The kidney and acid-base regulation

Bruce M. Koeppen
School of Medicine, University of Connecticut, Farmington, Connecticut

Koeppen BM. The kidney and acid-base regulation. Adv Physiol Educ 33: 275–281, 2009; doi:10.1152/advan.00054.2009.—Since the topic of the role of the kidneys in the regulation of acid-base balance was last reviewed from a teaching perspective (Koeppen BM. Renal regulation of acid-base balance. Adv Physiol Educ 20: 132–141, 1998), our understanding of the specific membrane transporters involved in H⁺, HCO₃⁻, and NH₄⁺ transport, and especially how these transporters are regulated in response to systemic acid-base disorders, has advanced considerably. In this review, these new aspects of renal function are presented, as are the broader and more general concepts related to the role of the kidneys in maintaining the acid-base balance. It is intended that this review will assist those who teach this aspect of human physiology to first-year health profession students.

Before considering the details of renal acid-base physiology, it is important for students to understand the role of the kidneys in relationship to the lungs in the maintenance of the systemic acid-base balance. This is shown in Fig. 1. In a typical diet, the majority of calories are ingested in the form of carbohydrates and fats. The complete metabolism of carbohydrates and fats requires O₂ and insulin and yields CO₂ and H₂O. With normal lung function, the CO₂ produced (20 mol/day) is excreted, and alterations in ventilation, by changing the PCO₂ of the blood, urine acidification

\[ \text{CO}_2 + \text{H}_2\text{O} \leftrightarrow \text{H}_2\text{CO}_3 \leftrightarrow \text{HCO}_3^- + \text{H}^+ \] (1)

The metabolism of the amino acids in protein may produce either acids or alkali depending on the specific amino acid. However, the metabolism of dietary protein produces net acids (e.g., HCl of H₂SO₄). These acids, often referred to as “nonvolatile acids,” are rapidly buffered:

\[ \text{HCl} + \text{NaHCO}_3 \rightarrow \text{NaCl} + \text{CO}_2 + \text{H}_2\text{O} \] (2)

\[ \text{H}_2\text{SO}_4 + 2\text{NaHCO}_3 \rightarrow \text{Na}_2\text{SO}_4 + 2\text{CO}_2 + 2\text{H}_2\text{O} \] (3)

The CO₂ generated in this buffering process is excreted by the lungs, whereas the Na⁺ salts of the acids are excreted by the kidneys, principally with NH₄⁺ [e.g., NH₄Cl and (NH₄)₂SO₄]. In the process of excreting NH₄⁺, HCO₃⁻ is generated and returned to the blood to replace the HCO₃⁻ lost in titrating the nonvolatile acid. This process is described later.

Other dietary constituents result in the generation of alkali. For example, when organic anions are metabolized to CO₂ and H₂O, H⁺ is consumed (i.e., HCO₃⁻ is produced). From a dietary perspective, fruits and vegetables result in the generation of alkali, whereas meat, grains, and dairy products generate acid. In addition, the diet may contain various acids and alkalis that, when absorbed via the gastrointestinal tract, contribute to the net acid/alkali load to the body. Finally, each day, HCO₃⁻ is lost in the feces and thus imparts an acid load to the body. In a healthy individual consuming a “typical Western diet,” there is a net addition of acid to the body. This acid, referred to as net endogenous acid production (NEAP), results in an equivalent loss of HCO₃⁻, which must then be replaced. Importantly, the kidneys excrete acid and, in the process, generate HCO₃⁻. Thus, the systemic acid-base balance is maintained when renal net acid excretion (RNAE) equals NEAP. RNAE excretion can be quantitated by measuring the excretion of NH₄⁺, titratable acid (TA), and HCO₃⁻ (note that the excretion of H⁺ is ignored, since even at a urine pH of 4.0, the concentration of H⁺ = 0.1 meq/l):

\[ \text{RNAE} = U_{\text{NH}_4} \times V + U_{\text{TA}} \times V - U_{\text{HCO}_3^-} \times V \] (4)

where U is the urine concentration and V is the urine flow rate. When a typical Western diet is ingested, NEAP is ~1 meq·kg body wt⁻¹·day⁻¹. As a consequence, RNAE must be the same.

It is important for students to recognize that RNAE excretion is accomplished by the transport of H⁺ and HCO₃⁻ by the cells of the nephron. Through the action of various H⁺ and HCO₃⁻ transporters, the kidneys reabsorb the filtered load of HCO₃⁻, titrate urinary buffers, excrete NH₄⁺, and acidify the urine. In the following sections each of these processes is reviewed.

HCO₃⁻ Reabsorption

The cells of the nephron secrete H⁺ into the tubular fluid and, in so doing, reabsorb the filtered load of HCO₃⁻. The contribution of each segment of the nephron to this process is shown in Fig. 2. At a plasma HCO₃⁻ concentration of 24 meq/l and a glomerular filtration rate of 180 l/day, the filtered load of HCO₃⁻ is >4,300 meq/day. Approximately 80% of this filtered load is reabsorbed by the proximal tubule. An additional 16% is reabsorbed by the thick ascending limb and distal convoluted tubule, and the remainder (4%) is reabsorbed by the collecting duct.

The cellular mechanisms by which H⁺ and HCO₃⁻ are transported across the apical and basolateral membranes of the proximal tubule are shown in Fig. 3. H⁺ secretion across the apical membrane occurs by two mechanisms. The primary mechanism is a Na⁺/H⁺ antiporter [Na⁺/H⁺ exchanger 3 (NHE3)]. It is estimated that two-thirds of proximal HCO₃⁻ reabsorption occurs via H⁺ secretion by NHE3. Vascular H⁺-ATPase provides another mechanism for apical H⁺ secretion and is responsible for approximately one-third of HCO₃⁻ reabsorption.

As shown in Fig. 3, carbonic anhydrase (CA) plays an important role in H⁺ secretion. In the proximal tubule, CA catalyzes the hydration of CO₂ to form H₂CO₃, which then undergoes dissociation to form H⁺ and HCO₃⁻.

In the distal nephron and collecting duct, H⁺ is secreted via the basolateral membrane into the peritubular capillary blood. The primary mechanism for H⁺ secretion in these segments is the apical membrane 

Address for reprint requests and other correspondence: B. M. Koeppen, Academic Affairs, Univ. of Connecticut School of Medicine, Farmington, CT 06030-1920 (e-mail: koeppen@nso.uchc.edu).
the cell, CA-II facilitates the generation of H⁺ and HCO₃⁻. The H⁺ is then secreted into the tubular fluid across the apical membrane, whereas the HCO₃⁻ exits the cell across the basolateral membrane. Membrane-bound CA (CA-IV) facilitates the production of H₂O and CO₂ from luminal carbonic acid.

Exit of HCO₃⁻ from the cell across the basolateral membrane occurs primarily via a 3HCO₃⁻/Na⁺ symporter [the electronegative Na⁺-HCO₃⁻ cotransporter (NBCe1)]. There is also evidence that some HCO₃⁻ exits the cell in exchange for Cl⁻ (anion exchanger 2 (AE-2)), and some by a K⁺-HCO₃⁻ symporter. Finally, the apical membrane Na⁺/H⁺ antiporter in the distal convoluted tubule may be the NHE2 isoform.

In the collecting duct, intercalated cells are responsible for H⁺ and HCO₃⁻ transport (see Fig. 4). Acid-secreting intercalated cells have vacuolar H⁺-ATPase and H⁺-K⁺-ATPase localized to the apical membrane, and HCO₃⁻ exits the cells across the basolateral membrane in exchange for Cl⁻ (AE-1). The less abundant HCO₃⁻-secreting cell has vacuolar H⁺-ATPase localized to the basolateral membrane and a different Cl⁻/HCO₃⁻ antiporter (pendrin) in the apical membrane.

TA

The H⁺ secreted into the tubular fluid can drive the reabsorption of the filtered load of HCO₃⁻ as just described. In addition, the secreted H⁺ can combine with other luminal constituents (termed urinary buffers), such as phosphate:

\[
\text{HPO}_4^{2-} + \text{H}^+ \rightarrow \text{H}_2\text{PO}_4^{-}
\]  

(5)

When the secreted H⁺ combines with a urinary buffer, a “new HCO₃⁻” is generated within the cell (see Fig. 5) and eventually replaces a HCO₃⁻ lost earlier in the titration of nonvolatile acids produced in cellular metabolism (NEAP). TA refers to the process whereby the kidney excretes H⁺ with urinary buffers. To quantitate this process, urine is titrated with alkali to raise the normally acidic pH to that of blood. Approximately one-third of RNAE is attributed to TA, with phosphate being the predominant buffer.
Ammoniagenesis and \( \text{NH}_4^+ \) Excretion

An important aspect of renal acid-base physiology is the production (ammoniagenesis) and excretion of \( \text{NH}_4^+ \). Figure 6 shows this process. The kidney takes glutamine and metabolizes it to two molecules each of \( \text{NH}_4^+ \) and \( \text{HCO}_3^- \). The \( \text{NH}_4^+ \) is excreted into the urine, and the \( \text{HCO}_3^- \), which is “new \( \text{HCO}_3^- \),” is returned to the blood, where it replaces the \( \text{HCO}_3^- \) lost earlier in the titration of nonvolatile acids. Figure 6 also shows the fate of the \( \text{NH}_4^+ \) that is returned to the blood rather than being excreted in the urine. When this occurs, the \( \text{NH}_4^+ \) is converted to urea by the liver, and, in that process, \( \text{H}^+ \) is generated. This \( \text{H}^+ \) is buffered by \( \text{HCO}_3^- \) and thus negates the process of renal “new \( \text{HCO}_3^- \)” generation. Thus, from the perspective of renal acid-base physiology, \( \text{NH}_4^+ \) produced by the kidney must be excreted into the urine and not returned to the blood. For every milliequivalent of \( \text{NH}_4^+ \) excreted, a milliequivalent of new \( \text{HCO}_3^- \) is returned to the blood. This process accounts for approximately two-thirds of RNAE.

A detailed depiction of \( \text{NH}_4^+ \) handling by the nephron is shown in Fig. 7. Glutamine is metabolized by proximal tubule

---

**Fig. 3.** Cellular mechanism for proximal tubule \( \text{H}^+ \) and \( \text{HCO}_3^- \) transport. CA, carbonic anhydrase. [Reprinted with permission from Ref. 6a.]

**Fig. 4.** Cellular mechanisms for \( \text{H}^+ \) and \( \text{HCO}_3^- \) secretion by intercalated cells of the collecting duct. [Reprinted with permission from Ref. 6a.]
The conversion of NH₄⁺ by the liver and, in that process, generate H⁺ but instead is returned to the blood, it will be metabolized to as a result of glutamine metabolism is not excreted in the urine of NH₄⁺ tubular fluid, a new HCO₃⁻ is produced. The HCO₃⁻ is returned to the blood as "new HCO₃⁻," and the NH₄⁺ is secreted into the tubular fluid. Regardless of the mechanism, for every NH₄⁺ secreted into the tubular fluid, a new HCO₃⁻ is returned to the blood.

In the thick ascending limb of the loop of Henle, significant amounts of NH₄⁺ are reabsorbed. Multiple routes exist for this reabsorption, including NH₄⁺ substituting for K⁺ on the apical membrane Na⁺-K⁺-2Cl⁻ symporter (NKCC2) and movement of NH₄⁺ through the paracellular pathway. NH₄⁺ movement out of the cell across the basolateral membrane can occur via K⁺ channels. This reabsorbed NH₄⁺ accumulates in the renal medullary interstitium.

As noted above, if the NH₄⁺ produced by the proximal tubule as a result of glutamine metabolism is not excreted in the urine but instead is returned to the blood, it will be metabolized to urea by the liver and, in that process, generate H⁺. If this occurs, the “new HCO₃⁻” generated by glutamine metabolism is negated. Thus, it is imperative that the NH₄⁺ reabsorbed by the thick ascending limb of the loop of Henle be resecreted into the tubular fluid. This occurs by the collecting duct and is dependent on the ability of the collecting duct to acidify the tubular fluid.

Our understanding of the mechanism of collecting duct NH₄⁺ secretion is evolving as a result of the discovery and characterization of Rh glycoproteins. Rh glycoproteins are NH₄⁺ transporters similar to those found in yeast, plants, and bacteria. To date, three mammalian Rh glycoproteins have been identified, and their role in renal NH₄⁺/NH₃ transport is being elucidated. RhAG is found in erythrocytes, whereas RhGB and RhGC have been localized to the kidneys (as well as other organs involved in NH₄⁺ transport, such as the liver and gastrointestinal tract). RhBG is found in distal nephron segments, beginning with the distal convoluted tubule and continuing through the inner medullary collecting duct. The expression in intercalated cells is greater than in principal cells. RhCG distribution along the nephron is similar to that of RhBG, and it is present on both the apical and basolateral membranes. Importantly, chronic acidosis increases RhCG expression in the outer and inner medullary collecting ducts, and translocation of the transporter from an intracellular pool to the apical membrane (note that RhBG expression does not change with chronic acidosis). Functional studies of Rh glycoprotein have attempted to define the nature of NH₄⁺/NH₃ transport, and, to date, the evidence is consistent with both electroneutral as well as electrogenic mechanisms. Evidence for Na⁺-H⁺ antiport also exists. Since acidification of the tubular fluid is required for NH₄⁺ secretion, the operation of NH₄⁺/H⁺ antiporters on both the apical and basolateral membranes of collecting duct cells, as shown in Fig. 7B, would explain this pH-dependent NH₄⁺ secretion.

The pH dependency of NH₄⁺ secretion has traditionally been explained by the process of nonionic diffusion of NH₃ with diffusion trapping of NH₄⁺ in the tubular fluid (see Fig. 7A). It remains to be determined how much of collecting duct NH₄⁺ secretion occurs via this mechanism and how much is mediated by RhCG or other NH₄⁺/NH₃ transporters.

Renal Response to Acid-Base Disorders

When systemic acid-base disorders occur, the kidneys respond by appropriately altering RNAE. Thus, with acidosis RNAE excretion increases, whereas RNAE decreases with...
alkalosis. Most of our understanding of the adaptive response of the kidneys to acid-base disorders has come from using models of metabolic acidosis. The following section describes our current understanding of how RNAE increases in this setting.

With acidosis RNAE increases. This response includes a reduction, if not elimination, of all HCO$_3^-$ from the urine and increases in TA and NH$_4^+$ excretion. The key elements of this response include the stimulation of H$^+$ and HCO$_3^-$ transport along the nephron, increased ammoniagenesis, and increased availability of urinary buffers (i.e., phosphate).

Acidosis can directly reduce the intracellular pH of renal tubular cells. This cellular acidosis has been shown to stimulate NHE3 activity via allosteric mechanisms, change transporter kinetics due to altered H$^+$ gradients across membranes, and cause exocytotic insertion of transporters into the plasma membrane from intracellular stores (e.g., H$^+$-ATPase and NHE3). It is uncertain as whether these effects of intracellular acidosis are mediated by pH alone or secondary to the activation of intracellular regulatory pathways or mechanisms. However, it is now clear that other factors also mediate the renal response to acidosis. For example, endothelin-1 (ET-1) and glucocorticoids clearly play a role in the stimulation of renal H$^+$ and HCO$_3^-$ transport during acidosis.

ET-1 is produced by both endothelial cells and proximal tubule cells in response to acidosis. Acting through the ET$_B$ receptor, both NHE3 and NBCe1 are phosphorylated, which then leads to their insertion into the apical and basolateral membranes, respectively. Cortisol secretion by the adrenal cortex is also stimulated by acidosis. Cortisol increases the abundance of NHE3 and NBCe1 in proximal tubule cells by increasing both mRNA levels and translation. Less is known about the effects of ET-1 and cortisol on distal H$^+$ and HCO$_3^-$ transport, although it is likely that they play a role in stimulating key acid-base transporters in these segments as well.

Acidosis also stimulates the secretion of parathyroid hormone (PTH). The increased levels of PTH act on the proximal tubule to inhibit phosphate reabsorption. In this way, more phosphate is delivered to the distal nephron, where it can serve as a urinary buffer and thus increase the capacity of the kidneys to excrete TA.

Ammoniagenesis by the proximal tubule is stimulated by acidosis. This is in part an effect of intracellular acidosis and also reflects a stimulatory effect of cortisol. As already noted above, acidosis increases the abundance of RhCG in the collecting duct, thus facilitating the secretion and ultimate excretion of NH$_4^+$. Thus, ammoniagenesis and NH$_4^+$ excretion are stimulated.

Figure 8 shows our current understanding of the response of the kidneys to acidosis. H$^+$ and HCO$_3^-$ transport are increased along the nephron. This results from a decrease in intracellular pH as well as effects of ET-1 and cortisol. Ammoniagenesis
and collecting duct secretion of NH₄⁺ are stimulated. Finally, proximal tubule phosphate reabsorption is inhibited, allowing the greater excretion of TA. The net effect is enhanced RNAE.

The most important component of the renal response to acidosis is the ability of the kidney to increase ammoniagenesis and NH₄⁺ excretion. In the setting of acidosis, it is often useful to calculate the urinary net charge (UNC):

\[
\text{UNC} = ([\text{Na}^+] + [\text{K}^+]) - [\text{Cl}^-]
\]  (6)

The concept of UNC assumes that the principle urine cations in this setting are Na⁺, K⁺, and NH₄⁺ (not measured), and, because urinary HCO₃⁻ excretion is essentially zero, the principle urine anion is Cl⁻. Thus, with acidosis, UNC as calculated by Eq. 6 should have a negative value, reflecting the excretion of NH₄⁺. Indeed, a value of zero or a positive value in this setting would be indicative of a defect in NH₄⁺ excretion.

The response of the kidneys to alkalosis is less well studied. Clearly, RNAE is reduced as a result of increased HCO₃⁻ excretion and reduced excretion of NH₄⁺ and TA. In general, this response is often said to reflect a reduction in those factors that are known to stimulate H⁺ and HCO₃⁻ transport, and ammoniagenesis as seen in the response to acidosis.

### Alterations in RNAE

Other factors can alter RNAE, but these are not directed at maintaining the acid-base balance. Rather, they can result in the development of acid-base disturbances (see Table 1). Because H⁺ and HCO₃⁻ transport are linked to Na⁺ in certain portions of the nephron, factors that alter renal Na⁺ transport [e.g., changes in extracellular fluid (ECF) volume] can have secondary effects on RNAE. For example, activation of the renin-angiotensin-aldosterone system in response to a decrease in ECF volume will result in enhanced proximal tubule HCO₃⁻ reabsorption, an effect mediated by ANG II (ANG II may also stimulate HCO₃⁻ reabsorption in the thick ascending limb and distal convoluted tubule). In addition, aldosterone stimulates intercalated cell H⁺ secretion and, thus, the generation of new HCO₃⁻ through the titration of urinary buffers (e.g., phosphate) and increased excretion of NH₄⁺. The opposite would occur with an expansion of ECF volume.

Hypo- and hyperkalemia also alter proximal tubule HCO₃⁻ reabsorption and ammoniagenesis (hypokalemia stimulates both, whereas hyperkalemia has the opposite effect). The mechanisms involved are not known with certainty but may be linked to changes in intracellular pH. Hypokalemia also increases the expression of H⁺-K⁺-ATPase in the intercalated cells of the collecting duct; this, in turn, stimulates H⁺ secretion.

### Summary

The role of the kidneys in the acid-base balance is to excrete net acid (RNAE) at an amount equal to daily NEAP. In so doing, the kidneys generate “new HCO₃⁻” to replace the HCO₃⁻ lost in the titration of net endogenous acids. RNAE reflects the transport of H⁺ and HCO₃⁻ by the cells of the nephron, which, in turn, serves to reabsorb the filtered load of HCO₃⁻, excrete TA, acidify the urine, and excrete NH₄⁺.

### Table 1. Some factors that alter RNAE

<table>
<thead>
<tr>
<th>Factor</th>
<th>Principle Nephron Site of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECF volume contraction</td>
<td>Proximal and distal tubules</td>
</tr>
<tr>
<td>Aldosterone</td>
<td>Proximal tubule and collecting duct</td>
</tr>
<tr>
<td>Hyperaldosteronism</td>
<td>Distal tubule and collecting duct</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>Proximal tubule and intercalated cells</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>Proximal tubule</td>
</tr>
</tbody>
</table>

RNAE, renal net acid excretion; ECF, extracellular fluid.
ACKNOWLEDGMENTS

This work has been previously presented at the American Physiological Society’s Renal Physiology Refresher Course on April 18, 2009, in New Orleans, LA.

REFERENCES