Effects of dexamethasone on renal and systemic acid-base metabolism

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Effects of dexamethasone on renal and systemic acid-base metabolism.
We carried out long-term balance studies in adrenalectomized (ADX)
dogs to evaluate the effects of small amounts of a glucocorticoid steroid
with minimal mineralocorticoid potency (dexamethasone; DEX) on
renal and systemic acid-base metabolism under conditions of constant
mineralocorticoid replacement and both normal and increased systemic
acid loads. We investigated the effects of low and high dosages of
dexamethasone (0.2 mg/day [normal-DEX] vs. 0.8 mg/day [high-DEX])
before and during hydrochloric acid feeding (5 mmol/kg/day) in paired
studies on ADX dogs ($N = 7$) maintained on constant mineralocorticoid
replacement (deoxycorticosterone, corticosterone, aldosterone). Prior
to hydrochloric acid feeding, no differences in plasma acid-base compo-
sition were observed between the two dosages despite greater endoge-
nous acid production with the higher dosage of DEX, evidenced by
greater rates of both net acid excretion (NAE) and the excretion of
urinary anions other than chloride, bicarbonate, and phosphate (urine
anion gap). During hydrochloric acid feeding, mean plasma bicarbonate
(P_{HCO_3}) decreased from 21.2 ± 0.4 to 13.7 ± 0.5 (normal-DEX) and from
21.1 ± 0.4 to 15.8 ± 0.4 mEq/liter (high-DEX). The difference in the
decrements in P_{HCO_3} between groups was significant ($P < 0.05$). With
continued hydrochloric acid feeding in both groups, increasing the DEX
dosage from 0.2 to 0.8 mg/day in the normal-DEX group resulted in a
significant increase in NAE ($\Sigma\Delta NAE$, $+161$ mEq, $P < 0.02$) and in
P_{HCO_3} ($+3.6 \pm 0.5$ mEq/liter, $P < 0.01$) to steady-state levels by day 10,
which were values not significantly different from those in high-DEX.
The DEX dose-related increase in NAE was greater than the corre-
sponding increase in endogenous acid production estimated from the
change in urine anion gap, and was due largely to an increase in
ammonium excretion, which, because urine pH did not decrease, could
not be attributed to increased intraluminal trapping of ammonia as a
result of more acidic tubular fluid. These studies indicate that the
severity of hydrochloric acid-induced metabolic acidosis in min-
eralocorticoid-replete ADX dogs can be mitigated by increasing the
dosage of exogenous glucocorticoid and suggest that this acidosis
mitigating effect is mediated in part by the increased NAE associated
with the stimulation of renal ammonia production. These studies further
indicate that the rate of production of fixed acids of metabolism
increases with an increased dosage of exogenous glucocorticoid, but
that this acidosis-producing effect is more than offset by independent
stimulation of renal net acid excretion, such that metabolic acidosis is
prevented (basal condition) or if present (hydrochloric acid feeding) is
significantly ameliorated.

**Effets de la dexaméthasone sur le métabolisme acido-basique rénal et
systémique.** Les études de bilan qui sont rapportées ont été réalisées
chez des chiens surrénalectomisés (ADX) pour évaluer les effets de
faibles quantités d'un stéroïde glucocorticoïde, ayant une activité
minéralocorticoïde faible (dexaméthasone; DEX), sur le métabolisme
acido-basique rénal et systémique dans des conditions de traitement
substitutif permanent de minéralocorticoïdes et de charge acide soit
normale soit élevée. Nous avons étudié les effets de doses de dexaméth-
asone (0,2 mg/jour; normale-DEX) ou 0,8 mg/jour (élevée-DEX) avant
et pendant l'administration d'acide chlorhydrique à raison de 5 mmol/
kg/jour dans des études appariées chez des chiens ADX ($N = 7$)
recevant un traitement substitutif par les minéralocorticoïdes (deoxy-
corticosterone acetate, corticosterone, aldosterone). Avant l'adminis-
tration d'acide chlorhydrique, il n'y avait pas de différence dans la
composition acido-basique du plasma selon les doses de DEX malgré
l'augmentation de production endogène d'acide sous l'effet de la dose la
plus élevée de DEX, augmentation traduite par une élévation de l'état
stationnaire d'excrétion nette d'acide (NAE) et de la somme des débits
d'excrétion des anions urinaires autres que le chlore, le bicarbonate et
le phosphate (trou anionique urinaire). Au cours de l'administration
d'acide chlorhydrique la concentration plasmatique moyenne de bicar-
bonate (P_{HCO_3}) a diminué de $21,2 \pm 0,4$ à $13,7 \pm 0,5$ (normale-DEX) et
de $21,1 \pm 0,4$ à $15,8 \pm 0,4$ mEq/litre (élevée-DEX). La différence des
diminutions de bicarbonate était significative ($P < 0,05$). Au cours de
l'administration prolongée d'acide chlorhydrique aux deux groupes
l'augmentation de la dose de DEX de 0,2 à 0,8 mg/jour dans le groupe
normale-DEX a eu pour résultat une augmentation significative de NAE
($\Sigma\Delta NAE$, $+161$ mEq, $P < 0,02$) et de P_{HCO_3} ($+3,6 \pm 0,5$ mEq/litre, $P <
0,01$), jusqu'à de nouveaux états stationnaires, le jour 10, non significa-
tivement différents de ceux observés dans le groupe élevée-DEX.
L'augmentation de NAE dépendant de la dose de DEX a été plus
grande que l'augmentation correspondante de la production endogène
d'acide estimée à partir de la modification du trou anionique urinaire,
elle était principalement due à une augmentation significative de l'excrétion d'am-
monium qui, du fait que le pH de l'urine n'a pas diminué, ne peut pas
être attribuée à une augmentation de la captation intraluminale d'am-
monia. Ces résultats indiquent que la sévérité de l'acidose métabolique
déterminée par acide chlorhydrique chez les chiens ADX recevant des
minéralocorticoïdes peut être atténuée par l'augmentation de la dose de
glucocorticoïdes exogènes et suggère que cet effet d'atténuation a pour
médiateur partiel l'augmentation de NAE associée à la stimulation de la
production rénale d'ammonia. Ces résultats indiquent, de plus, que le
débit de production des acides fixes augmente en même temps que la
dose de glucocorticoïdes exogènes mais que cet effet de production
d'acidose est plus que compensé par la stimulation indépendante de
l'excrétion rénale nette d'acide, de telle sorte que l'acidose métabolique
est empêchée (conditions basales) ou significativement améliorée au
cours de l'administration acide chlorhydrique.

Adrenal mineralocorticoid hormones with minimal glucocor-
ticoid activity stimulate renal net acid excretion such that states

of mineralocorticoid excess result in renal metabolic alkalosis [1, 2] and states of mineralocorticoid deficiency result in renal metabolic acidosis [3, 4]. Long-term administration of adrenal steroids with predominant glucocorticoid activity but with substantial mineralocorticoid effect as well (cortisol, cortisone) results in metabolic alkalosis and an increased excretion of potassium and net acid [5–8]. In humans, long-term administration of adrenocorticotrophin, which is known to result in sustained hypercortisolemia, results in hyperbicarbonatemia and hypokalemia [9]. In Cushing's syndrome, the degree of metabolic alkalosis is directly related to the degree of hypokalemia and hypercortisolemia [10]. The alkalosis-producing effect of cortisol is believed to reflect the "mineralocorticoid" properties of the hormone inasmuch as renal tubular reabsorption of sodium and chloride and renal secretion of potassium are stimulated by cortisol administration [7, 8] and the administration of the mineralocorticoid antagonist spironolactone at least partially reverses the apparent mineralocorticoid effects of hydrocortisone and adrenocorticotrophin [6, 9].

The effects of glucocorticoid steroids that exhibit minimal mineralocorticoid potency, such as dexamethasone or triamcinolone, on renal and systemic acid-base metabolism have not been specifically investigated. Dexamethasone has been shown to stimulate hydrogen ion secretion in isolated urinary epithelia of vertebrate species [11] and to stimulate renal ammonium excretion in man [12]. Triamcinolone has been demonstrated to increase renal ammonia production and plasma bicarbonate concentration in rats, but its effects on net acid excretion and plasma acidity were not assessed [13, 14]. The long-term administration of large amounts of triamcinolone in dogs stimulates the endogenous production of organic acids and an increase in net acid excretion sufficient to maintain normal acid-base equilibrium [15].

The present long-term balance studies were carried out in adrenalectomized dogs to evaluate the effects of small amounts of glucocorticoid steroid (dexamethasone) on renal and systemic acid-base metabolism under conditions of constant mineralocorticoid replacement and both normal and increased systemic acid loads.

Methods

Plasma and urine acid-base and electrolyte composition was determined in long-term balance studies in seven adrenalectomized female mongrel dogs weighing 13 to 26 kg. Throughout the studies, the dogs were fed a constant amount (30 g/kg/day) of a low-electrolyte synthetic diet [1] homogenized with distilled water (60 ml/kg) and supplemented with specified amounts of sodium chloride and potassium as the neutral phosphate salt. Bilateral adrenalectomy was performed at least 1 week before starting the metabolic diet. After surgery, the adequacy of adrenalectomy was confirmed by the positive finding of hyperkalemia and hyponatremia. Throughout all study periods and for at least three days before initiating control observations, each animal received in addition to the metabolic diet s.c. injections of *d*-aldosterone acetate (Ciba) in sesame oil, 60 µg/day; deoxycorticosterone acetate (Organon) in sesame oil, 0.15 mg/day; corticosterone (Sigma) in 95% ethanol, 3.0 mg/day; and dexamethasone sodium phosphate (Merck, Sharp and Dohme), 0.2 (study A) or 0.8 mg/day (study B). Studies A and B were performed on the same animals with an interval of 9 to 49 days between studies. The lower dosage of dexamethasone was

used in the postoperative period and between studies A and B. Each animal served as its own paired control.

We chose the 0.2-mg/day dosage of dexamethasone to be the low dosage, which is considerably lower than the replacement dosages (0.75 to 0.80 mg) used in dogs in previous studies [16–19]. The corticosterone and deoxycorticosterone replacement dosages were chosen to approximate the normal secretion rates in dogs [20, 21]. The aldosterone replacement dosage chosen is estimated to be the normal aldosterone requirement for dogs [22].

In both studies, following a steady-state control period of 6 to 12 days, in which plasma and urine acid-base and electrolyte composition were constant, hydrochloric acid (5.0 mmol/kg of body wt) was administered in the daily diet for 4 days to all seven dogs. In four dogs, acid feeding was continued for an additional 12 days in both studies. In study A, the dexamethasone dosage was increased to 0.8 mg/day beginning on day 4 of hydrochloric acid feeding. In study B, hydrochloric acid was continued with no change in the dexamethasone dose. The electrolyte supplement to the diet was identical in both studies and consisted of sodium chloride (2.5 mmoles/kg/day) and potassium (2.5 mEq/kg/day) as the neutral phosphate. Dogs that failed to eat spontaneously were tube fed. Studies were terminated if vomiting resulted in a cumulative loss greater than 1 dl. At 9 A.M., after the dogs were fasted overnight, arterial blood samples were obtained percutaneously, at intervals of 24 to 72 hours, in heparinized glass syringes from the femoral artery. Urine was collected through the stainless-steel surfaces of the metabolic cages, in which the animals were kept, into glass bottles containing mineral oil and thymol-chloroform preservative.

Analytical procedures. All determinations were performed in duplicate. The analytical methods used have been described in a previous report [3]. Urine inorganic sulfate concentration was determined by a modification of the method of Ma and Chan [23]. Urine calcium concentration was determined by atomic absorption spectrophotometry. The concentration of urinary total organic acid was determined by titration of phosphate-precipitated urine (prepared by the method of Van Slyke and Palmer [24]) from a pH of 2.7 to 8.0 by means of a Radiometer titrator (model 11) and an autoburette (model, ABU 1B) connected to a Radiometer pH meter (model PHM27). Net acid excretion was calculated as the sum of the urinary ammonium and the titratable acidity minus the bicarbonate. Unmeasured anion concentration (anion gap) was calculated as follows:

$$(P_{Na} + P_K) - (P_{Cl} + P_{HCO_3})$$

and as

$$(U_{NH_4} + U_{Na} + U_K) - (U_{Cl} + U_{HCO_3} + U_{HPO_4} + U_{H_2PO_4})$$

where the concentration of each species is expressed in mEq/liter. Statistical significance was determined by Student's *t* test [25].

Results

No significant differences in plasma acid-base composition were observed at the two dosages of dexamethasone prior to hydrochloric acid feeding (Table 1). The mean plasma sodium concentration and the anion gap were significantly greater in study B. The mean steady-state net acid excretion and urinary anion gap were significantly greater in study B than they were in

Table 1. Effect of dexamethasone dosage on steady-state plasma acid-base and electrolyte composition in mineralocorticoid-replete adrenalectomized dogs[a]

Dog no.	Arterial H^+ nEq/liter	Arterial P_{CO_2} mmHg	P_{HCO_3}	Anion gap	P_{Cl}	P_{Na}	P_K	$P_{creatinine}$ mg/dl	Body wt kg
					mEq/liter				
Study A, 0.2-mg/day dexamethasone									
134	39	32.8	20.5	13.7	106.9	136.7	4.3	0.56	14.2
159	41	34.2	20.2	15.9	108.1	139.8	4.5	0.61	18.6
165	45	37.9	20.5	18.0	106.0	140.1	4.4	0.53	24.9
197	42	35.2	20.7	13.9	107.8	137.7	4.6	0.56	13.9
198	39	36.4	22.7	17.9	103.9	139.8	4.7	0.85	15.6
200	39	35.1	22.0	16.1	104.1	137.5	4.6	0.94	19.0
203	40	35.7	21.7	16.2	105.9	139.3	4.5	0.56	20.6
Mean	41	35.3	21.2	16.0	106.1	138.7	4.5	0.66	18.1
± SEM	±1	±0.6	±0.4	±0.6	±0.6	±0.5	±0.1	±0.06	±1.5
Study B, 0.8-mg/day dexamethasone									
134	40	32.1	19.6	17.2	107.8	140.1	4.4	0.43	13.0
159	42	34.0	19.7	20.2	105.0	140.7	4.2	0.56	17.9
165	42	36.7	21.7	19.9	106.4	143.9	4.1	0.46	25.5
197	42	36.6	21.3	19.3	105.8	141.9	4.4	0.50	13.2
198	40	37.1	22.6	17.6	106.3	142.1	4.3	0.68	15.0
200	40	36.3	21.9	17.4	107.1	140.3	4.5	0.70	19.7
203	42	36.9	21.1	17.0	106.9	140.6	4.4	0.51	20.7
Mean	41	35.7	21.1	18.4[b]	106.5	141.4[c]	4.3[b]	0.55[c]	17.9
± SEM	±1	±0.7	±0.4	±0.5	±0.3	±0.5	±0.1	±0.04	±1.7

[a] Each value represents the mean of 5 to 8 determinations of plasma acid-base and electrolyte composition and body weight during steady-state control periods of 6 to 12 days' duration at each dose of dexamethasone (studies A and B) prior to hydrochloric acid feeding. Values for creatinine concentrations represent the mean of two determinations. An interval of 9 to 49 days separated studies A and B.
[b] $P < 0.05$, compared with study A.
[c] $P < 0.01$, compared with study A.

study A and by virtually identical amounts (study B minus study A) (Table 2). The difference in net acid excretion between studies was accounted for by the difference in urinary ammonium excretion. The difference in urinary anion gap between studies was accounted for, in part (42%), by the difference in organic acid plus sulfate excretion. The mean urinary calcium excretion was not significantly different. The mean urine pH was significantly greater during study B.

In response to an identical load of hydrochloric acid (5.0 mmol/kg/day) in the diet, the mean plasma bicarbonate concentration decreased to a significantly greater extent when the same animals were maintained on the lower dosage of dexamethasone (study B; Fig. 1), with the change in plasma bicarbonate (A vs. B, day 3) being -7.5 ± 0.6 vs. -5.3 ± 0.7 mEq/liter, $P < 0.05$. During hydrochloric acid feeding the mean arterial hydrogen ion concentration was significantly greater during the lower dosage of dexamethasone (48 ± 1 vs. 46 ± 1 nEq/liter, $P < 0.05$, day 1; 53 ± 2 vs. 51 ± 2 nEq/liter, day 4). A subsequent increase in dexamethasone to the higher dose with continued hydrochloric acid feeding caused the plasma bicarbonate concentration to significantly increase and thereby reversed the prior downward trend (Fig. 1). The increase in plasma bicarbonate concentration was associated with a significant cumulative increase in net acid excretion of 161 ± 35 mEq ($P < 0.02$) (days 3–5 to day 16) without a change in unmeasured anion excretion (Fig. 1). The increase in net acid excretion was due largely to ammonium without a reduction in urine pH. The plasma and urinary electrolyte response to hydrochloric acid is shown in Table 3.

Discussion

The results of the present studies in adrenalectomized dogs maintained on constant mineralocorticoid replacement indicate that a fourfold increase in the dosage of replacement glucocorticoid, administered as dexamethasone, increases net acid excretion in the steady state without altering the plasma acid-base composition. The increased rate of net acid excretion was accounted for entirely by an increased rate of ammonium excretion, which was not attributable to an increased luminal trapping of ammonia secondary to increased luminal acidity inasmuch as urine pH was significantly increased during the administration of the high dosage of dexamethasone. This finding indicates that the availability of cellular ammonia for diffusion into tubular fluid is increased, possibly as a result of an increased rate of renal ammonia production. This possibility is consistent with the observation that the rate of directly measured ammonia production from isolated perfused rat kidney is increased by an administration of triamcinolone [13], a steroid with predominantly glucocorticoid or mineralocorticoid potency similar to dexamethasone [26]. To what extent increased ammonia production reflects direct or indirect effects of the steroid on the kidney remains to be determined. Dexamethasone has been reported to increase the plasma concentration of glutamine, the major renal ammoniagenic precursor [12]. Neither potassium depletion nor systemic acidosis, factors known to stimulate renal ammoniagenesis [27], were present during the administration of the higher dosage of dexamethasone in the present studies.

Despite the significantly greater net acid excretion rate observed with the administration of the higher dosage of dexamethasone, the plasma bicarbonate concentration was not significantly different from that observed with the lower dose of dexamethasone (Tables 1 and 2), and there was no trend in the daily values of plasma bicarbonate concentration with either dosage in the basal state (Fig. 1). This finding suggests that the higher dosage of dexamethasone resulted in corresponding

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Table 2. Effect of dexamethasone dosage on steady-state urinary acid-base and electrolyte composition in mineralocorticoid-replete adrenalectomized dogs[a]

Dog no.	pH	TA_{calc}	TA_{tit}	NH_4	Net $acid_{calc\ TA}$	Net $acid_{tit\ TA}$	Na
				mEq/day			
Study A, 0.2-mg/day dexamethasone							
134	6.20	24.6	25.6	36.2	58.8	59.7	45.7
159	5.64	36.1	39.2	43.9	79.8	82.9	48.7
165	5.81	49.3	51.5	52.5	101.5	103.7	73.5
197	5.62	30.1	31.7	31.0	61.0	62.5	39.3
198	5.84	30.6	35.5	28.9	59.1	64.1	45.7
200	5.84	33.8	36.2	35.0	68.3	70.7	59.0
203	6.07	39.6	45.5	62.9	100.8	106.7	67.0
Mean	5.86	34.9	37.9	41.5	75.6	78.6	54.1
± SEM	±0.08	±3.0	±3.2	±4.7	±7.1	±7.4	±4.8
Study B, 0.8-mg/day dexamethasone							
134	6.34	20.6	23.0	52.6	69.4	71.9	46.2
159	5.88	36.6	40.2	62.4	98.6	102.2	48.8
165	6.13	43.7	49.6	75.4	117.1	123.0	78.0
197	6.00	27.0	30.5	44.8	71.1	74.6	42.6
198	6.04	28.2	29.6	37.4	65.0	66.5	34.0
200	5.93	38.5	42.4	41.7	79.7	83.6	61.1
203	6.11	36.2	38.7	59.0	93.7	96.2	61.3
Mean	6.06[c]	33.0	36.3	53.3[b]	84.9[b]	88.3[b]	53.1
± SEM	±0.06	±3.0	±3.4	±5.0	±7.2	±7.6	±5.5
Change, study B minus study A							
	+0.20[c]			+11.8[b]	+9.3[b]	+9.7[b]	
	±0.05			±3.4	±3.2	±4.0	

[a] Abbreviations used are OA, organic acids; TA_{calc}, calculated TA based on phosphate excretion and ionic strength correction for pK_a phosphate; TA^{tit}, TA by titration method; net $acid_{calc\ TA}$, net acid based on TA_{calc}; net $acid_{tit\ TA}$, net acid based on TA_{tit}. Each value represents the mean of 6 to 12 daily determinations of urinary acid-base, electrolyte, and nitrogen excretion during the steady-state control periods at each dose of dexamethasone (studies A and B) prior to hydrochloric acid feeding. An interval of 9 to 49 days separated studies A and B.

[b] $P < 0.05$, compared with study A.

[c] $P < 0.01$, compared with study B.

increases in the net daily systemic load of hydrogen ion destined for renal excretion (endogenous acid production) and in the set point of renal regulation of plasma bicarbonate. If endogenous acid production had been unchanged by the higher dosage of dexamethasone, a significantly greater plasma bicarbonate concentration would have been expected in comparison with that observed with the lower dosage owing to the increase in net renal input of bicarbonate to the systemic circulation that is coupled to an increase in net acid excretion [28]. But the inferred increase in endogenous acid production would have been expected to cause a decrease in plasma bicarbonate concentration if the set point for renal regulation of plasma bicarbonate concentration had not concomitantly been increased.

Consistent with the possibility that the rate of endogenous acid production was increased by the higher dose of dexamethasone is the observation that the urinary excretion of anions other than bicarbonate, phosphate, and chloride (that is, anion gap) increased significantly (Table 2). The increase in urine anion gap was essentially identical to that of ammonium and net acid excretion (Table 2). The close correspondence of the increase in urinary anion gap and ammonium suggests that the anion gap consists of conjugate bases that were generated in the body coupled to hydrogen ions, for example, the "so-called" fixed acids of metabolism. At least in part, such increased endogenous acid production was accounted for by the increased production of sulfuric and organic acids, inasmuch as approximately 42% of the increase in anion gap was accounted for by the measured increase in sulfate and organic acid excretion.

The factors responsible for preventing a decrease in plasma bicarbonate concentration and pH with the higher dosage of dexamethasone despite an apparently greater rate of endogenous acid production require further consideration. It is known from studies of chronic mineral acid feeding in dogs that the magnitude of the chronic reduction in plasma bicarbonate concentration and pH is determined in part by the chemical identity of the conjugate base (anion) of the acid administered. In the case of nitric acid feeding, plasma acid-base composition remains unchanged despite large increases in net systemic acid load [29]. It has been proposed that the magnitude of the steady-state reduction in plasma bicarbonate concentration during acid loading is directly related to the renal tubular reabsorbability of the acid anion administered, which determines *(1)* the magnitude of urinary losses of sodium and consequent stimulation of distal nephron avidity for sodium-hydrogen "exchange" and *(2)* the facility with which the increment in filtered anion load is delivered to terminal segments of the nephron where the accompanying cation is reabsorbed in exchange for hydrogen ion excreted in buffered form [29]. An additional possibility to account for the unchanged plasma bicarbonate concentration with the higher dosage of dexamethasone is that the magnitude of the increase in systemic acid load, an increment of approximately 10%, was insufficient to result in an appreciable reduction in plasma bicarbonate concentration, regardless of the identity of the associated anion or anions. An additional possibility to be considered is that dexamethasone directly stimulates renal acid excretion and that the increment in dexametha-

Table 2. continued

| K	Cl	Ca	OA + SO$_4$	iPO$_4$	N$_2$	Anion gap	Volume
	mEq/day			*mmol/day*	*g/day*	*mEq/day*	*ml/day*
Study A, 0.2-mg/day dexamethasone							
36.1	42.9	0.19	36.3	41.5	6.2	23.0	901
43.6	53.4	0.23	42.3	49.7	9.3	29.5	1089
67.7	70.4	0.70	63.7	71.9	11.8	44.9	1642
37.3	38.5	0.94	31.4	41.3	6.8	25.6	813
42.0	44.2	0.54	40.8	43.4	8.0	24.6	896
43.4	57.5	1.01	79.1	48.5	10.4	26.1	904
66.6	66.6	1.22	66.8	63.2	12.7	53.9	1061
48.1	53.4	0.69	51.5	51.4	9.3	32.5	1044
±5.0	±4.6	±0.15	±6.8	±4.5	±0.9	±4.5	±106
Study B, 0.8-mg/day dexamethasone							
36.2	45.2	0.21	45.1	38.7	7.0	37.1	959
45.7	47.2	0.38	61.0	53.6	10.0	49.8	1158
65.1	72.0	0.51	70.5	72.0	15.0	60.0	1729
37.1	40.6	0.48	66.8	41.7	9.2	35.9	899
41.9	33.7	0.41	36.0	42.7	8.1	30.6	890
53.6	59.7	0.31	47.3	56.5	11.2	32.3	1013
57.0	59.9	0.52	60.1	58.6	10.4	46.1	980
48.1	51.2	0.40	55.3	52.0	10.1	41.7[b]	1090
±4.1	±5.0	±0.04	±4.8	±4.5	±1.0	±4.0	±112
Change, study B minus study A							
						+9.2[b]	
						±3.4	
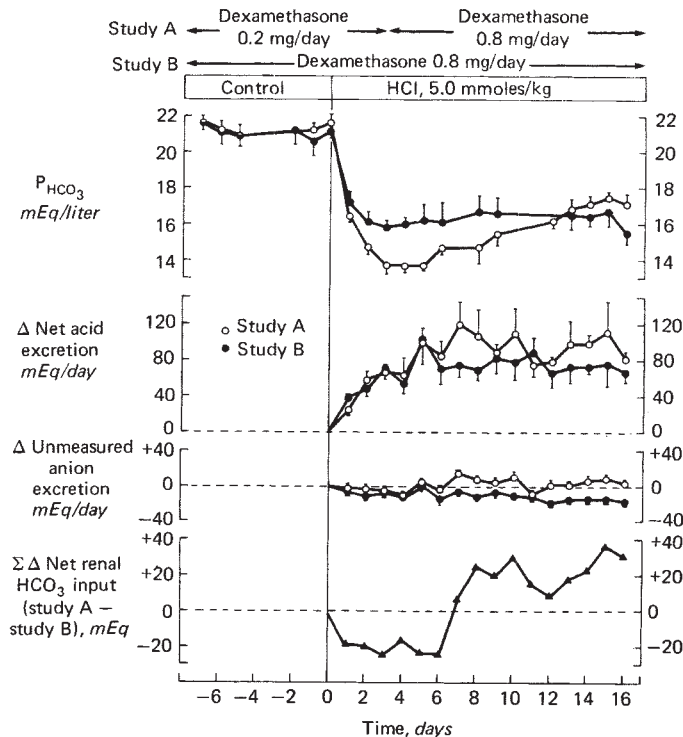
Fig. 1. *Systemic and renal acid-base response to long-term hydrochloric acid feeding in mineralocorticoid-replaced adrenalectomized dogs maintained on 0.2 or 0.8 mg of dexamethasone per day (study A vs. study B).* In study A, the dexamethasone dosage was increased from 0.2 to 0.8 mg/day on day 4 of hydrochloric acid feeding. Daily net renal bicarbonate input to the systemic circulation was calculated as the difference between the change in (Δ) net acid excretion and Δ unmeasured anion excretion (change from control) (see discussion).

sone dosage was sufficient to increase net acid excretion *pari passu* with the increase in endogenous acid production. The extent to which the dexamethasone-dependent stimulation of renal acid excretion is attributable to direct and indirect effects of dexamethasone on the kidney requires further investigation.

The occurrence of a dexamethasone-dependent stimulation of renal acid excretion was further investigated by comparing the renal and systemic acid-base response to an experimental increase in the systemic load of hydrogen ion in paired studies in the same animals on two different dosages of dexamethasone. The results of these studies indicate that a significantly greater degree of metabolic acidosis develops in response to hydrochloric acid loading during administration of the lower dosage of dexamethasone (study A).[1] Furthermore, a subsequent increase in dexamethasone dosage to the higher level used in study B stimulated net acid excretion sufficiently to significantly increase plasma bicarbonate concentration to levels similar to those in study B. The increase in net acid excretion that occurred when the dose of dexamethasone was increased during hydrochloric acid feeding was accounted for largely by the increased ammonium excretion unaccounted for by a lowering of urine pH. Urine pH in fact increased as ammonium excretion increased, suggesting that an increase in ammonia production occurred. To relate the increase in net acid excretion accompanying the increase in dexamethasone dosage to a

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[1]Although the rapidity and severity of the development of acidosis in study A precluded prolongation of the lower dose of dexamethasone, it has been demonstrated that plasma bicarbonate concentration does not increase above day-3 values with indefinite prolongation of acid feeding over a wide range of hydrochloric acid loads (3 to 7 mmol/kg) [29].

Table 3. Effect of dexamethasone dose on the plasma and urinary electrolyte response to chronic HCl feeding in mineralocorticoid-replete adrenalectomized dogs $(N = 7)$[a]

Period	P_{Na}	P_K	P_{Cl}	$P_{creatinine}$	$U_{Na}V$	U_KV	$U_{Cl}V$	$U_{iPO_4}V$	UV	Body wt
	mEq/liter			mg/dl	mEq/day			mmol/day	ml/day	kg
				Study A, 0.2-mg/day dexamethasone						
Control	138.7	4.5	106.1	0.66	54.1	48.1	53.4	51.4	1044	18.1
	±0.5	±0.1	±0.6	±0.06	±4.8	±5.0	±4.6	±4.5	±106	±1.5
HCl feeding										
Day 1	137.9	4.4	109.2[b]	0.61	56.5	62.4[b]	101.4[c]	48.9	1027	18.0
	±1.0	±0.1	±0.8	±0.07	±10.3	±7.6	±13.3	±6.7	±137	±1.5
Day 2	136.9	4.4	110.0[c]	0.63	69.4	57.8	138.9[c]	51.7	1196	17.8[b]
	±0.9	±0.1	±0.6	±0.07	±12.6	±5.4	±19.3	±5.1	±148	±1.5
Day 3	135.2[b]	4.3	110.8[d]	0.64	67.8[b]	55.2	150.3[d]	49.7	1188[b]	17.7[c]
	±1.1	±0.1	±1.0	±0.05	±6.3	±5.5	±13.0	±3.6	±122	±1.5
Day 4	135.3[b]	4.1[b]	109.2[b]	0.64	62.8	52.3	147.7[c]	46.1	1100	17.5[c]
	±1.3	±0.1	±1.1	±0.05	±8.8	±7.2	±21.1	±7.9	±143	±1.4
ΣΔ on day 4, mEq					+40[b]	+35[b]	+325[d]	+46		
					Study B, 0.8-mg/day dexamethasone					
Control	141.4 [f]	4.3 [e]	106.5	0.55 [f]	53.1	48.1	51.2	52.0	1090	17.9
	±0.5	±0.1	±0.3	±0.04	±5.5	±4.1	±5.0	±4.5	±112	±1.7
HCl feeding										
Day 1	139.8	4.2	109.0	0.56	72.3[b]	62.8[c]	124.0[d, e]	55.4	1189	17.7[b]
	±0.7	±0.1	±1.7	±0.04	±9.5	±6.1	±36.8	±5.6	±139	±1.7
Day 2	138.2[d]	4.4	108.9	0.54	56.1	54.8	127.0[d]	48.7	1056	17.6[b]
	±0.8	±0.1	±1.4	±0.04	±7.7	±6.5	±15.8	±5.1	±127	±1.7
Day 3	137.3[d, e]	4.3	108.4	0.56 [e]	61.5	50.6	142.9[d]	50.6	1120	17.6
	±0.6	±0.1	±1.0	±0.04	±8.4	±4.6	±14.9	±5.0	±131	±1.7
Day 4	136.9[c]	4.4 [e]	108.3	0.53 [f]	41.5	45.3	114.5	45.8	886	17.6[b]
	±0.8	±0.2	±0.8	±0.03	±7.5	±5.5	±15.1	±5.5	±139	±1.8
ΣΔ on day 4, mEq					+19	+21[b]	+304[d]	+46		

[a] Studies A and B designate protocol conditions wherein each animal underwent chronic hydrochloric acid (HCl) feeding (5.0 mmoles/kg/day) twice during two different dexamethasone replacement regimens. An interval of 9 to 49 days separated studies A and B. In study A, dexamethasone dose was increased to 0.8 mg/day on day 4 of HCl feeding. Cumulative change in excretion (ΣΔ) is the accumulated sum of the daily differences from the mean control daily excretion value. Values are means ± SEM.
[b] Significantly different from control (or from zero in the case of ΣΔ), $P < 0.05$; [c] $P < 0.01$; [d] $P < 0.001$.
[e] Significantly different from study A, $P < 0.05$; or [f] $P < 0.01$.

net increase in renal bicarbonate input to the systemic circulation, we "corrected" the values of net acid excretion for any associated increase in endogenous acid production by subtracting the daily change in anion gap from the daily change in net acid excretion (Fig. 1). This index of net renal bicarbonate input to the systemic circulation in comparing study A with study B shows that, with the lower dosage of dexamethasone, the more severe acidosis that occurred was associated with a lesser cumulative renal input of bicarbonate, and that with the increase in dexamethasone dosage, the subsequent reversal of the progressively worsening degree of acidosis was associated with a large increase in renal bicarbonate input.

The results of these studies do not permit inferences about the role of endogenous glucocorticoid steroids in the regulation of renal and systemic acid-base metabolism. Both plasma corticosterone (rats) and cortisol (dogs) concentrations have been observed to increase following mineral acid loading [30, 31]. In the rat, the increase in plasma corticosterone level in response to acid feeding can be prevented by prior hypophysectomy, a maneuver that also prevents the increase in urinary ammonium excretion that ordinarily occurs during acid feeding [31]. These results have led to the suggestion that, in the rat, the renal ammonium excretory response to acid loading is dependent on the increased adrenal secretion of ACTH-responsive steroids, secondary to stimulation of the pituitary gland by acidosis [31]. The results of the present studies are consistent

with this possibility and suggest a need for additional studies designed to investigate the role of endogenous glucocorticoid steroids in the regulation of acid-base homeostasis.

Acknowledgments

References

1. HULTER HN, SIGALA JF, SEBASTIAN A: K^+ deprivation potentiates the renal alkalosis-producing effect of mineralocorticoid. *Am J Physiol* 235:F298–F309, 1978
2. KASSIRER JP, LONDON AM, GOLDMAN DM, SCHWARTZ WB: On the pathogenesis of metabolic alkalosis in hyperaldosteronism. *Am J Med* 49:306–315, 1970
3. HULTER HN, ILNICKI LP, HARBOTTLE JA, SEBASTIAN A: Impaired H^+ secretion and NH_3 production in mineralocorticoid-deficient glucocorticoid-replete dogs. *Am J Physiol* 232:F136–F146, 1977
4. HULTER HN, LICHT JH, GLYNN RD, SEBASTIAN A: Renal acidosis in mineralocorticoid deficiency is not dependent on NaCl depletion or hyperkalemia. *Am J Physiol* 236:F283–F294, 1979

5. GROLLMAN AP, GAMBLE JL JR: Metabolic alkalosis, a specific effect of adrenocortical hormones. *Am J Physiol* 196:135–140, 1959

6. GWINUP G, GANTT CL, HAMWI GJ: The production of hypokalemic alkalosis with hydrocortisone in subjects with adrenal insufficiency. *Metabolism* 9:831–835, 1964

7. SELDIN DW, RECTOR FC JR: The generation and maintenance of metabolic alkalosis. *Kidney Int* 1:306–321, 1972

8. SPRAGUE RG, POWER MH, MASON HL, ALBERT A, MATHIESON DR, HENCH PS, KENDALL EC, SLOCUMB CH, POLLEY HF: Observations on the physiologic effects of cortisone and ACTH in man. *Arch Intern Med* 85:199–257, 1950

9. NUKI G, BODDY K, KENNEDY AC, KING P, DUNCAN AM, BUCHANAN WW: Potassium metabolism in patients with rheumatoid arthritis: Effects of treatment with depot tetracosactrin, spironolactone and oral supplements of potassium chloride. *Ann Rheum Dis* 34:506–514, 1975

10. CHRISTY NP, LARAGH JH: Pathogenesis of hypokalemic alkalosis in Cushing's Syndrome. *N Engl J Med* 265:1083–1088, 1961

11. LUDENS JH, FANESTIL DD: Aldosterone stimulation of acidification of urine by isolated urinary bladder of the Colombian toad. *Am J Physiol* 226:1321–1326, 1974

12. SAPIR DG, POZEFSKY T, KNOCHEL JP, WALSER M: The role of alanine and glutamine in steroid-induced nitrogen wasting in man. *Clin Sci* 53:215–220, 1977

13. WELBOURNE TC: Influence of adrenal glands on pathways of renal glutamine utilization and ammonia production. *Am J Physiol* 226:555–559, 1974

14. WELBOURNE TC, PHENIX P, THORNLEY-BROWN C, WELBOURNE CJ: Triamcinolone activation of renal ammonia production. *Proc Soc Exp Biol Med* 153:539–542, 1976

15. HULTER HN, LICHT JH, BONNER EL JR, GLYNN RD, SEBASTIAN A: Effects of glucocorticoid steroids on renal and systemic acid-base equilibrium. *Am J Physiol* 239:F30–F43, 1980

16. KURTZMAN NA, WHITE MG, ROGERS PW: Aldosterone deficiency and renal bicarbonate reabsorption. *J Lab Clin Med* 77:931–940, 1971

17. TANNEN RL, WEDELL E, MOORE R: Renal adaptation to a high potassium intake. *J Clin Invest* 52:2089–2101, 1973

18. BOYKIN J, deTORRENTE A, ERICKSON A, ROBERTSON G, SCHRIER RW: Role of plasma vasopressin in impaired water excretion of glucocorticoid deficiency. *J Clin Invest* 62:738–744, 1978

19. KAHN T, ALBERTINI BV, GOLDSTEIN M, LEVITT MV, BOSCH JP: Effect of increased NaCl or KCl intake on response to chronic furosemide administration. *Am J Physiol* 238:F509–F514, 1980

20. ROBB CA, DAVIS JO, JOHNSON JA, BLAINE EH, SCHNEIDER EG, BAUMBER JS: Mechanisms regulating the renal excretion of sodium during pregnancy. *J Clin Invest* 49:871–880, 1970

21. TAYLOR AA, DAVIS JO, JOHNSON JA: Control of deoxycorticosterone secretion in the dog. *Am J Physiol* 223:466–472, 1972

22. YOUNG DB, GUYTON AC: Steady-state aldosterone dose-response relationships. *Circ Res* 40:138–142, 1977

23. MA RSW, CHAN JCM: Endogenous sulphuric acid production: A method of measurement by extrapolation. *Clin Biochem* 6:82–87, 1973

24. VAN SLYKE DD, PALMER WW: Studies of Acidosis: XVI. The titration of organic acids in urine. *J Biol Chem* 41:567–585, 1920

25. SNEDICOR GW, COCHRAN WG: *Statistical methods* (6th ed.). Ames, Iowa, Iowa State Univ. Press, 1967

26. HAYNES RC JR, LARNER J: Adrenocorticotrophic hormone; adrenocortical steroids and their synthetic analogs; inhibitors of adrenocortical steroid biosynthesis, in the *Pharmacological Basis of Therapeutics* (5th ed.), edited by GOODMAN LS, GILMAN A, New York, Macmillan Co., 1975, pp. 1478–1485

27. TANNEN RL: Relationship of renal ammonia production and potassium homeostasis. *Kidney Int* 11:453–465, 1977

28. SCHWARZ WB, COHEN JJ: The nature of the renal response to chronic disorders of acid-base equilibrium. *Am J Med* 64:417–428, 1978

29. DeSOUSA RC, HARRINGTON JT, RICANATI ES, SHELKROT JW, SCHWARTZ WB: Renal regulation of acid-base equilibrium during chronic administration of mineral acid. *J Clin Invest* 53:465–476, 1974

30. PEREZ GO, OSTER JR, KATZ FH, VAAMONDE CA: The effect of acute metabolic acidosis on plasma cortisol, renin activity and aldosterone. *Hormone Res* 11:12–21, 1979

31. WELBOURNE TC: Acidosis activation of the pituitary-adrenal-renal glutaminase I axis. *Endocrinology* 99:1071–1079, 1976