CHAPTER

72 Disorders of Potassium and Acid–Base Metabolism in Association with Renal Disease

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In this chapter, we review disturbances in potassium and acid–base homeostasis seen in patients with renal disease. Our discussion is, however, limited to disorders of potassium and acid–base homeostasis seen in (1) patients with progressive chronic kidney disease (CKD) and (2) patients with renal insufficiency and defects in the renin–aldosterone axis or in the tubular response to aldosterone. We briefly review potassium and acid–base homeostasis in healthy humans before focusing on patients with underlying renal disease. We do not, however, discuss normal renal handling of potassium and only briefly review renal handling of hydrogen ion. These two topics are extensively reviewed in Chapter 6: Tubular Potassium Transport, and Chapter 7: Renal Acid–Base Transport, respectively.

POTASSIUM HOMEOSTASIS

Potassium is the most abundant cation in the body. The distribution of potassium is such that 98% of total body potassium is intracellular, whereas only 2% is extracellular. Serum potassium is normally between 3.8 and 5.0 mEq per liter, whereas the intracellular potassium concentration is 120 to 140 mEq per liter. The high intracellular to extracellular potassium ratio (K_i/K_o) is crucial to normal cell function, because it is the major determinant of the resting membrane potential. The body is able to maintain this distribution in a highly regulated and efficient fashion through the hormonal modulation of Na-K-ATPase pump activity.[1,2] Humans, as carnivorous intermittent eaters, are continuously challenged by large potassium loads. On a long-term basis, this challenge is met primarily by the renal excretion of potassium load; however, on a short-term basis, a significant amount of potassium is shifted intracellularly.[3] This shift temporarily buffers the expected change in the K_i/K_o ratio until potassium intake is balanced by a comparable output. Therefore, potassium homeostasis is regulated through both extrarenal as well as renal mechanisms (Fig. 72.1).[4]

Extrarenal Potassium Homeostasis

The kidney is able to excrete only about 50% of the administered potassium during the first 4 hours after intravenous or oral intake of potassium. Approximately 80% of the retained potassium is shifted intracellularly, and only 20% (or 10% of the total intake) remains in the extracellular space.[5–7] The retained potassium will be excreted completely over the next 24 hours.[8] The major regulators of this internal redistribution are: (1) insulin, (2) catecholamines, and (3) mineralocorticoids. In addition to these physiologic regulators, serum potassium is also regulated by acid–base status as well as plasma osmolality. Factors that increase or decrease plasma potassium concentration are noted in Figure 72.2.

Insulin

The ability of insulin to shift potassium intracellularly has been known for over 70 years[9] and has been used therapeutically for the treatment of hyperkalemia. Pancreatectomized dogs tolerate exogenous potassium loads poorly.[10] This is reversed by the exogenous replacement of insulin.[11,12] The partial inhibition of endogenous insulin in dogs by somatostatin infusion results in a twofold rise in serum potassium compared to controls.[6] If physiologic doses of insulin were added to the somatostatin infusion, potassium tolerance returned to normal. In healthy volunteers, somatostatin infusion in the postabsorptive state led to a 50% decline in the plasma insulin concentration and a 0.5 to 0.7 mEq per liter rise in serum potassium that was reversed by a physiologic infusion of exogenous insulin.[6] A similar phenomenon was observed in maturity-onset diabetic patients who have normal or increased fasting plasma insulin levels, but not in insulin-deficient juvenile diabetic patients.[13]

The primary sites of insulin-mediated potassium uptake include muscle and the liver, and to a lesser degree, adipose tissue.[14,15] In normal volunteers on variable insulin doses, the liver is the primary site of potassium uptake during the first hour.[15] However, during the second hour, despite a continued decrease in serum potassium, there is net release of potassium from the portal and splanchnic bed, indicating a shift of potassium uptake to the peripheral tissue, especially muscle.[15]

At the cellular level, insulin interacts with specific receptors on the plasma membrane,[16] increasing the activity

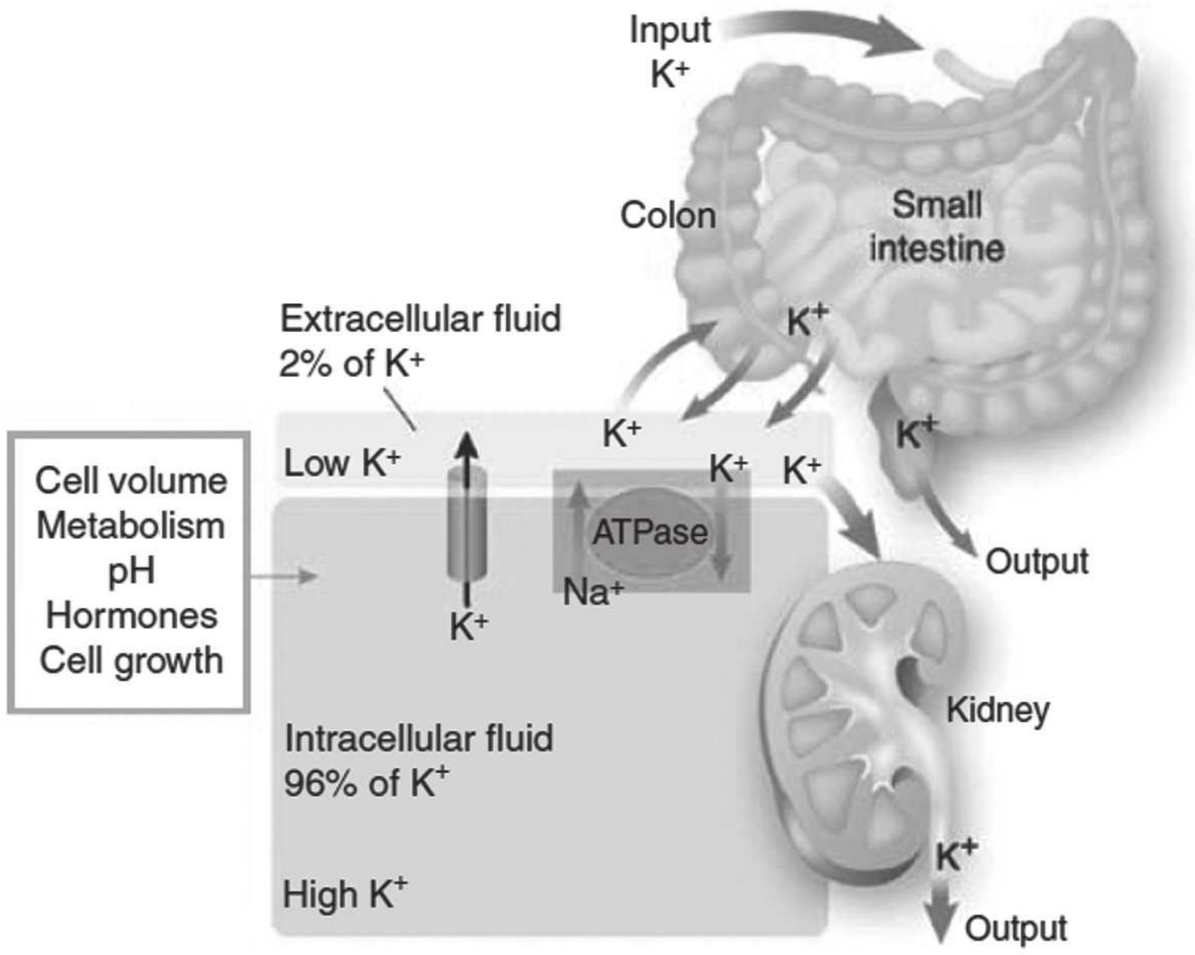

FIGURE 72.1 The distribution of potassium (K) in the body. Potassium is primarily located in cells (96%), with distribution controlled by a pump-leak mechanism involving both Na-K-ATPase and membrane potassium channels. The kidneys excrete more than 90% of the daily potassium load, and the intestines excrete the rest. (From Giebisch G, Krapf R, Wagner C. Renal and extrarenal regulation of potassium. *Kidney Int*. 2007;397, with permission.)

of the Na-K-ATPase pump in the skeletal and heart muscle, epithelial cells of the kidney and bladder, as well as liver and fat cells.[17] This results in a series of intracellular events leading to hyperpolarization of cell membranes.[17] The time course for this interaction is consistent with both an increase in enzyme activity as well as the rapid recruitment of Na-K-ATPase pumps to the cellular membrane. In contrast, chronic stimulation by insulin probably increases the total number of available pump sites. This occurs through the regulation of the Na-K-ATPase pump at the transcriptional and posttranscriptional levels by inducing the synthesis of new α and β subunits.[1] McDonough and Youn,[18] using a potassium clamp, have recently shown that after 10 days of potassium deprivation in rats Na-K-ATPase activity decreased by more than 50% and insulin-mediated potassium shift decreased by 94%, whereas in rats deprived of potassium for only 2 days the number of pumps did not decrease, but insulin-mediated potassium shift decreased by 80%. This would indicate that insulin resistance precedes a decrease in the number of pump expression during hypokalemia. The molecular mechanism underlying this response, however, remains poorly understood.[19] Several in vitro studies, including one study in humans, have shown that insulin-driven potassium uptake by both muscle and the liver is independent of glucose uptake.[15,20]

Catecholamines

D'Silva,[21] beginning in 1934, first observed a biphasic response of plasma potassium to epinephrine injection. Plasma potassium rose during the first 1 to 3 minutes, but

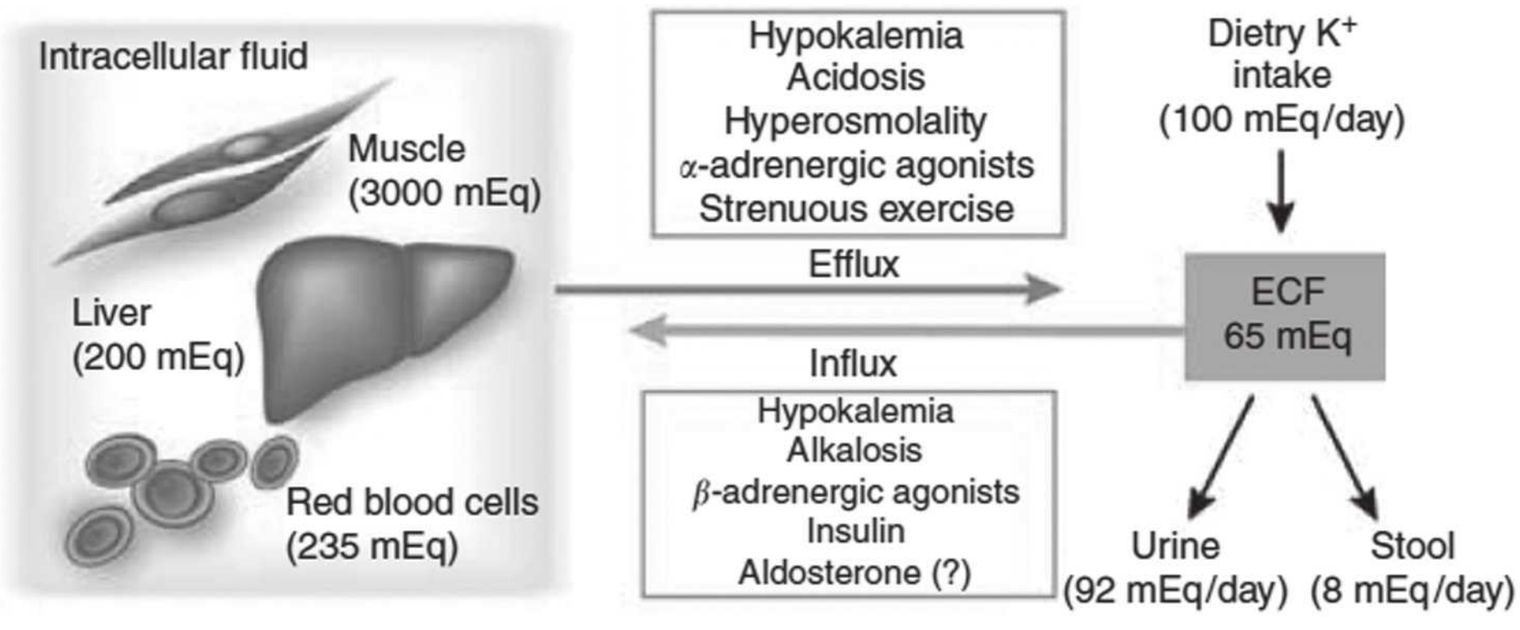

FIGURE 72.2 The distribution of potassium (K) between the intracellular and extracellular fluid compartments. Potassium distribution between the intra- and extracellular fluid is controlled by a pump-leak mechanism involving both Na-K-ATPase and membrane potassium channels. The factors noted in the figure drive potassium into or out of cells. (From Giebisch G, Krapf R, Wagner C. Renal and extrarenal regulation of potassium. *Kidney Int*. 2007;397, with permission.)

with continued infusion, fell and remained lower than baseline. Other investigators have shown increased potassium tolerance in animals infused with pharmacologic doses of epinephrine[22,23] despite a pancreatectomy or nephrectomy.[24] Brown and coworkers[25] have shown that the infusion of stress-level doses of epinephrine resulted in a decrease in serum potassium by 0.4 to 0.6 mEq per liter. Because epinephrine inhibits the renal excretion of potassium,[26,27] the decline in potassium concentration is entirely accounted for by enhanced cellular potassium uptake.

Specific receptors are involved in the cellular disposal of potassium by catecholamines. Alpha stimulation in humans by phenylephrine[28] significantly impairs cellular potassium tolerance, which is reversed by the α-antagonist phentolamine. This phenomenon may explain the initial rise in serum potassium after the infusion of catecholamine.[26,27] β_2-blockade impairs the catecholamine-induced shift of potassium into extrarenal tissues[29,30] and causes hyperkalemia despite an increase in renal excretion of this ion. In normal volunteers who exercise while taking β-adrenergic blocking agents, the serum potassium level is raised 2- to 2.5-fold higher than during similar exercise performed without a β blockade.[3,31] The effect of nonspecific β-blockers such as propranolol on serum potassium is mimicked by specific β_2-blockers[32] but not β_1-blockers. Although an important role for catecholamine-stimulated uptake of potassium by muscle has been demonstrated, the role of the liver remains controversial. The effect of potassium on catecholamine levels is less clear.

At the cellular level, epinephrine binds to the β_2-receptor resulting in the stimulation of adenyl cyclase and the conversion of adenosine triphosphate to cyclic 3′,5′-adenosine mono- phosphate (cAMP). It is postulated that cAMP then activates protein kinase A, which then phosphorylates the Na-K-ATPase pump, increasing its activity and promoting potassium influx into the cell and Na^+ efflux.[31] Binding catecholamines to the α receptor decreases cellular potassium uptake by inhibiting adenylate cyclase activity and decreasing Na-K-ATPase pump activity.[32] In addition, activation of the α-1 receptor alters cytoplasmic calcium, thereby increasing intracellular calcium concentration and opening calcium-activated potassium channels, which allow potassium to exit the cell.[32] Interestingly, the effect of insulin and epinephrine on plasma potassium is additive, which confirms a separate mechanisms of action.[31] In insulin-induced hypoglycemia, hypokalemia is therefore due to the combined effect of both insulin and the hypoglycemia-induced rise in catecholamines.[31]

Mineralocorticoids

Mineralocorticoids play a major role in external potassium homeostasis by increasing its excretion by the kidney,[33] colon,[34] salivary,[35] and sweat glands.[36] However, aldosterone's role in internal potassium homeostasis is less clear.[37,38] Anephric rats adapted to high potassium intake handle an acute potassium load more efficiently than do nonadapted rats. This adaptation is lost by prior adrenalectomy and restored by exogenous mineralocorticoid replacement.[39] However, Spital and Sterns[40,41] observed that during the 20 hours of fasting before a nephrectomy and acute potassium loading, these rats became potassium depleted owing to marked kaliuresis resulting from high serum potassium coupled with a high aldosterone level. In adrenalectomized dogs, Young and Jackson[42] have shown that plasma potassium concentration at any exchangeable potassium level was a function of aldosterone replacement dose. High-dose aldosterone in anephric rabbits delays death due to hyperkalemia.[43] Similarly, baseline potassium was significantly higher in hormonally deficient adrenalectomized rats despite negative potassium balance compared to exogenously replaced controls, thus supporting a defect in the cellular uptake of potassium.[5,44] This impairment was corrected by either aldosterone or epinephrine replacement. In rats, aldosterone has been shown to increase Na-K-ATPase pump activity by inducing the synthesis of new α- and β-subunits in heart and vascular smooth muscle.[1] This effect presumably represents the action of aldosterone on Na-K-ATPase pump gene expression and supports a role for aldosterone in cellular potassium homeostasis. In anephric humans treated with deoxycorticosterone acetate (DOCA), spironolactone, or placebo for 3 days, the baseline potassium was similar; however, the DOCA-treated subjects showed greater tolerance to acute potassium load than did the other two groups.[45] In a study of 15 patients on hemodialysis that were treated with 0.05 to 2.0 mg per day of fludrocortisone acetate, the serum K^+ decreased significantly.[46] Interestingly, the effect of exogenous mineralocorticoid was more pronounced in patients with a low compared to a high plasma aldosterone concentration. Low dose spironolactone (25 mg per day) was associated with an increase in a mean serum K^+ concentration of 0.3 mEq per liter over 4 weeks of therapy in 15 chronic hemodialysis patients.[47] In the largest study to date, serum potassium in 50 hemodialysis patients treated with 25 mg per day of spironolactone increased from baseline 4.96 to 5.16 in 2 weeks and remained stable for 6 months.[48] Very low dose spironolactone (25 mg thrice weekly), however, did not increase serum K^+ in hemodialysis patients,[49] whereas a very high dose (300 mg per day) induced a significant rise in plasma potassium (0.5 mEq per liter) and caused hyperkalemia after 3 weeks of therapy in nine chronically hemodialyzed end-stage renal disease (ESRD) patients (three were anephric).[50] In summary, these studies support a small but significant role for aldosterone in internal potassium homeostasis in anephric animals and ESRD patients.

Acid–Base Balance

The role of acid–base balance on the internal distribution of potassium[51] is based on the concept that during the development of acute acidemia, the hydrogen ion enters the cell in exchange for potassium and that the reverse occurs during the development of alkalemia.[51–53] This dynamic interrelationship has been simplified clinically to a general rule that

for each 0.1 U change in serum pH, the serum potassium changes in the opposite direction by 0.6 mEq per liter. However, the relationship between serum potassium and serum pH is much more complex and depends on the type and severity of the acid–base disorder, the anion accompanying hydrogen, the duration of acidosis, changes in plasma bicarbonate concentration independent of changes in pH and the extent of intracellular buffering, and renal adaptation as well as hormonal changes in response to the disorder.[54] In addition, in clinical settings, there are often other physiologic and pathophysiologic processes that may be present, which would affect both transcellular as well as the renal and extrarenal handling of potassium. The following generalizations should therefore be used with caution.

1. On the whole, acidosis is accompanied by a greater change in serum potassium than is alkalosis.[55]
2. Mineral acidosis (Fig. 72.3) causes the greatest shift (0.24 to 1.7 mEq per liter for each 0.1 U in pH change), whereas organic acidosis has a much smaller effect.[53,56,57] Mild mineral acidosis (a decrease in serum bicarbonate by 5 mEq per liter and an increase in hydrogen ion concentration by 0.45 nmol per liter), however, does not result in a significant change in serum potassium.[58]
3. Acute respiratory alkalosis paradoxically results in a small but significant rise in serum potassium (+0.30 mEq per liter with a drop in pCO_2 of 16 to 22.5 mm Hg). The rise was primarily due to stimulation of α-adrenergic receptors by catecholamine.[59] Chronic respiratory alkalosis, however, results in sustained hypokalemia due to a renal loss of potassium.[60]
4. The amounts of potassium shifted into the cell in metabolic and chronic respiratory alkalosis are approximately similar (0.1 to 0.4 mEq per liter for each 0.1 U of pH change).
5. Acute respiratory acidosis resulting in a decrease in pH to 7.24 had no effect on serum K^+.[61]
6. Changes in serum bicarbonate, independent of serum pH, have an inverse effect on the serum potassium concentration.
7. In chronic acidosis and alkalosis, the final serum K^+ is a function of the effect of acid–base disturbance on the renal handling of potassium, as well as on the transcellular distribution of this ion. In dogs with ammonium chloride–induced acidosis, Magner and associates[62] noted a fall in serum potassium below baseline by days 3 to 5, owing to severe kaliuresis.

Osmolality

The acute hyperkalemic effect of a sudden rise in plasma osmolality is probably caused by the shift of potassium-rich intracellular fluid by solvent drag.[63] Clinically, this phenomenon is most commonly observed in hyperosmolar diabetic patients (Fig. 72.4), with or without ketoacidosis[64–67] when insulin deficiency augments the rise in potassium. Although chronic hyperkalemia in diabetic patients is multifactorial, a sudden rise in plasma osmolality seems to play a contributory role. The infusion of hypertonic mannitol in healthy humans[68] or hypertonic saline[69] or hypertonic contrast media[70] in patients with chronic kidney disease results in a modest rise in serum potassium (0.4 to 0.6 mEq per liter). Hyperkalemia can be severe, especially in diabetic patients with little or no

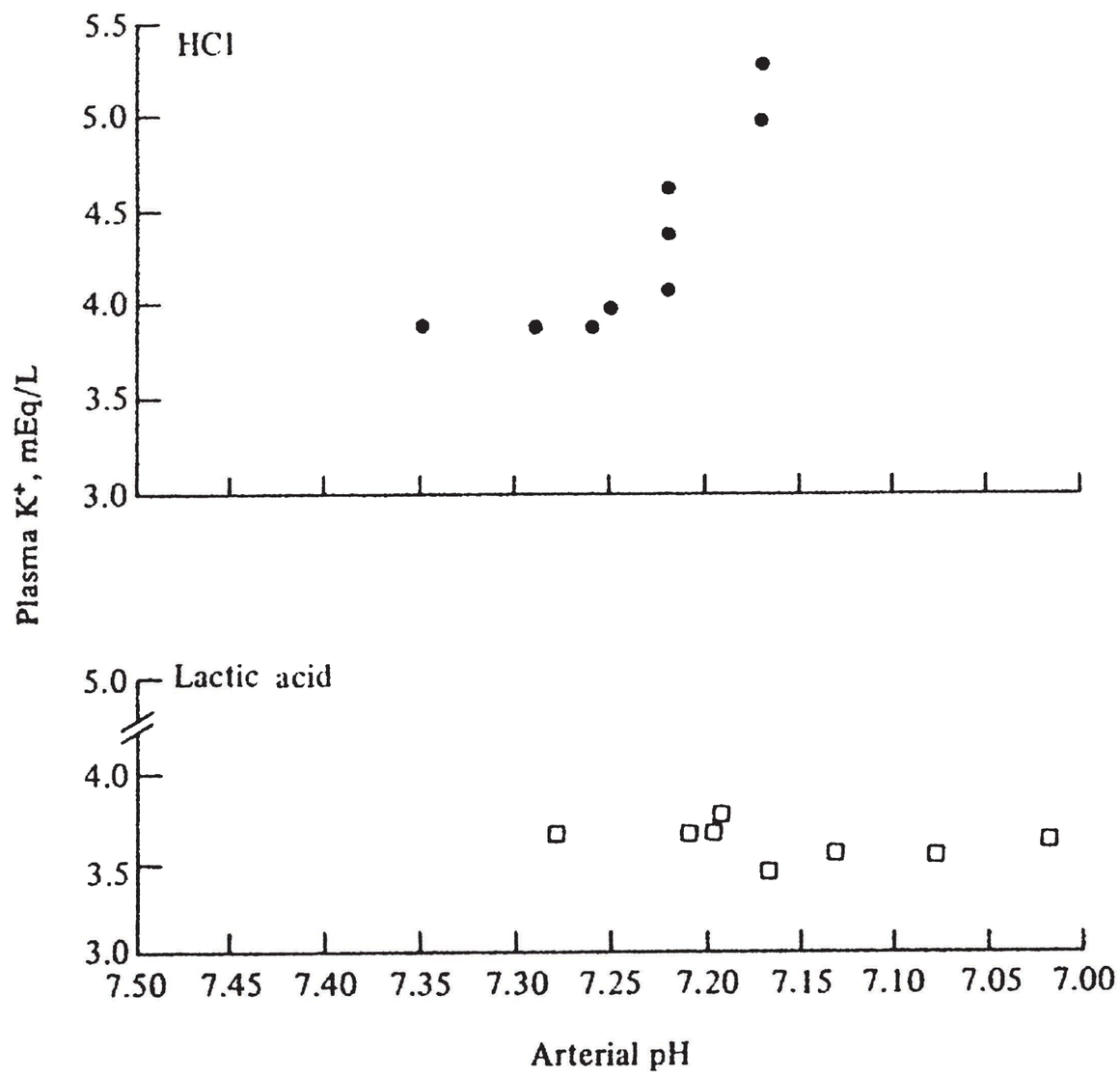

FIGURE 72.3 The effect of arterial pH on plasma potassium concentration in experimentally induced mineral acidosis (hydrochloric acid-HCl) and lactic acidosis in dogs. (From Perez GO, Oster JR, Vaamonde CA. Serum potassium concentration in acidemic states. *Nephron*. 1981;27:233, with permission.)

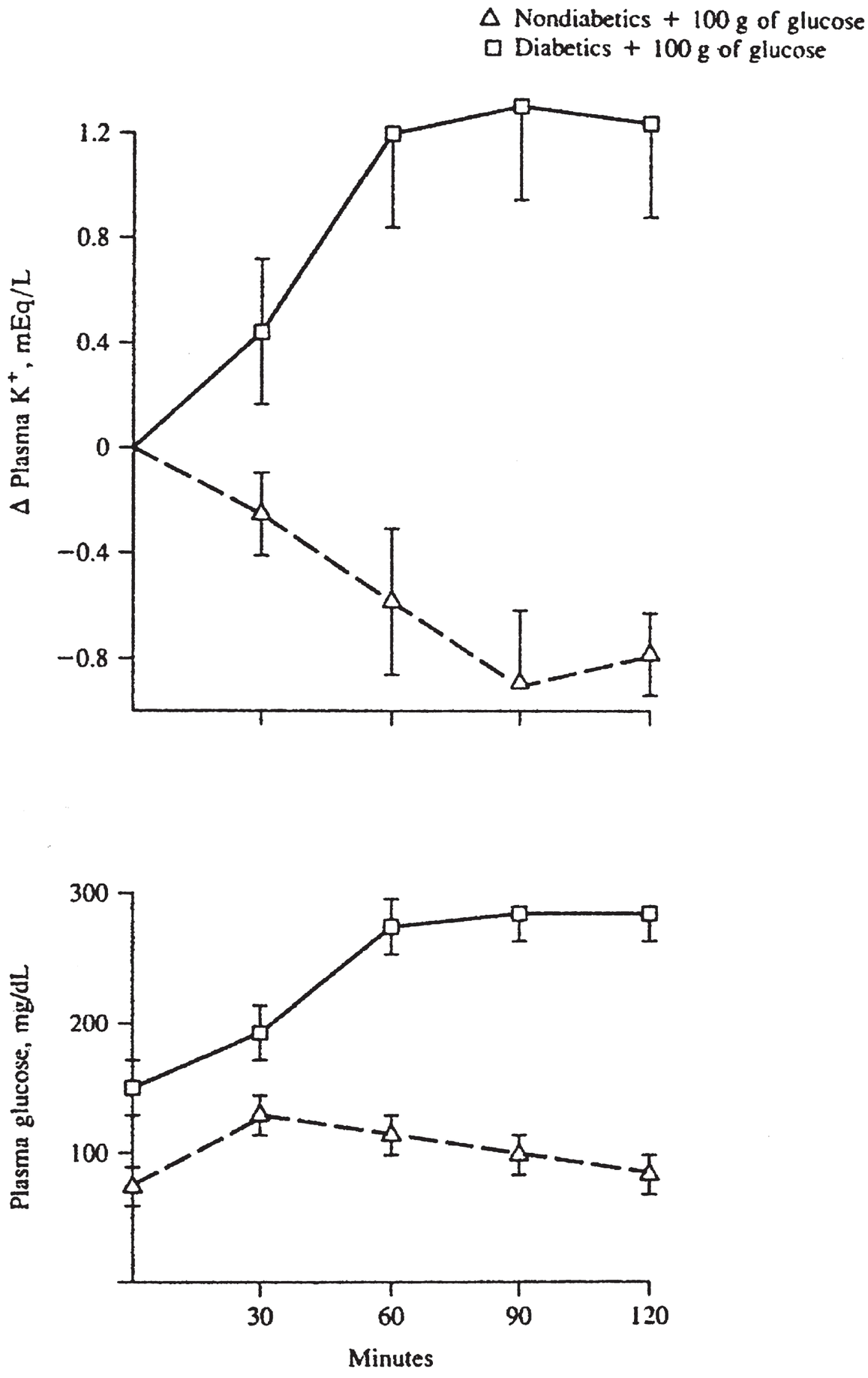

FIGURE 72.4 The effect of glucose infusion on plasma potassium and glucose concentrations in diabetics *(squares)* and normal subjects *(triangles)*. The plasma potassium rises in diabetics owing to the development of hyperosmolality (hyperglycemia) but falls in normal subjects as a result of the glucose-induced release of endogenous insulin. (From Nicolis GL, Kahn T, Sanchez A, et al. Glucose-induced hyperkalemia in diabetic subjects. *Arch Intern Med.* 1981;141:49, with permission.)

renal function facing sudden hyperglycemia.[71] These clinical observations support an independent role of sudden osmolar shifts in the regulation of serum potassium.

Feedback or Feedforward Control of Potassium Homeostasis. It is well known that an increase in potassium concentration directly stimulates renal potassium excretion through an increase in potassium secretion in the collecting duct. This is accomplished by the direct stimulation of Na-K-ATPase, an increased tubular flow, and an increase in aldosterone. However, as Rabinowitz et al.[72] first noted an increase in renal potassium excretion after meals in sheep was independent of change in serum potassium and aldosterone. In normal human subjects, urinary potassium excretion increased significantly 20 minutes after the ingestion of potassium salts before any change in serum potassium. Kaliuresis was more robust if potassium is ingested with meals rather than without meals or given intravenously. These and other observations support a role for a direct gut–kidney axis in potassium homeostasis favoring a feedforward rather than a feedback homeostatic mechanism (Fig. 72.5). The specific gut sensor and the gut–kidney loop remains speculative at this point. For a more detailed discussion, readers are referred to two recent reviews of this topic.[73,74]

POTASSIUM HOMEOSTASIS IN RENAL FAILURE

Patients with renal failure are able to maintain a near normal serum potassium concentration despite a marked decrease in glomerular filtration rate (GFR).[75–78] Although hyperkalemia could be due to increased potassium intake and/or rapid shifts of potassium from the cell, renal failure is the most important cause of hyperkalemia, accounting for 77% of the cases reported by Acker and coworkers.[79] In a random sample of 300 CKD patients (serum creatinine [Cr] levels

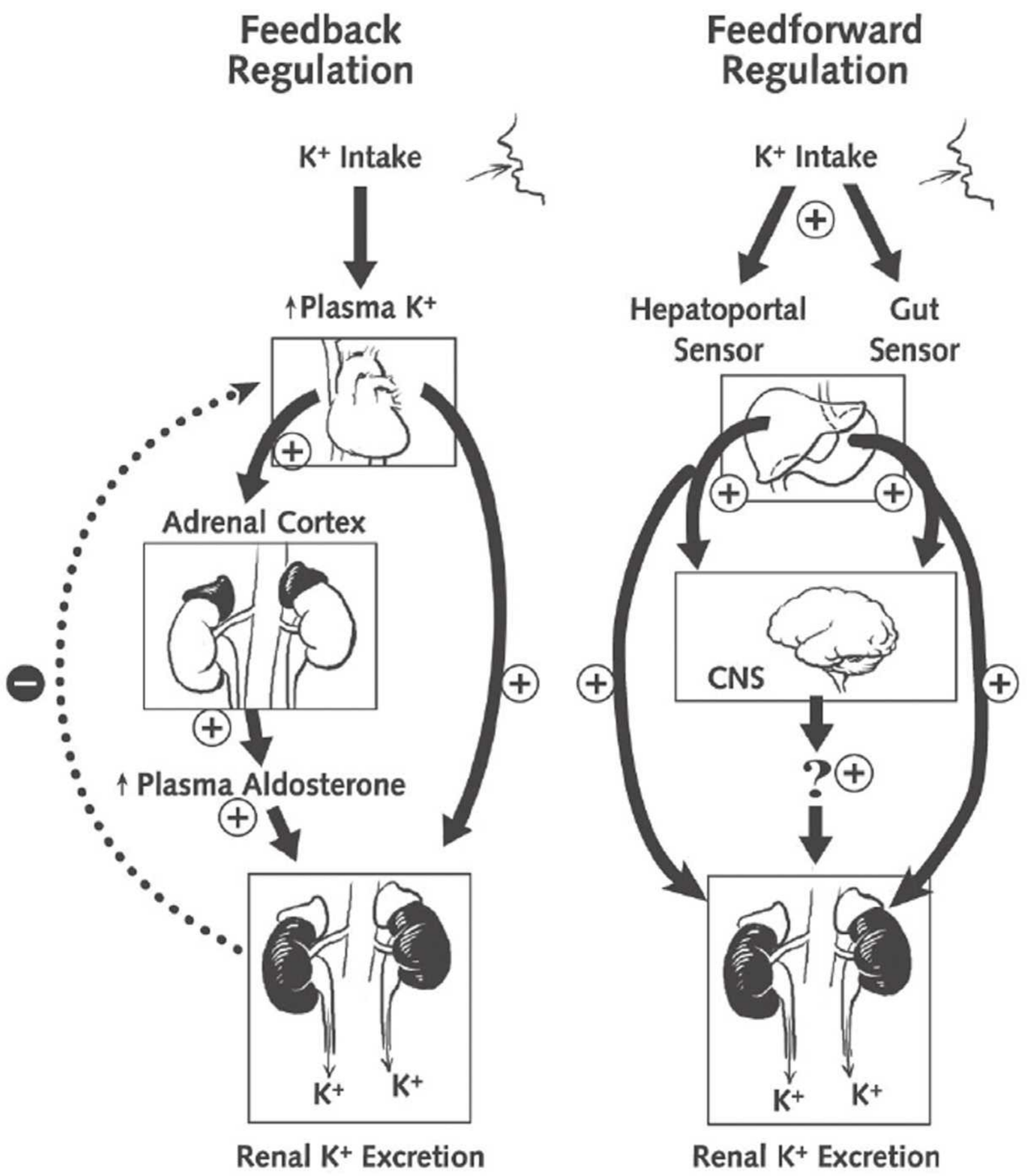

FIGURE 72.5 The integrated model of the regulation of body potassium balance: feedback and feedforward regulation. Renal potassium excretion is controlled by both feedback signals (plasma potassium concentration) and feedforward signals (liver and gut). CNS, central nervous system. (From Greenlee M, Wingo CS, McDonough AA, et al. Narrative review: evolving concepts in potassium homeostasis and hypokalemia. *Ann Intern Med.* 2009;150:619, with permission.)

1.5 to 6.0 mg per deciliter) not receiving drugs that interfered with potassium homeostasis, 55% were noted to have hyperkalemia ($K^+ \geq 5.0$ mEq per liter).[80] Treatment with drugs that interfere with potassium handling would be expected to further increase the development of hyperkalemia (see the following). Serum potassium rises with decreasing GFR; however, it often remains within normal range with GFR above 40 mL per minute.[75] In this study, the rate of hyperkalemia ($[K^+] > 5.0$) was 17% and was primarily limited to patients with CKD stage 4 and 5. However, under certain conditions, hyperkalemia may occur in patients with mild-to-moderate renal failure (Table 72.1). In a longitudinal study of patients with CKD, hyperkalemia ([K] > 5.5] was reported in only 8% of patients and, surprisingly, hypokalemia ([K] < 4.0) was more frequently seen in 15% of patients. Hypokalemia was not related to nutrition and was most likely secondary to the use of diuretics.[78] This observation would indicate that electrolyte disturbances in patients with CKD are partly related to the underlying disease and partly to medications used in the management of concomitant comorbidities such as fluid overload and hypertension. However, it should be emphasized that the risk of hyperkalemia in patients with CKD, including those treated with renin–angiotensin–aldosterone system (RAAS) blockers, is relatively small.[81]

In this section, we initially discuss total body potassium content in patients with renal failure before treatment with dialysis and then review internal and external potassium homeostasis in these patients. In the subsequent section, we discuss hyperkalemia seen in patients with renal insufficiency with a defect in the renin–angiotensin–aldosterone axis or in the tubular responsiveness to aldosterone.

72.1 Etiologies of Hyperkalemia in Patients with Renal Insufficiency

- GFR < 20 mL/min
- Defects in the renin–angiotensin–aldosterone axis
- Tubular defects in potassium secretion
- Potassium input (e.g., rhabdomyolysis, hemolysis, severe catabolic states, gastrointestinal bleeding, exogenous potassium administration)
- Shift of potassium from intracellular compartment
- Drugs that interfere with renal and extrarenal potassium homeostasis

GFR, glomerular filtration rate.

Total Body and Cellular Potassium Content in Renal Failure

Total body potassium content is a reflection of the balance between potassium intake and potassium output, whereas the cellular content reflects the distribution of potassium between the intracellular and the extracellular compartments. Exchangeable potassium (K_e) in pre-ESRD patients has been generally reported as lower than normal.[82] However, Berlyne and associates,[83] after excluding patients with intercurrent problems (such as vomiting, diarrhea, or malnutrition), reported a normal value. It should also be noted that malnutrition is common in patients with CKD and many serum and anthropomorphic measurements of protein-energy nutritional status show progressive decline with the progression of CKD.[84] As Patrick[85] has pointed out, the normal range for K_e is not well defined and depends on age, sex, and the reference points used (e.g., total body weight, lean body weight, intracellular water). These reference points may be distorted in patients with CKD. The measurement of total body potassium by the use of a naturally occurring isotope (^{40}K) also has given normal values.[86]

Cellular potassium content has been estimated by the use of muscle biopsy.[87–92] Bergstrom and colleagues[87] studied 102 patients with serum creatinine levels ranging from 4.8 to 25.0 mg per deciliter before therapy. In this and other studies, the intracellular potassium concentration was low owing to an increase in intracellular water despite normal intracellular potassium content.[87,90] However, Bilbrey and coworkers[93] and Montanari and coworkers[92] have reported normal intracellular potassium concentrations. Importantly, the intracellular potassium content was either low or normal (but not increased) in all four studies.[87,90–93] The low intracellular potassium (and high intracellular sodium content) has also been reported in erythrocytes[92,94,95] and leukocytes[82,96] from these patients. This bespeaks of a decrease in the number and/or the activity of the Na-K-ATPase pumps in the cell membrane. In chronic dialysis patients, the pump transport rate is higher immediately after fluid removal,[97,98] and the abnormal levels of intracellular sodium and potassium in uremic patients return to normal following several weeks of dialysis.[95] Because the number of pump sites inversely correlates with intracellular sodium, and a change in their number requires the production of new cells with lower intracellular sodium, the acute effect of fluid removal by dialysis may result from the removal of a volume-sensitive pump inhibitor.[99] In contrast, the long-term effect of dialysis reflects the production of new cells with lower intracellular sodium and a higher number of pump sites. For a detailed discussion, refer to the article by Kaji and Kahn.[99]

Internal Potassium Homeostasis in Chronic Kidney Disease

The role of cellular uptake of potassium in renal failure has been studied in both humans[76,77,100] and animals.[101–103] Schon and associates[103] have shown that the cellular uptake of potassium in rats with a remnant kidney is similar to that in normal rats maintained on a comparable diet but is lower than normal when both groups consume a high potassium diet. In contrast, in two different models of renal failure in rats, Bia and DeFronzo[101] showed impairment in the cellular disposal of an acute potassium load. Bourgoignie and associates[102] challenged chronically uremic dogs (remnant kidney model) that were adapted to different potassium intakes with an acute potassium load. Whereas the percentage of retained potassium that was shifted into the intracellular compartment was greater in normal dogs (90%), the absolute amount was significantly less than that in dogs with a remnant kidney (9.0 versus 20.5 mEq, respectively). They concluded that extrarenal cellular uptake was normal in the dogs with renal failure. Gonick and colleagues[76] challenged patients with moderate renal failure with an oral potassium load. Whereas serum potassium 5 hours postchallenge was slightly higher in patients than in controls (5.2 versus 4.7 mEq per liter), this result was entirely because of a lower urinary excretion. In a study of patients with tubulointerstitial disease, the absolute amount of potassium shifted into the cell was greater in patients compared with controls, but the relative amount (expressed as a percentage of total potassium retained) was similar.[100] In contrast, Kahn and colleagues[77] observed a significantly greater rise in serum potassium in patients compared with controls when dietary potassium was increased by 50 mEq per day. This study[77] cannot be strictly compared with others because they relied on 24-hour urinary potassium measurements, and their study reflected a long-term adaptation to a high potassium diet in patients with CKD. In hemodialysis patients, serum potassium rose significantly more in patients than in controls challenged with acute potassium load (1.06 versus 0.39 mEq per liter). However, the baseline potassium was significantly higher in patients than in controls (5.17 versus 3.59 mEq per liter), making the interpretation of this study difficult.[104] More recently, Allon and colleagues[105] noted a similar response in these patients with lower baseline potassium. Finally, the effect of vigorous exercise on serum potassium in hemodialysis patients was similar to the control group.[106] It is reasonable to conclude that the extrarenal cellular uptake of an acute potassium load in CKD patients is near normal.

As discussed previously, internal potassium homeostasis is regulated by insulin, catecholamines, and, to a lesser extent, aldosterone. Although the serum insulin level is increased in renal failure,[106–108] several studies provide strong support for normal insulin-stimulated potassium uptake[106,108,109] by the splanchnic as well as by the peripheral tissues.[109] Alvestrand and coworkers,[109] using the euglycemic insulin clamp technique, demonstrated a similar uptake of potassium by both splanchnic and leg tissues in patients with CKD. The inhibition of endogenous insulin by somatostatin results in a significantly greater rise in serum potassium in uremic rats than in controls (1.0 versus 0.2 mEq per

liter at 60 minutes).[110] The administration of glucose with potassium stimulates insulin secretion and attenuates the rise in potassium in patients on dialysis as well as normal controls.[105]

Elevated serum catecholamine levels have been reported in CKD.[106,111,112] Yang and coworkers[113] noted higher mean potassium in patients on propranolol. Infusion of epinephrine resulted in two different responses: In 4 of 10 patients, serum potassium did not fall; in the remaining 6, an exaggerated response was noted. The authors felt that the latter group of patients is those who have a propensity to develop hyperkalemia while on propranolol. Gifford and associates,[114] using a much lower epinephrine dose, could not show a hypokalemic response in patients with ESRD. Plasma aldosterone is normal or high in most CKD patients.[115–119] As noted, patients with ESRD who are taking DOCA, spironolactone, or placebo have similar baseline potassium levels; however, patients on DOCA can dispose an acute potassium load more promptly than the other groups.[45] In addition, ESRD patients on spironolactone have a small but significant rise in serum potassium levels.[48] These studies would support a minor role for aldosterone in internal potassium homeostasis in ESRD patients. In summary, extrarenal potassium homeostasis is near normal in patients with severe renal failure, although a cellular defect in potassium disposal due to abnormal response to catecholamines has been reported in a subgroup of patients on dialysis.

External Potassium Homeostasis in Severe Renal Failure

Renal Adaptation

Patients with a marked decrease in GFR are able to excrete the ingested dietary potassium load and maintain near normal potassium balance. This adaptive process is reflected by an increase in the fractional excretion of potassium (FE_K) modulated by an increase in secretory rate per functioning nephron. However, this adaptive response is limited and a sudden increase in potassium intake may result in life-threatening hyperkalemia. The quantitative aspects as well as the anatomic and functional characteristics of this adaptive response are briefly reviewed herein.

In conscious dogs with a 10% remnant kidney, Schultze and coworkers[119] showed that potassium excretion by the remnant kidney increased fourfold by 18 hours and approached 85% of the control value by the 7th day. Kunau and Whinnery[120] and Wilson and Sonnenberg[103] reported similar data in rats. In experiments by Schultze and associates,[119] animals with a remnant kidney manifested an exaggerated kaliuresis following a potassium load. In contrast to these data and independent of previous potassium intake, dogs with 25% remnant kidney were only able to excrete 30% to 37% of the load in 5 hours compared with 70% to 90% in the control animals.[102] There is no easy resolution to the differences in these two studies.[102,119]

Gonick and colleagues[76] documented that human subjects with CKD were able to excrete only 20% of an oral potassium load in 6 hours compared with 46% in normal controls. Similar data were reported by Perez and colleagues[100] in patients with tubulointerstitial disease. Kahn and colleagues[77] demonstrated in 10 patients with stable chronic kidney disease renal adaptation to increased dietary potassium. In summary, it can be concluded that residual renal tissue is able to maintain external potassium homeostasis in the postabsorptive state. However, the initial phase of this adaptation is impaired when an acute potassium load is administered.

The nephron sites involved in this adaptation have been studied using a variety of techniques in both rats and rabbits and appear to include both the distal convoluted tubule and the collecting duct.[103,119–123] The discrepancies reported in the literature most likely owe to interspecies and intraspecies differences as well as the anatomic definition of different distal tubular segments.

The mechanisms involved in this renal adaptation have been partially defined. In both humans[115] and rodents,[124] aldosterone has been shown to play an important role in the adaptive ability of the diseased kidney to maintain a normal rate of potassium excretion. This renal adaptation has been shown to be independent of dietary sodium intake.[125] Schultze and coworkers[119] argued that aldosterone is not important in the renal potassium adaptation that occurs following a reduction in renal mass, because uremic dogs maintained on constant aldosterone replacement maintained normal rates of potassium excretion. However, the replacement dose of aldosterone in this study was in the high pharmacologic range. Serum potassium concentration itself plays an important role in augmenting urinary potassium excretion.[81] Bourgoignie and colleagues[102] found a direct relationship between serum potassium and both the absolute and fractional potassium excretion (EE_k). The slope of the curve relating serum potassium to the absolute rate of urinary potassium excretion was much steeper in normal dogs than in dogs with a remnant kidney. However, the slope of the curve relating serum potassium to the FE_K was similar in the control and uremic dogs.

Microperfusion studies by Fine and associates[122] indicate that adaptation is an inherent characteristic of the renal tubular cells of uremic animals and, once learned, it can be retained in vitro, at least for short periods of time. Schon and associates[103] showed that augmented potassium excretion is associated with an increase in Na-K-ATPase in the outer medulla in animals subjected to a three-quarter nephrectomy. This increase is quite specific to this enzyme and occurs only in the kidney[103] and the colon.[126] Muto and colleagues[127] demonstrated that an increase in peritubular $[K^+]$ increased renal potassium excretion by also enhancing K^+ conductance (ROMK) and Na^+ conductance (ENaC) in principal cells (Fig. 72.6). Other mechanisms may include a higher rate of potassium delivery and an increase in tubular flow rate in the distal nephron.[120]

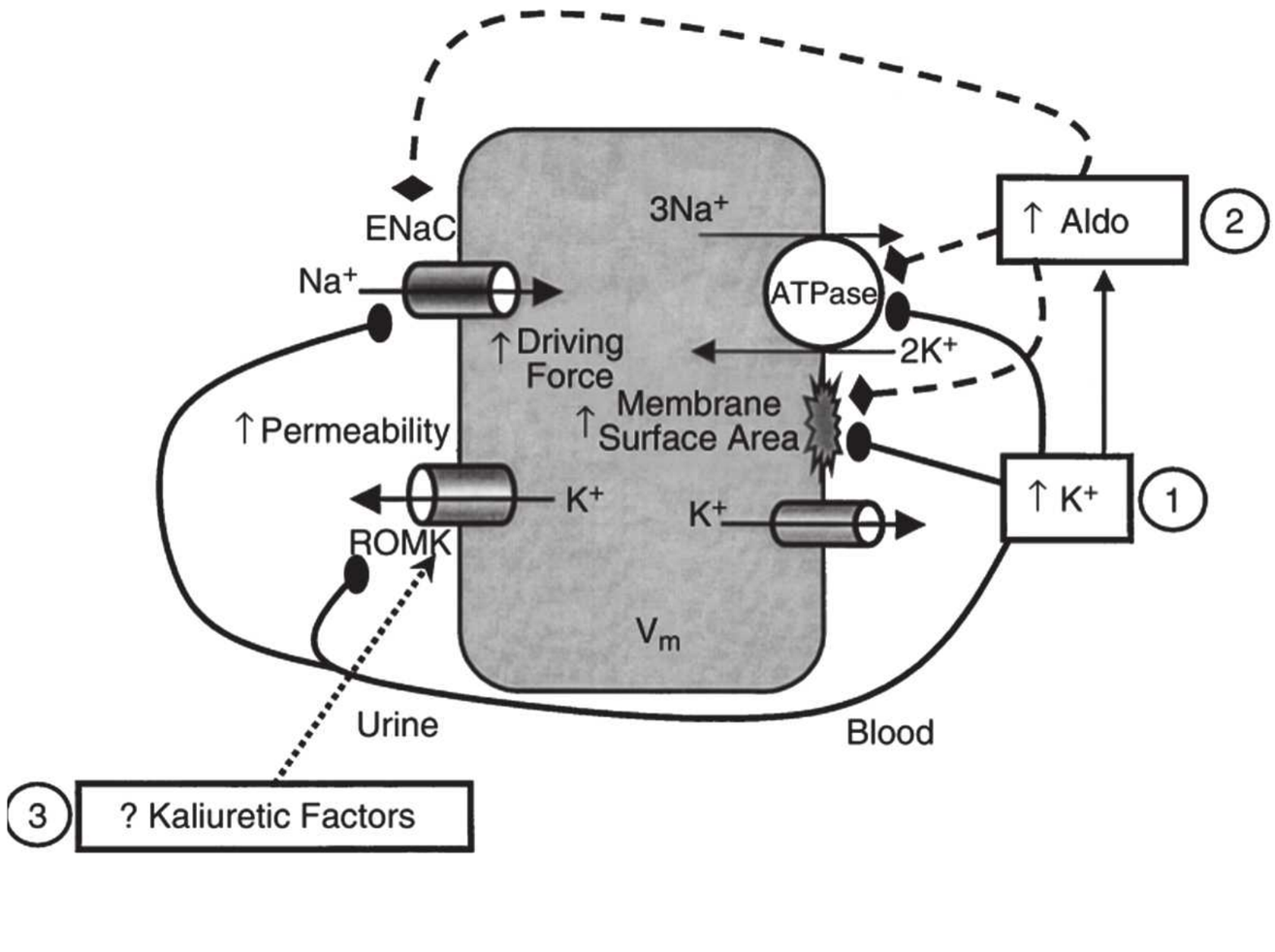

FIGURE 72.6 The major factors that regulate potassium secretion in principal cells. Sodium is reabsorbed across the luminal membrane through ENaC (epithelial sodium channels) with resultant cellular depolarization increasing the electrical driving force for potassium secretion through ROMK (potassium channels). The effects of aldosterone (Aldo) and hyperkalemia ($\uparrow K^+$) on potassium secretion are noted. (From Gennari FJ, Segal AS. Hyperkalemia: an adaptive response in chronic renal insufficiency. *Kidney Int.* 2002;62:1, with permission.)

Intestinal Potassium Excretion in Renal Failure

Patients with renal failure secrete more potassium in the stool than do normal controls.[115,128,129] Net colonic secretion of potassium is increased significantly above control levels in rats with renal insufficiency.[128] This increase is associated with an increase in Na-K-ATPase activity in colonic mucosa and is functionally similar to the increase seen with the administration of DOCA, glucocorticoids, or high dietary potassium.[130] Although the rise in fecal potassium concentration is significant, the absolute amount of K^+ lost through this route in patients with mild-to-moderate CKD is small and contributes only minimally to the external K^+ homeostasis. In patients with advanced renal insufficiency (GFR < 5 to 10 mL per minute), however, up to 30% to 40% of the ingested potassium load may be excreted in the stool.[129]

Acid–Base Homeostasis in Renal Failure

The ability of the kidney to excrete a hydrogen ion is progressively diminished with the diminution of GFR. A significant decrease in serum bicarbonate does not usually occur until GFR falls below 25 to 30 mL per minute.[75,131] Widmer and colleagues,[132] in 41 ambulatory patients with CKD who had multiple electrolyte measurements over time, noted a serum bicarbonate reduction from 28 to 22 mEq per liter in patients with a moderate renal failure defined as a creatinine level of 2 to 4 mg per deciliter and a further reduction to 19 mEq per liter in patients with a creatinine level of 4 to 14 mg per deciliter. The anion gap remained unchanged in the first group and rose significantly with a further decrease in GFR. This study is criticized for the use of serum creatinine to define severity of renal failure rather than the use of a more accurate measurement of renal function. The concept of orderly progression of metabolic acidosis of renal failure from hyperchloremic to anion gap acidosis, however, occurs in the minority of patients. Wallia and colleagues[133] studied the electrolyte pattern in 70 patients with ESRD just before dialytic therapy was begun. Five patterns were found: 14 patients with normal electrolytes; 14 with anion gap metabolic acidosis; 21 with hyperchloremic acidosis; 11 with mixed hyperchloremic and anion gap acidosis; and 10 with normal serum chloride, low serum bicarbonate, and normal anion gap. This last group, however, had the lowest serum sodium and therefore were relatively hyperchloremic. Therefore, among these 70 patients with ESRD, 31 (44%) had hyperchloremic acidosis, only 14 (20%) had classic anion gap acidosis, and interestingly, another 14 (20%) had normal electrolytes. Patients with an increased anion gap, however, had a slight but significantly higher serum creatinine than patients with pure hyperchloremic acidosis or with normal electrolytes (13.2 versus 10.0 versus 9.0 mg per deciliter, respectively). In addition, these two studies did not support the common impression that hyperchloremic acidosis occurs more often in patients with tubulointerstitial rather than glomerular disease.[132,133] Interestingly, diabetic patients with moderately severe renal failure (GFR < 30 mL per minute) have recently been reported to have milder metabolic acidosis than nondiabetic patients with similar renal function.[134]

Renal tubular acidosis (RTA) defines a group of disorders characterized by the presence of metabolic acidosis out of proportion to the decrease in GFR. The hallmark of these disorders is the presence of significant metabolic acidosis with hyperchloremia and a normal anion gap. Renal tubular acidosis in patients with mild-to-moderate renal insufficiency is often associated with significant hyperkalemia and is discussed later in this chapter.

The Pathophysiology of Metabolic Acidosis in Chronic Kidney Disease

Many studies have shown that acid production in renal failure is normal, and therefore, uremic acidosis reflects a decrease in net acid excretion, defined as the difference between proton excretion in the form of titratable acid and

ammonium ion (NH_4^+) and bicarbonate excretion.[135–137] Careful metabolic studies by Goodman and colleagues[137] documented that patients with chronic renal failure have a daily bicarbonate deficit of approximately 13 to 19 mEq. It is notable that despite this persistent deficit, serum bicarbonate in patients with CKD after an initial drop remains stable over long periods of time.[138,139] This is due chiefly to the buffering of excess hydrogen ions by bone buffers, including calcium carbonate.[138]

Renal Excretion of Bicarbonate

Several studies demonstrate that some patients with severe kidney disease have significant bicarbonate wasting.[135,140–144] In an early study by Schwartz and coworkers,[135] three out of four patients with renal failure had significant bicarbonaturia, which disappeared only after the fall of serum bicarbonate to below 20 mEq per liter. In a more detailed study in 17 uremic patients (serum creatinine of 5.6 to 18.9 mg per deciliter), the majority had significant bicarbonate wasting (fractional excretion of HCO_3 of 0% to 17.56%) despite the presence of metabolic acidosis (serum HCO_3 of 16 to 23 mEq per liter). After NH_4Cl loading, serum bicarbonate decreased to below 14 mEq per liter, and bicarbonaturia disappeared in all but four patients.[144] Interestingly, the bicarbonate wasting in these four patients also disappeared with the institution of a low-sodium diet.[144] These two studies support the presence of a diminished maximal tubular reabsorption (T_m) for bicarbonate in the majority of patients with renal failure. Further, they demonstrate that the low T_m is partly responsive to volume status.

Arruda and colleagues[143] and Wong and associates,[145] working with a remnant kidney model in dogs with variable levels of volume expansion and serum bicarbonate, noted that the ratio of absolute bicarbonate to sodium reabsorption was increased in CKD. In addition, Wong and associates,[145] using a micropuncture method, showed that this ratio was also higher at the beginning of the distal tubule, indicating avid bicarbonate absorption by the proximal tubule of the remnant kidney. Although absolute absorption was higher, the absolute amount of bicarbonate delivered to the distal tubule was also higher, reflecting the marked increase in filtered load per nephron owing to an increase in single nephron GFR.[145] In summary, the whole kidney T_m for bicarbonate is, in general, diminished in CKD despite an absolute increase in bicarbonate resorption at the single nephron. The discrepancy in these findings may reflect the variation in the experimental designs and the role of nonvolume regulators in bicarbonate handling by the kidney.

Renal Excretion of Titratable Acid

The excretion of titratable acids chiefly reflects the amount of urinary phosphate and the urinary pH. Most CKD patients are able to maximally acidify their urine,[135,146] and urine-serum PCO_2, as a measure of hydrogen pump activity in the distal tubule, is normal.[147] The amount of titratable acids in these patients is normal.[137,138–150] This is primarily owing to an increase in the fractional excretion of phosphate initiated by secondary hyperparathyroidism. It should be noted, however, that urinary phosphate does decrease with severe renal failure. This reflects both a decrease in dietary phosphate as well as the effect of phosphate binders commonly used in these patients.

Renal Excretion of Ammonium

Although bicarbonaturia may contribute to metabolic acidosis, the major abnormality is a decrease in renal excretion of ammonium. Ammonium is primarily produced by the deamination of amino acids, chiefly glutamine, in the proximal tubule and, to a much lesser extent, in the loop of Henle and the distal convoluted tubule.[130,131] This is reviewed in detail in Chapter 7, Renal Acid–Base Transport and will not be reviewed here. In CKD, fractional renal ammonium excretion initially increases by severalfold, thereby resulting in the maintenance of a normal absolute excretion rate.[151] However, as the GFR decreases below 20 mL per minute, despite a maximal increase in fractional excretion of ammonium, the absolute excretory rate decreases significantly. Thus, progressive metabolic acidosis results. This decrease in the rate of ammonium excretion also reflects a decreased ability of the kidney to trap ammonia in the collecting duct.[146] Warnock[139] has suggested that the decrease in ammonia trapping in the remnant kidney model may be secondary to excess delivery of bicarbonate to the collecting duct, thereby resulting in an unfavorable environment for the diffusion and trapping of ammonia.

The role of aldosterone in ammonium excretion is complex. Aldosterone increases the rate of Na^+-dependent and Na^+-independent H^+ secretion in the cortical and medullary collecting duct.[152,153] Hypoaldosteronism is associated with a decrease in the rate of H^+ secretion, whereas the ability to maintain a steep H^+ gradient between urine and plasma, as measured by urinary pH and urine minus blood PCO_2 in alkaline urine, is not affected.[154,155] The decrease in the rate of H^+ secretion is associated with a decrease in the availability of ammonium buffer in the urine that is not augmented appropriately in response to sodium sulfate infusion.[156,157] Hypoaldosteronism is universally associated with a decreased potassium excretion and hyperkalemia. Hyperkalemia decreases renal ammonium excretion significantly. A decrease in accumulation of ammonium in the renal interstitium despite normal production by the proximal tubule underlies this effect.[158] In the syndrome of hyperkalemic renal tubular acidosis, this mechanism probably plays the major role in the production of hyperchloremic acidosis seen early in the course of renal failure (Fig. 72.7).[159] Reversal of hyperkalemia with sodium binding resin,[160] mineralocorticoids,[161] or low-potassium diet[162] ameliorates the metabolic acidosis by increasing ammonium secretion.

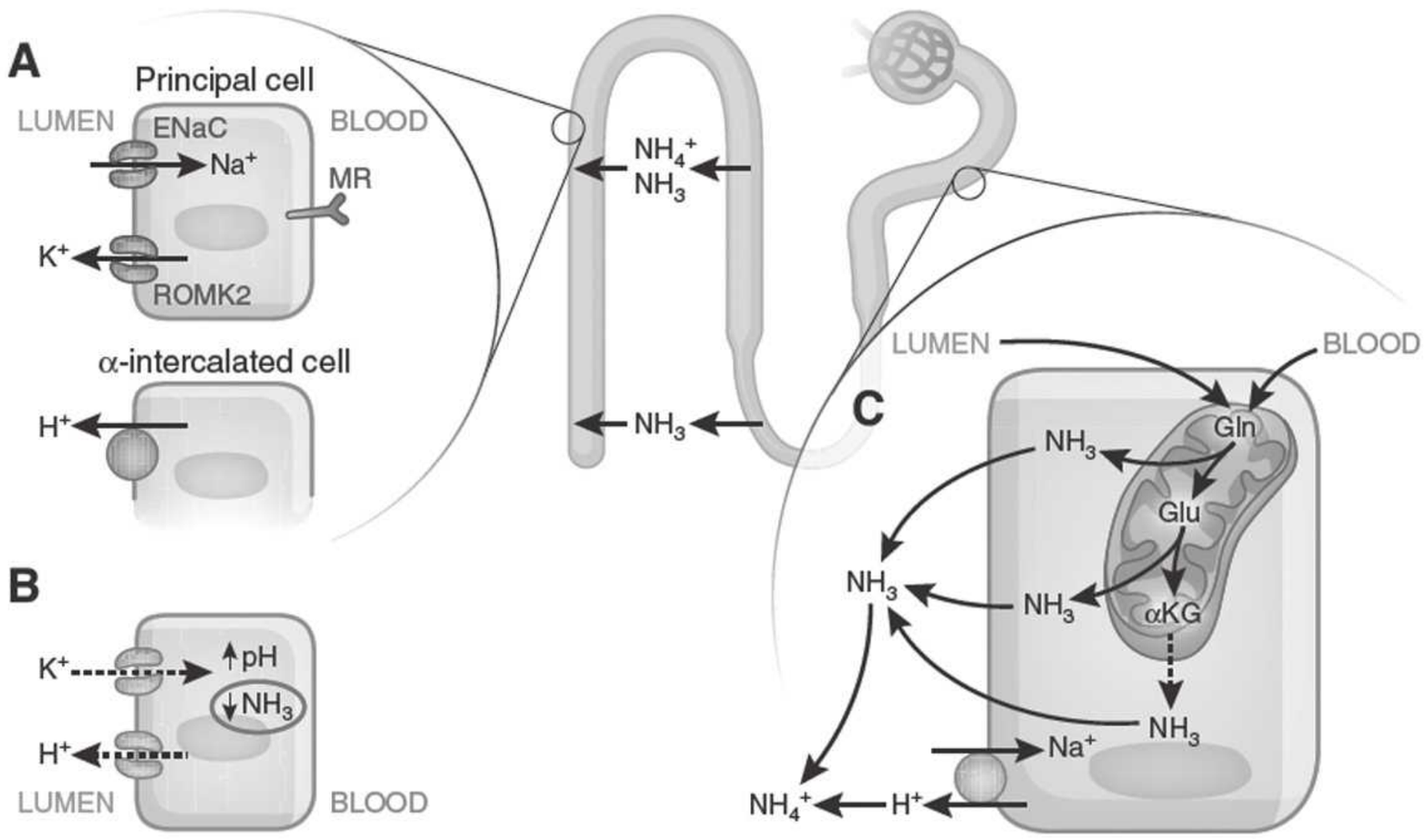

FIGURE 72.7 The factors involved in hyperkalemic acidosis. **A:** ENaC function at the apical surface of principal cells allows potassium secretion by ROMK (potassium channels) and the hydrogen ion by adjacent intercalated cells. **B:** Hyperkalemia increases intracellular pH by proton exchange, impairing the enzyme involved in ammoniagenesis. **C:** The process of ammoniagenesis involves deamination of glutamine, which allows ammonia to buffer the hydrogen ion in the urine. Ammonia and ammonium are reabsorbed in the medullary loop and are then excreted in the urine in the distal nephron. (From Karet FE. Mechanisms in hyperkalemic renal tubular acidosis. *J Am Soc Nephrol*. 2009;20:251, with permission.)

In summary, the metabolic acidosis develops universally in all patients with CKD as GFR decreases to below 20 mL per minute. The pathogenesis of this disorder is complex and reflects renal defect in both resorption as well as the generation of bicarbonate. The major mechanism, however, is in a decrease in absolute ammonia excretion despite the presence of acidosis.

HYPERKALEMIC RENAL TUBULAR ACIDOSIS OWING TO A DEFECT IN RENIN–ANGIOTENSIN–ALDOSTERONE AXIS OR TUBULAR UNRESPONSIVENESS TO ALDOSTERONE

Although a decrease in GFR may be associated with the development of significant hyperkalemia and hyperchloremic (HCA) or anion gap metabolic acidosis, this usually occurs only with severe reductions in GFR, below 15 to 20 mL per minute. However, some patients with underlying renal disease and mild-to-moderate azotemia present with striking hyperkalemia with or without HCA. The elevated serum potassium in these patients is primarily owing to a disturbance in the renin–angiotensin–aldosterone axis or to renal tubular responsiveness to aldosterone (see Fig. 72.6 and Table 72.2). Since the report by Hudson and associates,[163] numerous cases have been described in which hyperkalemia with or without HCA developed in the presence of only mild-to-moderate renal insufficiency.[164] The majority of these cases are diabetic or hypertensive nephropathy or chronic interstitial nephritis.[165] In 1972, Schambelan and colleagues[166] presented evidence linking hypoaldosteronism with hyporreninism in six patients with this syndrome. This association was verified in subsequent reports,[167–170] and the entity became known as hyporeninemic hypoaldosteronism (HHA). However, it quickly became clear that a significant minority of these patients had normal renin levels. DeFronzo,[171] in 1980, after reviewing 81 published cases, came to the conclusion that in 20% of cases the low plasma aldosterone levels could not be explained by renin deficiency, and therefore a primary abnormality in aldosterone synthesis had to be postulated. At the same time, some patients with sickle cell disease,[172,173] systemic lupus erythematosus,[174–177] and renal transplantation[178–180] have a renal tubular secretory defect resulting in hyperkalemia despite a normal renin–aldosterone axis. Therefore, at the present time, these patients can be divided into two large categories: (1) hyperkalemia resulting from hypoaldosteronism with or without hyporreninism; and (2) hyperkalemia resulting from a primary renal tubular potassium secretory defect. One could consider this entity as a spectrum ranging from pure aldosterone deficiency with normal tubular responsiveness to severe tubular resistance with normal aldosterone secretion. Between these two extremes there are many overlapping presentations in which either the defect in the hormonal axis or the tubular responsiveness dominates. Although Table 72.2 summarizes all the hormonal or tubular defects that can lead to hyperkalemia,

72.2 Etiology of Chronic Hyperkalemia Due to Disturbances in Renal Potassium Excretion

I. Decrease in GFR
   A. Acute renal failure
   B. Chronic kidney disease (GFR < 15–20 mL/min)
II. Defect in renal tubular secretion of potassium
   A. Disturbance in the renin–angiotensin–aldosterone axis
      1. Hyporeninism: associated with renal insufficiency (diabetes mellitus, interstitial nephritis)
      2. Disturbance in angiotensin II activation or function (captopril, saralasin)
      3. Hypoaldosteronism
         a. With glucocorticoid deficiency (Addison disease, enzyme deficiency)
         b. Block in aldosterone synthesis (heparin, 18-methyloxidase deficiency)
         c. Primary hypoaldosteronism
   B. Tubular resistance to the action of aldosterone (renal tubular hyperkalemia)
      1. Pseudohypoaldosteronism
      2. Hyperkalemia, hypertension, and normal renal function
      3. Hyperkalemia with mild-to-moderate renal insufficiency and variable plasma aldosterone levels (sickle cell disease, systemic lupus erythematosus, renal transplant, obstructive uropathy, miscellaneous)
      4. Pharmacologic inhibition of the tubular action of aldosterone (spironolactone, eplerenone, triamterene, amiloride, pentamidine, trimethoprim) in distal nephron

GFR, glomerular filtration rate.

often with HCA, our discussion is limited to the disturbances associated with renal insufficiency.

Hyperkalemic Renal Tubular Acidosis Owing to a Defect in Renin–Angiotensin–Aldosterone Axis

This group comprises approximately 80% of the patients with renal insufficiency and hyperkalemia.[171,181–183] The hallmark of this group is a low plasma aldosterone concentration. The majority (80%) of this group also has low plasma renin activity (PRA) and therefore represents the classic syndrome of HHA. However, 20% have a normal PRA. Clinically and physiologically, these patients present with fairly uniform features. Several large series[166,184] have defined the characteristics of these patients first summarized in a review by DeFronzo.[171] These include: (1) a mean age of about 60 years, (2) the presence of diabetes mellitus in about 50%, (3) the presence of mild-to-moderate renal failure in the majority, and (4) a lack of symptoms referable to hyperkalemia in 75%. Physiologic features include: (1) low or low-normal baseline and/or stimulated aldosterone levels, (2) normal plasma cortisol, (3) low baseline and/or stimulated renin values in 80%, (4) normal aldosterone response to angiotensin or adrenocorticotropic hormone (ACTH) stimulation in the minority, (5) presence of hyperchloremic acidosis in well over 50%, and (6) a lack of significant salt wasting.

To gain an understanding of the physiologic basis of this syndrome, we initially review the defect in renin secretion and then summarize our present understanding of aldosterone deficiency in this syndrome.

Hyporreninism

At present, no single abnormality can explain the low PRA seen in 80% of these patients.[171,182,183] Evidence has been presented in support of a defect in one or more physiologic regulators of renin secretion including volume, autonomic nervous system, serum potassium concentration, and prostaglandins.

Oh and colleagues,[169] Perez and colleagues,[185] and others[186,187] have demonstrated that long-term sodium and volume depletion in these patients is associated with a significant increase in the PRA. However, comparable data in normal controls with the same degree of volume depletion were not provided. In the report of Oh and colleagues,[169] after 3 to 6 weeks of salt depletion, the PRA rose into the normal range, but plasma aldosterone remained subnormal. In the study by Chan and coworkers, 8 of the 12 patients with hyporreninism responded to 2 weeks of furosemide with an increase in PRA without a similar response in plasma aldosterone.[187] In a study of four patients with acute postinfectious glomerulonephritis,[155] plasma renin and aldosterone concentrations were low during the acute phase, but returned to normal following recovery from acute nephritis. Interestingly, in two patients, the renin and aldosterone levels remained low during the acute phase despite an excellent response to diuretics. These two patients, however, responded appropriately to

physiologic doses of fludrocortisone. This study,[155] coupled with previous studies of acute glomerulonephritis,[188,189] supports the concept that although physiologic suppression of the renin–aldosterone axis by volume expansion may play a significant role in certain patients with glomerular disease, hypertension, and edema, other factors such as decreased GFR and damage to the juxtaglomerular apparatus play an important contributory role. Gordon and colleagues[190] have described a patient with hypertension, acidosis, hyperkalemia, and normal renal function associated with HHA. Prolonged sodium restriction resulted in a correction of these abnormalities. A similar pathophysiologic mechanism has been postulated in hypertensive patients with hyperkalemia and renal insufficiency.[191]

The autonomic nervous system plays an important physiologic role in the regulation of renin secretion. Sympathetic nerve terminals are known to innervate the juxtaglomerular apparatus, and renin secretion is stimulated by epinephrine.[192,193] Therefore, autonomic insufficiency could result in a state of hyporreninemia. This hypothesis has been investigated primarily in diabetic patients, in whom autonomic neuropathy is common and circulating catecholamine levels are often low.[194] In five diabetic patients with autonomic neuropathy, Tuck and colleagues[195] reported low basal PRA as well as diminished plasma aldosterone and norepinephrine concentrations. In addition, the infusion of isoproterenol, a β-adrenergic agonist, did not increase PRA, indicating a possible block at or beyond the receptor level. In contrast, normal circulating catecholamine levels have previously been reported in diabetic patients with the syndrome of hypoaldosteronism.[154,167,196,197] Fernandez-Cruz and coworkers[198] compared stimulated PRA in 16 normotensive diabetic patients without overt nephropathy and 9 age-matched controls. The stimulated PRA was significantly lower in these patients and correlated directly with the degree of autonomic dysfunction as measured by the velocity of esophageal peristalsis. de Chatel and colleagues,[199] however, were unable to demonstrate in a large group of diabetic individuals any correlation between the plasma epinephrine concentration and abnormalities in the renin–aldosterone axis. Therefore, although autonomic neuropathy may play a role in the development of hypoaldosteronism in some diabetic patients, it is not a uniform finding and certainly cannot explain the occurrence of this syndrome in nondiabetic patients.

Hyperkalemia is known to inhibit PRA[200]; consequently, one could hypothesize that hyporreninemia is not a primary defect but is secondary to hyperkalemia. In two studies,[166,170] short-term normalization of serum potassium did not increase PRA significantly; however, long-term studies have not been undertaken to examine this very important question.

Prostaglandins E_2, I_2, and D_2 are known stimulators of renin release,[201,202] whereas prostaglandins E_1 and E_2 directly increase aldosterone biosynthesis in vitro.[203] Furthermore, hyperkalemia has been reported following treatment with indomethacin, a potent prostaglandin inhibitor[204] as well as selective cyclooxygenase-2 (COX-2) inhibitors,[205] suggesting that a defect in prostaglandin synthesis may play a role in the development of HHA in some hyperkalemic patients. Consistent with this possibility, Tan and colleagues[206] found a strong correlation between urinary PGE_2 levels and the ratio of active to inactive renin in normal controls and in patients with the syndrome of hypoaldosteronism. In four of the nine patients, low urinary PGE_2 was associated with a low ratio of active to inactive renin. In normal controls, the inhibition of prostaglandin synthesis with indomethacin resulted in a similar decrease in this ratio. These authors postulated that prostaglandins may play a critical role in the activation of renin, and therefore hypoaldosteronism in these patients may be secondary to a prostaglandin deficiency. In two patients with diabetes mellitus and hypoaldosteronism, the total renin concentration was normal, whereas PRA was low.[207] The fractionation of the plasma yielded an inactive renin precursor (prorenin or "big renin"); unfortunately, prostaglandin levels were not measured in these diabetic patients. It should be noted, however, that other investigators have failed to find an association between prostaglandin deficiency and the development of HHA.[208]

Another hypothesis that links CKD with hyporreninism is fibrosis of the juxtaglomerular apparatus owing to intrinsic renal disease. Although occasional reports of juxtaglomerular apparatus fibrosis have appeared,[187] this is a rare finding. Besides, the presence of juxtaglomerular apparatus damage alone does not explain the development of hypoaldosteronism.

Hyperfiltration hypothesis has been linked to the development of HHA in both diabetic and nondiabetic CKD patients.[209] According to this hypothesis, as the number of nephrons is reduced, there is an adaptive increase in the renal plasma flow and GFR by the remaining functioning glomeruli. These alterations in renal hemodynamics serve to inhibit renin synthesis and release, leading secondarily to the development of hypoaldosteronism.

Hypoaldosteronism

The hallmark of the syndrome of HHA is a low basal or low stimulated plasma aldosterone level in spite of normal levels of glucocorticoids and other ACTH-dependent steroids such as DOCA or corticosterone. Aldosterone secretion is primarily stimulated by the renin–angiotensin system. However, ACTH and serum potassium, as well as other regulators, play independent roles.

As stated previously, hyporreninemia is present in 80% of patients with hypoaldosteronism,[171,179,183] and therefore it is logical to consider that the primary defect in these patients lies in renin synthesis or release. Schambelan and colleagues[183] showed that the stimulation of renin by volume contraction resulted in a rise in plasma aldosterone that was appropriate for the increase in PRA. The slope of the curve relating plasma renin and aldosterone was similar in patients with HHA and normal controls. Surprisingly, for any given level of PRA,

the plasma aldosterone concentration was disproportionately elevated, probably because of the independent stimulatory effect of plasma potassium on aldosterone secretion. Nevertheless, the highest levels of renin and aldosterone achieved in these patients were comparable only to the basal levels in control subjects. In contrast, as indicated, other investigators have found a clear disconnect between renin and aldosterone level after stimulation with volume depletion[185–187] and captopril.[187] In all studies, however, the response of aldosterone was significantly blunted despite increased renin and persistent hyperkalemia. In addition, most investigators have reported a marked impairment in the ability of angiotensin II (AT-II) to stimulate aldosterone secretion.[171,183] This finding, coupled with a subnormal aldosterone response to ACTH stimulation, and the failure of hyperkalemia to stimulate aldosterone secretion, has strengthened the possibility of a primary adrenal defect in some patients with hypoaldosteronism. This is further supported by the observation that 20% of patients with hypoaldosteronism have normal PRA.[171,179,183] It is possible that the poor response of aldosterone to ACTH, AT-II, and hyperkalemia may be secondary to long-term atrophy of the zona glomerulosa of the adrenal gland rather than to a specific enzymatic defect in aldosterone production. Consistent with this possibility, Fredlund and colleagues[210] provided evidence in isolated adrenal glomerulosa cells that the aldosterone response to hyperkalemia is dependent on the circulating angiotensin level. However, no study so far has evaluated the response of the adrenal gland to prolonged stimulation by AT-II in patients.

The serum potassium concentration is an important regulator of the plasma aldosterone level.[211–213] In nephrectomized patients, a significant correlation between serum potassium and plasma aldosterone exists,[214] and this relationship is independent of renin or ACTH. Therefore, in interpreting a given plasma aldosterone level, the effect of serum potassium must be considered. Schambelan and colleagues[183] categorized 31 patients into two groups based on the ratio of urinary aldosterone excretion to serum potassium concentration. Group A (23 patients) had a low ratio and was considered to have hypoaldosteronism. Group B (8 patients) had a normal ratio and was considered to have a primary tubular defect in potassium secretion. In group A, 20% had a normal PRA. Therefore, hypoaldosteronism in this group, in spite of normal PRA and high plasma potassium, is probably owing to a defect in aldosterone synthesis.

Another regulator of aldosterone secretion and plasma volume is atrial natriuretic factor (ANF). ANF has been shown to be a strong inhibitor of baseline as well as stimulated aldosterone in humans.[215,216] In normal humans, ANF also prevents a potassium-stimulated rise in the aldosterone level.[217] In addition, the ANF level is markedly elevated 10- to 50-fold in patients with hypoaldosteronism.[217] Although the rise in ANF (and the suppression of aldosterone) could be secondary to volume expansion, ANF also suppresses potassium, angiotensin, and ACTH-stimulated aldosterone secretion, supporting the presence of a common cellular mechanism for its action possibly through the stimulation of cyclic guanosine monophosphate (cGMP).[218]

Several investigators have explored the possibility of an enzymatic defect in aldosterone biosynthesis,[185,197,200] and an enzymatic block involving the conversion of 18-hydroxycorticosterone to aldosterone has been postulated, but these findings have not been supported by other studies.[219,220]

As indicated, diabetic patients constitute a large percentage of patients with HHA. To explain this high incidence, two other postulates have been presented. Insulin is an important regulator of potassium uptake by a variety of tissues, and chronic hypoinsulinemia (absolute or relative) might be expected to result in a state of intracellular potassium deficiency. Furthermore, intracellular potassium concentration is an important regulator of aldosterone synthesis.[171] Potassium-deficient cultured zona glomerulosa cells have a blunted aldosterone response to AT-II and ACTH.[210,221] Insulinopenia, by decreasing intracellular potassium, may lead to a defect in aldosterone synthesis and the syndrome of hypoaldosteronism. A second hypothesis is offered by Smith and DeFronzo[222] and involves the concept of tubuloglomerular feedback. Normal tubuloglomerular balance is disrupted in the presence of osmotic agents in the renal tubule,[223,224] including glucose.[225–227] It is postulated that, in diabetic patients with a high filtered glucose load, sodium chloride delivery out of the proximal tubule is enhanced, leading to an increased delivery of solute to the loop of Henle. Enhanced chloride reabsorption by the thick ascending limb of Henle (TALH) may inhibit renin secretion,[228] which secondarily leads to the development of hypoaldosteronism.

In summary, at present, a unified etiologic hypothesis cannot explain the occurrence of the syndrome of HHA in different patients. It is likely that this syndrome is quite heterogeneous and can be explained only by multiple etiologic abnormalities. In a given patient, the role of different regulatory systems (i.e., volume status, prostaglandins, ANF, autonomic nervous system, structural damage to the juxtaglomerular apparatus, enzymatic defects in aldosterone and renin biosynthesis, and intracellular adrenal potassium deficiency) should be considered and evaluated.

Hyperkalemic Renal Tubular Acidosis Owing to a Renal Tubular Secretory Defect

This group of disorders (see Table 72.2 and Fig. 72.8) includes patients who have hyperkalemia out of proportion to the degree of renal failure or hypoaldosteronism. The primary defect is a partial resistance to the physiologic effect of aldosterone to promote potassium secretion. Perez and coworkers[229] named this syndrome renal tubular hyperkalemia and divided it into three groups: group I, patients with pseudohypoaldosteronism; group II, patients with hyperkalemia, hypertension, and normal renal function; and group III, patients with hyperkalemia, mild-to-moderate renal insufficiency, and normal-plasma aldosterone (group IIIa), low-plasma aldosterone (group IIIb), or high-plasma aldosterone (IIIc) (Table 72.2).

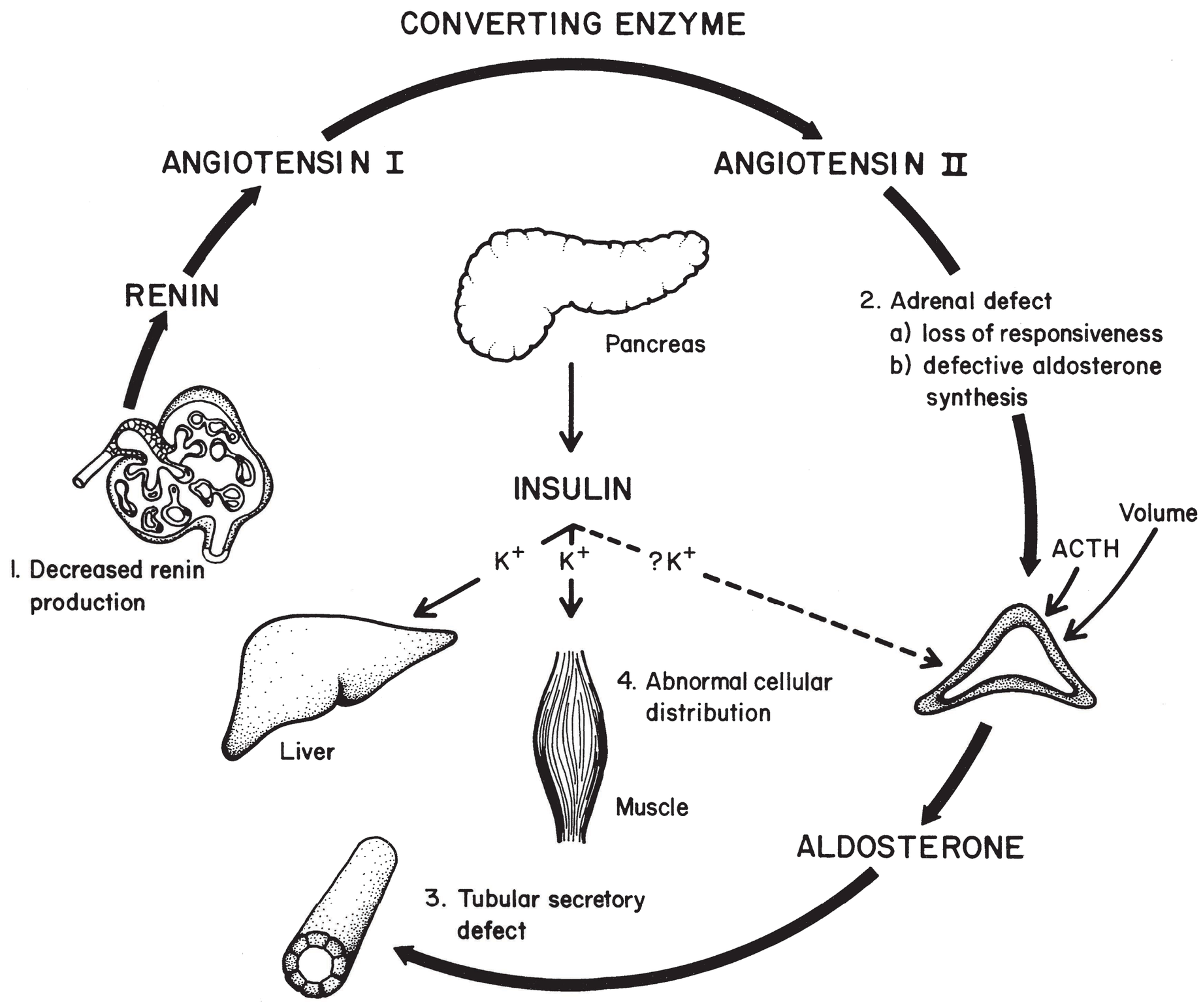

FIGURE 72.8 A schematic representation of potential hormonal, renal, and extrarenal defects resulting in hyperkalemia. Hyperkalemia may result from one of the following conditions: (**1**) decreased renin production, (**2**) decreased aldosterone production despite normal renin secretion (adrenal defect), (**3**) a renal tubular secretory defect, or (**4**) an abnormal distribution of potassium between intracellular and extracellular fluid compartments. ACTH, adrenocorticotropic hormone. (From DeFronzo RA, et al. Nonuremic hypokalemia: a possible role for insulin deficiency. *Arch Intern Med.* 1979;137:842, with permission.)

Groups I and II represent examples of a pure tubular secretory defect without renal insufficiency and are not discussed here. In this section we deal only with group III patients, who present with mild-to-moderate renal insufficiency, hyperkalemia, hyperchloremic acidosis, variable plasma renin and aldosterone levels, and resistance to physiologic doses of mineralocorticoids. This clinical entity has been described in patients with sickle cell disease, systemic lupus erythematosus, renal transplant, obstructive uropathy, AIDS, and a group of miscellaneous diseases including lead nephropathy and chronic interstitial nephritis.

Sickle Cell Disease

A renal tubular potassium secretory defect in sickle cell disease was first reported in patients with normal renal function and normal serum electrolyte concentrations[7] and, later, in patients with sickle cell nephropathy,[171,230] sickle cell trait,[172] and sickle cell disease.[173] Although basal and stimulated aldosterone levels were normal in all subjects, these patients were unable to excrete a potassium load normally. The infusion of potassium chloride, sodium sulfate, and furosemide failed to augment potassium secretion normally. This defect is thought to result from ischemic damage to the collecting tubules and medullary area by sickle cells. An immunologic reaction against a renal tubular antigen also has been suggested. It should be noted that the syndrome of HHA also occurs in sickle cell disease.[171,230]

Systemic Lupus Erythematosus

Patients with systemic lupus erythematosus (SLE) may have multiple tubular defects, including type I and IV RTA.[176,177] In the largest study of 30 patients with active SLE, 18 patients had defects in the handling of potassium, sodium, and/or hydrogen ions. Eight patients had distal renal tubular acidosis (dRTA) due to an isolated proton secretory defect. Five had dRTA of the gradient or acid back leak type.

Three had voltage-dependent dRTA. One individual had hyporeninemic hypoaldosteronism and one had dRTA plus hypoaldosteronism. Clinically, patients with the abnormal tubular study results more often presented with nephritis or nephrotic sediment, peripheral edema, or anemia.[176] A defect in potassium secretion, similar to the defect in sickle cell disease, has also been reported in several patients with SLE.[174,175] The defect is often accompanied by a defect in hydrogen ion secretion.[174,175,231] In a study of two patients with SLE and hyperkalemic RTA, Bastani and associates[232] showed the presence of autoantibodies to collecting duct cells in one patient. The serum from the patient with autoantibodies labeled the intercalated cell in rat kidney section. However, the serum from both patients did not react with the affinity-purified bovine H^+ATPase or human H^+ATPase beta subunit. This is in contrast to the finding in a single patient with Sjögren syndrome who had an absence of vacuolar H^+ATPase in intercalated cells.[233] These findings support the concept that cellular and molecular mechanisms in these patients probably are heterogeneous in nature.

Obstructive Uropathy

Hyperkalemic RTA, as a complication of obstructive uropathy, is common and best described in a report of 13 patients by Batlle and associates.[181] Two patterns were noted: (1) Five patients had normal plasma aldosterone levels but failed to increase urinary potassium excretion after the administration of acetazolamide, fludrocortisone, and sodium sulfate. The primary defect in this group is renal tubular unresponsiveness to aldosterone. (2) Eight patients had low plasma aldosterone levels but failed to augment renal potassium excretion with mineralocorticoid administration. As noted, this reflects a combined defect in this group. Furthermore, urinary acidification in response to systemic acidosis and sodium sulfate infusion was abnormal in 8 of 13 patients. In a rat model of acute ureteral obstruction, no change in the number or tubular distribution of vacuolar H^+ATPase was noted; however, the intracellular distribution was changed with a significant decrease in plasma membrane bound pumps in intercalated cells.[234] This finding may explain hyperchloremic metabolic acidosis (HMA), which is commonly noted in these patients.

Renal Transplantation

In the precyclosporine era, hyperkalemia was a relatively unusual phenomenon following a successful renal transplantation.[179,180,235] However, two series from Australia and the United States[179,180] and a series from Israel[236] have reported the occurrence of renal tubular hyperkalemia in this group. In the largest series, 23 of 75 patients with a successful kidney transplant had hyperkalemia unrelated to rejection episodes, renal failure, oliguria, or acidosis.[180] The renin–angiotensin–aldosterone axis was normal in these patients, and hyperkalemia did not respond to furosemide. The hyperkalemia was transient, disappearing spontaneously, and did not correlate with clinical or laboratory evidence of rejection. In contrast, in two patients studied by Batlle and coworkers,[235] hyperkalemia was associated with very low levels of aldosterone, which did not respond to volume contraction. Urinary potassium was low and did not respond to the infusion of sodium sulfate or acetazolamide. The etiology of this disorder is not clear, but immunologic damage to the renal tubular cells is postulated.[180] In the cyclosporine era, hyperkalemia is more common in kidney transplant recipients.[180,237,238]

In a study of 12 transplant patients on cyclosporine, Kamel et al.[238] noted low renin and aldosterone levels associated with a poor response to fludrocortisone. Transtubular potassium gradients (TTKGs), however, rose significantly with bicarbonaturia initiated with acetazolamide, supporting the hypothesis that a tubular defect was due to an inability to generate a favorable electrical and chemical gradient in the cortical collecting duct.[238] In a recent series of 567 transplant patients for more than 12 months and GFR $>$ 40 mL per minute, RTA was diagnosed in 76 (13%). Using standard tools including urine pH, urine anion gap, as well as bicarbonate loading, the authors divided the group as follows: 28 (37%) with classical RTA, 11 (14%) with classical RTA but with elevated potassium, and 37 (49%) with type IV RTA (some with normal potassium). In multivariate analysis, the presence of RTA correlated with lower GFR, higher parathyroid hormone (PTH) level, the use of tacrolimus, and renin–angiotensin blockers. It was estimated that the use of renin–angiotensin blockers accounted for 25% of patients with RTA.[180]

Hyperkalemic Renal Tubular Acidosis Associated with AIDS

Acid–base and electrolyte disturbances, with or without renal failure, are common in patients with AIDS. As reviewed by Perazella and Brown,[239] the incidence varies from 5% to 53% and is owing to a variety of causes including adrenal insufficiency, renal failure, type IV RTA, and finally as a complication of drugs used in these patients.[240] The syndrome of hyporenin–hypoaldosteronism is relatively uncommon and usually is associated with HIV-related nephropathy. Patients with AIDS are exposed to a variety of drugs that could result in hyperkalemia, which is often associated with HCA and/or renal insufficiency.

Miscellaneous Conditions

Renal tubular hyperkalemia has been reported in a variety of other renal diseases. These include chronic interstitial nephritis of unknown etiology,[241] nephrosclerosis,[184] diabetes mellitus,[183] postinfectious glomerulonephritis,[188,189] lead nephropathy,[242] and drug-induced acute interstitial nephritis.[243] Although in our experience this entity seems to be relatively common in nonspecific interstitial nephritis, no incidence or prevalence data are available.

Drugs Associated with Hyperkalemia in Patients with Kidney Disease

In patients with underlying kidney disease, prescribed drugs or over-the-counter medications and supplements play an increasingly dominant role in the development of hyperkalemia. It is therefore important to recognize that a variety of products are capable of elevating serum potassium concentration through multiple mechanisms (Table 72.3). Hyperkalemia, depending on the criteria used, has been reported to develop in anywhere from 1.3% to 10% of patients and is often multifactorial. Of the many factors involved, culprit medications, either alone or in association with other disturbances in potassium homeostasis, were a contributing cause of hyperkalemia in 35% to 75% of hospitalized patients.[244–248] Of note, kidney disease and older age (> 60 years) were important predisposing risk factors in many studies.[244–246]

Increased Potassium Input

Enteral and parenteral inputs of potassium are very common causes of hyperkalemia in hospitalized patients. Nonetheless, chronic hyperkalemia does not occur with these products unless an underlying defect in potassium homeostasis also is present. Deliberate potassium intake often lies at the root of hyperkalemia, although unsuspected potassium delivery also occurs. A 3.6% incidence of hyperkalemia among 4,921 patients taking physician-prescribed potassium supplements was documented in the Boston Collaborative Drug

72.3 Common Drugs That Cause Hyperkalemia and the Mechanism of Action

Medication	Mechanism of Action
Potassium supplement	Increase intake
Salt substitutes	Increase intake
Nutritional/herbal supplements	Increase intake
β_2-blocking agents	Decrease potassium movement into cells, decrease renin/aldosterone
Digoxin intoxication	Decrease Na^+-K^+-ATPase activity
Lysine, arginine, and ε-aminocaproic acid	Shift of potassium out of cells
Succinylcholine	Shift of potassium out of cells
Potassium-sparing diuretics	
Spironolactone, eplerenone, drospirenone	Aldosterone antagonism
Triamterene	Block Na^+ channels in principal cells
Amiloride	Block Na^+ channels in principal cells
NSAIDs, COX-2 selective inhibitors	Decrease renin/aldosterone Decrease RBF and GFR
ACE inhibitors and AT-II	Decrease aldosterone synthesis
receptor antagonists	Decrease RBF and GFR
Heparin	Decrease aldosterone synthesis
Trimethoprim and pentamidine	Block Na^+ channels in principal cells
Cyclosporine and tacrolimus	Decrease aldosterone synthesis Decrease Na^+-K^+-ATPase activity Decrease K^+ channel activity

NSAIDs, nonsteroidal anti-inflammatory drugs; COX-2, cyclooxygenase-2; GFR, glomerular filtration rate; ACE, angiotensin-converting enzyme; AT-II, angiotensin II.

Surveillance Program.[244] The mean peak K^+ concentration in these patients was 6.0 mEq per liter, whereas a level greater than 7.5 mEq per liter was noted in 13 of the 179 patients (7.3%). Azotemia and older age were more frequent among those with hyperkalemia. In addition, several other studies reveal that potassium supplements cause or contribute to hyperkalemia in 15% to 40% of hospitalized patients.[245–248]

The new Dietary Guidelines for Americans stresses the importance of reducing sodium intake and increasing dietary potassium. As a result, food manufacturers have focused on meeting these guidelines by replacing sodium in their products with potassium-based alternatives. Potassium salt substitutes and alternatives, which provide a rich source of potassium, are not new but are recently receiving a second look from food processors.[249] Pressure exerted by the government and public health advocates to reduce dietary sodium has led the food industry to experiment with salt substitutes. Manufacturers also assert that improved product formulas significantly reduce the metallic aftertaste often noted with potassium chloride, thereby making it more palatable. Some potassium salt substitutes contain 10 to 13 mEq of potassium per gram.[250]

A number of nutritional supplements contain as much as 49 to 54 mEq of potassium per liter, whereas foods prepared as low sodium contain greater amounts of potassium (because potassium replaces sodium in these foods). As a result, enteral feeds employing these products and some herbal remedies, such as noni juice (K^+, 56.3 mEq per liter) can deliver excessive amounts of potassium to patients with impaired potassium homeostasis.[251] An emerging source of potassium in foods is so-called "enhanced" fresh meat, which is injected with a solution of water with sodium and potassium salts. Food companies claim that this salt-based injection ensures that meat will be tender and tasty despite how it is cooked by the consumer. In an analysis of the potassium content of 36 fresh meat products purchased from local grocery stores, enhanced products often contained 2 to 3 times more potassium than comparable cuts of nonenhanced meat.[252] Most concerning was the absence of potassium content on most labels.

Another unsuspected source of potassium excess in the hospital includes the antibiotic penicillin G potassium (1.7 mEq of K^+ per 1 million units), which can cause hyperkalemia if administered in sufficiently high doses.[254] The urinary alkalinizing agent potassium citrate (2 mEq of potassium per 1 mL), and packed red blood cells transfused after 10 or more days of storage (7.5 to 13 mEq of K^+ per liter) can precipitate hyperkalemia in at risk patients.[255,256] A potassium-containing cardioplegia solution employed during cardiac surgery may also cause hyperkalemia in patients with a defect in potassium handling.

Impaired Cellular Potassium Homeostasis

As discussed previously, the cellular uptake of a potassium load is the primary mechanism by which the body acutely prevents the development of hyperkalemia. Several commonly prescribed drugs can impair this protective cellular response. β-Adrenergic–blocking drugs through the inhibition of renin secretion as well as cellular uptake of potassium have been associated with the development of mild and, on rare occasions, life-threatening hyperkalemia.[257,258] Hyperkalemia often develops rapidly, as one would expect with the disruption of cellular potassium homeostasis, but rarely develops in the absence of heavy exercise or other risk factors for hyperkalemia.[3,258] As an example, three renal transplant recipients developed severe hyperkalemia (K^+ range 6.0 to 8.3 mEq per liter) within hours of treatment with intravenous labetalol.[259] Most studies evaluating hyperkalemia in hospitalized patients have shown that β-adrenergic blockers have caused or at least contributed to hyperkalemia in anywhere from 4% to 17% of patients.[248,260–262] Not unexpectedly, the hyperkalemic potential of β-adrenergic blockers is increased by underlying renal insufficiency, the coexistence of diabetes mellitus or hypoaldosteronism, and concurrent therapy with other medications that reduce renal potassium excretion.[256,257]

Digoxin, by blocking the Na-K-ATPase pump function, has also been demonstrated to disrupt potassium homeostasis.[263] As a result of this effect, the impaired cellular uptake of potassium as well as reduced renal potassium excretion occurs. In general, therapeutic digoxin levels do not lead to hyperkalemia but, in rare circumstances, can be a contributing factor.[263] Nonetheless, digoxin intoxication will result in hyperkalemia, which at times is fatal.[263,264]

Both natural (lysine, arginine) and synthetic (ε-aminocaproic acid) amino acids have been associated with hyperkalemia.[265–269] This is owing to the shift of potassium out of cells.[265–269] Levinsky and colleagues[265] demonstrated lysine uptake into isolated rat muscle within 1 hour in an amount equivalent to the potassium lost from the muscle tissue. In intact animals, the infusion of lysine was associated with hyperkalemia, with a 1.0 to 1.5 mEq per liter rise in plasma K^+ concentration noted for every 10 mEq per liter increase in plasma lysine concentration.[266] Hyperkalemia has also been described with intravenous arginine administration.[267–269] In normal humans, serum potassium increased by approximately 1 mEq per liter following the infusion of 30 to 60 g of arginine, whereas patients with ESRD developed a mean increase in serum K^+ of 1.5 mEq per liter at 2 hours after 30 g of intravenous arginine.[268] In two patients with mild renal insufficiency and liver disease, K^+ concentrations were 7.5 and 7.1 mmol per liter, respectively, after the infusion of arginine.[269] Serum potassium concentrations increased as early as 45 minutes after arginine infusion and peaked between 2 to 6 hours following injection, bespeaking a disturbance in cellular potassium homeostasis.[268,269] Hyperkalemia can also develop in subjects treated with the synthetic amino acid, ε-aminocaproic acid, which is structurally similar to both lysine and arginine.[270] A study in nephrectomized dogs demonstrated a significant rise in serum K^+ in animals administered intravenous ε-aminocaproic acid as either a constant infusion (2 or 4 g per hour) or a bolus injection

of 2.5 g.[270] Clinical relevance in humans was demonstrated in a case report where hyperkalemia (potassium, 6.7 mEq per liter) developed acutely in a patient with chronic renal insufficiency treated with ε-aminocaproic acid (three boluses of 10 g) to reduce perioperative blood loss during cardiac surgery.[271] The rapid onset of hyperkalemia following ε-aminocaproic acid therapy in this patient suggested that a cellular release of potassium was the cause of this electrolyte disturbance. In addition, Perazella and coworkers[272] in a retrospective study in patients undergoing cardiac surgery noted higher intraoperative serum potassium concentrations (K^+, 5.9 mEq per liter) in 232 patients treated with intravenous ε-aminocaproic acid as compared with 371 well-matched controls (K^+, 5.5 mEq per liter) who did not receive this medication. Other possible confounding factors did not explain the rapid development of hyperkalemia in these patients. It is therefore likely that intravenous ε-aminocaproic acid causes hyperkalemia through the cellular release of potassium in exchange for this synthetic amino acid.

The anesthetic agent succinylcholine, by the depolarization of the cell membrane, can cause hyperkalemia.[273–275] A rapid cellular potassium leak induced by these agents, resulting in the abrupt onset of hyperkalemia, has been demonstrated in muscle preparations in intact animals and humans. Plasma K^+ increased by 0.5 mEq per liter within 3 to 5 minutes in patients with normal muscle, whereas increases as high as 3.0 mEq per liter occurred in patients afflicted by trauma or nervous system disease.[4,300] In 12 patients with renal insufficiency, plasma K^+ concentration rose by 1.2 mEq per liter in one patient and up to 0.7 mEq per liter in the rest.[275]

An interesting study that examined the effect of the dual inhibition of the RAAS with 4 weeks of spironolactone and lisinopril as compared with placebo (randomized, crossover in 18 participants) noted a higher serum potassium concentration with drug therapy (4.87 mEq per liter versus 4.37 mEq per liter). However, using an hourly measurement of renal potassium excretion following a 35 mEq oral potassium challenge, the reduction in renal excretion (0.44 mEq per liter) did not entirely explain the increase in serum potassium (0.67 mEq per liter), suggesting an effect to reduce cellular potassium disposition.[276]

Impaired Renal Potassium Excretion

Although an increase in K^+ intake can contribute to hyperkalemia, impaired renal excretion almost always plays the dominant role in this process. Potassium-sparing diuretics are used to enhance renal sodium losses and diminish potassium excretion in patients with hypertension and edematous states.[277,278] Two basic mechanisms underlie the pharmacologic actions of these diuretics, which act to modulate principal cells residing in the collecting duct.[279] The aldosterone antagonists, spironolactone and eplerenone, compete with aldosterone binding to cytoplasmic aldosterone receptors, thereby preventing the nuclear uptake of the receptor and blunting aldosterone's effects on the principal cell.[280,281] Amiloride and triamterene directly block sodium channel activity in the luminal membrane of the principal cell, effectively inhibiting sodium reabsorption through the epithelium and decreasing the driving force for potassium secretion.[282,283] Moderate-to-severe hyperkalemia has been reported in 4% to 19% of patients treated with these medications.[261,280–292] In one small study, treatment with the combination of triamterene and hydrochlorothiazide resulted in hyperkalemia in 26% of the patients.[283] In a retrospective chart review, five patients were noted to develop severe hyperkalemia (K^+ concentrations in the 9.4 to 11 mEq per liter range) within 8 to 18 days of combination therapy with amiloride/hydrochlorothiazide and an angiotensin-converting enzyme (ACE) inhibitor.[286] All of these patients had diabetes and three had underlying CKD.

The combination of spironolactone and losartan increased plasma K^+ by 0.8 mEq per liter (up to 5.0 mEq per liter) and decreased urinary potassium excretion (from 108 to 87 mEq per liter) in eight normal subjects studied.[288] Hyperkalemia occurred most frequently in patients with preexisting renal insufficiency or diabetes mellitus, and those taking K^+ supplements or another medication that also impairs potassium excretion.[285,286,289–292] Several studies have demonstrated a brisk increase in the incidence of hyperkalemia from the use of either spironolactone or eplerenone in patients with heart failure following the publication of the Randomized Aldactone Evaluation Study (RALES) and Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trials.[293,294] For example, the spironolactone prescription rate increased from 34 per 1,000 patients in 1994 to 149 per 1,000 patients in 2001 following the publication of RALES.[294] This was associated with an increase in the rate of hospitalization for hyperkalemia (2.4 per 1,000 patients in 1994; 11.0 per 1,000 patients in 2001) (Fig. 72.9) and mortality (0.3 per 1,000 patients in 1994; 2.0 per 1,000 patients in 2001) in heart failure patients treated with ACE inhibitors.[294] In the EPHESUS trial, significant hyperkalemia ($K^+ > 6.0$ mEq per liter) developed in 5.5% of treated patients versus 3.9% in placebo-treated patients.[295] Hyperkalemia ($K^+ > 6.0$ mEq per liter) was most prevalent in patients with impaired kidney function (creatinine clearance < 50 mL per minute) as 10.1% of eplerenone-treated patients developed this complication as compared with 5.9% of placebo-treated patients.[295] However, these data are refuted by a population-based longitudinal analysis of patients in Scotland who were treated with spironolactone for heart failure, cirrhosis, and resistant hypertension before and after the publication of RALES.[296] Using the record linkage database, the number of spironolactone prescriptions, hospital admissions for hyperkalemia, and hyperkalemia and kidney function without admission were analyzed. The authors found that despite a significant increase in spironolactone prescriptions (2,847 in the first half of 1999; 6,582 in the second half of 2001; and 8,619 by 2007), there was not an increase in the number of admissions for hyperkalemia in 1995 before the publication

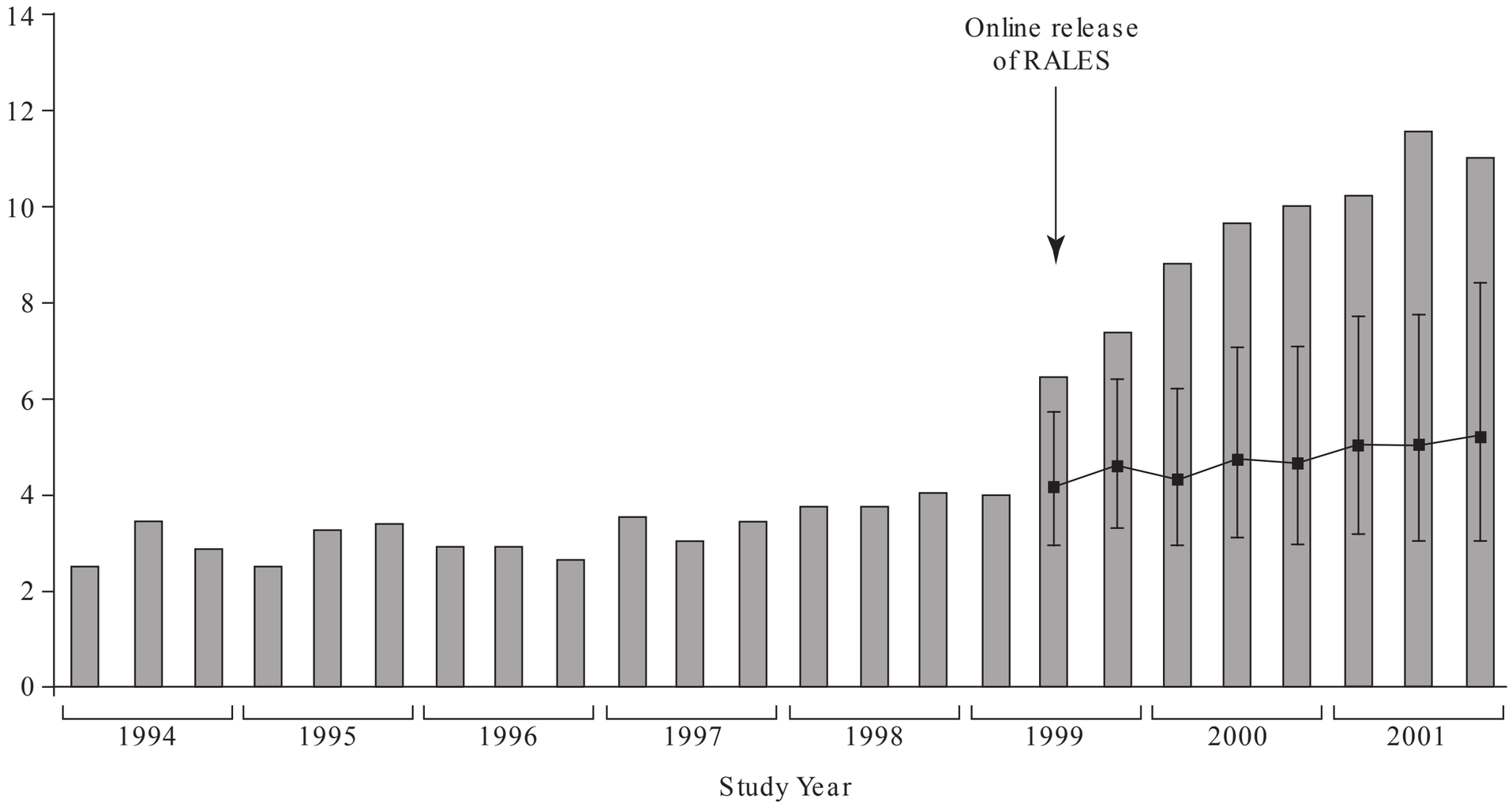

FIGURE 72.9 The rate of hospital admissions for hyperkalemia among patients recently hospitalized for heart failure who were receiving angiotensin-converting enzyme (ACE) inhibitors. Each bar demonstrates the rate of hospital admission for hyperkalemia per 1,000 patients during one 4-month interval. *RALES,* Randomized Aldactone Evaluation Study. (From Juurlink DN, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. *New Engl J Med.* 2004;351:543, with permission.)

of RALES and in 2001 and 2007 after the publication of RALES. A separate analysis of heart failure patients also prescribed ACE inhibitors demonstrated a significant increase in spironolactone prescriptions but no increase in outpatient hyperkalemia. Thus, it appears that spironolactone can be used safely with an appropriate monitoring in this group of patients. Another drug with the potential to induce hyperkalemia is drospirenone, which is combined with ethinyl estradiol, and is used for contraception, premenstrual syndrome, and postmenopausal osteoporosis. Drospirenone is a novel progestin and mineralocorticoid antagonist, which has the capacity to reduce renal potassium excretion and potentially cause hyperkalemia in patients with advanced kidney failure and/or in those who are receiving other medications that impair renal potassium excretion. Currently, no cases of serious hyperkalemia have been reported; however, plasma potassium does increase during therapy with this medication. A study in postmenopausal women aged 44 to 70 years (~one third diabetes mellitus) all on either an ACE-inhibitor or AT-II receptor blockers (ARB) were randomized to 28 days of drospirenone/ethinyl estradiol or placebo.[297] Baseline creatinine clearance was greater than 100 mL per minute in both groups. Serum potassium was higher in the drug arm, with hyperkalemia ($K^+ > 5.5$ mEq per liter) developing in 7.3% of drug-treated versus 2.6% in placebo-treated patients ($P = .13$).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely prescribed for a variety of inflammatory diseases and pain syndromes. Hyperkalemia is one of the many renal complications associated with NSAID therapy, and over-the-counter availability of these agents further increases the risk of drug toxicity.[298] NSAIDs disturb potassium homeostasis via the inhibition of renal prostaglandin synthesis, especially prostaglandin E2 (PGE2) and prostaglandin I2 (PGI2).[299] The inhibition of prostaglandin synthesis decreases potassium secretion through (1) a lack of activation of the renin–angiotensin system, (2) the direct inhibition of potassium channels in principal cells, and (3) the decreased renal blood flow and diminished delivery of sodium to the distal nephron.[204,298–301] Several reports have confirmed the hyperkalemic complication of NSAIDs prescribed to normal subjects, diabetic patients, and patients with underlying renal insufficiency.[250,300–305] This is especially problematic in patients with reduced effective renal perfusion such as those with intravascular fluid depletion, congestive heart failure (CHF), and third-spacing of intravascular fluid.[297–300] Predictably, NSAID-induced hyperkalemia occurs more often in patients with preexisting hyporeninemic hypoaldosteronism, renal insufficiency, and concomitant therapy with potassium-sparing diuretics and ACE inhibitors.[298–304] As with the traditional NSAIDs, selective COX-2 inhibitors (celecoxib) cause hyperkalemia in at risk patients.[305] The induction of hyporeninemic hypoaldosteronism, reduced sodium delivery to the cortical collecting duct, and renal insufficiency are the mechanisms by which these drugs promote hyperkalemia.[305]

A retrospective analysis of a large national cohort of patients cared for at the Veterans Health Administration (VHA) demonstrated an increased rate of hyperkalemia in CKD patients treated with RAAS antagonists (versus non-CKD

patients). Most concerning was the increased odds ratio of death within 1 day of the hyperkalemic event in patients with moderate (≥ 5.5 mEq per liter and < 6.0 mEq per liter) and severe hyperkalemia (≥ 6.0 mEq per liter) for all stages of CKD, suggesting that use of RAAS blockers in CKD patients should be monitored closely.[306]

ACE inhibitors indirectly reduce renal potassium excretion by inducing a state of hypoaldosteronism.[250,307,308] These drugs may additionally impair renal potassium excretion by reducing the effective GFR in patients with volume depletion, renal artery stenosis, and/or moderate-to-severe chronic renal insufficiency. In these conditions, ACE inhibitors interfere with AT-II production and blunt the postglomerular arteriolar constriction induced by this hormone, thereby lowering the effective filtration pressure and GFR. Ultimately, a reduction in the distal nephron delivery of sodium and water, together with decreased aldosterone production, may precipitate hyperkalemia.[307] In hospitalized patients, ACE inhibitors have been noted to be the culprit drug in 9% to 38% of patients who developed hyperkalemia.[261,262,309] In outpatients treated with an ACE inhibitor for 1 year, 10% developed a serum potassium concentration greater than 6.0 mEq per liter.[310] In this study, patients with renal impairment who were over the age of 70 years were at highest risk. Most studies suggest that the risk of ACE inhibitor–induced hyperkalemia is directly proportional to the existing degree of renal insufficiency.[261,262,307–309] However, serum potassium concentrations can rise significantly in patients with only modest renal insufficiency.[307,308,311] For example, a rise in serum K^+ concentration, a positive cumulative potassium balance, and a reduction in both plasma and urinary aldosterone were demonstrated in 22 of 23 patients treated with high-dose captopril for 10 days despite a creatinine clearance greater than 50 mL per minute.[308] In addition, another study noted a fall in aldosterone excretion and a rise in serum K^+ concentration (mean rise 0.8 mEq per liter) in 23 of 33 hypertensive patients after 1 week of captopril therapy.[307] In this study, all but 3 of the patients had a creatinine clearance above 60 mL per minute and the peak serum K^+ concentration was not predicted by the pretherapy serum creatinine concentration. In contrast, Memon and colleagues[309] demonstrated a significant positive correlation of hyperkalemia with serum creatinine and a negative correlation with creatinine clearance, emphasizing the importance of the underlying level of renal function. In patients with renal impairment, reducing the dose of an ACE inhibitor and initiating a low-potassium diet has been shown to decrease the development of hyperkalemia in a significant percentage of patients.[309,311] Unfortunately, as many as one-third of patients still require the discontinuation of this medication because of ongoing hyperkalemia.[309] Predictably, combination therapy with an ACE inhibitor and other medications capable of altering potassium homeostasis can increase plasma potassium and precipitate hyperkalemia in patients with only modest renal impairment.[250,307,308,312–317] As an example, elderly patients on an ACE inhibitor who were hospitalized for hyperkalemia were 27 times more likely to have been prescribed a potassium-sparing diuretic in the week prior to hospital admission.[318] Other notable risk factors include hypoaldosteronism and states of effective arterial volume depletion, such as CHF and cirrhosis.[250,307,308,319,320] Using patients with hypertensive CKD (GFR, 20 to 65 mL/min/1.73 m^2) from the AASK trial, Weinberg et al.[321] noted that ACE-I therapy was associated with an increased hazard ratio for hyperkalemia than either calcium channel blockers or β-receptor blockers. However, this effect was only present in patients with GFR 31 to 40 mL/min/1.73 m^2 (heart rate [HR], 3.61) and GFR < 30 mL/min/1.73 m^2 (HR, 6.81), because risk was not increased in those with GFR 41 to 50 mL/min/1.73 m^2. In addition, diuretic use reduced hyperkalemia risk by 59%.[321] Johnson et al.[322] analyzed a retrospective cohort of CKD patients in the Kaiser Health Maintenance Organization who were initiated on lisinopril and who developed hyperkalemia (potassium ≥ 5.5 mEq per liter or diagnosis code). They then used Cox regression to synthesize a risk score from a priori predictors in the medical record. They noted a 90-day hyperkalemia risk of 2.8% in the population and found seven predictors: age, estimated GFR, diabetes mellitus, heart failure, potassium supplements, potassium sparing diuretics, and high lisinopril dose. The risk score was able to separate high-risk from low-risk patients with excellent accuracy (predicted and observed risks agreed within 1% for each quintile). Although the risk score must be validated in other populations, it has the potential to help guide clinician practice in avoiding potentially lethal hyperkalemia.[322]

ARBs are a relatively new class of drugs marketed for the treatment of hypertension. Their action to block binding of AT-II to its receptor ultimately decreases AT-II–driven adrenal synthesis of aldosterone, causing hyperkalemia through the induction of hypoaldosteronism in a manner similar to ACE inhibitors. Data are conflicting with regard to the effect of this class of drugs on the development of hyperkalemia. In healthy patients with essential hypertension, the ARB, losartan (100 mg), and the ACE inhibitor, enalapril (20 mg), similarly depressed plasma aldosterone levels (50% decrease) and 24-hour urinary aldosterone excretion.[323] The effect of these two drugs on the RAAS did not include the evaluation of serum K^+ concentrations in these patients.[323] Data pooled from 16 double-blind clinical trials evaluating the safety of therapy with losartan as compared with ACE inhibitors in healthy patients with hypertension demonstrated no significant difference in the development of hyperkalemia (K^+ > 5.5 mEq per liter) between the two drug classes (1.3% versus 1.5%).[324] It is important to remember that the patients evaluated in these studies were healthy and at very low risk of developing hyperkalemia.[324] The evaluation of the effect of losartan in elderly patients demonstrated a significant rise in serum potassium (> 0.5 mEq per liter) in 19% of patients, whereas hyperkalemia actually developed in 7% of patients.[325] A clinical history of diabetic nephropathy and a serum creatinine greater than 1.3 mg per deciliter

were predictors of a significant increase in serum potassium. Bakris and colleagues[326] compared the effects of the ACE inhibitor, lisinopril, to the ARB, valsartan, on serum potassium concentration, urinary potassium excretion, and plasma aldosterone in 35 subjects with a mean GFR of approximately 71 mL/min/1.73 m^2.[326] After 4 weeks of therapy with lisinopril, serum K^+ increased (0.2 mEq per liter), whereas plasma aldosterone and urinary potassium excretion decreased. In contrast, serum potassium, plasma aldosterone, and urinary potassium excretion were essentially unchanged in the valsartan group.[326]

Combination therapy with ACE inhibitors and ARBs raises concerns that patients may experience an increase in the development of hyperkalemia from a more complete blockade of the RAS. The combined decline in GFR and the more pronounced suppression of aldosterone synthesis may promote serious hyperkalemia. A multicenter randomized active-controlled parallel group trial studied patients with renal insufficiency (average creatinine clearance 20 to 45 mL per minute).[327] Patients were randomized to either valsartan alone or in combination with benazepril. Dual therapy, however, was associated with a very low risk of hyperkalemia. Serum K^+ concentration rose in each group ranging from 0.28 mEq per liter to 0.48 mEq per liter. An identical percentage (4.5%) of patients on monotherapy and dual blockade developed a serum K^+ concentration greater than 6.0 mEq per liter. Other studies note similar rates of hyperkalemia, although small numbers of patients developed serum K^+ levels greater than 6.0 mEq per liter.[328] Weir and Rolfe[329] reviewed 39 studies that used RAAS inhibitors in the treatment of patients with hypertension, heart failure, or CKD and the rate of hyperkalemia. In patients without other risk factors for hyperkalemia, the incidence of hyperkalemia with drug monotherapy was $\leq$ 2%, whereas it increased to 5% with dual drug therapy. In patients with CKD or heart failure, hyperkalemia incidence increased to 5% to 10%, with serum potassium increases of 0.1 to 0.3 mEq per liter, but a low rate of drug withdrawal (1% to 5%). Thus, although RAAS inhibitor use in high-risk patients is fraught with more hyperkalemia, the actual increases are generally small and serious hyperkalemia is relatively rare.[329] Despite these generally reassuring data, a risk remains for the development of hyperkalemia when these drugs are used alone or in combination. Clinicians should therefore monitor follow-up serum K^+ levels within 1 to 2 weeks once therapy has been initiated.

Trimethoprim and pentamidine are antimicrobial agents employed to treat infections in both HIV-infected patients as well as other hosts. Hyperkalemia evolves through a reduction in renal potassium secretion, the result of competitive inhibition of sodium transport channels in the luminal membranes of the distal nephron by these drugs.[330] The blockade of epithelial sodium channel transport indirectly inhibits potassium secretion (Fig. 72.10),[349] because potassium movement into the distal nephron lumen is electrogenically linked to the movement of sodium out of the

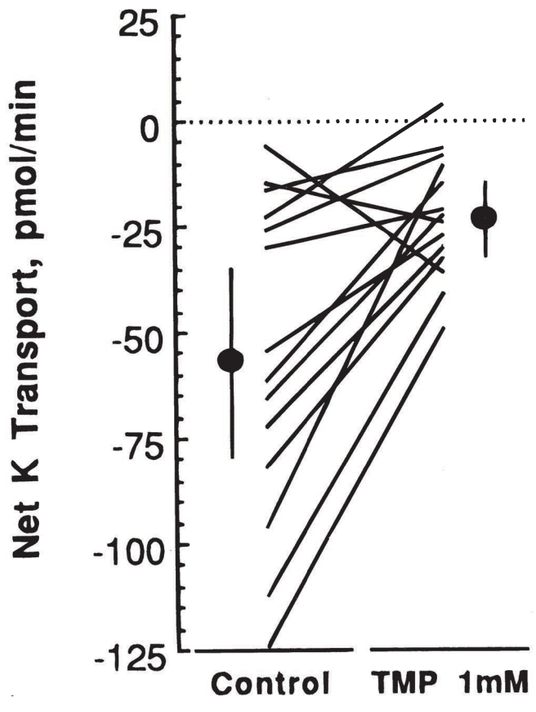

FIGURE 72.10 The net potassium transport during perfusion of 14 distal tubules with control and trimethoprim (TMP) solutions. Lines connect measurements in the same tubules. *Black circles* and *vertical lines* indicate means and confidence intervals. Positive values indicate absorption; negative values indicate secretion. (From Velazquez H, Perazella MA, Wright F, et al. Renal mechanism of trimethoprim-induced hyperkalemia. *Ann Intern Med.* 1993;119:296, with permission.)

lumen.[278,279,330] This action is identical to that exhibited by amiloride, which has a molecular structure very similar to both trimethoprim and pentamidine.[330] Hyperkalemia was first described in a patient treated with "high-dose" trimethoprim (20 mg/kg/day) for Pneumocystis carinii pneumonia.[331] Subsequently, a 50% incidence of mild hyperkalemia ($K^+ > 5.0$ mEq per liter) and a 10% to 12% incidence of severe hyperkalemia ($K^+ > 6.0$ mEq per liter) were observed in HIV-infected patients receiving high-dose trimethoprim.[330] Shortly thereafter, 21% of hospitalized non-HIV patients treated with standard dose trimethoprim (360 mg per day) developed hyperkalemia ($K^+ > 5.5$ mEq per liter).[332] Mild renal impairment (serum creatinine $\leq$ 1.2 mg per deciliter) was significantly associated with the development of a higher serum potassium concentration.[332] A prospective, randomized controlled study in healthy outpatients treated with standard-dose trimethoprim revealed that 18% (9/51) and 6% (3/51) of trimethoprim-treated patients developed serum K^+ concentrations greater than 5.0 and 5.5 mEq per liter, respectively.[333] Older age, diabetes mellitus, and a higher serum creatinine level appeared to predispose a patient to more severe hyperkalemia. Additionally, therapy with pentamidine also has been complicated by hyperkalemia.[334] A retrospective study in 32 patients with AIDS noted a significant increase in mean serum K^+ from 4.2 to 4.7 mEq per liter, with 24% of the patients developing severe hyperkalemia.[335] All cases of hyperkalemia were associated with renal insufficiency, providing an underlying risk factor in these patients. A sevenfold risk for hyperkalemia-associated hospitalization was noted within 14 days of concurrent trimethoprim-sulfamethoxazole and RAAS inhibitor therapy in a cohort of elderly patients. This population-

based, nested case-control study in Canadian residents did not note such a risk with other antibiotics (amoxicillin, ciprofloxacin, norfloxacin, or nitrofurantoin), suggesting that the potassium-sparing effects of trimethoprim combined with RAAS blockade should be avoided or used cautiously in the elderly.[335] However, in a study using the same population of patients, a further increased risk of trimethoprim-sulfamethoxazole–associated hospitalization for hyperkalemia with concurrent β-blocker use was not noted.[336]

Heparin and its congeners have been shown to inhibit adrenal aldosterone production and precipitate hyperkalemia in approximately 8% of patients treated with at least 10,000 U per day.[337] This drug reduces both the number and affinity of AT-II receptors in the adrenal zona glomerulosa, thus decreasing the principal stimulus for aldosterone synthesis.[337] Heparin also directly inhibits the final enzymatic steps of aldosterone formation (18-hydroxylation) and promotes atrophy of the zona glomerulosa in rats following prolonged administration, further reducing aldosterone production.[337] Finally, excess anticoagulation with heparin may rarely precipitate adrenal hemorrhage and induce frank adrenal insufficiency. Although heparin-associated hyperkalemia has been reported in normal subjects, patients with preexisting hypoaldosteronism, kidney disease, or diabetes mellitus and patients treated with other medications that disrupt K^+ homeostasis more commonly develop hyperkalemia.[337]

Cyclosporine and tacrolimus have been associated with the development of hyperkalemia in organ transplant recipients. In the precyclosporine era, 31% (23/75) of renal transplant patients were noted to develop transient hyperkalemia because of an underlying disturbance in potassium excretion.[235] Not unexpectedly, therapy with cyclosporine and tacrolimus increases the risk of this disorder in these patients.[180] Heering and Grabensee[237] documented the presence of incomplete RTA in 8 of 35 recipients on cyclosporine compared with none of the 15 on azathioprine. Four of the former group also had HHA syndrome. In a detailed study of 12 cadaveric recipients with hyperkalemia on cyclosporine, Kamel and colleagues[238] documented the presence of low urinary potassium excretion that did not respond to 0.2 mg of fludrocortisone. Renal K^+ excretion, however, responded to bicarbonaturia initiated by acetazolamide, suggesting a defect in generating a favorable electrochemical gradient in the distal tubule, leading to hyperkalemia and varying degrees of hyperchloremic acidosis. Recently, Yu and coworkers[338] demonstrated higher serum potassium concentrations and lower TTKGs in 35 renal transplant recipients receiving cyclosporine as compared with matched normal controls, thus supporting a disturbance in renal potassium excretion. Tacrolimus has similarly caused hyperkalemia in solid organ transplant patients. Hyperkalemia was noted in 26 of 49 (53%) pediatric heart transplant recipients treated with tacrolimus.[339] Of note, the majority of subjects who developed hyperkalemia had impaired renal function. The reduction in renal potassium excretion that occurs with these two drugs is likely owing to a dose-dependent decrease in the activity of the basolateral Na-K-ATPase pumps in principal cells in the distal nephron.[340,341] Calcineurin, which modulates sodium pump function through its regulation of phosphatase activity, is inhibited by both cyclosporine and tacrolimus.[341] In vitro inhibition of calcineurin by these two drugs has been shown to decrease Na-K-ATPase pump activity and probably explains the observed reduction in renal potassium excretion. Ling and Eaton[342] have also demonstrated the inhibition of apical secretory potassium channels by cyclosporine, providing yet another possible mechanism of decreased renal potassium excretion and hyperkalemia. Cyclosporine also impairs cellular potassium homeostasis and causes transient hyperkalemia by acutely increasing potassium efflux from cells.[343] Although the mechanism is currently unknown, cyclosporine may cause hyperkalemia through the impairment of Na-K-ATPase pumps in muscle and liver cell membranes.

Acute Treatment of Serious Hyperkalemia

Severe hyperkalemia is a potentially life-threatening disorder because of its toxic effect on cardiac and other excitable neuromuscular tissues. Importantly, patients with underlying renal disease and disturbances in potassium homeostasis can develop serious hyperkalemia. It is therefore imperative that this electrolyte disturbance is rapidly recognized and aggressively treated. Symptoms of hyperkalemia are sometimes impressive and quite obvious; however, serious hyperkalemia also may present with only very subtle symptoms or signs. Rarely, patients may have absolutely no clinical evidence of this disorder, the presence of renal impairment or other disturbances in potassium homeostasis providing the only clues to hyperkalemia. Nonspecific muscle weakness and generalized malaise are common, but severe muscle weakness, paresthesias, and ascending paralysis may rarely be seen in these patients with extreme elevations in serum potassium levels.[344] The cardiac toxicity of hyperkalemia may manifest as weakness or dizziness from arrhythmias that induce hypotension and cerebral hypoperfusion.[344] Cardiac monitoring or a 12-lead electrocardiogram (ECG) may reveal a rhythm suspicious of hyperkalemia. These include tenting of the T waves (K^+, 5.5 to 6.0 mEq per liter), lengthening of the P-R interval and widening of the QRS complex (K^+, 6.0 to 7.0 mEq per liter), disappearance of the P waves (K^+, 7.0 to 7.5 mEq per liter), and finally the sine wave pattern (K^+, 8.0 mEq per liter or greater). These ECG changes may occur at different concentrations (higher or lower) of potassium, depending on underlying heart disease and acuity of hyperkalemia.[344] The presence of hypocalcemia, hypomagnesemia, and hyponatremia potentiate the toxic effects of hyperkalemia on the cardiac conduction system and potassium concentrations in the 6.0 to 6.5 mEq per liter range can precipitate life-threatening arrhythmias.[344] Additionally, patients with underlying cardiac disease may deteriorate directly to a ventricular arrhythmia in the absence of other ECG changes.

Once the clinician judges that hyperkalemia warrants treatment (plasma $K^+ > 6.0$ to 6.5 mEq per liter, clinical

manifestations, or ECG changes), immediate therapy should be commenced. The stabilization of excitable cell membranes—in particular, cardiac tissue—is the most urgent priority in the treatment of hyperkalemia. Intravenous calcium, as either calcium gluconate (10% solution, calcium ion at 3 mEq per milliliter) or calcium chloride (10% solution, calcium ion at 13 mEq per milliliter), is the treatment of first choice and should be administered in a monitored setting (Table 72.4). Calcium acts within 1 to 3 minutes, and the effect persists for approximately a half hour.[344] If no effect is noted within 5 minutes following the first dose, repeated administration may provide benefit. Patients who have been treated with digoxin should receive a slower infusion of calcium (calcium mixed in 100 mL of 5% dextrose) over 10 to 20 minutes.[344]

Intravenous administration of regular insulin as a 10-U bolus followed by 50 mL of intravenous 50% dextrose (Table 72.4) should be the next therapeutic choice.[345,346] Twenty units of intravenous insulin may promote an even greater reduction in plasma K^+.[347] The beneficial effect of insulin is observed within 15 minutes and lasts approximately 3 to 6 hours.[345–347] Dextrose is given to prevent hypoglycemia in nondiabetic patients. However, because a high incidence of hypoglycemia occurs even with this regimen, it is prudent to monitor blood glucose levels and redose dextrose based on levels.[345–347] Dextrose should not be infused before insulin because an acute worsening of hyperkalemia can occur with hyperglycemia through a shift of potassium out of cells. Glucose levels should be checked prior to the administration of dextrose to diabetic patients.[345–347]

High-dose nebulized albuterol (10 to 20 mg), which is fourfold to eightfold higher than used to treat asthma, also effectively lowers potassium concentrations in patients with hyperkalemia (Table 72.4).[348] However, the potassium-lowering effect of albuterol is less reliable in ESRD patients, and as many as 40% of these patients are resistant to the potassium-lowering effect of this β-agonist.[348] In general, the plasma potassium concentration declines significantly at 30 minutes following albuterol inhalation and remains depressed for approximately 2 hours.[348] To date, no adverse cardiovascular effects from albuterol have been documented in ESRD patients.[348] Therefore, nebulized albuterol is useful to acutely lower plasma potassium concentration in most hyperkalemic patients; however, it should not replace insulin as the most important therapy to move potassium into cells. Subcutaneous terbutaline (7 μg per kilogram) was shown in a study of 14 CKD patients to significantly lower serum potassium (mean reduction, 1.31 +/− 0.5 mEq per liter), with reasonably good safety because the major adverse effect was asymptomatic tachycardia.[349]

Combined therapy with intravenous insulin and nebulized albuterol has been shown to be additive in the reduction of plasma K^+ concentrations.[348] Plasma K^+ decreases approximately 0.6 mEq per liter with 10 U of insulin, whereas 20 mg of nebulized albuterol lowers plasma K^+ to a similar degree[347]; however, the combination of these agents lowers plasma K^+ by approximately 1.2 mEq per L.[274] As a result, it is worthwhile to combine these two agents to treat severe hyperkalemia (Table 72.4). Combined therapy with sodium bicarbonate and insulin reduced plasma K^+ more effectively, whereas sodium bicarbonate plus nebulized albuterol was no better than monotherapy.[348]

Although sodium bicarbonate is listed as a useful treatment for hyperkalemia, the critical evaluation of the

72.4 Acute Treatment of Serious Hyperkalemia

Stabilize Excitable Tissues (Cardiac and Neuromuscular) Calcium gluconate (10% solution), given as a 10- to 20-mL intravenous bolus. Calcium chloride (10% solution), given as a 5-mL intravenous bolus. Each may be repeated every 5 min, if ECG appearance does not improve. Calcium gluconate should be mixed in 100 mL of 5% and infused over 10–20 min if the patient has been treated with digoxin.
Shift Potassium into Cells Regular insulin, 10 to 20 U plus 50% dextrose (50 mL), given as an intravenous bolus, followed by 10% dextrose at 50 mL/min until definitive therapy. Check glucose levels at 1- to 2-hr intervals. Albuterol (5 mg/mL), 10–20 mg, nebulized over approximately 10 min. Terbutaline, 7 mcg/kg, subcutaneous injection. Combination therapy of insulin/dextrose and nebulized albuterol.
Remove Potassium from the Body Acute hemodialysis (low potassium dialysate) to remove potassium in patients with severe renal insufficiency. Sodium polystyrene sulfonate (15–30 g) plus sorbitol (15–30 mL), oral ingestion (avoid in postsurgical patients and those with gastrointestinal disease).

ECG, electrocardiogram.

literature suggests that this agent is ineffective as an isolated therapy to acutely lower plasma potassium.[350,351] In studies where bicarbonate infusion successfully lowered plasma potassium concentrations in ESRD patients, the effect was not observed until at least 4 hours after treatment. Similarly, other studies have confirmed the use of sodium bicarbonate therapy in the chronic (not acute) lowering of plasma K^+ concentrations.[350,351] In contrast, patients with severe metabolic acidosis and concurrent hyperkalemia should receive bicarbonate to correct pH and stabilize cardiac tissue. In this setting, sodium bicarbonate (50 mEq) may be given intravenously to correct pH and serum bicarbonate levels in patients who are normokalemic and can tolerate the sodium load.[350,351]

THE WORKUP AND MANAGEMENT OF CHRONIC HYPERKALEMIC RENAL TUBULAR ACIDOSIS

Although acute hyperkalemia with or without significant HCA requiring immediate treatment occurs in patients with impaired potassium handling, the major challenge is the workup and treatment of chronic hyperkalemia seen in this setting. Given the frequency of this syndrome and the lack of individualized treatment for specific subgroups, most patients can be adequately managed without complex workups. However, in certain patients, it may be important to make a more specific pathophysiologic diagnosis. Although HCA is the dominant finding in some patients, hyperkalemia is the prominent presentation requiring workup and treatment.

Figure 72.11 summarizes a simple pathophysiologic approach to chronic hyperkalemia in these patients. The first question to be answered is, "Is the hyperkalemia owing to an increase in intake or a decrease in output?" Although dietary history and pertinent clinical data may be helpful, a specific laboratory test that would answer this question could simplify the workup. Urinary potassium concentration and the urinary to serum potassium ratio do not account for the variability in the urinary potassium concentration as a function of water reabsorption in the collecting duct. The fractional excretion of potassium (FE_{K^+}) normalizes potassium excretion for GFR; however, because potassium is primarily secreted (and therefore, less dependent on filtration), its clinical use is questionable.

Halperin and colleagues[58,352–354] have suggested correcting the urinary (U_K) to serum potassium (S_K) concentration by the ratio of urine (U_{Osm}) to serum osmolality (S_{Osm}) to normalize the data for water reabsorption. This ratio ($U_{K^+}/S_{K^+} X\ S_{Osm}U_{Osm}$), called the TTKG, attempts to approximate the gradient across potassium-secreting cells in the distal nephron. Despite several pitfalls (urine more diluted than the plasma or very low urinary sodium), a value less than 6 in patients with hyperkalemia suggests a lack of aldosterone or response to aldosterone; a value above 6 is in favor of an increase in potassium intake, with or without renal abnormality in potassium handling. It should, however, be noted that the published clinical experience with the use of TTKG is still very limited and often is limited to case reports. Therefore, the values given here should be used with caution and evaluated in light of other data.[355] If the TTKG is normal, one should search for excessive potassium intake, either externally (e.g., potassium supplements, salt substitutes) or internally (e.g., severe hemolysis, rhabdomyolysis, acidosis). In general, given the renal ability to handle a large oral potassium load (e.g., serum potassium rising by less than 1.0 mEq per liter on a 400-mEq diet), a significant increase in serum potassium is indicative of either a major internal shift of potassium or a decrease in urinary excretion output. If the TTKG is low in the face of hyperkalemia, the aldosterone level should be measured to separate the group with tubular unresponsiveness from that with low aldosterone. Patients also can be challenged with exogenous mineralocorticoids (0.05 to 1.0 mg of fludrocortisone). If the TTKG increases to 7 or above, hypoaldosteronism is probably the major factor in the development of hyperkalemia.[354,355] The role of renin–angiotensin in patients with hypoaldosteronism can be evaluated by measuring the renin level. A low renin associated with low aldosterone is the hallmark of the most common subgroup (i.e., hyporenin-hypoaldosteronism). If the renin level is normal, then either the generation of

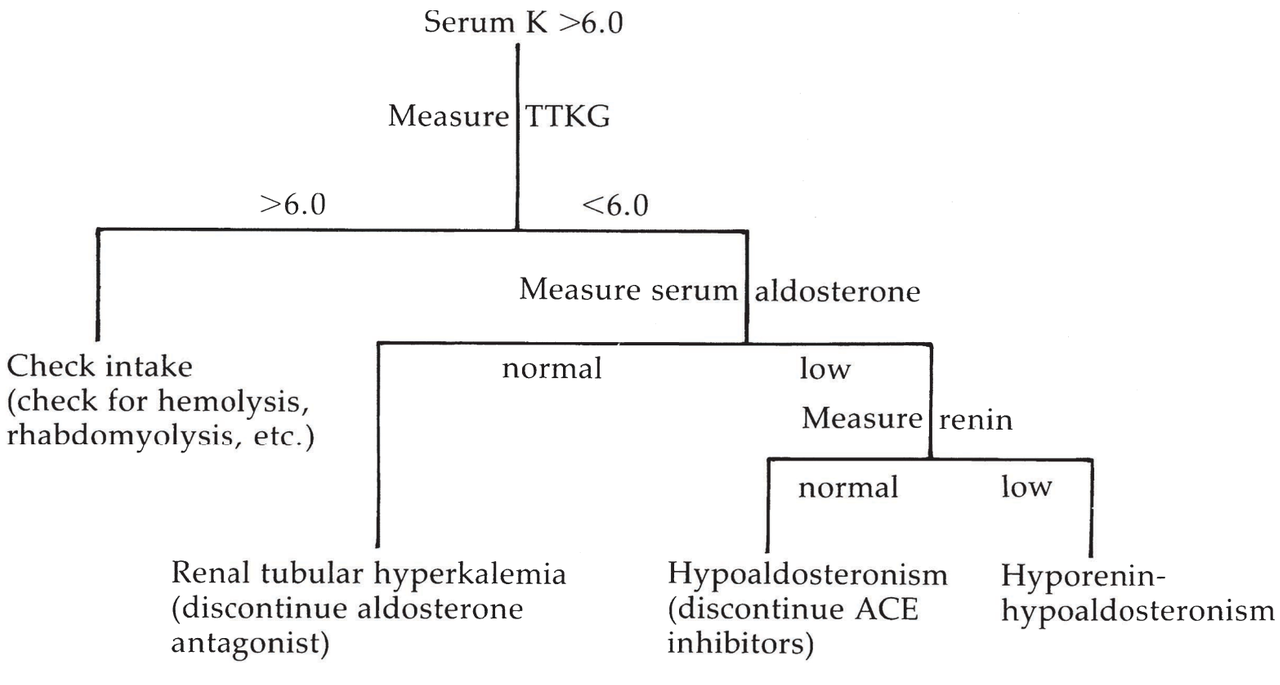

FIGURE 72.11 The pathophysiologic approach to chronic hyperkalemia. *ACE*, angiotensin-converting enzyme; *TTKG*, transtubular potassium gradient.

AT-II is abnormal (e.g., in patients on ACE inhibitors) or the synthesis and secretion of aldosterone are abnormal. The adrenal response to AT-II infusion would provide appropriate answers to this question.

In practice, this type of workup should be reserved for unusual patients who do not represent the commonly recognized groups with this syndrome (e.g., diabetic, hypertensive patients), or as part of a research protocol. In addition, it should be noted that this approach does not lead to an etiologic diagnosis, but only a pathophysiologic one. The etiologic diagnosis (as discussed elsewhere in this chapter) should depend on other diagnostic evaluations.

Some patients with type IV RTA present primarily with HCA. In these patients, the diagnostic workup should focus on the pathogenesis and etiology of this abnormality. The major defect leading to HCA is either a loss of bicarbonate, often through the gastrointestinal tract, or a decrease in the regeneration of bicarbonate by the kidney through the stimulation of ammoniagenesis. Urinary ammonium should be high in the former and low in the latter group. However, urinary ammonium is not commonly measured in clinical laboratories. Clinicians are forced to rely on measurements of surrogates for urinary ammonium excretion. The most commonly used surrogate is the urinary anion gap, which is the difference between major urinary cations (Na + K) and urinary anions (Cl + HCO_3). As the amount of bicarbonate is very small in acid urine (urine pH < 6.5), the difference between urinary Na^+, K^+, and Cl^- reflects the major missing ion (i.e., ammonium). Using this formula, one can demonstrate an inverse relationship between the urinary anion gap and the amount of ammonium in the urine (Fig. 72.12).[356,357] In the presence of extrarenal acidosis, the urinary ammonium excretion should increase severalfold, resulting in a very negative anion gap value. In contrast, in distal RTA, the urinary ammonium will remain low, resulting in a positive anion gap. The amount of ammonium in the urine also can be deduced from a modified urinary osmolar gap using the following formula:

$$\text{Urinary Ammonium} = 1/2\ (\text{Urine Osmolality} - 2(\text{Na} + \text{K}) + \text{Urea Nitrogen}/2.8 + \text{Glucose}/18) \quad (1)$$

This is based on the concept that NH_4^+, with its accompanying anion, is the major missing osmole accounting for the osmolar gap.[358] It should be noted that neither calculation predicts the exact amount of ammonium in the urine but rather provides a qualitative estimate of it. This is still helpful if used to answer the appropriate question in a patient with HCA.

The major use of urinary anion or osmolar gap is to differentiate renal from extrarenal causes of hyperchloremic acidosis such as diarrhea or the ingestion of hydrochloric acid or its equivalent where the gap is negative. However, a low or negative anion gap in itself does not establish the diagnosis of type IV RTA, because this is also seen in classic RTA as well as uremic acidosis. Batlle and colleagues[357]

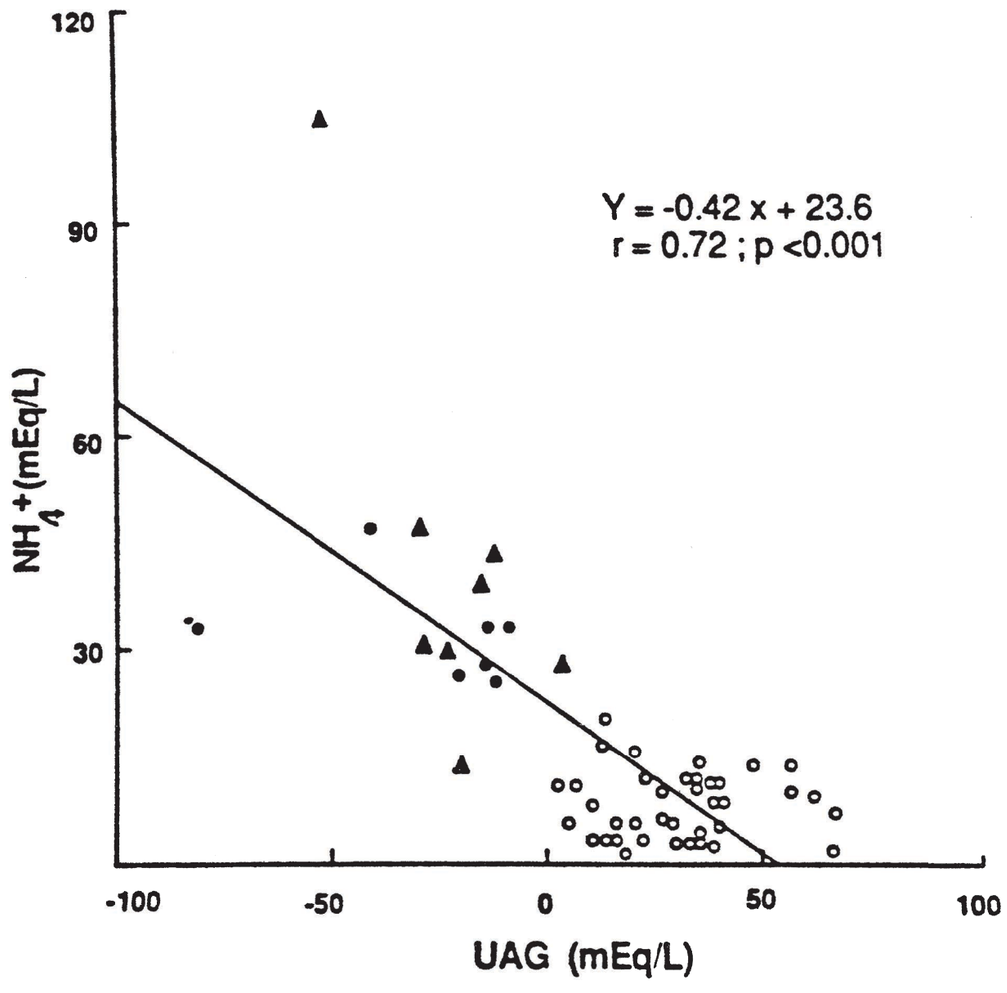

FIGURE 72.12 Urinary ammonium (NH_4^+) in relation to the urinary anion gap (UAG). The 38 patients with altered distal urinary acidification are represented by *open circles*; the 7 normal subjects receiving ammonium chloride are represented by *closed circles*; and the 8 patients with hyperchloremic metabolic acidosis associated with diarrhea are represented by *triangles*. (From Batlle DC, et al. The use of urinary anion gap in the diagnosis of hyperchloremic metabolic acidosis. *N Engl J Med.* 1988;318:594, with permission.)

studied a group of patients with classic RTA, hyperkalemic RTA, and selective aldosterone deficiency and compared the results to controls with a serum pH 7.30 to 7.35. These investigators noted a urinary anion gap of −20 ± 5.7 in controls and +23 ± 4.1, +30 ± 4.2, and +39 ± 4.2 mEq per liter in patients, respectively. The major pitfall in using urinary anion gap is the presence of a significant amount of bicarbonate or an unexpected charged molecule, such as penicillin or ketoacids, in the urine. In summary, urinary anion gap is a physiologic concept that indirectly assesses the amount of urinary ammonium. This measurement, in conjunction with other data, is helpful in establishing the pathogenesis of HCA in selected patients.[359]

In patients with hyperkalemic RTA, the treatment of chronic hyperkalemia should be instituted only when absolutely necessary (i.e., when clinical signs of hyperkalemia are present or plasma K^+ is over 6.0 mEq per liter). If therapy is deemed necessary, simple modalities should be tried first before more complex therapies with their associated side effects are instituted.

Discontinuation of Drugs That Cause Hyperkalemia

As these patients have an intrinsic difficulty in the excretion of potassium, any drugs that can cause hyperkalemia should

be immediately discontinued. The list of drugs that should be stopped includes those discussed in the previous section.

Dietary Intervention

The next step in patients with mild-to-moderate hyperkalemia is to decrease K^+ intake to less than 60 mEq per day. This can be done by the elimination of potassium-rich foods. This may be difficult if the patient is on a low-sodium diet because such a diet, by definition, contains foods that are high in potassium content. Also, an increased replacement of sodium with potassium by the food industry as well as "meat enhancing" will make potassium-containing foods more prevalent.

Treatment of Acidemia

Because HCA is commonly associated with hyperkalemia, the correction of the acidosis by sodium bicarbonate decreases the serum potassium concentration. The effect of bicarbonate is partly related to a change in H^+ concentration and is partly independent of pH change. As acidemia is corrected, H^+ moves out of cells in exchange for potassium. The inhibitory effect of acidemia on renal K^+ secretion also is removed. In addition, sodium bicarbonate, through volume expansion and the delivery of both sodium and bicarbonate to the distal potassium exchange site, may also increase renal excretion of potassium.

In some patients with significant metabolic acidosis ($HCO_3 < 16$ mEq per liter and/or pH < 7.30), it is important to treat acidosis with base replacement to prevent mobilization of bone calcium and protein catabolism. Bone provides a buffer sink for the hydrogen ion, resulting in a release of calcium and its loss in the urine.[137,360] This phenomenon is independent of vitamin D, the parathyroid hormone, and calcitonin.[361,362] In addition, there is increasing evidence for a catabolic role for metabolic acidosis independent of uremia in patients with chronic renal failure.[363] This is thought to result in muscle wasting secondary to the stimulation of muscle protein degradation through the ubiquitin-proteasome system.[364] Both effects can be reversed by alkali therapy. More recently, the relationship between serum bicarbonate and the rate of decline in renal function has been explored in several studies. Low serum bicarbonate in patients with CKD is associated with higher mortality.[365,366] In one study, the relationship between serum bicarbonate and mortality was U shaped, indicating that both low and high bicarbonate was associated with increased mortality.[366] Two studies have also shown that the treatment of metabolic acidosis with alkali improves both the nutritional state as well as decreases the rate of decline in kidney function[367,368] and the need for dialysis.[368] The mechanism of acidosis-induced injury is unclear and may involve complement activation and/or the induction of endothelin production resulting in tubulointerstitial injury.[368,369] Although these provocative findings will require further substantiation with randomized prospective studies, it is recommended that alkali therapy be used to raise serum bicarbonate to $>$ 22mEq per liter. The bicarbonate needed in these patients is close to 0.5 to 0.75 mEq/kg/day and can be easily supplied as citric acid-sodium citrate (Shohl) solution, which contains 1 mEq of bicarbonate equivalent per milliliter. Interestingly, such therapy is well tolerated and has not resulted in volume overload or worsening of hypertension.

Volume Expansion

Volume expansion may enhance potassium excretion by increasing distal fluid and sodium delivery. This therapy is especially effective in patients with chronic volume depletion owing to mild sodium wastage.

Diuretic Therapy

Use of most diuretics, especially loop blockers and thiazides, results in hypokalemic, hypochloremic metabolic alkalosis. In patients with hyperkalemia, the previously mentioned side effects may ameliorate hyperkalemia and, when present, metabolic acidosis. To prevent volume depletion with its resultant decrease in distal tubular sodium and fluid delivery, a high salt intake can be added to the diuretic regimen. Thiazide diuretics have proved effective in some patients with renal tubular hyperkalemia despite the failure of loop blockers such as furosemide.

Mineralocorticoids

Mineralocorticoid replacement represents the most logical approach to therapy in these patients. DeFronzo[171] reported an 84% success rate with this therapy; however, the effective dose of fludrocortisone (up to 0.4 to 1.0 mg per day) was much higher than the true physiologic dose. This observation suggests that most of these patients possess some degree of tubular resistance to the potassium stimulatory effect of mineralocorticoids. Surprisingly, although such high doses were needed to augment renal potassium excretion and normalize serum potassium levels, the sodium-retaining effects of aldosterone remained intact in some patients, resulting in marked edema formation, hypertension, and CHF. In general, if the dose of fludrocortisone required to maintain normokalemia exceeds 0.2 mg per day, side effects are common, and these drugs probably should be combined with diuretics or not employed at all. Use of mineralocorticoids should be limited to patients who have not responded to other maneuvers and continue to have clinically significant hyperkalemia.

Sodium-Potassium Exchange Resins

Sodium polystyrene sulfonate (SPS) resin was first used as a therapy to treat hyperkalemia in 1958 and a study in 1961 documented its efficacy in significantly lowering serum potassium (1.8 mEq per liter at the end of study) in 22 hyperkalemic patients.[370] Studies demonstrated a reliable lowering of serum potassium in hyperkalemic patients using oral SPS mixed either with water or the cathartic sorbitol, which was

added to reduce SPS retention and prevent obstipation.[371] In general, a decline in serum potassium requires at least 2 hours, peaks at 4 to 6 hours, and may take 10 hours or longer following oral administration. SPS retention enemas in water were found to be less efficacious. On average, SPS resin efficiency is approximately 33%; that is, 10 mEq of potassium is bound by 30 g of resin (compared with 1 mEq per gram of resin in vitro).[372] As a result, SPS mixed in sorbitol (33% or 70% sorbitol) became a standard therapy for hyperkalemia in both the acute and chronic setting. However, in 2009, the U.S. Food and Drug Administration (FDA) recommended against the "concomitant use of sorbitol" with SPS powder because of associated complications such as colonic necrosis, gastrointestinal injury (bleeding, ischemic colitis, perforation), and rectal stenosis. A close examination of the cases where complications developed reveals the following: (1) SPS enemas with 70% sorbitol were primarily associated with gastrointestinal injury, and (2) postsurgical patients and those with compromised gastrointestinal function were the group most often developing these complications. Although the incidence of complications is difficult to estimate, a study of 752 hospitalized patients treated with SPS resin mixed with sorbitol provides insight.[373] Only two cases of colonic necrosis developed and these patients were given the mixture within 1 week of surgery. This was an incidence of 1.8% in postsurgical patients. If the entire SPS-treated hospital group is examined, the incidence declines to 0.3%. Thus, it is reasonable to continue to use oral SPS mixed in 33% sorbitol in hyperkalemic patients who do not have gastrointestinal dysfunction or who are not in the immediate postsurgical period. Also, SPS enemas should never be employed as therapy for hyperkalemia.

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