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David C. Lowance, … , William D. Mattern, William B. Schwartz

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Research Article

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Normal dogs subjected to expansion demonstrated no change in net acid excretion or in plasma bicarbonate concentration even in the face of a marked diuresis of sodium and chloride and a reduction in plasma sodium concentration to approximately 110 mEq/liter. The animals did, however, regularly lose potassium, a finding that clearly indicates an acceleration of distal sodiumcation exchange. On the basis of these observations, and the findings in the expanded acidotic dogs, we suggest that in the expanded normal dogs acceleration of sodium-hydrogen exchange was responsible for preventing a bicarbonate diuresis and for stabilizing plasma bicarbonate […]

The Effect of Chronic Hypotonic Volume Expansion on the Renal Regulation of Acid-Base Equilibrium

DAVID C. LOWANCE, HOWARD B. GARFINKEL, WILLIAM D. MATTERN, and WILLIAM B. SCHWARTZ

From the Department of Medicine, Tufts University School of Medicine, and the Renal Laboratory of the New England Medical Center Hospitals, Boston, Massachusetts 02111

ABSTRACT Balance studies have been carried out to evaluate the influence of vasopressin-induced volume expansion on acid-base equilibrium in normal dogs and in dogs with steady-state metabolic acidosis induced by the administration of 5–7 mmoles/kg per day of hydrochloric acid.

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These studies clearly demonstrate that chronic hypotonic expansion exerts a major influence on the renal regulation of acid-base equilibrium. The exact nature of the mechanism responsible for the increase in sodium-hydrogen exchange during hypotonic expansion remains to be determined.

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INTRODUCTION

Little is known about the influence of chronic expansion of extracellular volume on the renal regulation of acid-base equilibrium. It is well recognized, however, that volume expansion produced by the syndrome of inappropriate secretion of antidiuretic hormone (SIADH),[1] is not accompanied by a reduction in plasma bicarbonate concentration, even in the face of renal sodium wasting and a reduction of as much as 30–40 mEq/liter in the plasma concentration of sodium and chloride (1). The explanation for the remarkable stability of bicarbonate concentration under these circumstances is obscure and it was this enigma that stimulated the studies reported here.

The present experiments were undertaken to explore the changes in acid-base equilibrium induced by the chronic administration of vasopressin and water. Studies were carried out both in normal dogs and in dogs with a steady state of metabolic acidosis induced by prolonged administration of hydrochloric acid. The data demonstrate that during hypotonic expansion in *normal* animals the renal loss of sodium and chloride, and the concomitant reduction in the plasma concentration of these electrolytes, was not accompanied by a parallel loss of bicarbonate or fall in plasma bicarbonate concentration. Hypotonic expansion in *acidotic* dogs produced a marked rise in net acid excretion and restored plasma bicarbonate concentration to normal even in the face of continued ingestion of hydrochloric acid. These

[1] *Abbreviation used in this paper:* SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

findings indicate that hypotonic expansion is a powerful stimulus to sodium-hydrogen exchange but they do not reveal the specific factors responsible for this striking alteration in tubular function.

METHODS

Balance studies were performed on 34 female mongrel dogs weighing 10–20 kg. Throughout the study each dog was fed 30 g/kg per day of a synthetic diet the composition of which has previously been described (2). The intrinsic electrolyte content of the diet was approximately 1 mEq of sodium, 0.3 mEq of chloride, and 0.1 mEq of potassium/100 g of diet. In all animals the diet was supplemented daily with 2.5 mEq/kg body weight of potassium as neutral potassium phosphate. In studies requiring a normal salt intake, the diet was supplemented daily with 2.5 mEq/kg of sodium as sodium chloride. Dogs that did not eat spontaneously were tube-fed.

Two protocols were employed. In the first, hypotonic volume expansion was induced by the administration of vasopressin (Pitressin Tannate in Oil [Parke Davis, Co., Detroit, Mich.], 5 U subcutaneously twice daily) and a liberal quantity of water (77 ml/kg per day) to normal dogs and to dogs with a metabolic acidosis induced by HCl feeding. Animals were accepted for study only if vasopressin administration reduced plasma osmolality to 240 mOsm/kg or below. In those animals that demonstrated no untoward effects during hypotonic volume expansion, vasopressin administration was continued until plasma osmolality fell to approximately 210–220 mOsm/kg. In those animals that developed signs of severe water intoxication (i.e., ataxia or seizures), vasopressin was immediately discontinued. If significant vomiting occurred (defined as a cumulative loss in excess of 100 ml) the study was terminated and the final balance day was taken as the one immediately before the termination day.

In the second protocol, vasopressin was administered (in the same dosage described above) to both normal and acidotic dogs but water intake was restricted (47 ml/kg per day) in order to prevent volume expansion. Any dog in which cumulative vomitus exceeded 100 ml was discarded.

All studies were initiated by a control period of 4–9 days. Dogs were accepted for further study only if control plasma bicarbonate concentrations were between 19–24 mEq/liter.

Protocol I: administration of vasopressin and a liberal quantity of water

A. Normal dogs (12 dogs). Six dogs received the normal NaCl diet and six the low NaCl diet. After the control period, vasopressin was administered for a period ranging from 4–14 days. Blood samples were drawn daily beginning on the 2nd or 3rd day of vasopressin administration.

B. Dogs with metabolic acidosis (14 dogs). Six dogs received the normal NaCl diet and eight the low NaCl diet. After the control period the diet was supplemented with 7 mmoles/kg of HCl in all dogs except for two in the low NaCl group that received 5 mmoles/kg of HCl. After 7–16 days of HCl feeding,[2] vasopressin was administered for 4–18 days; HCl feeding was continued throughout the vasopressin period. Blood samples were drawn daily beginning on the 2nd or 3rd day of vasopressin administration. In four animals in which severe hypotonicity was achieved uneventfully, vasopressin administration was continued for periods of 4–9 days beyond the day of lowest plasma osmolality.

In the dogs ingesting the low NaCl diet, observations on weight and plasma composition were carried out for 2–10 days after vasopressin was discontinued; during this post-vasopressin period HCl feeding was continued.

Protocol II: administration of vasopressin during restriction of water intake

A. Normal dogs (four dogs). All dogs received the normal NaCl diet. After the control period, water intake was restricted and vasopressin was administered for 6 days. Blood samples were drawn on 4 days of the vasopressin period (including the last 2 days) and the standard water intake was adjusted to maintain plasma osmolality in the range of 270–305 mOsm/kg.

B. Dogs with metabolic acidosis (four dogs). All dogs received the normal NaCl diet. After the control period, and the subsequent induction of metabolic acidosis, water intake was restricted and vasopressin was administered during a further 7 day period of HCl feeding. Blood samples were drawn daily beginning on the 3rd day of vasopressin administration and the standard water intake was adjusted to maintain plasma osmolality in the range of 270–305 mOsm/kg.

Balance technique and analytic methods

The details of the balance technique, calculations, and the analytic methods have been previously described (4, 5). Cumulative changes in balance and urinary electrolyte excretion during the vasopressin period were calculated on the basis of all days in the period up to and including the day of lowest plasma osmolality. Delta net acid excretion during this period was calculated using as a "control" the mean steady-state acid excretion during the last 3–4 days of the preceding HCl period. Plasma osmolalities were measured by freezing point depression. Plasma osmolalities were not measured in three dogs in protocol I A but were instead estimated by doubling plasma sodium concentration.

RESULTS

Values for the electrolyte composition of plasma and urine and cumulative balance data are shown in Figs. 1–8 and in Tables I–IV. The term significant is used throughout the paper to describe changes with a P value of less than 0.05 as determined by Student's t test (6).

Administration of vasopressin and a liberal quantity of water to normal dogs and to dogs with metabolic acidosis

A. Normal Dogs

Vasopressin period. Administration of vasopressin and water to the dogs ingesting the normal NaCl diet resulted in a significant increase in mean body weight from 16.1 to 16.5 kg while mean plasma osmolality de-

[2] Previous studies in dogs have shown that daily HCl feeding induces a steady state of metabolic acidosis within 4 days. This steady state has been documented for periods up to 21 days (3).

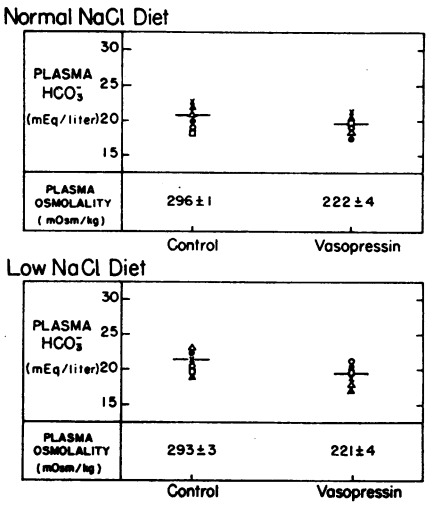

FIGURE 1 Effect of the chronic administration of vasopressin and a liberal quantity of water on plasma bicarbonate concentration in normal dogs. The values for the vasopressin period are those for the day of lowest plasma osmolality. Note that in neither the normal nor the low NaCl group was there a significant change in plasma bicarbonate concentration during hypotonic expansion.

creased from 296 to 222 mOsm/kg. In the low NaCl group mean body weight increased significantly from 13.3 to 14.2 kg while mean plasma osmolality decreased from 293 to 221 mOsm/kg.

Fig. 1 shows the plasma bicarbonate concentration in each study period for the six dogs ingesting the normal NaCl diet (upper panel) and the six dogs ingesting the low NaCl diet (lower panel). There was no significant change in plasma bicarbonate concentration in either group at a time when plasma osmolality had fallen to its nadir. Mean plasma bicarbonate concentration in the normal NaCl group was 20.7 mEq/liter during the control period and 19.6 mEq/liter on the day of lowest plasma osmolality and in the low NaCl groups was 21.3 mEq/liter and 19.4 mEq/liter. Mean P_{CO_2} and hydrogen ion concentration fell significantly in both groups. In the normal NaCl group P_{CO_2} fell from 35 to 29 mm Hg, and plasma hydrogen ion concentration fell from 41 to 35 nmoles/liter. In the low NaCl group mean P_{CO_2} fell from 37 to 30 mm Hg and mean plasma hydrogen ion concentration from 43 to 37 nmoles/liter.

As shown in Fig. 2 (column 1 of each panel) there was no significant change in net acid excretion in either the normal or the low NaCl group. There was, however, a significant increase in cumulative potassium excretion which averaged 52 mEq in the normal NaCl group and 66 mEq in the low NaCl group (column 2 of each panel). Plasma potassium concentration (Fig. 3) fell in every dog in the normal NaCl group, the final mean value of 2.7 mEq/liter being significantly lower than the control value of 3.7 mEq/liter. Plasma potassium concentration fell in five of the six animals in the low NaCl group, but the final mean value of 3.3 mEq/liter was not significantly different from the control value of 3.9 mEq/liter. It is noteworthy that no significant change in plasma potassium concentration or urinary

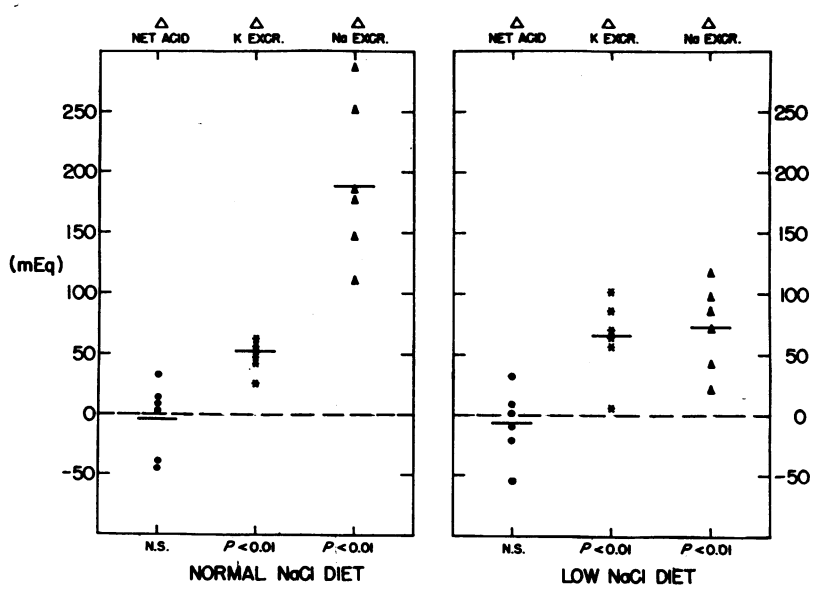

FIGURE 2 Cumulative changes in urinary excretion of net acid, potassium, and sodium during chronic administration of vasopressin and a liberal quantity of water to normal dogs ingesting either a normal or low NaCl diet. Note the significant increase in potassium excretion in both groups of dogs.

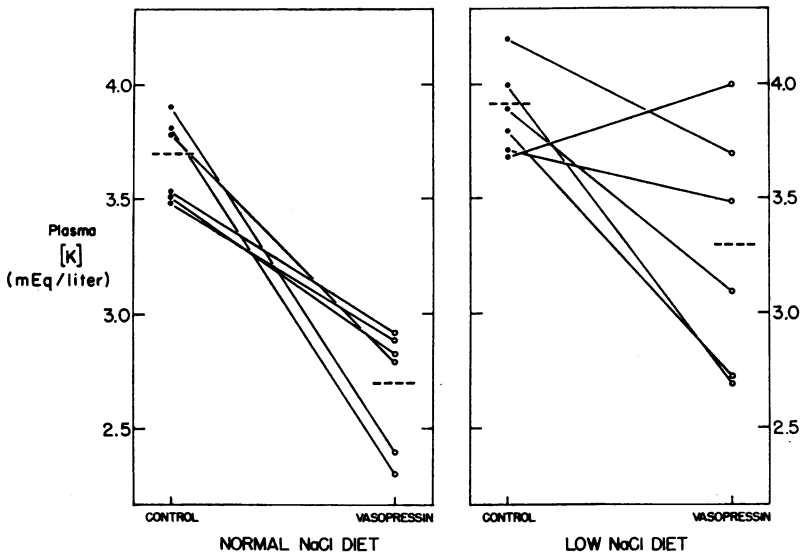

FIGURE 3 Effect of the chronic administration of vasopressin and a liberal quantity of water on plasma potassium concentration in normal dogs ingesting either a normal or low NaCl diet.

potassium excretion occurred in either group until plasma osmolality fell to approximately 240 mOsm/kg.

As shown in Fig. 2 (column 3 of each panel), there was a significant increase in cumulative sodium excretion which averaged 193 mEq in the normal NaCl group and 74 mEq in the low NaCl group. There was also a significant increase in chloride excretion in both groups. (Table I). In the normal NaCl group mean plasma sodium concentration fell from 146 to 114 mEq/liter and mean plasma chloride concentration from 113 to 78 mEq/liter. In the low NaCl group mean plasma sodium concentration fell from 145 to 110 mEq/liter and mean plasma chloride concentration from 109 to 76 mEq/liter.

B. Dogs with HCl-Induced Metabolic Acidosis

Fig. 4 illustrates the effects of hypotonic volume expansion on acid-base and electrolyte equilibrium in a representative dog ingesting HCl and the normal NaCl diet. When vasopressin was administered there was an increase in weight from 12.9 to 13.5 kg and a fall in plasma osmolality from 299 to 220 mOsm/kg. Cumulative net acid excretion increased by 97 mEq and plasma bicarbonate concentration rose from 14.2 to 21.4 mEq/liter. Sodium balance became negative by 136 mEq but there was no clear-cut change in potassium balance.

HCl period. HCl feeding in the normal NaCl group produced a significant fall in mean plasma bicarbonate concentration from 21.1 mEq/liter in the control period to 13.6 mEq/liter in the acidotic steady state (Fig. 5); in the low NaCl group mean plasma bicarbonate concentration fell from 22.4 to 14.3 mEq/liter (Fig. 6). In the normal NaCl group mean P_{CO_2} fell significantly from 37 to 30 mm Hg, and mean plasma hydrogen ion concentration rose from 42 to 54 nmoles/liter. In the low NaCl group mean P_{CO_2} fell significantly from 39 to 31 mm Hg, and mean plasma hydrogen ion concentration rose from 42 to 52 nmoles/liter. Mean cumulative delta potassium balance was significantly negative in both groups: −43 mEq in the normal NaCl group (Table II) and −42 mEq in the low NaCl group (Table III). Mean plasma potassium concentration fell significantly from 3.7 to 3.1 mEq/liter in the normal NaCl group (Table II) and from 4.1 to 3.6 mEq/liter in the low NaCl group (Table III). There was no significant change in sodium balance in either group (Tables II and III).

HCl plus vasopressin period. In the normal NaCl group mean body weight increased significantly from 15.3 kg in the acidotic steady state to 16.4 kg as mean plasma osmolality fell from 298 to 220 mOsm/kg (Table II). In the low NaCl group mean body weight increased significantly from 15.6 to 16.5 kg as mean plasma osmolality fell from 293 to 230 mOsm/kg (Table III). In the normal NaCl group mean plasma bicarbonate concentration rose from 13.6 to 20.6 mEq/liter ($P < 0.001$), a final value not significantly different from the control value of 21.1 mEq/liter (Fig. 5). In the low NaCl group mean plasma bicarbonate concentration rose from 14.3 to 20.1 mEq/liter ($P < 0.001$), a final value 2.3 mEq/liter less than the control value of 22.4 mEq/liter ($P < 0.05$) (Fig. 6). The rise in plasma bicarbonate concentration was not accompanied by a significant rise in P_{CO_2} in either group; in the normal NaCl group

TABLE I

Effect of Chronic Administration of Vasopressin and Water on Plasma

Dog No.	Control period: Plasma composition and body weight								Vasopressin and water period: Plasma composition and body weight*			
	Na	Cl	K	HCO_3	H	$Paco_2$	Osm	Wt	Na	Cl	K	HCO_3
		mEq/liter			*nmoles/liter*	*mm Hg*	*mOsm/kg*	*kg*		*mEq/liter*		
Normal NaCl diet‖												
377	143	111	3.9	20.3	41	35	294	17.6	117	80	2.4	19.1
378	145	112	3.5	21.5	42	37	296	18.0	111	78	2.8	18.5
384	145	115	3.8	19.8	40	33	297	10.7	108	75	2.3	19.2
385	148	112	3.5	21.9	41	38	300	17.3	114	77	2.9	21.3
388	146	112	3.6	20.3	39	33	292	18.3	107	73	2.9	18.2
390	150	115	3.8	20.3	40	34	295	14.4	124	84	2.8	21.0
Mean	146	113	3.7	20.7	41	35	296	16.1	114	78	2.7	19.6
SE	0.9	0.8	0.1	0.3	0.4	0.8	1.0	1.2	2.5	1.6	0.1	0.5
Low NaCl diet¶												
168	145	111	3.8	20.2	46	39	290	14.6	112	75	2.7	20.8
190	150	107	3.7	22.9	43	41	300	10.7	108	75	3.5	17.5
192	147	110	4.0	19.8	45	37	293	9.9	106	65	2.7	19.9
285	141	107	3.9	20.9	41	35	301	16.8	107	74	3.1	18.1
288	145	109	4.2	23.1	41	39	291	16.2	110	80	3.7	20.5
309	143	108	3.7	20.6	39	33	283	11.4	117	86	4.0	19.5
Mean	145	109	3.9	21.3	43	37	293	13.3	110	76	3.3	19.4
SE	1.3	0.7	0.1	0.6	1.1	1.2	3.0	1.2	1.6	2.9	0.2	0.5

* Values are those for the day of lowest plasma osmolality.
‡ Cumulative delta balance calculated on the basis of all days up to and including the day of lowest plasma osmolality.
§ K corrected for N.
‖ 2.5 mEq Na/kg per day.
¶ <0.5 mEq Na/kg per day.

$Paco_2$ was 30 mm Hg during acidosis and 32 mm Hg during expansion; in the low NaCl group it was 31 mm Hg during acidosis and 31 mm Hg during expansion. In both groups plasma hydrogen ion concentration fell significantly, from 54 to 37 nmoles/liter in the normal NaCl group and from 52 to 37 nmoles/liter in the low NaCl group. Each of these final hydrogen ion concentrations was significantly lower than the control value of 42 nmoles/liter observed in each group. Mean cumulative net acid excretion increased by 126 mEq in the normal NaCl group and by 87 mEq in the low NaCl group (Fig. 7, column 1 of each panel). This increase (due almost entirely to an increase in ammonium excretion) was more than sufficient to account for the observed rise in plasma bicarbonate concentration, even assuming that alkali distribution occurred throughout total body water.

There was no change in potassium excretion in the normal NaCl group but in the low NaCl group there was a significant increase in cumulative potassium excretion which averaged 46 mEq (Fig. 7). Mean plasma potassium concentration fell significantly from 3.1 to 2.1 mEq/liter in the normal NaCl group and from 3.6 to 2.6 mEq/liter in the low NaCl group.

There was a significant cumulative increase in sodium excretion which averaged 104 mEq in the normal NaCl group, but there was no significant change in sodium excretion in the low NaCl group (Fig. 7). In the normal NaCl group mean plasma sodium concentration fell from 146 to 110 mEq/liter and in the low NaCl group from 144 to 115 mEq/liter. Chloride excretion rose and plasma chloride concentration fell significantly in both groups (Tables II and III).

In nearly all instances the changes in urinary electrolyte and acid excretion began at a time when plasma osmolality had fallen to a level of approximately 260 mOsm, but the major changes occurred beginning at a level of approximately 240 mOsm. The alterations in acid excretion were usually promptly accompanied by a rise in plasma bicarbonate concentration.

One of the four dogs that received vasopressin for a prolonged period after the day of lowest plasma osmo-

Composition, Body Weight, and Cumulative Delta Balance in Normal Dogs

Vasopressin and water period									
Plasma composition and body weight*				Cumulative delta balance‡					
H	Pa_{CO_2}	Osm	Wt	Na	Cl	K	Kn§	N	Net acid
nmoles/liter	*mm Hg*	*mOsm/kg*	*kg*	*mEq*				*g*	*mEq*
36	29	229	18.2	−203	−174	−69	−36	−12	13
40	31	222	18.5	−237	−175	−65	−41	−9	−40
31	25	210	11.0	−147	−145	−62	−39	−9	14
35	31	219	18.1	−194	−169	−71	−27	−17	15
35	26	216	18.5	−326	−247	−90	−49	−15	−38
33	29	236	14.7	−155	−79	−51	−8	−16	32
35	29	222	16.5	−210	−165	−68	−33	−13	−1
1.2	1.0	4.0	1.3	26.8	22.2	5.2	5.8	1.4	12.4
36	32	223	15.6	−121	−130	−107	−80	−10	−9
40	29	216	11.1	−89	−68	−66	−32	−12	32
36	30	212	10.0	−73	−105	−86	−67	−7	9
35	26	213	18.2	−98	−75	−74	−65	−4	−20
38	33	225	18.4	−23	−17	−40	−20	−8	1.3
38	31	237	12.0	−51	−46	−28	−15	−5	−54
37	30	221	14.2	−76	−73	−67	−46	−8	−7
0.7	0.9	4.0	1.5	14.4	16.5	11.9	11.3	1.3	11.8

lality showed an escape from the water-retaining effect of the hormone; weight fell from 13.7 to 12.7 kg while plasma osmolality rose from 234 to 272 mOsm/kg. Simultaneously, plasma bicarbonate concentration fell from 18.0 to 11.7 mEq/liter, a value identical to that observed in the pre-expansion steady state of acidosis. The other three animals showed only a partial escape from the effects of vasopressin, plasma osmolality rising slightly from its nadir but always remaining below 270 mOsm/kg. During this period of prolonged hypotonic expansion (illustrated by the two dogs shown in Fig. 8) plasma bicarbonate concentration remained significantly above the initial acidotic levels, passing through a cycle characterized by an initial moderate fall and a subsequent rise to final values only slightly below control. Each of the final values for bicarbonate was some 6–7 mEq/liter above the level seen in the previous unexpanded acidotic steady state.

Recovery period. The fall in weight and rise in plasma osmolality that followed vasopressin withdrawal in the low NaCl group was accompanied by a significant fall ($P < 0.001$) in the mean plasma bicarbonate concentration to 15.3 mEq/liter; this final value was 1.0 mEq/liter higher ($P < 0.02$) than that previously seen in the acidotic steady state (Fig. 6).

Administration of vasopressin during restriction of water intake

A. Normal Dogs

When vasopressin was administered in association with a restricted water intake to four dogs ingesting the normal NaCl diet (Table IV) there were no significant changes in plasma osmolality or in the plasma concentration of sodium, chloride, potassium, or hydrogen ion over the 6 day period of study. There was a slight fall in mean plasma bicarbonate concentration from 21.0 to 19.4 mEq/liter ($P < 0.02$), and a reduction in mean Pa_{CO_2} from 36 to 33 mm Hg ($P < 0.02$). There was an increase in mean body weight from 13.6 to 13.9 kg ($P < 0.05$). There were no significant changes in the excretion of potassium, sodium, or chloride.

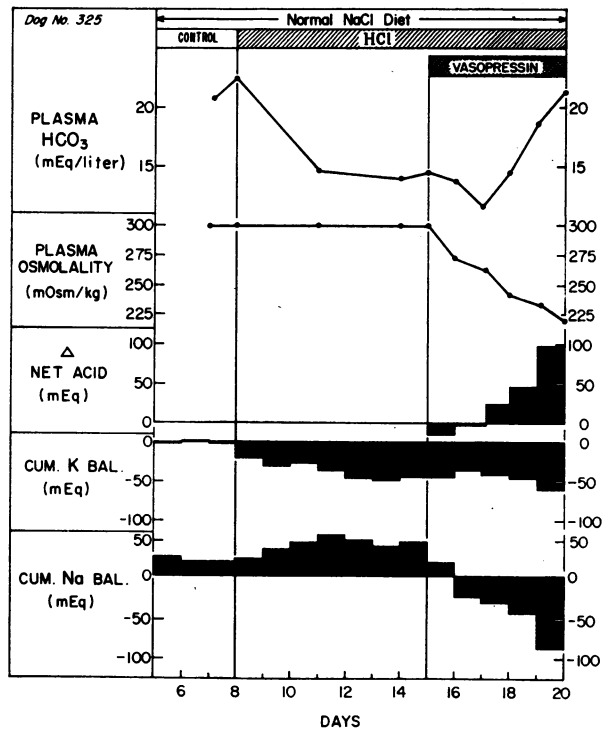

FIGURE 4 Effect of the chronic administration of vasopressin and a liberal quantity of water on electrolyte and acid-base equilibrium in a representative dog with HCl-induced metabolic acidosis (normal NaCl diet). Note that the fall in plasma osmolality to 220 mOsm/kg was accompanied by a marked increase in net acid excretion and a rise in plasma bicarbonate concentration from 14 mEq/liter to a normal level of 21 mEq/liter.

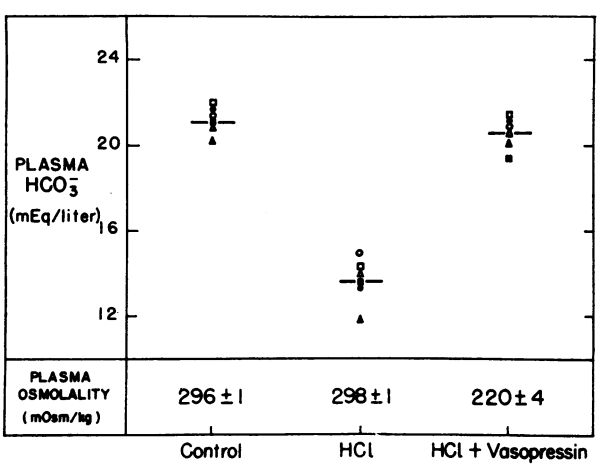

FIGURE 5 Effect of the chronic administration of vasopressin and a liberal quantity of water on plasma bicarbonate concentration in all dogs with HCl-induced metabolic acidosis ingesting a *normal* NaCl diet. Note that plasma bicarbonate concentration rose from a mean of 13.6 mEq/liter in the acidotic steady state to a mean of 20.6 mEq/liter on the day of lowest plasma osmolality.

B. Dogs with HCl-Induced Metabolic Acidosis

When vasopressin was administered in association with a restricted water intake to four dogs with steady-state HCl-induced metabolic acidosis ingesting the normal NaCl diet (Table IV), there was no change in mean plasma bicarbonate concentration over the 7 day period of study. Furthermore, there were no significant changes in body weight, plasma osmolality, P_{CO_2}, or in the plasma concentration of hydrogen ion, potassium, sodium, or chloride. There were no significant changes in the excretion of net acid, potassium, sodium, or chloride.

DISCUSSION

Response of the acidotic dog to hypotonic expansion. The present studies demonstrate that hypotonic expansion produced by the chronic administration of vasopressin can fully correct severe HCl-induced metabolic acidosis in dogs ingesting a normal NaCl diet. In the face of chronic acid feeding (7 mmoles/kg per day) water retention caused a marked increase in acid excretion and a rise in plasma bicarbonate concentration from a mean steady-state value of 14 mEq/liter to a normal value of 21 mEq/liter. In the dogs ingesting a low NaCl diet there was also a striking increase in acid excretion, in this case accompanied by a rise in plasma bicarbonate concentration from 14 to 20 mEq/liter. Withdrawal of vasopressin or escape from vaso-

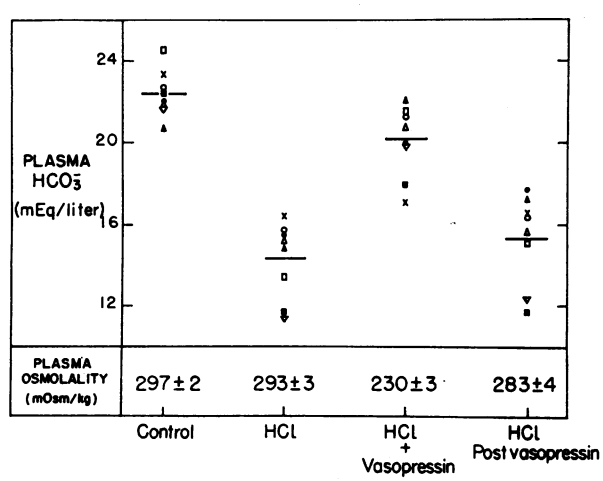

FIGURE 6 Effect of the chronic administration of vasopressin and a liberal quantity of water on plasma bicarbonate concentration in all dogs with HCl-induced metabolic acidosis ingesting a *low* NaCl diet. Note that plasma bicarbonate concentration rose from a mean of 14.3 mEq/liter in the acidotic steady-state to a mean of 20.1 mEq/liter on the day of lowest plasma osmolality. Note also that after vasopressin withdrawal and restoration of normal plasma osmolality, plasma bicarbonate concentration fell to pre-expansion acidotic levels.

TABLE II

*Effect of Chronic Administration of Vasopressin and Water on Plasma Composition, Body Weight, and Cumulative Delta Balance in Dogs with HCl-Induced Metabolic Acidosis Ingesting a Normal NaCl Diet**

Dog No.	Plasma composition and body weight								Cumulative delta balance‡					
	Na	Cl	K	HCO_3	H	P_{CO_2}	Osm	Wt	Na	Cl	K	Kn§	N	Net acid
		mEq/liter			*nmoles/liter*	*mm Hg*	*mOsm/kg*	*kg*		*mEq*			*g*	*mEq*
HCl period														
323	145	119	3.0	14.9	50	31	298	17.3	−46	133	−22	−45	8	‖
324	147	121	3.2	13.3	57	31	301	14.5	−51	73	−71	−63	−3	‖
325	148	122	2.7	14.2	52	31	299	12.9	29	147	−32	−49	6	‖
329	144	120	3.4	13.6	53	30	297	14.5	−41	124	−38	−43	2	‖
330	145	120	2.7	14.0	52	31	299	17.4	−6	147	−55	−65	4	‖
331	146	124	3.6	11.8	58	28	294	15.2	−55	108	−43	−37	−2	‖
Mean	146	121	3.1	13.6	54	30	298	15.3	−29	122	−43	−50	3	
SE	0.6	0.7	0.2	0.4	1.3	0.5	1.0	0.7	13.5	11.5	7.0	4.6	1.8	
Vasopressin and water plus HCl period¶, **														
323	114	78	2.3	20.9	38	33	229	19.1	−82	−102	5	38	−12	192
324	110	74	1.9	21.0	35	31	220	15.5	−95	−171	−41	−11	−11	132
325	112	74	2.2	21.4	36	33	220	13.5	−124	−148	−2	26	−11	97
329	103	67	2.1	19.4	36	30	206	15.2	−144	−221	−85	−46	−15	182
330	115	79	2.1	20.6	39	34	229	19.2	−78	−134	26	53	−10	108
331	108	69	2.0	20.1	39	33	215	15.7	−187	−194	−59	−25	−13	46
Mean	110	74	2.1	20.6	37	32	220	16.4	−118	−162	−26	6	−12	126
SE	1.8	2.0	0.1	0.3	0.7	0.6	4.0	0.9	17.3	17.5	17.4	15.9	0.7	22.0

* 2.5 mEq Na/kg per day.

‡ Cumulative changes in balance for each period are calculated using the steady-state daily balance of the immediately preceding period as the control.

§ K corrected for N.

‖ Net acid excretion during HCl period (representing endogenous acid production plus increased acid excretion due to HCl feeding) served as the control for calculating delta net acid during subsequent vasopressin plus water period.

¶ Values for plasma composition and body weight are those for the day of lowest plasma osmolality.

** Cumulative delta balance calculated on the basis of all days in the period up to and including the day of lowest plasma osmolality.

pressin was followed by a prompt fall in plasma bicarbonate concentration to acidotic levels. When vasopressin was administered in association with a restricted water intake, and expansion thus prevented, there was no significant increase in acid excretion nor rise in plasma bicarbonate concentration; this finding clearly indicates that vasopressin per se cannot be invoked as the factor responsible for the correction of metabolic acidosis during hypotonic expansion.

What was the mechanism responsible for the striking changes in acid-base equilibrium induced by water retention? In over-all terms it is clear that the central event was an acceleration of sodium-hydrogen exchange, most likely occurring in the distal portion of the nephron. The factor serving as the link between hypotonic expansion and increased acid excretion is far less clear but three candidates for the role of mediator deserve consideration: first, the increased delivery of sodium to the distal nephron produced by expansion; second, the expansion of volume per se; and third, the reduction in body fluid osmolality.

The first of these possibilities, that increased sodium delivery enhanced hydrogen ion secretion, is particularly attractive in view of the evidence that a considerable portion of the sodium diverted from the proximal tubule can be conserved more distally (7, 8), chiefly by reabsorption in the loop of Henle (9–11) but also to a small extent by sodium-potassium exchange in the distal tubule (9). It seems only a small further step to hypothesize that an untapped capacity for distal sodium-hydrogen exchange can be mobilized in the same fashion; indeed, acidosis and increased acidity of the renal tubular cells might well be visualized as facilitating such a process. The major difficulty in this hypothesis arises from an examination of the estimated distal delivery of sodium in our normal as compared to

TABLE III

*Effect of Chronic Administration of Vasopressin and Water on Plasma Composition, Body Weight, and Cumulative Delta Balance in Dogs with HCl-Induced Metabolic Acidosis Ingesting a Low NaCl Diet**

Dog No.	Plasma composition and body weight								Cumulative delta balance‡					
	Na	Cl	K	HCO_3	H	P_{CO_2}	Osm	Wt	Na	Cl	K	Kn§	N	Net acid
		mEq/liter			*nmoles/liter*	*mm Hg*	*mOsm/kg*	*kg*		*mEq*			*g*	*mEq*
HCl period														
236	145	118	4.1	15.5	51	33	299	17.6	−10	189	−33	−30	−1	‖
239	148	117	3.7	15.6	51	33	299	10.9	−4	112	−47	−43	−2	‖
240	147	118	3.6	15.2	54	34	303	13.7	−7	91	−97	−93	−2	‖
241	146	115	3.0	16.4	52	36	296	17.7	10	214	38	14	9	‖
266	139	117	4.0	13.4	52	29	285	16.8	4	181	−48	−80	12	‖
267	139	116	3.3	11.7	52	26	289	12.9	−17	118	−96	−77	−7	‖
296	142	121	3.2	11.4	56	27	287	17.5	−11	147	−31	−26	−2	‖
298	144	118	3.6	14.8	49	30	285	17.3	−3	117	−21	−44	8	‖
Mean	144	118	3.6	14.3	52	31	293	15.6	−5	146	−42	−47	2	
SE	1.2	0.6	0.1	0.7	0.7	1.3	3.0	0.9	3.0	15.5	15.3	12.3	2.4	
Vasopressin and water plus HCl period¶, *														
236	122	86	2.3	20.0	40	33	240	18.5	−31	−121	−75	−60	−6	85
239	117	80	2.6	21.3	38	34	231	11.5	−31	−58	−29	−8	−8	73
240	116	78	2.1	20.8	37	32	236	14.9	−48	−73	−29	−20	−4	21
241	118	87	1.9	17.1	46	33	233	19.2	−43	−81	−36	−18	−7	75
266	112	79	3.5	21.6	33	30	218	18.5	−26	−178	−13	17	−11	239
267	116	87	4.3	18.0	35	27	234	13.7	15	12	45	54	−3	63
296	119	86	2.8	19.7	35	29	232	18.4	−14	−94	−17	10	−10	29
298	104	67	2.5	22.1	31	29	216	17.6	−137	−213	−96	−50	−17	108
Mean	115	81	2.6	20.1	37	31	230	16.5	−39	−101	−31	−9	−8	87
SE	1.9	2.5	0.3	0.6	1.6	0.9	3.0	1.0	15.5	24.8	15.0	13.0	1.6	24.0

* <0.5 mEq Na/kg per day.

‡ Cumulative changes in balance for each period are calculated using the steady-state daily balance of the immediately preceding period as the control.

§ K corrected for N.

‖ Net acid excretion during HCl period (representing endogenous acid production plus increased acid excretion due to HCl feeding) served as the control for calculating delta net acid during subsequent vasopressin plus water period.

¶ Values for plasma composition and body weight are those for the day of lowest plasma osmolality.

** Cumulative delta balance calculated on the basis of all days in the period up to and including the day of lowest plasma osmolality.

our low sodium chloride group. If the availability of sodium delivered distally was the determinant of the level of hydrogen secretion, one might expect that the animals ingesting HCl and a liberal quantity of NaCl would, in the pre-expansion phase, have a higher steady-state plasma bicarbonate concentration than acid-fed animals on a low NaCl diet. Such in fact was not the case; both groups during acid feeding demonstrated virtually identical steady-state reductions in plasma bicarbonate concentrations. It is conceivable, of course, that even in the high NaCl group the amount of sodium traversing the distal nephron (30–35 mEq/day) was too small to produce a significant effect on acid secretion and that only during increased delivery of sodium to exchange sites in response to expansion could notable acceleration occur. This explanation seems unlikely in view of the fact that delivery of sodium to the distal tubule (as estimated from increased chloride excretion) in the expanded low NaCl dogs barely reached the level seen during pre-expansion in the normal NaCl group. The role of sodium delivery per se thus requires further study.

The second possibility deserving consideration is that expansion per se stimulated sodium-hydrogen exchange. Studies with the shrinking drop technique suggesting that distal sodium reabsorption is accelerated by an increase in extracellular volume (12) would make this hypothesis appealing. On the other hand, free flow and

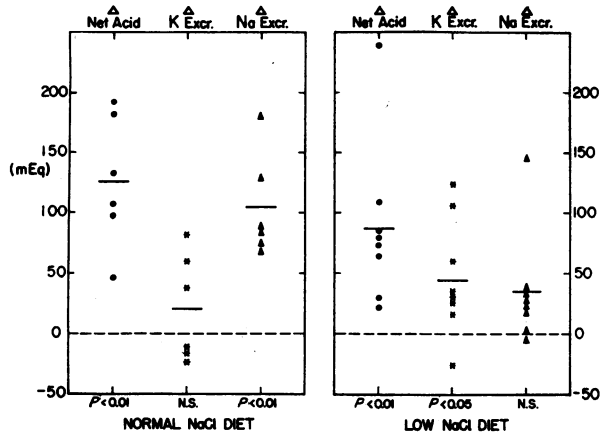

FIGURE 7 Cumulative changes in urinary excretion of net acid, potassium, and sodium during chronic administration of vasopressin and a liberal quantity of water to dogs with HCl-induced metabolic acidosis ingesting either a normal or low NaCl diet. Note the significant increase in net acid excretion in both groups of animals. Note also the significant increase in sodium excretion in the normal NaCl group and in potassium excretion in the low NaCl group.

microperfusion studies of the distal tubule during expansion have not yielded evidence of accelerated sodium reabsorption (13, 14). If we assume for a moment, however, that sodium-hydrogen exchange is accelerated by expansion, the key question relevant to the present experiments is whether the extracellular volume of the low (as well as the normal) NaCl group was in fact increased to an abnormally high level by the administration of vasopressin. There is, of course, no question that the extracellular fluid volume of the normal NaCl animals was considerably expanded; these animals had no evidence of contraction during the initial acid loading period (no significant sodium loss or reduction in body weight) and underwent a 1 kg increase in weight and a 20% increase in "chloride space" during subsequent vasopressin administration. Determination of the final volume status of the low NaCl group is, however, somewhat more complicated. By virtue of a restricted sodium intake before acid loading, one might have presumed that the base line extracellular fluid volume was considerably reduced; however, recent studies have demonstrated that the amount of contraction that occurs

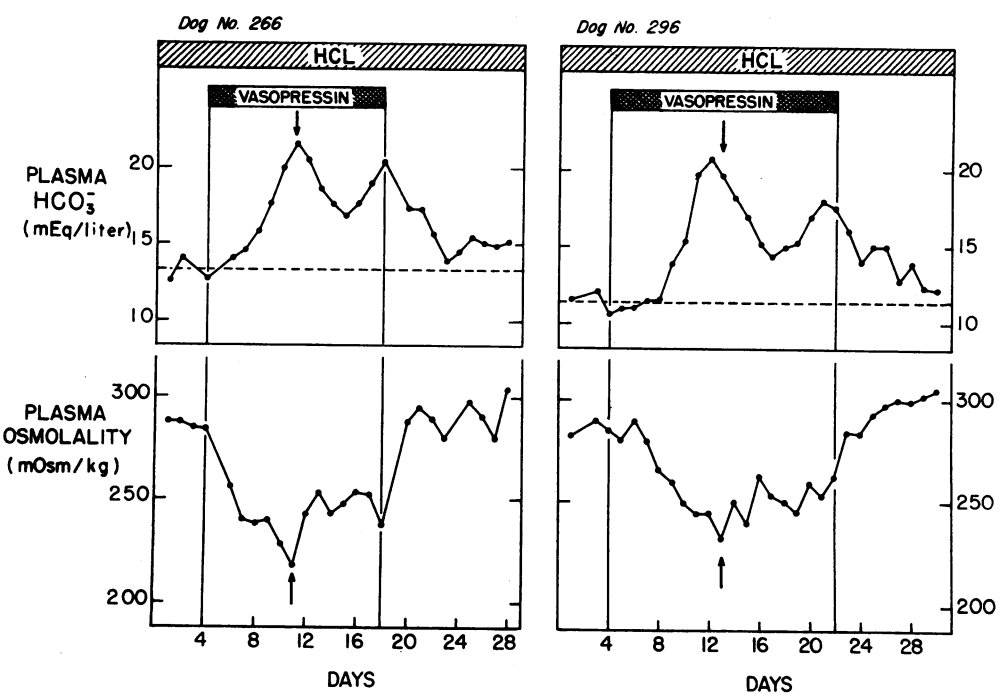

FIGURE 8 Effect of the prolonged administration of vasopressin and a liberal quantity of water on plasma bicarbonate concentration and osmolality in two dogs with HCl-induced metabolic acidosis (low NaCl diet). Note that in both animals plasma bicarbonate concentration reached normal levels on the day of lowest plasma osmolality. Note also that as plasma osmolality rose from its nadir, bicarbonate concentration fall from its peak value but always remained significantly above its pre-expansion level. After vasopressin withdrawal and restoration of normal plasma osmolality, bicarbonate concentration fell to the levels seen before hormone administration.

TABLE IV

*Effect of Chronic Administration of Vasopressin and a Restricted Water Intake on Plasma Composition and Body Weight in Normal Dogs and in Dogs with HCl-Induced Metabolic Acidosis Ingesting a Normal NaCl Diet**

Dog No.	Na	Cl	K	HCO_3	H	Pa_{CO_2}	Osm	Wt	Na	Cl	K	HCO_3	H	Pa_{CO_2}	Osm	Wt
	Normal dogs															
	Control period								Vasopressin period							
	mEq/liter				*nmoles/liter*	*mm Hg*	*mOsm/kg*	*kg*	*mEq/liter*				*nmoles/liter*	*mm Hg*	*mOsm/kg*	*kg*
171	143	110	3.7	20.5	46	39	300	11.0	134	100	3.5	19.5	47	38	279	11.4
172	143	107	3.8	22.1	39	36	297	15.1	143	110	3.8	19.7	40	32	295	15.6
173	145	108	4.3	21.5	38	34	299	15.0	139	102	4.2	19.8	38	31	285	15.2
175	144	108	3.6	19.9	43	35	300	13.1	144	109	3.4	18.7	42	32	297	13.2
Mean	144	108	3.9	21.0	42	36	299	13.6	140	105	3.7	19.4	42	33	289	13.9
SE	0.3	0.5	0.2	0.5	1.7	1.2	1.0	1.0	2.3	2.5	0.2	0.2	1.9	1.6	4.0	1.0
	Dogs with metabolic acidosis															
	HCl period								Vasopressin period							
345	148	119	3.3	14.0	56	33	291	17.1	145	119	3.0	13.0	57	31	288	16.8
348	148	122	3.7	14.9	54	34	291	14.0	145	119	3.2	14.9	55	34	292	13.7
349	147	115	3.2	16.8	48	34	288	16.6	144	111	3.2	16.3	48	33	273	16.2
350	148	116	3.0	13.5	51	29	287	10.5	149	116	3.1	14.0	51	30	284	16.5
Mean	148	118	3.3	14.8	52	32	289	14.6	146	117	3.1	14.6	53	32	284	14.3
SE	0.3	1.6	0.1	0.7	1.8	1.1	1.0	1.5	1.0	2.0	0.0	0.7	2.0	0.9	4.0	1.4

when a normal dog is changed from an NaCl intake identical to that used here, to a sodium-free diet, is relatively small, i.e., there is virtually no weight loss or change in sodium balance.[3] This fact, taken together with the absence of sodium loss during acid feeding and a subsequent weight gain of 1 kg (and an expansion of 20% in chloride space) during vasopressin administration, strongly suggests that final extracellular fluid volume in the low NaCl dogs was substantially larger than normal.

The observation that the distal delivery of sodium (estimated from increased chloride excretion) during expansion of the low NaCl dogs was no larger than that seen in the normal NaCl dogs before expansion probably is accounted for by the hyponatremia of the expanded state. It is well known that hyponatremia blunts the sodium diuresis that accompanies volume expansion (15), apparently by promoting a relatively more effective proximal reabsorption (16). Thus in an expanded hypotonic animal sodium delivery to the distal nephron might well be lower than in an isotonic dog with a normal extracellular volume. Taking all of our experimental findings, it therefore seems reasonable to conclude that expansion was present in both the high and low NaCl groups given vasopressin and water and that it could have been the common denominator responsible for the accelerated sodium-hydrogen exchange. Direct evidence in support of this hypothesis is, of course, not available from the present data.[4]

What then of the third possibility, that hyposmolality of the body fluids was directly responsible for the acceleration of sodium-hydrogen exchange? Such an hypothesis cannot be excluded but at present there is no experimental evidence for its support. It must, therefore, remain as a possibility requiring further investigation.

Response of the normal dog to hypotonic expansion. The present studies demonstrate that the sodium diuresis produced by the administration of vasopressin and water to normal dogs is accompanied by a loss of chloride without a concomitant loss of bicarbonate. The absence of a bicarbonate diuresis, a striking finding, might be accounted for in one of two ways. It is possible that sodium shunted from proximal to distal tubule by volume expansion was accompanied exclusively by chloride. It is far more likely, however, that the sodium was accompanied by bicarbonate as well as chloride and

[3] Cohen, J. J., A. Gougoux, W. D. Kaehny, and W. B. Schwartz. Unpublished data.

[4] One further observation provides clear evidence that the level of dietary NaCl intake before expansion influenced the response of organism during expansion. In the normal NaCl group there was a significant increase in the excretion of sodium but not of potassium when vasopressin and water were administered, whereas in the low NaCl group there was an increase in excretion of potassium but not of sodium. The relationship of this finding to the mechanism responsible for acceleration of sodium-hydrogen exchange remains obscure.

that accelerated distal sodium-hydrogen ion exchange, analogous to that demonstrated in the expanded acidotic dogs, conserved the shunted bicarbonate and prevented an alkali diuresis.[5] The striking increase in potassium excretion which occurred during expansion in the normal dogs indirectly supports this interpretation, giving clear indication of enhanced distal sodium-cation exchange.

The present data reveal a notable similarity between the response of plasma bicarbonate concentration in the normal dog given vasopressin and water and that of man suffering from the syndrome of inappropriate secretion of antidiuretic hormone. Under both circumstances hypotonic expansion does not produce a significant depression of plasma bicarbonate concentration despite a marked reduction in plasma sodium concentration (1). We suggest, therefore, that the mechanism proposed here for the stability of the plasma bicarbonate level in normal dogs, namely, conservation of bicarbonate by acceleration of distal hydrogen secretion, is also operative in man. Several observations on potassium equilibrium during hypotonic expansion in man are consistent with this interpretation, suggesting as they do acceleration of distal cation exchange. In the one study of human subjects made markedly hypotonic by exogenous vasopressin administration, potassium wasting and hypokalemia were commonly encountered (17). Hypokalemia has also been seen with significant frequency among patients with SIADH in whom hypotonicity was of a severity comparable to that which led to potassium wasting in the present studies; analysis of a large group of cases of SIADH (1) indicates that among eight patients in which serum sodium concentration was below 110 mEq/liter, serum potassium concentration was less than 3.5 mEq/liter in four. By contrast, hypokalemia occurred in only 6 of 54 instances in which serum sodium concentration was above 110 mEq/liter.[6]

A final issue deserving comment is the striking and unexplained respiratory alkalosis which was a feature of the present studies. During expansion of the HCl-loaded dogs, as plasma bicarbonate concentration rose to normal or near normal values the P_{CO_2} remained at the low level characteristic of the earlier acidotic state. Thus, at a time when bicarbonate concentration had risen to 20–21 mEq/liter, P_{CO_2} was 8 mm Hg below control in the normal NaCl group and 5 mm Hg below control in the low NaCl group. As a result, mean plasma hydrogen concentration in each group fell to a value 5 nmoles/liter below control. A similar degree of hypocapnia and alkalosis occurred in the normal dogs during expansion, a finding which indicates that the persistence of hypocapnia observed during the correction of acidosis cannot be attributed to a lag in the restoration of normal ventilation (18–20), but instead must be attributed to the vasopressin protocol.[7]

It should also be noted that the development of alkalosis during hypotonic expansion gives clear evidence that the normal plasma bicarbonate concentration observed in the expanded dogs represented a significant "overshoot" on the part of the kidneys; chronic hypocapnia of the degree found here, in the absence of complicating factors, should have been associated with a bicarbonate concentration significantly below that observed in our expanded animals (21).

In summary, the present studies indicate that vasopressin-induced hypotonic expansion served as a stimulus to renal hydrogen ion secretion sufficiently powerful to restore plasma bicarbonate concentration to control or near control levels in the face of continued ingestion of large quantities of acid and to prevent a bicarbonate diuresis in normal animals. The significance of this finding for the physiologic regulation of acid-base equilibrium must await clarification of the specific factor(s) responsible for the augmented hydrogen secretory activity.

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[5] In the acidotic dogs, the amount of bicarbonate in filtrate shunted to the distal tubule was presumably smaller than in the normals, a phenomenon which would explain why a significant fraction of the enhanced hydrogen ion secretion produced by expansion could be detected as an increase in net acid excretion.

[6] Cases were included for analysis only if the case report gave no indication of vomiting, diuretic administration, steroid therapy, or other factors that might be expected to produce potassium depletion.

[7] It should be noted that the normal dogs given vasopressin but prevented by water restriction from undergoing expansion also had a reduction in P_{CO_2} (3 mm Hg) but one that was significantly smaller than in the expanded animals. Given this finding, it is difficult to assess the relative roles of vasopressin per se and of water retention in producing hypocapnia.

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