The Critical Role of the Adrenal Gland in the Renal Regulation of Acid-Base Equilibrium during Chronic Hypotonic Expansion

EVIDENCE THAT CHRONIC HYPONATREMIA IS A POTENT STIMULUS TO ALDOSTERONE SECRETION

JORDAN J. COHEN, HENRY N. HULTER, NEIL SMITHLINE, JAMES C. MELBY, and WILLIAM B. SCHWARTZ

From the Department of Medicine, Tufts University School of Medicine, Boston 02111, the Renal Service of the New England Medical Center Hospital, Boston 02111, and the Department of Medicine, Boston University School of Medicine, Boston, Massachusetts 02115

ABSTRACT Recent studies have shown that chronic hypotonic volume expansion (HVE) induced by administration of vasopressin and water stimulates distal hydrogen ion secretion and thereby (*a*) permits dogs with HCl-acidosis to restore acid-base equilibrium to normal despite continued acid feeding and (*b*) permits normal dogs to conserve filtered bicarbonate quantitatively despite the natriuresis induced by water retention.

To examine whether these effects of chronic HVE are mediated by augmented mineralocorticoid secretion, urinary and plasma aldosterone levels were monitored during prolonged administration of vasopressin. In HCl-fed animals, the HVE-induced rise in plasma [HCO_3] (from 13.8 to 21.3 meq/liter) was associated with a rise in aldosterone excretion from 0.45 to 0.88 μg/day ($P < 0.02$). In normal animals, in which plasma [HCO_3] remained stable during HVE (21.9 vs. 20.0 meq/liter), aldosterone excretion rose from 0.51 to 2.28 μg/day ($P < 0.02$) and plasma aldosterone concentration rose from 8.1 to 39.8 ng/100 ml ($P < 0.01$).

Vasopressin and water were also administered to adrenalectomized animals maintained on glucocorticoids and a slightly subphysiologic replacement schedule of mineralocorticoids. In the HCl-fed adrenalectomized group, plasma [HCO_3], instead of rising to normal, showed no significant change (16.9 vs. 15.0 meq/liter). In the non-HCl-fed adrenalectomized group, plasma [HCO_3], rather than remaining stable, fell significantly (20.3 vs. 16.5 meq/liter, $P < 0.1$).

Two conclusions can be drawn from this study: (*a*) the well-known inhibitory effect of volume expansion on aldosterone secretion can be overridden by a potent stimulatory effect on the adrenal produced by severe chronic hypotonicity, and (*b*) the response of plasma [HCO_3] observed during severe chronic HVE is mediated by augmented mineralocorticoid secretion. These findings, furthermore, offer a possible explanation for the puzzling observation that plasma [HCO_3] in patients with the syndrome of inappropriate antidiuretic hormone secretion is maintained at normal levels even in the face of severe hyponatremia.

INTRODUCTION

Chronic hypotonic expansion of the body fluids, induced by the prolonged administration of vasopressin and water, produces a marked enhancement of distal hydrogen ion secretion in dogs with HCl-induced acidosis (1). The resulting increase in renal acid excretion is enough to restore plasma bicarbonate concentration completely to normal, even in the face of the continued daily administration of a large acid load.

The present study was designed to explore the mechanism responsible for this striking effect of hypotonic

Dr. Hulter's current address is: U. S. Public Health Service, San Francisco, Calif. and Dr. Smithline's is: Tucson Medical Center, Department of Medicine, Tucson, Ariz.

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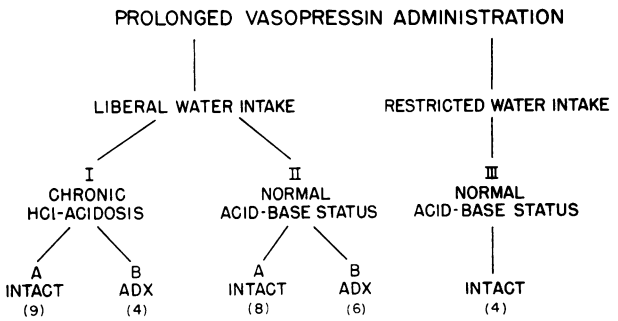

FIGURE 1 Schematic representation of protocol designed to determine effects of hypotonic volume expansion on aldosterone levels. Note that all animals received vasopressin but that animals differed in level of water intake, acid-base status, and presence or absence of adrenals. The number of dogs in each subgroup is shown in parentheses.

expansion on the renal regulation of acid-base equilibrium. Because there is no evidence that either hyponatremia or volume expansion stimulates distal hydrogen ion secretion directly, it would appear that some as yet undefined factor must mediate the observed enhancement of acid excretion. More particularly, since several studies have indicated that hyponatremia can, under certain acute experimental circumstances, cause the release of aldosterone from the adrenal gland (2–6), we hypothesized that aldosterone might play such a mediating role.

To test this hypothesis, aldosterone levels in plasma and urine were determined during prolonged administration of vasopressin to normal dogs and to dogs made acidotic by the chronic administration of HCl. The data indicate that aldosterone secretion is indeed markedly augmented by chronic hyponatremia. Moreover, when augmentation of aldosterone secretion was prevented by prior adrenalectomy, the striking response of plasma bicarbonate concentration to chronic hypotonic volume expansion (HVE)[1] was abolished.

We have concluded from these observations that severe chronic hypotonicity is a sufficiently potent stimulus to aldosterone secretion to override the well-established inhibitory effects of volume expansion. We also conclude that augmented mineralocorticoid secretion plays a critical role in the renal regulation of acid-base equilibrium during chronic HVE.

METHODS

31 studies were carried out on female mongrel dogs weighing between 9 and 27 kg. Animals were utilized for study only if average control plasma bicarbonate concentration was between 18 and 24 meq/liter. Each dog was fed 30 mg/kg per day of a synthetic diet containing 1 meq of sodium, 0.3 meq of chloride, and 0.1 meq of potassium per 100 g (7). The daily diet was supplemented with 2.5 meq potassium/kg body wt as neutral phosphate and 2.5 mM sodium chloride/kg body wt. Unless otherwise noted, water intake was held constant at 77 ml/kg body wt per day throughout the study. Dogs that failed to eat spontaneously were tube-fed. Studies were terminated if vomiting resulted in a cumulative loss greater than 100 ml; in such instances, data from the day on which vomiting occurred and from the previous day were excluded.

Fig. 1 summarizes the various protocols employed in this study. As can be seen, animals were treated identically with respect to vasopressin administration Pitressin tannate in oil, Parke, Davis & Company, Detroit, Mich. (5 U subcutaneously twice daily for 5–8 days) but differently with respect to the conditions under which they were studied, i.e., level of water intake, state of acid-base equilibrium, and presence or absence of adrenal glands.

As shown on the left-hand side of the figure, the animals maintained on a liberal water intake were divided into two groups; group I (n = 13) with chronic HCl-induced acidosis, and group II (n = 14) with normal acid-base status. Each of these groups was further divided into two subgroups: A, containing intact and B, containing adrenalectomized (ADX) animals. All animals included in groups I and II achieved a nadir value for plasma osmolality of 245 mosmol/kg or less during vasopressin administration; several other animals treated identically failed to meet this criterion and were not included for study.

As shown on the right-hand side of the figure, the animals maintained on a restricted water intake constituted group II; each had normal acid-base status and intact adrenal glands.

In all animals subjected to adrenalectomy, the surgical procedure was performed at least 10 days before study. The adequacy of adrenalectomy was confirmed in each animal by demonstrating that the 24-h urinary excretion of 17-hydroxysteroids, invariably less than 5 mg, remained unchanged after ACTH administration. Glucocorticoid replacement was provided as dexamethasome sodium phosphate (Decadron, Merck Sharp & Dohme, Div. of Merck Co., Inc., West Point, Pa.) 0.8 mg/day subcutaneously.

Mineralocorticoid replacement was provided by a combination of aldosterone, corticosterone, and desoxycorticosterone, the salt-active hormones known to be secreted by the canine adrenal gland (8). A slightly subphysiologic dose of each hormone was administered in an effort to avoid mineralocorticoid excess and the attendant expansion of extracellular fluid volume. In a series of preliminary studies, the following dosage schedules of mineralocorticoids was found to provide the desired, subphysiologic effect, as evidenced by mild but persistent hyponatremia: d-aldosterone acetate, 0.06 mg/day subcutaneously in sesame oil; desoxycorticosterone acetate, 0.1 mg/day subcutaneously in sesame oil; and corticosterone, 3.0 mg/day subcutaneously in 95% ethanol.

Urinary aldosterone excretion and plasma aldosterone concentration were measured in all animals with intact adrenal glands on two control days and on the second and all subsequent days of vasopressin administration.

Group I—intact and ADX animals with chronic HCl acidosis given vasopressin and a liberal water intake

A. Intact dogs (n = 9). Hydrochloric acid, 7 mM/kg body wt, was added to the daily diet at least 7 days before vasopressin administration to induce stable metabolic acidosis

[1] *Abbreviations used in this paper*: ADH, antidiuretic hormone; ADX, adrenalectomized; HVE, hypotonic volume expansion.

TABLE I

Change in Plasma Osmolality and Acid-Base Equilibrium in Response to Vasopressin and a Liberal Water Intake in Intact and ADX Animals with Chronic HCl-Acidosis (Group I)

Dog	HCl, 7 mM/kg/day*					HCl, 7 mM/kg/day, + vasopressin and water‡				
	Osmolality	HCO_3	$PaCO_2$	H	Weight	Osmolality	HCO_3	$PaCO_2$	H	Weight
	mosmol/kg	*meq/liter*	*mm Hg*	*neq/liter*	*kg*	*mosmol/kg*	*meq/liter*	*mmHg*	*neq/liter*	*kg*
Intact animals (group I-A)										
1	302	15.1	36	59	11.3	231	22.1	41	47	11.9
2	298	12.2	28	56	26.8	258	15.3	28	45	27.4
3	308	15.1	33	54	19.0	258	18.6	33	44	20.1
4	308	13.6	33	60	11.6	246	18.0	30	42	11.8
5	302	18.1	36	49	13.1	243	25.6	35	34	13.6
6	299	13.7	32	61	13.1	273	12.9	31	60	13.1
7	297	13.5	30	54	14.5	271	16.0	32	49	14.7
8	302	11.7	28	58	15.1	286	13.3	30	55	14.7
9	294	11.3	26	57	15.3	249	15.6	29	46	16.2
Mean	301	13.8	31	56	15.5	257	17.5	32	47	15.9
ADX animals (group I-B)										
1	272	17.6	32	45	10.3	233	15.9	26	39	10.4
2	278	16.1	30	44	10.0	227	15.1	26	41	9.8
3	271	15.8	28	43	8.4	252	11.9	23	46	7.9
4	287	17.9	32	43	12.6	251	17.2	29	42	12.5
Mean	277	16.9	31	44	10.3	241	15.0	26	42	10.2

* The individual values shown are the mean of three observations obtained during the steady state of HCl-induced metabolic acidosis.

‡ The individual values shown are the mean of observations obtained on days 4 and 5 of vasopressin administration.

(9); acid feeding was continued throughout the 5–8 days of vasopressin administration.

B. ADX dogs ($n = 4$). As in group I-A, hydrochloric acid, 7 mM/kg body wt, was added to the daily diet at least 7 days before and throughout 8 days of vasopressin administration.

Group II—intact and ADX animals with normal acid-base status given vasopressin and a liberal water intake

A. Intact dogs ($n = 8$). All animals in this group received vasopressin for 6 days.

B. ADX dogs ($n = 6$). Water intake was held constant at the standard rate of 77 ml/kg per day during the control period but was adjusted daily during the vasopressin administration to achieve a rate of decline in plasma osmolality similar to that observed in group II-A, (see Results).

Group III—intact animals with normal acid-base status given vasopressin and a restricted water intake ($n = 4$)

Water intake was restricted to 47/ml/kg per day during a 6-day control period and, when necessary, was restricted further to maintain plasma osmolality above 280 mosmol/kg during 6 days of vasopressin administration.

Analytic methods

Detailed description of the analytical methods employed in this laboratory for plasma electrolytes, osmolality, hydrogen-ion concentration, and carbon dioxide tension have been previously described (10). Urinary aldosterone was measured by a modified method of Mayes et al. (11). Plasma aldosterone was measured as the gamma-lactone by a radioimmunoassay method patterned after that of St. Cyr et al. (12). Plasma samples for aldosterone determinations were obtained at approximately 9:00 a.m.

RESULTS

Control values for each animal were averaged to provide a base line for assessing the influence of subsequent vasopressin administration. The mean of the values obtained on the 4th and 5th days of vasopressin administration (ADH days 4 and 5) was selected for most comparisons because, as previously noted (1), during this interval, HVE typically induces most of the increment in net acid excretion and plasma bicarbonate observed in HCl-fed animals.

TABLE II

Response of Urinary Aldosterone Excretion and Plasma Aldosterone Concentration to Prolonged Vasopressin Administration

Dog	Control*		Vasopressin‡	
	Aldosterone excretion	Plasma aldosterone	Aldosterone excretion	Plasma aldosterone
	μg/24 h	*ng/100 ml*	*μg/24 h*	*ng/100 ml*
Group I-A (HCl-acidosis)				
1	0.24	8.0	0.47	13.5
2	0.89	19.4	1.11	12.0
3	0.34	8.9	0.59	9.5
4	0.37	22.1	0.85	44.7
5	0.60	7.9	2.02	37.8
6	0.36	6.1	1.10	15.7
7	0.44	7.9	0.53	7.0
8	0.50	6.8	0.75	16.4
9	0.32	7.5	0.50	8.3
Mean	0.45	10.5	0.88	18.3
Group II-A (no HCl)				
1	1.70	10.0	5.60	34.0
2	—	5.0	—	90.0
3	0.26	9.0	1.24	26.0
4	0.30	8.0	1.21	29.0
5	0.29	6.0	3.50	52.0
6	0.56	12.6	2.75	49.5
7	0.31	8.5	0.69	13.4
8	0.14	5.8	1.00	24.5
Mean	0.51	8.1	2.28	39.8
Group III (water-restricted)				
1	0.29	18.0	0.44	17.5
2	0.23	8.5	0.34	11.0
3	0.11	8.5	0.35	8.0
4	0.35	16.0	0.23	8.0
Mean	0.25	12.8	0.34	11.1

* Control values represent the means of two observations obtained before vasopressin administration.

‡ Vasopressin values represent the means of the observations obtained on days 4 and 5 of vasopressin administration.

Group I-intact and ADX animals with chronic HCl acidosis given vasopressin and a liberal water intake

A. Intact dogs. The administration of vasopressin to the intact HCl-fed animals produced changes in plasma electrolyte composition quite similar to those observed in an identically treated group of dogs reported previously from this laboratory (1). Values for plasma osmolality and acid-base equilibrium are shown in Table I. As plasma osmolality fell, plasma bicarbonate concentration rose, the peak level for individual animals occurring between ADH days 5 and 8; the average of the peak bicarbonate levels was 21.3 meq/liter, a value not significantly different from the mean bicarbonate concentration of 21.1 meq/liter observed before acid feeding. Plasma sodium concentration fell from a mean value of 145 meq/liter during HCl-acidosis to a low of 115 meq/liter during vasopressin administration ($P < 0.1$). Mean plasma potassium concentration fell from 3.0 to 2.3 meq/liter ($P < 0.01$).

As shown in Table II, aldosterone excretion averaged 0.45 μg/24 h during the HCl acidosis and rose to a mean of 0.88 μg/24 h by ADH days 4 and 5

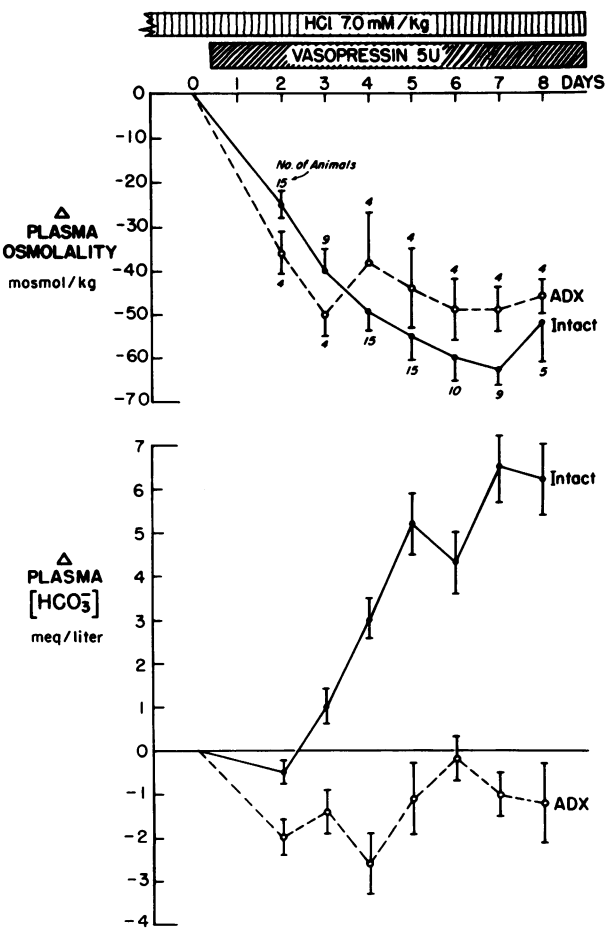

FIGURE 2 Mean change (±SEM) in plasma osmolality and bicarbonate concentration during administration of 5 U vasopressin twice a day and water to intact and to ADX dogs with chronic HCl-acidosis. Data from six intact animals studied previously (1) are included with the present observations. Note that the response of plasma osmolality was similar in both the intact and ADX dogs, but that the response of plasma bicarbonate was markedly different.

TABLE III

Change in Plasma Osmolality and Acid-Base Equilibrium in Response to Vasopressin and a Liberal Water Intake in Intact and ADX Animals Given Vasopressin and Water (no HCl Supplement)

Dog	Control*					Vasopressin‡ and water				
	Osmolality	HCO_3	$PaCO_2$	H	Weight	Osmolality	HCO_3	$PaCO_2$	H	Weight
	mosmol/kg	*meq/liter*	*mm Hg*	*neq/liter*	*kg*	*mosmol/kg*	*meq/liter*	*mm Hg*	*neq/liter*	*kg*
Intact animals (group II-A)										
1	298	22.3	42	47	15.8	239	20.5	37	43	15.8
2	303	22.5	39	42	13.2	254	18.9	30	41	13.1
3	300	22.1	37	41	12.3	244	21.4	30	35	12.7
4	296	19.9	35	43	18.6	235	20.3	29	35	19.6
5	297	20.2	37	44	12.3	273	20.5	36	42	12.2
6	299	23.6	41	43	16.5	265	22.7	36	38	16.7
7	296	22.2	38	42	21.3	250	20.0	32	39	21.9
8	298	22.2	39	43	11.9	240	21.1	32	37	12.0
Mean	298	21.9	39	43	15.2	250	20.7	33	39	15.5
ADX animals (group II-B)										
1	293	20.4	35	42	21.2	232	15.9	27	42	23.1
2	294	21.4	36	41	14.9	241	17.3	30	42	15.8
3	292	18.8	32	42	23.5	233	15.5	25	39	25.3
4	292	20.3	34	41	16.5	234	18.2	28	37	17.7
5	296	20.1	35	43	15.9	239	16.6	26	38	16.4
6	291	20.5	42	49	13.5	234	15.5	25	40	13.4
Mean	293	20.3	36	43	17.6	236	16.5	27	40	18.6

* The individual values shown are the mean of two or three observations obtained during the control period.

‡ The individual values shown are the mean of observations obtained on days 4 and 5 of vasopressin administration.

($P < 0.02$). Plasma aldosterone concentration, also shown in Table II, averaged 10.5 ng/100 ml during the HCl period and 18.3 ng/100 at ADH days 4 and 5; these values were not significantly different from one another. However, by the final day of study, mean plasma aldosterone concentration had risen to 30.7 ng/100 ml, a value that did differ significantly from that observed during the HCl period ($P < 0.05$).

B. ADX dogs. As can be seen in Table I, the acidosis produced in ADX animals by prolonged HCl feeding was no greater than that produced in intact animals. Mean plasma osmolality was slightly lower in the ADX group during control,[2] but there was virtually no difference in the pattern of fall in plasma osmolality during administration of vasopressin, as illustrated in Fig. 2. Note that the data for intact animals used in this figure include not only observations from the present study but also from a previous study of six intact animals treated identically (1).

Fig. 2 also shows that plasma bicarbonate concentration, which rose strikingly in the intact animals during vasopressin administration, remained virtually unchanged in the ADX animals. Note also that on ADH days 4 and 5, the interval used above in assessing the aldosterone response of intact animals, plasma bicarbonate concentration differed significantly between the intact and ADX groups ($P < 0.02$).

Group II—intact and ADX animals with normal acid-base status given vasopressin and a liberal water intake

A. Intact dogs. Values for plasma osmolality and acid-base composition are shown in Table III. As can be seen, the administration of vasopressin to the intact group of animals resulted in changes in plasma acid-base and electrolyte composition similar to those observed in an identically treated group of dogs reported previously from this laboratory (1). As plasma osmolality fell progressively, there was only a transient fall in mean plasma bicarbonate concentration (from a control value of 21.9 to a minimum value of 19.2 meq/liter on ADH day 2); thereafter, plasma bicarbonate gradually returned to control levels, reaching a mean level of 20.7 meq/liter by ADH days 4 and 5 and 21.0 meq/liter by the final day of the study.

[2] This difference in osmolality reflects a significant difference in sodium concentration ($P < 0.01$), which we attribute to the low-dose mineralocorticoid replacement schedule intentionally employed in the ADX animals.

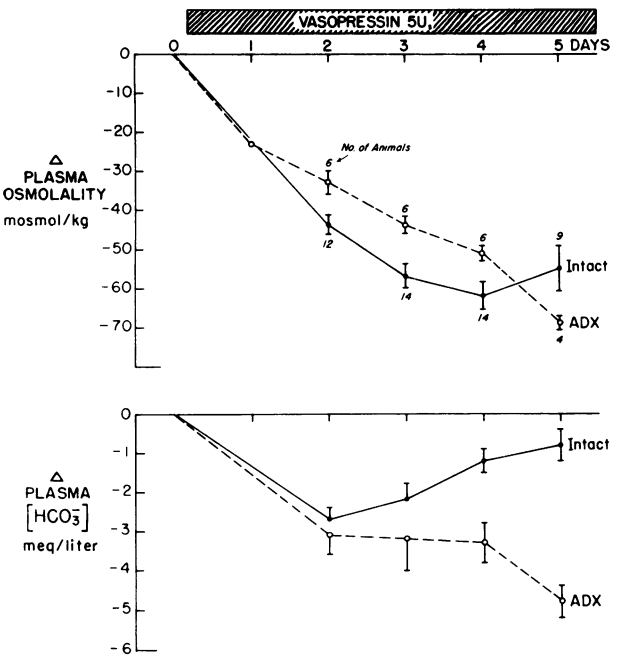

FIGURE 3 Mean change (±SEM) in plasma osmolality and bicarbonate concentration during administration of 5 U vasopressin twice a day and water to intact and to ADX dogs with normal acid-base status. Data from six previously studied intact animals (1) are included with the present observations. Note that plasma bicarbonate fell initially in both groups but remained below normal only in the ADX animals.

Plasma sodium concentration fell from a mean control value of 145 to a low value of 114 meq/liter during vasopressin administration ($P < 0.01$). Mean plasma potassium concentration fell from 3.9 to 3.1 meq/liter ($P < 0.01$).

The observed changes in osmolality and plasma bicarbonate concentration were associated with a marked increase in urinary aldosterone excretion; as can be seen in Table II, aldosterone excretion rose from a mean control value of 0.51 μg/24 h to a value of 2.28 μg/24 h by ADH days 4 and 5 ($P < 0.02$). A significant change in plasma aldosterone concentration also occurred (Table II), the mean level rising from 8.1 ng/100 ml to 39.8 ng/100 ml on ADH days 4 and 5 ($P < 0.01$).

B. ADX dogs. As can be seen in Table III, plasma bicarbonate, Pa_{CO_2}, and plasma hydrogen ion concentration in the intact and ADX groups were not significantly different during the control period. Mean plasma osmolality was slightly lower in the ADX animals during control ($P < 0.01$), but, as shown in Fig. 3, the pattern of fall during vasopressin administration was virtually identical in the intact and ADX groups. Note that the data for intact animals used in this figure include not only those obtained from the present study but also those from a previous study of six intact animals studied by an identical protocol (1). As can be seen, plasma bicarbonate concentration fell to a similar extent on ADH day 2 in both groups (Δ plasma bicarbonate was −2.7 vs. −3.1 meq/liter). Thereafter, however, the response was clearly divergent; bicarbonate concentration in the ADX group failed to rise over the subsequent days of the period, remaining at a mean level 4.8 meq/liter below control on ADH day 5. The difference between the mean bicarbonate concentrations observed in the two groups on both ADH days 4 and 5 was significant ($P < 0.01$).

Group III—intact animals with normal acid-base status given vasopressin and a restricted water intake

Administration of vasopressin to water-restricted animals resulted in only minor variations in plasma osmolality and electrolyte composition, a finding in keeping with previous observations (1). As shown in Table II, no significant change was observed either in urinary aldosterone excretion or in plasma aldosterone concentration; aldosterone excretion averaged 0.25 and 0.34 μg/24 h, and plasma aldosterone averaged 12.8 and 11.1 ng/100 ml during control and ADH day 4–5, respectively.

DISCUSSION

Two principle conclusions can be drawn from the present studies: (*a*) a marked increase in aldosterone secretion occurs when chronic HVE is induced by prolonged administration of vasopressin and water and (*b*) this increase in aldosterone secretion mediates the striking effects of HVE on renal acid-base regulation. The following discussion will consider, in turn, the implications of these two conclusions.

Regulation of aldosterone secretion: The interplay of hypotonicity and extracellular volume. The finding that aldosterone secretion can be augmented during chronic HVE appears, on the surface, to be contrary to the well-established fact that expansion of extracellular fluid volume is a potent inhibitor of aldosterone release. This apparent contradiction is all the more remarkable when one recalls that the means by which volume expansion was first demonstrated to be a crucial regulator of aldosterone secretion was the very means by which volume was expanded in the present experiments; water retention induced by daily vasopressin administration was clearly shown by Bartter et al. as early as 1956 to cause a prompt reduction in urinary aldosterone excretion (13).

There is, however, one substantive difference between this earlier study and ours: in the earlier study, serum sodium concentration was reduced to a

level of only 120–125 meq/liter (13), whereas in the present study, sodium concentration was lowered to an average of 115 meq/liter and frequently as low as 108 meq/liter.

We would suggest that this difference in sodium concentration is the key factor accounting for the divergent aldosterone responses. On the basis of both present and previous data, it would appear that HVE produces two distinctly different effects on aldosterone secretion; one, an inhibiting effect related to volume expansion and the other, a stimulating effect related to hypotonicity.[3] Whether aldosterone levels are suppressed or augmented during HVE seems to depend upon the balance of these two opposing forces. In chronic HVE of only moderate severity, as in the studies of Bartter et al., the dampening effects of expansion override the stimulating effects of hypotonicity. This interpretation gains considerable support from several acute studies in which even modest degrees of hypotonicity, produced without concomitant expansion, have been clearly shown to augment aldosterone release from the adrenal gland (2–6).

When severe hypotonic expansion is produced, as in the present study, there is a shift in the balance of forces that leads to a rise in aldosterone levels. The marked reduction in serum sodium concentration apparently causes a sufficiently potent stimulus to aldosterone secretion to more than offset the inhibitory effect of the associated volume expansion. It should be noted, incidentally, that the potency of this stimulus is further attested to by the failure of moderate hypokalemia and potassium deficiency to block the aldosterone response.

The effects of HVE on renal acid-base regulation. Previous studies from this laboratory have indicated that the renal response to HVE causes a striking increase in plasma bicarbonate concentration in animals with chronic HCl acidosis and prevents the anticipated fall in plasma bicarbonate concentration in normal animals (1). In the present study, these effects on acid-base equilibrium were found to be associated temporally with the rise in aldosterone levels. Given the well-known effect of aldosterone on sodium and hydrogen ion transport in the kidney, such a temporal association raised the strong possibility that the observed augmentation in aldosterone secretion mediated the response of plasma bicarbonate concentration. To assess this possibility, we carried out additional experiments in which enhanced mineralocorticoid secretion was prevented by prior adrenalectomy. The results provide further compelling evidence that aldosterone plays a critical role in the renal response to HVE; adrenalectomized animals fed HCl failed to increase plasma bicarbonate concentration (Fig. 2) and non-HCl fed, ADX animals failed to maintain normal bicarbonate levels (Fig. 3).[4]

Of course, since adrenalectomy prevents the secretion of all adrenal hormones, we cannot exclude the possibility that some hormone other than aldosterone could have been the actual mediator of the renal response to HVE. However, in view of the very high levels attained by aldosterone itself, this possibility seems quite remote.

We should also point out that these data provide a possible explanation for the remarkable stability of plasma bicarbonate concentration in hyponatremic patients with the syndrome of inappropriate secretion of ADH. It is well known that even in the face of severe hyponatremia (sodium concentrations of 100–115 meq/liter), bicarbonate concentration in patients with this syndrome usually remains at normal or nearly normal levels (14), but no explanation for this remarkable finding has previously been proposed. On the basis of the present observations, it would seem reasonable to suggest that a rise in aldosterone secretion induced by hyponatremia is responsible for the protection of acid-base equilibrium. Whether this explanation is, in fact, correct remains to be determined; elevated levels of aldosterone have been noted in some patients with this syndrome (15–19), but such increases have not been found consistently (20–23). It thus seems clear that a systematic study of aldosterone secretion in these patients will be necessary to clarify the interplay between tonicity, aldosterone, and acid-base equilibrium.

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[3] It is clear that the factor responsible for the sustained elevation in aldosterone levels observed during HVE was hypotonicity rather than vasopressin administration itself; control animals given vasopressin but a restricted water intake failed to manifest an aldosterone response.

[4] Our interpretation of the role of aldosterone in maintaining steady-state plasma bicarbonate concentration during HVE in normal animals is further supported by the observation that a transient fall in plasma bicarbonate concentration occurs (see Fig. 3), but is corrected concomitant with the increase in aldosterone secretion.

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