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EDITORIAL REVIEW

Pathogenesis of distal renal tubular acidosis

Distal renal tubular acidosis (RTA) is a syndrome characterized by hyperchloremic metabolic acidosis and an inappropriately high urine pH relative to the degree of acidosis. The clinical presentation is frequently complicated by nephrocalcinosis, hypercalciuria, and nephrolithiasis. Less frequent presenting manifestations include hypokalemia and osteomalacia (for review of clinical features, see Refs. 1–4). Initially, all cases of renal tubular acidosis were considered to have similar pathophysiologic mechanisms, but subsequent studies have subdivided the group into abnormalities of bicarbonate reabsorption (proximal RTA), disorders of net acid excretion (distal or classical), and defects of ammonium production. In the present review, we will limit our discussion to the pathogenesis of distal RTA.

Gradient hypothesis of distal renal tubular acidosis

Distal RTA has generally been attributed to an inability to produce or maintain steep hydrogen ion concentration gradients in the collecting duct without an impairment of hydrogen ion secretory capacity. This hypothesis was based on the following observations: *(1)* During severe metabolic acidosis, the urine pH could not be lowered below 6.0 [1, 4]. *(2)* Total hydrogen ion secretion, as estimated by the bicarbonate reabsorptive capacity, was not decreased [5, 6]. *(3)* Titratable acid excretion could be increased normally during the infusion of the buffer phosphate [5]. Thus, these patients had an inability to maximally acidify the urine during severe metabolic acidosis despite the absence of a detectable limit to total hydrogen ion secretion during bicarbonate or buffer infusion. The logical conclusion was that either the distal nephron could not secrete hydrogen ions against a steep concentration gradient, or that a steep hydrogen ion concentration gradient could not be maintained because of increased back-diffusion of hydrogen ions through an abnormally permeable collecting duct membrane [2]. This gradient hypothesis explained most of the physiologic observations and survived virtually unchallenged for 20 years (1954 to 1974).

Diminished distal hydrogen ion secretion hypothesis of distal renal tubular acidosis

Because hydrogen ion secretion would not be impaired in the absence of a hydrogen ion gradient, both gradient-limited hydrogen ion secretory models of distal RTA should have normal distal nephron hydrogen ion secretion if the hydrogen ion concentration in the fluid of the collecting duct were significantly lower than that of the renal tubular cell. With this in mind, we evaluated the distal hydrogen ion secretory capacity in patients with distal RTA by measuring the urine minus blood P_{CO_2} gradient in alkaline urine (U-B P_{CO_2}).[1] In three of these patients, the urine pH was above 8.0. Because there was no rise in the U-B P_{CO_2}, we inferred that a post-papillary rise in the urine pH did not occur. Therefore, the collecting duct fluid pH must have been equal to the urine pH and was clearly higher than any value we might reasonably expect to exist in the secretory cells of the collecting duct. As the hydrogen ion concentration gradient clearly favored the transfer of hydrogen ions into the collecting duct lumen, we argued that the failure of the U-B P_{CO_2} to rise was incompatible with the gradient hypothesis, and on this basis we suggested that distal RTA was due to an isolated hydrogen ion secretory defect in the distal nephron rather than to a gradient defect [8].

Subsequently, Steinmetz, Al-Awqati, and Lawton questioned whether the urine bicarbonate concentrations were high enough in our patients with distal RTA to adequately test the hydrogen ion secretory limit hypothesis [9]. To reexamine this issue, we determined the relationship between U-B P_{CO_2} and

[1] For an explanation of the physiologic basis for the U-B P_{CO_2}, as well as a comment on the role of the urine bicarbonate concentration in the causation of the high P_{CO_2} values observed in alkaline urine, see Ref. 7. For convenience, these arguments are summarized in the appendix.

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urine bicarbonate concentration in 15 patients with distal RTA and 20 normal subjects. The results are shown in Fig. 1 [10]. These data include the original patients with distal RTA and normal subjects reported in our earlier paper [8], as well as an additional 5 patients with distal RTA and 10 normal subjects. The results clearly establish that the U-B P_{CO_2} is significantly higher in normal subjects than in patients with distal RTA at all concentrations of urine bicarbonate. Thus, patients with distal RTA do not have comparable rates of distal hydrogen ion secretion at equivalent urine bicarbonate concentrations.

Sebastian, McSherry, and Morris suggested an alternative explanation for the observations that the patients with distal RTA cannot elevate the P_{CO_2} of their urine [11]. Because the postpapillary rise in the U-B P_{CO_2} is dependent on the presence of a carbonic acid concentration in the collecting duct in excess of the equilibrium value, the inability of patients with distal RTA to evaluate the urine P_{CO_2} value above that in blood could be the result of dissipation of the disequilibrium pH by excessive back-diffusion of carbonic acid from the collecting duct or from accelerated dehydration of carbonic acid due to exposure of luminal fluid to carbonic anhydrase. In this case, the U-B P_{CO_2} would lose its utility as an index of distal hydrogen ion secretion. Based on these considerations, their proposal was that distal RTA was a single structural abnormality of the distal nephron, permitting the back flux of carbonic acid from alkaline urine and hydrogen ions from acid urine (that is, a gradient defect).[2]

Animal models of distal renal tubular acidosis

Amphotericin B. It is well established that amphotericin B increases membrane permeability to a variety of ions, including the hydrogen ion [13]. Because amphotericin B has been reported to cause distal RTA [14], we examined the utility of the U-B

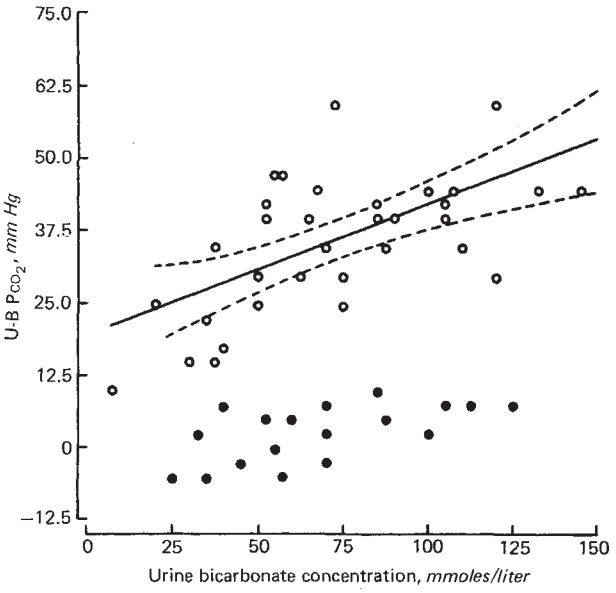

Fig. 1. *Urine-blood P_{CO_2} gradient (U-B P_{CO_2}) plotted as a function of the urine bicarbonate concentration in normal subjects (○) and patients with distal renal tubular acidosis (RTA) (●).* The U-B P_{CO_2} is lower at all concentrations of urine bicarbonate in distal RTA patients. (Reprinted with permission of S. Karger AG Basel.)

P_{CO_2} as an index of distal hydrogen ion secretion in this model in which the acidification defect is thought to be due to a gradient type of distal RTA, that is, increased back-diffusion of secreted hydrogen ions due to an increase in collecting duct permeability. In a group of 24 rats treated with 5 mg of amphotericin B per kilogram of body weight, 12 rats developed a defect in urine acidification. The ability to elevate the U-B P_{CO_2} during bicarbonate loading was not compromised in these rats with the amphotericin-B-induced acidification defect. Therefore, amphotericin B produced an acidification defect by increasing hydrogen ion permeability without altering the permeability to carbonic acid. We concluded that U-B P_{CO_2} is a valid index of distal hydrogen ion secretion in this model of distal RTA, which is presumed to be due to an increase in membrane permeability [15].

Julka, Arruda, and Kurtzman have confirmed our observations that chronic amphotericin B administration produced an acidification defect characterized by an inability to maximally acidify the urine associated with a normal capacity to elevate the U-B P_{CO_2} in alkaline urine [16]. They also found, however, that the acute i.v. administration of amphotericin B to bicarbonate-loaded rats depressed the urine P_{CO_2} out of proportion to its effect on the urine bicarbonate concentration, thus resulting in a rise in the urine pH. They proposed that this effect

[2] Both the "failure to secrete" and the "back-diffusion of carbonic acid" hypotheses are compatible with the observation that distal RTA patients increase their titratable acidity as a result of phosphate infusion and have normal bicarbonate reabsorptive capacities. With respect to titratable acid excretion, the pH of the distal tubular fluid is about 6.4 during acidemia [12]. Thus, more than two thirds of the titratable acid is produced by the titration of phosphate (pK = 6.8) prior to reaching the collecting duct. Phosphate infusion would augment the quantity of titratable acid formed as a result of the titration of phosphate by both the proximal and distal convoluted tubules. Similarly, with regard to bicarbonate reabsorption, this parameter is primarily the function of hydrogen ion secretion in the proximal tubule, and the presence or absence of collecting duct hydrogen ion secretion would not be likely to affect this parameter significantly.

was a result of an amphotericin-B-induced increase in permeability to carbonic acid. An equally plausible explanation for this observation is that the disproportionate fall in urine P_{CO_2} was the result of a significant increase in sodium and/or chloride permeability with resultant impairment of voltage-dependent hydrogen ion secretion (vide infra).

Amiloride. Amiloride administration has been shown to cause a rise in urine pH, bicarbonaturia, and a decrease in net acid excretion [17, 18]. Arruda et al have recently shown that these differences are the results of a distal acidification defect similar to that of distal RTA [19]. These investigators demonstrated that ammonium-chloride-loaded rats given amiloride could not lower the urine pH to a degree comparable to that of control rats despite a similar degree of acidemia and that this relative alkaluria could not be corrected by sodium sulfate administration. Furthermore, during bicarbonate infusion the U-B P_{CO_2} did not rise as a result of buffer administration.

Lithium-induced distal RTA. Clinical studies have demonstrated that lithium produces hyperchloremic metabolic acidosis and a defect in urinary acidification [20]. To investigate the pathophysiology of this acquired acidification defect, we studied the effect of acute lithium administration on the U-B P_{CO_2} of bicarbonate-loaded rats. Our results demonstrated that lithium caused a decline in the U-B P_{CO_2} without significantly altering bicarbonate excretion [21]. We interpreted these results to indicate that lithium caused a decrease in distal nephron hydrogen ion secretion. Subsequently, Nascimento et al noted that lithium lowered the U-B P_{CO_2} of bicarbonate-loaded dogs as well, but they found that sodium sulfate administration to their lithium-treated animals resulted in a very acidic urine. Similarly, Arruda et al demonstrated that phosphate infusion elevated the P_{CO_2} in lithium-treated dogs in a manner and degree similar to that of control animals [23].

The postobstructed kidney (POK). Walls et al noted the development of an acidification defect following the release of unilateral ureteral obstruction (POK) in rats [24]. This disorder was found to be associated with a decrease in distal bicarbonate reabsorption and an impaired ability to elevate the U-B P_{CO_2}. They concluded that the defect was most likely due to decreased distal (collecting duct) hydrogen ion secretion, but pointed out that marked alteration in the bicarbonate absorption in juxtamedullary nephrons could not be excluded. Walls et al considered this possibility unlikely in view of the absence of an increased splay in their bicarbonate titration studies and the failure of the urine P_{CO_2} to rise in alkaline urine [24].

Thirakomen et al subsequently confirmed the findings of Walls et al and further demonstrated that POK animals could not acidify their urine following sodium sulfate or raise the U-B P_{CO_2} as a result of buffer infusion [25]. They interpreted these results as most compatible with a diffuse distal secretory defect for hydrogen and potassium.

In vitro studies in models of distal nephron

In many respects the acidification mechanism of the reptilian and amphibian bladders resemble that of the mammalian collecting duct [26]. Both can acidify the luminal contents, absorb sodium, and have a low passive permeability to hydrogen ions. Therefore, the turtle bladder and the Colombian toad bladder have been subjected to extensive investigation in an attempt to clarify forces responsible for hydrogen ion secretion under controlled conditions [26, 27]. These studies have demonstrated that net hydrogen ion flux can be dissected into active and passive components. The active component is a function of the electrochemical gradient against which secretion takes place. The pH-dependent component is highest in the absence of a pH gradient and ceases when the concentration gradient is near 3 pH units [26]. The electrical component of the gradient also influences the hydrogen ion secretory rate. Because the lumen is usually electrically negative with respect to the serosal or peritubular fluid as a consequence of sodium reabsorption, the electrical potential difference (PD) tends to accelerate hydrogen ion secretion. This electrical (voltage-dependent) component can be abolished by nullifying the PD by means of a voltage clamp (short-circuit current), by removing sodium from the media, or by blocking sodium transport with ouabain or amiloride [28, 29]. The passive component of hydrogen ion transport is usually very small in "tight" urinary epithelia, such as the turtle bladder and probably the collecting tubule, and therefore makes only a minor contribution to the net rate [26].

An additional possibility that arises for consideration from the studies of amphibian bladders is augmented bicarbonate addition to the luminal fluid. A bicarbonate/chloride exchange system has been demonstrated in the turtle bladder [30], and augmentation of this pathway could be responsible for an acidification defect. Support for this possibility is obtained from observations by McKinney

and Burg that bicarbonate secretion can be observed sporadically in in vitro perfused rabbit tubules and that this pathway can be induced by dietary manipulations [31, 32].

Pathogenesis of experimental distal renal tubular acidosis

If the turtle bladder is an appropriate model for collecting duct hydrogen ion secretion in mammals, then several distinctive physiologic abnormalities could affect distal acidification. These are *(1)* defective hydrogen ion secretion due to an intrinsic defect or cell destruction; *(2)* abnormalities of voltage-dependent hydrogen ion secretion due to increased permeability to sodium or chloride or defective sodium reabsorption; *(3)* increased permeability to hydrogen ion; *(4)* increased secretion by ionic bicarbonate; *(5)* a bicarbonate leak from the proximal tubule.

Thus, distal RTA might result from differing physiologic mechanisms. Of these five theoretical possibilities, abnormalities of pH-dependent and voltage-dependent hydrogen ion secretion are likely to be responsible for most examples of distal RTA. This conclusion is based on the fact that these two mechanisms should impair the ability to elevate the U-B P_{CO_2} whereas the other three physiologic defects of hydrogen ion secretion should exhibit a normal capacity to elevate the U-B P_{CO_2} in alkaline urine. Because all the clinical cases of distal RTA that we have observed have exhibited an inability to elevate the U-B P_{CO_2} during bicarbonate loading, we conclude that disorders of hydrogen ion secretion (*1* and *2*) are most likely responsible for the usual case of distal RTA.

We emphasize that these five types of acidification defects are not mutually exclusive. For example, an agent that produces an acidification defect by increasing the permeability to hydrogen ion might also impair voltage-dependent hydrogen ion secretion by increasing the transcellular permeability to sodium or chloride. Of the various experimental manipulations that produce distal RTA, amphotericin B [33, 34], amiloride [19, 35], and lithium [36] have been well studied in the amphibian bladder, and the results yield insight into the probable mechanisms by which these agents impair distal acidification.

Amphotericin B. Amphotericin B impairs the ability of the short-circuited turtle bladder to generate steep hydrogen ion gradients, but does not alter hydrogen ion secretion in the absence of hydrogen ion gradient [33]. These findings were interpreted to suggest that there was a permeability defect to hydrogen ions, and this hypothesis was subsequently confirmed by direct studies of hydrogen ion permeability [34]. These studies established that a hydrogen ion permeability defect is the primary abnormality in amphotericin-B-induced distal RTA but do not exclude an impairment in voltage-dependent hydrogen ion secretion, because serosal-mucosal permeability to both sodium and chloride was increased by amphotericin B, and the effect of amphotericin B on hydrogen ion secretion in the open-circuited turtle bladder was not evaluated. An additional possibility is that chronic amphotericin B administration leads to morphologic damage [37], which could impair distal hydrogen ion secretion.

Amiloride. Ziegler, Fanestil, and Ludens found that the hydrogen ion secretory rates of amiloride-treated Columbian toad bladders were similar to those of short-circuited bladders, but significantly less than that of bladders allowed to develop a spontaneous PD [28]. Furthermore, by the imposition of a voltage similar in magnitude to those developed in nontreated open-circuited bladders, they were able to restore the hydrogen ion secretion of amiloride bladders to normal values. They concluded that amiloride acted primarily by inhibiting voltage-dependent acidification. These results were recently confirmed by Arruda et al [19], and by Husted and Steinmetz [35]. Husted and Steinmetz also observed a 30% reduction in hydrogen ion secretion in short-circuited turtle bladders following the addition of amiloride [35]. They proposed that this inhibition resulted from hyperpolarization of luminal cell membrane resulting in the imposition of a voltage opposing active hydrogen ion secretion. These results are all compatible with the hypothesis that amiloride produces a distal secretory defect by altering the PD, which normally potentiates pH-dependent hydrogen ion secretion.

Lithium. Arruda et al have examined the effect of lithium on hydrogen ion secretion in the turtle bladder. They noted that in the presence of 1% carbon dioxide, lithium did not alter hydrogen ion secretion in the short-circuited bladder, but that it had an inhibitory effect on lithium-treated open-circuited bladders. Furthermore, they were able to demonstrate that superimposition of a voltage in lithium-treated bladders similar to that observed in open-circuited control bladders abolished the inhibitory effect of lithium. Finally, direct measurement of hydrogen ion permeability in lithium-treated bladders

ruled out the possibility of a gradient defect. These studies indicate that lithium, as well as amiloride, produces an acidification defect by blocking voltage-dependent hydrogen ion secretion.

Attempts to classify distal renal tubular acidosis in vivo

Nascimento et al proposed that distal RTA can be classified according to the response to sodium sulfate or phosphate infusion [38]. They observed that sodium sulfate infusion lowered the urine pH, and that phosphate administration elevated the urine P_{CO_2} in animals with lithium-induced distal RTA, but that neither of these responses were obtained in animals with POK-induced distal RTA. From these observations, Kurtzman and Arruda suggested that lithium-induced distal RTA was due to a distal permeability defect whereas the acidification defect due to POK resulted from defective distal hydrogen ion secretion [39]. But, as a result of a subsequent demonstration that both amiloride and lithium exert their influence in the turtle bladder by blocking voltage-dependent acidification [19, 36], Kurtzman has suggested an alternative (and in our view more plausible) explanation for the differing effects of buffer and sulfate on the amiloride and lithium models of distal RTA. According to his proposal, lithium acts as a competive inhibitor of sodium transport and, therefore, its inhibition of voltage-dependent acidification can be nullified by increasing distal sodium delivery. By contrast, Kurtzman believes that the amiloride-induced inhibition of sodium transport and voltage-dependent acidification is noncompetitive in nature and therefore unaffected by sulfate or buffer administration [40]. Regardless of the ultimate explanation for the differential effect of buffer and sulfate on these experimental-dependent defects of acidification, however, the turtle bladder data of Arruda et al demonstrates that sulfate and buffer administration cannot be used to separate distal RTA into pathogenetic subtypes [19, 36].

Summary. Most of the experimental observations in patients with distal RTA can be explained in terms of either the "failure to secrete" or the "back-diffusion" of hydrogen ions and carbonic acid hypotheses. Because distal RTA can result from a variety of causes, it is possible that either mechanism might be operative in certain instances, or even that both mechanisms could play a role in the same patient. Further elucidation of which of these pathophysiologic mechanisms is more important in any particular type of distal RTA must await more sophisticated methodology for the detection of distal hydrogen ion secretion in vivo.

BOBBY J. STINEBAUGH
FRANCIS X. SCHLOEDER
S. C. TAM
MARC B. GOLDSTEIN
MITCHELL L. HALPERIN
Houston, Texas, and Toronto, Ontario, Canada

Appendix

Evaluation of distal hydrogen ion secretion. Highly permeable compounds like carbon dioxide are present in the collecting duct fluid and are very likely to be in diffusion equilibrium with medullary structures. Thus, the fluid leaving the collecting duct should have a P_{CO_2} similar to that of the renal medulla. Nevertheless, the urine P_{CO_2} is elevated above this value in normal subjects presumably as a result of distal nephron hydrogen ion secretion. Hydrogen ions, which are secreted into the luminal fluid of the distal nephron, react with bicarbonate to form carbonic acid. Because carbonic anhydrase is not present on the luminal aspect of these cells, the dehydration of carbonic acid is not instantaneous [41]. Therefore, a portion of the carbonic acid produced as a result of hydrogen ion secretion in the distal nephron arrives in the renal pelvis and undergoes dehydration in the lower urinary tract. The dehydration of carbonic acid leads to a rise in the urine pH and causes the release of hydrogen ions from buffers. These hydrogen ions combine with bicarbonate ions and ultimately result in a rise in the P_{CO_2} in a portion of the nephron where the surface area to volume relationship is not conductive to back-diffusion of carbon dioxide [41]. During bicarbonate infusion, the arterial blood P_{CO_2} closely approximates that of the renal medulla [42]. Thus, the ability to elevate the urine P_{CO_2} above that of arterial blood (U-B P_{CO_2}) has been used as a qualitative index of distal nephron ion secretion [8].

The ampholyte hypothesis. Arruda et al have questioned the importance of hydrogen ion secretion in the generation of U-B P_{CO_2} [43]. They demonstrated that the U-B P_{CO_2} is a linear function of the urine bicarbonate concentration and that this interrelationship is similar to that obtained by mixing crystalline sodium bicarbonate with water (ampholyte effect of bicarbonate). Accordingly, they proposed that a large component of the U-B P_{CO_2} was a result of the elevated urine bicarbonate concentration resulting from water abstraction and only that portion of the U-B P_{CO_2} that was in excess of that obtained by mixing bicarbonate and water could be interpreted as resulting from hydrogen ion secretion [44]. We have recently confirmed that there is a linear relationship between the U-B P_{CO_2} and the urine bicarbonate concentration in the dog, but showed that a similar relationship does not occur in the rabbit [7]. Our observations in the rabbit are difficult to reconcile with the concept that the ampholyte properties of bicarbonate are a major factor in the elevation of the U-B P_{CO_2}, because this physicochemical mechanism should produce an invariable elevation of the U-B P_{CO_2} at high bicarbonate concentrations.

Theoretical considerations also cast doubt on the ampholyte hypothesis [7]. The elevation of the P_{CO_2} by the addition of sodium bicarbonate to water according to the net reaction, $2HCO_3^- \rightarrow CO_2 + CO_3^=$ requires an initial excess of bicarbonate relative to CO_2 and $CO_3^=$. This condition exists in a container of crystalline sodium bicarbonate, but not in plasma, because all components of the bicarbonate buffer system are in equilibrium in an aqueous solution. Furthermore, the high urine bicarbonate concentrations are achieved by reabsorption of tubular fluid in excess of bicarbonate, and this process would tend to elevate concentrations of HCO_3^-, CO_2, H_2CO_3, and $CO_3^=$ equally and would

not result in the relative bicarbonate excess required by the ampholyte hypothesis. Only the secretion of ionic bicarbonate into the tubular fluid will produce the conditions required by the ampholyte hypothesis, and it is unlikely that this mechanism is responsible for a significant portion of the urinary bicarbonate. Therefore, we concluded that the ampholyte hypothesis is unlikely to be a significant factor in the causation of the U-B P_{CO_2} and that other mechanisms must be responsible for the observed linear relationship between the U-B P_{CO_2} and the urine bicarbonate concentration in the dog [7]. Alternate explanations of this relationship include the simulation of distal hydrogen ion secretion by the luminal bicarbonate concentration [44] and the Reid and Hills suggestion of the production of a disequilibrium pH by concentrations of the components of the bicarbonate buffer system with simultaneous back-diffusion of carbon dioxide [45].

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Reprint requests to Dr. B. J. Stinebaugh, Department of Medicine, Renal Section, The Methodist Hospital, 6565 Fannin, Houston, Texas 77030, USA

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