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Clinical and pathophysiologic spectrum of acquired distal renal tubular acidosis

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Clinical and pathophysiologic spectrum of acquired distal renal tubular acidosis. Urinary acidification was studied in nine patients with hyperchloremic metabolic acidosis. The aim of this study was to investigate the mechanism(s) of impaired distal acidification by the systematic administration of sodium sulfate and neutral phosphate. No impairment of proximal acidification was apparent because all patients had a fractional bicarbonate excretion below 5% at plasma bicarbonate concentrations above 22 mEq/liter. All patients except two were unable to lower urine pH below 5.5 despite systemic metabolic acidosis. The two patients who lowered urine pH normally were hyperkalemic and had selective aldosterone deficiency. Six patients failed to lower the urine pH below 5.5 with sodium sulfate (6.04 ± 0.16) and were unable to achieve a normal urine minus blood (U-B) P_{CO_2} gradient with neutral phosphate (2.8 ± 3.5 mm Hg). Control subjects, the two patients with selective aldosterone deficiency, and the remaining patient lowered the urine pH below 5.5 and increased the U-B P_{CO_2} gradient above 25 mm Hg in response to sodium sulfate and neutral phosphate infusion, respectively. The abnormal response to these agents exhibited by six patients strongly suggests that the mechanism of impaired distal acidification was that of secretory failure of the proton pump. The normal response of the remaining three patients indicates that the proton pump was able to secrete hydrogen ions normally under maximal stimulation. This pattern is totally predictable in patients with isolated selective aldosterone deficiency who are also capable of lowering the urine pH normally in the presence of systemic metabolic acidosis. The distinctive acidification pattern of the remaining patient who was also hyperkalemic can be explained on the basis of a voltage-dependent type of distal renal tubular acidosis. This type may be disclosed by the findings of impairment of both hydrogen ion and potassium secretion.

Aspects clinique et physiopathologique de l'acidose tubulaire distale acquise. L'acidification urinaire a été étudiée chez neuf malades ayant une acidose métabolique hyperchlorémique. Le but de ce travail était d'étudier le mécanisme de l'altération de l'acidification distale par l'administration de sulfate de sodium et de phosphate neutre. Il n'est pas apparu d'altération de l'acidication proximale puisque tous les malades avaient une excrétion fractionnelle de bicarbonate inférieure à 5% à des concentrations de bicarbonate plasmatique supérieures à 22 mEq/litre. Tous les malades sauf deux étaient incapables d'abaisser leur pH urinaire au dessous de 5,5 malgré l'acidose métabolique. Les deux malades qui abaissaient le pH de l'urine à des valeurs normales étaient hyperkaliémiques et avaient un déficit sélectif d'aldostérone. Six malades n'ont pu abaisser leur pH urinaire en dessous de 5,5 avec le sulfate de sodium (6,04 ± 0,16) et ont été incapables de réaliser un gradient de P_{CO_2} normal urine-sang sous phosphate neutre (2,8 ± 3,5 mm Hg). Les sujets contrôles, les deux malades ayant un déficit d'aldostérone et le dernier malade ont abaissé le pH de l'urine au dessous de 5,5 et augmenté le gradient de P_{CO_2} à plus de 25 mm Hg en réponse aux administrations de sulfate de sodium et de phosphate neutre, respectivement. La résponse anormale des six malades suggère fortement que le mécanisme de l'altération de l'acidification distale est un défaut de fonctionnement de la pompe à protons. La réponse normale des trois derniers malades indique que la pompe était capable de secréter des ions hydrogène dans des conditions de stimulation maximales. Cette modalité est prévisible chez les malades qui ont un déficit sélectif et isolé d'aldostérone et qui sont aussi capables d'abaisser le pH de leur urine en présence d'une acidose métabolique systémique. La modalité d'acidification particuliére du dernier malade qui était en même temps hyperkaliémique peut être expliquée par un mécanisme dépendant de la différence de potentiel. Cette situation peut être reconnue par la constatation d'un désordre portant à la fois sur la secrétion de ions hydrogène et celle de potassium.

It is useful to divide patients with renal tubular acidosis (RTA) into two main categories based on two major patterns of bicarbonate excretion [1–10]. Patients who excrete more than 15% of the filtered bicarbonate at normal plasma bicarbonate concentrations are said to have proximal RTA [6]. Patients with distal renal tubular acidosis (DRTA) excrete less than 5% of the filtered bicarbonate at normal plasma bicarbonate concentrations [6]. Patients with proximal RTA may be able to lower urine pH below 5.5 when plasma bicarbonate falls below their tubular threshold for bicarbonate reabsorption [5,6]. Patients with "pure" DRTA are unable to lower urine pH normally in the presence of systemic metabolic acidosis regardless of its severity [1–12]. Overlaps between proximal and distal RTA occur as shown by the fact that some patients with significant bicarbonate wastage are not able to lower urine pH even when they are profoundly acidotic (type III RTA) [1, 6]. In both proximal and distal RTA, impaired acid excretion results in hyperchloremic metabolic acidosis and often is complicated by potassium depletion [1–10].

It has been widely accepted that the mechanism responsible for DRTA is the inability of the distal nephron to develop and maintain a steep hydrogen ion gradient between the extracellular fluid and the tubular urine [1–4, 6, 9, 12]. Hence, DRTA is also referred to as gradient limitation RTA (synonymous terms include type 1 RTA and classical RTA). This notion was challenged by Halperin et al, who suggested that DRTA results

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Table 1. Clinical and biochemical features in patients with hyperchloremic metabolic acidosis[a]

Patient no.	Renal disease/ associated conditions	Age/sex	Race	Plasma creatinine *mg/dl*	S_{Na}	S_K	S_{Cl}	S_{HCO_3}	Anion gap *mEq/liter*	Blood pH	Blood P_{CO_2} *mm Hg*	Urine pH	FE_{HCO_3}[b] %
					mEq/liter								
1*	Nephrocalcinosis/Htn	64 F	C	1.5	139	3.4	110	16	16.4	7.27	36	6.80	0.60
2	Liver cirrhosis, unknown nephropathy pancreatic insufficiency, hypoproteinemia	54 M	C	2.0	135	3.4	110	17	11.5	7.29	35	5.75	0.88
3	Renal transplant/Htn	41 F	B	1.7	140	4.7	113	15	16.0	7.29	34	5.97	0.36
4	Renal transplant/Htn	27 F	S	2.0	140	4.2	110	16	18.2	7.33	32	6.44	0.85
5	Neurogenic bladder/DM	52 F	B	4.5	141	4.3	116	15	14.0	7.31	32	7.56	4.20
6*	SC Hemoglobinopathy/Htn	50 M	B	1.9	140	5.6	116	11	18.6	7.26	24	6.05	0.70
7	Toxic interstitial nephritis (?)/Htn	59 M	B	3.9	136	6.0	108	15	19.0	7.28	32	6.24	0.28
8	Hyporeninemic hypoaldosteronism/DM	53 M	B	1.7	141	5.7	111	21	15.0	7.28	46	5.04	0.02
9	Hyporeninemic hypoaldosteronism/DM	70 M	C	2.2	138	5.8	108	18	18.0	7.32	36	4.79	0.02

[a] The above values were obtained during spontaneous acidosis or ammonium-chloride-induced acidosis (indicated by asterisk) in two patients. Htn is hypertension; DM, diabetes mellitus; B, Black; C, Caucasian; S, Spanish.

[b] The fractional excretion of bicarbonate (FE_{HCO_3}) was obtained on a separate occasion when plasma bicarbonate was above 22 mEq/liter except in patients 8 and 9.

from an impairment of hydrogen ion secretion rather than from an inability to maintain a steep pH gradient between blood and urine [13]. Experimental studies using membranes analogous to the human collecting duct have provided conclusive evidence that mechanisms other than a secretory failure can also result in deranged distal acidification [14–16].

Based on animal models of defective distal acidification, our idea was that the mechanism of DRTA could be characterized by assessing the response to sodium sulfate and neutral phosphate administration [17–22]. A normal response to either sodium sulfate or neutral phosphate would indicate that the distal mechanism for hydrogen ion secretion is sufficiently intact to respond to maneuvers which stimulate acidification. Failure to lower the urine pH with sodium sulfate and the inability to elevate the U-B P_{CO_2} gradient with phosphate would strongly support the concept that DRTA is due to an isolated secretory defect in the distal nephron.

There are occasional observations in the literature on the use of these agents in patients with DRTA [23–31]. Both tests, however, were never applied in a combined and systematic fashion. By examining the response to sodium sulfate and neutral phosphate administration in normal subjects and in patients with hyperchloremic metabolic acidosis, this study seeks to characterize the pathophysiologic mechanism(s) responsible for the generation of distal acidification defects in humans.

Methods

Nine patients with hyperchloremic metabolic acidosis and three normal subjects were studied. Each patient had mild or moderate renal insufficiency with persistent hyperchloremic metabolic acidosis (Table 1). The clinical characteristics of the renal disease of these patients satisfied the criteria of interstitial nephritis [32]. The main clinical diagnosis and other associated conditions are listed in Table 1. The diagnosis of DRTA was made by the inability to lower the urine pH below 5.5 in spite of spontaneous systemic acidosis (blood pH below 7.33, plasma bicarbonate of 15 mEq/liter or below) in seven patients. Two of them (patients 1 and 6) were further studied after an oral acid loading test with ammonium chloride (0.1 g/kg of body wt daily for 3 days). The remaining two patients (8 and 9) lowered the urine pH below 5.5 with spontaneous metabolic acidosis as they had isolated hypoaldosteronism (see below). Fractional bicarbonate excretion (clearance bicarbonate divided by clearance creatinine × 100) was measured in all patients to rule out a proximal leak in bicarbonate reabsorption. When proximal RTA is present, the fractional bicarbonate excretion usually exceeds 15% at normal plasma bicarbonate concentrations [6]. All our patients had a value of fractional bicarbonate excretion below 5%, which, thus, excludes a significant leakage of bicarbonate from the proximal nephron. In addition, a bicarbonate titration study was performed in two patients (6 and 7). Both patients exhibited normal bicarbonate reabsorption at normal or high levels of plasma bicarbonate concentration.

The studies were carried out on out-patient basis at the University of Illinois Hospital with the approval of its Institutional Review Committee; written consent from each patient was obtained. The patients were allowed to continue their normal diets at the time of all the studies. If they had been taking any diuretics, alkalinizing solutions, or other medications that could affect urinary acidification, these drugs were discontinued for 1 week prior to the studies. All studies were performed in the morning. After obtaining blood and urine samples for baseline determination of electrolytes, we instructed the patients to empty their bladders completely; timed urine collections were then begun. The urine was collected under mineral oil for measurement of urine pH and carbon dioxide tension. Because inability to achieve a minimum urine pH in the supine position has been previously observed [33], all patients were instructed to urinate in the upright position. Tap ice-water was given ad lib to guarantee an adequate urinary output. Venous blood was obtained from a heparinized indwelling catheter at the midpoint of each collection. The urine collections were of approximately 30 to 60 min duration. Glomerular

filtration rate (GFR) was measured either by the clearance of endogenous creatinine or by the administration of I^{125}-iothalamate in a dose of 10 μCi with 0.1 ml of epinephrine s.c. 1 hour before starting the clearance collections. Two basic protocols were followed:

(1) Sodium sulfate infusion. In this protocol, the patients and controls were given 1 mg of fludrocortisone orally the night before the study to guarantee that sufficient levels of mineralocorticoid were present, thus ensuring a state of sodium avidity in all cases. Two control clearance collections of approximately 30 to 60 min each were obtained and followed by the i.v. administration of a 500-ml solution of 4% sodium sulfate, which was infused over a period of 45 to 60 min. Four clearance collections were completed at 60, 120, 180, and 240 min after the beginning of the sodium sulfate infusion.

(2) Neutral phosphate infusion. This study was performed on a separate day. After completion of two control clearance collections of 30 to 60 min each, a solution of 0.2 M neutral phosphate was infused at a rate of 1 to 1.5 ml/min for 120 to 180 min. The study was terminated if the urinary P_{CO_2} failed to rise 3 hours after the beginning of the infusion in spite of a urinary phosphate concentration above 15 mM. In the subjects in which the urinary pH was not close to the pK of the phosphate system (6.8), a solution of 0.9 M sodium bicarbonate was infused prior to the infusion of phosphate to achieve a urinary pH as close as possible to 6.8.

Plasma and urine electrolytes were measured as previously described [34]. Titratable acidity was measured as the amount of 0.1 N sodium hydroxide required to titrate 1 ml of urine sample from the urine pH up to the blood pH. Ammonium was measured by the formalin titrimetric method of Cunnarro and Weiner [35].

Plasma cortisol (at 9 A.M.) and plasma aldosterone were determined using a standard radioimmunoassay kit (Diagnostic Products Corp., Los Angeles). Plasma renin activity was measured by radioimmunossay (E. R. Squibb and Sons, Inc., Princeton). Acute volume contraction was induced by the administration of three oral doses of 40 mg of furosemide the day before the determinations (at 6 P.M., 12 midnight, and 6 A.M.). Blood samples were obtained at 9 A.M. The normal values obtained in our laboratory with this protocol are 3.6 ± 1.2 ng/ml/hr for plasma renin activity and 26.5 ± 4.76 ng/dl for plasma aldosterone. To account for the effect of plasma potassium on plasma aldosterone levels, we used the ratio of plasma aldosterone/plasma potassium. Hyperkalemic patients with isolated hypoaldosteronism exhibit a ratio of plasma aldosterone/plasma potassium below 3 [36]. Fractional excretion of sodium and potassium were calculated by the formulas: clearance of sodium divided by GFR × 100 and clearance of potassium divided by GFR × 100, respectively. Statistical analyses were done using the Student's *t* test for paired or unpaired data when appropriate. Data are presented as the means ± SEM. No adverse side effects occurred during these studies.

Results

General data. As shown in Table 1, the population of patients included in this study was heterogeneous. Some suffered from clinical disorders such as nephrocalcinosis, sickle cell (SC) disease, bladder dysfunction, or had undergone renal transplantation. One patient (patient 2) had liver cirrhosis, pancreatic insufficiency, hypoalbuminemia, and hyperglobulinemia. Patient 7 presented with advanced renal failure and a long-standing history of hypertension; he had been exposed to several heavy metals, mainly chromium and lead. Heavy metal nephropathy may result in proximal RTA [6], but this patient exhibited a normal maximal bicarbonate reabsorption pattern during a bicarbonate titration study. Because hypertensive nephrosclerosis is not associated with DRTA, we tentatively ascribed the etiology of his distal acidification defect to toxic interstitial nephritis. Patients 8 and 9 were diabetic and fulfilled the criteria for the diagnosis of the syndrome of hyporeninemic hypoaldosteronism (see below).

Table 2. Renin-aldosterone and aldosterone-potassium relationship after acute volume contraction[a]

Patient no.	S_K *mEq/liter*	PRA *ng/ml/hr*	Plasma aldosterone *ng/dl*	P_{Aldo}/P_K	Minimal urine pH during acidosis
1	3.4	2.8	28.0	8.2	6.8
2	3.4	0.17	1.0	0.3	5.75
3	4.7	13.9	39.9	10.2	5.97
4	3.7	2.9	7.4	2.1	6.44
5	4.3	0.17	9.1	2.1	7.30
6	5.6	4.4	25.7	4.6	6.05
7	5.8	0.36	8.3	1.4	6.24
8	5.7	0.10	3.9	0.7	5.04
9	5.6	0.14	2.7	0.5	4.79

[a] All the above values were obtained from blood collected after acute volume contraction induced by furosemide. The minimal urine pH observed during acidosis is included for comparison purposes.

Table 1 also summarizes the biochemical features of the patients. Plasma creatinine was elevated in all of the patients ranging from 1.5 to 4.5 mg/dl. All of them had spontaneous hyperchloremic metabolic acidosis (mean blood pH, 7.29 ± 0.01; mean blood P_{CO_2}, 34 ± 1.9 mm Hg; mean plasma bicarbonate, 14.9 ± 1.5 mEq/liter; mean plasma chloride, 111 ± 1.0 mEq/liter; mean anion gap, 16.3 ± 0.8 mEq/liter) while untreated or after 1 week of discontinuation of all medications. Despite the presence of chronic metabolic acidosis, seven patients failed to lower the urine pH below 5.5. Two patients (8 and 9) lowered the urine pH normally with systemic acidosis. Fractional bicarbonate excretion measured at plasma bicarbonate concentrations above 22 mEq/liter was less than 5% in all of the patients.

Plasma potassium was normal in three patients (3, 4, and 5), intermittently low in two (1 and 2) and elevated in the remaining four (7, 6, 8, and 9). The hypokalemia of patient 2 was ascribed to diarrhea from pancreative insufficiency. Potassium excretion was not higher in the hyperkalemic patients (53.5 ± 17 μEq/min) than that of controls (69 ± 15 μEq/min) or the remaining five patients (46.8 ± 4.1 μEq/min). Potassium excretion corrected for GFR was lower in the hyperkalemic patients (126 ± 27 μEq/dl of GFR) than that of the remaining patients (170 ± 67 μEq/dl of GFR); this difference was not statistically significant. Plasma cortisol levels were normal in all cases ranging from 12.5 to 23 μg/dl.

Following acute volume contraction induced by furosemide (Table 2), four patients (1, 3, 4, and 6) exhibited normal values of plasma renin activity, plasma aldosterone, and plasma aldosterone/plasma potassium ratio. One patient (5) had subnormal

Table 3. Effect of sodium sulfate on urinary acidification[a]

Patient no.	GFR, *ml/min*		Blood pH		Urine pH		TA Ex *μEq/dl GFR*		NH_4 Ex *μEq/dl GFR*		Net acid Ex *μEq/dl GFR*		FE_{Na} %		FE_K %	
	C	SO_4	C	SO_4	C	SO_4	C	SO_4	C	SO_4	C	SO_4	C	SO_4	C	SO_4
1	68	64	7.36	7.36	6.80	6.77	3.4	4.7	5.8	16	−0.4	−5.9	0.9	5.1	18	194
2	39	54	7.29	7.28	5.75	5.58	46	40	55	74	99	120	1.8	3.5	20	30
3	43	48	7.31	7.35	5.93	5.82	39	32	37	27	67	56	3.7	5.5	32	44
4	38	31	7.40	7.43	6.69	6.16	13	18	62	72	56	81	3.1	4.1	40	85
5	11	11	7.32	7.24	7.69	6.00	0	98	189	100	54	182	4.2	11	99	135
7	14	17	7.33	7.33	5.96	5.94	56	62	23	32	73	85	2.5	8.5	35	78
Mean	35.5	37.5	7.33	7.33	6.47	6.04	26	43	62	53	58	86	2.7	6.3	41	94
±SEM	±8.6	±8.6	±0.01	±0.02	±0.29	±0.16	±10	±14	±26	±13	±13	±26	±0.5	±1.2	±12	±25
6	41	53	7.32	7.34	6.26	5.02	67	112	71	186	134	299	1.5	9.2	15	67
8	97	99	7.33	7.34	5.04	5.03	32	21	14	8.8	46	30	1.0	3.6	20	30
9	45	45	7.27	7.33	4.97	4.84	57	63	41	33	97	96	2.5	4.3	22	35
Mean	61	66	7.31	7.33	5.42	4.96	52	65	42	102	92	141	1.6	5.7	19	44
±SEM	±18	±17	±0.01	±0.002	±0.41	±0.05	±10	±26	±16	±44	±25	±81	±0.4	±1.7	±15	±11
							Controls									
10	147	115	7.42	7.19	6.64	4.69	3.3	20	4.7	17	4.7	36	0.6	2.8	15	36
11	111	126	7.37	7.36	6.30	5.20	5.4	14	11	15	15	30	0.5	3.3	10	47
12	146	131	7.43	7.41	5.27	4.35	31	50	17	23	47	74	0.04	2.7	13	41
Mean	135	124	7.40	7.32	6.07	4.74	13	28	10.7	18.5	22	47	0.4	2.9	12.5	41
±SEM	±11	±4.7	±0.01	±0.06	±0.4	±0.24	±9	±11	±3.4	±2.4	±13	±8	±0.2	±0.1	±1.6	±2.9

[a] TA Ex is titratable acid excretion; NH_4, ammonium; FE_{Na} and FE_K, fractional sodium and potassium excretion; C, control; SO_4, sodium sulfate infusion.

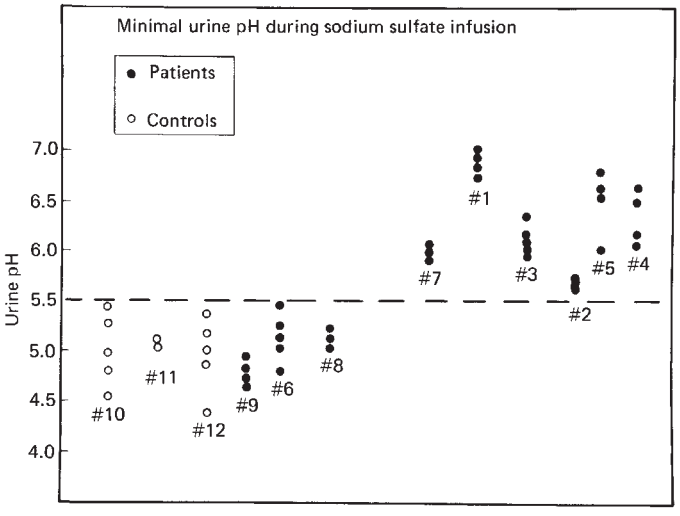

Fig. 1. *Urine pH values achieved by controls and patients during several clearance collections obtained after sodium sulfate infusion.* The controls and three patients consistently lowered the urine pH below 5.5. The remaining six patients failed to lower the urine pH below 5.5.

plasma renin activity but plasma aldosterone and the plasma aldosterone/plasma potassium ratio were not diminished. The remaining four patients (2, 7, 8, and 9) exhibited low levels of plasma renin activity, plasma aldosterone, and plasma aldosterone/plasma potassium ratio after acute volume contraction. Two of them (8 and 9) suffered from prolonged diabetes, had hyperkalemic hyperchloremic metabolic acidosis, and were able to lower the urine pH normally in the presence of spontaneous acidosis. Thus, they fulfilled the criteria for the diagnosis of the syndrome of isolated hyporeninemic hypoaldosteronism [36–40]. The inability to lower the urine pH normally despite systemic acidosis in the remaining two patients (2 and 7), who also exhibited low levels of aldosterone, suggested that factors in addition to selective aldosterone deficiency were responsible for the generation of DRTA (see below). The low plasma aldosterone of patient 2 could have been the result of chronic potassium depletion due to diarrhea.

Response to sodium sulfate infusion. The capacity for distal acidification in patients with DRTA, was investigated by sodium sulfate administration (Table 3 and Fig. 1). The three normal control subjects lowered the urine pH maximally (4.74 ± 0.24). This decrease in urine pH was accompanied by an increase in absolute ammonium excretion, titratable acidity (TA) excretion, and net acid excretion. In contrast, six patients failed to lower the urine pH below 5.5 (6.04 ± 0.16). In these six patients, sodium sulfate infusion also failed to produce a significant increase in ammonium excretion, TA excretion, or net acid excretion.

A response to sodium sulfate similar to that of controls was observed only in patient 6 who responded with a sharp fall in his urine pH from 6.26 to 5.02; ammonium excretion, TA excretion, and net acid excretion increased markedly. Because his normal response to sodium sulfate contrasted with the abnormal response of the remaining six patients who were unable to lower the urine pH during spontaneous acidosis, this patient was further challenged with ammonium chloride administration. This maneuver resulted in a fall in blood pH from 7.33 to 7.26; his urine pH, however, fell to only 5.75.

The two patients (8 and 9) who were able to lower the urine pH normally with spontaneous acidosis also lowered the urine pH with sodium sulfate. The latter maneuver, however, failed to produce an increase in ammonium excretion, TA excretion, or net acid excretion.

It is noteworthy that most of the remaining six patients had a high rate of ammonium excretion corrected for GFR in spite of their high urine pH. Prior to sodium sulfate infusion, the mean

Table 4. Urine acidification measured by the urine-blood (U-B) P_{CO_2} during phosphate infusion[a]

Patient no.	GFR *ml/min*		P_{PO_4} *mmoles/liter*		P_{HCO_3} *mEq/liter*		$P_{P_{CO_2}}$ *mm Hg*		$U_{P_{CO_2}}$ *mm Hg*		Urine pH		U_{PO_4} *mmoles/liter*		U-B P_{CO_2} *mm Hg*	
	B	P	B	P	B	P	B	P	B	P	B	P	B	P	B	P
1	68	63	1.1	2.8	17	14	29	27	19	19	6.84	6.57	5	20	−10	−8
2	38	39	1.0	1.9	25	24	48	43	46	49	6.72	6.40	6	28	−2	6
3	34	47	1.9	2.1	16	22	32	37	27	48	5.97	7.02	8	33	−5	11
4	31	29	1.2	5.3	19	25	34	32	29	44	6.35	6.74	4	27	−5	12
5	9	17	1.8	2.5	18	22	38	41	21	44	5.71	7.20	15	15	−17	3
7	15	15	1.6	3.9	21	21	45	42	45	35	6.24	6.61	10	16	0	−7
Mean	32.5	35	1.3	3.1[b]	19	21	38	37	31	40	6.3	6.7	8.0	23.2[b]	−6.5	2.8
±SEM	±8.2	±8	±0.1	±0.5	±1	±1.6	±3	±3	±5	±5	±0.2	±0.1	±1.6	±3.0	±2.5	±3.5
6	55	53	1.3	3.2	16	16	29	29	43	64	7.29	7.10	9	55	14	35
8	52	48	1.4	2.5	20	30	44	40	40	80	4.9	7.07	15	15	−4	40
							Controls									
10	110	114	1.2	3.2	27	29	39	40	56	70	5.72	6.87	37	86	17	30
11	146	161	1.0	3.2	26	27	42	42	30	81	6.30	6.64	6	26	−12	39
12	44	39	1.0	3.1	23	24	45	50	57	75	5.19	6.40	10	30	12	25
Mean	100	104	1.1	3.1[b]	25.4	26.8	42	44	47.6	75.5	5.73	6.61	18	47[b]	5.6	31[b]
±SEM	±29	±35	±0.06	±0.0	±1.2	±1.6	±2	±3	±8.6	±3.1	±.31	±.15	±9	±19	±8.9	±4

[a] B denotes baseline; P, neutral phosphate infusion.
[b] $P < 0.02$ as compared to prephosphate infusion values.

blood pH of the patients with DRTA, however, was significantly lower than that of the controls (7.33 ± 0.02 vs. 7.39 ± 0.02, $P < 0.01$). Most likely, the relatively high acid excretion of patients with DRTA as compared with controls was due to the presence of metabolic acidosis in the patients but not in the controls. Table 3 includes renal potassium excretion in response to sodium sulfate infusion. Notice that this agent resulted in an increase in fractional potassium excretion in patients and controls. This, was associated with a comparable increase in fractional sodium excretion in all cases.

Response to neutral phosphate infusion. The results obtained with the neutral phosphate infusion are summarized in Table 4 and Fig. 2. The urinary pH during the neutral phosphate infusion ranged from 6.40 to 7.20 (patients, 6.83 ± 0.08; controls, 6.61 ± 0.15). Before phosphate infusion neither patients nor controls displayed a significant elevation of U-B P_{CO_2} gradient. Following phosphate infusion, urinary phosphate concentration increased in all cases to above 15 mM. As a result of phosphate infusion, the U-B P_{CO_2} gradient increased above 25 mm Hg in all controls (from a mean of 5.6 ± 8.9 to 31.3 ± 4.1 mm Hg, $P < 0.02$). Two of the three patients (6 and 8) who had lowered the urine pH normally with sodium sulfate also were able to achieve a similarly large U-B P_{CO_2} gradient (Table 3). The third patient (9) was not tested with neutral phosphate. The remaining six patients failed to achieve a substantial U-B P_{CO_2} gradient (2.8 ± 3.5 mm Hg) during phosphate infusion in spite of similar conditions of urinary pH and phosphate buffer concentration. These six patients also had failed to lower the urine pH normally with sodium sulfate.

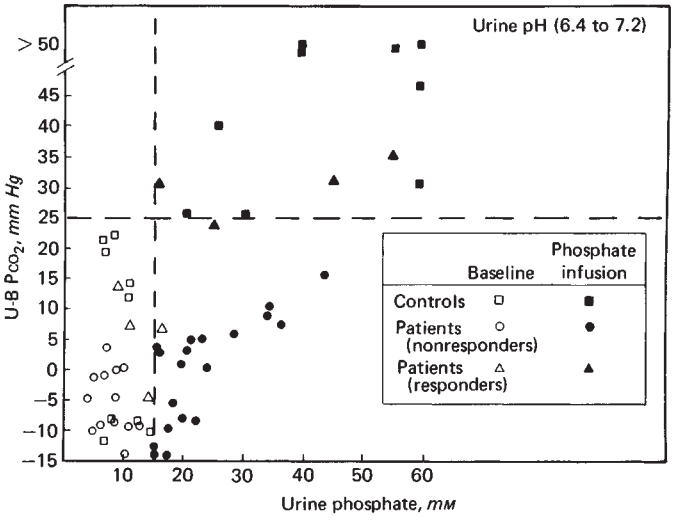

Fig. 2. *Relationship between urine-blood P_{CO_2} and urine phosphate concentration at a urine pH close to 6.8 (ranging from 6.4 to 7.2).* With urine phosphate concentrations above 20 mM, the controls and two patients (responders) achieved a urine-blood P_{CO_2} above 25 mm Hg. The remaining six patients (nonresponders) exhibited a urine-blood P_{CO_2} consistently lower than 15 mm Hg at comparable levels of urine phosphate concentration.

Discussion

The diagnosis of DRTA is generally made by the inability to lower the urine pH to normal minimum levels (that is, below 5.5) in the presence of systemic metabolic acidosis. The failure to lower the urine pH, however, does not indicate the mechanism responsible for impaired distal acidification which leads to hyperchloremic metabolic acidosis. As suggested by Steinmetz, "there is not an a priori reason why there should be a single mechanism for the different disease entities associated with DRTA or for that matter, for an individual case of DRTA" [3]. This contention is gaining support from experimental models of distal acidification defects, which indicate that more than one mechanism is capable of impairing distal acidification [14–20].

The urine pH reaches its lowest value in the distal nephron, presumably in the collecting duct [41]. Active proton secretion appears to be dependent on the integrity of a proton specific pump and is influenced by the electrical and chemical gradients against which the pump operates [3, 4]. The electrical gradient is influenced by the rate of sodium transport and the amount and nature of anions present in the lumen of the distal nephron.

Table 5. Pathophysiologic features of secretory, voltage-dependent DRTA and selective aldosterone deficiency

Type	Mechanism	Urine pH		U-B P_{CO_2}			FE_K		Example
		Acidemia	Na_2SO_4	HCO_3 loading	PO_4 loading	P_K	Baseline	Stimulated	
I. Secretory DRTA	Intrinsic H^+ pump failure	>5.5	>5.5	<10	<10	Normal or ↓	Normal or ↑	↑	Classical DRTA
II. Reversible voltage-dependent DRTA[a]	Impairment of distal Na transport or enhanced Cl permeability	>5.5	<5.5	<10[b]	>25	↑	↓	↑	SC disease
III. Aldosterone deficiency	Decreased H^+ conductance; decreased Na reabsorption; decreased ammonia production	<5.5	<5.5	>25	>25	↑	↓	↓	Isolated hyporeninemic hypoaldosteronism

[a] An irreversible type of voltage-dependent defect should be associated with all the features of a secretory defect plus impaired potassium excretion during stimulation [48]. A pattern similar to that of a reversible voltage-dependent defect could be expected in DRTA secondary to acid backleak (that is, amphotericin B toxicity). In this case, however, potassium excretion would be increased with attendant hypokalemia.

[b] A subnormal U-B P_{CO_2} during bicarbonate loading is predictable based on animal models of voltage-dependent DRTA [15, 16].

The chemical hydrogen ion gradient is obviously dependent on the luminal pH and probably on the intracellular pH as well. The rate of hydrogen ion secretion is modulated by aldosterone, a hormone that increases the proton conductance of the distal nephron and enhances luminal electronegativity by increasing sodium transport [42]. The acidification process also includes a passive component that relates to the backleak of acid from lumen to blood and the leak of bicarbonate from blood to lumen; the significance of the passive component is still uncertain.

Theoretically, impaired distal acidification could result from a defect in any of the above mentioned components of acidification. The view that has prevailed for about 30 years is that DRTA results from the inability of the distal nephron to maintain a steep hydrogen ion gradient between the extracellular fluid and the tubular urine (gradient DRTA) [1–4, 6, 9–12]. This view was challenged by the findings that patients with DRTA failed to increase the U-B P_{CO_2} (an index of distal hydrogen ion secretion) when a favorable hydrogen ion gradient was imposed by maximal alkalinization of the urine [13]. Based on these findings, Halperin et al proposed that the mechanism responsible for DRTA was that of a secretory defect for hydrogen ions [13]. An objection to this proposal is that a low U-B P_{CO_2} during bicarbonate loading could also be the result of backleak of secreted acid (hydrogen ions or carbonic acid) because the rise in the U-B P_{CO_2} is dependent on the present of sufficient carbonic acid concentrations in the collecting duct [43].

Failure to secrete hydrogen ions would likely be manifested by the inability to acidify the urine normally with any of the various maneuvers known to stimulate the distal acidification apparatus. In this study, the mechanism(s) responsible for DRTA was investigated by the systematic administration of sodium sulfate and neutral phosphate. Sodium sulfate results in a prompt fall in urine pH in normal subjects and patients with chronic renal failure retaining salt avidly [44, 45]. It favors the electrical gradient for hydrogen ion secretion by increasing distal delivery of sodium and a poorly reabsorbable anion [44]. Neutral phosphate not only stimulates acidification by increasing the electrical gradient, but also by minimizing the pH gradient against which hydrogen ions are secreted by virtue of its buffer properties.[1]

Our findings that six of our seven patients with DRTA failed to lower the urine pH with sodium sulfate (Fig. 1) and also failed to achieve a normal U-B P_{CO_2} with neutral phosphate (Fig. 2) provide the strongest evidence available that DRTA in these patients was due to an isolated secretory defect in the distal nephron (secretory DRTA). It must be emphasized, however, that definitive support for this mechanism awaits the demonstration of a normal response to these agents in patients with DRTA due to a nonsecretory mechanism (that is, increased backleak of acid[2]).

One patient (patient 6) with DRTA had a distinctive pattern of urinary acidification. He failed to lower the urine pH normally during systemic acidosis, but he responded normally to both sodium sulfate and neutral phosphate administration. This pattern could be the result of a partial secretory defect for hydrogen ion ("weak proton pump"), which responds to maximal stimulation of the distal acidification apparatus. This patient, however, was also distinctive in that he was hyperkalemic despite a normal plasma aldosterone concentration. An increase in luminal electronegativity facilitates both hydrogen ion and potassium secretion; this may be achieved by sodium sulfate administration. That this patient was able to lower the urine pH and increase potassium excretion with sodium sulfate infusion is consistent with a reversible form of voltage-dependant DRTA (see below). In contradistinction, all the remaining six patients with DRTA increased potassium excretion but they

[1] Providing that the urine pH is closed to the pK of the phosphate buffer system in the urine (that is, 6.8), phosphate binds the secreted hydrogen ions and later releases hydrogen ions which react with bicarbonate ions; thus, a normal secretory capacity for hydrogen ions is reflected by an increase in urine P_{CO_2} [18].

[2] Acid backleak is the likely mechanism of DRTA induced by amphotericin B, a drug well known to increase membrane permeability. In this case, sodium sulfate infusion could result in a normal fall in urine pH by increasing lumen electronegativity and thereby restricting back diffusion of secreted acid. Likewise, neutral phosphate infusion could result in a normal acidification response by buffering secreted hydrogen ions, which would be less diffusible.

failed to lower the urine pH in response to sodium sulfate infusion (Table 3). This pattern suggests that they were able to generate a transtubular electrical gradient and thereby increase potassium excretion. The failure to lower the urine pH in this setting further suggests thay they had an isolated failure of the proton pump as the mechanism responsible for their DRTA.

That some patients with DRTA (that is, patient 6) are hyperkalemic despite normal aldosterone suggests the presence of a distinctive type of distal tubular dysfunction. A diffuse distal tubular defect for both hydrogen ion and potassium secretion is not likely since the great bulk of potassium is derived into the lumen of the distal nephron by passive translocation [46]. Therefore, it seems logical to speculate that the hyperkalemic DRTA of our patient 6 was the consequence of inability to generate a transtubular electrical gradient for hydrogen ion and potassium secretion (voltage-dependent DRTA). The most likely cause for a voltage-dependent defect is a primary impairment in sodium reabsorption. In support of this contention are the recent findings of impaired maximal sodium conservation in a patient with voltage-dependent DRTA associated with hemoglobinopathy S [47]. Depending on the nature of the defect for sodium transport, impairment for hydrogen ion and potassium secretion may or may not be reversed by enhanced distal sodium delivery (that is, sodium sulfate infusion). A voltage-dependent type of acidification defect can be induced experimentally with amiloride administration [16]. In this case, sodium sulfate does not correct the defect presumably because the presence of amiloride irreversibly blocks the cellular channels for sodium transport. A pattern of impaired hydrogen ion and potassium secretion similar to that caused by amiloride is present in patients and animals with obstructive uropathy [20, 48]. A reversible form of voltage-dependent DRTA can be induced experimentally by lithium administration [15]. This is associated with a normal response to sodium sulfate and neutral phosphate infusions [18, 19]. The pattern of hydrogen ion and potassium excretion in response to sodium sulfate observed in patient 6 is consistent with a reversible type of voltage-dependent DRTA.

It should be noted that voltage-dependent DRTA may result from enhanced chloride reabsorption rather than decreased sodium transport in some patients. A patient recently described by Shambelan, Sebastian, and Rector appears to represent this mechanism of a "chloride shunt" [49]. In this case, hypertension was present and plasma renin activity and plasma aldosterone were low while on a normal salt diet, presumably reflecting volume expansion from enhanced salt retention [49]. A normal increase in potassium excretion was demonstrated when the patient was given sodium sulfate after salt restriction [49].

In our study, hyperkalemia was recognized in three other patients. Two of these patients (8 and 9) had the typical features of selective aldosterone deficiency [36–40]. This entity is considered a form of RTA (type IV RTA) by some authors [40]. Urinary acidification in this syndrome is characterized by a maximally acidic urine during acidosis as well as a normal U-B P_{CO_2} during alkalinization of the urine [36–40]. Predictably, our study shows that these patients are also able to generate a normal U-B P_{CO_2} gradient during neutral phosphate infusion.

Selective aldosterone deficiency was also present in the third hyperkalemic patient (7, Table 2). This patient failed to acidify the urine during acidosis and after sodium sulfate and neutral phosphate administration. Clearly, he had a distal acidification defect that could not be solely accounted by aldosterone deficiency. Thus, it is worthy of emphasis that aldosterone deficiency can coexist with an intrinsic distal acidification defect [48].

Table 5 summarizes the features of secretory DRTA, voltage-dependent DRTA, and selective aldosterone deficiency. This table is based on the findings of this study and the pathogenetic mechanisms discussed above. Although the U-B P_{CO_2} during bicarbonate loading was not measured in the present study, an abnormal response to alkalinization of the urine is expected in any patient that responds abnormally to sodium sulfate and neutral phosphate administration.

Summary. Our study indicates that many patients with DRTA do not acidify the urine normally with either sodium sulfate or neutral phosphate administration. This pattern is the strongest evidence available against the theory that DRTA results from inability to maintain a transtubular pH gradient. It rather suggests the presence of a "broken" hydrogen ion secretory pump (secretory DRTA). In these patients potassium excretion is not impaired when aldosterone deficiency is not present. On the other hand, a normal response to either sulfate or phosphate indicate that the hydrogen ion pump is either intact or less severely damaged. In hyperkalemic patients, the kaliuretic and acidification response to sodium sulfate can be used to reveal a voltage-dependent type of distal tubular dysfunction.

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