# 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 $H^+$:

$$[7.7.1] \qquad CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons HCO_3^- + H^+$$

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:

$$[7.7.2] \qquad CO_2 + H_2O \rightleftharpoons HCO_3^- + H^+$$

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 $200\ mL\ min^{-1} \times 1440\ min\ day^{-1} / 22.4\ L\ mol^{-1} \approx 13$ mol of $CO_2$ 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:

$$[7.7.3] \qquad 2C_5O_{11}NO_2S + 15H_2O \Rightarrow 4H^+ + 2SO_4^{2-} + CO(NH_2)_2 + 7H_2O + 9CO_2$$

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 $pH = \log K_A = -\log K_D = pK$. 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 $[H^+]$. 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:

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




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Here 6.10 is the p$K$ when $[HCO_3^-]$ 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 $P_{a_{CO_2}}$, 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 $P_{a_{CO_2}}$ is inversely proportional to the alveolar ventilation, $Q_A$. Thus increasing the breathing rate and depth increases $Q_A$ and decreases $P_{a_{CO_2}}$. 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:

$$[7.7.5] \qquad CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons HCO_3^- + H^+$$

Thus increasing $P_{CO_2}$ increases $[CO_2]$, 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 $[H^+]$ 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 $[HCO_3^-]$

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, $\log([HCO_3^-]/0.0308\ P_{CO_2})$ is too low. It can be corrected by lowering $P_{CO_2}$, which is the respiratory component of compensation, or by raising $[HCO_3^-]$, 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 $[CO_2]$ by hyperventilation, or by raising $[HCO_3^-]$, 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 $[HCO_3^-]$, 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 $[HCO_3^-]$, 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 $H^+$,$K^+$-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

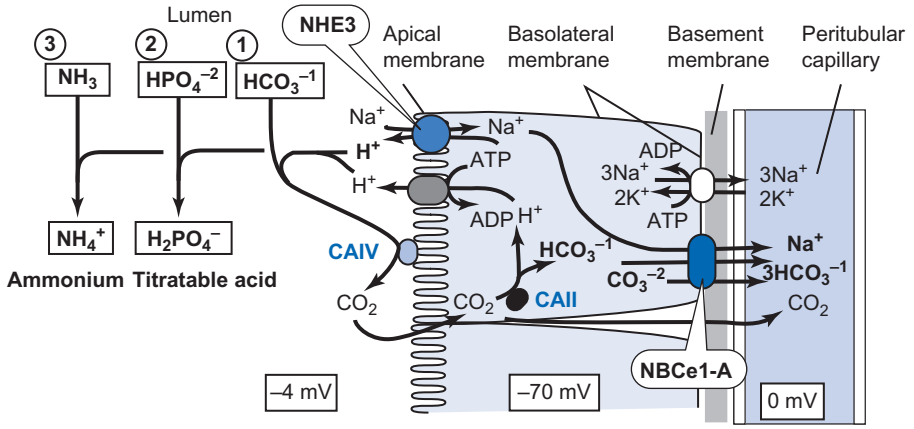


**FIGURE 7.7.1** Mechanism of reabsorption of $HCO_3^-$ in proximal tubule cells. $H^+$ ions within the tubule cell are actively secreted into the lumen across the apical membrane by the operation of primary active transport ($H^+$-ATPase) or secondary active transport ($Na^+$–$H^+$ exchanger). The secreted $H^+$ 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 $Na^+$ $HCO_3^-$ from the lumen and appearance of $Na^+$ $HCO_3^-$ in the blood. Secreted $H^+$ ions can also combine with other filtered buffers. The figure shows binding of secreted $H^+$ with $Na_2HPO_4$, which has a $pK = 7.21$. According to the Henderson–Hasselbalch equation, an acid is half neutralized when the pH = 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 **$Na^+$–$HCO_3^-$ 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 TITRATABLE 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 $[HCO_3^-]$. The increased $HCO_3^-$ binds plasma $H^+$, thereby reducing the $[H^+]$ 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 $[HCO_3^-]$.

## AMMONIA DOES NOT SHOW UP AS TITRATABLE ACID BECAUSE ITS p*K* IS TOO HIGH

The acid dissociation of $NH_4^+$ is written as

$$[7.7.6] \qquad NH_4^+ \rightleftharpoons NH_3 + H^+: \; K_D = 6.3 \times 10^{-10} \text{ M}$$

The p*K* for this reaction is 9.2. The Henderson–Hasselbalch equation for this reaction is as follows:

$$[7.7.7] \qquad pH = 9.2 + \log \frac{[NH_3]}{[NH_4^+]}$$

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 [$NH_3$] will be much smaller than [$NH_4^+$]. 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 p*K*. 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:

$$\text{Net } HCO_3^- \text{ gain} = \text{titratable acid} + NH_4^+ - HCO_3^- \quad [7.7.8]$$

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 $NH_3$ 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

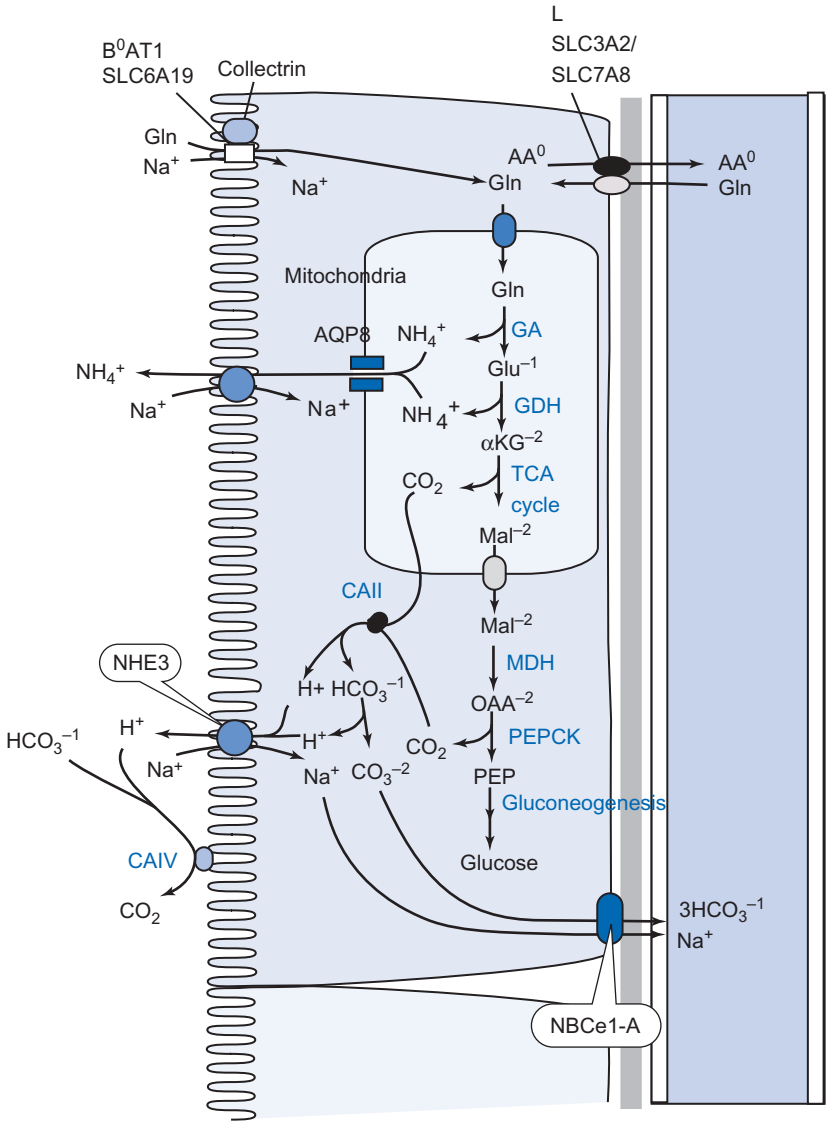


**FIGURE 7.7.2** Mechanism of generation of ammonia in proximal tubule cells. Deamination of glutamine occurs in two steps: conversion to glutamic acid and conversion to α-ketoglutaric acid. Ammonia generated in this way quickly is protonated to ammonium, which can be transported across the apical cell membrane by the $Na^+$–$H^+$ 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, $B^0AT1$, 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 $NH_3$ liberated from these reactions nearly instantly equilibrates with the cells' $[H^+]$, with only a small fraction remaining free as $NH_3$. The $NH_4^+$ crosses the apical membrane, probably carried by the $Na^+$–$H^+$ exchanger. Some free $NH_3$ may also diffuse across the apical membrane because it is uncharged and lipophilic. In the tubule fluid, $NH_3$ 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 $NH_3$ diffuses across the membrane and then becomes trapped in the acid environment as $NH_4^+$. For every $NH_4^+$ excreted, there is the equivalent of one $H^+$ excreted that is linked to transfer of new $HCO_3^-$ 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 $HCO_3^-$ is reabsorbed in the proximal tubule. Distal tubule fluid has about the same $[HCO_3^-]$ as the late proximal tubule. Because water is reabsorbed in the loop of Henle, this means that significant $HCO_3^-$ reabsorption must occur in the loop, about 10–15% of the filtered load. In addition, much of the $NH_4^+$ 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

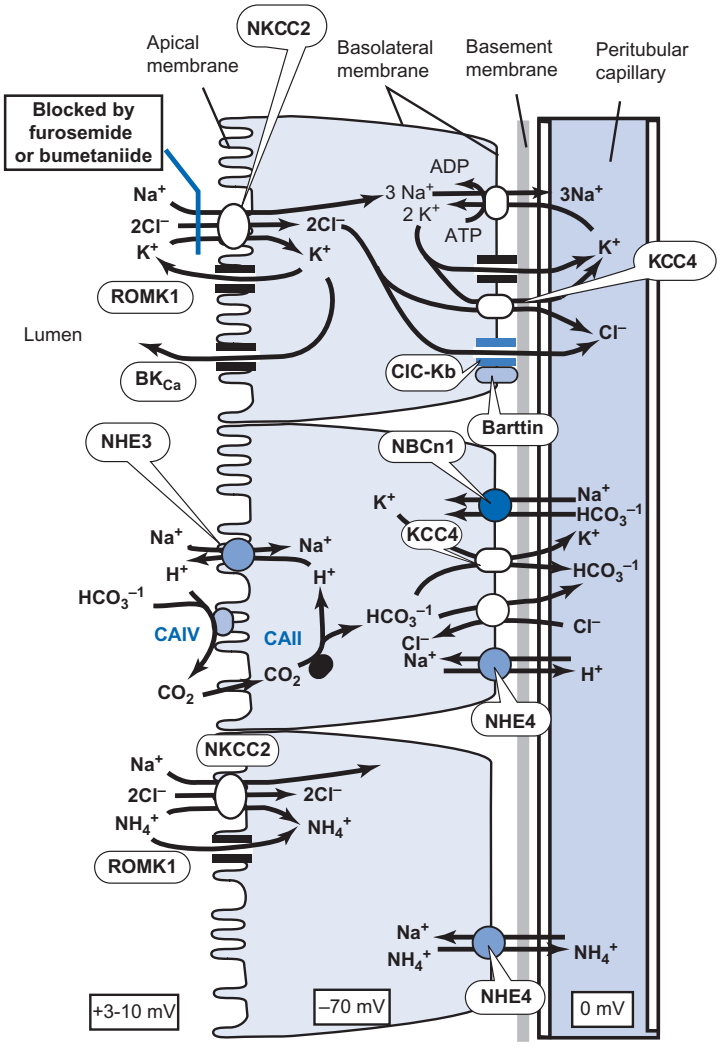


**FIGURE 7.7.3** Mechanisms of $H^+$ secretion, $HCO_3^-$ reabsorption, and $NH_4^+$ reabsorption in thick ascending limb. Top, mechanisms of $Na^+$, $K^+$, and $Cl^-$ transport. Middle, mechanisms of $HCO_3^-$ reabsorption. Bottom, mechanisms of $NH_4^+$ transport. The mechanism of $H^+$ secretion is 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. $HCO_3^-$ in the tubule fluid is neutralized by the secreted $H^+$, while a new $HCO_3^-$ ion made in the cell is transported out of the cell by multiple mechanisms that include $Cl^-$–$HCO_3^-$ exchange, and $K^+$–$HCO_3^-$ cotransport, probably over KCC4. $NH_4^+$ in the fluid may enter the cell through the Na:K:2Cl cotransporter or through $K^+$ channels. $NH_4^+$ exits the cell over the $Na^+$–$H^+$ exchanger, NHE4.

acid secretion occurs through the $Na^+-H^+$ 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 $Cl^--HCO_3^-$ exchange and $K^+-HCO_3^-$ cotransport probably mediated by KCC4. Cells in the thick ascending limb express NBCn1, a $Na^+-HCO_3^-$ 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 Na:K:2KCl transporter or through an apical $K^+$ channel (ROMK). Most $NH_4^+$ exits the cells by the NHE4, a $Na^+-H^+$ exchanger that can carry $NH_4^+$. The net result of these transport processes is to reabsorb $NaHCO_3^-$ and to add $NH_3/NH_4^+$ to the kidney interstitium. This sets up another countercurrent multiplier that concentrates $NH_3/NH_4^+$ 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 $NH_3/NH_4^+$ enters the collecting duct by diffusion trapping driven by the acid pH of the collecting duct fluid.

Increasing $[K^+]$ 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 $H^+$-ATPase and the $H^+,K^+$-ATPase. This secretion of $H^+$ is linked to the formation of new $HCO_3^-$ within the cell, which exits the basolateral membrane over a $Cl^--HCO_3^-$ exchanger, AE1. The $Cl^--HCO_3^-$ exchange is a product of alternate gene splicing of the same gene that produces the $Cl^--HCO_3^-$ exchanger of the red blood cells. $HCO_3^-$ can also exit the cell over a $Cl^--HCO_3^-$ 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 $H^+$-ATPase primary active transport on the basolateral membrane that pumps $H^+$ into the peritubular fluid rather than into the lumen as in the case

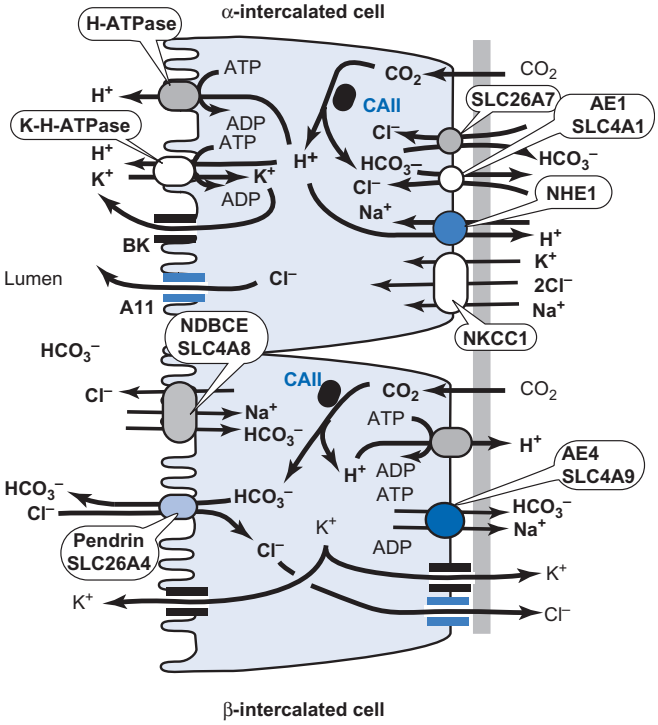


**FIGURE 7.7.4** Mechanism of acid and base secretion by α-intercalated cells (top) and β-intercalated cells (bottom) in the distal nephron. The α-intercalated cells secrete acid whereas the β-intercalated cells secrete base. α-intercalated cells secrete $H^+$ on the apical membrane by primary active 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 $Cl^--HCO_3^-$ exchanger, Pendrin (SLC4A8). $HCO_3^-$ 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 $Cl^--HCO_3^-$ 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 unwieldly 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 $P_{CO_2}$ 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

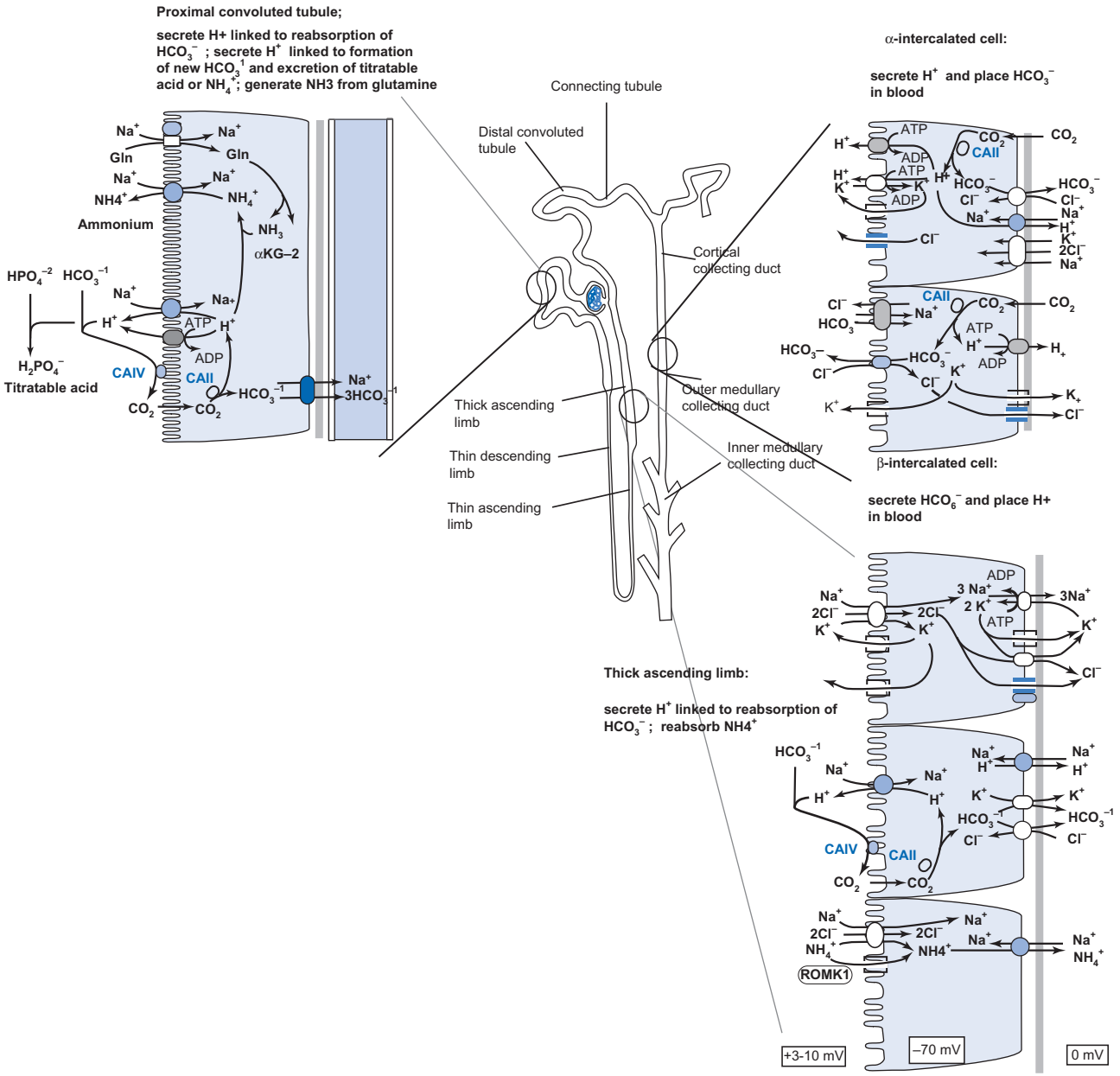


**FIGURE 7.7.5** Synopsis of transport mechanisms related to acid–base handling by the nephron. The proximal tubule secretes $H^+$ by $Na^+$–$H^+$ exchange, powered by the basolateral Na,K-ATPase that creates a gradient for $Na^+$ entry into the cell. The secreted $H^+$ can combine with filtered $HCO_3^-$ 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 $H_2PO_4^{-1}$, 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 $[H^+]$ because this gradient requires energy. As the gradient gets large, the pump is inhibited. These pumps can maximally concentrate $[H^+]$ 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 $P_{a_{CO_2}}$ levels in the dog reveals increasing $HCO_3^-$ reabsorption (which is approximately equal to acid secretion) with increasing $P_{a_{CO_2}}$. Thus hypoventilation that increases $P_{a_{CO_2}}$ and causes respiratory acidosis is met with increasing renal $H^+$ secretion. Figure 7.7.6 illustrates the relationship between $P_{a_{CO_2}}$ 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.

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 $[HCO_3^-]$

In respiratory acidosis, the $P_{a_{CO_2}}$ 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 $P_{a_{CO_2}}$ driving an increased plasma $[H^+]$ and acidosis. There is also an increased $[HCO_3^-]$, 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 $[HCO_3^-]$. 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 $[HCO_3^-]$ is not normal.

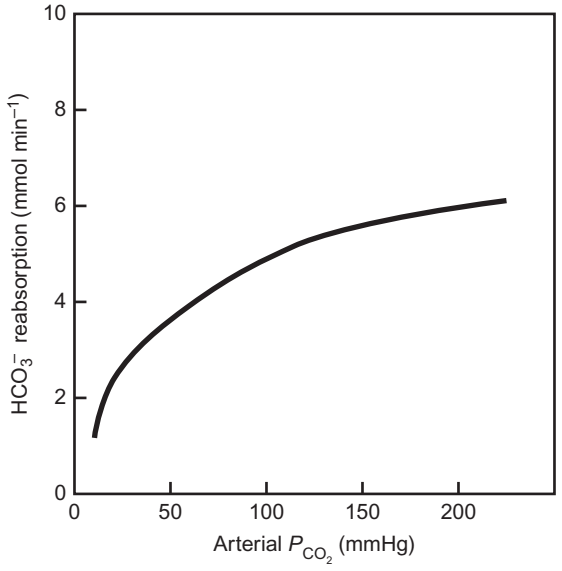


**FIGURE 7.7.6** Relationship between arterial $P_{CO_2}$ and the rate of $HCO_3^-$ reabsorption in the dog. Since $HCO_3^-$ reabsorption requires $H^+$ secretion, this illustrates how $H^+$ secretion is driven by $H^+$ supply to the tubule cells through hydration of $CO_2$. *From F.C. Rector, D.W. Seldin, 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.*

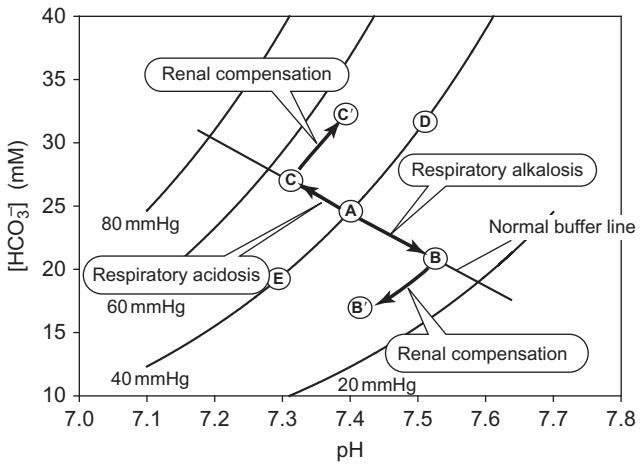


**FIGURE 7.7.7** pH–$HCO_3^-$ diagram showing the renal compensation of respiratory acidosis and alkalosis. The normal pH situation is indicated as A. Respiratory acidosis entails an increase in $P_{CO_2}$ and $[HCO_3^-]$ along the normal buffer line, indicated as point C. Renal compensation is to increase the plasma $[HCO_3^-]$ 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 $[HCO_3^-]$ along the normal buffer line (point B). Renal compensation consists of lowering $[HCO_3^-]$ 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)

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

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 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.

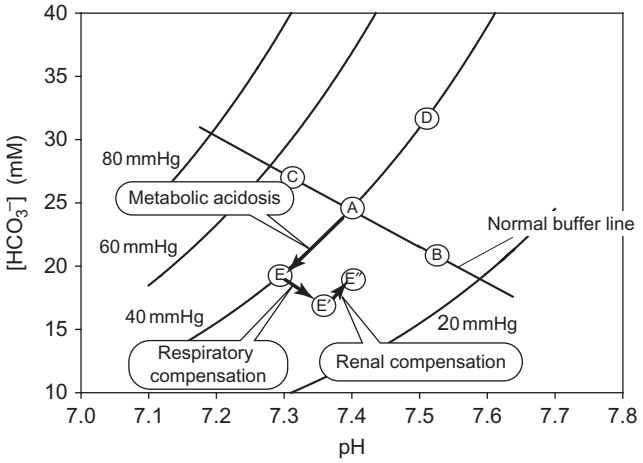


**FIGURE 7.7.8** Respiratory and renal compensation of metabolic acidosis. The normal pH status is indicated by point A. Metabolic acidosis is indicated by point E. Acid stimulates ventilation to cause an excursion parallel to the normal buffer line, to point E′. This respiratory compensation occurs 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.

### 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 is all of the filtered $HCO_3^-$ and $HCO_3^-$ lost in an alkaline urine (see Figure 7.7.9).

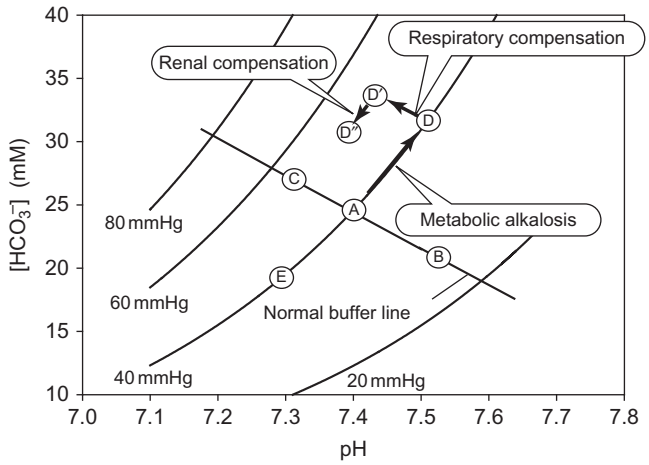


**FIGURE 7.7.9** Respiratory and renal compensation of metabolic alkalosis. The normal pH status is indicated by point A. Metabolic alkalosis is indicated by point D. Alkalosis inhibits ventilation to cause an excursion parallel to the normal buffer line, to point D′. This respiratory compensation occurs 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.

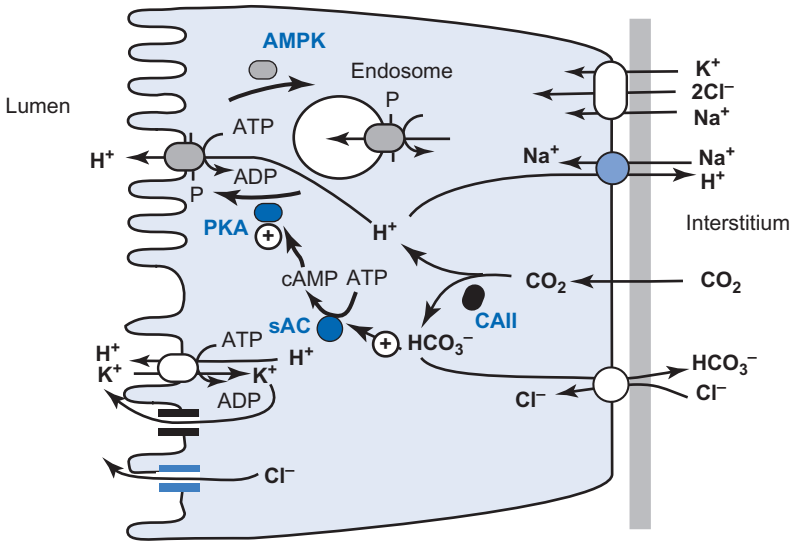


**FIGURE 7.7.10** Regulation of acid secretion in type A-intercalated cells. The apical membrane H-ATPase resides in reservoir endosomal vesicles. Movement to the apical membrane is stimulated by phosphorylation by PKA and inhibited by phosphorylation at a different site by AMPK. PKA is activated by increased concentrations of cAMP that is produced by a soluble adenylyl cyclase that is activated by $HCO_2^-$. 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 with a metabolic alkalosis** and, conversely, **hyperkalemia is often associated with metabolic acidosis**.

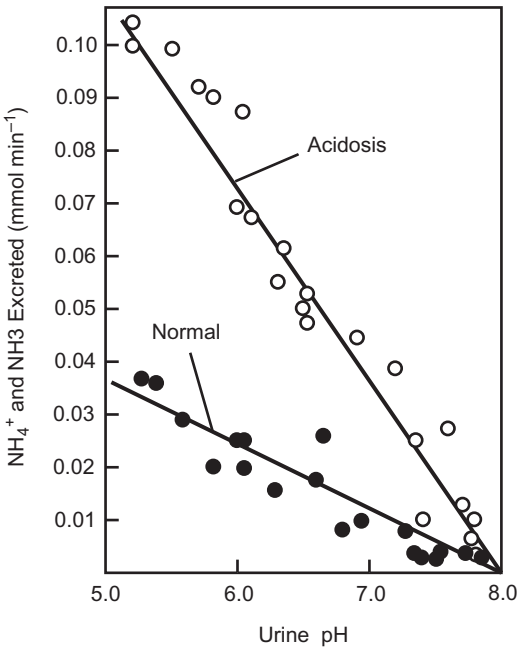


**FIGURE 7.7.11** Excretion of $NH_4^+ + NH_3$ when urine pH is varied by infusion of $NaHCO_3$ under normal conditions and during chronic acidosis produced by feeding $NH_4Cl$. Data were obtained in a single dog. *From R.F. Pitts, The renal excretion of acid,* Fed. Proc. *7:418, 1948.*

## 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 xproduced 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 $NH_4^+$.

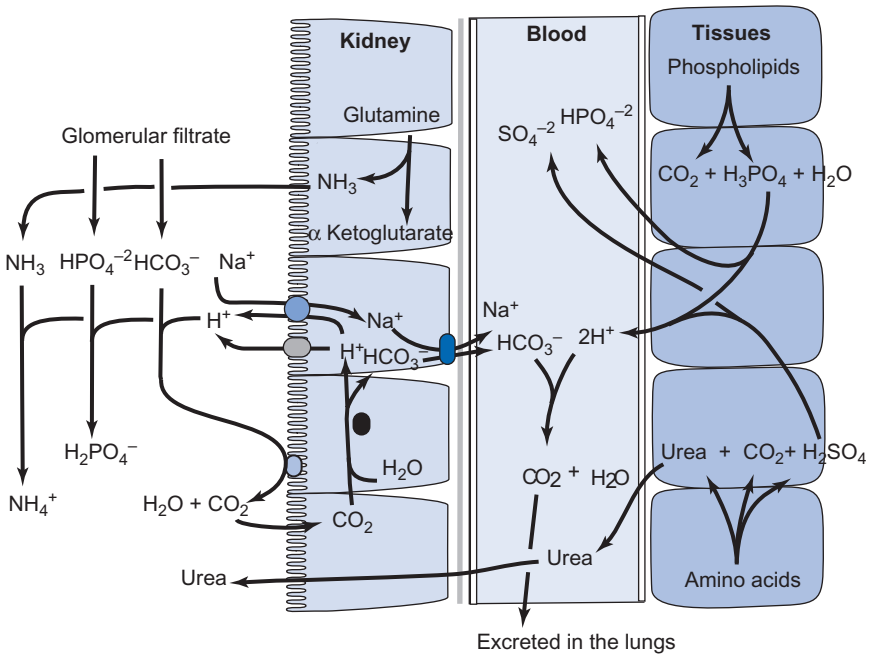


**FIGURE 7.7.12** Overall function of the kidneys in acid–base balance. The tissues generally produce acid at a rate that depends largely on protein intake. The acid is buffered in the blood by $HCO_3^-$, which forms $CO_2$ and $H_2O$. The lungs eliminate the $CO_2$ from the body. This buffering action 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 $HCO_3^-$–$Cl^-$ exchanger or the apical membrane $H^+$-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 $[H^+]$ 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 $P_{a_{CO_2}}$. During acidosis, respiration is stimulated, resulting in decreased $P_{a_{CO_2}}$. According to the Henderson–Hasselbalch equation:

$$pH = 6.1 + \log([HCO_3^-]/0.0308\ P_{a_{CO_2}})$$

decreasing $P_{a_{CO_2}}$ increases the pH. Thus acidosis evokes a compensatory respiratory alkalosis. Similarly, alkalosis inhibits respiration so that $P_{a_{CO_2}}$ 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 $P_{a_{CO_2}}$. 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 $Na^+-H^+$ 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 $[HCO_3^-]$ 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?