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RENAL 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 NH_4^+ plays in the ability of the kidneys to generate new HCO_3^-. 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 HCO_3^- 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 HCO_3^-. Finally, the important role of NH_4^+ production and excretion in the generation of new HCO_3^- is reviewed and highlighted.

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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 HCO_3^- 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 HCO_3^- 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 HCO_3^- 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 HCO_3^- 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 HCO_3^-,'' 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 NH_3.

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 NH_4^+ have changed dramatically in recent years, and it is now clear that NH_3 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 NH_3/NH_4^+ in renal acid excretion. In addition, students must understand the role of the kidneys as they relate to the

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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.

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

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 P_{CO_2} and HCO_3^- concentration ($[HCO_3^-]$). Thus acid-base balance can be effected by both the lungs and the kidneys, the lungs through control of P_{CO_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

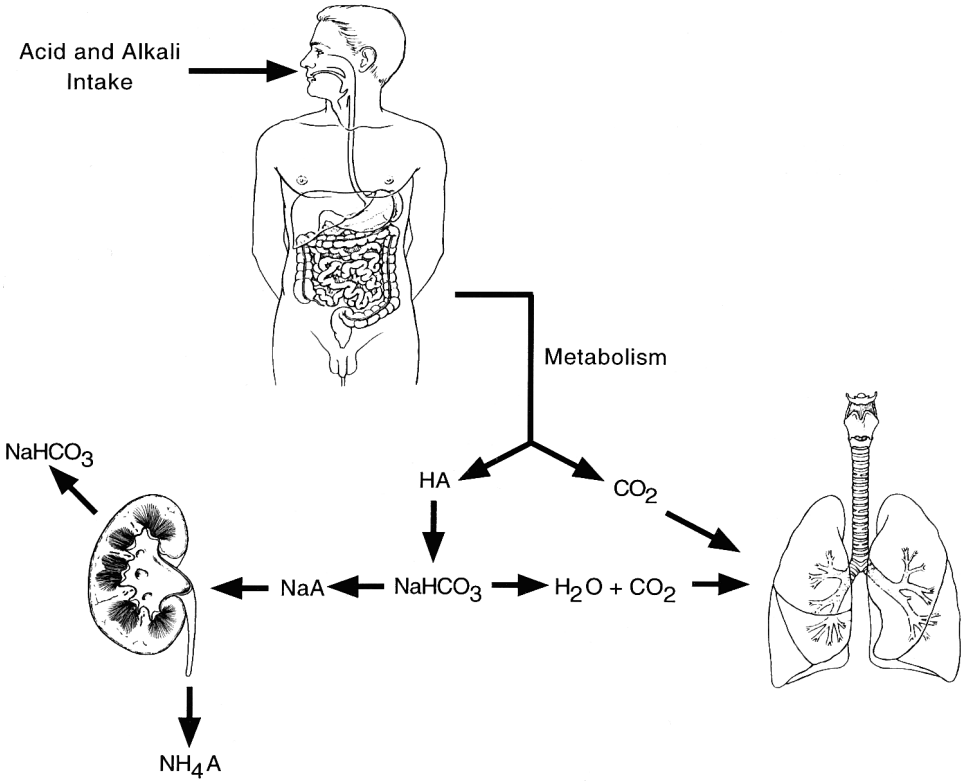

FIG. 1.
Overview of role of kidneys in acid-base balance. See text for details. HA, nonvolatile acid.

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excretion of CO_2 does not impact acid-base balance (3). However, as indicated by *reaction 1*, retention of CO_2 (production > excretion) will produce an increase in $[H^+]$ and thus the development of acidosis. Conversely, if CO_2 production is less than excretion, there will be a decrease in $[H^+]$, and alkalosis results. Acid-base disorders resulting from primary alterations in the P_{CO_2} are termed ''respiratory'' disorders.

As depicted in Fig. 1, nonvolatile acids are buffered by HCO_3^- (other non-HCO_3^- buffers are also involved in this process). Thus, if nonvolatile acid production exceeds the excretion of acid from the body, $[HCO_3^-]$ 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 $[HCO_3^-]$ 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 $[HCO_3^-]$.

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 CO_2 and H_2O. On a typical diet, ~15–20 mol of CO_2 are produced. Normally, this large quantity of CO_2 is effectively eliminated by the lungs, and there is no impact of this metabolically derived CO_2 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 CO_2 and H_2O 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 O_2) or treatment with insulin, many of these nonvolatile acids are then further metabolized to CO_2 and H_2O. In this later process, much of the HCO_3^- 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 HCO_3^- 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

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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

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

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 amounted 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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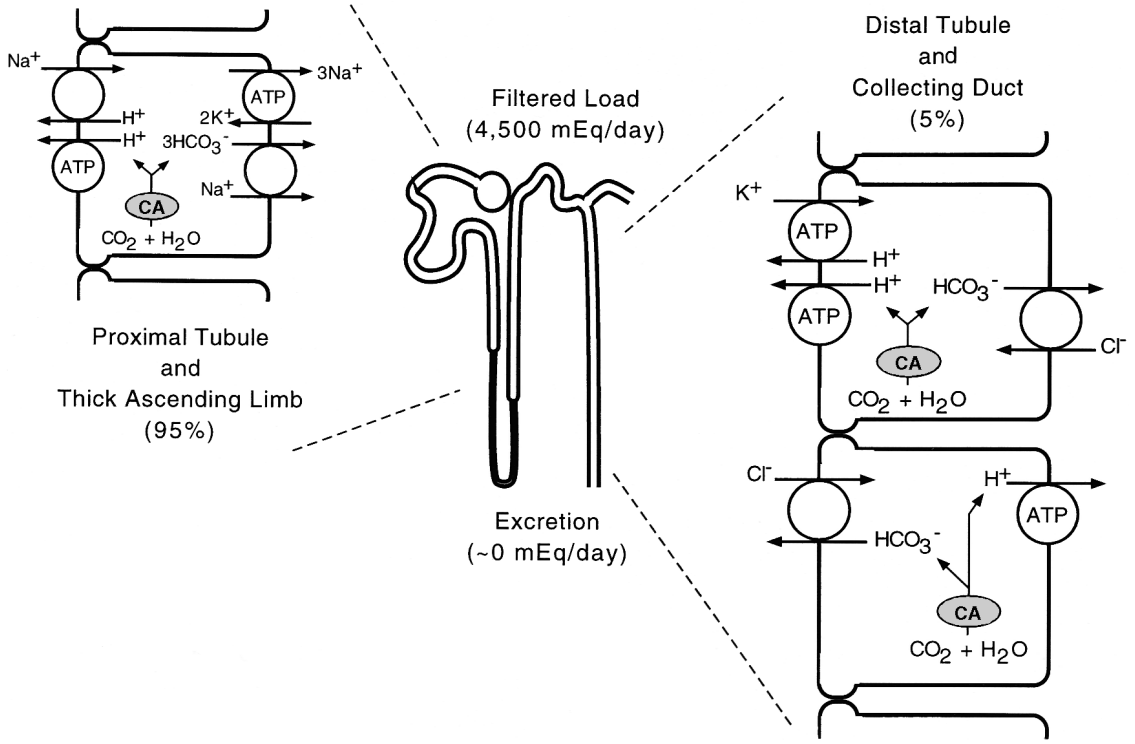

FIG. 2.
Summary of cellular mechanisms of H^+ secretion (HCO_3^- reabsorption) along nephron. Approximately 80% of filtered load of HCO_3^- is reabsorbed by proximal tubule and 15% by thick ascending limb of Henle's loop. Collecting duct contains both H^+-secreting and HCO_3^--secreting intercalated cells.

intercalated cells of the collecting duct (Refs. 4, 5; see below).

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 HCO_3^- from CO_2 and H_2O. 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).

HCO_3^- generated in the cell from the hydration of CO_2 exits the cell across the basolateral membrane by a symporter that couples the movement of 3 HCO_3^- with 1 Na^+. An additional portion of basolateral HCO_3^- exit may also occur in exchange for Cl^-.

The distal tubule and collecting duct reabsorb the portion of the filtered load of HCO_3^- that escapes reabsorption by the proximal tubule and thick ascending limb of Henle's loop (~5% of the filtered load). HCO_3^- 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 HCO_3^-. The predominant mechanism for HCO_3^- exit across the basolateral membrane is via a Cl^-/HCO_3^- 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 HCO_3^- (see Fig. 2). Because of nonvolatile acid production, and thus the need to excrete acid, H^+ secretion predominates in the collecting duct. However, HCO_3^-

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TABLE 1
Factors influencing H^+ secretion by the nephron

Factor	Principal Nephron Site of Action
Increase H^+ secretion	
Primary	
Decrease in plasma [HCO_3^-] (↓ pH)	Entire nephron
Increase in blood P_{CO_2}	Entire nephron
Secondary (not directed at maintaining acid-base balance)	
Increase in filtered load of HCO_3^-	Proximal tubule
Decrease in ECF volume	Proximal tubule
Increase in angiotensin II	Proximal tubule
Increase in aldosterone	Collecting duct
Hypokalemia	Proximal tubule
Decrease H^+ secretion	
Primary	
Increase in plasma [HCO_3^-] (↑ pH)	Entire nephron
Decrease in blood P_{CO_2}	Entire nephron
Secondary (not directed at maintaining acid-base balance)	
Decrease in filtered load of HCO_3^-	Proximal tubule
Increase in ECF volume	Proximal tubule
Decrease in aldosterone	Collecting duct
Hyperkalemia	Proximal tubule

secretion is important in states of metabolic alkalosis, when renal HCO_3^- 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 [HCO_3^-] and pH) or respiratory (increased P_{CO_2}) 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 [HCO_3^-] and pH) and respiratory (increased P_{CO_2}) 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 HCO_3^- 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 HCO_3^-) reabsorption in volume depletion and decreasing reabsorption during volume expansion.

PRODUCTION AND EXCRETION OF NH_4^+

Although the reabsorption of the filtered load of HCO_3^- is quantitatively an important process, simply preventing the loss of HCO_3^- in the urine does not replenish the HCO_3^- lost during the titration of nonvolatile acid. This later process is accomplished through the excretion of H^+ with urine buffers (titratable acid) and by the production and excretion of NH_4^+. 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, NH_4^+ production and excretion by the kidneys is regulated to effect acid-base balance. Thus understanding how the kidneys produce and excrete NH_4^+ is critical to understanding the role of the kidneys in acid-base balance.

Traditionally, the excretion of NH_4^+ has been taught from the perspective of urinary buffering. Specifically, NH_3 was viewed as a urinary buffer that could accept

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H^+. HCO_3^- was generated in this process from the hydration of CO_2 within the intercalated cell (i.e., the H^+ was secreted into the tubular fluid and the HCO_3^- returned to the blood). However, new knowledge regarding the production and excretion of NH_4^+ makes it clear that NH_3 cannot be viewed simply as a urinary buffer (2).

The essential features of NH_4^+ production and excretion are summarized in Fig. 3. Glutamine is metabolized by the kidneys to produce $2NH_4^+$ and $2HCO_3^-$. The NH_4^+ is excreted in the urine, and the HCO_3^- is returned to the body to replenish that which was lost earlier during the titration of nonvolatile acids. For every equivalent of NH_4^+ excreted in the urine, an equivalent of HCO_3^- is returned to the body. Figure 3 also illustrates what happens if the kidneys are unable to excrete NH_4^+. When this occurs, NH_4^+ returns to the liver, where it is metabolized to urea. The net result of this process is that 2 NH_4^+ are converted to urea with the production of 2 H^+. These 2 H^+ are then titrated by 2 HCO_3^-, thus negating the efforts of the kidneys to generate HCO_3^- from the metabolism of glutamine.

The details of NH_4^+ 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 NH_4^+ and the tricarboxylic acid cycle intermediate 2-oxoglutarate$^=$, which is then further metabolized to $2HCO_3^-$ (2). The HCO_3^- is returned to the body, and the NH_4^+ is secreted by the cell into the tubular fluid.

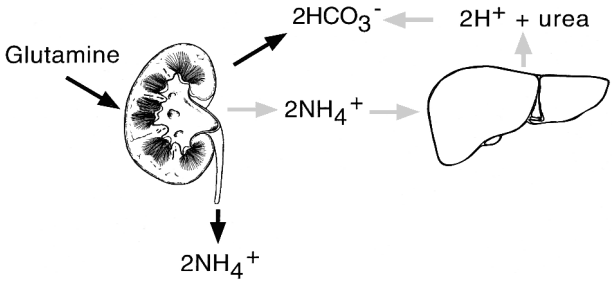

FIG. 3.
Overview of NH_4^+ production and excretion by kidneys. Glutamine is metabolized by kidneys to produce 2 NH_4^+ and 2 HCO_3^-. NH_4^+ is excreted in urine, and HCO_3^- is returned to body ("new HCO_3^-"). Shaded arrows illustrate what happens to NH_4^+ if it is not excreted in urine. When this occurs 2 NH_4^+ are converted to urea by liver, in a process yielding 2 H^+. This production of urea from NH_4^+ negates production of HCO_3^-, which occurred in kidneys from metabolism of glutamine.

NH_4^+ secretion by the proximal tubule cells occurs by two mechanisms. The majority is exchanged for Na^+ via the Na^+/H^+ antiporter (NH_4^+ substituting for H^+). An additional small portion leaves the cell as NH_3 and is reprotonated in the lumen. At this point the process of generating HCO_3^- is complete (i.e., NH_4^+ has been secreted into the tubular fluid and HCO_3^- returned to the blood). However, NH_4^+ must still be eliminated from the body, because as already noted, if any NH_4^+ is reabsorbed by the nephron it will be metabolized to urea by the liver and in that process consume the HCO_3^- produced from ammoniagenesis (see Fig. 3). Unfortunately, significant amounts of NH_4^+ are reabsorbed by the thick ascending limb of Henle's loop. Unlike the other portions of the nephron, which are highly permeable to NH_3 but not NH_4^+, the thick ascending limb has the opposite characteristics (low permeability to NH_3 and high permeability to NH_4^+). The reabsorption of NH_4^+ 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 (NH_4^+ substituting for K^+) and movement across the basolateral membrane via K^+ channels. Paracellular reabsorption of NH_4^+ is driven by the lumen positive potential difference. The reabsorbed NH_4^+ accumulates in the interstitial fluid of the medulla by the processes of countercurrent multiplication and countercurrent exchange. As a result, this accumulated NH_4^+, which is in chemical equilibrium with NH_3 ($pK_a = 9$), is available for secretion into the tubular fluid by the cells of the collecting duct.

The secretion of NH_4^+ by the collecting duct is indirect and involves nonionic diffusion of NH_3 and diffusion trapping of the NH_4^+ in the acidic tubular fluid. As indicated in Fig. 4, the secretion of NH_4^+ by the collecting duct is critically dependent on H^+ secretion. If H^+ secretion is impaired in any way, reduced amounts of NH_4^+ will also be secreted and more NH_4^+ will be returned to the body. It should be emphasized that even though the secretion of NH_4^+ by the collecting duct requires H^+ secretion, no additional HCO_3^- is generated in this process (i.e., the HCO_3^- generated in the intercalated cell titrates the H^+ generated in the

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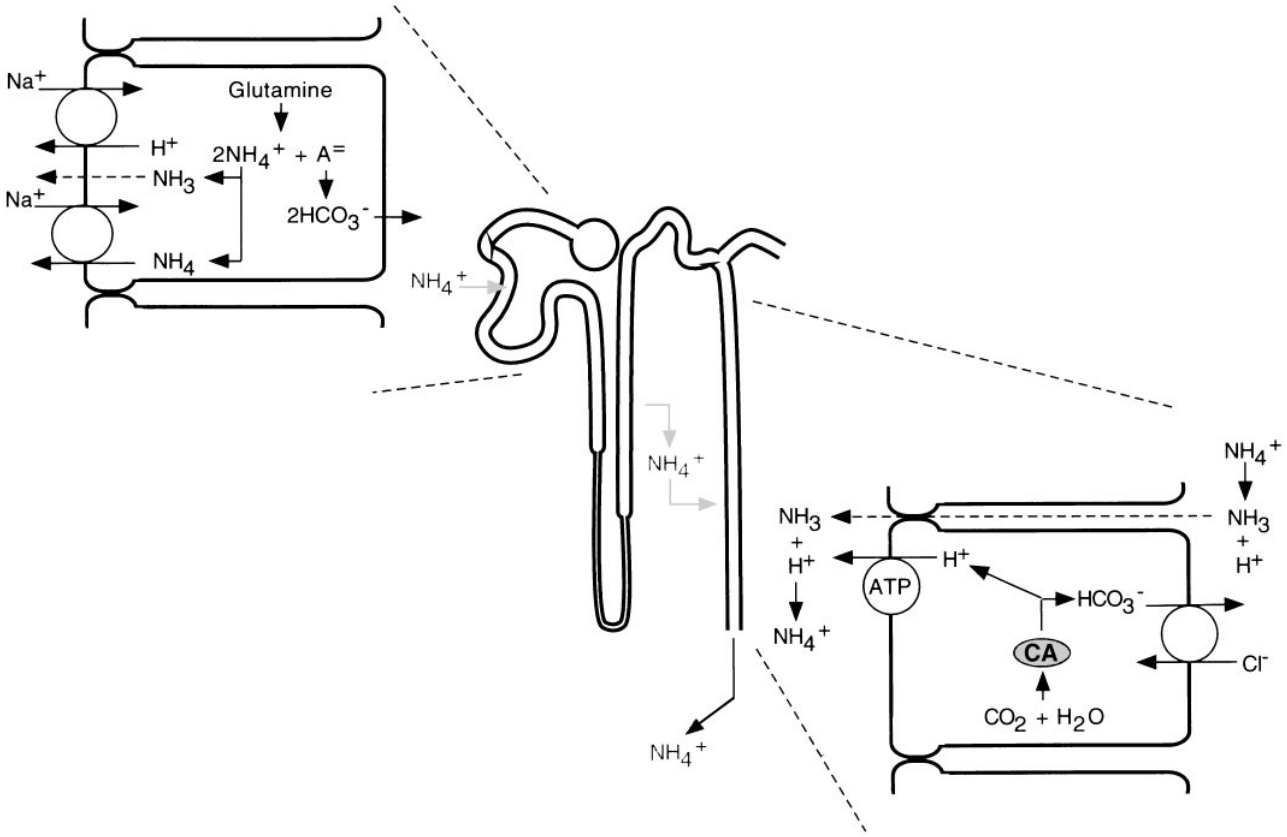

FIG. 4.

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$^=$.

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 DISTURBANCES), 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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measuring the urinary concentrations of Na^+, K^+, and Cl^- (6)

$$\text{urine anion gap} = [Na^+] + [K^+] - [Cl^-] \quad (3)$$

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 P_{CO_2}. Given the mechanics of breathing, P_{CO_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 P_{CO_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 [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 [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

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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

Halperin, M. L., and M. B. Goldstein. *Fluid, Electrolyte, and Acid-Base Physiology* (2nd ed.). Philadelphia, PA: Saunders, 1994, chapt. 1.

Koeppen, B. M., and B. A. Stanton. *Renal Physiology* (2nd ed.). St. Louis, MO: Mosby Year Book, 1997, chapt. 8.

Rose, B. D., and H. G. Rennke. *Renal Pathophysiology—The Essentials*. Baltimore, MD: Williams and Wilkins, 1994, chapt. 6.

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References

1. **Ambühl, P. M., M. Amemiya, M. Danczkay, M. Lotscher, B. Kaissling, O. W. Moe, P. A. Preisig, and R. J. Alpern.** Chronic metabolic acidosis increases NHE3 protein abundance in rat kidney. *Am. J. Physiol.* 271 (*Renal Fluid Electrolyte Physiol.* 40): F917–F925, 1996.
2. **Brosnan, J. T., M. Lowry, P. Vinay, A. Gougoux, and M. L. Halperin.** Renal ammonium production—une vue canadienne. *Can. J. Physiol. Pharmacol.* 65: 489–498, 1987.
3. **Gamble, J. L., Jr.** Moving more closely to acid-base relationships in the body as a whole. *Perspect. Biol. Med.* 39: 593–600, 1996.
4. **Gluck, S. L., M. Iyori, L. S. Holliday, T. Kostrominova, and B. S. Lee.** Distal urinary acidification from Homer Smith to the present. *Kidney Int.* 49: 1660–1664, 1996.
5. **Gluck, S. L., D. M. Underhill, M. Iyori, L. S. Holliday, T. Y. Kostrominova, and B. S. Lee.** Physiology and biochemistry of the kidney vacuolar H^+-ATPase. *Annu. Rev. Physiol.* 58: 427–445, 1996.
6. **Goldstein, M. B., R. Bear, R. M. A. Richardson, P. Marsden, and M. Halperin.** The urine anion gap: a clinically useful index of ammonium excretion. *Am. J. Med. Sci.* 292: 198–202, 1986.
7. **Hays, S. R.** Mineralocorticoid deficiency inhibits apical membrane H pump and basolateral membrane Cl/HCO_3 exchange in parallel in the inner stripe of the outer medullary collecting duct ($OMCD_i$) (Abstract). *J. Am. Soc. Nephrol.* 2: 702, 1991.
8. **Hays, S. R.** Mineralocorticoid modulation of apical and basolateral membrane $H^+/OH^-/HCO_3^-$ transport processes in the rabbit inner stripe of outer medullary collecting duct. *J. Clin. Invest.* 90: 180–187, 1992.
9. **Laghmani, K., P. Borensztein, P. Ambühl, M. Froissart, M. Bichara, O. W. Moe, R. J. Alpern, and M. Paillard.** Chronic metabolic acidosis enhances NHE-3 protein abundance and transport activity in the rat thick ascending limb by increasing NHE-3 mRNA. *J. Clin. Invest.* 99: 24–30, 1997.
10. **Moe, O. W.** Sodium-hydrogen exchange in renal epithelia: mechanisms of acute regulation. *Curr. Opin. Nephrol. Hypertens.* 6: 440–446, 1997.
11. **Sabolic, I., D. Brown, S. L. Gluck, and S. L. Alper.** Regulation of AE1 anion exchanger and H^+-ATPase in rat cortex by acute metabolic acidosis and alkalosis. *Kidney Int.* 51: 125–137, 1997.
12. **Sly, W. S., and P. Y. Hu.** Human carbonic anhydrases and carbonic anhydrase deficiencies. *Annu. Rev. Biochem.* 64: 375–401, 1995.
13. **Tsuruoka, S. and G. J. Schwartz.** Metabolic acidosis stimulates H^+ secretion in the rabbit outer medullary collecting duct (inner stripe) of the kidney. *J. Clin. Invest.* 99: 1420–1431, 1997.
14. **Wakabayashi, S., M. Shigekawa, and J. Pouyssegur.** Molecular physiology of vertebrate Na^+/H^+ exchangers. *Physiol. Rev.* 77: 51–74, 1997.
15. **Wingo, C. S., and A. J. Smolka.** Function and structure of H-K-ATPase in the kidney. *Am. J. Physiol.* 269 (*Renal Fluid Electrolyte Physiol.* 38): F1–F16, 1995.

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