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THE RENAL AND ELECTROLYTE RESPONSE TO RESPIRATORY ACIDOSIS IN THE ADRENALECTOMIZED RAT†

The renal response to respiratory acidosis is characterized in the rat[1,2] and in the dog[3] by chloruresis, a negative chloride balance, an elevated tubular reabsorption of bicarbonate with renal conservation of bicarbonate, and increased urinary excretion of acid. The depression of chloride and elevation of bicarbonate in the serum at equilibrium during sustained exposure to carbon dioxide depend on these changes in renal tubular function.[1]

It has been shown that exposure to carbon dioxide stimulates adrenocortical activity in the dog,[4] and in the rat.[5-7] Both aldosterone and hydrocortisone accelerate renal tubular sodium-hydrogen and sodium-potassium exchange;[8] the former reaction is important for tubular reabsorption of bicarbonate.[9] In adrenal insufficiency there is impaired renal excretion of acid in response to metabolic acidosis.[10] These relationships motivated the present study of the renal response to respiratory acidosis in adrenalectomized rats. It is concluded that the chloruresis and increased tubular reabsorption of HCO_3 produced by respiratory acidosis are not dependent on adrenal cortical hormones.

METHODS

Sprague Dawley rats weighing 180-240 grams were used. After bilateral adrenalectomy, rats were maintained either by drinking, ad lib, normal saline (150 MEq/L) (Group A) or by a daily subcutaneous injection of 0.5 milligrams desoxycorticortisone acetate in oil and two milligrams of cortisone acetate (Group B) for one week. The rats were trained to eat their total daily intake of an artificial low residue, high caloric diet in a 40-minute period, as previously described,[1] to avoid the inevitable diminution of intake during exposure to CO_2. The diet contained 0.11 mEq. of sodium, 0.13 mEq. of potassium, and 0.10 mEq. of chloride per gm. by analysis. The addition of five per cent sucrose to the saline increased intake of the solution and

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† This study was supported by research grants from the National Institute of Health (USPHS HE-00834, AM-5015) and the American Heart Association.
Received for publication 15 December 1965.

TABLE 1. EFFECT OF 8 PER CENT CO_2 ON THE SERUM ELECTROLYTES OF CONTROL AND ADRENALECTOMIZED RATS
(Group A on saline; Group B on exogenous steroid)

	Control rats		*Adrenalectomized rats*			
			Group A		*Group B*	
	(9 rats) Room air	*(7 rats) 8% CO_2*	*(6 rats) Room air*	*(8 rats) 8% CO_2*	*(6 rats) Room air*	*(7 rats) 8% CO_2*
CO_2 mM/L	23.3 ± 2.3‡	35.1 ± 2.6*	22.9 ± 2.4	34.5 ± 3.8*	25.4 ± 1.7	36.9 ± 3.4*
Cl mEq/L	103.6 ± 1.5	94.6 ± 2.0*	104.1 ± 4.1	90.8 ± 2.7*	97.2 ± 2.8	91.0 ± 4.1*
Na mEq/L	143.0 ± 3.0	144.8 ± 3.6	143.5 ± 5.7	142.8 ± 4.6	144.2 ± 2.8	145.3 ± 4.1
K mEq/L	4.49 ± 0.21	5.01 ± 0.36*	6.56 ± 1.24	6.59 ± 1.48	4.09 ± 0.48	4.45 ± 0.89

* $p = <0.01$ when compared with value for similar rats in each group in room air.
‡ Values are mean ± S.D.

improved the condition of rats in Group A, especially during the initial dietary training period. Glycosuria was tested for daily and was absent. When at least the preoperative weights were reached, metabolic balance was performed in individual cages in air, as previously described, for three control days, followed by 24 hours in a lucite chamber with a controlled inflow of eight per cent CO_2 in air. Rats were stimulated to pass urine at the end of each 24-hour period by making them sniff ether. Urine was collected under mineral oil and preserved with thymol. Immediately after removal from carbon dioxide, blood was obtained from the abdominal aorta in syringes filled with mineral oil, and samples of thigh muscle were taken. Similar blood and muscle specimens were obtained from normal controls and from normal rats and adrenalectomized rats maintained in room air. In the experimental groups the completeness of adrenalectomy was confirmed at autopsy.

Serum, urine and muscle sodium and potassium were measured on a flame photometer with an internal lithium standard, serum and urine chloride on the Cotlove chloridometer, and serum and urine bicarbonate by the method of Van Slyke and Neill. Methods of preparation of muscle for analysis have been described previously[11] as have methods for urine creatinine and ammonia.[1] Samples of air in the chamber were analyzed for CO_2 and O_2 content using a Beckman gas analyzer. The mean carbon dioxide in the three experiments was 8.7 per cent (range 8.2 to 9.3%) and mean oxygen 18.4 per cent (range 17.9 to 19.1%). No animals died during exposure to CO_2. Mean changes in body weight during CO_2 were $+0.4 \pm 2.7$ per cent for controls, -0.3 ± 2.3 per cent for Group A, and -2.1 ± 1.7 per cent for Group B (mean $\pm$ S.D.).

RESULTS

Serum electrolytes

Exposure of adrenalectomized rats maintained on either saline or steroids to eight per cent carbon dioxide for 24 hours induces a significant rise in serum bicarbonate and a decrease in serum chloride equal to that seen for similarly treated normal rats. (Table 1.) Serum potassium rose in the control and steroid-treated rats. While in room air the rats maintained on saline alone had an elevated serum potassium, but did not show a further increase when exposed to carbon dioxide.

Electrolyte balance

During exposure to carbon dioxide each of the three groups shown in A, B, and C of Table 2 had a chloruresis with negative chloride balance significantly different from the balance of the previous day. Potassium balance became less positive in all groups, with an increase in urinary excretion, but levels of statistical significance as compared to the previous day were reached only in the two experimental groups. Sodium balance changed significantly in carbon dioxide only in the saline-maintained adrenalectomized rats but this can be ascribed to a marked reduction in sodium intake as compared to the previous day ($p < 0.025$) because of

TABLE 2 A. ELECTROLYTE BALANCE DATA OF CONTROL RATS EXPOSED TO 8 PER CENT CO_2

	No.		Room air			8% CO_2	p value
			Day 1	Day 2	Day 3	Day 4	
Chloride, mEq.	7	Intake	0.46 ± 0.12†	0.62 ± 0.01	0.60 ± 0.03	0.58 ± 0.02	
		Output	0.50 ± 0.16	0.60 ± 0.03	0.56 ± 0.12	0.79 ± 0.03	
		Balance	—0.04 ± 0.05	+0.02 ± 0.03	+0.04 ± 0.05	—0.21 ± 0.06	$p < 0.001$*
Sodium mEq.	7	Intake	0.50 ± 0.14	0.68 ± 0.03	0.62 ± 0.11	0.63 ± 0.11	
		Output	0.35 ± 0.03	0.54 ± 0.15	0.45 ± 0.12	0.53 ± 0.12	
		Balance	+0.15 ± 0.07	+0.14 ± 0.06	+0.17 ± 0.06	+0.10 ± 0.05	NS
Potassium, mEq.	7	Intake	0.63 ± 0.16	0.84 ± 0.02	0.78 ± 0.03	0.78 ± 0.03	
		Output	0.45 ± 0.02	0.46 ± 0.01	0.55 ± 0.14	0.61 ± 0.02	
		Balance	+0.18 ± 0.09	+0.38 ± 0.08	+0.23 ± 0.16	+0.17 ± 0.09	NS
Creatinine, mg.	7	Output	3.34 ± 0.46	3.34 ± 0.41	3.36 ± 0.41	3.07 ± 0.46	$p < 0.025$
Ammonia, mEq.	5	Output	0.47 ± 0.16	0.46 ± 0.14	0.63 ± 0.26**	0.60 ± 0.29	NS
Titratable acid, mEq.	5	Output	0.12 ± 0.06	0.10 ± 0.02	0.03 ± 0.03**	0.22 ± 0.08	$p < 0.01$
Bicarbonate, mM.	5	Output	0.054 ± 0.045	0.072 ± 0.075	0.142 ± 0.097	0.040 ± 0.032	$p < 0.05$
Net acid excretion‡	5	Output	0.52 ± 0.24	0.41 ± 0.10	0.43 ± 0.13	0.73 ± 0.13	$p < 0.02$

† Results are expressed as mean ± S.D. per 100 gm. of rat per 24 hours.
‡ Net acid excretion (NH_4 + TA — HCO_3).
* p value for balance or output in CO_2 as compared to that for the preceding day.
** An unexplained increase in ammonium excretion and simultaneous decrease in titratable acid excretion is noted on the third day of control rats in room air. These values are distinctly different from values obtained repeatedly under similar control conditions in this laboratory. The reciprocal changes of increased ammonium with decreased titratable acid are seen with fecal contamination and or urinary tract infection. These altered values prevent a significant difference from being apparent during the fourth day in CO_2. To establish the point further, a repeat experiment was done for control and adrenalectomized animals (drinking saline) exposed to carbon dioxide for 24 hours, this time collecting the urine in a receptacle containing 1 ml. of 0.1N sulphuric acid. In control animals a significant increase in ammonium excretion from 0.35 mEq. on day 3 to 0.62 on day 4 in CO_2 ($n = 4$) was observed while adrenalectomized rats showed no change in ammonium excretion (0.46 on day 3 in air and 0.49 on day 4 ($n = 4$) in CO_2).

TABLE 2 B. ELECTROLYTE BALANCE DATA OF ADRENALECTOMIZED RATS, DRINKING SALINE AND EXPOSED TO 8 PER CENT CO_2

	No.		Room air			8% CO_2	p value
			Day 1	Day 2	Day 3	Day 4	
Chloride, mEq.	9	Intake	5.21 ± 2.48†	5.89 ± 1.97	6.40 ± 2.37	3.62 ± 2.77	
		Output	4.93 ± 1.91	5.27 ± 2.14	5.46 ± 1.78	4.05 ± 2.33	
		Balance	+0.28 ± 0.78	+0.62 ± 0.34	+0.94 ± 1.26	−0.43 ± 0.71	$p < 0.01$*
Sodium, mEq.	9	Intake	5.24 ± 2.48	5.98 ± 2.13	6.31 ± 2.25	3.67 ± 2.76	
		Output	4.54 ± 1.72	4.98 ± 2.11	5.40 ± 1.66	3.88 ± 2.36	
		Balance	+0.70 ± 0.64	+1.00 ± 0.30	+0.91 ± 1.01	−0.21 ± 0.54	$p < 0.01$
Potassium, mEq.	9	Intake	0.38 ± 0.02	0.54 ± 0.02	0.59 ± 0.01	0.63 ± 0.01	
		Output	0.33 ± 0.02	0.29 ± 0.02	0.28 ± 0.01	0.45 ± 0.01	
		Balance	+0.05 ± 0.22	+0.35 ± 0.20	+0.34 ± 0.20	+0.18 ± 0.16	$p = 0.05$
Creatinine, mg.	9	Output	3.66 ± 0.67	3.27 ± 0.56	3.34 ± 0.44	3.65 ± 0.71	NS
Ammonia, mEq.	6	Output	0.82 ± 0.75	0.63 ± 0.12	0.87 ± 1.00	1.32 ± 1.02	NS
Titratable acid, mEq.	6	Output	0.18 ± 0.13	0.53 ± 0.83	0.45 ± 0.70	0.07 ± 0.09	NS
Bicarbonate, mM.	6	Output	0.328 ± 0.254	0.310 ± 0.110	0.371 ± 0.110	0.380 ± 0.331	NS
Net acid excretion‡	6	Output	0.75 ± 0.62	0.86 ± 0.70	0.95 ± 0.65	1.00 ± 0.60	NS

† Results are expressed as mean ± S.D. per 100 gm. of rat per 24 hours.
‡ Net acid excretion (NH_4 + TA − HCO_3).
* p value for balance or output in CO_2 as compared to that for the preceding day.

the diminished drinking of saline during exposure to CO_2.

Control rats increased urinary acid excretion significantly in CO_2 (Table 2) as the result of an increase in titratable acid and diminished bicarbonate excretion (see footnote to Table 2A). There was no significant rise in ammonia or titratable acidity, or fall in urine bicarbonate in either experimental group. Urine bicarbonate excretion in saline-maintained animals was higher than controls ($p < 0.005$ on day 3) and did not alter during exposure to CO_2. During the initial three-day observation period in air, all three groups of rats were in positive balance for sodium and potassium, but chloride balance was slightly negative in the steroid-maintained Group B, which was the group with the lower serum chloride. Total acid excretion while in room air was higher in both adrenalectomized groups than in controls, but highest in Group B, which had the higher serum bicarbonate.

Muscle electrolytes

Muscle potassium in control rats fell significantly in CO_2 but was unaltered by exposure to CO_2 in both of the experimental groups. The level of muscle potassium in the steroid-treated group B was lower than control rats ($p < 0.05$) in air. (Table 3.)

DISCUSSION

In the normal rat, hypercapnia induces a rise in serum bicarbonate with a decrease in serum chloride and an increase in the urinary excretion of chloride and acid.[1,2] Adrenalectomized rats also respond to respiratory acidosis with a rise in serum bicarbonate and hypochloremia and with chloruresis similar in magnitude to that seen in normal rats. Uniquely different, however, is the unaltered rate of urinary excretion of acid. This indicates that the increase in serum bicarbonate is primarily derived from extra-renal buffering. Extra-renal buffering in response to hypercapnia has been observed in the nephrectomized dog.[13] Additional evidence of extra-renal buffering has been presented by Schwartz and coworkers[8] who showed that the rise in serum bicarbonate in the dog exposed to carbon dioxide for 24 hours is not associated with changes in acid excretion, although acid excretion does increase as exposure to carbon dioxide is continued. Although the increased bicarbonate in the serum is derived from extra-renal sources in these experiments, an increase in the tubular reabsorption of bicarbonate is a prerequisite to its retention.

In the dog exposed to chronic respiratory acidosis, the maximum reabsorption of bicarbonate is not reached for several days and it has been suggested that steroids play a role in this adaptive response.[13] Dogs

TABLE 2 C. ELECTROLYTE BALANCE DATA OF ADRENALECTOMIZED RATS, RECEIVING STEROIDS, AND EXPOSED TO 8 PER CENT CO_2

	No.		Room air			8% CO_2	p value
			Day 1	Day 2	Day 3	Day 4	
Chloride, mEq.	8	Intake	0.44 ± 0.09†	0.52 ± 0.16	0.50 ± 0.10	0.48 ± 0.10	
		Output	0.56 ± 0.19	0.57 ± 0.11	0.59 ± 0.18	0.73 ± 0.11	
		Balance	−0.12 ± 0.14	−0.05 ± 0.13	−0.09 ± 0.14	−0.25 ± 0.13	$p < 0.05$*
Sodium, mEq.	8	Intake	0.49 ± 0.12	0.57 ± 0.18	0.55 ± 0.09	0.53 ± 0.12	
		Output	0.38 ± 0.12	0.53 ± 0.12	0.47 ± 0.13	0.58 ± 0.14	
		Balance	+0.09 ± 0.13	+0.04 ± 0.15	+0.08 ± 0.21	−0.05 ± 0.14	NS
Potassium, mEq.	8	Intake	0.60 ± 0.12	0.70 ± 0.21	0.67 ± 0.14	0.61 ± 0.14	
		Output	0.50 ± 0.03	0.51 ± 0.02	0.55 ± 0.24	0.61 ± 0.14	
		Balance	+0.10 ± 0.08	+0.19 ± 0.05	+0.12 ± 0.20	−0.01 ± 0.24	$p < 0.05$
Creatinine, mg.	8	Output	3.53 ± 0.33	3.31 ± 0.36	3.70 ± 0.62	3.16 ± 0.55	$p < 0.025$
Ammonia, mEq.	5	Output	0.93 ± 0.38	1.22 ± 0.52	1.41 ± 1.15	0.94 ± 0.32	NS
Titratable acid, mEq.	5	Output	0.04 ± 0.07	0.08 ± 0.10	0.06 ± 0.06	0.11 ± 0.07	NS
Bicarbonate, mM.	5	Output	0.134 ± 0.189	0.073 ± 0.106	0.161 ± 0.209	0.069 ± 0.143	NS
Net acid excretion‡	5	Output	0.84 ± 0.17	1.09 ± 0.75	1.23 ± 0.95	1.00 ± 0.50	NS

† Results are expressed as mean ± S.D. per 100 gm. of rat per 24 hours.
‡ Net acid excretion (NH_4 + TA − HCO_3).
* p value for balance or output in CO_2 as compared to that for the preceding day.

TABLE 3. EFFECT OF 8 PER CENT CO_2 ON ELECTROLYTE COMPOSITION OF RAT MUSCLE IN CONTROL AND ADRENALECTOMIZED RATS

	Control rats		*Adrenalectomized rats*			
			Group A		*Group B*	
	(10 rats) Room air	*(7 rats) 8% CO_2*	*(6 rats) Room air*	*(9 rats) 8% CO_2*	*(5 rats) Room air*	*(8 rats) 8% CO_2*
% H_2O	77.9 ± 0.4‡	76.0 ± 0.7†	78.2 ± 1.0	78.1 ± 0.9	76.8 ± 1.5	75.3 ± 1.7
% Fat	0.9 ± 0.2	1.0 ± 0.6	0.4 ± 0.1	0.8 ± 0.5	0.5 ± 0.04	1.1 ± 0.5*
Fat-free dry solids						
Na mEq/100 gm.	10.6 ± 0.8	9.55 ± 2.2	8.65 ± 2.4	12.23 ± 3.2*	8.16 ± 1.5	10.10 ± 2.1
K mEq/100 gm.	49.1 ± 0.8	46.1 ± 2.7†	48.7 ± 2.5	48.6 ± 2.8	46.2 ± 3.6	46.0 ± 3.0

‡ Values are means ± S.D.
* P value < 0.05 as compared to controls for that group in air.
† P value < 0.005 as compared to controls for that group in air.
Per cent water value for Group A rats in CO_2 were significantly higher than those of both control and Group B rats in CO_2 ($P < 0.001$).

pretreated with desoxycorticosterone acetate rapidly develop an increase in tubular reabsorption of bicarbonate, but it is difficult to dissociate this effect from associated potassium deficiency.[14] Roth and Gamble[15, 16] have stated that chronic DOCA administration in the dog has a direct effect that increases the tubular reabsorption of bicarbonate independently of potassium depletion. The present experiments show that the elevation of serum bicarbonate produced by respiratory acidosis in the rat is not related either directly or in a permissive sense to the presence of, or variation in the level of, adrenal cortical hormones. Hypercapnia, a known potent stimulus to the tubular reabsorption of bicarbonate[17, 18] is apparently the sole factor responsible for the changes observed under these experimental conditions.

Sartorius, *et al.*[10] showed that adrenalectomized rats challenged with metabolic acidosis have a markedly diminished renal response with 80 per cent less titratable acid and 50 per cent less ammonium excretion when compared with normal rats similarly challenged. These observations indicate that adrenalectomized rats also have an impaired ability to increase acid excretion in response to respiratory acidosis. This deficit persists in spite of apparently adequate replacement therapy and suggests that an increase in urinary excretion of acid in response to respiratory acidosis requires an increase in the endogenous production of steroids.

The serum chloride fell to lower levels ($p < 0.01$) in saline-maintained rats than in control rats during CO_2 exposure and there was a greater negative chloride balance. This is most probably the result of the diminished saline intake during carbon dioxide exposure and is reflected in the negative sodium balance in this group. The negative chloride balance was in excess of the sodium balance and in some animals in which sodium balance remained positive, chloruresis was still observed. Adrenalectomized rats whose intake of sodium chloride is abruptly reduced excrete more sodium than chloride in the urine and develop a marked metabolic acidosis.[19] This is in marked contrast to the findings in these rats whose sodium chloride intake was moderately reduced while exposed to carbon dioxide. The chloruresis that occurs in response to exposure to carbon dioxide is clearly dependent upon factors other than saluresis, kaluresis, and increased excretion of ammonium.

Adrenalectomized rats maintained on steroids had a lower serum chloride and serum potassium as well as a slight decrease in muscle potassium, associated with a higher serum bicarbonate and slightly increased net acid excretion. These changes are compatible with minimal potassium deficiency induced by the perhaps excessive dose of steroid. To the extent that potassium deficiency was present it would not be

expected to alter the response to hypercapnia since it has been shown that significant potassium deficiency does not alter the serum and urinary response to hypercapnia, except that muscle potassium, already low, does not decrease further.[20] The higher net acid excretion in the saline-treated adrenalectomized rats while maintained in air with the same dietary intake and the same serum bicarbonate suggests a greater endogenous hydrogen ion production following adrenalectomy without steroid replacement.

The fall in muscle potassium and the rise in serum potassium in normal rats[11] exposed to carbon dioxide has been confirmed in these experiments. The lack of fall of muscle potassium in the adrenalectomized rats suggests that the fall seen in normal animals may be in some way steroid dependent.

SUMMARY

Control and adrenalectomized rats, maintained on normal saline or by exogenous steroid, were exposed to carbon dioxide for 24 hours. In response to respiratory acidosis, adrenalectomized rats developed hypochloremia, an elevation of serum bicarbonate, and a chloruresis similar to that found in controls. Unlike the reaction in controls, net acid excretion did not increase during exposure to carbon dioxide. The rise in serum bicarbonate is attributed to tissue buffering, which is maintained by an increase in tubular reabsorption of bicarbonate. It is concluded that the increase in renal reabsorption of bicarbonate and the chloruresis occurring during exposure to carbon dioxide in the rat is not dependent on adrenal cortical hormones.

ACKNOWLEDGMENTS

We acknowledge the valuable contributions made in the laboratory by Mrs. Corinne Wilson, Mrs. Nadia Myketey, and Mrs. Lorraine Pozika.

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