THE RENAL RESPONSE TO ACUTE RESPIRATORY ACIDOSIS [1]

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It is well known that patients suffering from acute and chronic ventilatory insufficiency or in whom there exists an impaired diffusion of carbon dioxide across the alveolo-capillary membrane may develop an acid-base disorder (respiratory acidosis) characterized by decrease in arterial pH and elevation of the total CO_2 content of the arterial blood (1–5). This syndrome of carbon dioxide retention has been noted clinically in patients with pulmonary emphysema, tracheal or laryngeal obstruction, during the coma of severe barbiturate and morphine poisoning, and in both acute paralytic and convalescent phases of poliomyelitis, where the common factor is failure of CO_2 elimination by the lungs.

Previous studies (6, 7) indicate that carbon dioxide is buffered by body buffers, principally hemoglobin of whole blood, and that the increase in plasma bicarbonate concentration characterizing respiratory acidosis occurs more or less in proportion to the degree of CO_2 retention. This increase is compensatory, minimizing the fall in blood pH which would otherwise ensue.

The inhalation of carbon dioxide mixtures has been shown to produce a diuresis with decrease in urine osmolarity, and increase in excretion of ammonia and titratable acid (8, 9). Since the plasma bicarbonate concentration is elevated in consequence of the buffering of retained carbon dioxide, one would anticipate from *a priori* considerations that a part of the renal compensation in acute respiratory acidosis would consist in an enhancement of the tubular reabsorption of bicarbonate bound base so as to maintain plasma bicarbonate concentration at supranormal levels.

The studies reported below indicate that acute respiratory acidosis induced by respiring carbon dioxide-oxygen mixtures does in fact result in enhancement of the renal reabsorption of bicarbonate bound base, and that the elevation of carbon dioxide tension of the body fluids rather than lowering of pH is primarily responsible for this increase. Additional data to be presented suggest that bicarbonate bound base is reabsorbed by a process of ion exchange.

METHODS

A total of 39 experiments was performed on 12 mongrel female dogs. Intravenous sodium pentobarbital was used to induce and maintain anesthesia; dosage was variable, but did not exceed 30 mg. per Kg. In all experiments the dog was intubated with an endotracheal airway equipped with an inflatable rubber cuff. During control periods the dog respired ambient room air. Mixtures of CO_2 and O_2 were administered as desired by connecting the endotracheal tube to a non-rebreathing Digby-Leigh valve, the inspiratory side of which was connected to a Douglas bag containing the mixtures to be breathed. The dogs breathed spontaneously throughout; artificial respiration was not employed. This arrangement insured the maintenance of an adequate airway and eliminated the necessity of a tracheotomy, thereby permitting repeated studies to be performed on each animal.

Solutions were infused intravenously at desired rates using a calibrated pump. Urine samples were collected using a Foley catheter connected to a length of rubber tubing which dipped under mineral oil in the collecting graduate. Exposure to air with resultant loss of CO_2 was thereby minimized. Each collection period was terminated by manual compression of the abdomen, facilitating bladder emptying. Arterial blood samples were obtained at the midpoint of each period from an indwelling needle in the femoral artery. One portion, collected with heparin as the anticoagulant, was used for the determination of creatinine, sodium and potassium. A second portion was collected in an oiled syringe containing two drops of saturated potassium oxalate. Two cc. were delivered into a Van Slyke pipette for determination of pH; the remainder was delivered under mineral oil into a tube, which was then sealed with paraffin, centrifuged and analyzed for CO_2 content within two hours. Creatinine was determined in urine and protein-free filtrates of plasma precipitated with tungstic acid, by the method of Phillips (10). Total CO_2 in plasma and urine was determined by the manometric extraction technique of Van Slyke and Neill (11). The pH of whole blood and urine was determined using a water-jacketed Cambridge condenser-type glass electrode, at a uniform temperature of 37°C. Concentrations of bicarbonate and dissolved CO_2 were calculated from the Henderson-Hasselbach equation, employing a pK′ for

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TABLE I

Experiments illustrating the effect of acute respiratory acidosis on the renal reabsorption of bicarbonate bound base

Concurrent time	Gas respired	Glom. filt. rate	Urine flow	Plasma			Urine			$BHCO_3$			
				pH	$BHCO_3$	pCO_2	pH	$BHCO_3$	pCO_2	Filt.	Excr.	Reabsorbed	
Minutes		*ml./min.*	*ml./min.*		*mEq./L.*	*mm. Hg*		*mEq./L.*	*mm. Hg*	*mEq./min.*	*mEq./min.*	*mEq./min.*	*mEq./100 ml. filtrate*
Experiment No. 5. Dog B—20.9 Kg.													
−82		Start infusion: Creatinine 2.66 Gm./L.; $NaHCO_3$ 16.6 Gm./L. @ 5.5 ml./min.											
−78		Prime: Creatinine 1.3 Gm.; $NaHCO_3$ 5.3 Gm.											
0–20	Room	99.9	2.23	7.58	32.9	36.2	8.10	266	87.4	3.29	0.59	2.70	2.70
20–40	Air	90.0	2.06	7.57	34.1	38.6	8.14	250	74.4	3.08	0.52	2.56	2.86
55–75	12% CO_2–	104	2.50	7.33	38.9	76.1	7.94	221	104	4.05	0.55	3.50	3.36
75–95	88% O_2	104	3.00	7.33	40.2	78.6	7.92	210	104	4.19	0.63	3.56	3.42
110–130	Room	104	4.29	7.54	36.7	44.2	8.04	247	90.6	3.80	1.06	2.74	2.65
130–150	Air	101	4.10	7.49	37.0	50.2	8.05	247	90.6	3.74	1.01	2.73	2.70
Experiment No. 8. Dog A—15.7 Kg.													
−80		Start infusion: Creatinine 2.3 Gm./L.; $NaHCO_3$ 18.0 Gm./L. @ 5.0 ml./min.											
−73		Prime: Creatinine 1.5 Gm.; $NaHCO_3$ 5.0 Gm.											
0–20	Room	63.5	3.30	7.48	41.4	57.1	7.96	256	113	2.76	0.84	1.92	3.02
20–40	Air	62.4	3.30	7.45	41.8	61.8	7.99	261	110	2.74	0.86	1.88	3.02
75–95	12% CO_2–	65.0	2.75	7.29	45.4	87.4	7.89	254	133	3.10	0.70	2.40	3.71
95–115	88% O_2	65.2	3.23	7.30	45.2	94.9	7.85	255	146	3.10	0.82	2.28	3.49
130–150	Room	75.1	4.52	7.48	42.1	58.5	7.89	252	133	3.33	1.14	2.19	2.92
150–170	Air	72.7	4.25	7.44	42.2	64.2	7.96	252	113	3.22	1.08	2.14	2.94

carbonic acid of 6.1, and 0.0591 α equal to 0.0301 for plasma and 0.0309 for urine. It was not considered necessary to adjust these factors for the ionic strength of plasma or urine. Sodium and potassium concentrations in plasma and urine were determined using an internal standard flame photometer.

The creatinine clearance was taken as equal to the glomerular filtration rate. The amount of each ion filtered in unit time was calculated as the product of its plasma concentration and the glomerular filtration rate, corrected for Donnan distribution across the glomerular membrane. A factor of 0.95 was taken for Na^+ and K^+, and 1.05 for Cl^- and HCO_3^-. The rate of excretion was calculated as the product of urine concentration and urine flow. The rate of reabsorption of each ion was calculated as the difference between the rates of filtration and excretion. Since in the dog and in man the reabsorption of bicarbonate per unit time has been shown to be a rectilinear function of glomerular filtration rate (12), the rate of reabsorption was also expressed in terms of the amount reabsorbed per 100 ml. of filtrate. This was done by dividing the absolute rate of reabsorption (mEq. per min.) by the GFR (ml. per min.) and multiplying by 100.

RESULTS

The effect of acute respiratory acidosis induced by breathing 12 per cent CO_2–88 per cent O_2 on the renal reabsorption of bicarbonate bound base was determined in eight experiments. Data from two representative experiments of this group are presented in Table I. In these experiments, the plasma concentration of bicarbonate was elevated to a level adequate to insure frank excretion and was maintained at approximately 37 to 44 mEq. per liter by infusing sodium bicarbonate at a constant rate. During the first two periods the dog respired room air; this was changed to 12 per cent CO_2–88 per cent O_2 during the middle two periods, and the dog again respired room air during the final two periods. Plasma pH, initially elevated by the bicarbonate infusion, dropped during the inhalation of CO_2, returning to control levels when air breathing was resumed. Plasma pCO_2 rose from essentially normal values on room air to approximately 90 mm. Hg [3] during CO_2 breathing, to fall toward control values when air was restored.

The final two columns of this table demonstrate the effect of acute respiratory acidosis on the re-

[3] Variability in pCO_2 in animals breathing 12 per cent CO_2 is the result of a number of factors including: leakage of room air into the system, differences in composition of tank gas, and variable respiratory depression from anesthesia.

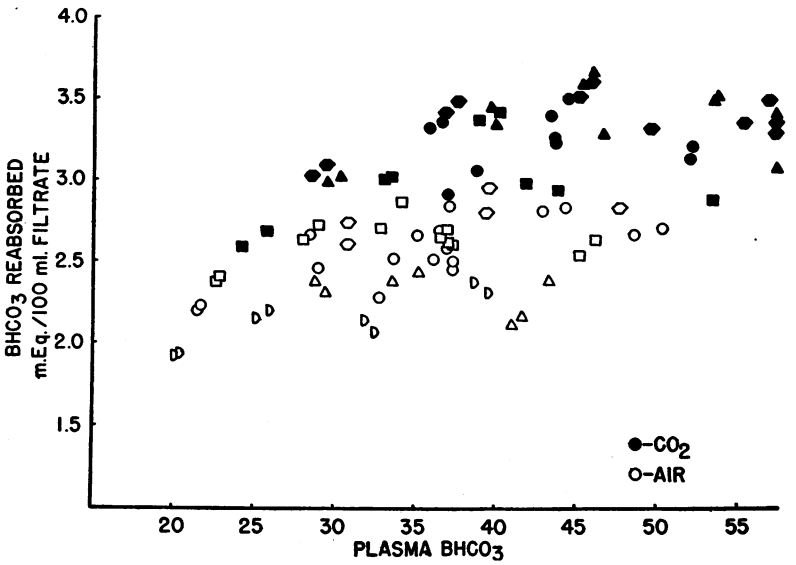

FIG. 1. THE RENAL REABSORPTION OF BICARBONATE BOUND IN THE DOG, AS A FUNCTION OF PLASMA BICARBONATE CONCENTRATION

Open circles: Respiring room air.
Solid circles: Respiring 12 per cent CO_2–88 per cent O_2.

nal tubular reabsorption of bicarbonate bound base. It is clear that the induction of respiratory acidosis was followed by a prompt and significant elevation in reabsorption of bicarbonate bound base, whether expressed in absolute terms of mEq. per min. or in relative terms of mEq. per 100 ml. glomerular filtrate. Expressed in the latter units, reabsorption on Dog A rose from an average control value of 2.48 to 3.45 during respiratory acidosis. With the resumption of breathing room air, reabsorption fell rapidly toward control values.

In order to determine the effect of CO_2 inhalation at various plasma bicarbonate levels, paired experiments were performed on each of five dogs. In these experiments, plasma bicarbonate concentration was elevated in stepwise increments from normal values to approximately 55 mEq. per liter. In the first experiment of each pair, the dog breathed room air throughout. In the second, it breathed 12 per cent CO_2–88 per cent O_2.

Data from these experiments are presented in graphical form in Figure 1. It is evident that, over the entire range of plasma bicarbonate concentration investigated, renal tubular reabsorption of bicarbonate bound base was increased by CO_2 inhalation.

Our attention was next directed toward determining which of the changes associated with respiratory acidosis was primarily effective in enhancing renal tubular reabsorption of bicarbonate bound base. The data presented thus far confirm the well-established observation that respiratory acidosis is associated with two changes in body fluid composition: elevation of pCO_2 and depression of pH (7). Stanbury and Thomson (13), and Ochwadt (14), on the basis of studies of bicarbonate excretion during hyperventilation in normal human subjects, concluded that the change in plasma pH rather than change in pCO_2 is the important stimulus effecting a change in bicarbonate reabsorption, which was decreased in their experiments. Similar conclusions were drawn by Elkinton, based on studies on hyperventilation (15) and CO_2 inhalation (16) in normal human subjects.

On the other hand, Brazeau and Gilman (17) employing controlled ventilation, as well as CO_2 inhalation in curarized dogs, varied arterial pCO_2 over a wide range (25 to 110 mm. Hg) and concluded that bicarbonate reabsorption expressed as mM per 100 ml. filtrate is practically a linear function of arterial pCO_2.

In Figure 2A, our data on bicarbonate reabsorption are plotted as a function of blood pH. It is seen that there exists a fair correlation between reabsorption of bicarbonate bound base and blood

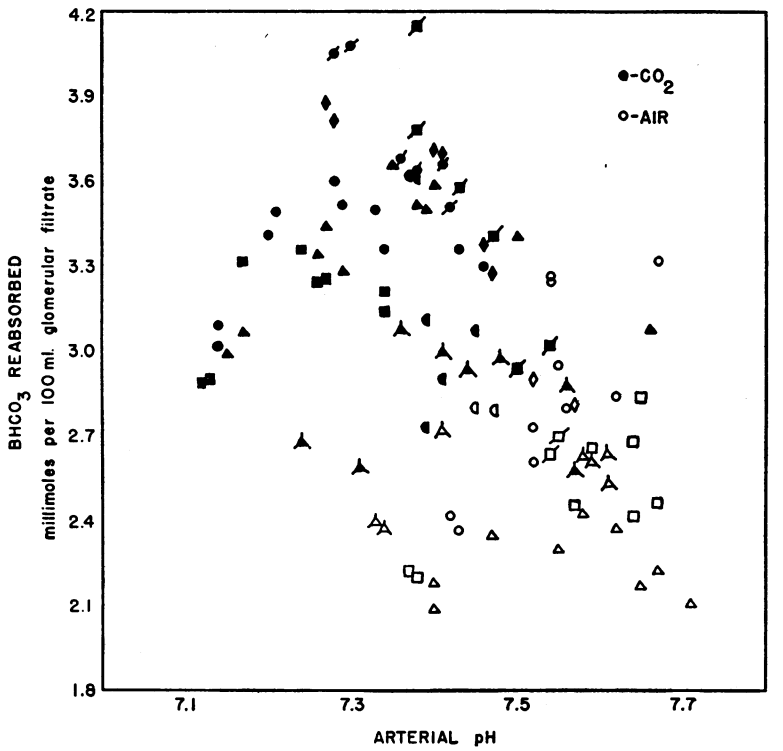

FIG. 2A. RENAL REABSORPTION OF BICARBONATE BOUND BASE, AS A FUNCTION OF ARTERIAL pH

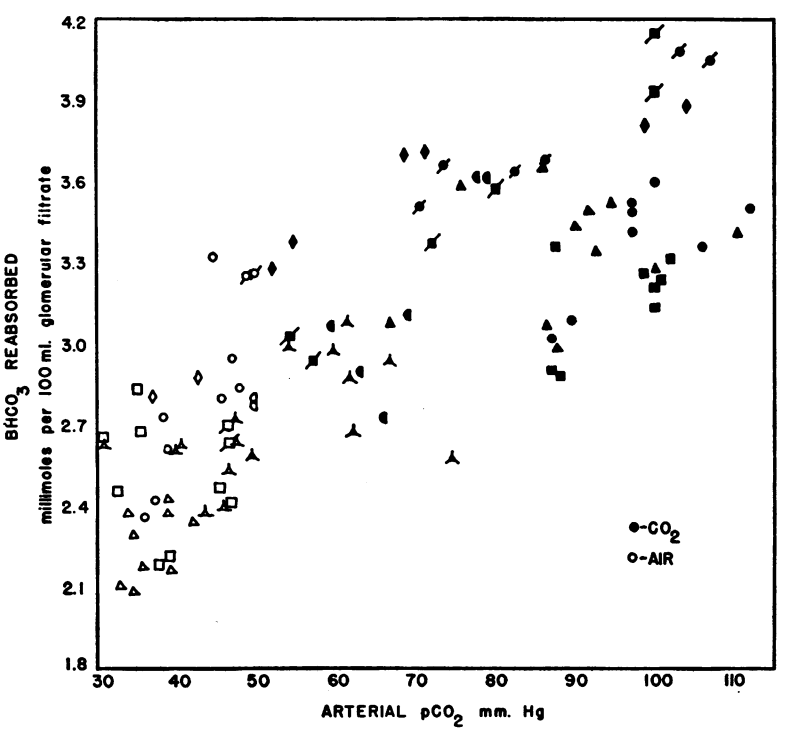

FIG. 2B. RENAL REABSORPTION OF BICARBONATE BOUND BASE, AS A FUNCTION OF ARTERIAL pCO_2

TABLE II

Experiments illustrating the effect of an elevated arterial pCO_2, with no concomitant significant change in arterial pH, on the renal reabsorption of bicarbonate bound base

Concurrent time	Glom. filt. rate	Urine flow	Plasma			Urine			$BHCO_3$			
			pH	$BHCO_3$	pCO_2	pH	$BHCO_3$	pCO_2	Filt.	Excr.	Reabsorbed	
Minutes	*ml./min.*	*ml./min.*		*mEq./L.*	*mm. Hg*		*mEq./L.*	*mm. Hg*	*mEq./min.*	*mEq./min.*	*mEq./min.*	*mEq./100 ml. filtrate*
Experiment No. 33. Dog A—15.5 Kg.												
−65	Start infusion No. I: Creatinine 2.0 Gm./L.; $NaHCO_3$ 8.0 Gm./L. @ 5.0 ml./min.											
−60	Prime: Creatinine 1.3 Gm.; $NaHCO_3$ 4.0 Gm. Dog respiring room air											
0–15	50.9	1.64	7.49	34.8	47.3	7.97	257	116	1.86	0.42	1.44	2.82
15–30	51.0	1.64	7.50	34.9	46.3	7.97	259	116	1.87	0.43	1.44	2.82
30–45	46.9	1.51	7.49	34.2	46.3	8.00	255	106	1.69	0.38	1.31	2.80
135	Start infusion No. II: Creatinine 0.67 Gm./L.; $NaHCO_3$ 20.0 Gm./L. @ 20.0 ml./min.											
145	Prime: $NaHCO_3$ 18.0 Gm. Dog respiring 12% CO_2–88% O_2											
170–180	54.4	18.7	7.49	89.1	120.9	7.79	174	116	5.10	3.24	1.86	3.42
180–190	55.4	19.0	7.48	92.2	127.9	7.76	176	126	5.35	3.34	2.01	3.64
190–200	53.0	18.8	7.48	94.5	131.1	7.74	177	133	5.25	3.32	1.93	3.64
Experiment No. 37. Dog L—14.5 Kg.												
−55	Start infusion No. I: Creatinine 2.0 Gm./L.; $NaHCO_3$ 8.0 Gm./L. @ 5.0 ml./min.											
−45	Prime: Creatinine 1.2 Gm.; $NaHCO_3$ 4.0 Gm. Dog respiring room air											
0–15	54.9	2.69	7.47	30.4	43.2	7.48	38.2	51.5	1.75	0.10	1.65	3.01
15–30	56.3	4.11	7.47	29.4	41.9	7.38	31.5	53.8	1.74	0.13	1.61	2.86
30–45	58.2	3.97	7.45	28.8	42.5	7.46	31.0	43.7	1.76	0.12	1.64	2.82
65	Prime: $NaHCO_3$ 18.0 Gm. Dog respiring 12% CO_2–88% O_2											
80	Start infusion No. II: Creatinine 0.5 Gm./L.; $NaHCO_3$—20.0 Gm./L. @ 20 ml./min.											
100–110	48.4	15.1	7.47	69.2	98.0	7.67	115	100	3.52	1.74	1.78	3.68
110–120	52.4	16.7	7.47	71.3	101	7.67	112	97.1	3.92	1.87	2.05	3.91
120–130	51.1	18.3	7.48	73.8	102	7.65	113	104	3.96	2.06	1.90	3.72

pH. However, low blood pH in these experiments was invariably associated with an elevated arterial pCO_2; and when bicarbonate reabsorption is plotted as a function of arterial pCO_2 (Figure 2B), the correlation is at least as good and probably better.

In order to determine whether change in pH or change in pCO_2 was the stimulus effective in enhancing reabsorption of bicarbonate bound base, two further types of experiments were performed.

In the first type of experiment, the animal breathed room air initially, and sodium bicarbonate was infused at a rate just sufficient to insure frank excretion, with slight elevation of the blood pH. After several control periods, a mixture of 12 per cent CO_2–88 per cent O_2 was respired and plasma bicarbonate level was further raised by the more rapid infusion of sodium bicarbonate. The concomitant elevations of plasma pCO_2 and bicarbonate concentration were so balanced that blood pH did not change significantly from control values.

Data from two typical experiments of this variety are presented in Table II. In the first of these (Experiment 33), blood pH averaged 7.49 during the control periods. With the initiation of the CO_2 breathing and increased bicarbonate infusion, blood pH did not change significantly. However, concomitant with an increase in arterial pCO_2 from an average control value of 46.3 mm. Hg to 127 mm. Hg on CO_2 breathing, reabsorption of bicarbonate bound base rose from an average control value of 2.81 mEq. per 100 ml. glomerular filtrate to 3.57.

Similar results were obtained in Experiment 37, data from which are also presented in Table II. In this experiment control values of blood pH averaged 7.46, with no significant change with the induction of respiratory acidosis and increased infusion of bicarbonate. However, associated with an elevation of arterial pCO_2 from an average value of 42.5 mm. Hg while breathing room air, to 100 mm. Hg on breathing CO_2, reabsorption of bicarbonate bound base again rose significantly, from

2.90 mEq. per 100 ml. glomerular filtrate on room air to 3.77 on breathing CO_2.

In Table III are presented data from the second type of experiment. Here, arterial pCO_2 was held approximately constant, while blood pH was increased by stepwise increments in plasma bicarbonate concentration. In spite of a marked increase in blood pH during the course of the experiment, renal reabsorption of bicarbonate bound base remained approximately constant, presumably associated with a virtually constant arterial pCO_2.

From a consideration of these data it seems clear that increase in arterial pCO_2, rather than decrease in pH, is the stimulus effective in enhancing reabsorption of bicarbonate bound base.

DISCUSSION

The data presented thus far indicate that the renal tubular response to an acutely induced respiratory acidosis consists principally in an enhancement of the reabsorption of bicarbonate bound base, both in absolute (mEq. per min.) and relative (mEq. per 100 ml. filtrate) terms. Furthermore, the effective stimulus for this increase in reabsorption appears to be the increase in pCO_2 of the body fluids.

The mechanism of reabsorption of bicarbonate bound base proposed by Pitts and Lotspeich (12) postulated a specific transport mechanism localized to the proximal tubule, by which some 80 per cent

TABLE III

Experiments illustrating the effect of an elevation in blood pH, with virtually constant arterial pCO_2, on the renal reabsorption of bicarbonate bound base

Concurrent time	Glom. filt. rate	Urine flow	Plasma			Urine			$BHCO_3$			
			pH	$BHCO_3$	pCO_2	pH	$BHCO_3$	pCO_2	Filt.	Excr.	Reabsorbed	
Minutes	*ml./min.*	*ml./min.*		*mEq./L.*	*mm. Hg*		*mEq./L.*	*mm. Hg*	*mEq./min.*	*mEq./min.*	*mEq./min.*	*mEq./100 ml. filtrate*
Experiment No. 18. Dog E—26.5 Kg. Breathing 12% CO_2–88% O_2 throughout												
–45	Infuse: Creatinine 3.8 Gm./L.; Mannitol 50 Gm./L. @ 5.0 ml./min.											
–44	Prime: Creatinine 2.0 Gm.											
0–15	78.6	1.70	7.14	28.7	87.0	5.78	0.95	66.1	2.37	0.0016	2.37	3.02
15–30	80.0	2.13	7.14	29.5	89.5	6.00	2.31	96.9	2.48	0.0049	2.47	3.08
30	Infuse: $NaHCO_3$ 14 Gm./L. @ 5.0 ml./min. Prime: $NaHCO_3$—6.8 Gm.											
50–65	80.3	3.46	7.21	37.7	97.1	7.55	105	123	3.16	0.36	2.80	3.49
65–80	99.0	4.12	7.20	36.9	97.1	7.52	101	126	3.82	0.42	3.41	3.41
80	Infuse: $NaHCO_3$ 28 Gm./L. @ 5.0 ml./min. Prime: $NaHCO_3$ 6.8 Gm.											
100–115	81.0	5.74	7.29	45.2	97.1	7.69	171	146	3.84	0.98	2.86	3.52
115–130	100	6.96	7.28	45.8	100	7.71	177	143	4.84	1.24	3.60	3.60
130	Infuse: $NaHCO_3$ 56 Gm./L. @ 5.0 ml./min. Prime: $NaHCO_3$ 6.8 Gm.											
150–165	108	14.3	7.34	55.4	106	7.76	187	136	6.30	2.66	3.64	3.36
165–180	89.5	12.1	7.33	57.1	112	7.75	184	136	5.36	2.23	3.13	3.50
180	Infuse: $NaHCO_3$ 84 Gm./L. @ 5.0 ml./min. Prime: $NaHCO_3$ 6.8 Gm.											
200–215	101	20.1	7.46	69.0	100	7.73	196	153	7.28	3.94	3.34	3.30
215–230	98.6	19.5	7.43	70.7	110	7.79	205	140	7.31	4.00	3.31	3.36
Experiment No. 19. Dog G—15.0 Kg. Breathing room air throughout												
–50	Infuse: Creatinine 2.0 Gm./L.; Mannitol 50 Gm./L. @ 5.0 ml./min.											
–25	Prime: Creatinine 1.0 Gm.											
0–15	39.2	4.13	7.39	19.5	33.9	6.79	3.97	26.2	0.82	0.02	0.80	2.04
15–30	35.8	2.87	7.39	19.4	33.2	6.74	3.56	26.2	0.73	0.01	0.72	2.01
47	Infuse: Creatinine 2.0 Gm./L.; $NaHCO_3$ 6.0 Gm./L. @ 5.0 ml./min.											
50	Prime: $NaHCO_3$ 4.5 Gm.											
75–90	46.9	3.47	7.50	26.0	34.2	7.77	70.5	48.9	1.28	0.24	1.04	2.20
90–105	51.8	3.20	7.52	25.1	31.9	7.83	78.2	47.2	1.37	0.25	1.12	2.15
105	Infuse: Creatinine 2.0 Gm./L.; $NaHCO_3$ 12.0 Gm./L. @ 5.0 ml./min. Prime: $NaHCO_3$ 4.5 Gm.											
125–140	56.9	6.43	7.60	32.6	34.2	7.94	120	55.0	1.95	0.77	1.18	2.07
140–155	56.2	4.93	7.60	31.8	33.6	7.96	136	61.5	1.88	0.67	1.21	2.14
160	Infuse: Creatinine 2.0 Gm./L.; $NaHCO_3$ 20.0 Gm./L. @ 5.0 ml./min. Prime: $NaHCO_3$ 4.5 Gm.											
175–190	52.3	6.80	7.65	39.6	37.2	7.98	141	61.5	2.18	0.96	1.21	2.32
190–205	50.6	5.44	7.65	38.7	36.2	8.01	158	61.5	2.06	0.86	1.20	2.38

TABLE IV

Experiment illustrating the effect of No. 6063 on the renal tubular response to respiratory acidosis

Concurrent time	Gas breathed	Glom. filt. rate	Urine flow	Plasma			Urine			$BHCO_3$			
				pH	$BHCO_3$	pCO_2	pH	$BHCO_3$	pCO_2	Filt.	Excr.	Reabsorbed	
Minutes		*ml./min.*	*ml./min.*		*mEq./L.*	*mm. Hg*		*mEq./L.*	*mm. Hg*	*mEq./min.*	*mEq./min.*	*mEq./min.*	*mEq./100 ml. glom. filt.*
Experiment No. 21. Dog A—15.0 Kg.													
-80	Infuse: Creatinine 2.3 Gm./L.; $NaHCO_3$ 8.0 Gm./L. @ 5.0 ml./min. Prime: Creatinine 1.5 Gm.; $NaHCO_3$ 4.0 Gm.												
0–15	Room	56.8	1.80	7.43	36.1	56.2	8.00	228	93.9	2.15	0.41	1.74	3.07
15–30	Air	54.8	1.76	7.43	36.4	56.5	8.05	236	84.1	2.09	0.42	1.68	3.06
50–65		54.5	1.44	7.30	39.4	82.9	7.85	188	107.0	2.26	0.27	1.98	3.65
65–80	12%	52.3	1.37	7.25	40.4	95.0	7.83	192	116.6	2.21	0.26	1.95	3.72
80	CO_2–	Infuse: Creatinine 2.3 Gm./L.; $NaHCO_3$ 12.0 Gm./L.; No. 6063 1.0 Gm./L. @ 5.0 ml./min. Prime: $NaHCO_3$ 4.0 Gm.; No. 6063 0.15 Gm.											
100–115	88% O_2	48.7	5.50	7.24	45.1	108.8	7.70	202	165.0	2.31	1.11	1.20	2.46
115–130		50.4	5.50	7.21	44.4	114.8	7.69	203	168.2	2.35	1.12	1.24	2.45
150–165	Room	50.9	6.01	7.40	39.8	66.1	7.83	199	119.9	2.13	1.19	0.94	1.84
165–180	Air	49.6	5.33	7.39	38.5	65.9	7.84	206	119.9	2.01	1.18	0.83	1.67

of bicarbonate reabsorption was believed to be effected under isohydric conditions. The remaining 20 per cent was believed to be reabsorbed in the distal tubules by a process of ion exchange. This process could be depressed by sulfonamide compounds, presumably by virtue of their inhibition of the enzyme carbonic anhydrase, which accelerates the hydration of molecular CO_2 to carbonic acid.

However, it has recently been shown that half or more of the bicarbonate normally reabsorbed may be excreted under the influence of the carbonic anhydrase inhibitor 2-acetylamino-1,3,4-thiadiazole-5-sulfonamide (No. 6063)[4] (18). Therefore, it is our present conception that all reabsorption of bicarbonate bound base is mediated by a process of ion exchange in which the hydration of carbon dioxide to carbonic acid is an essential link.

The data in Table IV illustrate the effect of No. 6063 on the enhancement of bicarbonate reabsorption induced by breathing 12 per cent CO_2. As indicated in the first column, room air was breathed during the first and second, and also during the seventh and eighth periods. Sodium bicarbonate was infused so as to produce a moderate elevation in plasma bicarbonate concentration. Between the fourth and fifth periods, a priming dose of No. 6063 was given, and this was followed by a sustaining infusion containing No. 6063.

As may be seen from the last two columns of this table, the inhalation of 12 per cent CO_2 elicited the customary increase in reabsorption of bicarbonate bound base. Under these conditions, the infusion of No. 6063 resulted in a reduction in reabsorption of bicarbonate to values below those of the control periods. However, the further significant reduction of bicarbonate reabsorption which accompanied the resumption of breathing room air indicates that the elevation in pCO_2 of the body fluids was still effective in enhancing bicarbonate

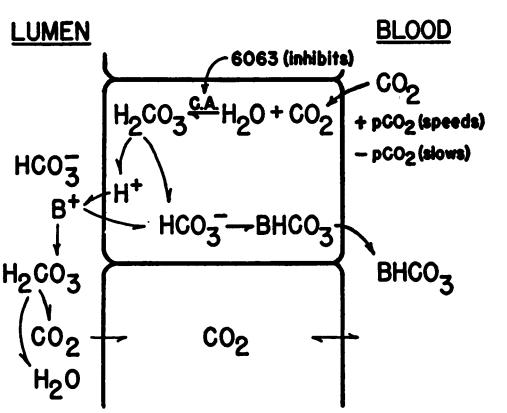

FIG. 3. PROPOSED SCHEMA OF THE PROCESSES INVOLVED IN THE REABSORPTION OF BICARBONATE BOUND BASE BY THE RENAL TUBULES

[4] We are indebted to the American Cyanamid Company for a supply of No. 6063.

reabsorption despite the inhibition of a considerable amount of carbonic anhydrase activity.

These and other data from our laboratory and from the laboratories of others (17, 19) can be explained in terms of the schema presented in Figure 3. Carbon dioxide is hydrated to carbonic acid within the tubular cells. This carbonic acid in turn dissociates to yield hydrogen ions which are exchanged for base bound by bicarbonate in the tubular urine. Carbonic anhydrase accelerates the hydration of carbon dioxide and increases the available supply of hydrogen ions. The action of No. 6063 in blocking the enzymatically facilitated hydration process reduces reabsorption of base. However, reabsorption continues, albeit at a reduced rate, for hydration occurs even though this enzyme is inactivated to a considerable degree. An increase in pCO_2 speeds the hydration process and consequently increases the reabsorption of base. A decrease in pCO_2 slows the hydration process and reduces reabsorption of base. According to this schema, the bicarbonate ion which accompanies the base into the peritubular blood is not that which accompanied it from plasma into the glomerular filtrate. This latter bicarbonate ion, first transformed into carbonic acid, dehydrates in part to form CO_2 and water in the tubular lumen. The CO_2 then diffuses back into the renal venous blood stream. Hence, in a strict sense, one should not speak of reabsorption of bicarbonate ion; rather, one must consider the reabsorption of the base bound by bicarbonate ion. How energy is cycled into this mechanism, to bring about the exchange of hydrogen ions for base, is beyond our present comprehension of the problem.

SUMMARY AND CONCLUSIONS

In normal dogs receiving infusions of sodium bicarbonate, acute respiratory acidosis induced by breathing 12 per cent CO_2 results in a significant increase in the rate of reabsorption of bicarbonate bound base, whether expressed in absolute or relative terms.

In acute respiratory acidosis, a change in pCO_2 of the body fluids is the effective stimulus in enhancing the reabsorption of bicarbonate bound base. A change in pH does not *per se* affect this reabsorptive mechanism.

The hypothesis proposed to account for these observations postulates a mechanism involving exchange of hydrogen ions for basic ions, operating throughout the renal tubule. This mechanism, enzymatically facilitated by carbonic anhydrase, is depressed by carbonic anhydrase inhibitors such as No. 6063.

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