Kidney International, Vol. 11 (1977), pp. 453–465

Relationship of renal ammonia production and potassium homeostasis

RICHARD L. TANNEN

Department of Medicine, College of Medicine, University of Vermont, Burlington, Vermont

The renal production of ammonia is classically perceived as a regulatory system which responds to perturbations in the acid-base status of the organism [1–4]. A growing body of evidence suggests that ammonia production is also intimately related to potassium homeostasis, and that these two parameters may form the components of a feedback system with an important regulatory function [5–7]. It has been proposed that potassium homeostasis regulates renal ammonia production, which in turn influences both urinary potassium and hydrogen ion excretion [5–7]. The first section of this review will focus on the clinical and physiologic observations supporting an ammonia production-potassium relationship, and the second portion will consider the data currently available concerned with the biochemical mechanisms whereby potassium modulates renal ammoniagenesis.

Physiology of potassium-ammonia metabolism interaction

Potassium depletion. Dating back to the 1950's, a variety of observations with both clinically and experimentally induced potassium depletion in humans and animals have suggested that potassium depletion may modify renal ammonia metabolism. An absolute increase in urinary ammonium excretion, a high urine pH with normal amounts of ammonium excretion, or a high rate of ammonium excretion relative to urine pH have all been described in situations of potassium depletion in humans, including laxative abuse [8], primary hyperaldosteronism [9–16], and fasting [17, 18], as well as experimentally induced potassium-depleted states [19–24]. Similar findings have been reported with potassium depletion in rats and dogs [25–27]. In addition, several investigators have described an inability of the potassium-depleted human to diminish urine pH normally in response to either an acute or chronic acid load [19, 24, 28].

These studies, which were largely descriptive, did not clearly elucidate the mechanism responsible for the apparent abnormalities in urine pH and ammonium excretion, but they did focus attention on several possibilities. The explanation most commonly proposed was that potassium depletion resulted in a primary defect in the ability to generate a normal transtubular hydrogen ion gradient, i.e., an acquired incomplete syndrome of distal renal tubular acidosis (RTA) [24, 28]. Indirect support for this possibility is provided by the defect in gastric acid secretion in the potassium deficient rat [29]. Although incomplete distal RTA does not result in systemic acidosis, both a high urine pH and a high rate of ammonium excretion relative to urine pH are exhibited with this condition [28]. Absolute rates of ammonium excretion in excess of normal, however, do not appear to be a manifestation of this disorder [5].

A second possibility, which could account for both the elevated urine pH and ammonium excretion, is that potassium depletion results in a primary increase in renal ammonia production. Direct experimental support for this interpretation was first obtained in 1963 in patients with cirrhosis [30]. Acute, diuretic-induced, potassium depletion increased renal venous ammonium concentration, while potassium repletion simultaneously diminished both renal venous ammonium concentration and urinary ammonium excretion, suggesting an effect on renal ammonia production. It was proposed that potassium depletion might precipitate hepatic coma in this fashion, since the patient with hepatic dysfunction would be unable to adequately detoxify the increased ammonia load by the liver and thereby be subjected to high systemic ammonia levels. Subsequently, Gabuzda and Hall, using *in vivo* methodology, reported an increase in renal ammonia production in acutely potassium-depleted dogs, which reversed rapidly upon potassium repletion [31]. Studies from my laboratory of experimental potassium depletion in normal men, which

were rigorously controlled for other factors affecting urine pH and ammonium excretion, demonstrated a simultaneous increase in urine pH, ammonium, and net acid excretion [5]. This combination of events strongly supported a primary increase in ammonia diffusion into the urine consistent with an increase in renal ammonia production.

It should be pointed out, however, that these studies do not exclude the possible coexistence of a hydrogen ion gradient defect. With standard acid-loading procedures, the decrease in urine pH is a reflection of both the capability to generate a transtubular hydrogen ion gradient and the coexisting rate of renal ammonia production [32]. Hence, an elevated urine pH, when accompanied by an increase in ammonium excretion, could represent an increase in ammonia production either alone or in combination with an inability to achieve a normal maximum hydrogen ion gradient. Theoretically, an investigative technique could be devised in which a maximal decrease in urine pH is achieved regardless of the rate of ammonia production; however, no acidification testing procedure currently utilized has been shown to accomplish this goal. Until the problem is studied in this fashion, a hydrogen ion gradient abnormality cannot be ruled out with complete confidence.

In addition to the *in vivo* observations, several *in vitro* studies of kidney slices from potassium-depleted rats have shown an increase in ammonia production [33–36]. Therefore, it seems well documented that potassium depletion can increase renal ammonia production.

Changes in plasma bicarbonate concentration during potassium depletion require brief consideration in view of their potential relationship to urinary acid-base parameters. The work of Schwartz, van Ypersele de Strihou, and Kassirer [37] and Bleich, Tannen, and Schwartz [38] indicates that although potassium depletion is an invariable feature of metabolic alkalosis, the alkalosis in humans is usually primarily the result of chloride depletion or mineralocorticoid excess; however, potassium depletion may play a causitive role, especially when it is exceedingly severe [39, 40]. Some of the controversy regarding the plasma acid-base status with potassium depletion may result from a species difference and a variable effect of different magnitudes of potassium loss. In general, primary isolated potassium depletion of moderate degree in humans is not accompanied by a significant increase in plasma bicarbonate concentration [5, 20–23, 41]. In the rat, modest depletion also appears to be associated with normal plasma bicarbonate levels [42, 43], while severe degrees of depletion can cause an alkalosis independent of other abnormalities [43–45]. By contrast, in the dog, uncomplicated potassium depletion results in a decline in plasma bicarbonate levels [43, 46].

Since in the dog metabolic acidosis appears to precede the changes in urinary ammonium excretion, Burnell, Teubner, and Simpson suggested that the acidosis was responsible for the changes in ammonia production accompanying potassium depletion [46]. This interpretation is difficult to reconcile with the events in other species, since the rat develops metabolic alkalosis, and the human either maintains normal acid-base balance or becomes slightly alkalotic, although both have an increase in ammonia production. If ammonia production is altered via a similar mechanism in all these species, it would not appear to be systemic acidosis. Furthermore, since during potassium depletion urine pH is increased in the dog with metabolic acidosis [46] and the human with normal plasma bicarbonate concentration [5], it would appear that the changes in urine pH, like the changes in ammonia metabolism, are not primarily related to plasma acid-base status.

Potassium-loading. The influence of a high potassium intake on urinary acidification and ammonia metabolism has received substantially less attention than the depleted state. Acute administration of potassium chloride suppresses net acid excretion and usually results in an alkali diuresis [47–49]. Kamm has shown that chronic ingestion of a high potassium diet in the rat results in a simultaneous decrease in urine pH and ammonium excretion [49, 50]. In my laboratory, we have studied the effects of chronic potassium-loading on urine acidification in both humans and dogs [6].

It is of interest to contrast our investigation of potassium-loading in humans with our studies of potassium-depleted humans [5], since the experimental design was similar in both instances. In both studies, potassium homeostasis was altered by five days of dietary manipulation, and on the sixth day the responses to a standardized acute ammonium chloride load was assessed.[a] In each instance the data were analyzed in relation to a paired study, utilizing the subject as his own control, which was carried out after ingesting an identical diet of normal potassium content. In the figures presented, the points represent the differences between experimental and control de-

[a] In the potassium-loading studies, a constant intake of either 3.0, 4.5, or 6.0 mmoles/kg/day of potassium was ingested. Potassium depletion was produced by ingesting a virtually potassium-free diet, in some instances in combination with Kayexalate on the first two days. With potassium-loading, average retention of potassium approximated 219 mmoles, while the average amount of depletion was 200 mmoles.

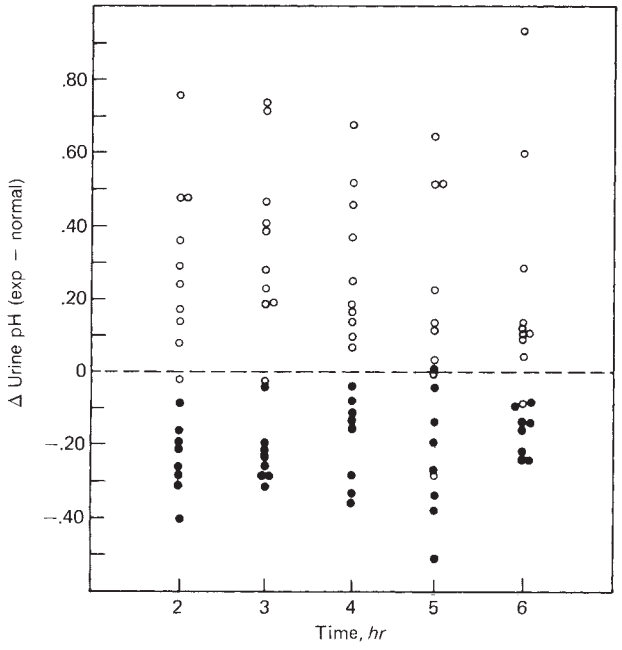

Fig. 1. *Effect of altered potassium homeostasis on urine pH.* The *points* shown represent the urinary pH response of potassium-depleted and chronically potassium-loaded humans following an acute ammonium chloride load. In this and subsequent figures relating to these studies, the data are depicted as the difference between an identical study performed on the same subjects under conditions of normal potassium homeostasis. *Open circles* = potassium-depleted; *closed circles* = potassium-loaded.

terminations obtained at identical times following ammonium chloride ingestion.

As shown in Figure 1, urine pH in the potassium-loaded state was lower than the control, contrasting with the increase in pH found during potassium depletion. Mean urine pH was decreased 0.21 U with potassium-loading and increased by 0.29 U with depletion. Neither potassium depletion nor loading had any detectable effect on plasma acid-base status in these studies, nor were changes apparent in urine flow rate or nonvolatile buffer excretion (i.e., phosphate, creatinine, and organic acids) which might account for the alterations in urine acidification.

The relationship between urine pH and both net acid and ammonium excretion in the potassium-depleted and potassium-loaded state is shown in Figure 2. The change in urine pH correlated positively and significantly with both the change in net acid ($N = 83$, $r = 0.29$, $P < 0.01$) and ammonium ($N = 87$, $r = 0.55$, $P < 0.001$) excretion. Since changes in both net acid and ammonium excretion should be more apparent with larger changes in pH, potassium-depleted and potassium-loaded data with a change in urine pH greater than 0.20 U are isolated on the figure and were analyzed separately. It is apparent from these data with large increments in urine pH that the increase seen with potassium depletion is accompanied by an increase in both ammonium (9.8 μmoles/min, $P < 0.001$) and net acid (6.2 μmoles/min, $P < 0.01$) excretion. By contrast, with potassium-loading, the decrement in pH is accompanied by a decrease in both ammonium (7.9 μmoles/min, $P < 0.01$) and net acid (7.5 μmoles/min, $P < 0.01$) excretion.

These findings are consistent with a primary decrease in ammonia diffusion into the urine during potassium adaptation, and the opposite effect during potassium depletion. Furthermore, they emphasize that the direct correlation between urine pH and ammonia seems to hold throughout the full spectrum of changes in potassium homeostasis, from depletion to excess. Ammonia diffusion into the urine could be modified by changes in renal blood flow and/or by changes in renal ammonia production. Theoretically, a decrease in renal blood flow could enhance urinary ammonium excretion, and an increase in flow could diminish urinary ammonium excretion by altering the

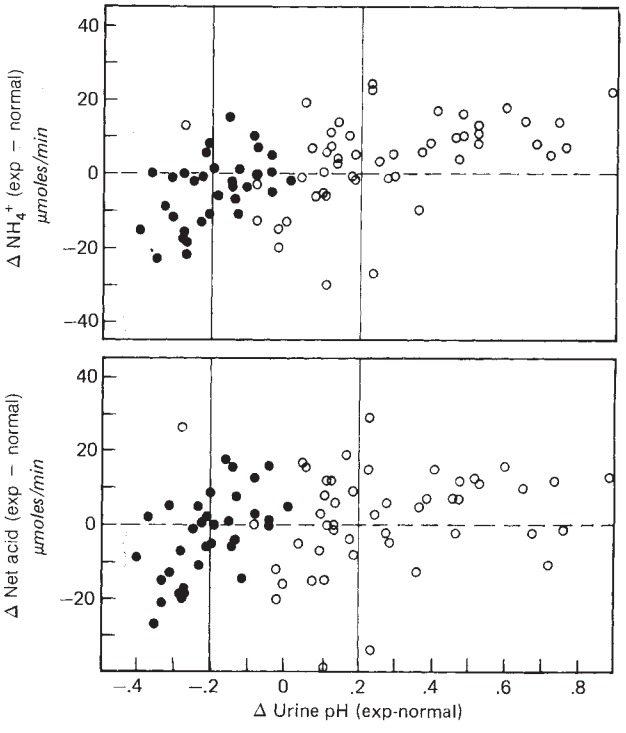

Fig. 2. *Relationship of urine pH to net acid and ammonium excretion.* Changes in urine pH correlate positively and significantly with both the change in net acid and ammonium excretion. Urine pH changes of greater than 0.20 U are isolated in the figure by *horizontal lines.* With potassium depletion, the larger increases in urine pH are associated with a significant increase in net acid and ammonium excretion, while with potassium-loading the larger decrements in urine pH are accompanied by a significant decrease in net acid and ammonium excretion. *Open circles* = potassium-depleted; closed circles = potassium-loaded.

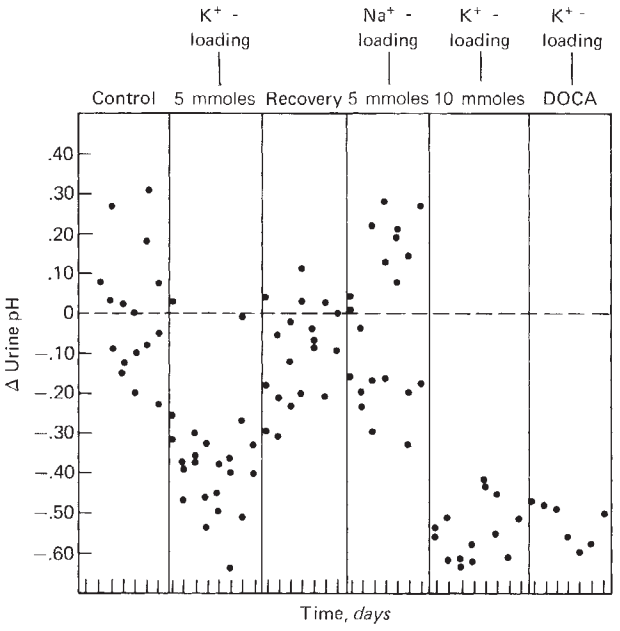

Fig. 3. *Urinary pH response of adrenalectomized dogs to potassium-loading.* The urine pH response in relation to a control period on a normal diet is shown for adrenalectomized dogs on maintenance doses of mineralocorticoid and glucocorticoid, ingesting 2 mmoles/kg of body wt per day of hydrochloric acid. Potassium-loading resulted in a sustained decrease in urine pH; a comparable sodium load had no effect on urine pH; and supplemental doses of DOCA did not modify the potassium-induced decrement in urine pH. (From TANNEN, WEDELL, MOORE [6].)

fraction of renal ammonia production entering the urine. Since renal blood flow is diminished during potassium depletion [51, 52] and increased with a high potassium intake [52], this could represent one factor contributing to the change in urinary ammonium excretion. A change in renal blood flow, however, might also alter ammonia production by modifying the amount of substrate (glutamine) presented to the renal tubular cells [53]. This effect would tend to counterbalance the effects of blood flow on ammonia distribution between urine and blood, since ammonia production would correlate directly with renal blood flow. At present, the overall effect of altered renal blood flow is unresolved.

As noted previously, there is substantial evidence indicating that renal ammonia production is increased with potassium depletion; however, the situation during potassium adaptation is not as well defined. *In vitro* studies of rat renal cortical slices have demonstrated only minimal decreases in ammonia-producing capability during potassium-loading; but, as will be discussed subsequently in more detail, impressive decrements have been found with outer medullary tissue [36]. Therefore, there is some evidence to suggest that the urinary changes accompanying potassium-loading are related, at least in part, to changes in ammonia production.

Longer term experiments in dogs receiving a modest daily acid load also demonstrate that urine pH diminishes during potassium-loading. Urine pH remained low as long as a high potassium intake was maintained, indicating that this phenomenon was not transient and therefore could reflect a chronic homeostatic mechanism. Furthermore, as shown in Figure 3, studies with adrenalectomized animals, receiving maintenance doses of glucocorticoid and mineralocorticoid, point out that the change in urine pH is independent of the increase in aldosterone secretion which accompanies potassium-loading. Finally, these animal studies suggest that some factor in addition to a decrease in ammonia production may contribute to the diminution in urine pH. If a primary decrease in ammonia production were the only event accompanying potassium-loading, a decrease in ammonium and net acid excretion would be anticipated; however, no changes in daily net acid or ammonium excretion were detected concomitant with the decrement in urine pH, and plasma bicarbonate concentration did not fall during potassium-loading. Therefore, it would appear that some mechanism in addition to a lower rate of ammonia production may be contributing to the decrease in pH and may be sustaining a normal rate of acid excretion. This possibility will be considered in more detail subsequently.

It is of interest that the effect of high potassium on ammonia production was invoked recently to explain the decrease in ammonium excretion and metabolic acidosis in a patient with hypoaldosteronism [54], and a similar pathophysiologic mechanism has been proposed in dogs with experimentally induced mineralocorticoid deficiency [55]. These observations raise the possibility that when other components of the potassium control mechanism, i.e., aldosterone, are completely deficient that decreased acid excretion and acidosis might ensue.

Physiologic implications. The observations with potassium depletion and loading suggest that renal ammonia production is responsive to potassium homeostasis, with low potassium stimulating ammoniagenesis in excess of normal and high potassium depressing it. Figure 4, which details the change in urinary potassium excretion compared with the change in urinary ammonium excretion, further emphasizes that the relationship between potassium and ammonium metabolism represents a continuum. This observation, along with the depression of ammonia production with a high potassium intake, a normal occurrence with certain dietary habits, and the increase in ammonia production with modest (approxi-

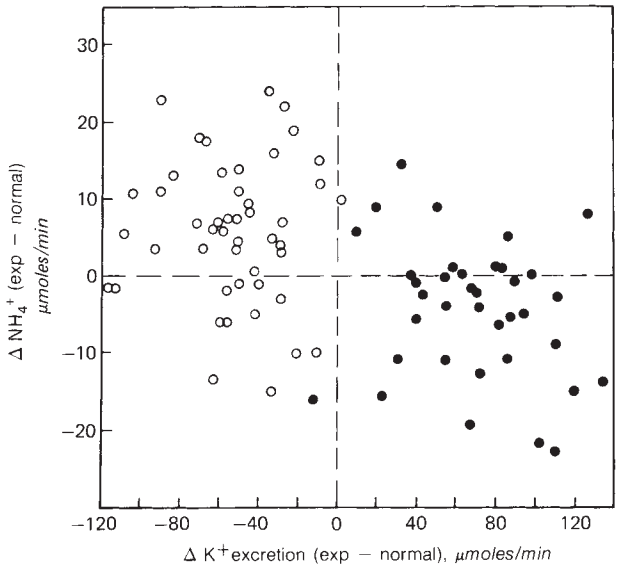

Fig. 4. *Relationship between changes in potassium and ammonium excretion.* Changes in potassium excretion correlate negatively with changes in ammonium excretion ($N = 86$, $r = -0.43$, $P < 0.001$). This suggests that the spectrum from potassium depletion to loading represents a continuum and raises the possibility that alterations in ammonium excretion might modify potassium excretion. *Open circles* = potassium-depleted; *closed circles* = potassium-loaded.

mately 6%) deficits in body potassium stores, suggests that the process is a physiologic rather than pathologic phenomenon. Its potential role in potassium and acid-base homeostasis can be appreciated better if the changes in sodium metabolism accompanying modifications in potassium homeostasis are addressed first.

This topic has been considered by Sealey and Laragh in a recent symposium issue of this journal [56], and will be reviewed here only in reference to its potential interplay with ammoniagenesis.[b] Potassium depletion increases plasma renin activity and decreases aldosterone secretion, presumably via a direct effect on the adrenal gland. It also appears to result in an increase in sodium reabsorption at proximal tubular sites [60, 61] and a decrease at distal sites [5], the latter presumably mediated, in part, by the decrease in aldosterone. By contrast, potassium-loading diminishes renin activity and stimulates aldosterone secretion. Recent micropuncture findings suggest that it decreases sodium reabsorption by the proximal tubule [42, 62, 63] and stimulates reabsorption at more distal nephron sites [63]. The distal reabsorption is enhanced due to a combination of increased aldosterone activity and an increase in the activity of sodium-potassium-adenosine triphosphatase (Na-K-ATPase) [64].

Given the hazard of extrapolation regarding tubular sites of electrolyte transport from net urinary excretion data, the changes in electrolyte metabolism described in experimental animals appear to pertain to humans also. Potassium depletion is associated with sodium retention [65] and potassium-loading with a natriuresis [6], presumably reflecting the effect of potassium on sodium-handling by the proximal nephron. Following ammonium chloride ingestion, the influence of potassium on distal tubular sodium-handling appears to be unmasked [5, 6]. As shown in Figure 5, urinary chloride excretion is unaltered in both the potassium-depleted and potassium-loaded state, while potassium excretion is diminished in depleted subjects and enhanced with potassium-loading. These changes in potassium excretion are counterbalanced by an increase in sodium excretion in the potassium-depleted state and a diminution with potassium-loading, consistent with a decrease and increase in distal sodium reabsorption, respectively.

These intrarenal adjustments in sodium reabsorption presumably serve to maintain both sodium and potassium homeostasis in the face of modifications in potassium intake. A decrease in potassium results in less sodium delivery to tubular sites where sodium-potassium exchange takes place, and in addition, the decrease in aldosterone diminishes the stimulus for sodium reabsorption at this site. Hence, relative so-

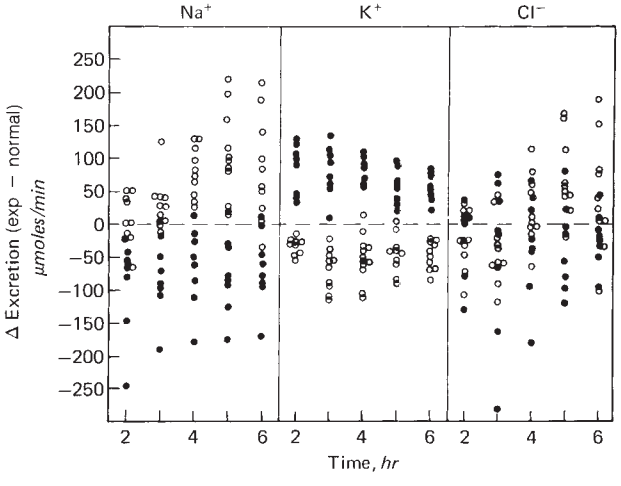

Fig. 5. *Effect of potassium homeostasis on electrolyte excretion.* Electrolyte excretion following the acute ammonium chloride load is depicted. Chloride excretion was unaltered by the state of potassium homeostasis. Potassium excretion was diminished and sodium excretion increased during potassium depletion (*open circles*), while the opposite results were obtained with potassium-loading (*closed circles*).

[b] Although the formulation proposed for the sodium, potassium, renin, aldosterone relationship is generally accepted, some of the issues are controversial [57–59].

dium balance can be maintained while potassium excretion is diminished. A high potassium intake acts in the opposite fashion. Sodium delivery to sodium-potassium exchange sites is increased, and reabsorption at these sites is stimulated by increases in aldosterone and Na-K-ATPase, thereby enhancing potassium excretion while maintaining sodium balance.

Several observations suggest that an increase in sodium reabsorption at distal exchange sites is associated with an increase in hydrogen ion excretion [66–75]. Quite possibly these changes in distal sodium reabsorption account, in part, for the modifications in urinary pH which are found with potassium depletion and loading. On the other hand, they cannot explain the accompanying changes in net acid and ammonium excretion which respond in a direction opposite to that anticipated. A combination of events related to distal sodium reabsorption and ammonia production could account for the observed phenomena.

If sodium reabsorption at distal tubular exchange sites influences hydrogen ion as well as potassium excretion, with an increase stimulating acid excretion and a decrease resulting in a dimunition, some mechanism may exist to minimize the change in acid-base homeostasis when the rate of distal sodium reabsorption is modified. Ammonia production could serve this function. With potassium-loading, the enhanced rate of distal sodium reabsorption is accompanied by a diminution in ammonia production. This decreased availability of ammonia to buffer hydrogen would result in a lower urine pH, an increased transtubular gradient for hydrogen ion secretion, and presumably serve as a mechanism to impede excessive net acid excretion. Likewise, with potassium depletion, an increase in ammonia production coincides with a decrease in distal sodium reabsorption, thereby preventing an accompanying diminution in acid excretion. Hence, the potassium responsive change in renal ammonia production can serve as a mechanism for maintaining relatively normal hydrogen ion homeostasis during manipulations in potassium intake.

Furthermore, by virtue of providing an alternative cation (i.e., ammonium) to exchange with sodium, the ammonia production mechanism might also play a role in regulating the ultimate rate of potassium excretion, as suggested by the correlation shown in Figure 4. Thus, with potassium-loading, a decrease in ammoniagenesis would tend to decrease hydrogen ion secretion and thereby favor sodium reabsorption in exchange for potassium. (The term "exchange" used in this context is not meant to imply a linked transport mechanism, but rather to describe net changes in cation movement.) Conversely, with potassium depletion, the enhanced rate of ammonia production might serve as a potassium-sparing mechanism.

Recent experiments from our laboratory suggest the likelihood of this possibility [7]. Utilizing glutamine ingestion as a mechanism to increase renal ammonia production independent of changes in systemic acid-base status, an increase in renal ammonia production and urinary excretion is accompanied by a reciprocal decrease in urinary potassium excretion (Fig. 6). Furthermore, if the influence of glutamine on ammonia production is obviated by pre-feeding sodium bicarbonate, its effects on postassium excretion are diminished. These studies suggest, therefore, that ammonia production independent of other events can influence potassium excretion.

The specific mechanism whereby ammonia production might influence potassium excretion has not been investigated; however, based on current understanding of renal tubular transport mechanisms, the following could be hypothesized. If hydrogen ion flux in the distal nephron is gradient-limited in a fashion similar to its transport characteristics in amphibian membranes [76], ammonia production could alter hydrogen ion secretion and excretion by modifying the transtubular pH gradient. The increase in urine pH and acid excretion accompanying a glutamine-induced stimulation of renal ammonia production provides indirect evidence supporting this possibility [7]. Although hydrogen and potassium are not transported by a coupled mechanism, an alteration in hydrogen ion flux at distal nephron sites might modify potassium secretion by altering the passive forces influencing its transport [77].

The specific mechanism and tubular sites of an ammonia-potassium interaction are only some of the unanswered questions. No direct evidence is available that a diminution in ammonia production increases urinary potassium excretion. The magnitude of the effect of ammoniagenesis on potassium excretion in the chronic setting, and thereby its quantitative importance for potassium control, is unknown. Its major role could be to maintain hydrogen ion homeostasis when potassium is manipulated. The potassium-ammonia relationship would appear to present several problems for additional fruitful research.

Finally, if the ammonia production mechanism plays a role in the renal response to potassium intake, it is appropriate to consider what transpires under conditions of alkali ingestion. Although this question has not undergone rigorous examination, it would

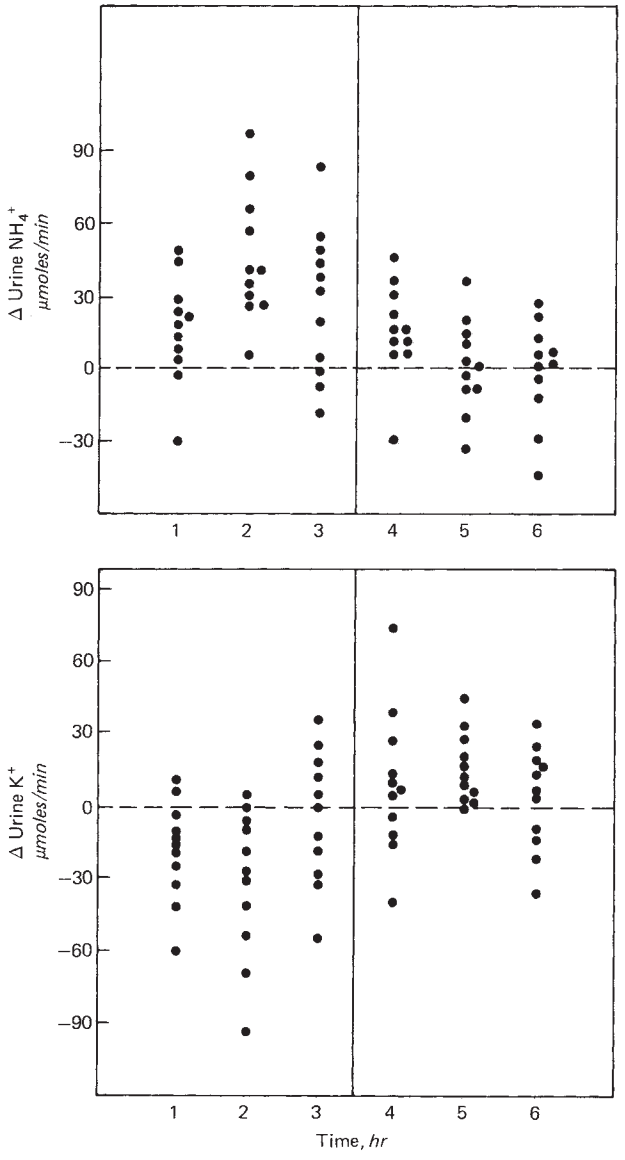

Fig. 6. *Effect of increased ammonia production on potassium excretion.* Urinary ammonium excretion is increased significantly for the first three hours following glutamine ingestion, when compared with an identical paired study performed in the absence of glutamine. This increase in ammonium excretion is accompanied by a significant decrease in potassium excretion, which reached maximal effect at two hours concomitant with the peak in ammonium excretion. (From TANNEN and TERRIEN [7].)

appear *a priori* that so long as excess bicarbonate is present in the tubular fluid no need exists for an alternate buffer mechanism (i.e., ammonia) to play a role in regulating hydrogen ion or potassium homeostasis. The constraints placed on the organism subjected to an alkali load differ substantially from those confronted during acid ingestion. The mechanism required must deal with excretion of bicarbonate (an anion), rather than the control of acid excretion (a cation), in the face of varying requirements for potassium excretion. Maintaining simultaneous acid-base and potassium control with potassium-loading does not pose an obvious problem; the only requirement is to excrete increased amounts of potassium along with bicarbonate in the urine. With uncomplicated potassium depletion, the bicarbonate load must be ingested with sodium, since ingestion with potassium would presumably correct the abnormality. This situation may be more complex since enhanced sodium bicarbonate reabsorption by the proximal tubule may transpire [78, 79]. Presumably, a new steady state will be established when sufficient alkalosis and/or volume expansion has occurred, so that excretion of sodium bicarbonate is comparable to the ingested daily load. Thus, the mechanisms responsible for regulating bicarbonate reabsorption and volume should be adequate to maintain both potassium and hydrogen ion homeostasis, when potassium intake is altered in the presence of an alkali load. When the requirement for excretion of acid is lacking, there would appear to be no need for ammonia to partake in the potassium regulatory mechanism.

Biochemistry of potassium-ammonia interaction

In view of the physiologic and clinical observations suggesting an interaction between potassium and ammonia production, it is of interest to consider how potassium modifies renal ammonia metabolism. Pertinent questions include the specific effector mechanism whereby potassium influences ammonia production, the specific metabolic events altered by this process, and finally, the specific nephron sites at which these events transpire.

Before considering these questions, it will be helpful to briefly recount the metabolic events related to ammonia production. For a detailed discussion of this issue, the reader is referred to several recent reviews [1–4, 80].

The metabolic pathways for ammonia metabolism are diagrammed in Figure 7. Glutamine, the major ammoniagenic substrate, can be converted to ammonia by several metabolic pathways. In the cytosol, these include *1)* the glutaminase II (transaminase) pathway and *2)* the glutamyl transferase or transpeptidase reaction, which may be synonymous with phosphate-independent glutaminase in some species [81–85]. The ammonia producing process can be reversed by *3)* the glutamine synthetase reaction. In addition, *4)* a purine nucleotide cycle was recently described, which is cytosolic in location and uses aspartate as substrate along with catalytic amounts of purine nucleotides [86]. Despite these varying pathways located in the cytosol, *5)* the intramito-

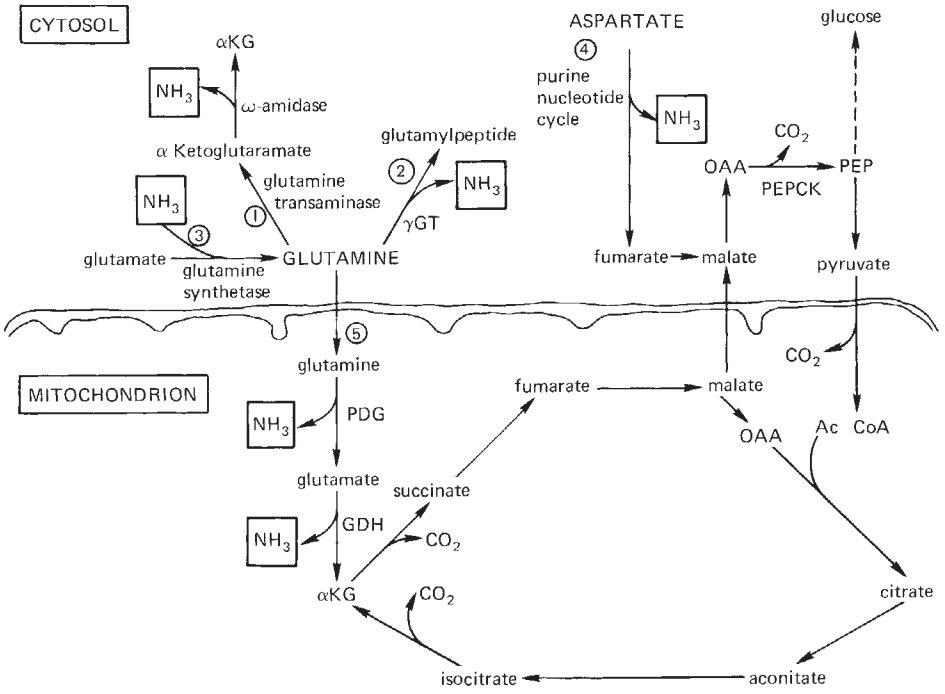

Fig. 7. *Pathways for renal ammonia production.* Abbreviations: αKG = α-ketoglutarate, γGT = gamma glutamyl transferase or transpeptidase, OAA = oxaloacetate, PEPCK = phosphoenolpyruvate carboxykinase, Ac CoA = acetyl CoA, PDG = phosphate-dependent glutaminase, GDH = glutamate dehydrogenase. Five key reactions are numbered and are depicted as occurring in either the cytosol or mitochondrion.

chondrially located phosphate-dependent glutaminase pathway is generally considered to represent the major renal ammonia-producing mechanism. Regulation of this pathway has been proposed to reside at the glutamine entry step, the activity of the glutaminase enzyme itself, and the rate of glutamate deamination, which is influenced by the quantity of oxidized purine nucleotides as well as the end products of this reaction. Disposal of its end product α-ketoglutarate may be dependent on extramitochondrial malate transport [87, 88], or on the rate of conversion to phosphoenolpyruvate, a cytosolic event in the rat controlled by the rate limiting enzyme phosphoenolpyruvate carboxykinase (PEPCK).

In Table 1 the metabolic changes which have been identified with potassium depletion in rats are compared to those found with metabolic acidosis. Potassium depletion has been shown to: *1)* increase ammonia production by renal cortical slices from both glutamine and glutamate [32–35], *2)* increase the enzyme activities of the transaminase pathway [89], *3)* decrease glutamate conversion to glutamine [34], *4)* increase the activity of the purine nucleotide cycle [86], *5)* increase mitochondrial ammonia production both in the absence and presence of rotenone, which inhibits glutamate deamination [45, 90], *6)* increase mitochondrial glutamine entry [90], *7)* increase phosphate-dependent glutaminase (PDG) activity [25, 27, 44, 45], *8)* increase glutamine and glutamate conversion to both carbon dioxide and glucose with cortical tissue slices [33–36, 91], *9)* alter radioactive carbon dioxide ($^{14}CO_2$) production from uniformly labelled ^{14}C-glutamine by mitochondria [92], *10)* increase the rate of citrate decarboxylation [93], and *11)* increase PEPCK activity [34].

Thus, every potential ammoniagenic pathway is stimulated, and every key control point is activated by potassium depletion. These findings are identical to those described with chronic metabolic acidosis in the rat and lead to the same uncertainties regarding the primary and most critical rate-limiting events responsible for the alteration in ammonia production [1–4, 80]. Investigation of species other than the rat has been limited to measurements of glutaminase activity in dogs. In contrast to metabolic acidosis in which no changes in enzyme are apparent in this species, potassium depletion may increase assayable glutaminase activity in the dog, but the data on this point are conflicting [26, 31].

The similarity in the metabolic response to chronic metabolic acidosis and potassium depletion has led to the suggestion that both respond to a common effec-

tor mechanism. In view of the relationship between potassium and intracellular hydrogen ion concentration, reviewed by Adler and Fraley in this symposium [94], a logical possibility for a common effect is an intracellular acidosis in both conditions. The observation that alterations in citrate metabolism by rat muscle, potassium-depleted *in vitro*, appear to be the result of a diminution in intracellular pH supports this hypothesis [95]. The pH of renal tubular cells, however, has not been directly measured with potassium depletion induced *in vivo*, and the effect on intracellular pH of acute *in vitro* changes in renal tissue potassium content is unclear [96, 97]. Furthermore, there is a significant question as to whether intracellular pH is in fact the mediator of the metabolic changes accompanying chronic metabolic acidosis, since a decrease in pH *in vitro* appears to decrease rather than increase ammonia production [98]. Hence, the role of intracellular pH in mediating the renal metabolic changes with potassium depletion is unclear at this time. Of interest, although cellular bicarbonate concentration was increased, no changes in muscle intracellular pH were detected in the potassium-loaded rat when analyzed by means of a bicarbonate-sensitive microelectrode; however, these animals, for reasons which are unclear, had an elevated blood carbon dioxide tension [99].

Table 1. Metabolic changes identified with potassium depletion in rats compared to those found with metabolic acidosis[a,b]

Metabolic pathway	Potassium depletion	Metabolic acidosis
Cytosol		
1) Transaminase (glutaminase II)		
a) Enzyme activity	↑	↑
2) γ-glutamyl transferase and/or transpeptidase (phosphate-independent glutaminase)		
a) Enzyme activity	—	NC
b) NH_3 production	—	NC
3) Glutamine synthetase		
a) Glutamine production from glutamate	↓	↓
4) Purine nucleotide cycle		
a) Enzyme activity	↑	↑
Mitochondria		
5) Phosphate-dependent glutaminase pathway		
a) Mitochondrial NH_3 production	↑	↑
b) Glutamine entry step	↑	↑
c) Deamidation		
i) PDG activity	↑	↑
ii) Mitochondrial NH_3 production with rotenone	↑	↑
d) Deamination		
i) NH_3 production glutamate (intact tissue)	↑	↑
e) TCA cycle		
i) $^{14}CO_2$ production from [U-^{14}C]gln (slices)	↑	↑
ii) $^{14}CO_2$ production from [U-^{14}C]gln (mitochondria)	↑ ↓	↑ ↓
iii) Citrate utilization	↑	↑
iv) Malate exit	—	↑
f) Glucose production[c]		
i) PEPCK activity	↑	↑
ii) Glucose production glutamine	↑	↑

[a] The symbols are ↑ = increase, ↓ = decrease, NC = unchanged, — = undescribed.

[b] References for the events depicted are provided in the text. Both potassium depletion and metabolic acidosis refer solely to events in the rat.

[c] This process is initiated in the mitochondrion and completed in the cytosol.

It has also been suggested that cellular potassium concentration may be the common denominator for the effect of potassium depletion and metabolic acidosis on ammonia production, since both conditions appear to affect renal potassium content in similar fashion [34, 100]. We have found little evidence that potassium concentration, *per se*, at some critical site exerts a direct influence on ammonia production. *In vitro* alteration of the potassium concentration in the bathing medium and tissue, with associated changes in the transcellular gradient for potassium, exerted no detectable influence on ammonia production by rat renal cortical slices [36]. Similarly, changes in the potassium concentration of the incubation media for cortical mitochondria had no significant effect [45]. These observations, coupled with the absence of measurable alterations in mitochondrial potassium concentration during potassium depletion [101], suggest that potassium content at some critical site is not the key modulator for the change in ammonia production which accompanies *in vivo* aberrations of potassium homeostasis.

Several notes of caution, however, are appropriate regarding interpretation of these data. The potassium content of isolated mitochondria may not reflect the actual situation *in vivo*, and the changes in the renal tissue diffusable pool of potassium may be greater [34, 102], and possibly more important physiologically, than the alterations in total renal tissue content. *In vitro* electrolyte manipulations of renal slices must be interpreted cautiously since the tissue does not maintain a normal intracellular potassium concentration when the potassium in the bathing medium approximates normal extracellular fluid concentrations [36]. Furthermore, it is possible that a time variable not achieved with short term *in vitro* studies is required or, alternatively, that potassium exerts its effects through one or more intermediaries not manifested during *in vitro* studies. Thus, a direct effect of potassium has not been definitively excluded, but there is little positive evidence favoring this possibility.

Chronic potassium-loading has been the subject of relatively few metabolic investigations. Kamm found no significant change in rat renal cortical slice ammonia production by potassium-loaded rats [49]. In our laboratory, utilizing a different model for potassium-loading and different analytical techniques, we found a very modest (mean, 5%) but statistically significant decrease ($P < 0.05$) in cortical slice ammonia production [36]. Studies of outer (red) medulla, however, yielded strikingly different results. As shown in Figure 8, outer medulla from potassium-loaded rats exhibited an impressive 36% diminution in ammonia production. Furthermore, no increase in ammonia production by outer medulla was apparent with potassium depletion. Similarly no increase is found with chronic metabolic acidosis. (TANNEN RL, unpublished observation.) Thus, it appears that ammoniagenesis is depressed in response to potassium-loading and that different tubular segments respond to deficits and excesses in potassium.

Utilizing microanalytical techniques, it has been shown that in metabolic acidosis PDG increases only in proximal convoluted tubules [103]. Potassium depletion, which affects only cortical tissue, is associated with an increase in phosphate-dependent glutaminase activity and results in an increase in mitochondrial ammoniagenesis. Presumably, it, like metabolic acidosis, affects mainly proximal convoluted tubule ammoniagenesis; however, similar tubule specific enzymatic assays have not been reported with potassium depletion.

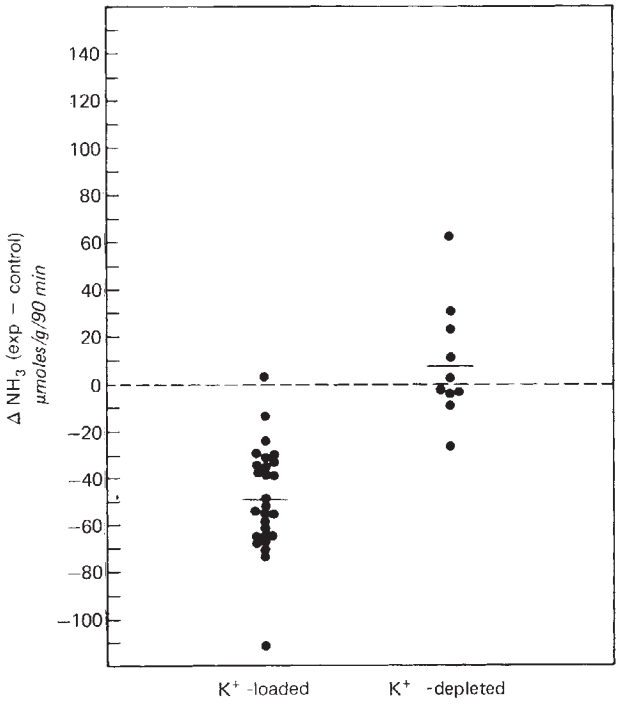

Fig. 8. *Influence of potassium homeostasis on outer medullary ammoniagenesis.* Ammonia production by outer medullary slices from potassium-loaded or potassium-depleted rats were compared in a paired fashion with tissue from pair fed normal controls. Potassium-loading resulted in a significant decrease in ammonia production, while no changes were apparent with potassium depletion. (From TANNEN and MCGILL [36].)

Potassium-loading, on the other hand, must influence either straight proximal tubules, ascending limbs, or collecting ducts, all of which are found in outer medulla [104]. Its minor effect on cortex may be related to the presence of modest amounts of these tubular segments in cortical tissue. Which specific tubular segments it influences and which metabolic pathway is primarily affected is undefined at this time. Chronic potassium-loading does not affect ammonia production by renal cortical mitochondria [45, 90] and has little effect on assayable phosphate-dependent glutaminase activity from either cortex or outer medulla [90, 105]. Studies using *d*-glutamine as substrate suggest it does not selectively inhibit the activity of the gamma glutamyl transferase pathway [105], which has a high baseline level of activity in straight proximal tubules [103]. Thus, definition of the specific nephron site affected and the metabolic pathway involved requires further investigation. In addition, a word of caution should be added concerning *in vitro* study of outer medullary slices, since the ideal conditions for such investigation still require additional definition. Finally, the physiologic significance of the specific sites for the metabolic effect of potassium on ammonia production is a fascinating question, which may provide additional clues regarding the transport dynamics interrelating these two variables.

Summary

Renal ammonia production appears to be intimately related to potassium homeostasis, and the two may comprise the components of a closed loop regulatory system. Studies with both intact organisms and *in vitro* systems indicate that potassium depletion stimulates and chronic potassium-loading suppresses renal ammonia production. An increase in ammoniagenesis has been shown to decrease potassium excretion. These observations suggest that changes in potassium modulate ammonia production, which in turn maintains hydrogen ion homeostasis and influences potassium excretion.

Potassium depletion increases rat renal cortical ammonia production by altering metabolism in a fashion identical to metabolic acidosis, but there is no convincing evidence that both processes are mediated by similar changes in either cellular hydrogen ion or

potassium concentration. By contrast, potassium-loading, which depresses ammonia production, appears to affect primarily the outer medulla, a region that is not influenced by potassium depletion. Thus, potassium-loading apparently affects different portions of the renal tubule than depletion does, but the specific mechanism and physiologic significance of the different sites of action is unknown.

Acknowledgments

This work was done during the tenure of an Established Investigatorship of the American Heart Association. The studies were supported in part by U.S. Public Health Service Grant AM-14225 and Grant in Aid 73-889 from the American Heart Association with funds contributed in part by the Vermont Heart Association.

Reprint requests to Dr. R. Tannen, Department of Medicine, University of Vermont, College of Medicine, Burlington, Vermont 05401, U.S.A.

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