RENNAL REGULATION OF ACID-BASE BALANCE

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This article reviews the role of the kidneys in the regulation of acid-base balance. It is intended as a guide for those who teach this aspect of renal physiology to health professions students. An approach is described, which begins with an overview of acid-base balance and then proceeds to describe the details of renal H⁺ transport and the important role the production and excretion of NH₄⁺ plays in the ability of the kidneys to generate new HCO₃⁻. In the overview, the role of the kidneys in acid-base balance is placed in context for the student by examining the impact of diet and cellular metabolism on acid-base balance. Also, the interactions between the kidneys and lungs to maintain extracellular HCO₃⁻ concentration within a narrow range are described. This is followed by a detailed look at the cellular mechanisms of H⁺ secretion along the nephron, how these mechanisms are regulated, and how they result in the reabsorption of the filtered load of HCO₃⁻. Finally, the important role of NH₄⁺ production and excretion in the generation of new HCO₃⁻ is reviewed and highlighted.


Key words: urine acidification; renal ammoniagenesis

Our knowledge of renal acid-base physiology has progressed over the years as we have been able to study and understand the mechanisms of H⁺ and HCO₃⁻ transport in increasing detail (i.e., from the level of specific nephron segments to single renal tubule cells, individual cell membranes, and, most recently, the membrane transporters themselves). In general, the teaching of renal acid-base physiology has paralleled this progression of knowledge and has focused on the mechanisms and regulation of H⁺ secretion in the various portions of the nephron.

Typically, students are taught that the kidneys reabsorb the filtered load of HCO₃⁻ and in addition excrete acid by titrating urinary buffers, with both processes being the result of specific H⁺ secretory mechanisms. Traditionally, and for simplicity of presentation to students, the processes of HCO₃⁻ reabsorption and acid excretion are ascribed to different portions of the nephron. Accordingly, the proximal tubule is the primary site in which the filtered load of HCO₃⁻ is reabsorbed, and the distal portions of the nephron are involved in acid excretion. Acid excretion assumes central importance in this scheme because it results in the generation of "new HCO₃⁻," which is returned to the body to replenish that lost during the titration of metabolically produced acids. The principal urinary buffers used for acid excretion are usually said to be phosphate and NH₃.

Although much of this simplified scheme of renal acid-base physiology is essentially correct, our understanding of the mechanisms involved in the production and excretion of NH₄⁺ have changed dramatically in recent years, and it is now clear that NH₃ cannot simply be viewed as a urinary buffer. Consequently, the teaching of renal acid-base physiology must emphasize our new understanding of the role of NH₃/NH₄⁺ in renal acid excretion. In addition, students must understand the role of the kidneys as they relate to the
function of other organs that also influence acid-base balance (e.g., lungs and liver).

In this article the role of the kidneys in the maintenance of acid-base balance is reviewed from the perspective of teaching this material to health professions students. First, an overview of the role of the kidneys in acid-base balance is presented. The cellular mechanisms of $H^+$ secretion along the nephron are then briefly reviewed, with recent discoveries from molecular biological studies highlighted. This is followed by a description of our current understanding of renal $NH_4^+$ production and excretion. Finally, the integrated function of the kidneys and lungs in the setting of acid-base disturbances (i.e., compensation) is considered.

**OVERVIEW**

Figure 1 provides a general overview of acid-base balance and the role of the kidneys. Also depicted is the role of the lungs in the excretion of metabolically produced $CO_2$. The interrelationships between $H^+$, $CO_2$, and $HCO_3^-$ are central to understanding acid-base balance and reflect the physiological importance of the $CO_2/HCO_3^-$ buffer system.

$$CO_2 + H_2O \leftrightarrow H_2CO_3 \leftrightarrow H^+ + HCO_3^- \quad (1)$$

The $CO_2/HCO_3^-$ buffer system is not only of quantitative importance in acid-base balance [extracellular fluid (ECF) contains 350–400 meq of $HCO_3^-$], but the $H^+$ concentration ([H$^+$])/pH of the body fluids is influenced by both $PCO_2$ and $HCO_3^-$ concentration ([H$CO_3^-$]). Thus acid-base balance can be effected by both the lungs and the kidneys, the lungs through control of $PCO_2$ and the kidneys through control of $[HCO_3^-]$. This dual impact of $CO_2$ and $[HCO_3^-]$ on pH has led to the distinction between $CO_2$-derived or “volatile acid” and “nonvolatile acid” such as lactic acid. Although this distinction is in widespread use, it is important to recognize that $CO_2$ itself is not an acid, and under normal conditions the production and

**FIG. 1.**
Overview of role of kidneys in acid-base balance. See text for details. HA, nonvolatile acid.
excretion of CO₂ does not impact acid-base balance (3). However, as indicated by reaction 1, retention of CO₂ (production > excretion) will produce an increase in [H⁺] and thus the development of acidosis. Conversely, if CO₂ production is less than excretion, there will be a decrease in [H⁺], and alkalosis results. Acid-base disorders resulting from primary alterations in the Pco₂ are termed “respiratory” disorders.

As depicted in Fig. 1, nonvolatile acids are buffered by HCO₃⁻ (other non-HCO₃⁻ buffers are also involved in this process). Thus, if nonvolatile acid production exceeds the excretion of acid from the body, [HCO₃⁻] decreases and [H⁺] increases (see reaction 1), and acidosis results. Conversely, if nonvolatile acid production is less than the excretion of acid from the body, then [HCO₃⁻] increases and [H⁺] decreases, and alkalosis results. Acid-base disorders resulting from nonvolatile acid or alkali are termed “metabolic” disorders. They are readily detected by the associated change in [HCO₃⁻].

Each day, acid and alkali are ingested in the diet. In addition, cellular metabolism produces acid-base equivalents. The majority of energy (i.e., the largest source of calories) is derived from the metabolism of dietary carbohydrates and fats. When tissue perfusion is adequate, and insulin is present at normal levels, cellular metabolism of carbohydrates and fats results in the production of CO₂ and H₂O. On a typical diet, ~15–20 mol of CO₂ are produced. Normally, this large quantity of CO₂ is effectively eliminated by the lungs, and there is no impact of this metabolically derived CO₂ on whole body acid-base status.

With inadequate tissue perfusion, hypoxia, or in the absence of insulin, the cellular metabolism of carbohydrates and fats does not yield CO₂ and H₂O but instead results in the production of significant quantities of nonvolatile acids such as lactic acid and ketoacids. With restoration of tissue perfusion (i.e., delivery of adequate amounts of O₂) or treatment with insulin, many of these nonvolatile acids are then further metabolized to CO₂ and H₂O. In this later process, much of the HCO₃⁻ lost during titration of the nonvolatile acids is regenerated.

Cellular metabolism of other dietary constituents also impacts acid-base balance. Amino acid metabolism results in the addition of either acid or alkali to the body. For example, the sulfur-containing (e.g., methionine) and cationic (e.g., arginine) amino acids result in acid production on metabolism, whereas alkali results from the metabolism of anionic (e.g., aspartate) amino acids. Given the mix of amino acids in the typical diet, acid production exceeds alkali production. Organic anions (e.g., citrate), when metabolized, result in the generation of alkali.

Several points must be considered when one is trying to determine the impact of nonvolatile acid and alkali on acid-base balance.

1) The source of the nonvolatile acid and alkali is multifactorial and not limited to cellular metabolism. Direct ingestion of acid or alkali can and does occur and, depending on diet, can have a significant impact on acid-base balance.

2) Acid and alkali can be and are lost from the body. For example, vomiting results in the loss of gastric acid, which from an acid-base perspective is equivalent to adding alkali to the body. As a result, vomiting can result in the development of a metabolic alkalosis. Conversely, diarrhea results in the loss of alkali (equivalent to addition of acid), and can result in metabolic acidosis.

3) The impact on acid-base balance of nonvolatile acid or alkali derived from cellular metabolism is highly variable and critically dependent on diet. The ingestion of a vegetarian diet, for example, results in a much reduced acid load to the body, and in some instances may even impart a net alkali load.

Most textbooks state that the direct intake of acid and alkali in a typical diet, the normal loss of some HCO₃⁻ in the feces, and the production of nonvolatile acid and alkali from metabolism result in the net addition of acid to the body. Collectively, these processes are referred to as nonvolatile acid production and ascribed a value of ~1 meq·kg body wt⁻¹·day⁻¹ (70 meq/day for an average adult). It should be apparent from the previous discussion that using 70 meq/day as a value for nonvolatile acid production may not always be accurate. Nevertheless, for the purposes of this review, and to illustrate to students the role of the kidneys in acid-base balance, we will assume that
there is net addition of this amount of nonvolatile acid to the body on a daily basis.

Nonvolatile acids are quickly buffered throughout the body. This buffering occurs in both the intracellular fluid (ICF) and the ECF. As already noted, HCO$_3^-$ is a major ECF buffer, and in this titration process it is consumed producing the sodium salts of the nonvolatile acids. To maintain acid-base balance, the kidneys must excrete the anions of the nonvolatile acids and replenish the HCO$_3^-$ lost during the titration process. This later process, frequently referred to as “new HCO$_3^-$ generation,” results from the excretion of titratable acid (i.e., the excretion of H$^+$ with urine buffers) and from the production and excretion of NH$_4^+$. In addition, the kidneys must reabsorb the filtered load of HCO$_3^-$ to prevent its loss in the urine, because any lost in the urine would be equivalent to the addition of acid to the body. This overall process is termed “net acid excretion” (NAE) and is quantitated as

$$\text{NAE} = [(U_{NH_4^+} \times V) + (U_{TA} \times V) - (U_{HCO_3^-} \times V)]$$  \hspace{1cm} (2)

where $U$ is the urine concentration, $V$ is the urine flow rate, $U_{NH_4^+} \times V$ is the amount of NH$_4^+$ excreted, $U_{TA} \times V$ is the amount of titratable acid excreted, and $U_{HCO_3^-} \times V$ is the amount of HCO$_3^-$ excreted. To maintain acid-base balance, net acid excretion must equal nonvolatile acid production. If nonvolatile acid production exceeds net acid excretion, metabolic acidosis results (serum [HCO$_3^-$] and pH decrease). Conversely, if nonvolatile acid production is less than net acid excretion metabolic alkalosis results (serum [HCO$_3^-$] and pH increase).

Several important points regarding net acid excretion by the kidneys require comment and emphasis.

1) NH$_4^+$ excretion, titratable acid excretion, and HCO$_3^-$ reabsorption all result from H$^+$ secretion along the nephron.

2) Very little acid is excreted by the kidneys as “free H$^+$.” Even with urine of pH 4.0, only 0.1 meq/l of H$^+$ is excreted in this form.

3) Titratable acid represents H$^+$ excreted with urinary buffers, with the principal urinary buffer being phosphate.

4) When urine pH is <6.5, very little HCO$_3^-$ is excreted, and therefore NAE is simply equal to the sum of titratable acid and NH$_4^+$ excretion.

5) The production and excretion of NH$_4^+$ is critically important in this process, because it is regulated by the kidneys in response to alterations in acid-base balance. The role of NH$_4^+$ excretion in renal acid-base physiology is emphasized in Fig. 1, in which the anions of the nonvolatile acids are shown as being excreted with NH$_4^+$. Importantly, for every NH$_4^+$ excreted in the urine an HCO$_3^-$ is returned to the body.

H$^+$ TRANSPORT ALONG NEPHRON

H$^+$ secretion by the cells of the nephron serves to reabsorb the filtered load of HCO$_3^-$, lower the pH of the urine, titrate urinary buffers, and cause the excretion of NH$_4^+$. Of these processes, the reabsorption of the filtered load of HCO$_3^-$ is quantitatively the most important, because the filtered load of HCO$_3^-$ is ~4,500 meq/day, whereas the amount of H$^+$ required for NH$_4^+$ excretion plus the amount excreted with urine buffers is generally <100 meq/day.

Figure 2 summarizes H$^+$ secretion (HCO$_3^-$ reabsorption) along the nephron. The proximal tubule reabsorbs ~80% of the filtered load of HCO$_3^-$, and an additional 15% is reabsorbed by the thick ascending limb of Henle’s loop. The cellular mechanisms involved are essentially the same in these segments. H$^+$ secretion occurs by two apical membrane transporters, Na$^+$/H$^+$ antiporter and H$^+$-ATPase. Of these transporters the Na$^+$/H$^+$ antiporter is the predominant pathway for H$^+$ secretion. Thus H$^+$ secretion is dependent on the lumen-to-cell Na$^+$ gradient. Because of this coupling, factors that regulate Na$^+$ transport in these segments will secondarily effect H$^+$ secretion (see below).

Recent studies on the molecular biology of Na$^+$/H$^+$ antiporters found that the Na$^+$/H$^+$ exchanger 3 (NHE-3) isoform is present in the apical membrane of both the proximal tubule and thick ascending limb cells and is the physiologically important antiporter for H$^+$ secretion in these segments (14). The H$^+$-ATPase provides a parallel pathway for H$^+$ secretion across the apical membrane. The isoform in the proximal tubule appears to be different from the isoform found in the

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Carbonic anhydrase plays an important role in H⁺ secretion by the cells of the proximal tubule and thick ascending limb. It is found in the cytoplasm of these cells, in which it catalyzes the production of H⁺ and HCO₃⁻ from CO₂ and H₂O. In the proximal tubule, but not the thick ascending limb, carbonic anhydrase is also found in the apical membrane. The isoforms for the cytoplasmic (CA-II) and apical membrane enzymes (CA-IV) differ (12).

HCO₃⁻ generated in the cell from the hydration of CO₂ exits the cell across the basolateral membrane by a symporter that couples the movement of 3 HCO₃⁻ with 1 Na⁺. An additional portion of basolateral HCO₃⁻ exit may also occur in exchange for Cl⁻.

The distal tubule and collecting duct reabsorb the portion of the filtered load of HCO₃⁻ that escapes reabsorption by the proximal tubule and thick ascending limb of Henle’s loop (~5% of the filtered load). HCO₃⁻ is reabsorbed as a result of H⁺ secretion by the intercalated cells found in this region of the nephron. H⁺ secretion occurs by two transporters, H⁺-ATPase and H⁺-K⁺-ATPase. The H⁺-ATPase, as already noted, is a distinct isoform from that found in the proximal tubule. The H⁺-K⁺-ATPase is similar to, but distinct from, the isoform found in the gastric parietal cells (15). As in the proximal tubule and thick ascending limb cells, CA-II catalyzes the intracellular production of H⁺ and HCO₃⁻. The predominant mechanism for HCO₃⁻ exit across the basolateral membrane is via a Cl⁻/HCO₃⁻ antiporter similar to that found in red blood cells (i.e., Band-3).

In addition to the H⁺-secreting intercalated cell, there is a second intercalated cell subtype that secretes HCO₃⁻ (see Fig. 2). Because of nonvolatile acid production, and thus the need to excrete acid, H⁺ secretion predominates in the collecting duct. However, HCO₃⁻ reabsorption by the proximal tubule and thick ascending limb of Henle’s loop (≈5% of the filtered load). HCO₃⁻ is reabsorbed as a result of H⁺ secretion by the intercalated cells found in this region of the nephron. H⁺ secretion occurs by two transporters, H⁺-ATPase and H⁺-K⁺-ATPase. The H⁺-ATPase, as already noted, is a distinct isoform from that found in the proximal tubule. The H⁺-K⁺-ATPase is similar to, but distinct from, the isoform found in the gastric parietal cells (15). As in the proximal tubule and thick ascending limb cells, CA-II catalyzes the intracellular production of H⁺ and HCO₃⁻. The predominant mechanism for HCO₃⁻ exit across the basolateral membrane is via a Cl⁻/HCO₃⁻ antiporter similar to that found in red blood cells (i.e., Band-3).
secretion is important in states of metabolic alkalosis, when renal HCO₃⁻ excretion must be enhanced.

H⁺ secretion by the cells of the nephron is regulated by a number of factors (see Table 1). From a cellular perspective, an important factor regulating the secretion of H⁺ across the apical membrane is the cell-to-tubular fluid gradient for H⁺. This gradient depends on the pH of the tubular fluid relative to the pH within the tubular cells. Acidosis, whether of metabolic (decreased [HCO₃⁻] and pH) or respiratory (increased P CO₂) origin, decreases intracellular pH, creating a more favorable cell-to-tubular fluid H⁺ gradient, and thus stimulates H⁺ secretion along the entire nephron. Alternatively, metabolic (increased [HCO₃⁻] and pH) and respiratory (increased P CO₂) alkalosis inhibit H⁺ secretion by their effect to increase intracellular pH. Although changes in intracellular pH can directly influence the cell-to-tubular fluid H⁺ gradient and thereby H⁺ secretion across the apical membrane of the cell, there is also evidence that changes in intracellular pH, perhaps mediated by other intracellular messengers, also alter the activity and expression of key H⁺ and HCO₃⁻ transporters in the cell (1, 4, 5, 9–11, 13, 14). For example, H⁺-secreting intercalated cells in the collecting duct respond to acidosis by exocytotically inserting more H⁺-ATPase into the apical membrane (4, 5, 11, 13). Also, the abundance of Na⁺/H⁺ antiporter in proximal tubule cells is increased in chronic metabolic acidosis (1, 9, 10, 14).

Other factors may alter renal H⁺ excretion, but their influence is not directed at the maintenance of acid-base balance (see Table 1). Because, as noted, H⁺ secretion is linked to Na⁺ reabsorption in both the proximal tubule and thick ascending limb of Henle’s loop, factors that are primarily related to Na⁺ reabsorption also influence renal H⁺ secretion. These include alterations in the filtered load (i.e., glomerulotubular balance) and changes in ECF volume. The effect of alterations in ECF volume are mediated by the renin-angiotensin-aldosterone system, with angiotensin II acting on the cells of the proximal tubule to stimulate the Na⁺/H⁺ antiporter and aldosterone acting on the intercalated cells of the collecting duct to stimulate the H⁺-ATPase (7, 8, 10). Alterations in peritubular Starling forces that occur with changes in ECF volume also are involved in enhancing proximal tubule fluid (and HCO₃⁻) reabsorption in volume depletion and decreasing reabsorption during volume expansion.

## PRODUCTION AND EXCRETION OF NH₄⁺

Although the reabsorption of the filtered load of HCO₃⁻ is quantitatively an important process, simply preventing the loss of HCO₃⁻ in the urine does not replenish the HCO₃⁻ lost during the titration of non-volatile acid. This later process is accomplished through the excretion of H⁺ with urine buffers (titratable acid) and by the production and excretion of NH₄⁺. It should be emphasized that the availability and thus excretion of urinary buffers is not regulated to meet the requirements for acid-base balance. For example, the most abundant urinary buffer is phosphate, the excretion of which is regulated not to effect acid-base balance but in response to phosphate balance needs. In contrast, NH₄⁺ production and excretion by the kidneys is regulated to effect acid-base balance. Thus understanding how the kidneys produce and excrete NH₄⁺ is critical to understanding the role of the kidneys in acid-base balance.

Traditionally, the excretion of NH₄⁺ has been taught from the perspective of urinary buffering. Specifically, NH₃ was viewed as a urinary buffer that could accept
H⁺. HCO₃⁻ was generated in this process from the hydration of CO₂ within the intercalated cell (i.e., the H⁺ was secreted into the tubular fluid and the HCO₃⁻ returned to the blood). However, new knowledge regarding the production and excretion of NH₄⁺ makes it clear that NH₃ cannot be viewed simply as a urinary buffer.

The essential features of NH₄⁺ production and excretion are summarized in Fig. 3. Glutamine is metabolized by the kidneys to produce 2NH₄⁺ and 2HCO₃⁻. The NH₄⁺ is excreted in the urine, and the HCO₃⁻ is returned to the body to replenish that which was lost earlier during the titration of nonvolatile acids. For every equivalent of NH₄⁺ excreted in the urine, an equivalent of HCO₃⁻ is returned to the body. Figure 3 also illustrates what happens if the kidneys are unable to excrete NH₄⁺. When this occurs, NH₄⁺ returns to the liver, where it is metabolized to urea. The net result of this process is that 2 NH₄⁺ are converted to urea with the production of 2 H⁺. These 2 H⁺ are then titrated by 2 HCO₃⁻, thus negating the efforts of the kidneys to generate HCO₃⁻ from the metabolism of glutamine.

The details of NH₄⁺ production and excretion are summarized in Fig. 4. The cells of the proximal tubule are the site of ammoniagenesis. Here glutamine is metabolized to 2 NH₄⁺ and the tricarboxylic acid cycle intermediate 2-oxoglutarate, which is then further metabolized to 2HCO₃⁻ (2). The HCO₃⁻ is returned to the body, and the NH₄⁺ is secreted by the cell into the tubular fluid.

NH₄⁺ secretion by the proximal tubule cells occurs by two mechanisms. The majority is exchanged for Na⁺ via the Na⁺/H⁺ antiporter (NH₄⁺ substituting for H⁺). An additional small portion leaves the cell as NH₃ and is reprotonated in the lumen. At this point the process of generating HCO₃⁻ is complete (i.e., NH₄⁺ has been secreted into the tubular fluid and HCO₃⁻ returned to the blood). However, NH₄⁺ must still be eliminated from the body, because as already noted, if any NH₄⁺ is reabsorbed by the nephron it will be metabolized to urea by the liver and in that process consume the HCO₃⁻ produced from ammoniagenesis (see Fig. 3). Unfortunately, significant amounts of NH₄⁺ are reabsorbed by the thick ascending limb of Henle’s loop. Unlike the other portions of the nephron, which are highly permeable to NH₃ but not NH₄⁺, the thick ascending limb has the opposite characteristics (low permeability to NH₃ and high permeability to NH₄⁺). The reabsorption of NH₄⁺ by the thick ascending limb occurs via transcellular and paracellular routes. Transcellular reabsorption involves uptake into the cell across the apical membrane via the Na⁺-K⁺-2Cl⁻ symporter (NH₄⁺ substituting for K⁺) and movement across the basolateral membrane via K⁺ channels. Paracellular reabsorption of NH₄⁺ is driven by the lumen positive potential difference. The reabsorbed NH₄⁺ accumulates in the interstitial fluid of the medulla by the processes of countercurrent multiplication and countercurrent exchange. As a result, this accumulated NH₄⁺, which is in chemical equilibrium with NH₃ (pKₐ = 9), is available for secretion into the tubular fluid by the cells of the collecting duct.

The secretion of NH₄⁺ by the collecting duct is indirect and involves nonionic diffusion of NH₃ and diffusion trapping of the NH₄⁺ in the acidic tubular fluid. As indicated in Fig. 4, the secretion of NH₄⁺ by the collecting duct is critically dependent on H⁺ secretion. If H⁺ secretion is impaired in any way, reduced amounts of NH₄⁺ will also be secreted and more NH₄⁺ will be returned to the body. It should be emphasized that even though the secretion of NH₄⁺ by the collecting duct requires H⁺ secretion, no additional HCO₃⁻ is generated in this process (i.e., the HCO₃⁻ generated in the intercalated cell titrates the H⁺ generated in the
interstitial fluid from the dissociation of $NH_4^+$ to $NH_3$).
All the $HCO_3^-$ derived from ammoniagenesis was generated during the process of glutamine metabolism in the proximal tubule. The $H^+$ secreted by the collecting duct in the process of $NH_4^+$ secretion simply prevents the $NH_4^+$ from being returned to the liver and converted to urea (see Fig. 3).

Importantly, $NH_4^+$ production and excretion is regulated by the kidneys. With acidosis ammoniagenesis is enhanced, and as already noted, $H^+$ secretion by the nephron is increased. Thus more $NH_4^+$ is excreted, and more $HCO_3^-$ is generated and returned to the body. This response to acidosis, frequently termed renal compensation (see COMPENSATION DURING ACID-BASE DISRUPTIONS), involves upregulation of the enzymes involved in proximal tubule glutamine metabolism. Therefore, hours to days are required for the full response.

Assessing $NH_4^+$ excretion by the kidneys is done indirectly, because assays of urine $NH_4^+$ are not routinely available. Consider, for example, the situation of metabolic acidosis. In the setting of metabolic acidosis, the appropriate renal response is to increase net acid excretion. Accordingly, little or no $HCO_3^-$ will appear in the urine, the urine will be acidic, and $NH_4^+$ excretion will be increased. To assess this, and especially the amount of $NH_4^+$ excreted, the “urinary net charge” or “urine anion gap” can be calculated by

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**FIG. 4.**
$NH_4^+$ production and excretion. Two $NH_4^+$ and two $HCO_3^-$ are produced in proximal tubule from glutamine. $HCO_3^-$ is returned to body as new $HCO_3^-$, and $NH_4^+$ is secreted into tubular fluid. A significant amount of $NH_4^+$ is reabsorbed by thick ascending limb, in which it accumulates in interstitial fluid of renal medulla. Some of this $NH_4^+$ is secreted into tubular fluid by collecting duct. This secretion process is indirect and involves nonionic diffusion and diffusion trapping. Shaded arrows emphasize pathway for $NH_4^+$ through nephron. $A^-$, 2-oxoglutarate.$}\]
measuring the urinary concentrations of Na\(^+\), K\(^+\), and Cl\(^-\) \((6)\)

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\text{urine anion gap} = [\text{Na}^+] + [\text{K}^+] - [\text{Cl}^-] \tag{3}
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The concept of urine anion gap assumes that the major cations in the urine are Na\(^+\), K\(^+\), and NH\(_4^+\), and that the major anion is Cl\(^-\) (with urine pH < 6.5, virtually no HCO\(_3^-\) is present). As a result, the urine anion gap will yield a negative value when adequate amounts of NH\(_4^+\) are being excreted. Indeed, the absence of a urine anion gap or the existence of a positive value indicates a renal defect in NH\(_4^+\) production and excretion.

**COMPENSATION DURING ACID-BASE DISTURBANCES**

When there is a disturbance of acid-base balance the body uses several mechanisms to minimize the impact on the pH of the body fluids. These mechanisms are compensatory in that they do not correct the underlying disorder and include buffering (intracellular and extracellular), respiratory compensation, and renal compensation.

Buffering is the first line of defense because of the rapidity at which it occurs. Extracellular buffering is virtually instantaneous and involves titration of H\(^+\) by HCO\(_3^-\), phosphate, and serum proteins (histidine groups). Intracellular buffering can take several minutes and utilizes the same buffering species. Although it is difficult to estimate, ~50% of nonvolatile acid and 70% of nonvolatile alkali is buffered in the extracellular fluid and the remainder is buffered inside cells.

With metabolic acidosis or alkalosis there is respiratory compensation. This compensatory response is mediated by changes in ventilatory rate, which in turn occur in response to H\(^+\). With metabolic acidosis there is an increase in the ventilatory rate, which drives down Pco\(_2\). Given the mechanics of breathing, Pco\(_2\) can be reduced to 10–15 mmHg in a young adult. However, lesser degrees of hypocapnia can be achieved in elderly or weakened patients. Conversely, there is a decrease in ventilatory rate with metabolic alkalosis. The concomitant hypoxia that develops as a result of hypoventilation limits the range of this response, and in general Pco\(_2\) cannot be maintained above 60 mmHg. The respiratory compensation to metabolic acidosis and alkalosis is not as fast as the intracellular and extracellular buffers. However, an appropriate response can be developed in several minutes to hours.

As already noted, the kidneys respond to acidosis (metabolic and respiratory) by increasing H\(^+\) secretion by the nephron segments and by increasing the production and excretion of NH\(_4^+\). Both responses are necessary to eliminate all HCO\(_3^-\) from the urine and to generate HCO\(_3^-\). If the kidneys are responding to a metabolic acidosis, the serum \([\text{HCO}_3^-]\) will still be less than the normal value but not as low as would be the case if the renal compensatory response had not occurred. In contrast, the serum \([\text{HCO}_3^-]\) is increased above normal in response to respiratory acidosis, because additional HCO\(_3^-\) is added to the normal levels present before the development of the respiratory acidosis. Because of the need for upregulation of acid-base transporters and the enzymes involved in ammoniagenesis, the renal compensatory response can take a day or more to become fully developed.

The renal response to alkalosis is more complicated and can differ for metabolic and respiratory disorders. In general, it is expected that renal H\(^+\) secretion and ammoniagenesis are reduced, resulting in loss of HCO\(_3^-\) in the urine and reduced generation of HCO\(_3^-\). Enhanced HCO\(_3^-\) secretion by the collecting duct also contributes to enhancing HCO\(_3^-\) excretion. These mechanisms typify the response seen in respiratory alkalosis and many cases of metabolic alkalosis. However, metabolic alkalosis can be seen in a setting of volume depletion. When this occurs, it is difficult for the kidneys to increase HCO\(_3^-\) excretion, because of the overriding need to reduce NaCl excretion. For example, loss of gastric contents produces a metabolic alkalosis and reduces extracellular fluid volume (volume depletion). The volume depletion in turn results in a decrease in the glomerular filtration rate, which limits the filtered load of HCO\(_3^-\). In addition, proximal tubule Na\(^+\) reabsorption is stimulated, resulting in enhanced HCO\(_3^-\) reabsorption because H\(^+\) secretion and Na\(^+\) reabsorption are linked via the Na\(^+\)/H\(^+\) antiporter (see H\(^+\) TRANSPORT ALONG NEPHRON). Finally, collecting duct H\(^+\) secretion is also stimulated by the elevated aldosterone levels seen in the setting.
of volume depletion. As a result, the kidneys cannot increase the excretion of HCO$_3^-$ until the ECF volume is restored and the stimuli for enhancing renal NaCl reabsorption are turned off.

**SUMMARY**

The role of the kidneys in acid-base balance is to excrete acid in an amount equal to nonvolatile acid production. In this way HCO$_3^-$ is generated and returned to the body to replenish that lost during the titration of nonvolatile acids. The process of acid excretion involves the secretion of H$^+$ by cells of the nephron. The secreted H$^+$ serve to reabsorb the filtered load of HCO$_3^-$, acidify the urine, titrate urine buffers, and excrete NH$_4^+$. Because the production and excretion of NH$_4^+$ can be regulated by the kidney, it assumes central importance in understanding the physiology of renal acid-base balance.

**Suggested Reading for Students**


Address reprint requests to the author at Univ. of Connecticut Health Ctr., MC-1915, Farmington, CT 06030.

**References**


