal compensation would return the acid–base situation toward the normal isobar.

HCO_3^- INCREASES ACID SECRETION BY A-INTERCALATED CELLS THROUGH A SOLUBLE ADENYLYL CYCLASE

The apical membrane H-ATPase in type A-intercalated cells is recruited from a population of pumps on endosomes. Translocation to the surface is activated by PKA (protein kinase A) and is inhibited by AMPK (AMP-activated protein kinase, a metabolic sensor that responds to metabolic stress when ATP levels fall). These two protein kinases phosphorylate the H-ATPase at distinct sites. PKA responds to the acid–base condition through the actions of a soluble adenylyl cyclase, sAC, which is activated by elevated HCO_3^- levels within the cell, which is, in turn, rapidly equilibrated with the P_{CO_2} in the cells through carbonic anhydrase (see Figure 7.7.10). Elevated HCO_3^- activates sAC to increase cAMP levels within the cell, which then activates PKA and recruits more of the H-ATPase to the apical membrane. This increases the acid secretion of the A-intercalated cells and increases HCO_3^- reabsorption or the formation of new HCO_3^- linked to the excretion of titratable acid or ammonium. This seems paradoxical: why would these cells increase acid secretion when cellular HCO_3^- is high, only to further increase HCO_3^- ? This is exactly what happens, however, and may be the mechanistic explanation behind the observation of Figure 7.7.6 that shows the monotonic relationship between P_{CO_2} and the rate of acid secretion by the kidney. In the pH– HCO_3^- diagrams, all cases in which HCO_3^- is elevated is accompanied by increased H^+ secretion. In some cases, such as respiratory acidosis, HCO_3^- increases and the renal compensation is the reabsorption of filtered HCO_3^- and formation of new HCO_3^- . In other cases, such as metabolic alkalosis with respiratory compensation, the kidneys secrete more acid, but the filtered load of HCO_3^- is increased more, so that the kidney actually wastes HCO_3^- despite increasing its acid secretion.

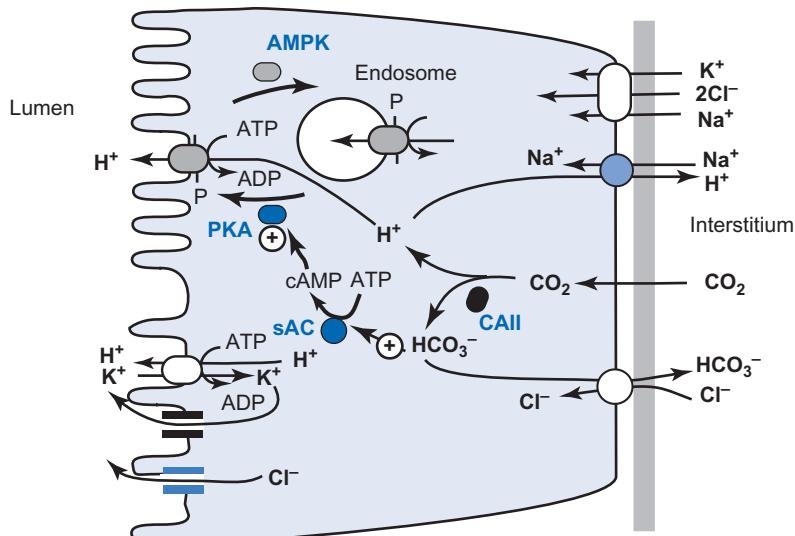


FIGURE 7.7.10 Regulation of acid secretion in type A-intercalated cells. The apical membrane H-ATPase resides in reservoir endosomal vesicles. Movement to the apical membrane is stimulated by phosphorylation by PKA and inhibited by phosphorylation at a different site by AMPK. PKA is activated by increased concentrations of cAMP that is produced by a soluble adenylyl cyclase that is activated by HCO_3^- . Thus increased P_{CO_2} results in increased HCO_3^- through the action of carbonic anhydrase, CA, that results in increased secretion of acid. Similar mechanisms pertain to the proximal tubule.

CHRONIC ACIDOSIS INCREASES EXCRETION OF NH_4^+

During normal acid–base balance, the kidneys filter about 20% of the plasma glutamine, but the arterial–venous difference is only about 3%. This means that most of the filtered glutamine is returned to blood and is not metabolized by the kidneys. Acute metabolic acidosis alters this metabolism. Within 3 hours of the onset of acute metabolic acidosis, the net extraction of glutamine by the kidneys climbs to 35%, exceeding the filtered load. Thus the kidneys import glutamine from the blood across the basolateral membrane and metabolize it to produce NH_4^+ . In addition, plasma glutamine levels rise due to release from muscle. In chronic metabolic acidosis, plasma glutamine levels normalize, but glutamine extraction remains high. Chronic metabolic acidosis causes an upregulation of several kidney enzymes that metabolize glutamine including glutaminase (GA), glutamic acid dehydrogenase (GDH), and phosphoenol pyruvate carboxykinase (PEPCK, see Figure 7.7.2). Thus chronic metabolic acidosis increases the production of ammonia. Figure 7.7.11 illustrates that the urinary excretion of NH_4^+ increases with decreasing urinary pH, but, at any given pH, it is increased by chronic acidosis.

POTASSIUM AND ACID–BASE BALANCE INTERACT

Potassium concentrations and H^+ concentrations in cells are generally inversely related: when K is depleted, H^+ is increased and therefore acid secretion by renal tubule cells is increased. Thus hypokalemia is often associated

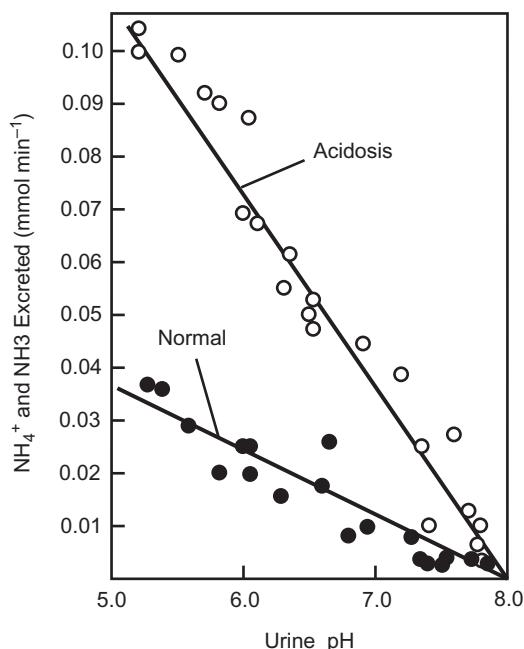


FIGURE 7.7.11 Excretion of $\text{NH}_4^+ + \text{NH}_3$ when urine pH is varied by infusion of NaHCO_3 under normal conditions and during chronic acidosis produced by feeding NH_4Cl . Data were obtained in a single dog. From R.F. Pitts, *The renal excretion of acid*, Fed. Proc. 7:418, 1948.

with a metabolic alkalosis and, conversely, hyperkalemia is often associated with metabolic acidosis.

VOLUME CONTRACTION INCREASES ACID SECRETION

Volume contraction, or loss of fluid volume, activates the renin–angiotensin–aldosterone system through the mechanisms described in Chapter 7.6. In this case, both ANG II and aldosterone are elevated. These increase ENaC activity in the principal cells of the distal nephron, which increase Na^+ uptake and K^+ secretion, and they also activate H^+ secretion from A-intercalated cells. Thus volume contraction tends to produce metabolic alkalosis. Volume expansion has opposite effects.

THE OVERALL PICTURE

Normal metabolism produces excess acid that must be excreted in the urine. Accordingly, the urine is typically acidic, with a pH normally around 6.0. This is accompanied by modest amounts of NH_4^+ and titratable acid, so that normally the kidney returns more HCO_3^- to the body than is filtered. This combines with plasma H^+ and is excreted to the air as CO_2 . Thus the acid that is produced in the tissues is removed by its being linked to the final excretion of the same amount of acid in the urine. The total amount of extra base delivered to the blood as HCO_3^- is equal to the titratable acid + ammonia – excreted HCO_3^- , as described in Eqn (7.7.8). In the steady state, the excretion of acid must match its metabolic production. In acidosis, the kidneys must excrete more H^+ and produce more HCO_3^- linked to the excretion of titratable acid and ammonium. In alkalosis, HCO_3^- is lost from the body by not reabsorbing all of the filtered load of HCO_3^- . Table 7.7.1 lists typical values for excretion of titratable acid, ammonium, and HCO_3^- in various conditions of acid–base balance. The overall response of the kidneys to acid–base disturbances is shown in Figure 7.7.12.

TABLE 7.7.1 Typical Approximate Values for the Excretion of Titratable Acid, NH_4^+ , and HCO_3^- During Normal Acid–Base Balance, Alkalosis, and Acidosis

Kidney Acid/Base Excretion	Acid–Base Status		
	Normal	Alkalosis	Acidosis
Titratable acid (mmol day^{-1})	20	0	40
NH_4^+ (mmol day^{-1})	40	0	160
HCO_3^- excreted (mmol day^{-1})	5	80	0
Net HCO_3^- gain (mmol day^{-1})	+55	-80	+200
Urinary pH	6.0	8.0	4.6

In the normal situation, the kidney produces new HCO_3^- to balance the net acid production from metabolism. During alkalosis, acid–base status is returned to normal by excreting base as HCO_3^- . During acidosis, there is an increase in new HCO_3^- formation that is linked mainly to increased excretion of NH_4^+ .

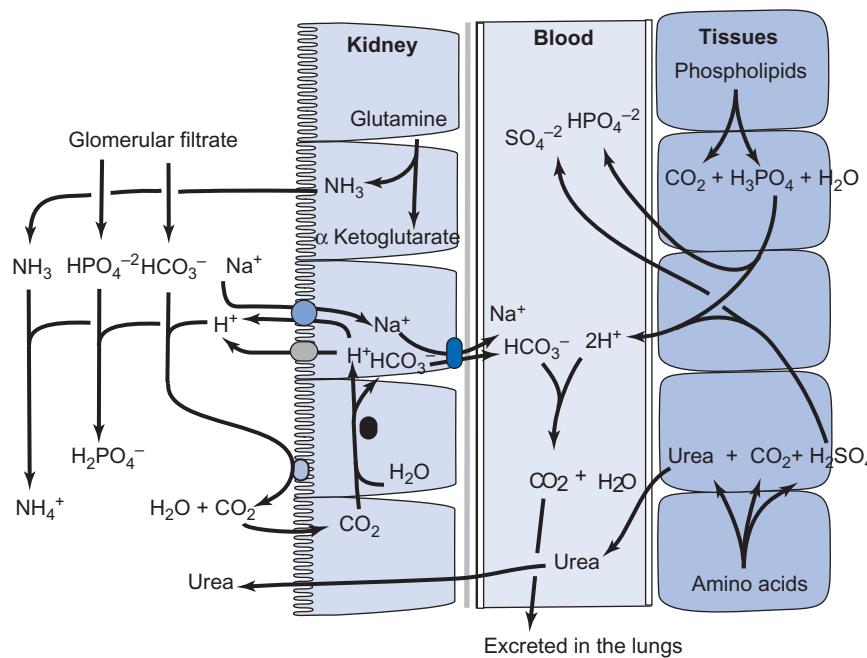


FIGURE 7.7.12 Overall function of the kidneys in acid–base balance. The tissues generally produce acid at a rate that depends largely on protein intake. The acid is buffered in the blood by HCO_3^- , which forms CO_2 and H_2O . The lungs eliminate the CO_2 from the body. This buffering action depletes the blood of HCO_3^- . The exact amount of HCO_3^- can be replenished by linking H^+ excretion in the kidneys to new HCO_3^- production. Thus, under steady-state circumstances, the kidney excretes the same amount of acid that is produced by the tissues, except that the acid does not derive directly from the tissues.

Clinical Applications: Renal Tubular Acidosis

Continual production of acid by metabolism necessitates excretion of an acid urine. Failure to secrete acid by the kidney will cause an acidosis that is classified as metabolic acidosis but is due to kidney failure. The failure can have multiple causes. The term “renal tubular acidosis” is reserved for cases in which insufficient urinary acidification occurs in otherwise adequate renal function.

There are two major categories of renal tubular acidosis: Type 1 is distal renal tubular acidosis, caused by failure of the α -intercalated cells to secrete enough acid. The urine cannot be acidified below pH 5.3. This can lead to: (1) acidemia; (2) hypokalemia; (3) urinary stone formation; (4) nephrocalcinosis (calcification of the kidney tissue); and (5) bone demineralization.

Causes of distal renal tubular acidosis include autoimmune diseases, hereditary mutations of the basolateral $\text{HCO}_3^- - \text{Cl}^-$ exchanger or the apical membrane $\text{H}^+ - \text{ATPase}$, and chronic urinary obstruction, among others.

Type 2 is proximal renal tubular acidosis. It is due to a failure of the proximal tubule cells to adequately reabsorb sufficient quantities of the filtered bicarbonate, leading to wasting of bicarbonate and acidemia. Because the distal tubule intercalated cells are generally normal, the urine can still be acidified and the acidemia is less severe than in distal renal tubular acidosis.

Proximal renal tubular acidosis may sometimes present as a solitary defect, but more usually it is associated with a general failure of proximal tubule transport called Fanconi’s syndrome, where there is phosphaturia, glucosuria, aminoaciduria, uricosuria, and proteinuria.

Treatment of distal renal tubular acidosis requires correction of the acidemia by oral bicarbonate. Hypokalemia that presents is addressed with potassium citrate, which also prevents nephrocalcinosis by complexing calcium. Treatment of proximal tubular acidosis also uses bicarbonate to reverse the acidosis.

SUMMARY

Defense against acid–base imbalance is accomplished through three interacting systems: the chemical buffers of the blood, the respiratory system, and the renal system.

The chemical buffers resist changes in plasma pH by binding H^+ ions when they are in excess and dissociating to form H^+ ions when the $[\text{H}^+]$ falls. The most important chemical buffer is the HCO_3^- buffer because

it can be adjusted by both the respiratory and renal systems.

The respiratory system adjusts plasma pH by adjusting P_{aCO_2} . During acidosis, respiration is stimulated, resulting in decreased P_{aCO_2} . According to the Henderson–Hasselbalch equation:

$$\text{pH} = 6.1 + \log([\text{HCO}_3^-]/0.0308 P_{\text{aCO}_2})$$

decreasing P_{aCO_2} increases the pH. Thus acidosis evokes a compensatory respiratory alkalosis. Similarly, alkalosis inhibits respiration so that P_{aCO_2} rises, and the acidosis is countered by a respiratory compensation.

The respiratory compensation is never complete because there must be residual pH imbalance to maintain the respiratory response that elevates or reduces P_{aCO_2} . The renal compensation, however, is complete. The renal system adjusts pH by either excreting HCO_3^- by failing to reabsorb all of the filtered HCO_3^- or by forming new HCO_3^- linked to the excretion of titratable acid or NH_4^+ . The main activity of the kidneys is to secrete H^+ through either an H^+ -ATPase or an $\text{Na}^+ - \text{H}^+$ exchanger located on the apical membrane. Secreted H^+ then either combines with filtered HCO_3^- , or with filtered buffers such as Na_2HPO_4 , or with NH_3 . Every secreted H^+ causes HCO_3^- to appear in the plasma. Thus when secreted H^+ ions combine with filtered HCO_3^- , the overall process is equivalent to reabsorption of filtered HCO_3^- ; when H^+ combines with titratable acid or NH_3 , the kidney effectively places new HCO_3^- in plasma.

Thus the kidney can excrete HCO_3^- in an alkaline urine, thereby reducing the $[\text{HCO}_3^-]$ in blood. By the Henderson–Hasselbalch equation, this would lower blood pH. Alternatively, the kidney can fight acidosis by adding HCO_3^- to blood, alkalinizing the blood while excreting an acid urine.

REVIEW QUESTIONS

1. How are filtered HCO_3^- ions reabsorbed?
2. What happens if the amount of acid secreted exceeds the amount of filtered HCO_3^- ?
3. In metabolic acidosis, what is the respiratory response? What is the renal response? Do the kidneys excrete more or less acid after respiratory compensation for metabolic acidosis compared to normal? Do they excrete more or less acid after respiratory compensation for metabolic acidosis, compared to normal?
4. What is the renal response to respiratory acidosis?
5. What drives H^+ secretion?
6. Why does hyperkalemia predispose to acidosis?