CHAPTER
ELEVEN

REGULATION OF ACID-BASE BALANCE

INTRODUCTION

Acid-base homeostasis can be easily understood if it is viewed in terms of the HCO_3^-/CO_2 buffering system:

$$H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow H_2O + CO_2 \qquad (11\text{-}1)$$

At equilibrium, the relationship between the reactants can be expressed by the law of mass action (see Chap. 10),

$$[H^+] = 24 \times \frac{P_{CO_2}}{[HCO_3^-]} \qquad (11\text{-}2)$$

or by the Henderson-Hasselbalch equation,

$$pH = 6.10 + \log \frac{[HCO_3^-]}{0.03P_{CO_2}} \qquad (11\text{-}3)$$

This system plays a central role in the maintenance of acid-base balance, because the HCO_3^- concentration and the P_{CO_2} can be *regulated independently*, the former

by changes in renal H^+ excretion and the latter by changes in the rate of alveolar ventilation.

These processes are extremely important, because acids and to a lesser degree bases are continually being added to the body through endogenous metabolic processes. The metabolism of carbohydrates and fats (primarily derived from the diet) results in the production of approximately 15,000 mmol of CO_2 per day. Since CO_2 combines with H_2O to form H_2CO_3, severe acidemia would ensue if this CO_2 were not excreted by the lungs.

In addition, the metabolism of proteins and other substances results in the generation of noncarbonic acids and bases.[1-3] The H^+ ions are derived mostly from the oxidation of sulfur-containing (methionine and cysteine) and cationic (arginine and lysine) amino acids, and the hydrolysis of that component of dietary phosphate that exists as $H_2PO_4^-$:

$$\begin{aligned}
\text{Methionine} &\rightarrow \text{glucose} + \text{urea} + SO_4^{2-} + 2H^+ \\
\text{Arginine}^+ &\rightarrow \text{glucose (or } CO_2) + \text{urea} + H^+ \\
\text{R-}H_2PO_4 + H_2O &\rightarrow ROH + 0.8\,HPO_4^{2-}/0.2\,H_2PO_4^- + 1.8\,H^+
\end{aligned}$$

The major sources of alkali, on the other hand, are the metabolism of anionic amino acids (glutamate and asparatate) and the oxidation or utilization for gluconeogenesis of organic anions (such as citrate and lactate):

$$\begin{aligned}
\text{Glutamate}^- + H^+ &\rightarrow \text{glucose} + \text{urea} \\
\text{Citrate}^- + 4.5O_2 &\rightarrow 5CO_2 + 3H_2O + HCO_3^- \\
\text{Lactate}^- + H^+ &\rightarrow \text{glucose} + CO_2
\end{aligned}$$

(The consumption of H^+ ions in the first and third reactions is equivalent to the generation of new HCO_3^- ions in the body.) On a normal western diet, the net effect is the production of *50 to 100 meq of H^+ per day* in adults.[1-3]

The homeostatic response to these acid and base loads occurs in three stages:

- Chemical buffering by the extracellular and intracellular buffers (see Chap. 10).
- Changes in alveolar ventilation to control the P_{CO_2}
- Alterations in renal H^+ excretion to regulate the plasma HCO_3^- concentration

As an example, the H_2SO_4 produced from the oxidation of sulfur-containing amino acids is initially buffered in the extracellular fluid by HCO_3^-:

$$H_2SO_4 + 2NaHCO_3 \rightarrow Na_2SO_4 + 2H_2CO_3 \rightarrow 2H_2O + CO_2 \quad (11\text{-}4)$$

Although this reaction minimizes the increase in the extracellular H^+ concentration, the excess H^+ ions must still be excreted by the kidney to prevent progressive depletion of HCO_3^- and the other body buffers and the development of metabolic acidosis. The CO_2 generated by this reaction is excreted by the lungs.

Under normal conditions, the steady state is preserved, as renal H^+ excretion varies directly with the rate of H^+ production (Fig. 11-1).[1,3] If acid generation is enhanced, for example, some of the excess H^+ is initially retained, resulting in a slight reduction in the plasma HCO_3^- concentration (which may be less than 1 meq/L) and pH.[3] This minimal degree of acidemia, which may be too small to be detected clinically, is at least part of the stimulus to increase net renal acid excretion to a level similar to the new higher rate of acid generation.

The net effect is that the plasma H^+ concentration and pH are maintained within narrow limits. The normal values for these parameters are:

	pH	$[H^+]$, nanoeq/L	P_{CO_2}, mmHg	$[HCO_3^-]$, meq/L
Arterial	7.37–7.43	37–43	36–44	22–26
Venous	7.32–7.38	42–48	42–50	23–27

The decrease in pH (and increase in H^+ concentration) in venous blood is due to the uptake of metabolically produced CO_2 in the capillary circulation.

The remainder of this chapter will mostly discuss the general mechanisms involved in renal H^+ excretion and the factors responsible for the regulation of

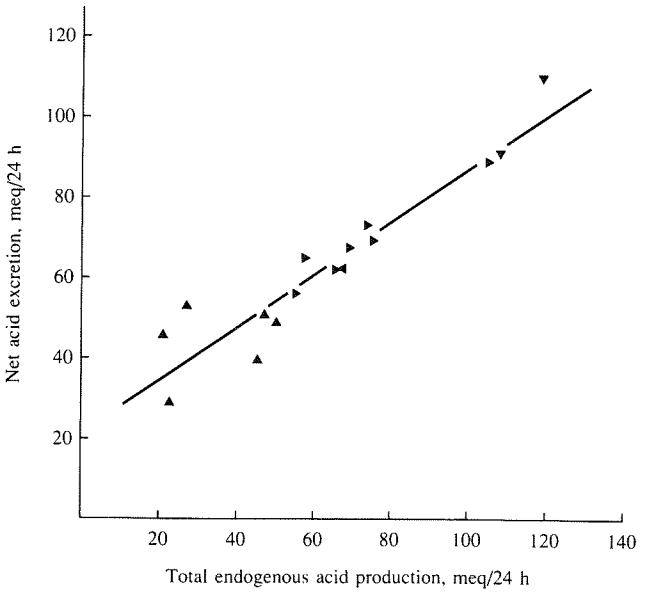

Figure 11-1 Relationship between net renal acid excretion and endogenous acid production in the steady state in normal subjects ingesting different diets with varying acid content. (*From Kurtz I, Maher T, Hulter HN, et al,* Kidney Int *24:670, 1983; and Lennon EJ, Lemann J Jr, Litzow JR,* J Clin Invest *45:1601, 1966. Reprinted by permission from* Kidney International *and the American Society for Clinical Investigation.*)

these processes. It is useful to summarize the steps involved in this complex process in advance:

- The kidneys must excrete the 50 to 100 meq of noncarbonic acid generated each day.
- This is achieved by H^+ secretion, although the major mechanisms are different in the proximal tubule and thick ascending limb of the loop of Henle (Na^+-H^+ exchange) and in the collecting tubules (active H^+-ATPase pump).
- The daily acid load cannot be excreted as free H^+ ions, since the free H^+ concentration in the urine is extremely low (< 0.05 meq/L) in the physiologic pH range.
- The daily acid load also cannot be excreted unless *virtually all of the filtered HCO_3^- has been reabsorbed*, because HCO_3^- loss in the urine is equivalent to adding H^+ ions to the body.
- Secreted H^+ ions are excreted by binding either to filtered buffers, such as HPO_4^{2-} and creatinine, or to NH_3 to form NH_4^+. NH_4^+ is generated from the metabolism of glutamine in the proximal tubule; the rate at which this occurs can be varied according to physiologic needs.
- The extracellular pH is the primary physiologic regulator of net acid excretion. In pathophysiologic states, however, the effective circulating volume, aldosterone, and the plasma K^+ concentration all can affect acid excretion, independent of the systemic pH.

RENAL HYDROGEN EXCRETION

The kidneys contribute to acid-base balance by regulating H^+ excretion so that the plasma HCO_3^- concentration remains within appropriate limits. This involves two basic steps: (1) reabsorption of the filtered HCO_3^- and (2) excretion of the 50 to 100 meq of H^+ produced per day.

It is essential to appreciate that loss of filtered HCO_3^- in the urine is equivalent to the addition of H^+ to the body, since both are derived from the dissociation of H_2CO_3. As a result, virtually all of the filtered HCO_3^- must be reabsorbed before the dietary H^+ load can be excreted. The quantitative importance of this process should not be underestimated. A normal subject with a glomerular filtration rate (GFR) of 180 L/day (125 mL/min) and a plasma HCO_3^- concentration of 24 meq/L filters and then must reabsorb approximately *4300 meq* of HCO_3^- each day.

The second step in renal acid-base regulation, excretion of the 50 to 100 meq daily H^+ load, is accomplished by the combination of H^+ ions either with urinary buffers such as HPO_4^{2-} (referred to as titratable acidity) or with ammonia to form amonium—$NH_3 + H^+ \rightarrow NH_4^+$. These processes are important, because the *excretion of free H^+ ions is minimal.* The lowest urine pH that can be achieved in humans is 4.5. Although this is almost 1000 times (3 log units) more acid than the extracellular pH, it still represents an extremely low free H^+ concentration of

less than 0.04 meq/L. Remember that the free H^+ concentration at an extracellular pH of 7.40 is only 40 nanomol/L, *one-millionth* the size of the daily acid load.

The reabsorption of HCO_3^- and the formation of titratable acidity and NH_4^+ all involve H^+ secretion from the tubular cell into the lumen (Figs. 11-2 to 11-4).[4,5] Three initial points need to be emphasized:

- The secreted H^+ ions are generated within the tubular cell from the dissociation of H_2O. This process also results in the equimolar production of OH^- ions.
- These OH^- ions bind to the active zinc-containing site of intracellular *carbonic anhydrase*; they then combine with CO_2 to form HCO_3^- ions, which are released into the cytosol and returned to the systemic circulation across the basolateral membrane.[4,6] The net effect is that the *secretion of each H^+ ion is associated with the generation of one HCO_3^- ion in the plasma.* If the secreted H^+ combines with filtered HCO_3^-, the result is HCO_3^- reabsorption (Fig. 11-2). This maintains the plasma HCO_3^- concentration by preventing HCO_3^- loss in the urine. If, however, the secreted H^+ combines with HPO_4^{2-} or NH_3, a *new HCO_3^-* is added to the peritubular capillary (Figs. 11-3 and 11-4). This results in an increase in the plasma HCO_3^- concentration to *replace the HCO_3^- lost in buffering the daily H^+ load* [Eq. (11-4)].
- Different mechanisms are involved in proximal and distal acidification (see below).

Net Acid Excretion

Since the urinary concentration of free H^+ is negligible, the net quantity of H^+ excreted in the urine is equal to the amount of H^+ excreted as titratable acidity and NH_4^+ minus any H^+ added to the body because of urinary HCO_3^- loss:

$$\text{Net acid excretion} = \text{titratable acidity} + NH_4^- - \text{urinary } HCO_3^- \qquad (11\text{-}5)$$

In the steady state, the net amount of H^+ excreted is roughly equal to the normal H^+ load of 50 to 100 meq/day (Fig. 11-1). However, this value can exceed 300 meq/day (primarily through enhanced NH_4^+ excretion) if acid production is increased (see below). Net H^+ excretion also can have a negative value if a large amount of HCO_3^- is lost in the urine. This may appropriately occur after the ingestion of citrate-containing fruit juices, since the metabolism of citrate results in the generation of HCO_3^-. How the kidney is able to make these homeostatic adjustments will be discussed below (see "Regulation of Renal Hydrogen Excretion: Extracellular pH," below).

Proximal Acidification

The primary step in proximal acidification is the secretion of H^+ by the Na^+-H^+ exchanger (or antiporter) in the luminal membrane.[7-10] This transport protein,

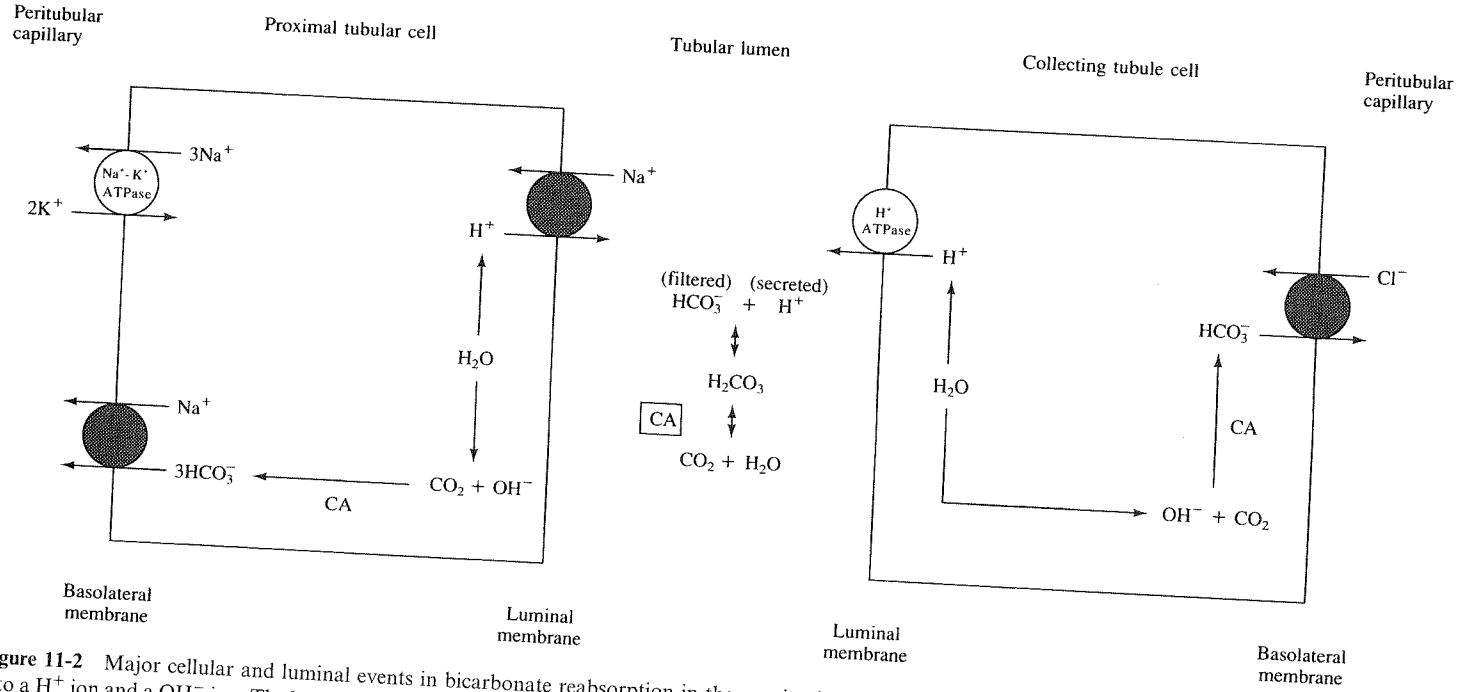

Figure 11-2 Major cellular and luminal events in bicarbonate reabsorption in the proximal tubule and the collecting tubules. Intracellular H_2O breaks down into a H^+ ion and a OH^- ion. The latter combines with CO_2 to form HCO_3^-, via a reaction catalyzed by carbonic anhydrase (CA). In the proximal tubule, the H^+ is secreted into the lumen by the Na^+-H^+ exchanger, whereas the HCO_3^- is returned to the systemic circulation primarily by a Na^+-$3HCO_3^-$ cotransporter. These same processes occur in the collecting tubules, although they are respectively mediated by an active H^+-ATPase pump in the luminal membrane and a Cl^--HCO_3^- exchanger in the basolateral membrane. The secreted H^+ ions combine with filtered HCO_3^- to form carbonic acid (H_2CO_3) and then $CO_2 + H_2O$, which can be passively reabsorbed. This dissociation of carbonic acid is facilitated when luminal carbonic anhydrase (CA in box) is present, as occurs in the early proximal tubule (see text). The net effect is HCO_3^- reabsorption, even though the HCO_3^- ions returned to the systemic circulation are not the same as those that were filtered. Although not shown, the collecting tubule cells also have H^+-K^+-ATPase pumps in the luminal membrane that are primarily involved in K^+ reabsorption.

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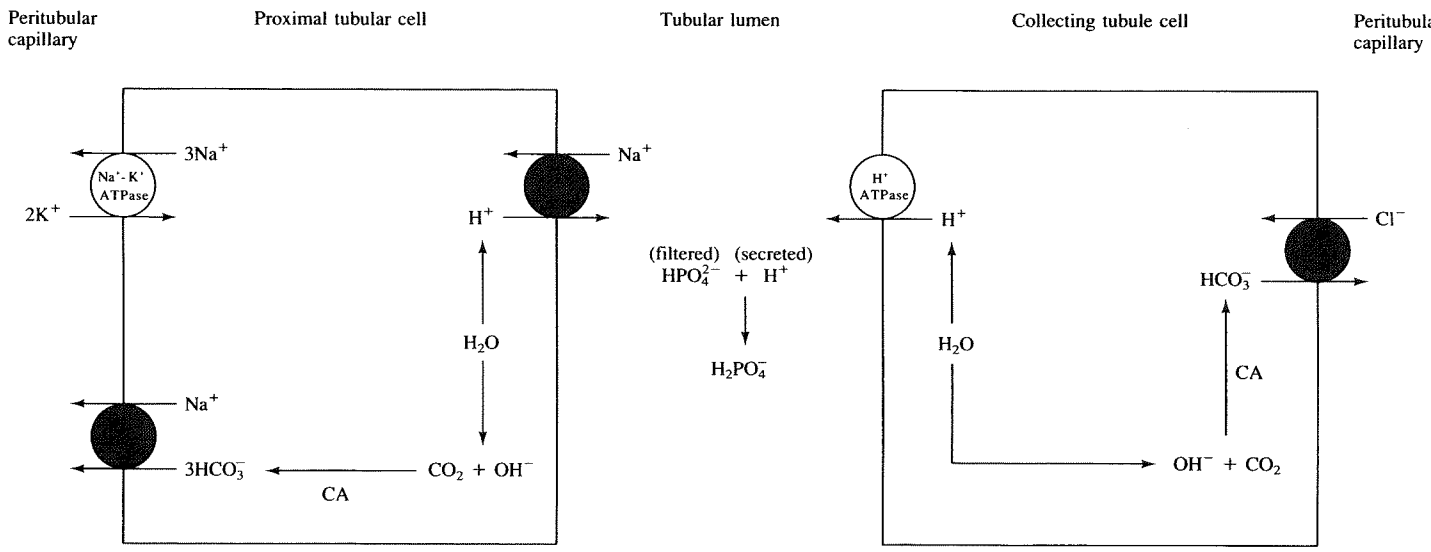


Figure 11-3 Formation of titratable acidity, which is primarily due to buffering of secreted H^+ by filtered HPO_4^{2-} and, to a lesser degree, other buffers such as creatinine. Note that a new HCO_3^- ion is returned to the peritubular capillary for every H^+ ion that is secreted.

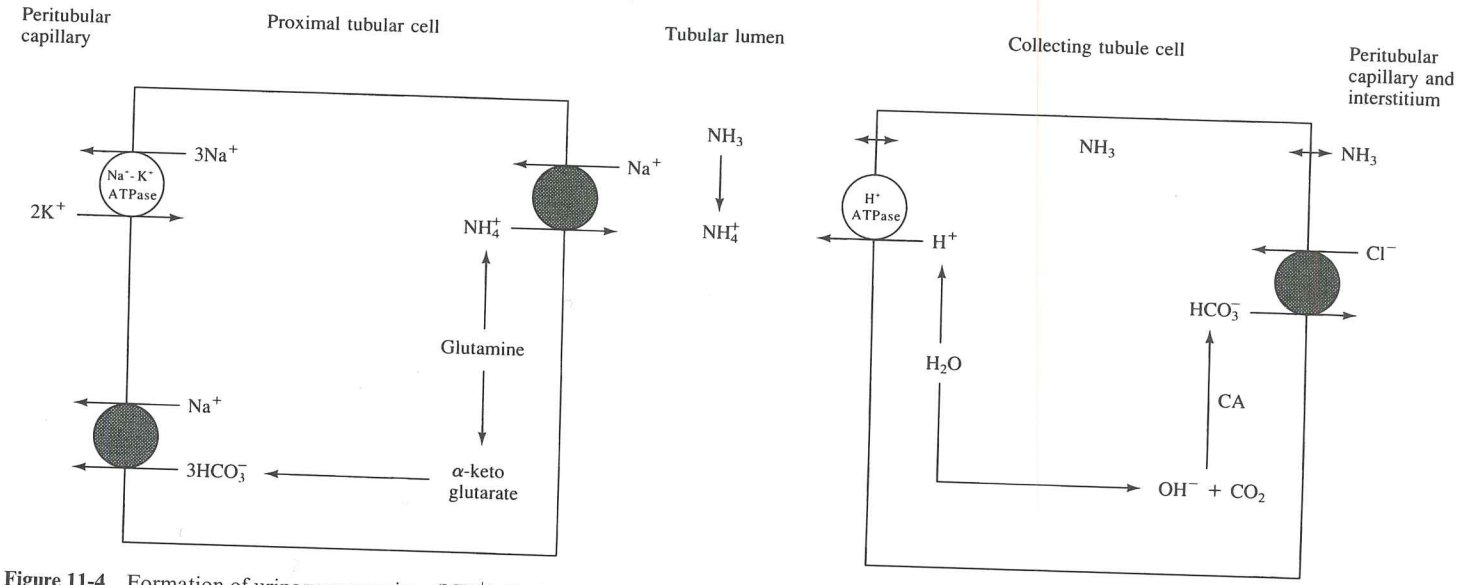


Figure 11-4 Formation of urinary ammonium (NH_4^+). In the proximal tubule, glutamine is taken up by the cells and metabolized into NH_4^+ and α-ketoglutarate. Utilization of the latter results in the generation of HCO_3^-, whereas NH_4^+ substitutes for H^+ on the Na^+-H^+ exchanger and is then secreted directly into the lumen. The mechanism is different in the collecting tubules; nonpolar, lipid-soluble NH_3 diffused from the interstitial fluid into the lumen, where it combines with secreted H^+ to form NH_4^+. Ammonium is lipid-insoluble and is therefore unable to back-diffuse out of the lumen. Note that each NH_4^+ ion that is excreted is associated with the generation of a new HCO_3^- ion that is returned to the peritubular capillary.

which also appears to mediate most of HCO_3^- reabsorption in the thick ascending limb of the loop of Henle,[11,12] preferentially binds filtered Na^+ at its external site and intracellular H^+ at its internal site (Fig. 11-2).[10]

A H^+-ATPase pump, similar to that in the distal nephron, is also present in the proximal tubule.[8,13] Via the use of different experimental methodologies, including genetic deletion, it appears that the Na^+-H^+ exchanger is responsible for approximately two-thirds of proximal H^+ secretion, with the H^+-ATPase pump being responsible for the remainder.[9,14]

The *energy for Na^+-H^+ exchange is indirectly provided by the Na^+-K^+-ATPase pump in the basolateral membrane*. As described in Chap. 3, this pump transports reabsorbed Na^+ into the peritubular capillary and also has two other important effects: It maintains the effective cell Na^+ concentration at a relatively low level (10 to 30 meq/L), and it creates a negative electrical potential in the cell interior. The negative potential is induced by the loss of cation from the cell, because of the $3Na^+ : 2K^+$ stoichiometry of the pump and the back-diffusion of this K^+ out of the cell through K^+ channels in the basolateral membrane. The low cell Na^+ concentration creates a favorable gradient for the passive diffusion of luminal Na^+ into the cell that is large enough to drive H^+ secretion against a concentration gradient via electroneutral Na^+-H^+ exchange.

Proximal acidification also requires that the HCO_3^- formed within the cell be returned to the systemic circulation. As depicted in Fig. 11-2, this is primarily achieved by a Na^+-$3HCO_3^-$ cotransporter* in the basolateral membrane, although a Cl-HCO_3^- exchanger also is present, particularly in the S_3 segment.[11–17] The Na^+-$3HCO_3^-$ transporter (which may actually function as a $Na^+ : CO_2^{2-} : HCO_3^-$ carrier)[17] results in the net movement of negative charge. The energy for this process is provided by the electronegative potential within the cell that is created by the Na^+-K^+-ATPase pump.[18]

Distal Acidification

H^+ secretion in the distal nephron primarily occurs in the *intercalated cells* in the cortical collecting tubule and in the cells in the outer and inner medullary collecting tubules,[19–22] the distal tubule also may contribute but appears to be quantitatively less important.[23] As illustrated in Fig. 11-2, there are three main characteristics of distal acidification:

- H^+ secretion is mediated by active secretory pumps in the luminal membrane.[24–28] Both H^+-ATPase and H^+-K^+-ATPase pumps are present.[24,29,30] The latter is an exchange pump, leading to H^+ secretion and K^+ reabsorption; its main role may be in minimizing K^+ loss during hypokalemia rather than in regulating acid-base balance (see page 393).[24,27,31] Following appro-

* The Na^+-$3HCO_3^-$ has an additional function in that it provides the major mechanism by which metabolic acid-base changes are sensed within the cell (see "Regulation of Renal Hydrogen Excretion: Extracellular pH," below).

Figure 11-4 Formation of urinary ammonium (NH_4^+). In the proximal tubule, glutamine is taken up by the cells and metabolized into NH_4^+ and α-ketoglutarate. Utilization of the latter results in the generation of HCO_3^-, whereas NH_4^+ substitutes for H^+ on the Na^+-H^+ exchanger and is then secreted directly into the lumen. The mechanism is different in the collecting tubules; nonpolar, lipid-soluble NH_3 diffused from the interstitial fluid into the lumen, where it combines with secreted H^+ to form NH_4^+. Ammonium is lipid-insoluble and is therefore unable to back-diffuse out of the lumen. Note that each NH_4^+ ion that is excreted is associated with the generation of a new HCO_3^- ion that is returned to the peritubular capillary.

priate stimuli, such as systemic acidemia (see below), cytoplasmic vesicles containing the H^+-ATPase pumps move to fuse with the luminal membrane, resulting in H^+ secretion.[32] Electroneutrality is maintained in this setting by concurrent secretion of Cl^- via voltage-dependent mechanisms.[19,21]

Note that the Na^+-H^+ antiporter would not be an efficient mechanism of distal acidification, since the *activity of this carrier is limited by the transcellular Na^+* gradient that provides the energy for H^+ secretion. This gradient is diminished in the collecting tubules as a result of the reduction in the tubular fluid Na^+ concentration, which can fall below 30 meq/L in the cortical collecting tubule and, in states of volume depletion, below 5 meq/L in the inner medullary collecting tubule. Furthermore, the gradient against which H^+ must be secreted is markedly increased in these segments. A urine pH of 4.8, for example, represents a H^+ concentration that is 400 times (2.6 log units) greater than that in the extracellular fluid. The net effect is that H^+ secretion by Na^+-H^+ exchange would require a nonphysiologic cell Na^+ concentration well below 1 meq/L. (There is evidence of a basolateral Na^+-H^+ exchanger in the medullary collecting duct; it is likely that this transporter is primarily involved in the regulation of cell pH rather than systemic acid-base balance.[33,34])

- The H^+ secretory cells in the distal nephron do not transport Na^+, since they have few if any of the luminal membrane Na^+ channels or transporters that are required for the entry of luminal Na^+ into the cell.[19,35] However, H^+ secretion by the intercalated cells in the cortical collecting tubule is indirectly influenced by Na^+ reabsorption in the adjacent *principal* cells. The transport of cationic Na^+ through Na^+ channels in the luminal membrane makes the tubular fluid relatively electronegative. This electrical gradient can affect acid handling in two ways: It promotes H^+ accumulation in the lumen by minimizing the degree of back-diffusion,[36,37] and it facilitates the passive reabsorption of HCO_3^-.[23]
- Bicarbonate exit is mediated by a Cl^-/HCO_3^- exchanger in the basolateral membrane, thereby returning HCO_3^- to the systemic circulation.[17,38] This protein is a truncated form of the Cl^-/HCO_3^- exchanger in red cells (which is also called band 3 protein).[39] The energy for Cl^-/HCO_3^- exchange is provided by the inward gradient for Cl^- entry, since the Cl^- concentration in the cells is relatively low.

Regulation of the H^+-ATPase secretory pumps appears to be mediated by a process of membrane insertion and recycling that is similar to the effect of antidiuretic hormone on luminal membrane water channels (see Chap. 6).[32,40] In the medullary collecting tubule and many of the intercalated cells in the cortical collecting tubule, cytoplasmic H^+ pumps are inserted into the luminal membrane with an acid load, thereby facilitating excretion of the excess acid. On the other hand, an alkaline load results in recycling of these transporters from the luminal membrane to cytoplasmic vesicles.[40]

The net effect of H^+ secretion in the collecting tubules is illustrated in Fig. 11-5. The tubular fluid pH falls by about 0.6 units in the proximal tubule; is relatively stable in the loop of Henle and distal tubule, which do not play a major role in urinary acidification; and then falls to its lowest level in the collecting tubules (represented in Fig. 11-5 as the difference between the distal tubule and the final urine).[41]

Impairment of this distal H^+ secretory process results in a reduced net acid excretion, metabolic acidosis, and urine pH that is inappropriately high; this disorder is called type 1 (distal) renal tubular acidosis. A number of different defects can directly or indirectly cause this problem. Patients with Sjögren's syndrome have been described in whom there is complete absence of H^+-ATPase pumps in the intercalated cells.[42,43] How immunologic injury leads to this change is not known. Another mechanism is a mutation in the basolateral Cl^-/HCO_3^- exchanger.[44]

The preceding discussion has emphasized the function of the type A intercalated cells. There is also a second type of intercalated cell (type B) in the cortical collecting tubule that can insert the H^+ pumps into the luminal membrane with an acid load or into the basolateral membrane with an alkaline load.[40] The latter process allows HCO_3^- to be appropriately secreted rather than reabsorbed (see below).

Bicarbonate Reabsorption

Approximately 90 percent of the filtered HCO_3^- is reabsorbed in the proximal tubule, and most of this occurs in the first 1 to 2 mm of this segment.[45,46] The marked reabsorptive capacity of the early proximal tubule appears to be mediated

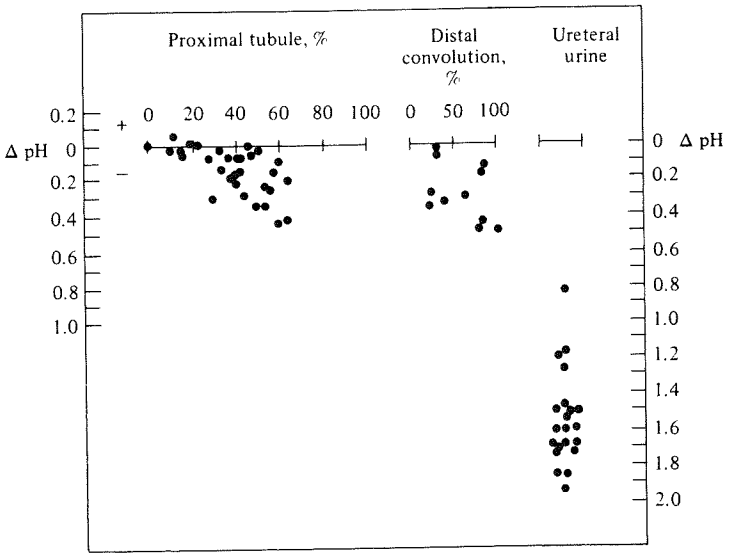


Figure 11-5 Change in pH (ΔpH) of the tubular fluid along the nephron of the rat. (*From Gottschalk CW, Lassiter W, William E, Mylle M*, Am J Physiol *198:581, 1960, with permission.*)

by an increased number of Na^+-H^+ exchangers and enhanced permeability to HCO_3^-.[47] The remaining 10 percent of the filtered HCO_3^- is reabsorbed in the more distal segments,[4] and most of this occurs in the thick ascending limb (primarily by Na^+-H^+ exchange)[11,12] and in the outer medullary collecting tubule.[19-21]

Carbonic anhydrase and disequilibrium pH Carbonic anhydrase within the tubular cells plays a central role in HCO_3^- reabsorption by facilitating the formation of HCO_3^- from the combination of OH^- ions with CO_2 (Fig. 11-2).[6,48-51] The role of *luminal* carbonic anhydrase in the proximal tubule is less well appreciated. As H^+ ions are secreted, two separate reactions occur in the tubular lumen (Fig. 11-2): (1) the combination of H^+ with filtered HCO_3^- to form H_2CO_3 and (2) the dehydration of H_2CO_3 into $CO_2 + H_2O$, which are then reabsorbed:

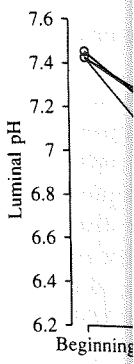
$$H^+ + HCO_3^- \overset{1}{\leftrightarrow} H_2CO_3 \overset{2}{\leftrightarrow} CO_2 + H_2O \qquad (11\text{-}6)$$

Step 2, the dehydration of H_2CO_3 into $CO_2 + H_2O$, normally proceeds relatively slowly. However, this reaction is accelerated in the early proximal tubule because the brush border of the tubular cells contains carbonic anhydrase.[48,49] Consequently, there is no accumulation of H_2CO_3 in the proximal tubular fluid. From the law of mass action, the maintenance of a low H_2CO_3 concentration drives reaction 1 in Eq. (11-6) to the right, thereby keeping the free H^+ concentration at a relatively low level. In general, the tubular fluid pH falls only 0.6 pH unit (from 7.40 in the filtrate to about 6.80 by the end of the proximal convoluted tubule), despite the reabsorption of the majority of the filtered HCO_3^- (Fig. 11–5).[41]

This response is extremely important, since, as noted above, the gradient against which H^+ is secreted by the Na^+-H^+ antiporter cannot exceed the favorable inward gradient for Na^+. By minimizing the increase in the tubular fluid H^+ concentration, luminal carbonic anhydrase minimizes the gradient against which H^+ is secreted, thereby allowing continued H^+ secretion and HCO_3^- reabsorption.

The contribution of this system can be appreciated from the response to the administration of a carbonic anhydrase inhibitor that enters the cells to a limited degree and therefore inhibits the luminal but not the intracellular enzyme.[48,49] In this setting, the dehydration of H_2CO_3 in the lumen is slowed, resulting in increases in the H_2CO_3 and H^+ concentrations and thereby *impairing proximal H CO_3^- reabsorption by up to 80 percent*.[49] This ability to induce a HCO_3^- diuresis makes a carbonic anhydrase inhibitor useful in the treatment of some patients with metabolic alkalosis (see Chap. 18).

The role of luminal carbonic anhydrase can also be appreciated by comparing the function of the middle (S_2) and late (S_3) segments of the proximal tubule (see Fig. 3-2). Luminal carbonic anhydrase is present in the former, but absent in the latter.[51,52] As shown in the tubular perfusion experiments in Fig. 11-6, both segments can lower the tubular fluid pH by 0.6 to 0.8 unit. This is associated with a marked reduction in the luminal HCO_3^- concentration in the early proximal tubule, as a result of a relatively high rate of HCO_3^- reabsorption. In



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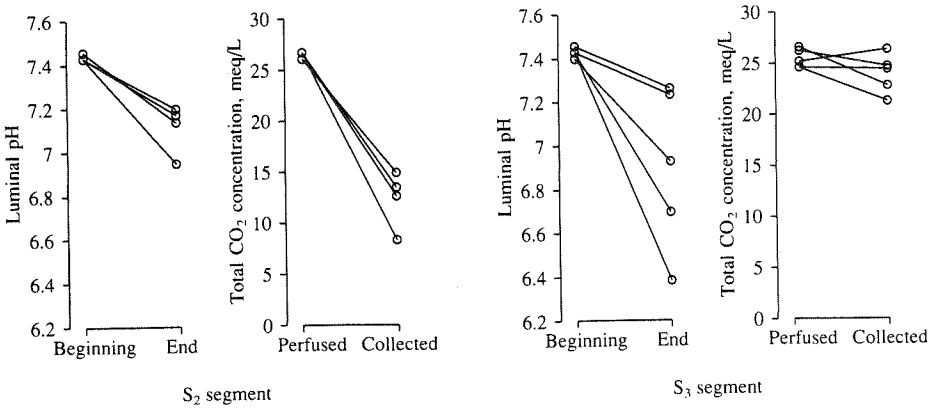

Figure 11-6 Changes in luminal (tubular fluid) pH and total CO_2 concentration as perfusion fluid flows through S_2 (mid) and S_3 (late) segments of the proximal tubule. The total CO_2 concentration is equal to the sum of the concentrations of HCO_3^- and of dissolved CO_2 (equal to $0.03 \times P_{CO_2}$; see page 310). The S_2 segment contains carbonic anhydrase in the lumen; as a result, H^+ secretion results in a fall in luminal pH and in total CO_2 concentration, since a substantial amount of HCO_3^- reabsorption has occurred. In comparison, the S_3 segment lacks luminal carbonic anhydrase. Consequently, the luminal pH falls to a similar degree, even though there has been a relatively small amount of H^+ secretion that is insufficient to lower the total CO_2 concentration. This segment also demonstrates a disequilibrium pH, as the measured value is 6.89, while the calculated value is 7.35 (similar to that in the initial perfusate). The lack of change in the calculated pH from that in the perfusate is a reflection of the stable total CO_2 concentration, whereas the reduction in the measured pH is a reflection of the accumulation of H_2CO_3. There is no disequilibrium pH in the S_2 segment, as the measured and calculated values are the same. (*Adapted from Kurtz I, Star R, Balaban RS, et al.* J Clin Invest *78:989, 1986, by copyright permission of the American Society for Clinical Investigation.*)

comparison, there is relatively little HCO_3^- transport in the S_3 segment, since, in the absence of luminal carbonic anhydrase, secreted H^+ ions and H_2CO_3 accumulate in the tubular fluid, producing a rapid fall in luminal pH that limits further H^+ secretion.

It is also possible to demonstrate a *disequilibrium pH* in those segments that lack luminal carbonic anhydrase (the S_3 segment, the cortical collecting tubule, and most of the medullary collecting tubule).[48,52-54] If, for example, the tubular fluid P_{CO_2} and HCO_3^- are measured in the late proximal tubule, the pH can be calculated from the Henderson-Hasselbalch equation [Eq. (11-3)]. However, the *measured pH is almost 0.5 pH unit below the calculated value* (6.89 versus 7.35 in the S_3 segment), a difference that is referred to as a *disequilibrium pH*.[48,52]

The error in the calculated pH results from the fact that the pK_a' of 6.10 can be applied to Eq. (11-6) only when the H_2CO_3 concentration is relatively low in relation to the dissolved CO_2 and HCO_3^- concentrations (see page 308). The 0.5-unit pH difference in this setting is presumably due to the accumulation of excess acid as H_2CO_3. The disequilibrium pH can be dissipated by the addition of

carbonic anhydrase to the tubular fluid and is absent in those segments that contain this enzyme.[52,54]

The uneven distribution of luminal carbonic anhydrase may play an important role in urinary acidification. The early proximal tubule has this enzyme and is able to reabsorb about 90 percent of the filtered HCO_3^-. The middle part of the outer medullary collecting tubule also contains luminal carbonic anhydrase[54] and is the most important distal site of HCO_3^- reabsorption.[21] The other distal segments, in comparison, lack luminal carbonic anhydrase and are less able to reabsorb HCO_3^-; however, they play an *essential role in* NH_4^+ *excretion*, since the exaggerated reduction in tubular fluid pH promotes the diffusion of NH_3 into the lumen, where it combines with the excess H^+ and is trapped as NH_4^+ (see "Ammonium Excretion," below).[5,52-54]

Bicarbonate secretion Virtually all of the filtered HCO_3^- is reabsorbed in normal subjects, in whom there is a requirement to excrete the daily acid load. However, loss of HCO_3^- in the urine is an appropriate response in patients with metabolic alkalosis (high arterial pH, high plasma HCO_3^- concentration). Although this HCO_3^- diuresis can be achieved by reabsorbing less of the filtered HCO_3^-, it appears that *HCO_3^- secretion by the type B intercalated cells in the cortical collecting tubule* also contributes to this response.[20,40,55,56]

These cells differ from HCO_3^- reabsorbing type A intercalated cells in that the *polarity of the membrane transporters can be reversed.* H^+ and HCO_3^- ions are still produced within the cell; however, the H^+ ions are secreted into the peritubular capillary by the H^+-ATPase pump, which is now inserted in the basolateral, rather than the luminal, membrane (Fig. 11-7).[40,56] The HCO_3^- ions, in comparison, are secreted into the tubular lumen by an anion exchanger in the luminal membrane.[55,56]

Titratable Acidity

Several weak acids are filtered at the glomerulus and may act as buffers in the urine. Their ability to do so is proportional to the quantity of the buffer present and to its pK_a. The latter is important, since maximum buffering occurs at ± 1.0 pH unit from the pK_a (see Fig. 10-2). Because of its favorable pK_a of 6.80 and its relatively high rate of urinary excretion, HPO_4^{2-} is the major urinary buffer (Fig. 11-3), with lesser contributions from other weak acids, such as creatinine ($pK_a = 4.97$) and uric acid ($pK_a = 5.75$).

This process is referred to as *titratable acidity*, since it is measured by the amount of NaOH that must be added to a 24-h urine collection to titrate the urine pH back to the same pH as that in the plasma (approximately 7.40 in normal subjects). Under normal conditions, 10 to 40 meq/day of H^+ is buffered by these weak acids.

The ability of phosphate to buffer H^+ can be illustrated by the following example (Table 11-1). From the Henderson-Hasselbalch equation for the $HPO_4^{2-}/H_2PO_4^-$ system,

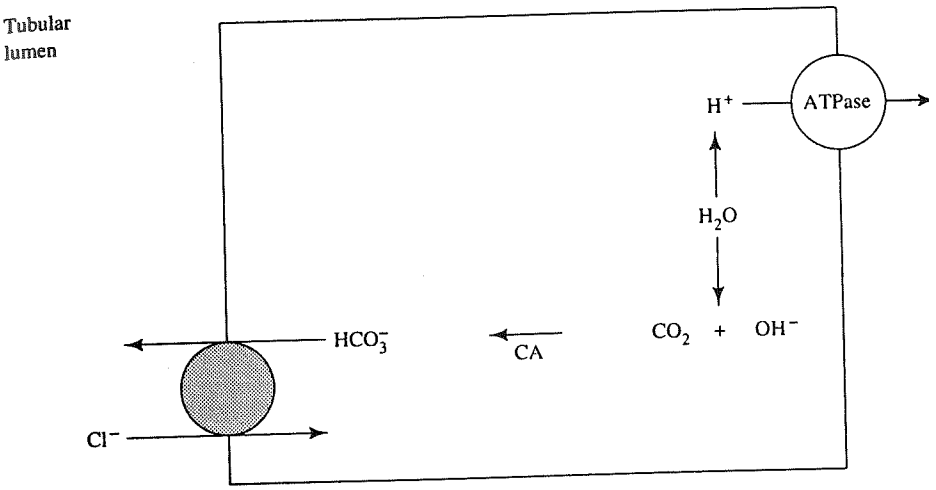

Figure 11-7 Transport mechanisms involved in the secretion of bicarbonate into the tubular lumen in the type B intercalated cells in the cortical collecting tubule. Water within the cell dissociates into hydrogen and hydroxyl anions. The former are secreted into the peritubular capillary by H^+-ATPase pumps in the basolateral membrane. The hydroxyl anions combine with carbon dioxide to form bicarbonate in a reaction catalyzed by carbonic anhydrase (CA). Bicarbonate is then secreted into the tubular lumen via chloride-bicarbonate exchangers in the luminal membrane. The favorable inward concentration gradient for chloride (lumen concentration greater than that in the cell) provides the energy for bicarbonate secretion.

$$\text{pH} = 6.80 + \log \frac{[HPO_4^{2-}]}{[H_2PO_4^-]} \qquad (11\text{-}7)$$

the ratio of HPO_4^{2-} to $H_2PO_4^-$ is 4:1 at an arterial pH of 7.40. If 50 mmol of phosphate is excreted in the urine (the remainder of the filtered phosphate being reabsorbed), then 40 mmol exists as HPO_4^{2-} and 10 mmol as $H_2PO_4^-$ in the glomerular filtrate. If the tubular fluid pH in the proximal tubule is lowered to 6.8 by H^+ secretion, then, from Eq. (11-7), the ratio of HPO_4^{2-} to $H_2PO_4^-$ will fall to 1:1.

As a result, there will now be 25 mmol each of HPO_4^{2-} and $H_2PO_4^-$ in the tubule. This represents the buffering of 15 mmol (or 15 million nanomol) of H^+ by

Table 11-1 Effects of a tubular fluid pH on buffering by HPO_4^{2-} if 50 mmol of phosphate is excreted

Segment	pH	Quantity (in mmol) of HPO_4^{2-}	Quantity (in mmol) of $H_2PO_4^-$	Amount buffered by HPO_4^{2-}, mmol
Filtrate	7.40	40	10	0
Proximal tubule	6.80	25	25	15
Final urine	4.80	0.5	49.5	39.5

HPO_4^{2-}, which an increase in the free H^+ concentration from 40 nanomol/L (pH of 7.40) to only 160 nanomol/L (pH of 6.80). Thus, over 99.99 percent of the secreted H^+ has been buffered. If the tubular fluid pH in the collecting tubules is lowered further to 4.8 (H^+ concentration of 0.016 mmol/L), essentially all the HPO_4^{2-} will be converted to $H_2PO_4^-$, as a total of 39.5 mmol of H^+ will have been buffered by the conversion of HPO_4^{2-} to $H_2PO_4^-$ (Table 11-1).

In summary, the *amount of H^+ buffered by HPO_4^{2-} increases as the tubular fluid pH is reduced.* However, once the urine pH falls below 5.5, virtually all of the urinary phosphate exists as $H_2PO_4^-$ and further buffering cannot occur unless there is an increase in phosphate excretion. To some degree, acid loading decreases proximal phosphate reabsorption[59] by decreasing the activity of the Na^+-phosphate cotransporter that is responsible for the entry of luminal phosphate into the cell.[60,61] This effect may be mediated both by decreased affinity for the interaction with Na^+[61] and by conversion of HPO_4^{2-} to $H_2PO_4^-$, which binds less avidly to the cotransporter.[62] In addition, some of the excess H^+ ions may compete for the Na^+ site on the cotransporter, further decreasing phosphate reabsorption.[61]

Nevertheless, the ability to enhance net acid excretion by acidemia-induced phosphaturia is usually limited, and it is *increased NH_4^+ excretion that generally constitutes the major adaptation to an acid load.* An exception occurs in diabetic ketoacidosis, where large amounts of β-hydroxybutyrate ($pK_a = 4.8$) are excreted in the urine (see Chap. 25). These ketoacid anions can act as urinary buffers, augmenting titratable acid excretion by as much as 50 meq/day.[63] This effect is due both to the high concentration of ketoacid anions present and to the proximity of the pK_a of β-hydroxybutyrate to the acid urine pH.

Ammonium Excretion

The ability to excrete H^+ ions as ammonium adds an important degree of flexibility to renal acid-base regulation, because the rate of NH_4^+ production and excretion can be varied according to physiologic needs. The mechanism by which this process occurs has been considered to begin with ammonia (NH_3) production by the tubular cells.[64] Some of the excess NH_3 then freely diffuses into the tubular lumen, where it combines with secreted H^+ ions to form NH_4^+:

$$NH_3 + H^+ \rightarrow NH_4^+ \qquad (11\text{-}8)$$

These NH_4^+ ions are lipid-insoluble and are therefore "trapped" in the lumen, since back-diffusion cannot occur.

This sequence also explains how NH_3 can act as an effective buffer, even though the pK_a of this system is 9.0, well above that of the plasma or urine. At a urine pH of 6.0, for example, the ratio of NH_3 to NH_4^+ is 1 : 1000. The combination of this small amount of NH_3 with secreted H^+ ions should rapidly utilize all of the available buffer. This does not occur, however, since the ensuing reduction in the tubular fluid NH_3 concentration results in the diffusion of more NH_3 into the lumen. This ability to replenish the quantity of buffer is not present with

titratable acidity; once HPO_4^{2-} has been converted to $H_2PO_4^-$ further buffering by this system cannot occur.

It is now clear that this model represents an oversimplification and that NH_4^+ excretion can be viewed as occurring in three major steps: (1) NH_4^+ is produced, primarily in the early proximal tubular cells; (2) luminal NH_4^+ is partially reabsorbed in the thick ascending limb and the NH_3 is then recycled within the renal medulla; and (3) the medullary interstitial NH_3 reaches high concentrations that allow NH_3 to diffuse into the tubular lumen in the medullary collecting tubule, where it is trapped as NH_4^+ by secreted H^+, as predicted from the classic theory.[64,65]

NH_4^+ production The initial step in NH_4^+ excretion is the generation of NH_4^+ within the tubular cells from the metabolism of amino acids, particularly but not solely glutamine[2,64,66]:

$$\text{Glutamine} \rightarrow NH_4^+ + \text{glutamate} \rightarrow NH_4^+ + \alpha\text{-ketoglutarate}^{2-}$$

The first of these reactions is catalyzed by phosphate-dependent glutaminase and the second by glutamate dehydrogenase.[67] The subsequent metabolism of α-ketoglutarate results in the generation of two HCO_3^- ions,[2] which are then returned to the systemic circulation by the Na^+-$3HCO_3^-$ cotransporter in the basolateral membrane (Fig. 11-4).

Notice that it is primarily NH_4^+, not NH_3, that is produced by these reactions, which occur mostly in the proximal tubule.[68,69] Lipid-solute NH_3 can freely diffuse out of the cell across both the luminal and basolateral membranes.[70] In comparison, lipid-insoluble NH_4^+ can be secreted only into the tubular lumen, since the required transmembrane transporters are present only in the luminal membrane.[70] This process of NH_4^+ secretion appears to be mediated at least in part by the Na^+-H^+ antiporter, which can also function as a Na^+-NH_4^+ exchanger (Fig. 11-4).[70-72]

Medullary recycling The NH_4^+ that is produced within the proximal tubule and secreted into the lumen exists in equilibrium with a much smaller quantity of NH_3. This NH_3 is capable of diffusing out of the lumen into the peritubular capillary, thereby reducing net acid excretion. This effect is minimized by the low urine pH, which can lower urinary NH_3 levels well below the level in the plasma. As depicted in Fig. 11-5, however, the urine does not become maximally acidified until the end of the collecting tubules. It is therefore possible that significant quantities of NH_3 could be lost from the lumen, particularly in the medullary collecting tubule, where progressively higher luminal concentrations of NH_4^+ and NH_3 are achieved.

These potential losses of luminal NH_3 are minimized because more than 75 percent of the tubular fluid NH_4^+ is *recycled within the medulla*, thereby maintaining a high interstitial NH_3 concentration (Fig. 11-8).[65,69,73] The primary step in this process is reabsorption in the thick ascending limb by substitution of NH_4^+ for K^+ both on the Na^+-K^+-$2Cl^-$ carrier and, to a much lesser degree, through the K^+ channels in the luminal membrane (see Fig. 4-2).[65,74] The movement of reab-

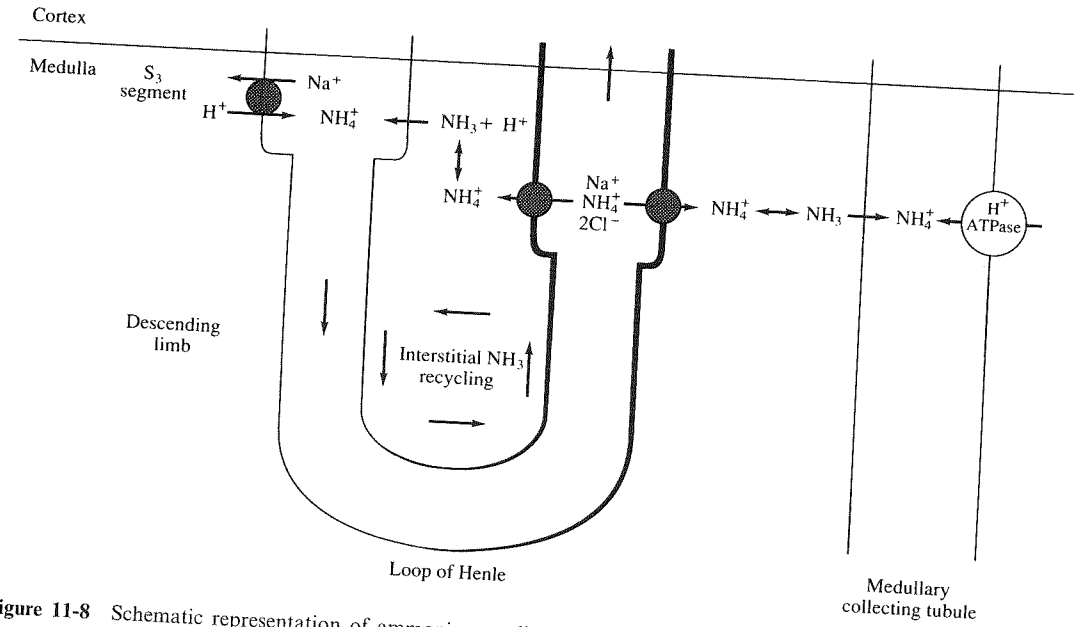

Figure 11-8 Schematic representation of ammonia recycling within the renal medulla. Although NH_4^+ production occurs predominantly in the proximal tubule, most of the NH_4^+ is then reabsorbed in the thick ascending limb, apparently by substitution for K^+ on the Na^+-K^+-$2Cl^-$ carrier in the luminal membrane. Partial dissociation into NH_3 and H^+ then occurs in the less acid tubular cell. The NH_3 diffuses into the medullary interstitium, where it reaches relatively high concentrations; it then diffuses back into those segments that have the lowest pH and therefore have the most favorable gradient: the S_3 segment of the late proximal tubule and, more importantly, the medullary collecting tubule, where the secreted NH_3 is trapped as NH_4^+ and then excreted.

sorbed NH_4^+ into the less acid tubular cell drives Eq. (11-8) to the left, resulting in the formation of NH_3 and H^+. The H^+ ions are then resecreted into the lumen via a Na^+-H^+ exchanger, where they promote HCO_3^- reabsorption by combining with HCO_3^- that is delivered out of the proximal tubule.[75,76]

In comparison, the luminal membrane has the unusual characteristic of being impermeable to NH_3.[76] As a result, the NH_3 formed within the cell will diffuse out across the basolateral membrane into the medullary interstitium, and then into those compartments that have the lowest NH_3 concentration, which in the tubules is a function of both delivery and the tubular fluid pH. As described above, a relatively small amount of H^+ secretion can lead to a large reduction in pH (and the generation of a disequilibrium pH) in those nephron segments that lack luminal carbonic anhydrase (Fig. 11-6). Thus, some of the NH_3 will diffuse into the S_3 segment of the proximal tubule and then be recycled again in the thick ascending limb.[52,74] The net effect is the maintenance of a high medullary interstitial NH_3 concentration, which promotes secretion into the medullary collecting tubule.

Ammonium reabsorption in the thick limb is reduced by hyperkalemia (probably due to competition for the reabsorptive site on the Na^+-K^+-$2Cl^-$ cotransporter, see "Plasma Potassium Concentration," below) and is enhanced by chronic metabolic acidosis due to increased NH_4^- production in and delivery out of the proximal tubule.[73,77] The latter represents an appropriate response, since the ensuing increase in ammonia recycling will facilitate NH_4^- excretion and therefore excretion of the acid load.

NH_3 secretion into the cortical and medullary collecting tubule The fluid entering the collecting tubules has a relatively low NH_3 concentration because of removal in the loop of Henle. Furthermore, there is no luminal carbonic anhydrase in most of the collecting tubule segments.[28,54] As a result, continued H^+ secretion (by the H^+-ATPase pump) produces a maximally acid urine that further reduces the tubular fluid NH_3 levels. The net effect is that there is a relatively large gradient favoring the free diffusion of interstitial NH_3 into the tubular lumen, where it forms NH_4^+ (Fig. 11-8).[5,69]

For luminal NH_4^+ accumulation to occur with maximum efficiency, the NH_3 and NH_4^+ permeabilities must be different from those in the loop of Henle. In the latter segment, the luminal membrane is permeable to NH_4^+ but not to NH_3; these characteristics permit luminal NH_4^+ to be reabsorbed without NH_3 back-diffusion into the lumen. In contrast, the cell membranes in the collecting tubules are highly permeable to NH_3 but have only a negligible permeability to NH_4^+.[78] As a result, interstitial NH_3 can passively diffuse into the tubular lumen, where it is then trapped as NH_4^+.

The net effect is that NH_3 is secreted into the lumen throughout the collecting tubules.[65] The gradient is greatest in the inner medulla, where the interstitial concentration is highest. However, there is a roughly equivalent degree of NH_3 secretion in the cortex and outer medulla, which have a higher NH_3 permeability, as a result of both an increase in unit permeability and a greater luminal surface area.[65,67]

...relatively high concentrations; it then diffuses back into those segments that have the lowest pH and therefore have the most favorable gradient: the S_3 segment of the late proximal tubule and, more importantly, the medullary collecting tubule, where the secreted NH_3 is trapped as NH_4^+ and then excreted.

Response to changes in pH According to this model, NH_4^+ excretion can be increased in one of two ways: by increasing proximal NH_4^+ production from glutamine and by lowering the urine pH, which will increase NH_3 diffusion into the lumen in the medullary collecting tubule (Fig. 11-9).[65] In humans given an acid load, for example, NH_4^+ excretion begins to increase within 2 h, mostly as a result of the formation of a more acid urine, which increases the efficiency of NH_3 secretion into the medullary collecting tubule.[79] Total NH_4^+ excretion reaches its maximum level at 5 to 6 days, a time at which there is an elevation in both glutamine uptake by the kidney and tubular NH_4^+ production (Fig. 11-10).[5,79-81]

Animal models provide confirmation of this sequence. Phosphate-dependent glutaminase activity increases on the first day and glutamate dehydrogenase activity by day 2 to 3 after an acid load.[82,83] However, NH_4^+ excretion begins to rise on the first day and is much greater than can be explained by the increase in enzyme activity; this response may reflect enhanced efficiency of NH_4^+ trapping or increased glutamine uptake by the cells.[82,83]

The adaptive increase in glutamine metabolism with acidemia begins with increased uptake by the proximal tubular cells.* Under normal conditions, most of the filtered glutamine is reabsorbed by cotransport with Na^+, being driven by the favorable electrochemical gradient for passive Na^+ entry into the cells (see page 75). In the presence of acidemia, however, Na^+-dependent glutamine uptake also occurs from the peritubular capillary across the basolateral membrane.[84,85] The peritubular capillary is a fertile source of glutamine, since only 20 percent of the renal plasma flow and therefore only 20 percent of the glutamine presented to the kidney normally undergoes glomerular filtration.

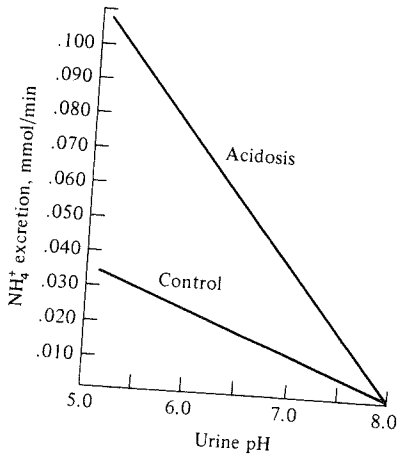

Figure 11-9 Effect of urinary and arterial pH on NH_4^+ excretion. Lowering the arterial pH (that is, acidemia) increases cellular NH_4^+ production from glutamine. Lowering the urine pH enhances the trapping of NH_3 as NH_4^+ in the medullary collecting tubule. (*Redrawn from Pitts RF,* Fed Proc *7:418, 1948, with permission.*)

* The increment in renal glutamine uptake leads to an initial reduction in circulating glutamine levels.[80] This is then followed by increased glutamine release from skeletal muscle, due in part to activation of glutamine synthetase.

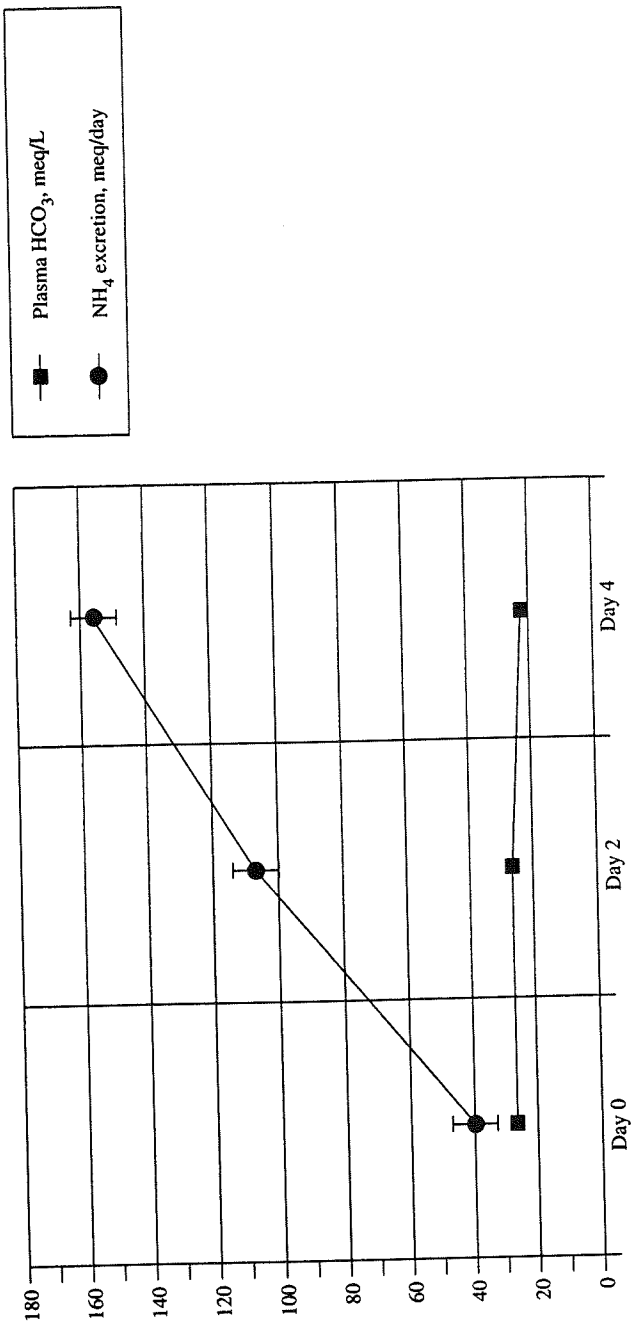

Figure 11-10 Effect of a dietary acid load on the plasma HCO_3^- concentration and urinary NH_4^+ excretion. The latter increases approximately fourfold with a reduction of only a few milliequivalents per liter in the plasma HCO_3^- concentration. (*Data from Welbourne T, Weber M, Bank N,* J Clin Invest *51:1852, 1972, with permission.*)

Once glutamine is within the tubular cells, its proximal metabolism is pH-dependent, appropriately increasing with acidemia and decreasing with alkalemia.[68,69] How this occurs is incompletely understood, as several factors may play an important role. With acidemia, for example, the rise in NH_4^+ production may be largely mediated by enhanced activity of the enzymes involved in NH_4^+ production, including phosphate-dependent glutaminase (promoting the metabolism of glutamine to glutamate), glutamate dehydrogenase (promoting the metabolism of glutamate to α-ketoglutarate), and α-ketoglutarate dehydrogenase (promoting the metabolism of α-ketoglutarate).[66,82] These changes in enzyme activity are limited to the proximal tubule,[82] which is consistent with this segment being the site of increased NH_4^+ production in acidemic states.[68]

It is presumed that proximal glutamine metabolism responds to alterations in cell pH that parallel those in the extracellular fluid (see "Extracellular pH," below). In particular, it may be an alteration in the *pH gradient between the cytosol and the mitochondria* that constitutes the signal to change the rate of NH_4^+ production.[66,86] Other, mostly unidentified circulating factors may also contribute, including increased release of glucocorticoids.[87,88]

Regardless of the exact mechanisms involved, the net effect is that NH_4^+ excretion can increase from its normal value of 30 to 40 meq/day to over 300 meq/day with severe metabolic acidosis.[63,89] This response, which is in marked contrast to the limited ability to enhance titratable acid excretion, is appropriate; each NH_4^+ produced results in the equimolar generation of HCO_3^- from the metabolism of α-ketoglutarate.[2] Return of this HCO_3^- to the systemic circulation then raises the plasma HCO_3^- concentration toward normal.

Urine pH

As depicted in Fig. 11-5, the tubular fluid pH falls progressively, reaching its lowest level in the medullary collecting tubule. In humans, the minimum urine pH that can be achieved is 4.5 to 5.0; this represents a maximum plasma-to-tubular fluid H^+ gradient of almost 1 : 1000 (3 log units). The inability to make the urine more acid may reflect a limit on the strength of the H^+-ATPase pump or on the impermeability of the tubular epithelium, which is required to prevent the passive backflux of secreted H^+ ions out of the lumen.

This ability to lower the urine pH is important, because the formation of both titratable acidity and NH_4^+ is pH-dependent, with both increasing as the urine is made more acid (Table 11-1, Fig. 11-9). If the minimum urine pH were higher, at 5.5 to 6.0 (which is still less than that of the plasma), titratable acid and NH_4^+ excretion would fall, and excretion of the daily H^+ load might be prevented. This appears to be the mechanism responsible for the acidemia in patients with type 1 (distal) renal tubular acidosis (see Chap. 19).

The pH dependence of titratable acidity and NH_4^- formation also means that these processes (as well as HCO_3^- reabsorption) occur throughout the nephron as the urine is made more acid. The sites at which they are most likely to occur can be

appreciated from the isohydric principle, which states that all three buffer systems must be in equilibrium:

$$pH = 6.1 + \log\frac{[HCO_3^-]}{0.03P_{CO_2}} = 6.8 + \log\frac{[HPO_4^{2-}]}{[H_2PO_4^-]} = 9.0 + \log\frac{[NH_3]}{[NH_4^+]}$$

Thus, a secreted H^+ ion will preferentially be buffered by that system with the highest concentration and/or the pK_a closest to that of the tubular fluid pH.[69] In the proximal tubule, most secreted H^+ ions are utilized for HCO_3^- reabsorption because of the high concentration of HCO_3^- and the ability to minimize the reduction in pH by the action of luminal carbonic anhydrase. This segment also represents the site in which most NH_4^+ is secreted into the lumen and in which about one-half of the available HPO_4^{2-} is buffered (Table 11-1). In contrast, most H^+ ions secreted in the medullary collecting tubule (where the urine pH is reduced to its lowest value) combine with secreted NH_3, since virtually all the HCO_3^- has been reabsorbed and most of the HPO_4^{2-} has already been buffered (which occurs when the urine pH is below 5.8, that is, more than 1 pH unit from the pK_a of 6.8).

REGULATION OF RENAL HYDROGEN EXCRETION

The preceding section discussed how the kidney excretes H^+ ions. In this section, we will review the factors that determine exactly how much H^+ is excreted. The *extracellular pH* (which is most often measured clinically on a specimen of arterial blood) is the major physiologic regulator of this process, as it allows acid excretion to vary with day-to-day changes in the dietary acid load. In addition, the rate of H^+ secretion also can be influenced by the effective circulating volume, aldosterone, the plasma K^+ concentration, and parathyroid hormone.

Extracellular pH

Net acid excretion tends to vary inversely with the extracellular pH. Acidemia, for example, is characterized by a fall in extracellular pH (or a rise in H^+ concentration) and is associated with an increase in both proximal and distal acidification.[90-93] This is manifested in the proximal tubule by four changes:

- Enhanced luminal Na^+-H^+ exchange,[90,91,94] a response that may be mediated both by binding of excess intracellular H^+ ions to a modifier site on the exchanger[90] and by the synthesis of new exchangers, as evidenced by a rise in mRNA for the Na^+-H^+ antiporter[95]
- Enhanced activity of the luminal H^+-ATPase[13]
- Increased activity of the Na : $3HCO_3^-$ cotransporter in the basolateral membrane, thereby allowing HCO_3^- formed within the cell to be returned to the systemic circulation[91,94,96]
- Increased NH_4^+ production from glutamine[68]

In the collecting tubules, on the other hand, the increase in acidification appears to involve the insertion of preformed cytoplasmic H^+-ATPase pumps into the luminal membrane of the acid-secreting cells,[40,57,97] particularly those in the outer medullary collecting duct.[97] The ensuing reduction in the tubular fluid pH in these segments will promote the diffusion of interstitial NH_3 into the lumen, where it will be trapped as NH_4^+ (Fig. 11-4).[79] The net effect of this increase in acid excretion is enhanced generation of HCO_3^- by the tubules. Return of this HCO_3^- to the systemic circulation will then raise the extracellular pH toward normal.

The extracellular pH is thought to affect net acid excretion in part by *parallel, although lesser, alterations in the renal tubular cell pH.*[98-100] The importance of this local effect, which is independent of other circulating factors, has been demonstrated in experiments with cultured renal proximal tubule cells. Lowering the pH of the bathing medium in this setting leads to a significant increase in the activity of the luminal Na^+-H^+ exchanger.[100] This effect is thought to be mediated by activation of pH-sensitive proteins.[101]

The mechanism by which the intracellular pH changes with the extracellular pH varies with the cause of the acid-base disorder. An elevation in the P_{CO_2}, for example, will lower the pH of the extracellular fluid; this will induce a similar and rapid acidification in the cells, because CO_2 can freely cross cell membranes.

The effect of alterations in the plasma HCO_3^- concentration are less direct, since transcellular diffusion of this anion is limited by the lipid bilayer of the cell membrane. However, the carrier-mediated HCO_3^- exit steps in the basolateral membrane of the proximal tubule (Na^+-$3HCO_3^-$ cotransport)[98,99] and the distal nephron (Cl-HCO_3^-) exchange)[102] are affected by the transmembrane HCO_3^- gradient. Lowering the extracellular pH by reducing the HCO_3^- concentration will make this gradient more favorable, therby promoting HCO_3^- exit from the cell and reducing the cell pH (Fig. 11-11).[98,99] The ensuing increase in acid excretion then raises both the systemic and the intracellular pH toward normal; thus, it may actually be the *intracellular pH* that is primarily being regulated.[102,103]

These adaptive changes in cell pH are determined by the extracellular pH itself, not by the HCO_3^- concentration or P_{CO_2} alone. There is *no alteration in the cell pH* if both the HCO_3^- concentration and the P_{CO_2} are lowered or raised to a similar degree, so that the extracellular pH remains constant.[98] In this setting, there is also no change in net acid excretion.[92]

Metabolic acidosis Metabolic acidosis is characterized by acidemia that is due to a *reduced* plasma HCO_3^- concentration. Net acid excretion is appropriately and often dramatically increased in this disorder, beginning within a day and reaching its maximum in 5 to 6 days (Fig. 11-10).[5,79,104] This response is mostly due to enhanced NH_4^+ excretion, which is mediated both by increased proximal NH_4^+ secretion[68,79] and by increased distal hydrogen secretion.[40,97]

In comparison, titratable acid excretion is generally limited by the amount of phosphate in the urine, which is modestly increased by an acidemia-induced inhibition of proximal phosphate reabsorption.[59-62] An exception to this rule occurs in

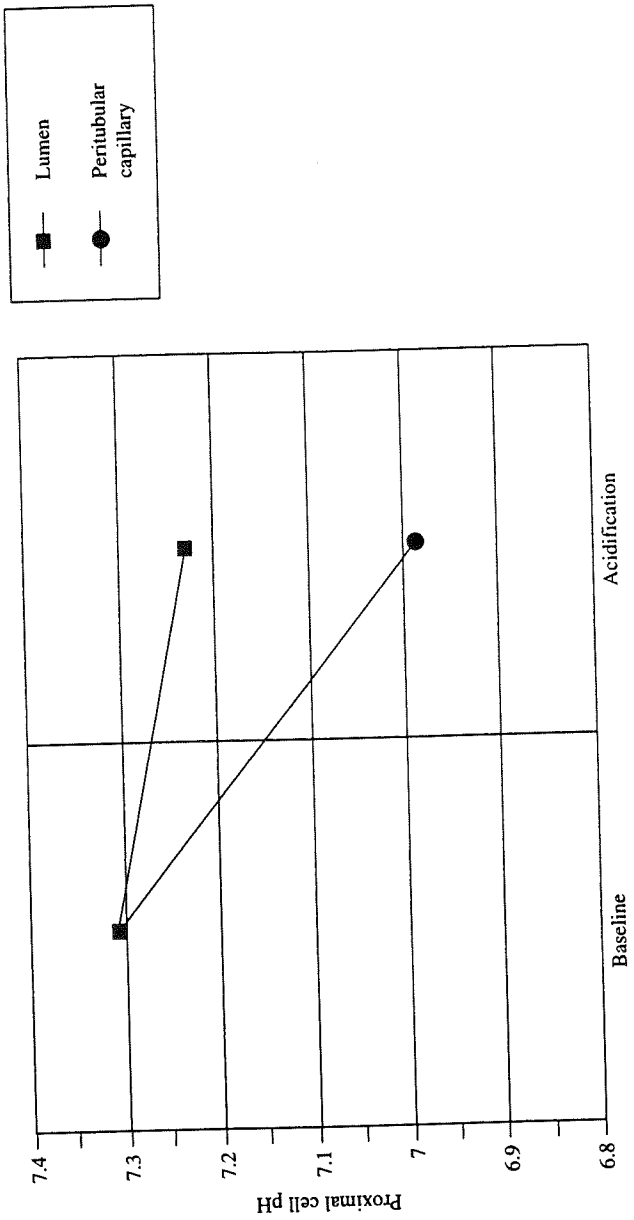

Figure 11-11 Effect of lowering the HCO_3^- concentration and pH in the fluid in the tubular lumen (squares) or in the peritubular capillary (circles) on the proximal tubular cell pH. Only the change in peritubular capillary pH significantly lowers the cell pH, an effect that appears to be mediated by the Na^+:$3HCO_3^-$ cotransporter. (*Data from Alpern RJ, Chambers M,* J Clin Invest *78:502, 1986, with permission.*)

diabetic ketoacidosis, where urinary ketone anions (particularly β-hydroxybutyrate) can act as titratable acids. In this setting, net acid excretion can exceed 500 meq/day,[63,89] resulting in the generation of an equivalent quantity of HCO_3^- ions in the extracellular fluid.

The relationship between cell pH and net acid excretion can also be understood in terms of the steady state. Suppose a normal subject increases acid generation by going on a high-protein diet. Over a period of days, net acid excretion will rise until it meets the new level of acid production. At this time, the patient is back in a new steady state, but the plasma HCO_3^- concentration must have fallen to provide the signal (lower cell pH) for the higher level of acid excretion. This process is reasonably efficient. As shown in Fig. 11-10, for example, lowering the plasma HCO_3^- concentration by 4 to 5 meq//L leads to a fourfold increase in NH_4^+ excretion.

Metabolic alkalosis Metabolic alkalosis, on the other hand, is characterized by an alkaline extracellular pH that results from an *elevation* in the plasma HCO_3^- concentration. The normal response to a HCO_3^- load is to excrete the excess HCO_3^- in the urine, both by diminishing its rate of reabsorption and by HCO_3^- secretion in the cortical collecting tubule.[21,55,56] As described above, the latter process occurs in a subpopulation of cortical intercalated cells that are able, in the presence of an elevated pH, to insert H^+-ATPase pumps into the basolateral rather than the luminal membrane (Fig. 11-7).[40]

This protective bicarbonaturic response is extremely efficient. For example, the administration of as much as 1000 meq of $NaHCO_3$ per day to normal subjects induces only a minor elevation in the plasma HCO_3^- concentration, as virtually all of the excess HCO_3^- is excreted in the urine.[105] Thus, maintenance of metabolic alkalosis requires the presence of a defect in HCO_3^- excretion, which is most often due to effective volume and chloride depletion (see below).

Respiratory acidosis and alkalosis Disturbances in alveolar ventilation induce changes in CO_2 elimination and, consequently, in the P_{CO_2}. Primary hyperventilation, for example, enhances CO_2 loss, resulting in a fall in the P_{CO_2} (hypocapnia) and a rise in pH that is called *respiratory alkalosis*. Primary hypoventilation, on the other hand, impairs CO_2 elimination, producing an elevation in the P_{CO_2} (hypercapnia) and a reduction in pH that is called *respiratory acidosis*. Although correction of either of these conditions requires the restoration of normal alveolar ventilation, the kidney can minimize the changes in arterial pH by varying H^+ excretion and HCO_3^- reabsorption.

From Eq. (11-3), the extracellular pH is a function of the HCO_3^-/P_{CO_2} ratio. Thus, the *pH may remain near normal in respiratory acid-base disorders if the P_{CO_2} and HCO_3^- concentration change in the same direction and to a similar degree.* Consequently, an elevation in the plasma HCO_3^- concentration is an appropriate response to hypercapnia, and a reduction in the plasma HCO_3^- concentration is an appropriate response to hypocapnia (see Chaps. 20 and 21).

These changes occur because the P_{CO_2}, via its effect on intracellular pH, is an important determinant of H^+ secretion and HCO_3^- reabsorption (Fig. 11-12).[57,92,93] With chronic respiratory acidosis, for example, there is an increase in net acid excretion (primarily and NH_4^+), resulting in the generation of new HCO_3^- ions in the plasma.[106] The net effect in the steady state (which is achieved within 5 to 6 days) is that the rise is P_{CO_2} is partially offset by an increase in the plasma HCO_3^- concentration that *averages 3.5 meq/L for every 10-mmHg elevation* in the P_{CO_2}.[107]

The renal response is reversed in chronic respiratory alkalosis. In this setting, the concurrent rise in intracellular pH diminishes H^+ secretion, resulting in HCO_3^- loss in the urine and decreased NH_4^+ excretion.[108,109] These changes are manifested by a fall in the plasma HCO_3^- concentration that averages *5 meq/L for every 10-mmHg decline* in the P_{CO_2}.[108]

Chronic metabolic acidosis versus chronic respiratory acidosis Although chronic metabolic and respiratory acid-base disturbances can produce similar changes in extracellular pH, there are major differences in the renal response that illustrate the role of the intracellular pH in determining the degree of acidification that occurs.[110,111] In chronic metabolic acidosis, for example, the daily acid load must be increased to sustain the acidemia (as with chronic diarrhea). Consequently, net acid and NH_4^+ excretion are persistently above normal (Fig. 11-13).

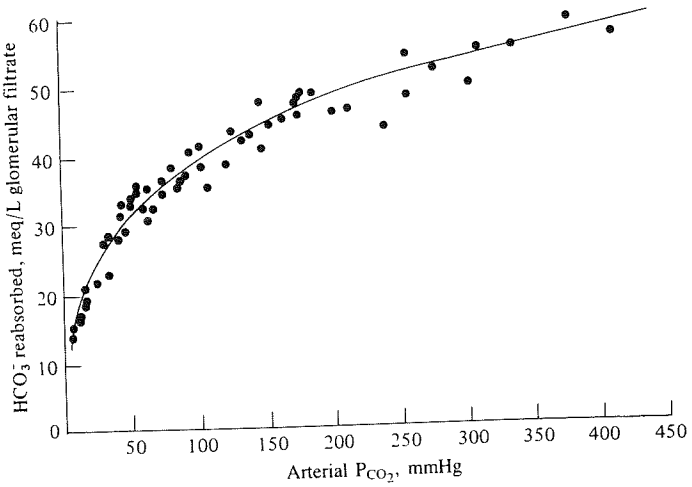

Figure 11-12 Relationship between arterial P_{CO_2} and HCO_3^- reabsorption. Note that the curve is steepest in the physiologic range (P_{CO_2} of 15 to 90 mmHg). (*From Rector FC Jr, Seldin DW, Roberts AD Jr, Smith JS,* J Clin Invest *39:1706, 1960, by copyright permission of the American Society for Clinical Investigation.*)

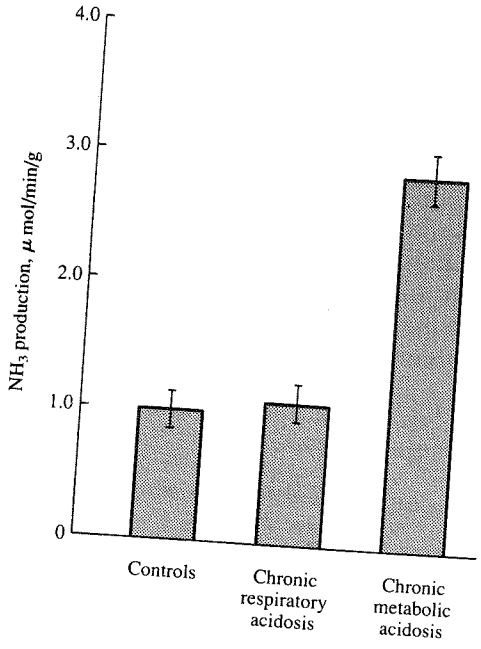

Figure 11-13 Ammonia production by the isolated perfused kidney from control rats and those with chronic respiratory acidosis or chronic metabolic acidosis of 3 days duration. Ammonia production is enhanced only in metabolic acidosis, despite a similar reduction in pH to about 7.30 in both acidotic groups. (*From Rodriguez-Nichols F, Laughrey E, Tannen RL,* Am J Physiol *247:F896, 1984, with permission.*)

The same response is seen in respiratory acidosis, as new HCO_3^- ions must be generated to produce the compensatory rise in the plasma HCO_3^- concentration.[92,106] In the new steady state, the pH will be partially corrected, but the daily acid load generated from protein metabolism *will be normal* (assuming that there is no change in dietary intake). As a result, there is *no necessity for increased* NH_4^+ *excretion* in chronic respiratory acidosis, which returns to a level similar to that in controls (Fig. 11-13).[110]

To summarize, net acid and NH_4^+ excretion are enhanced in chronic metabolic but not respiratory acidosis, despite a similar degree of acidemia in both conditions. This seemingly paradoxical finding may be *explained by differences in proximal tubular cell pH.*[111,112] Both metabolic and respiratory acidosis will produce a similar effect at the basolateral membrane: lowering the cell pH by HCO_3^- exit down a more favorable gradient in metabolic acidosis and by CO_2 entry in respiratory acidosis.[98,99]

The responses are quite different, however, at the luminal membrane. The plasma HCO_3^- concentration and, therefore, the filtered HCO_3^- load are reduced in metabolic acidosis. As a result, less HCO_3^- is reabsorbed in the proximal tubule by Na^+-H^+ exchange. In comparison, the plasma HCO_3^- concentration and filtered HCO_3^- load are elevated in chronic respiratory acidosis. This increase in the tubular HCO_3^- concentration allows more HCO_3^- to be reabsorbed.[113] It is important to remember that proximal acidification is limited by the transcellular Na^+ gradient that provides the energy for the Na^+-H^+ antiporter. When more buffer (as HCO_3^-) is present, more H^+ secretion can occur without an excessive reduction in tubular fluid pH.[113]

The net effect of this increase in H^+ extrusion from the cell is that the *proximal tubular cell pH returns toward normal in chronic respiratory acidosis.*[111,112]* As a result, there is now no stimulus to increase proximal NH_4^+ secretion, incomparison to chronic metabolic acidosis, where the cell pH is persistently reduced.[112] Similar factors may explain why mRNA expression for the Na^+-H^+ exchanger is increased in metabolic acidosis but unchanged in chronic respiratory acidosis.[98]

Effective Circulating Volume

Bicarbonate reabsorption can be influenced by the effective circulating volume, with the most important effect being an increase in HCO_3^- reabsorptive capacity with volume depletion.[113-115] As shown in Fig. 11-14, for example, raising the plasma HCO_3^- concentration by infusing $NaHCO_3$ leads to a plateau in HCO_3^- reabsorption at a level of about 26 meq//L (see page 88). This is a proper response, since it allows virtually all of the filtered HCO_3^- to be reabsorbed as long as the plasma HCO_3^- concentration is within the normal range. Once the latter exceeds 26 meq/L, inappropriate HCO_3^- retention is prevented by excretion of the excess HCO_3^- in the urine.

In contrast, if hypovolemia is induced by the prior administration of a diuretic, then net HCO_3^- reabsorption continues to increase, even at a level above 35 meq/L (Fig. 11-14). This effect can be demonstrated in normals simply by the ingestion of a low-salt diet (10 meq/day), which is sufficient to increase HCO_3^-

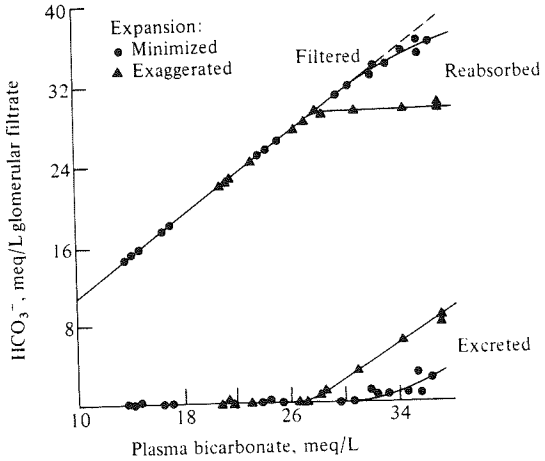

Figure 11-14 Relationship between arterial P_{CO_2} and HCO_3^- reabsorption. Note the curve is steepest in the physiologic range (P_{CO_2} of 15 to 90 mmHG). (*From Rector FC Jr, Seldin DW, Roberts AD Jr, Smith JS,* J Clin Invest *39:1706, 1960, by copyright permission of the American Society for Clinical Investigation.*)

* It seems likely that distal acidification is similar in metabolic and respiratory acidosis,[93] since the confounding effect of increased HCO_3^- reabsorption is primarily limited to the proximal tubule. However, this preservation of distal function in chronic respiratory acidosis does not lead to a significant increase in net acid excretion, since virtually all of the urinary NH_4^+ is produced proximally.[68,69] Thus, the absence of an elevation in proximal NH_4^+ production in this disorder[110] limits the degree to which distal H^+ secretion can enhance net acid excretion.

reabsorptive capacity by 4 meq/L even though the subject is clinically euvolemic.[116]

The relationship between volume depletion and HCO_3^- transport becomes clinically important in patients with metabolic alkalosis, in whom the inability to excrete the excess HCO_3^- prevents the spontaneous restoration of acid-base balance.[117] In this setting, *the attempt to maintain volume by preventing further* Na^+ *loss as* $NaHCO_3$ *occurs at the expense of the systemic pH.*

At least four factors may contribute to this effect on HCO_3^- excretion: (1) a reduction in glomerular filtration rate, (2) activation of the renin-angiotensin-aldosterone system, (3) hypochloremia, and (4) concurrent hypokalemia due to urinary or gastrointestinal losses (see below).[114,127-129] A decline in GFR, for example, may play a permissive role in selected patients. It is not likely to be of primary importance, however, since the rise in the plasma HCO_3^- concentration results in a filtered load of HCO_3^- that is often not diminished. Furthermore, many patients maintain a GFR that is relatively normal; in this setting, increased tubular reabsorption must be responsible for the absence of HCO_3^- excretion.[117,119]

Renin-angiotensin-aldosterone system The hypovolemia-induced increase in renin release can enhance net H^+ secretion and therefore HCO_3^- reabsorption in several ways. Angiotensin II, acting in the early proximal tubule, is a potent stimulator of HCO_3^- transport by increasing the activity of both the luminal Na^+-H^+ antiporter and the basolateral Na^+-$3HCO_3^-$ cotransporter.[120,121]

However, the physiologic significance of this response for acid-base balance is uncertain. Angiotensin II does increase HCO_3^- reabsorption in the early proximal tubule, but the ensuing decrease in delivery out of this segment may result in an equivalent delivery-dependent reduction in HCO_3^- transport in the late proximal tubule.[122,123] Thus, there may be a net neutral effect on HCO_3^- handling, as the major function of the proximal action of angiotensin II is to increase NaCl and water reabsorption, thereby appropriately expanding the extracellular volume.[122]

Aldosterone may play a more important role by stimulating the Na^+-independent H^+-ATPase pump throughout the distal nephron, including the intercalated cells in the critical collecting tubule and the cells in the outer and inner medullary collecting tubule.[124-128]* Aldosterone also increases the activity of the second step in distal acidification, promoting HCO_3^- extrusion from the cell into the peritubular capillary via the basolateral Cl-HCO_3^- exchanger.[102,127]

In addition, aldosterone can indirectly increase net H^+ secretion by the stimulation of Na^+ transport in a different cell population, the principal cells in the cortical collecting tubule (see Chap. 6).[36,37,114] The reabsorption of cationic Na^+ ions creates a lumen-negative potential difference; this electrical gradient then promotes H^+ accumulation in the lumen by minimizing the degree of back-diffusion.

* This ability of aldosterone to increase urinary H^+ loss can promote the development of metabolic alkalosis in disorders of primary mineralocorticoid excess, such as primary hyperaldosteronism (see Chap. 18).

Chloride depletion Hypochloremia is a common concomitant of metabolic alkalosis, since both H^+ and Cl^- ions are lost in most patients, such as those with vomiting or diuretic therapy. This reduction in the filtered Cl^- concentration can enhance H^+ secretion and HCO_3^- reabsorption through both *Na^+-dependent and Na^+-independent* factors. It has been proposed, for example, that the effect of hypochloremia is related to the high level of Na^+ reabsorption seen in volume depletion, often leading to a urine Na^+ concentration below 5 to 10 meq/L. If, as in normal subjects, the filtrate Na^+ concentration is 145 meq/L and the filtrate Cl^- concentration is 115 meq/L, then only 115 meq/L of Na^+ can be reabsorbed with Cl^-. Since Cl^- is the only quantitatively important reabsorbable anion in the filtrate, *further Na^+ reabsorption must be accompanied by H^+ or K^+ secretion to maintain electroneutrality*. These secretory processes, which primarily occur in the collecting tubules, become more important in the presence of hypochloremia, a setting in which less of the filtered Na^+ can be reabsorbed with Cl^-. The net effect is enhanced H^+ secretion, increased HCO_3^- reabsorption, and persistence of the metabolic alkalosis.

The importance of both volume status and the reabsorbability of the anion can be illustrated by the response to an infusion of Na_2SO_4 (SO_4^{2-} being a poorly reabsorbed anion). When given to a euvolemic subject, Na_2SO_4 is rapidly excreted in the urine. In a volume-depleted subject, however, the Na^+ will be retained (in part under the influence of aldosterone), and, since SO_4^{2-} cannot be reabsorbed, H^+ and K^+ secretion must be increased (Fig. 11-15).[129] In contrast, the administration of NaCl in this setting results in both Na^+ and Cl^- reabsorption without affecting H^+ and K^+ secretion.

The reabsorbability of the anion creates a paradoxical situation in patients with hypovolemia and metabolic alkalosis in that the *administration of acid will not necessarily correct the alkalemia*. If, for example, HNO_3 is given (NO_3^- being relatively nonreabsorbable), it will be buffered by extracellular HCO_3^-:

$$HNO_3 + NaHCO_3 \rightarrow NaNO_3 + H_2CO_3 \rightarrow CO_2 + H_2O$$

As the $NaNO_3$ is presented to the cortical collecting tubule, Na^+ will be retained and H^+ excretion enhanced. This is similar to the fate of Na_2SO_4, shown in Fig. 11-15. The net effect is the excretion of the administered HNO_3 as NH_4NO_3.[130] As

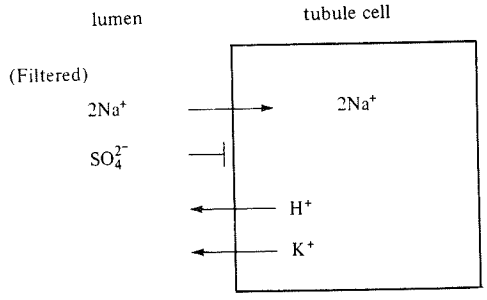

Figure 11-15 Events occurring after Na^+ reabsorption across the luminal membrane of the cortical collecting tubule cell. In a sodium-avid state, the presentation of Na^+ with a nonreabsorbable anion to the cortical collecting tubule enhances H^+ and K^+ secretion. In contrast, if NaCl is presented to this segment, Na^+ will be reabsorbed with Cl^-, with little effect on H^+ and K^+ secretion.

a result, the arterial pH will be unchanged, since an acid urine is excreted despite the presence of systemic alkalemia.

If, in comparison, acid is given as HCl, buffering by $NaHCO_3$ will lead to the generation of NaCl. When this reaches the cortical collecting tubule, the Na^+ will be reabsorbed with Cl^- and not exchanged for H^+. Therefore, the administered H^+ will be retained and the alkalemia will be corrected.

Rather than by giving HCl, the alkalemia can be reversed more easily by promoting HCO_3^- excretion in the urine. This can be achieved by expanding the effective circulating volume with NaCl, eventually allowing the excess HCO_3^- to be excreted as $NaHCO_3$. In comparison, the administration of Na^+ with a different, nonreabsorbable anion, such as SO_4^{2-}, will be ineffective. Thus, the correction of metabolic alkalosis in a volume-depleted (Na^+-avid) subject requires the *administration of the only reabsorbable anion, Cl^-, as either NaCl, HCl, or, if hypokalemia is present, KCl* (see Chap. 18).

The importance of Cl^- may also be related to direct effects on acid-base handling that are *independent of Na^+*.[118,131] In particular, both HCO_3^- secretion by the type B intercalated cells in the cortical collecting tubule and H^+ secretion in the distal nephron can be affected by the local Cl^- concentration.

HCO_3^- secretion into the lumen in the type B intercalated cells appears to be mediated by a Cl-HCO_3^- exchanger in the luminal membrane, the energy for which is provided by the favorable inward gradient for Cl^- (Fig. 11-7).[55,56] Lowering the tubular fluid Cl^- concentration will diminish this gradient, minimizing the ability to secrete HCO_3^-.

With H^+ secretion by the H^+-ATPase pump, Cl^- appears to be passively cosecreted to maintain electroneutrality.[25] The gradient for Cl^- secretion and therefore the ability to secrete H^+ may be enhanced when the tubular fluid Cl^- concentration is reduced.[131]

Both diminished HCO_3^- secretion and enhanced H^+ secretion will contribute to maintenance of the high plasma HCO_3^- concentration and persistence of the alkalemia.

In summary, the effects of hypochloremia on net HCO_3^- reabsorption are most prominent in the collecting tubules. Thus, the appropriate HCO_3^- diuresis induced by fluid and chloride repletion is mostly mediated by decreased net distal HCO_3^- reabsorption (which probably includes a component of HCO_3^- secretion.[132]

Plasma Potassium Concentration

Potassium is another potential influence on renal H^+ secretion, as a reciprocal relationship has been demonstrated between the plasma K^+ concentration and HCO_3^- reabsorption (Fig. 11-16).[133-135] The major proposed mechanism for this relationship is that alterations in K^+ balance lead to *transcellular cation shifts* that affect the intracellular H^+ concentration (Fig. 11-17).

As an example, gastrointestinal or urinary K^+ losses lead to a reduction in the plasma K^+ concentration. As a result, intracellular $K6^+$ moves into the extracellular fluid (through K^+ channels in the cell membrane) down a favorable concen-

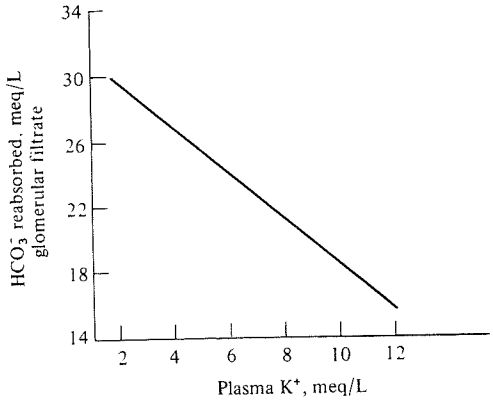

Figure 11-16 Renal tubular reabsorption of HCO_3^- as a function of the plasma K^+ concentration. (*Adapted from Fuller GR, MacLeod MB, Pitts RF,* Am J Physiol *182:111, 1956, with permission.*)

tration gradient to replete the extracellular stores. To maintain electroneutrality, H^+ (and Na^+) enter the cell,[136] resulting in an intracellular acidosis.[112,137,138]

This increase in H^+ concentration in the renal tubular cells may account for the enhanced H^+ secretion, HCO_3^- reabsorption, and NH_4^+ excretion observed with K^+ depletion.[133,138,139] In the proximal tubule, for example, hypokalemia is associated with increased activity of both the luminal Na^+-H^+ antiporter and the basolateral Na^+-$3HCO_3^-$ cotransporter, which are required for the elevations in H^+ secretion and HCO_3^- reabsorption.[140]

These changes are reversed with a rise in the plasma K^+ concentration, as K^+ moves into and H^+ out of cells.[141] The ensuing intracellular alkalosis may then account for the associated reductions in HCO_3^- reabsorption and NH_4^+ excretion.[133,138,139]

Factors other than these transcellular shifts also may contribute to the potassium-induced changes in urinary acidification. For example, hyperkalemia reduces NH_4^+ excretion in rats; there is, however, no change in NH_4^+ delivery out of the

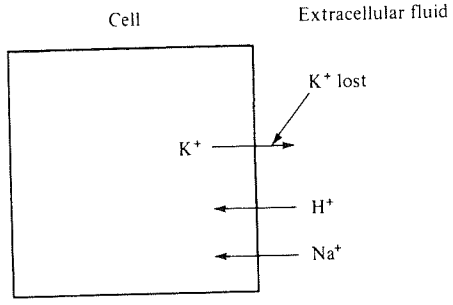

Figure 11-17 Reciprocal cation shifts of K^+, H^+, and Na^+ between the cells, including renal tubular cells, and the extracellular fluid. In the presence of hypokalemia, K^+ moves out of the cells down a concentration gradient. Since the cell anions (primarily proteins and organic phosphates) are unable to cross the cell membrane, electroneutrality is maintained by the entry of Na^+ and H^+ into the cell. The increase in cell H^+ concentration may be responsible for the increased H^+ secretion and HCO_3^- reabsorption seen with hypokalemia. On the other hand, hyperkalemia causes H^+ and Na^+ to leave the cells, resulting in a fall in H^+ secretion and HCO_3^- reabsorption.

proximal tubule, suggesting that segments distal to the proximal tubule must be involved.[142] There are at least two mechanisms by which distal K^+ and H^+ handling might be related:

- Medullary recycling of NH_4^+ is initiated by substitution of NH_4^+ for K^+ on the Na^+-K^+-$2Cl^-$ carrier in the luminal membrane of the thick ascending limb (Fig. 11-8).[74] Increased luminal K^+ in hyperkalemia could competitively inhibit this process, thereby limiting ammonia accumulation in the medullary interstitium, subsequent secretion into the medullary collecting tubule, and total urinary NH_4^+ excretion.[142,143]
- H^+ secretion in the distal nephron is mediated in part by an electroneutral H^+-K^+-ATPase that also actively reabsorbs K^+.[24,27,29] Active K^+ reabsorption by this pump appears to be stimulated by hypokalemia,[27,144-146] an effect that could in part explain the concurrent increase in H^+ secretion. The net result is that hypokalemia and aldosterone, which stimulate the H^+-K^+-ATPase and H^+-ATPase pumps, respectively, can have a potentiating effect on distal hydrogen secretion and therefore on the development and maintenance of metabolic alkalosis.[147] This synergism has potential clinical importance, since many of the causes of metabolic alkalosis (such as diuretic therapy, vomiting, and primary hyperaldosteronism) are associated with both a reduction in the plasma K^+ concentration and increased aldosterone release (see Chap. 18).

In summary, hypokalemia tends to increase net acid excretion, which promotes the development of metabolic alkalosis. Hyperkalemia, via opposite mechanisms, reduces net acid excretion, which, by causing H^+ retention, favors the development of metabolic acidosis. In some patients with hyperkalemia due to hypoaldosteronism, for example, the associated metabolic acidosis can be corrected solely by lowering the plasma K^+ concentration.[139]

Parathyroid Hormone

Parathyroid hormone (PTH) diminishes proximal HCO_3^- reabsorption by reducing the activity of the Na^+-H^+ exchanger in the luminal membrane[148,149] and the Na^+-$3HCO_3^-$ cotransporter in the basolateral membrane.[150] However, the extra HCO_3^- delivered out of the proximal tubule is mostly picked up in the loop of Henle and more distal segments. Although there may be a slight increase in HCO_3^- excretion, this is generally counteracted by enhanced excretion of phosphate, which can increase net acid excretion by buffering secreted H^+ ions.[151]

This response may be physiologically important, since an acid load stimulates PTH secretion. PTH then minimizes the change in extracellular pH both by promoting bone buffering and by increasing acid and phosphate excretion in the urine.[151,152]

The effect of a chronic excess of PTH on acid-base balance is less clear. Patients with primary hyperparathyroidism, who are also hypercalcemic, tend to

have a metabolic acidosis.[153] However, the chronic, continuous administration of PTH to normal humans increases net acid excretion and produces a small elevation, not reduction, in the plasma HCO_3^- concentration.[154]

EFFECT OF ARTERIAL pH ON VENTILATION

Alveolar ventilation provides the oxygen necessary for oxidative metabolism and eliminates the CO_2 produced by these metabolic processes. It is therefore appropriate that the main physiologic stimuli to respiration are an elevation in the P_{CO_2} and a reduction in the P_{O_2} (hypoxemia).[155,156] The CO_2 stimulus to ventilation primarily occurs in chemosensitive areas in the respiratory center in the brain stem, which appear to respond to CO_2-induced changes in the cerebral interstitial pH.[157] This effect is extremely important in the maintenance of the acid-base balance, since roughly 15,000 mmol of CO_2 is produced daily from endogenous metabolism, added to the capillary blood, and then eliminated via the lungs. In contrast, hypoxemia is primarily sensed by peripheral chemoreceptors in the carotid bodies, which are located near the bifurcation of the carotid arteries.[156,158]

Respiratory Compensation in Metabolic Acidosis and Alkalosis

Alveolar ventilation also is affected by metabolic acid-base disorders.[159-165] In metabolic acidosis, for example, minute ventilation can increase from the normal of approximately 5 L/min to greater than 30 L/min as the arterial pH falls from 7.40 to 7.00 (Fig. 11-18). The initial rise in ventilation is mediated primarily by the peripheral chemoreceptors in the carotid bodies, which immediately sense the reduction in pH. However, the ensuing fall in P_{CO_2} produces an acute *elevation* in cerebrospinal fluid and cerebral interstitial pH, since CO_2 but not HCO_3^- rapidly crosses the blood-brain barrier. As a result, the central chemoreceptors sense alkalemia and act to diminish ventilation, thereby limiting the ventilatory response.[159] If the acidemia persists for hours to days, however, the cerebral pH will fall, as a result of ionic diffusion or the formation of new cerebrospinal fluid that reflects the change in systemic pH.[159,160] This cerebral adaptation allows the full degree of hyperventilation to be seen, usually with 12 to 24 h.[159,161]

The increase in ventilation with metabolic acidosis is an appropriate compensatory response, since the concomitant reduction in P_{CO_2} will return the extracellular pH toward normal.[162,163] Conversely, hypoventilation with a consequent elevation in P_{CO_2} lowers the pH toward normal in metabolic alkalosis, where the plasma HCO_3^- concentration is increased.[164,165]

The potential importance of these respiratory compensations to metabolic acidosis and alkalosis can be appreciated from the following hypothetical example. In diabetic ketoacidosis (see Chap. 25), the increased production of ketoacids is buffered in part in the extracellular fluid, resulting in a decline in the plasma

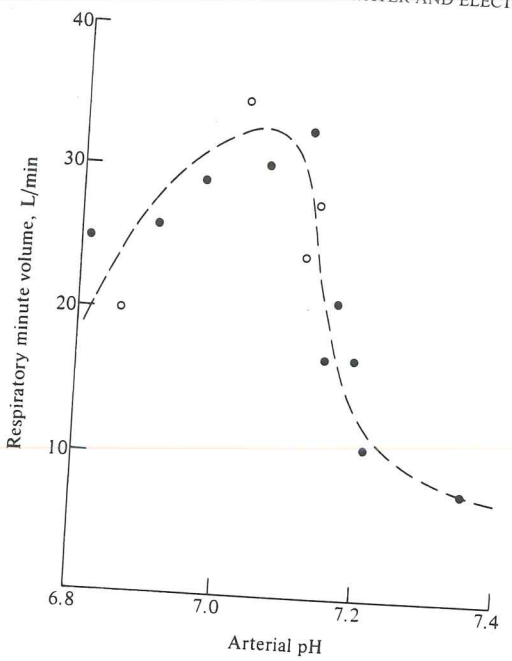

Figure 11-18 Relationship between respiratory minute volume and arterial pH in patients with diabetic ketoacidosis. (*Reproduced from Kety SS, Polis BD, Nadler CS, Schmidt CF,* J Clin Invest *27:500, 1948, by copyright permission of the American Society for Clinical Investigation.*)

HCO_3^- concentration. If the latter were reduced to 6 meq/L and the P_{CO_2} remained at the normal 40 mmHg, then

$$pH = 6.1 + \log \frac{6}{0.03 \times 40} = 6.80$$

However, if ventilation were stimulated by the acidemia and the P_{CO_2} fell to 15 mmHg, then

$$pH = 6.1 + \log \frac{6}{0.03 \times 15} = 7.22$$

Thus, the respiratory compensation has turned a life-threatening reduction in pH into one that is much less dangerous.

Limitation of Respiratory Compensation

Despite the effectiveness of the respiratory compensation, the pH is protected for only a few days, since the initially beneficial change in P_{CO_2} then alters renal HCO_3^- reabsorption. In metabolic acidosis, for example, the compensatory fall in P_{CO_2} decreases HCO_3^- reabsorption (Fig. 11-12) and, therefore, the plasma HCO_3^- concentration. The net effect is that, after several days, the *extracellular pH is the same as it would have been if no respiratory compensation had occurred,* since the decline in P_{CO_2} is balanced by a further reduction in the HCO_3^- concentration (Table 11-2).[166] Fortunately, most forms of severe metabolic acidosis

Table 11-2 Arterial pH in chronic metabolic acidosis with and without respiratory compensation

Clinical state	Arterial		
	pH	$[HCO_3^-]$, meq/L	P_{CO_2}, mmHg
Baseline	7.40	24	40
Metabolic acidosis			
No compensation	7.29	19	40
Compensation			
Acute	7.37	19	34
Chronic	7.29	16	34

are acute (ketoacidosis, lactic acidosis, ingestions), so that the associated hyperventilation does protect the pH.

Similar considerations apply to the compensatory hypoventilation seen with chronic metabolic alkalosis. The rise in P_{CO_2} in this setting leads to increased H^+ secretion, a further elevation in the plasma HCO_3^- concentration, and no net improvement in the alkalemia.[167]

It is presumed that alterations in renal tubular cell pH are responsible for these changes in H^+ secretion. In metabolic acidosis, for example, the fall in plasma HCO_3^- concentration will produce a parallel reduction in the cell pH that is probably the signal to enhance H^+ secretion. Returning the extracellular pH toward normal by increasing ventilation will also raise the cell pH, since reducing the P_{CO_2} will result in CO_2 diffusion out of the cell. This will lead to an initially lower level of net acid excretion and therefore a further reduction in the plasma HCO_3^- concentration.

These observations once again illustrate the importance of the steady state. A patient with chronic metabolic acidosis who produces an extra 100 meq of acid per day will enter the steady state only when daily acid excretion increases by 100 meq. The signal to maintain this increment in H^+ secretion is probably a reduction in the cell pH; furthermore, the *required level of cellular acidification to enhance acid excretion by 100 meq will be the same whether or not respiratory compensation has occurred.* Thus, the extracellular pH will also be the same in both settings, since it is the primary determinant of changes in the cell pH.[98]

SUMMARY

From the Henderson-Hasselbalch equation, the arterial pH is a function of the $[HCO_3^-]/0.03P_{CO_2}$ ratio. Three processes are involved in the maintenance of the arterial pH: (1) The extracellular and intracellular buffers act to minimize changes in pH induced by an acid or base load, (2) the plasma HCO_3^- concen-

tration is held within narrow limits by the regulation of renal H^+ excretion, and (3) the P_{CO_2} is controlled by variations in alveolar ventilation. How these processes interact to protect the pH can be appreciated from the response to a HCl load (Fig. 11-19).

- Extracellular buffering of the excess H^+ by HCO_3^- occurs almost immediately.
- Within several minutes, the respiratory compensation begins, resulting in hyperventilation, a decrease in the P_{CO_2}, and an increase in the pH toward normal.
- Within 2 to 4 h, the intracellular buffers (primarily proteins and organic phosphates) and bone provide further buffering, as H^+ ions enter the cells in exchange for intracellular K^+ and Na^+. These responses act to prevent wide swings in the arterial pH until acid-base homeostasis can be restored by the renal excretion of the H^+ load as NH_4^+ and tritratable acidity.
- The corrective renal response begins on the first day and is complete within 5 to 6 days.[5,79,104]

This sequence tends to be reversed with a $NaHCO_3$ load. The corrective renal response tends to be more rapid than after an acid load, as the excess HCO_3^- is quickly excreted in the urine. Both decreased reabsorption and HCO_3^- secretion in the cortical collecting tubule play a contributory role in this setting.[19-21,55]

Alterations in pH induced by changes in the P_{CO_2} produce a somewhat different response. There is virtually no extracellular buffering, since HCO_3^- cannot effectively buffer H_2CO_3 (see page 313). Similarly, there is no compensatory change in alveolar ventilation, since the primary disturbance is one of abnormal respiration. Thus the intracellular buffers (including hemoglobin) and changes in renal H^+ excretion constitute the only protective mechanisms against respiratory acidosis or alkalosis.

If, for example, the P_{CO_2} is increased, the intracellular buffers will act to increase the plasma HCO_3^- concentration, thereby minimizing the degree of acidemia (Fig. 11-20). This process is complete within 10 to 30 min.[168] The intracellular buffers increase the plasma HCO_3^- concentration by only 1 meq/L for each

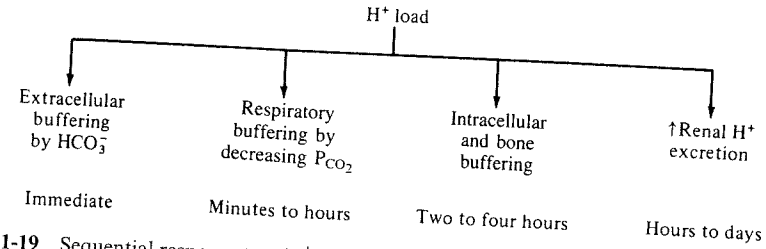

Figure 11-19 Sequential response to a H^+ load, culminating in the restoration of acid-base balance by the renal excretion of the excess H^+.

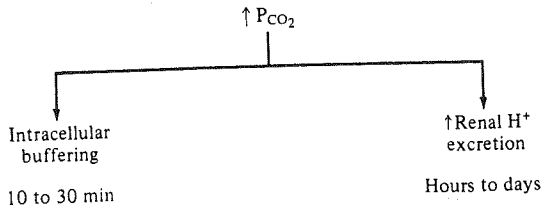

Figure 11-20 Response to an increase in the P_{CO_2}. Although these changes raise the pH toward normal, acid-base homeostasis will not be restored until ventilation is normalized.

10-mmHg rise in the P_{CO_2} and are therefore relatively ineffective in protecting the pH.* If the hypercapnia persists, however, there will be an appropriate increase in renal H^+ excretion, resulting in a further elevation in the plasma HCO_3^- concentration.

It is this renal compensation, which begins within several hours but is not complete for several days,[106] that constitutes the main defense against respiratory acidosis. Even if the P_{CO_2} is chronically elevated at 80 mmHg, the pH usually is not much lower than 7.30 because of the effectiveness of the renal compensation. This sequence is reversed with respiratory alkalosis, as there is an appropriate reduction in the plasma HCO_3^- concentration as a result of intracellular buffering and decreased net acid excretion.[108,109]

The renal responses to alterations in the P_{CO_2} are compensatory but not corrective. Acid-base homeostasis will not be restored unless alveolar ventilation is normalized.

PROBLEMS

11-1 The daily H^+ load is excreted in the urine as titratable acidity and NH_4^+. Would H^+ retention leading to metabolic acidosis occur if there were:

(a) a marked reduction in titratable acid excretion, as a result of a decrease in the plasma phosphate concentration?

(b) a marked reduction in NH_4^+ formation?

11-2 Equal amounts of H^+, as HCl or H_2SO_4, are given over several days to a volume-depleted subject. Which acid will produce the greater degree of acidemia?

11-3 Two patients with a normal GFR of 180 L/day are studied, one with normal acid-base balance and one with metabolic acidosis. The following laboratory data are obtained from the first patient:

$$\text{Plasma } [HCO_3^-] = 24 \text{ meq/L}$$

$$\text{Titratable acidity} = 30 \text{ meq/day}$$

$$NH_4^+ \text{ excretion} = 50 \text{ meq/day}$$

$$\text{Urine pH} = 5.5$$

Similar values in the second patient are

* The changes in the plasma HCO_3^- concentration seen with acute and chronic respiratory acidosis and alkalosis are presented in detail in Chaps. 20 and 21.

$$\text{Plasma } [HCO_3^-] = 6\,\text{meq/L}$$

$$\text{Titratable acidity} = 75\,\text{meq/day}$$

$$NH_4^+ \text{ excretion} = 140\,\text{meq/day}$$

$$\text{Urine pH} = 5.0$$

Assuming that all the filtered HCO_3^- is reabsorbed, which is indicated by the low urine pH, calculate:

(a) net acid excretion

(b) total H^+ secretion (which includes that utilized for reabsorption of the filtered HCO_3^-)

11-4 The following values are obtained on a 24-h urine collection:

$$\text{Phosphate} = 60\,\text{mmol}$$

$$\text{pH} = 5.8$$

If the arterial pH is 7.40 and the pK_a for phosphate is 6.80, how many millimoles of H^+ are excreted as titratable acidity using HPO_4^{2-} as a buffer? Is NH_4^+ excretion included in the measurement of titratable acidity?

11-5 A patient with persistent vomiting develops metabolic alkalosis as a result of the loss of HCl in gastric juice. Why isn't the condition corrected spontaneously by excretion of the excess HCO_3^- in the urine?

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