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EFFECTS OF CHRONIC HYPERCAPNIA ON ELECTROLYTE AND
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THE ADAPTIVE AND RECOVERY PROCESS AS
EVALUATED BY PROVISION OF ALKALI *

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Previous studies have characterized the changes in acid-base equilibrium in dogs exposed over a prolonged period to a 12 per cent carbon dioxide atmosphere (1). Plasma bicarbonate concentration rose in a gradual curvilinear fashion over several days and became stabilized at maximal levels of 35 to 38 mEq per L. This adaptive response was not influenced by the level of sodium chloride intake. After the return of the dogs to room air, however, plasma bicarbonate concentration remained significantly elevated in dogs ingesting a low-salt diet. The resulting alkalosis persisted until chloride was provided, and then normal acid-base equilibrium was rapidly restored (2).

During hypercapnia, the urine remained almost free of bicarbonate and it was therefore not possible to define fully the effects of hypercapnia on the mechanism for bicarbonate reabsorption; the capacity to reabsorb completely as much as 38 mEq of bicarbonate per L of filtrate may have been rapidly engendered by hypercapnia, but not fully employed for several days because of slow renal generation of bicarbonate. In order to evaluate further the effect of a high carbon dioxide tension on the renal threshold for bicarbonate, observations have been carried out in dogs whose diets were supplemented with large quantities of sodium bicarbonate. Under these circumstances, the rise in plasma bicarbonate concentration ought not to be limited by renal ability to generate bicarbonate, but rather by renal reabsorptive capacity. Observations have also been carried out

to assess the renal reabsorptive capacity after restoration of normal carbon dioxide tension in animals maintained on a high-bicarbonate, low-chloride intake.

METHODS

Balance studies were carried out on 7 female mongrel dogs weighing between 13 and 18 kg. Observations were made during a 4- to 7-day control period, a 6- to 13-day period in a high CO₂ atmosphere, and a 9- to 23-day period of recovery.

Each day the animals were fed 30 g per kg of body weight of a synthetic diet of previously described composition (1). The intrinsic electrolyte content of the diet was 1 mEq sodium, less than 1 mEq chloride, and less than 0.1 mEq potassium per 100 g. The daily intake was supplemented with 5.5 to 6.5 mmoles per kg of body weight of sodium bicarbonate and with 2.5 to 3.0 mEq per kg of potassium as phosphate, 4 HPO₄²⁻/1 H₂PO₄⁻. The daily intake was fed in two parts throughout the study. Additional electrolytes were provided as described below. The study was divided into the following three periods.

Period I. Adaptation to high CO₂ atmosphere. The animals were maintained in a 12 ± 1 per cent CO₂ atmosphere according to a technique previously described (1). On day 1, 1 or 2 hours after the morning feeding, the CO₂ concentration in the cage was increased to approximately 12 per cent over a period of 2 to 3 hours. Each morning and evening, the animals were removed briefly from the cage for feeding and other routine procedures; the total time out of the high CO₂ atmosphere was about 30 to 40 minutes daily. All blood samples were taken while the dogs breathed a mixture of 12 per cent CO₂, 20 per cent oxygen, and 68 per cent nitrogen through a mask.

Period II. Recovery—return to room air. The atmosphere in the cage was abruptly restored to normal, and metabolic observations were continued until plasma bicarbonate was stabilized for at least 2 days. Then, 4 dogs were provided for a period of 4 to 5 days with an additional daily intake of electrolytes—2 to 3 mmoles per kg of KHCO₃ for dogs C, E, and Z, and 3 mmoles per kg of sodium bicarbonate for dog D—and were then returned to their basal intake for 2 to 4 days.

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Period III. Recovery—administration of chloride supplement. Dogs L, S, B, and D were provided with 3 to 6 mmoles per kg per day NaCl and dogs Z, C, and E, with 2 to 3 mmoles per kg per day KCl for 1 to 5 days. Observations were continued in five dogs for 3 to 5 days after withdrawal of the chloride load, but since no significant change occurred over this interval, detailed data are not presented.

The analytic methods have been described previously (3). Net alkali excretion has been calculated as $[\text{HCO}_3^- - (\text{NH}_4 + \text{titratable acid})]$. Delta net alkali is expressed as the change from the average output during the last 3 to 7 days of the preceding period. The daily balance was calculated as the net intake minus the combined output in urine, stool, and blood sample. Each 20 ml of blood withdrawn was considered to contain 2 mEq of chloride and 3 mEq of sodium. In dog D, the urine was contaminated on Day 7 of hypercapnia by vomitus; analysis for electrolytes was performed on a nitric acid digest of the mixture.

Supplementary studies on acute changes in plasma bicarbonate concentration and bicarbonate excretion after bicarbonate feeding. Three additional dogs were placed in 12 per cent CO_2 for 2 hours and then force-fed with half their daily diet and half their supplementary NaHCO_3 . Over the next 5 to 6 hours, multiple blood samples were drawn for determination of CO_2 , pH, and other electrolytes. In two animals, voided or catheterized urine specimens were obtained for measurement of pH and CO_2 content at intervals throughout this period. These studies were conducted in unanesthetized animals, without interruption of hypercapnia, by use of an environmental chamber.

RESULTS

At the end of the control period, average plasma concentrations were: 147 mEq per L sodium, 23 mEq per L bicarbonate, 109 mEq per L chloride, and 3.9 mEq per L potassium. Urine bicarbonate

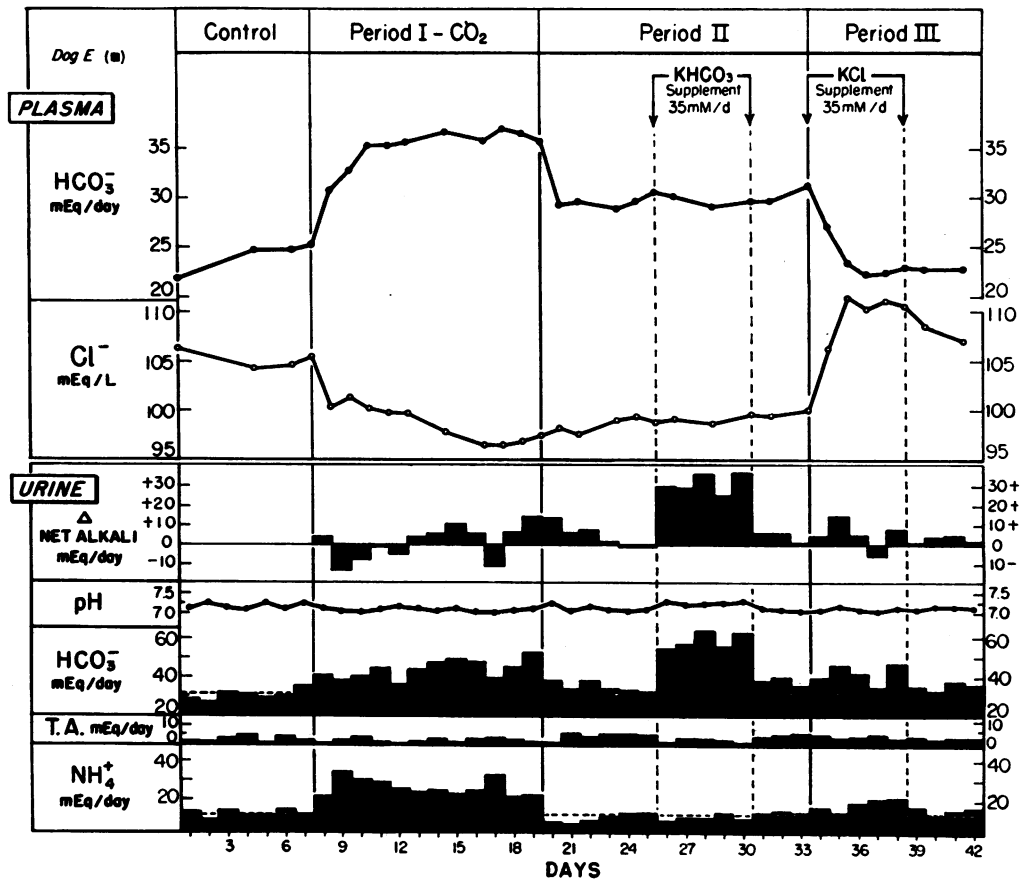


FIG. 1. CHANGES IN ACID-BASE EQUILIBRIUM AND PLASMA CHLORIDE CONCENTRATION DURING ADAPTATION TO AND RECOVERY FROM CHRONIC HYPERCAPNIA IN A DOG INGESTING SODIUM BICARBONATE (6.5 MMOLES PER KG PER DAY). Dashed horizontal lines represent mean daily excretion during the control period. Values for net alkali excretion [bicarbonate - (ammonium + titratable acid)] represent changes from mean daily excretion during the control period.

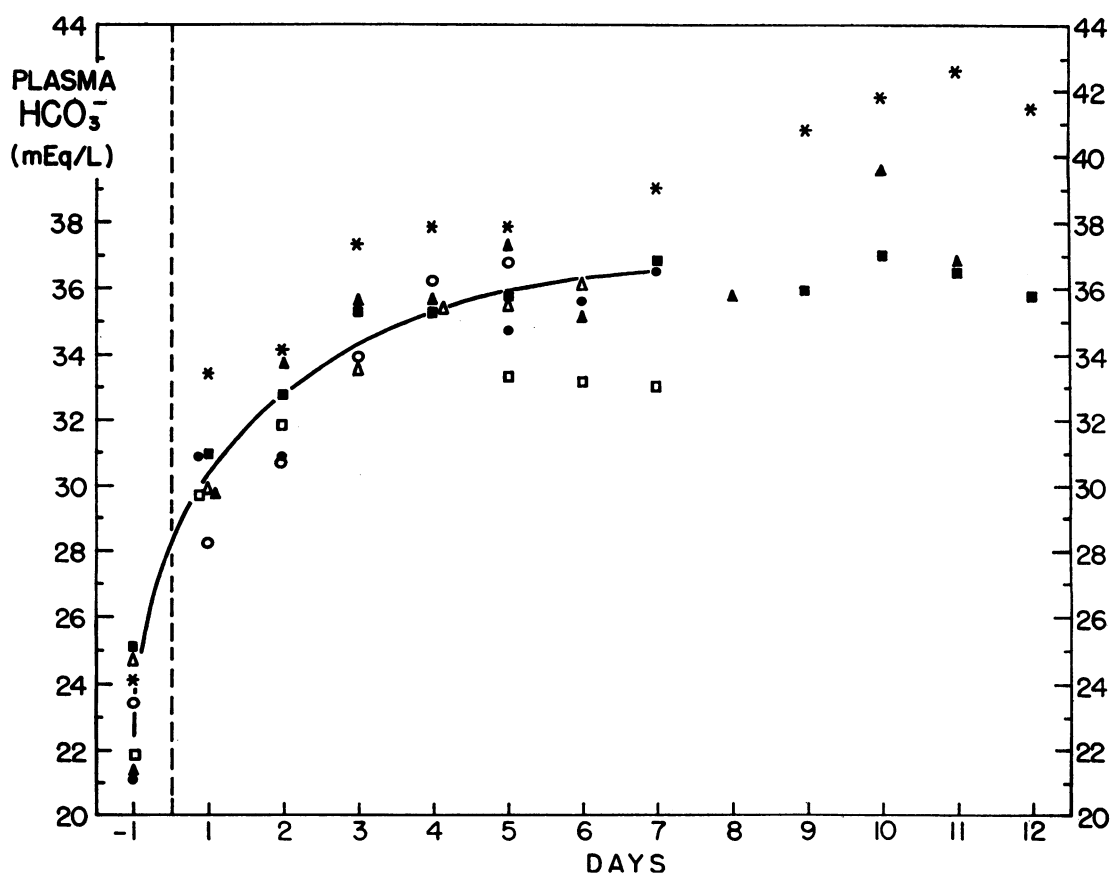


FIG. 2. PLASMA BICARBONATE CONCENTRATION DURING EXPOSURE TO A HIGH CO₂ ATMOSPHERE IN DOGS INGESTING SODIUM BICARBONATE (5.5 TO 6.5 MMOLES PER KG PER DAY). Day -1 refers to the last day of the control period. Dog D (*) vomited on Day 7. The solid curved line has been taken from a previous paper (1) describing changes in plasma bicarbonate in dogs exposed to a 12 per cent CO₂ atmosphere while ingesting an alkali-free intake.

excretion averaged 35 mEq per day, with a range from 26 to 54 mEq. Figure 1 presents in detail the results of a typical study. The remaining figures and Table I show collective data.

Period I. High CO₂ atmosphere

Acid-base balance. As seen in Figure 2, plasma bicarbonate concentration rose after one day in the high CO₂ atmosphere to a mean value of 30 mEq per L. On subsequent days, plasma bicarbonate continued to rise slowly, reaching a plateau of approximately 36 mEq per L 3 to 4 days after induction of hypercapnia. At the end of the period, plasma pH was in the range of 7.20 to 7.25. On day 1, alkali excretion rose above control levels in six of seven animals, with an average delta net alkali of +10 mEq, owing entirely to an in-

crease in HCO₃ excretion (Figure 1). Over the next 2 to 3 days, as plasma bicarbonate rose to its maximal level, net alkali excretion fell. Cumulative delta net alkali excretion over days 2 to 4 averaged -41 mEq, with a range from -20 to -112 mEq. This fall was due entirely to an increase in ammonia excretion; bicarbonate excretion remained at or above control levels throughout the period.

Chloride, sodium, and potassium. On the first day, plasma chloride concentration fell to an average of 105 mEq per L. Over the next 5 to 6 days there was a further drop to a level of approximately 98 mEq per L (Figure 1). Moderate chloruresis occurred during the first 3 to 6 days, and then chloride excretion fell to control levels. The cumulative chloride losses for the period ranged from 39 to 83 mEq (Table I). There

were no significant changes in plasma sodium concentration or in sodium balance. By the end of the period, plasma potassium concentration had fallen to an average of 3.4 mEq per L. Potassium excretion increased on the first day in CO_2 by an average of 26 mEq, but subsequently returned to approximately control levels. Balance data are shown in Table I.

Period II. Recovery—return to room air

Acid-base balance. By the end of 1 day in room air, plasma bicarbonate had dropped by an

average of 6 mEq to a mean level of 30 mEq per L (Figure 3). pH rose from its previously acidotic levels to an average of 7.48. The fall in plasma bicarbonate concentration was accompanied by a rise in the unmeasured anion level, averaging +3 mEq per L, and a decrease in sodium concentration, averaging -3 mEq per L. During the subsequent 5 to 6 days, there were no further significant changes. There was no significant difference in the daily net alkali excretion rate as compared with either the end of the CO_2 period or the control period. In the four animals given

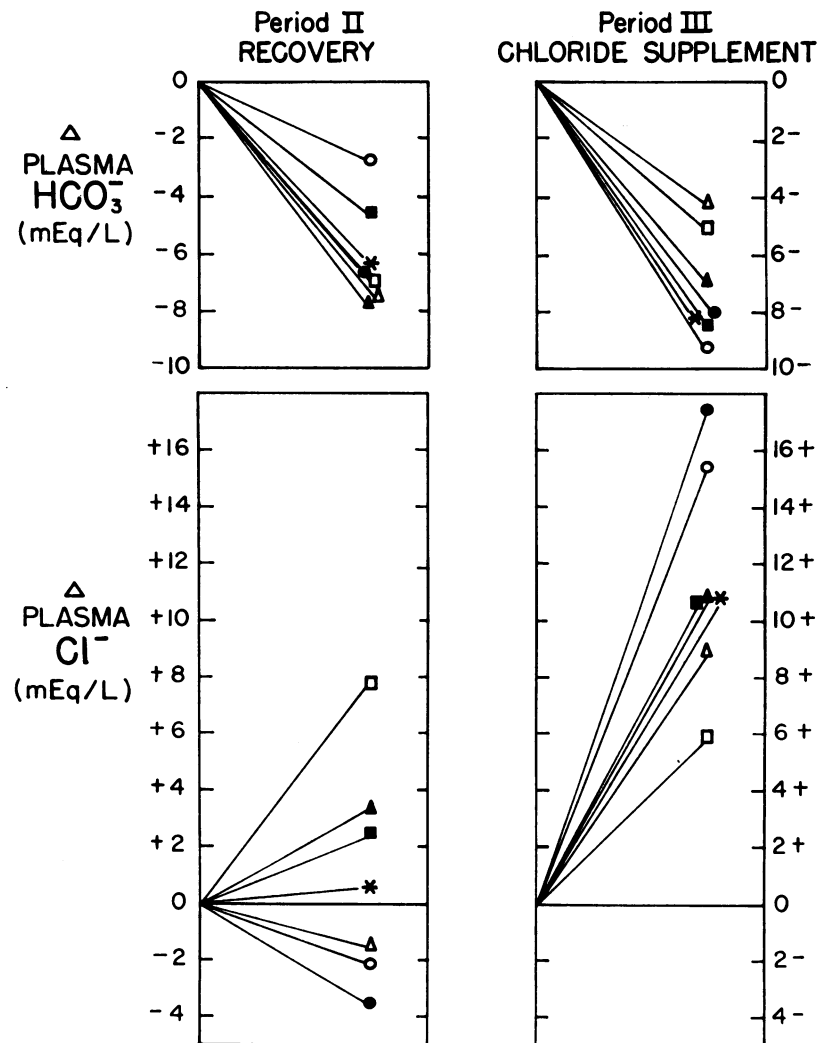


FIG. 3. CHANGES IN PLASMA BICARBONATE AND CHLORIDE CONCENTRATIONS DURING RECOVERY FROM CHRONIC HYPERCAPNIA. For Period II, changes have been calculated as the difference between plasma concentration on the last day in CO_2 and the last day before chloride administration; for Period III, as the difference between the last day before chloride administration and the last day of chloride repletion.

TABLE I
 Changes in electrolyte balance*

Experimental period	Dog	Time	Weight		External balance					
			Initial	Final	Cl	Na	Cl - $\frac{Na}{1.3}$	K	K corrected for N †	N
		<i>days</i>	<i>kg</i>	<i>kg</i>	<i>mEq</i>	<i>mEq</i>	<i>mEq</i>	<i>mEq</i>	<i>mEq</i>	<i>g</i>
I. High CO ₂ atmosphere	L	6	13.0	11.8	-39	-28	-17	-24	-20	-1.7
	S	13	18.4	17.3	-66	+54	-107	-8	-5	-1.0
	B	7	16.1	16.3	-51	-13	-41	-78	-61	-6.1
	D	12	13.2	12.9	-82‡	+65	-132	+7	-18	+9.1
	Z	7	16.1	14.8	-83	-34	-57	-49	-7	-15.4
	C	7	14.8	14.0	-47	+18	-61	-3	-18	+5.2
	E	12	13.0	12.5	-50	+15	-62	-31	-33	+0.3
II.	L	6	11.8	11.6	-10	-3	-8	-13	-9	-1.5
	S	5	17.3	17.1	0	+9	-7	-23	-40	+6.4
	B	7	16.3	15.2	-3	+56	-46	+14	+1	+5.1
	D	14	12.9	12.9	+4	+87	-63	+6	-47	+19.6
	Z	14	14.8	14.8	-2	+129	-101	+22	-26	+17.5
	C	11	14.0	13.8	-6	-6	-1	-63	-113	+18.6
	E	14	12.7	12.5	-5	+31	-29	+14	-20	+12.7
III. Chloride supplement §	L	1	11.6	11.8	+68	+66	+17	+17	+7	+3.5
	S	3	17.1	17.4	+97	+95	+24	+44	+24	+7.1
	B	4	15.2	15.7	+66	-10	+74	+14	+4	+3.8
	D	2	12.9	13.2	+63	+26	+43	+19	+15	+1.5
	Z	4	14.8	15.0	+93	+24	+75	+54	+49	+1.6
	C	5	13.8	14.3	+120	+66	+69	+65	+32	+12.2
	E	5	12.5	13.0	+63	+18	+49	+33	+18	+5.6

* The cumulative balances refer only to the changes that occurred during the individual period.

† 2.7 mEq potassium per g of nitrogen.

‡ Value includes approximately 30 mEq lost in vomitus on day 7.

§ Chloride provided as NaCl to Dogs L, S, B, and D and as KCl to Dogs Z, C, and E.

supplements of sodium or potassium bicarbonate, the increment in alkali load was recovered in the urine; plasma bicarbonate concentration was unaffected.

Chloride, sodium, and potassium. Plasma chloride concentration showed no consistent or significant trend during the recovery period (Figures 1 and 3) and averaged 99 mEq per L. Cumulative balances are shown in Table I. Plasma potassium fell to a mean level of 2.9 mEq per L. The sodium and potassium bicarbonate supplements produced no significant change either in plasma composition or in electrolyte balance.

Period III. Recovery—administration of chloride

Acid-base balance. During the administration of chloride, as either NaCl or KCl, plasma bicarbonate concentration fell to an average of 23 mEq per L, and pH returned to the normal range. The total fall in bicarbonate concentration averaged 7 mEq per L (Figure 3). There was a cumulative increase in net alkali excretion averaging 13 mEq.

Chloride, sodium, and potassium. Plasma chloride concentration rose by an average of 14 mEq

per L to a mean level of 113 mEq per L (Figures 1 and 3). Cumulative chloride retention ranged from 63 to 120 mEq (Table I). Plasma potassium rose to an average level of 3.9 mEq per L. Cumulative retention of electrolytes is shown in Table I.

Miscellaneous. Calculated extracellular fluid volume decreased by an average of 0.3 L during hypercapnia, remained stable over Period II, and rose by an average of 0.4 L after chloride administration. Phosphate excretion remained at control levels throughout the study except for a slight increase, averaging 6 mmoles, during the first day of hypercapnia and a moderate decrease, averaging 14 mmoles, during the first day in room air. There was significant retention of nitrogen during Periods II and III (Table I).

Throughout the study, from Periods I through III, plasma creatinine, organic acid excretion, and sulfate excretion (measured in dog E only) showed no significant change. The electrolyte losses in the stool remained essentially in the control range throughout, and averaged 4 mEq sodium, 1 mEq potassium, and less than 1 mEq chloride daily.

Supplementary studies on acute changes in plasma bicarbonate concentration after bicarbonate feeding. Studies were carried out in three animals after a feeding of half the daily sodium bicarbonate supplement. Plasma bicarbonate concentration rose over a period of 1 to 3 hours to peak levels of 36.0, 34.5, and 33.5 mEq per L, and fell slowly thereafter. The following morning the mean plasma bicarbonate concentration was 30.0 mEq per L. Peak values observed after feeding fell short by 3.0, 4.0, and 2.5 mEq per L, respectively, of the final levels achieved after 4 to 6 days of exposure to CO₂. As the plasma bicarbonate concentration rose after feeding, 16 and 17 mEq bicarbonate were excreted by the two animals from which urine was collected. Significant alkali excretion—24 and 25 mEq—continued as plasma bicarbonate subsequently fell from the peak level toward preabsorptive concentrations.

These studies exclude the theoretical possibility that an elevation in renal bicarbonate threshold to 36 to 38 mEq per L was masked by rapid absorption and excretion of bicarbonate; if rapid intestinal absorption had led to an abrupt rise of plasma bicarbonate concentration far above 36 to 38 mEq per L, a large fraction of the administered bicarbonate might have been spilled by the kidney before significant equilibration with extravascular fluids had occurred.

DISCUSSION

The present study demonstrates that despite provision of liberal quantities of alkali, plasma bicarbonate concentration did not reach maximal levels until 3 to 4 days after induction of hypercapnia. Over this interval, bicarbonate excretion continued at a high level, indicating that a gradual rise in bicarbonate reabsorptive capacity limited the rate at which the plasma bicarbonate concentration increased. It is of interest to note, as shown in Figure 2, that the pattern of rise in plasma bicarbonate was similar to that shown previously in animals ingesting an alkali-free intake (1).¹ It thus appears that the rise in plasma

¹ In the previous study on an alkali-free intake (1), the data were interpreted as indicating a slight rise in plasma concentration between days 4 and 7. Exact definition, however, of the slope between these latter points is difficult in view of the wide scatter of the data. Whether or not there is a significant difference between the two studies over this interval cannot be decided.

concentration in these previous studies closely reflected the gradual rise in the threshold for bicarbonate; since these animals excreted urine almost free of bicarbonate, it would seem that the rate of bicarbonate generation and the rise in threshold were closely linked.

The highest spontaneous reabsorptive capacity² seen in the present chronic studies corresponds closely to the forced reabsorptive capacity³ observed during acute hypercapnia (4, 5). Despite this superficial resemblance, closer examination reveals striking differences in the characteristics of the reabsorptive mechanisms under these two circumstances. In acute respiratory acidosis, during intravenous administration of sodium bicarbonate, there was a continuous and increasing excretion of bicarbonate as plasma level was elevated above 30 mEq per L. The maximal bicarbonate reabsorption of 38 mEq per L was achieved only at plasma concentrations significantly higher than 38 mEq per L. If this degree of incomplete reabsorption persisted during prolonged hypercapnia, plasma bicarbonate concentration could not be spontaneously sustained above 30 mEq per L. The present data demonstrate that only after 3 to 4 days of hypercapnia is the bicarbonate reabsorptive capacity sufficiently enhanced so that no bicarbonate is excreted at plasma levels below 36 to 38 mEq. Only at that time can plasma bicarbonate concentration rise to approximately 36 mEq per L.

Just as the spontaneous reabsorptive capacity increases during adaptation, so the forced reabsorptive capacity rises, reaching a final level as high as 50 to 55 mEq per L, at plasma bicarbonate concentrations of 70 to 80 mEq per L (6). Bicarbonate excretion, however, begins at plasma levels well below those necessary to saturate reabsorptive capacity (6) and, as demonstrated in the present study, is so great that even a large oral intake of bicarbonate fails to raise the plateau

² The term *spontaneous reabsorptive capacity* is used to designate the amount of bicarbonate reabsorbed per unit of glomerular filtrate in the fasting animal. For all practical purposes this value can be assumed to equal the plasma bicarbonate concentration in the fasting animal.

³ The term *forced reabsorptive capacity* will be used to designate the maximum amount of bicarbonate reabsorbed per unit of glomerular filtrate when plasma bicarbonate is markedly elevated by intravenous loading.

level in the plasma above that observed on an alkali-free intake (1).

It is apparent that a direct augmentation of hydrogen transfer by way of a mass action effect of CO_2 cannot account for the progressive rise in spontaneous reabsorptive capacity that occurs in the presence of a constant elevation of pCO_2 . The mechanism responsible for this adaptation remains obscure, although it is clear that some rate limit present in acute respiratory acidosis is modified by long-sustained hypercapnia. It has previously been demonstrated that in acute respiratory acidosis the relationship between plasma bicarbonate concentration and rate of bicarbonate reabsorption exhibited the characteristics of Michaelis-Menten kinetics (4).⁴ It was proposed that an enzymatic reaction was rate-limiting in the reabsorptive process, and it was further suggested that the rate limit may be determined by the activity of carbonic anhydrase. If such were the case, it might be postulated that chronic exposure to hypercapnia leads to an increased carbonic anhydrase activity that is responsible for the adaptive process. Although *in vitro* studies in rats exposed chronically to CO_2 do not show an increase in renal carbonic anhydrase activity (8), this type of observation in no way excludes the possibility that there is an *in vivo* increase in activity. On the other hand, it is possible that either some other enzyme or that some factor of a nonenzymatic nature is responsible for both the original rate limit and its removal. If, for example, chronic hypercapnia were directly responsible for inhibiting chloride reabsorption, this change itself could conceivably account for the rise in bicarbonate threshold (9).

The data suggest that the abrupt rise in plasma bicarbonate concentration observed on the first day of exposure to carbon dioxide was the result of tissue buffering, since on this day alkali excretion

actually rose above control levels. Over the subsequent 2 to 3 days, net alkali excretion fell sufficiently to account fully for the further rise in extracellular bicarbonate concentration and, in most animals, to account for a comparable degree of alkalization throughout body water. It is of interest that the fall in net alkali excretion was less than half as large as the increase in net acid excretion previously reported in hypercapnic dogs ingesting a bicarbonate-free intake (1). Since the increment in plasma bicarbonate concentration was virtually identical in both studies, it seems possible that this discrepancy could be the result of differences in endogenous acid load during the period of hypercapnia. This view is suggested by the observation that, in the present study, there were no significant changes in nitrogen balance, whereas in previous studies nitrogen balance was strongly negative (1).

During the first 24 hours after the animals' removal from the CO_2 atmosphere, plasma bicarbonate concentration fell by an average of 6 mEq per L to a mean of 30 mEq per L, where it remained despite a continued high bicarbonate intake. These data demonstrate a reduction in bicarbonate threshold in the face of persistent chloride deficiency. They further suggest that the post-hypercapnic fall in plasma bicarbonate concentration observed previously on a low-chloride, bicarbonate-free diet was due to a reduction in threshold rather than to failure of the kidney to regenerate bicarbonate lost as the result of tissue buffering (2).

SUMMARY

Large quantities of alkali have been administered to seven dogs during and after chronic exposure to a 12 per cent carbon dioxide atmosphere in order to evaluate the characteristics of the adaptive and recovery process. It has been demonstrated that despite provision of 5.5 to 6.5 mmoles of sodium bicarbonate per kg of body weight, plasma bicarbonate concentration did not reach its maximal level of approximately 36 mEq per L until 3 to 4 days after induction of hypercapnia. These data suggest that a constant elevation of pCO_2 induces a slow adaptive process that is responsible for the progressive increase in the capacity of the kidney to completely reabsorb bi-

⁴ Over plasma bicarbonate concentrations of 25 to 55 mEq per L, the data were found to fit a rectangular hyperbola. It has subsequently been reported that at higher plasma concentrations the reabsorptive rate deviates from this pattern (5). Such findings in no way argue against the possibility that at lower and more physiological substrate concentrations a step characterized by Michaelis-Menten kinetics may be rate-limiting; it is well known that deviations from ideal Michaelis-Menten kinetics occur commonly *in vitro* at high substrate concentrations (7).

carbonate. This pattern of rise in plasma bicarbonate concentration is similar to that previously observed in animals on an alkali-free intake; since the animals in these earlier studies excreted an almost bicarbonate-free urine, it appears that in chronic hypercapnia the rate of bicarbonate generation by the kidney and the rise in bicarbonate threshold are closely linked.

After the animals' return to room air, plasma bicarbonate level fell to approximately 30 mEq per L, a response identical to that previously noted in animals on a low-chloride, alkali-free diet. Acid-base equilibrium was subsequently restored to normal, with plasma bicarbonate 23 mEq per L, when chloride was administered as either the sodium or potassium salt. These findings indicate that the increase in renal reabsorptive capacity induced by chronic hypercapnia can be partly eliminated by restoration of a normal plasma carbon dioxide tension without change in the degree of chloride deficiency or hypochloremia.

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