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Research Article

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Regulation of Acid-Base Equilibrium in Chronic Hypocapnia

EVIDENCE THAT THE RESPONSE OF THE KIDNEY IS NOT GEARED TO THE DEFENSE OF EXTRACELLULAR [H^+]

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ABSTRACT It is generally believed that the reduction in plasma [HCO_3] characteristic of chronic hypocapnia results from renal homeostatic mechanisms designed to minimize the alkalemia produced by the hypocapneic state. To test this hypothesis, we have induced chronic hypocapnia in dogs in which plasma [HCO_3] had previously been markedly reduced (from 21 to 15 meq/liter) by the prolonged feeding of HCl. The P_{CO_2} of chronically acid-fed animals was reduced from 32 to 15 mm Hg by placing the animals in a large environmental chamber containing 9% oxygen. In response to this reduction in P_{CO_2}, mean plasma [HCO_3] fell by 8.6 meq/liter, reaching a new steady-state level of 6.4 meq/liter. This decrement in plasma [HCO_3] is almost identical to the 8.1 meq/liter decrement previously observed in normal (nonacid-fed) animals in which the same degree of chonic hypocapnia had been induced. Thus, in both normal and HCl-fed animals, the renal response to chronic hypocapnia causes plasma [HCO_3] to fall by approximately 0.5 meq/liter for each millimeter of Hg reduction in CO_2 tension.

By contrast, the response of plasma [H^+] in the two groups was markedly different. Instead of the fall in [H^+] which is seen during chronic hypocapnia in normal animals, [H^+] in HCl-fed animals rose significantly from 53 to 59 neq/liter (pH 7.28–7.23). This seemingly paradoxical response is, of course, an expression of the constraints imposed by the Henderson equation and reflects the fact that the percent fall in [HCO_3] in the HCl-fed animals was greater than the percent fall in P_{CO_2}.

These findings clearly indicate that in chronic hypocapnia the kidney cannot be regarded as the effector limb in a homeostatic feedback system geared to the defense of systemic acidity.

INTRODUCTION

It is well known that the fall in plasma hydrogen ion concentration produced by chronic hyperventilation is partially ameliorated by a secondary reduction in bicarbonate concentration which results largely from renal adaptive mechanisms. Most students of acid-base physiology have regarded this change in bicarbonate to be the result of homeostatic mechanisms that serve specifically to defend systemic acid-base equilibrium. Indeed, it is the conventional wisdom that all disturbances of acidity initiate homeostatic responses on the part of the kidney which are keyed to the stabilization of extracellular hydrogen ion concentration.

Recent observations of prolonged mineral acid feeding have, however, raised considerable doubts about the central role of pH in the renal regulation of acid-base equilibrium (1) and have stimulated us to reexamine the hypothesis that alkalemia is a critical factor in the adaptation to chronic hypocapnia. To this purpose, we produced severe metabolic acidosis in dogs by the prolonged feeding of HCl (7 mM/kg per day) and then studied the effects of superimposed chronic hypocapnia on acid-base equilibrium.

The data demonstrate that chronic hypocapnia, superimposed upon the HCl-induced acidosis, causes plasma bicarbonate concentration to fall by an amount virtually identical to that observed previously during chronic

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hypocapnia in normal dogs. In consequence, hydrogen ion concentration, rather than falling, actually rose to levels even higher than those observed in the pre-hypocapneic state.

METHODS

Studies were carried out on seven female mongrel dogs, ranging in weight from 12.1 to 19.2 kg. All animals were fed 30 g/kg per day of a synthetic diet for at least 3 days before the control period and throughout the period of study. The diet contained less than 1.0 meq sodium/100 g, less than 0.1 meq potassium/100 g, and less than 0.5 meq chloride/100 g (2). The daily diet was homogenized with twice its weight of distilled water and supplemented with 2.5 meq/kg body weight of potassium as neutral phosphate and 2.5 mM/kg of body weight of sodium chloride. Animals that did not eat spontaneously were tube-fed and animals that vomited were excluded from further study. Blood samples were obtained by percutaneous arterial puncture; rectal temperature was measured at the time of blood sampling. During each period of study, an animal was judged to be in a steady state when plasma values obtained on 3 consecutive days varied by no more than 2 meq/liter for bicarbonate and by no more than 5 mm Hg for P_{CO_2}.

Experimental protocol

Control period. A control period of at least 3 days duration was obtained to establish a normal base line.

Period I: Uncomplicated metabolic acidosis. Hydrochloric acid, 7 mM/kg body weight, was added to the daily diet and observations were carried out for 7 days, a period sufficient to insure the development of a new steady state (1).

Period II: Metabolic acidosis plus severe chronic hypocapnia. During continued acid feeding, the animals were placed within a large environmental chamber (3) and the ambient oxygen concentration was lowered from 21 to 9% in a stepwise fashion over a period of 2–3 days. The chamber atmosphere was maintained at a level of 9% oxygen until the 7th day of the period, by which time a new steady state of acid-base equilibrium had been established in all animals.

Period III: Metabolic acidosis plus stepwise recovery from chronic hypocapnia. Prolonged observations were obtained at two intermediate oxygen concentrations (11.5 and 16%) thus allowing the development of two additional steady-state levels of chronic hypocapnia. The animals were then returned to room air, and hydrochloric acid feeding was continued for a final 7-day period.

Analytical methods

Methods used for determining sodium, potassium, chloride, phosphorus, ammonium, titratable acid, net acid, creatinine, and nitrogen have been reported previously (4). The balance techniques employed in this study have also been described earlier (4). Total CO_2, pH, and P_{O_2} were measured directly; bicarbonate concentration and P_{CO_2} were calculated from the Henderson-Hasselbalch equation. pH, pK′ and the solubility coefficient of CO_2 were corrected for temperature; pK′ was also corrected for pH (5–7). Blood lactate and pyruvate were determined by specific enzymatic methods (8–9).

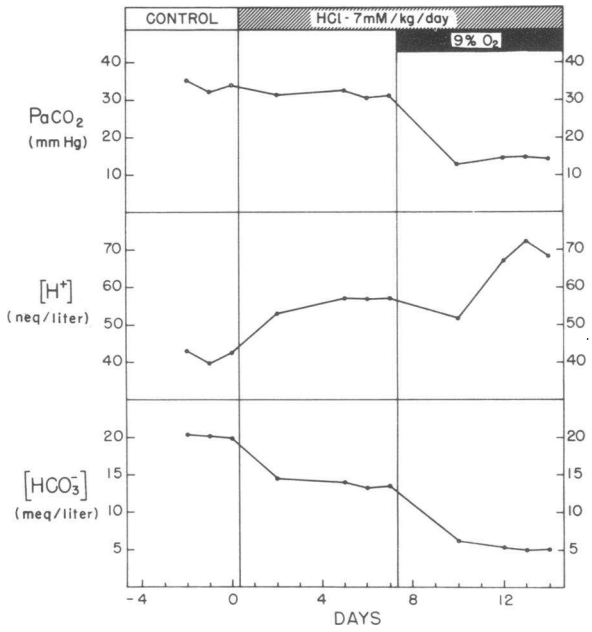

FIGURE 1 Changes in plasma acid-base composition produced by prolonged, severe hypocapnia in a representative animal with chronic HCl-acidosis. Note that the marked reduction in P_{CO_2} achieved by exposure to 9% oxygen caused such a marked fall in plasma $[HCO_3]$ that the plasma $[H^+]$ rose to an even higher level than observed during HCl feeding alone.

RESULTS

Throughout the text the terms "significant" or "significantly different" will be used to describe a difference which has a P value of less than 0.01.

Fig. 1 depicts, for a representative animal, the changes in plasma acid-base composition induced by chronic HCl administration and by the subsequent superimposition of severe chronic hypocapnia. As can be seen, bicarbonate concentration, which fell sharply during HCl feeding, fell even further when P_{CO_2} was lowered during exposure of the animals to 9% oxygen. Hydrogen ion concentration, which had risen during the period of HCl feeding alone, rose even further during the state of superimposed hypocapnia.

Mean steady-state plasma values for the group as a whole are presented in Table I. Values for the control period and each experimental period were obtained for each animal by averaging the three plasma determinations made during the respective steady-state intervals.

Period I: Uncomplicated metabolic acidosis. Administration of 7.0 mM of HCl/kg per day led to a significant decrease in plasma bicarbonate concentration from a mean control value of 21.4 to 15.0 meq/liter and a significant decrease in mean P_{CO_2} from 36 to 32 mm Hg. Plasma hydrogen ion concentration increased significantly from a control value of 41 to a value of 53

TABLE I

*Changes in Plasma Composition Produced by Graded Degrees of Chronic Hypocapnia in Dogs with HCl-Induced Metabolic Acidosis**

Period	P_{CO_2}	HCO_3	H^+	Na	K	Cl	Unmeasured anions‡
	mm Hg	*meq/liter*	*neq/liter*	*meq/liter*	*meq/liter*	*meq/liter*	*meq/liter*
Control	36±0.5	21.4±0.4	41±0.7	145±0.4	3.4±0.1	109±0.8	19±0.8
HCl-room air	32±0.7	15.0±0.6	53±2.1	146±0.3	2.9±0.1	117±0.8	16±0.7
HCl-9% O_2	15±0.3	6.4±0.3	59±2.1	144±0.5	2.8±0.1	125±1.3	16±1.1
HCl-11.5% O_2	20±0.4	7.9±0.4	61±1.4	143±0.4	2.8±0.1	124±0.6	13±0.3
HCl-16% O_2	26±0.8	10.7±0.4	59±1.6	142±0.2	2.6±0.1	122±0.6	11±0.6
HCl-room air (Recovery)	31±0.9	14.3±0.7	53±1.6	145±0.3	2.6±0.1	118±0.8	14±0.6

* Values presented are the means±1 SE, $n = 7$.
‡ $(Na + K) - (HCO_3 + Cl)$.

neq/liter. These changes in plasma acid-base parameters, as well as in plasma electrolyte composition (Table I), are virtually identical to those observed previously in animals given the same dose of HCl (1). No significant changes in phosphate or creatinine concentrations or in hematocrit were noted.

Period II: Metabolic acidosis plus severe chronic hypocapnia. All seven HCl-fed animals remained alert and active during exposure to the 9% O_2 atmosphere. As can be seen in Table I, hyperventilation caused a significant reduction of P_{CO_2} from 32 to 15 mm Hg and a significant reduction in plasma bicarbonate concentration from 15.0 to 6.4 meq/liter. As a consequence, mean plasma hydrogen ion concentration increased significantly from 53 to 59 neq/liter.

Plasma sodium concentration decreased significantly from 146 to 144 meq/liter. Plasma potassium concentration did not change significantly, but chloride concentration increased significantly from 117 to 125 meq/liter. Unmeasured anion concentration (defined as the sum of sodium and potassium minus the sum of bicarbonate and chloride) remained virtually constant. Plasma lactate and pyruvate concentrations, measured during the last 2 days of the steady-state interval, averaged to 1.8 mM/liter and 0.1 mM/liter, respectively; both of these values are within the normal range. Phosphate concentration rose significantly from 1.2 to 1.4 mM/liter. Plasma creatinine did not change. Hematocrit rose significantly from 38.7 to 51.7%.

Period III: Metabolic acidosis plus stepwise recovery from chronic hypocapnia. Statistical evaluation of the data obtained during graded degrees of chronic hypocapnia was carried out by means of analysis of variance. As can be seen in Table I, when oxygen concentration was increased to 11.5% and then to 16%, steady-state P_{CO_2} rose to 20 and 26 mm Hg, respectively. In response to these stepwise increments in P_{CO_2}, mean steady-state plasma bicarbonate concentration rose significantly to 7.9 meq/liter and then to 10.7 meq/liter. Mean hydrogen ion concentration during these two periods was 61 and 59 neq/liter, respectively; both of these values were significantly higher than the value observed during the period of uncomplicated HCl acidosis. When the animals were once again allowed to breath room air, mean P_{CO_2}, bicarbonate concentration, and hydrogen ion concentration all returned to values virtually identical to those observed during the initial experimental period.

Regression of bicarbonate concentration and hydrogen ion concentration on P_{CO_2}. Fig. 2 depicts the steady-state relationship between P_{CO_2} and both plasma bicarbonate (lower panel) and hydrogen ion concentrations (upper panel) for the full range of carbon dioxide tensions studied. The regression lines shown in the figure were calculated from the pooled data by the method of least squares. In both cases, the slope value was significantly different from zero and neither relationship was significantly improved by the addition of a quadratic term.[1] The correlation coefficient was 0.95 for bicarbonate vs. P_{CO_2} and −0.47 for hydrogen ion vs. P_{CO_2}.

Changes in electrolyte and acid excretion. The cumulative changes in urinary electrolyte and net acid excretion during the initial period of severe hypocapnia (Period II) were estimated for each animal by summing the differences between the mean daily excretion during Period I (uncomplicated metabolic acidosis) and the daily excretion for each of the first 5 days of Period II; a 5-day interval was used because all animals had reached a steady state of acid-base and electrolyte composition by this time.

[1] It is recognized, of course, that the mathematical constraints inherent in the Henderson equation make it impossible for strictly linear regressions to govern the relationship both of bicarbonate and P_{CO_2} and of hydrogen ion concentration and P_{CO_2} simultaneously. The present data indicate, however, that the degree of curvature which must be present in one or both of these relationships is slight.

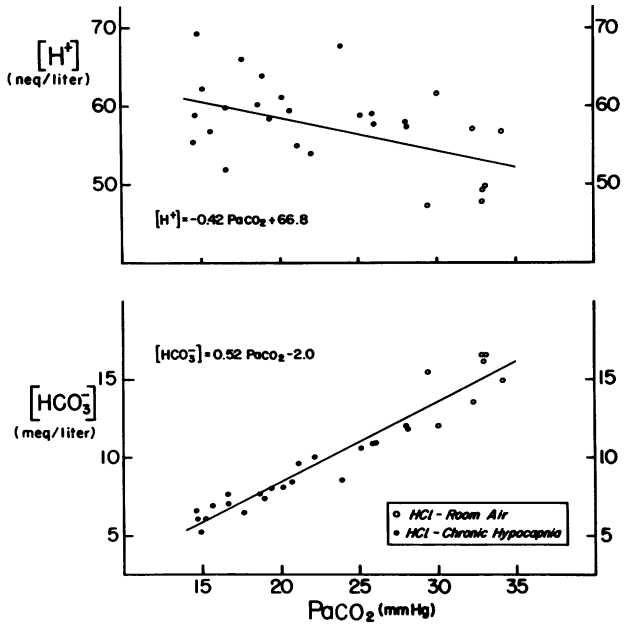

FIGURE 2 Steady-state relationship between $Paco_2$ and plasma $[HCO_3]$ (lower panel) and between $Paco_2$ and plasma $[H^+]$ (upper panel) during graded degrees of chronic hypocapnia in dogs with HCl-induced metabolic acidosis. Each point represents the mean of observations obtained on 3 steady-state days; open circles designate observations obtained during exposure to room air; closed circles designate observations obtained during exposure to 9, 11.5, or 16% oxygen. The least squares regression lines drawn through the points were calculated from the pooled data.

As shown in Fig. 3, the induction of hypocapnia was accompanied by a loss of sodium which averaged 40 meq ($P < 0.05$) and a retention of phosphate which averaged 22 meq; no significant changes were observed in the excretion of either potassium or chloride. This pattern of change in electrolyte excretion was remarkably similar, both qualitatively and quantitatively, to that observed previously during induction of chronic hypocapnia in normal dogs (10). There were no notable changes in fecal sodium, potassium, or chloride excretion. Consequently, the cumulative changes in electrolyte balance shown in Table II are largely reflective of the changes in urinary excretion. Mean body weight fell slightly from 13.5 to 13.2 kg.

TABLE II

Cumulative Changes in Electrolyte and Nitrogen Balance Produced by Prolonged Severe Hypocapnia in Dogs with HCl-Induced Metabolic Acidosis

Dog no.	Na	Cl	K	Kn*	Nitrogen
		meq			*g*
524	−80	−51	−40	−27	−5
528	−31	+5	+25	+11	+5
529	−65	−72	−28	−22	−2
558	−6	+54	+8	−2	+4
559	+12	+162	+33	+12	+8
561	−41	+1	−8	−9	0
562	+16	+47	+11	+7	+2
Average	−28	+21	0	−4	+2

* Kn = K corrected for N.

TABLE III

Cumulative Changes in Urinary Excretion Produced by Prolonged Severe Hypocapnia in Dogs with HCl-Induced Metabolic Acidosis

Dog no.	Titratable acidity	Bicarbonate	Ammonium	Estimated ammonium* (Unaccounted charge balance)
	meq	*meq*	*meq*	*meq*
524	−4.6	−0.1	−11.9	−93
528	−21.4	0.6	11.7	−40
529	−1.4	0.2	23.9	−26
558	−16.0	−0.1	−99.7	−60
559	−35.0	−0.1	−118.7	−140
561	−7.0	−1.6	−17.6	−66
562	−16.1	0.1	−37.3	−38
Average	−14.5	−0.1	−35.7	−66
±1 SE	±4.4	±0.3	±20.5	±15
P	<0.02	NS	NS	<0.01

* This estimate was obtained by subtracting the cumulative delta excretions of sodium, potassium, and titratable acidity from that of chloride, phosphate, and bicarbonate (see text).

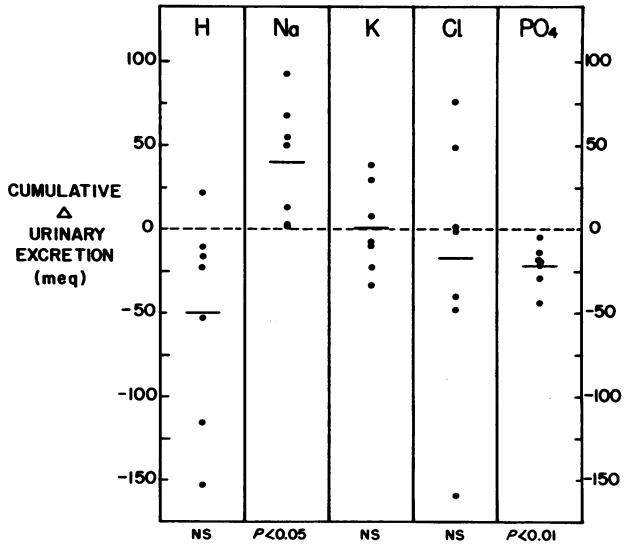

FIGURE 3 Cumulative changes in urinary net acid (H) and electrolyte excretion during the 5-day period of adaptation to severe hypocapnia in dogs with chronic HCl-acidosis. The significance level for each of the mean values (horizontal solid lines) is indicated below the panels.

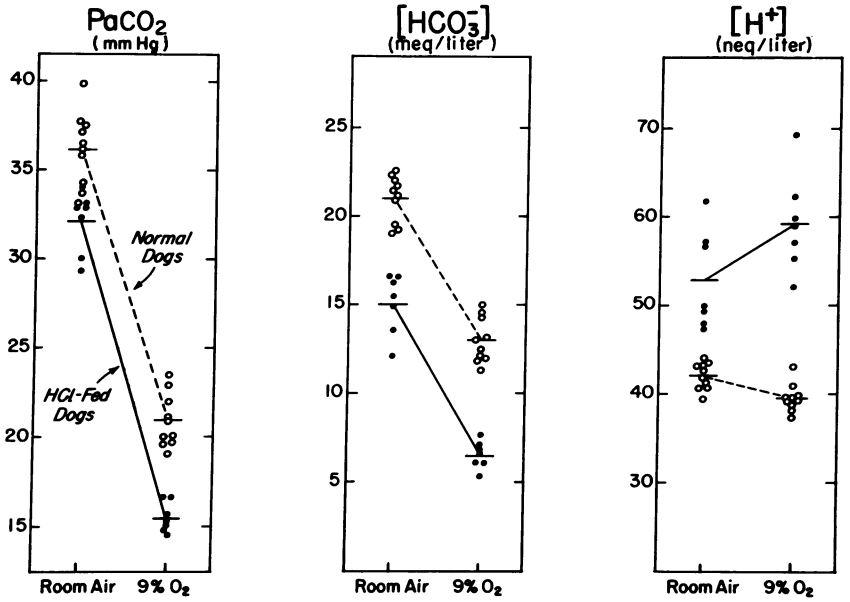

FIGURE 4 Changes in plasma acid-base parameters observed during prolonged exposure of normal dogs and dogs with chronic HCl-acidosis to 9% oxygen. Each point represents the mean of observations obtained on 3 steady-state days; values for the normal dogs were obtained by Gennari et al. (10). Note that the virtually identical decrements in P_{CO_2} induced in both groups led to nearly equivalent reductions in plasma [HCO_3] but to divergent changes in plasma [H^+].

As shown in Table III, adaptation to hypocapnia was accompanied by a significant reduction in the excretion of titratable acid ($P < 0.02$) but not by a significant reduction in the excretion of ammonium. It is noteworthy that in a previous study of normal dogs made similarly hypocapneic, (10) a significant reduction in ammonium excretion was observed but averaged only 28 meq over the 5-day interval of adaptation. Such a small reduction, if present in the current studies, would almost certainly have gone undetected because of the difficulty in obtaining a reliable estimate of base-line ammonium excretion in the face of large daily acid loads. Ammonium excretion, which averaged well over 100 meq/day during acid feeding in the present group, typically varied by some 50 meq from day to day; by contrast, ammonium excretion, which averaged less than 30 meq/day in normals, typically varied by only some 15 meq.

It was reasoned that the small changes in ammonium excretion being sought might still be detected, albeit indirectly, from an examination of the unaccounted charge balance created by changes in the other major urinary ions, the base-line excretions of which were quite stable. For this purpose, the cumulative changes in the excretion of sodium, potassium, and titratable acid were subtracted from that of chloride, phosphate, and bicarbonate for each animal. As can be seen in Table III, a consistent discrepancy was observed and averaged —66 meq ($P < 0.01$). The only reasonable possibility to account for this large a discrepancy in charge balance is that ammonium excretion was, in fact, reduced; no more than a small fraction of this discrepancy could have been the consequence of changes in the excretion of other urinary ions.[2]

DISCUSSION

The present study provides strong evidence that the response of the kidney to chronic hypocapnia is not keyed to the defense of extracellular hydrogen ion concentration. This is illustrated in Fig. 4 which compares the steady state plasma acid-base composition observed before and during forced hyperventilation in normal animals (10) and animals made acidotic by the daily feeding of hydrochloric acid. As can be seen, virtually identical steady-state decrements in plasma bicarbonate concentration were maintained by the kidney during comparable degrees of chronic hypocapnia in both groups of animals. The net effect of these similar bicarbonate decrements on plasma hydrogen ion concentration was,

[2] It is noteworthy that in normal, nonacid-fed animals that were made similarly hypocapneic (10), the suppression of ammonium excretion estimated from the unaccounted charge balance was similar to that estimated here (— 40 vs. — 66 meq). As noted, however, it was possible to detect directly a significant fall in ammonium excretion in these animals in which the base-line level of ammonium excretion could be established more accurately.

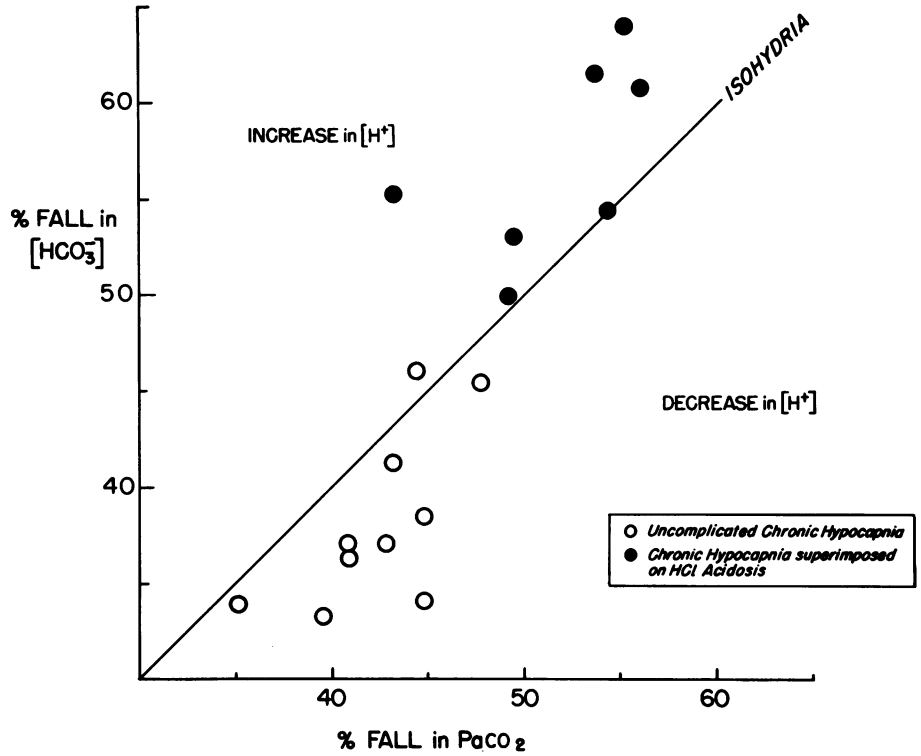

FIGURE 5 Percent fall in steady state [HCO_3] and P_{CO_2} produced by exposure of normal dogs (open circles) and of dogs with chronic HCl acidosis (closed circles) to 9% oxygen. Values for the normal dogs were calculated from the data of Gennari et al. (10). Points falling on the diagonal line signify no change in plasma [H^+]. Note that all but one of the normal animals yielded points below the diagonal, in the zone of decreased [H^+], whereas all but one of the HCl-fed animals yielded points above the diagonal, in the zone of increased [H^+].

however, markedly different; steady-state hydrogen ion concentration, which is reduced by chronic hypocapnia in normal animals, actually rose in the acid-fed animals, reaching levels appreciably higher than those observed during HCl feeding alone.

The explanation for this seemingly paradoxical response of plasma hydrogen ion concentration in the acid-fed dog is, of course, inherent in the mathematic relationships defined by the Henderson equation. As shown in Fig. 5, the hydrogen ion response in the acidotic group reflects the fact that the percent fall in plasma bicarbonate concentration was greater than the percent fall in P_{CO_2}, whereas in the normals the reverse was true.

It seems clear from these observations that the apparent homeostatic regulation of extracellular hydrogen ion concentration observed in the normal organism during chronic hypocapnia is simply a fortuitous by-product of the effect of lowered carbon dioxide tension on renal hydrogen ion secretion and bicarbonate reabsorption, an effect which is independent of the initial level of plasma bicarbonate concentration (Fig. 4). The resulting relationship between P_{CO_2} and steady-state plasma bicarbonate concentration is highly proportional over the entire range of P_{CO_2} studied (Fig. 2) and is reflected by the expression: $\Delta [HCO_3]/\Delta P_{CO_2} = 0.5$.

The fall in plasma bicarbonate that occurred during adaptation to severe hypocapnia can be reasonably ascribed, as in the normals, to a transient retention of hydrogen ion by the kidney. The observed reduction in titratable acid excretion, coupled with the estimated reduction in ammonium excretion (Table III), strongly suggests that renal acid excretion fell by an amount well within that needed to account for the observed decrement in plasma bicarbonate.

It is important to emphasize, however, that whether the decrement in plasma bicarbonate concentration occurred as a result of suppressed renal acid excretion, or as the consequence of extrarenal adjustments, there can be no doubt that it was sustained in the new steady state as a result of suppressed renal bicarbonate reabsorption. This being the case, what can we conclude from the present data about the mechanisms underlying this steady-state renal response? Perhaps most noteworthy is that the kidney, as discussed above, is not the effector limb in a negative feedback system keyed to the defense

of extracellular hydrogen ion concentration. The present data do not, of course, permit us to exclude with equal certainty the possibility that the renal response is mediated by changes in intracellular (e.g. renal tubular cell) hydrogen ion concentration. We think, however, that this explanation is most unlikely in view of the finding that during sustained hypocapnia, bicarbonate reabsorption was reduced to a nearly identical degree in both the HCl-fed and normal dogs. If changes in cellular acidity were indeed responsible for the renal response, such an equal reduction in bicarbonate reabsorption would presuppose that in both groups there was a reduction in intracellular hydrogen ion concentration of equal magnitude. Considering the marked differences in extracellular acid-base composition of the HCl-fed and normal dogs, it is hard to imagine that a given steady-state decrement in P_{CO_2} would induce in each group an identical change in cellular acidity; only if severe HCl acidosis itself has no influence on intracellular bicarbonate concentration would a given reduction in P_{CO_2} be expected to exert the same effect on intracellular acid-base composition of both the normal and the HCl-fed animals. Studies of the effect of HCl acidosis on intracellular bicarbonate concentration argue against this possibility (11–13).

If carbon dioxide tension does not exert its effect on the kidney through a change in cellular acidity, how might it influence the steady-state rate of bicarbonate reabsorption? One possibility is that P_{CO_2} directly influences the reabsorptive process, perhaps through a change in bicarbonate or hydrogen ion permeability or through a change in the activity of carbonic anhydrase. A second possibility is that carbon dioxide tension exerts its effect indirectly through an enhancement of chloride reabsorption. The present data do not permit us to choose between these alternatives. However, the concept that changes in chloride reabsorption are the key to the kidney's behavior in chronic hypocapnia is attractive because it serves to unify the present observations with recent data indicating that anion reabsorbability is a critical determinant of acid excretion and bicarbonate reabsorption in metabolic acid-base disorders (1, 4, 14–16).

Finally, it should be noted that the present observations may well have important implications for the clinical evaluation of mixed acid-base disturbances. Currently, an increase in the severity of acidemia in a patient with metabolic acidosis would be ascribed, without exception, either to a worsening of the metabolic process or to an element of respiratory acidosis. It is now evident, however, that there is a third possibility to be considered, namely, chronic respiratory alkalosis. On this basis, we would suggest that the very term, "chronic respiratory alkalosis" is a misnomer and should be discarded in favor of the more noncommital expression, chronic hypocapnia.

ACKNOWLEDGMENTS

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