Digestive Diseases and Sciences, Vol. 42, No. 1 (January 1997), pp. 119–128

Effect of Fludrocortisone and Spironolactone on Sodium and Potassium Losses in Secretory Diarrhea

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The response of the colon to aldosterone is believed to be an important adaptive mechanism to excessive sodium losses in diarrhea. However, the degree to which mineralocorticoid activity actually influences fecal output of sodium in people with diarrhea is unknown. To gain insight into this question, 10 normal people were treated with placebo, fludrocortisone (an aldosterone agonist), and spironolactone (an aldosterone antagonist) during three experimental periods lasting nine days. On days 5–8, diarrhea was induced by ingestion of phenolphthalein. Diet was controlled. Fecal sodium was 40 meq/day on placebo and 29 meq/day on fludrocortisone, consistent with mineralocorticoid stimulation of intestinal sodium absorption. However, contrary to our expectations, spironolactone therapy was also associated with a fall in fecal sodium output, to 28 meq/day. To explain this paradoxical effect of spironolactone, we suggest that sodium depletion caused by spironolactone's natriuretic action on the kidney caused the release of an unknown stimulant of intestinal sodium absorption, whose action more than overcame the reduced colonic absorption resulting from inhibition of aldosterone activity by spironolactone. This interpretation implies that the intestinal adaptation to sodium depletion in diarrhea involves both aldosterone and an aldosterone independent factor, working in concert to reduce fecal sodium output.

KEY WORDS: fludrocortisone; spironolactone; secretory diarrhea; sodium absorption; intestinal adaptation.

The response of the colon to aldosterone is believed to be an important mechanism of adaptation to excessive fecal sodium losses in people with secretory diarrhea. This concept is based on two observations. First, sodium depletion from diarrhea causes aldosterone release from the adrenal gland (1–5). Second, mineralocorticoids have been shown to promote sodium absorption by the colon (6–10). Therefore, sodium depletion from diarrhea may be mitigated by aldosterone-induced colonic sodium conservation. This adaptation presumably comes at the price of fecal potassium wasting, since aldosterone also causes the colon to secrete potassium (6, 9, 10).

Although there is clear evidence that mineralocorticoids exert a major regulatory influence on colonic transport of sodium and potassium in rats (6–10), the degree to which they influence fecal output of sodium and potassium in people is uncertain (11). The only well controlled human study showing a major effect was limited to the rectum (12). Furthermore, high levels of mineralocorticoid activity have pronounced effects on the kidney, and the resulting physiological changes might initiate a chain of events that increase or decrease fecal output of sodium and potassium.

Manuscript received April 10, 1996; revised manuscript received August 29, 1996; accepted September 10, 1996.

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These indirect effects of mineralocorticoids on the intestine might mask or accentuate any direct effects that mineralocorticoids may have on fecal output of cations.

The objective of the present research was to determine the net effect of mineralocorticoid activity on the fecal excretion of sodium and potassium in people with diarrhea. To accomplish this, three different states of mineralocorticoid activity were created in 10 normal volunteers by treating them for nine days with either placebo, fludrocortisone (a mineralocorticoid agonist), or spironolactone (an inhibitor of the action of mineralocorticoids). Starting on day 5, the subjects ingested phenolphthalein to induce secretory diarrhea. Normal volunteers with induced diarrhea were used in preference to patients with various other causes of diarrhea so that experimental conditions could be standardized and proper controls could be employed.

MATERIALS AND METHODS

Rationale of Study Design. The decision to investigate the effect of several days of drug treatment, rather than the effect of a single dose, was based on two considerations. First, animal studies have shown that stimulation of mineralocorticoid-dependent sodium absorption by the colon increases slowly over a period of several days (7), whereas maximal changes in the renal tubules are attained within 4 hr (13). Second, in order to have pathophysiological significance in diarrheal diseases, mineralocorticoid effects would have to persist after initial adjustments to mineralocorticoid status.

To create excess mineralocorticoid activity, we used fludrocortisone, a synthetic corticosteroid with potent mineralocorticoid activity. The dose recommended for therapeutic purposes ranges between 0.05 and 0.3 mg/day (14). We gave our subjects 2 mg of fludrocortisone per day, ensuring a major increase in mineralocorticoid activity.

Spironolactone is an antagonist of aldosterone that modifies electrolyte metabolism only in the presence of aldosterone-like compounds. It reverses all electrolyte-regulating effects of aldosterone, regardless of the tissue studied (15). After oral intake, the drug is absorbed nearly completely and reaches its maximal effect after two or three days of ongoing treatment (14, 15). When spironolactone is used clinically as a diuretic, the usual recommended dose ranges between 25 and 200 mg/day. We gave the subjects 200 mg/day of spironolactone, a dose approved for the treatment of hyperaldosteronism (16).

To induce diarrhea, we used phenolphthalein, because it is safe and causes secretory diarrhea by inhibition of sodium absorption and by stimulation of active chloride secretion in both small and large intestine (17–19). Its mechanism of action has been studied in the rabbit ileum *in vitro*, where it inhibits sodium chloride absorption and chloride/bicarbonate exchange when applied to the mucosal (but not serosal) side of the intestine, without an increase in cyclic nucleotides (19).

Since the aim of the study was to assess the effect of different states of mineralocorticoid activity on fecal excretion of sodium and potassium, and since excretion is partly dependent on dietary intake, it was necessary to maintain the same diet for all treatment periods. During treatment with fludrocortisone, it was anticipated that serum potassium concentration would fall, perhaps to dangerously low levels, unless the subjects ingested a diet that contained a plentiful amount of potassium (20). The subjects were therefore placed on a high potassium diet. In an effort to limit fluid retention during mineralocorticoid administration, and thereby prevent a clinically significant increase in blood pressure, dietary sodium was moderately restricted. Because serum potassium concentration can rise during treatment with spironolactone, serum electrolyte concentrations were measured frequently during the course of all three experimental periods.

Subjects. Ten normal subjects (seven men and three women), ranging in age from 24 to 49 years, volunteered for the study. They had no evidence of any medical disorder as judged by history, physical examination, and routine laboratory tests, and they were on no medications. The subjects had participated in previous studies conducted in this laboratory, which included quantitative stool collections. They were known to be highly compliant in adhering to strict protocols. These studies were approved by the Institutional Review Board for Human Protection of Baylor University Medical Center, and informed consent was obtained.

Protocol. A study period consisted of one preexperimental day (day 0) and nine experimental days. During the experimental days subjects ate a standard diet and ingested either placebo (empty gelatin capsules), 2 mg/day (20 tablets of 0.1 mg) of fludrocortisone acetate (Florinef Acetate; E.R. Squibb & Sons Inc., Princeton, New Jersey) given as a single daily dose, or 200 mg/day of spironolactone (Aldactone, G.D. Searle Co., Chicago, Illinois) administered in two divided doses. A research dietician designed a diet for each of the test days that was moderately high in potassium and moderately low in sodium. All food consumed during the study was provided to the subjects, and each subject ate exactly the same food on a given study day. By food table analysis, the diet provided an average of 2594 kcal, 131 meq sodium and 150 meq potassium per day. The daily diets were also assayed in triplicate (after acid digestion) for sodium and potassium content. The measured content averaged 132 meq for sodium and 155 meq for potassium, which were very close to the values calculated from food tables. Intake of water was unrestricted. On days 5–8, diarrhea was induced by phenolphthalein (Medilax, Mission Pharmacal Co., San Antonio, Texas), 960 mg/day given in four divided doses. Urine was collected quantitatively on days 0–8. Daily stools were collected quantitatively in plastic containers during the diarrhea phase of the study and were stored in portable ice chests. Specimens were returned to the laboratory on the morning following each 24-hr collection.

Subjects reported to the laboratory each morning at 8:00 AM after having eaten breakfast and having been upright for at least 2 hr. Urine and stool collections from the previous 24 hr were delivered and refrigerated. Subjects were

Table 1. Aldosterone and Plasma Renin Activity

	Serum aldosterone (pg/ml)		*Plasma renin (ng/ml/hr)*		*Urine Aldosterone (μg/day)*
	Standing	*Lying*	*Standing*	*Lying*	
Day 0					
Spironolactone	114 ± 16	69 ± 10	4.2 ± 1.0	2.1 ± 0.6	8.9 ± 1.9
Placebo	100 ± 16	61 ± 12	3.7 ± 0.9	1.5 ± 0.3	6.6 ± 1.3
Fludrocortisone	96 ± 11	59 ± 7	3.7 ± 1.1	1.6 ± 0.4	9.6 ± 2.0
RM ANOVA	>0.5	>0.5	>0.5	>0.5	>0.5
Day 4					
Spironolactone	434 ± 61	325 ± 42	13.0 ± 3.0	6.8 ± 1.2	43.9 ± 6.5
Placebo	253 ± 38	159 ± 23	5.2 ± 1.4	4.1 ± 1.2	15.0 ± 2.9
Fludrocortisone	40 ± 6	22 ± 2	1.1 ± 0.2	0.5 ± 0.1	1.7 ± 0.5
RM ANOVA	<0.001	<0.001	<0.001	<0.001	<0.001
Day 8 or 9					
Spironolactone	606 ± 72[a]*	431 ± 50[a]	22.0 ± 4.3[a]	13.2 ± 2.6[a]	56.3 ± 6.5[b]
Placebo	203 ± 24[a]	115 ± 11[a]	3.7 ± 0.6[a]	1.7 ± 0.2[a]	13.6 ± 2.1[b]
Fludrocortisone	52 ± 25[a]	35 ± 20[a]	1.7 ± 0.7[a]	0.4 ± 0.1[a]	1.5 ± 1.0[b]
RM ANOVA	<0.001	<0.001	<0.001	<0.001	<0.001

* [a], day 9; [b], day 8.

weighed, and blood pressure and heart rate were measured after lying supine for 5 min and again after standing for 1 min. On days 0 (baseline), 4, and 9, a blood specimen was obtained upon entering the laboratory while subjects were upright, for determination of plasma renin activity and serum aldosterone. After lying supine for 30 min, blood was again drawn for plasma renin activity and aldosterone. Serum electrolyte concentrations were measured on days 0, 2, 4, 7, and 9. Serum albumin concentrations were measured on days 0, 4 and 9.

Analytical Methods. Stool was homogenized using a commercial blender. A 30-g aliquot was centrifuged at 64,000*g* for 45 min to obtain supernatant for analysis. Fecal sodium, potassium, chloride, bicarbonate, calcium, phosphorus, magnesium, and ammonium concentrations were measured in stool supernatant by standard methods. The concentration of fecal bicarbonate equivalent was calculated as ([Na] + [K]) − [Cl] (21). The concentration of organic acids was measured by a previously published method (22). Fecal water output was measured by lyophilization. Assessment of fecal output of sodium, potassium, calcium, magnesium, and phosphorus was based on analysis of acid-digested stool (23); fecal output of chloride, bicarbonate, ammonium, and organic acids were calculated by multiplying concentration in stool supernatant by daily fecal water output.

Daily urine was mixed by manual agitation of the container and was analyzed for sodium and potassium concentration by flame photometry. An aliquot of urine was frozen for later analysis of aldosterone concentration. Aliquots of plasma and serum were frozen for later analysis of renin activity and aldosterone concentration, respectively. Plasma renin activity was measured with a commercial radioimmunoassay kit (Incstar Corp., Stillwater, Minnesota). Serum and urine aldosterone concentrations were measured by radioimmunoassay (Diagnostic Systems Laboratories Inc., Webster, Texas).

Data were expressed as mean ± SEM. Statistical analyses were made using repeated measures ANOVA and all-pairwise multiple comparisons (24). Differences of means were considered statistically significant when $P < 0.05$.

RESULTS

Renin and Aldosterone Levels. The results are shown in Table 1, presented in order of increasing mineralocorticoid activity (lowest with spironolactone, highest with fludrocortisone). Apart from the expected effect of posture on serum aldosterone and plasma renin (a fall in the respective levels when subjects went from the standing into the lying position), three points deserve emphasis. First, when subjects ingested placebo and the standard diet, aldosterone and renin activity increased significantly (compared to pretreatment levels); this can be explained by the high potassium and limited sodium content in the diet (25, 26). Second, when subjects ate the same diet but were treated with fludrocortisone, there was a statistically significant fall in aldosterone and renin activity; this can be explained by fludrocortisone-induced sodium retention resulting in intravascular and extracellular volume expansion (27, and see below). Third, when subjects ingested spironolactone, there was a statistically significant increase in plasma renin and aldosterone levels; this can be explained by spironolactone-induced sodium depletion leading to intravascular and extracellular volume contraction (see below).

Body Weight, Serum Electrolytes, Serum Albumin, and Vital Signs. As shown in Figure 1, subjects treated with placebo lost about 2.5 lb over the course of the experiment, presumably related to the restriction in dietary sodium intake. Average serum sodium concentrations remained between 140 and 142 meq/liter, and serum potassium concentration rose slightly

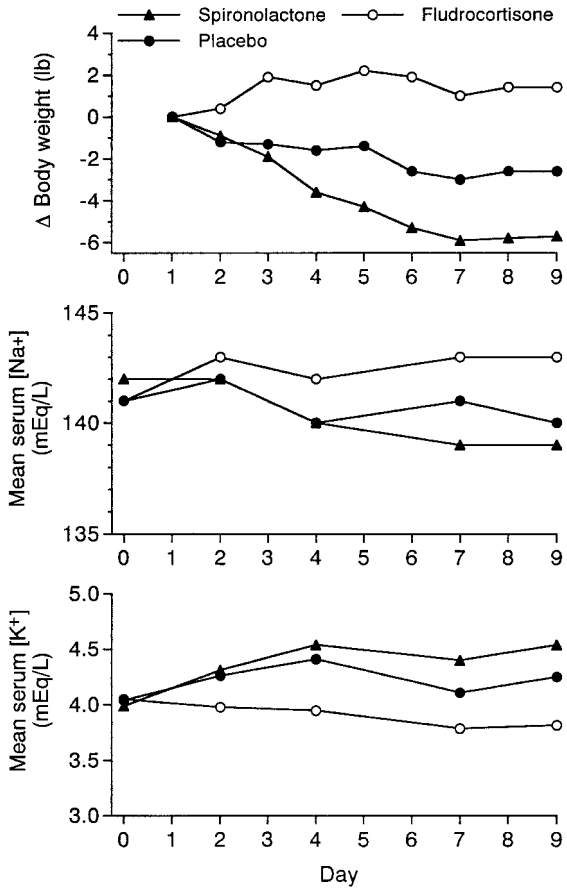

Fig 1. Effect of fludrocortisone and spironolactone on body weight and serum sodium and potassium concentrations in 10 normal subjects eating a high-potassium/low-sodium diet. Differences in average values were statistically significant by RM ANOVA with *P* values ranging from <0.04 to <0.00001.

in association with the relatively high dietary potassium intake. When the subjects were treated with fludrocortisone, there was a weight gain of about 1.5 lb and, compared to results on placebo, the average serum sodium concentration was higher and the potassium concentration was lower. The lowest individual serum potassium concentration on fludrocortisone was 3.30 meq/liter. By contrast, spironolactone therapy was associated with an average weight loss of almost 6 lb, a slightly lower serum sodium concentration, and a slightly higher serum potassium concentration.

Serum albumin concentration rose by 7 ± 1.7% on spironolactone therapy, rose by 2 ± 1.9% on placebo therapy, and fell by 5 ± 3.8% on fludrocortisone therapy (data not shown). These changes are consistent with contraction of the intravascular and extracellular volumes on spironolactone and expansion of these volumes on fludrocortisone.

There were no significant changes in average blood pressure or pulse rate from the beginning of the study through its duration, and there were no differences in average blood pressure between the three treatment groups (data not shown).

Sodium and Potassium Balance. Dietary intake was known, urinary output was measured on each day of the experiment, and fecal output was measured during the diarrhea phase of the study. Since fecal sodium and potassium outputs are trivial in the absence of diarrhea, with or without exogenous administration of mineralocorticoids (11, 20, 28), sodium and potassium balance can be calculated from these results.

As shown in Figure 2, when subjects were treated with placebo, sodium balance was −83 meq on day 1, due to the restricted dietary sodium intake. Cumulative balance fell to −142 meq by day 3, and rose progressively thereafter so that by day 8 cumulative balance was +27 meq. When subjects were treated with spironolactone, sodium balance on day 1 was −110 meq, and by day 3 cumulative sodium balance was −320 meq; daily balance was positive thereafter, and by the end of the experiment cumulative sodium balance was −180 meq. When subjects were treated with fludrocortisone, sodium balance on day 1 was +30 meq and cumulative balance rose steadily thereafter, reaching +265 meq at the end of the study.

After day 3, the sodium balances depicted in Figure 2 were essentially parallel for the three treatment groups. This was due to the fact that after day 3 the combined output of sodium in stool and urine was approximately equal to dietary sodium intake, regardless of mineralocorticoid status. (As shown in the previous section, differences in body weight and serum sodium concentration persisted throughout the experimental period). Sodium balance did not fall during the diarrhea phases of the study, regardless of mineralocorticoid status, because as fecal sodium losses increased, urinary losses decreased.

Cumulative potassium balance was positive during all treatments, because of the high potassium diet. Initially, there was less positive balance on fludrocortisone and a greater positive balance on spironolactone, but by the end of the experiment the cumulative balance values were similar on all three treatments (Figure 2).

Comparison of Body Weight and Sodium Balance. On each of the three treatments, there was good agreement between directional change in body weight and initial directional change in sodium balance.

TABLE 2. AVERAGE FECAL OUTPUTS DURING PHENOLPHTHALEIN-INDUCED DIARRHEA UNDER THREE STATES OF MINERALOCORTICOID ACTIVITY

	Total weight (g/day)	*Water (g/day)*	*Na (meq/day)*	*K (meq/day)*	*Cl (meq/day)*	*HCO_3 (meq/day)*	*Equivalent HCO_3 (meq/day)*	*OA (meq/day)*	*Ca (meq/day)*	*P (mmol/day)*	*Mg (meq/day)*	*NH_4 (meq/day)*
Spironolactone	458 ± 46	404 ± 43	28 ± 5	29 ± 3	19 ± 2	6 ± 1	32 ± 6	47 ± 5	45 ± 2	24 ± 2	29 ± 2	5 ± 1
Placebo	599 ± 39	535 ± 36	40 ± 4	36 ± 2	29 ± 2	10 ± 1	41 ± 5	62 ± 6	45 ± 5	26 ± 3	34 ± 3	6 ± 1
Fludrocortisone	498 ± 37	438 ± 36	29 ± 4	36 ± 3	22 ± 2	8 ± 1	36 ± 3	51 ± 5	44 ± 5	28 ± 2	33 ± 3	4 ± 1
P values, RM ANOVA	<0.02	<0.02	<0.02	<0.05	<0.002	<0.08	<0.13	<0.03	<0.86	<0.08	<0.06	<0.03
All pairwise comparisons, $P < 0.05$												
P vs S	Yes	Yes	Yes	Yes	Yes	No	No	Yes	No	No	Yes	No
P vs F	Yes	Yes	Yes	No	Yes	No	No	Yes	No	No	No	Yes
S vs F	No	No	No	No	No	No	No	No	No	Yes	No	Yes

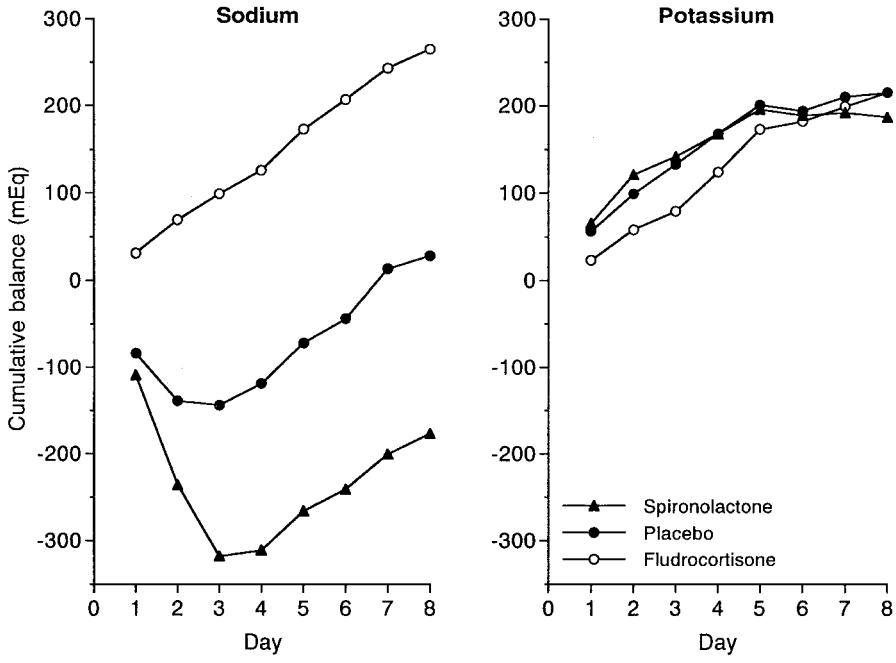

Fig 2. Cumulative balance of sodium and potassium in 10 normal subjects eating a high-potassium/low-sodium diet, during treatment with placebo, spironolactone, and fludrocortisone. Depicted values on day 1 represent the start of the cumulative balance, but also represent the actual balance values for day 1. Subsequent values represent cumulative balance only, but the balance on any given day can be estimated from the change from the previous day. Differences in average values for sodium balances were statistically significant by RM ANOVA, with $P < 0.002$. The differences in average values for potassium balance were significant by RM ANOVA on days 1, 2, and 3 ($P < 0.04$), but not on subsequent days.

However, during the latter part of the experiment sodium balances were positive by 10–50 meq/day (Figure 2), but there was no increase in body weight (Figure 1). This discrepancy is most likely due to the fact that we did not measure sodium losses in sweat. It is known from the work of others that sweat contains substantial amounts of sodium and that balance results that do not account for sweat sodium are artifactually positive (29).

Fecal Output of Water, Cations, and Anions During Phenolphthalein-Induced Diarrhea. When normal subjects eat food and refrain from laxatives, stool weight averages about 100 g/day (30, 31), stool water output averages about 70 g/day (30, 31), potassium output averages about 10 meq/day (11, 20, 28, 32), and sodium output averages about 2.5 meq/day (20, 28, 32). As shown in Table 2, when our normal subjects ingested phenolphthalein plus a placebo, water output was 535 ml/day, sodium output was 40 meq/day, and potassium output was 36 meq/day. The sum of sodium plus potassium outputs was 76 meq/day; when multiplied by 2 (to account for accompanying anions), the sum of electrolyte outputs was 152 meq/day. Since stool water was 0.535 liters/day, the concentration of electrolytes in stool water was 284 meq/liter (152 ÷ 0.535). Assuming a plasma osmolality of 290 mosm/kg, the calculated osmotic gap (21) was negligible at 6 meq/liter, consistent with a secretory diarrhea. The calculated osmotic gap was also small when the subjects were treated with phenolphthalein plus spironolactone or fludrocortisone.

Compared to phenolphthalein–placebo therapy, phenolphthalein–fludrocortisone therapy was associated with an 18% reduction in fecal water, a 28% reduction in fecal sodium, no change in fecal potassium, and a 24% reduction in fecal chloride. Phenolphthalein–spironolactone therapy was associated with a 24% reduction in fecal water, a 30% reduction in fecal sodium, a 19% reduction in fecal potassium, and a 34% reduction in fecal chloride.

The fecal outputs of several other measured substances also tended to be lower on both fludrocortisone and spironolactone than on placebo, with variable degrees of statistical significance as shown in Table 2.

DISCUSSION

For reasons explained in Materials and Methods, the effect of fludrocortisone and spironolactone on fecal cation output was evaluated several days after drug therapy was initiated. This raised safety concerns, especially in regard to hypokalemia and hypertension during treatment with such large doses of fludrocortisone. The subjects were therefore placed on a diet that moderately increased potassium intake and moderately restricted sodium intake. In retrospect, the experimental diet was both necessary and effective because the serum potassium concentration did fall on fludrocortisone, but not to dangerous levels, and because subjects in all treatment groups did well otherwise. During the placebo part of the experiment there was a doubling of serum aldosterone levels, due to the reduced-sodium and high-potassium diet.

Several lines of evidence make it clear that our experimental protocol actually achieved three different mineralocorticoid states. These include differences in sodium balance, changes in body weight, changes in serum sodium, and changes in potassium and albumin concentrations. Moreover, the differences we observed in plasma renin activity and aldosterone levels are consistent with the expected response to the experimental diet and to fludrocortisone and spironolactone therapy. As alluded to at the beginning of this paper, any observed effect of differences in mineralocorticoid status on fecal output might be mediated either by a direct influence of mineralocorticoid activity on the intestine or by an indirect physiological change resulting from the influence of mineralocorticoid status on renal cation transport. These two mechanisms might work synergistically or in opposition.

During treatment with placebo, phenolphthalein-induced diarrhea was characterized by a fecal water output that averaged 535 g/day, a fecal sodium output of 40 meq/day, and a fecal chloride output of 29 meq/day. When the subjects were treated with fludrocortisone, fecal water, sodium, and chloride outputs were reduced by 18–28%. These results suggest that high levels of mineralocorticoid activity stimulate the absorption of sodium chloride and water in people with secretory diarrhea. Since the levels of mineralocorticoid activity were already somewhat elevated when the subjects were treated with placebo (due to the nature of the diet they were ingesting), it is possible that the percentage reduction in fecal output of sodium chloride and water during treatment with fludrocortisone would have been even greater had the mineralocorticoid levels been lower during placebo therapy.

In planning this experiment, we anticipated that the experimental diet might elevate mineralocorticoid activity during the placebo period, and thereby might blunt the calculated effect of fludrocortisone therapy. We therefore included a spironolactone treatment period and intended to calculate the effect of mineralocorticoid activity on the intestine by the difference in fecal cation outputs on spironolactone and fludrocortisone. In other words, we expected fludrocortisone and spironolactone to have opposite effects on the excretion of sodium and potassium by the intestine, as they did on the excretion of these cations by the kidney (see Figure 2). However, we found that spironolactone therapy was associated with a reduction in fecal output of sodium and chloride, to the same levels observed during treatment with fludrocortisone.*

We can think of two explanations for this apparent paradox. First, it is possible that the dose of spironolactone employed in this experiment blocks the effect of mineralocorticoids on the kidney, but not on the intestine. If this were the case, spironolactone-induced volume contraction (mediated by its effect on the kidney) would lead to increased endogenous release of aldosterone. Under this supposition, high aldosterone would not influence renal transport because it is blocked by spironolactone; however, if spironolactone did not block aldosterone effects on the intestine, intestinal sodium absorption would be stimulated and stool volume would be reduced. To the best of our knowledge, no one has previously suggested such a differential organ sensitivity to spironolactone. Previous studies have indicated that spironolactone inhibits aldosterone stimulation of intestinal sodium absorption or potassium secretion (7, 27, 33–39), but they do not deal with the relative sensitivity of the intestine and kidney to such inhibition.

A second explanation is that spironolactone did inhibit aldosterone activity on the intestine, but in addition it resulted in the release of an aldosterone-independent regulatory force that stimulated sodium chloride absorption. For convenience, we will designate this force as factor X, and we suggest that it is

* It seems worth noting that the conclusions of our study would have been completely different had any one of the three treatment arms been eliminated. For example, had we only compared spironolactone and fludrocortisone, and omitted the placebo arm of the experiment, we would have concluded that mineralocorticoid status has no effect on fecal output of sodium in humans with diarrhea.

released and acts according to the following sequence: spironolactone × natriuresis × sodium depletion × factor X × stimulation of intestinal sodium absorption × decreased fecal sodium output. If the proabsorptive effect of factor X were more potent than the antiabsorptive effect of aldosterone inhibition, the net effect of spironolactone would be a fall in fecal sodium output. If this interpretation is correct, when sodium depletion develops due to secretory diarrhea, the intestine adapts by two mechanisms, one regulated by aldosterone and one regulated by an aldosterone-independent factor.

Although our results do not differentiate between the two suggested explanations for the paradox, the potassium output data favor an aldosterone-independent mechanism. We found that average fecal output of potassium was lower on spironolactone than during placebo therapy, but that fludrocortisone treatment and placebo therapy were associated with exactly the same average fecal potassium output. These results are consistent with mineralocorticoid stimulation of potassium secretion, lowest on spironolactone (assuming that aldosterone activity on the intestine was blocked), rising to a maximal extent with moderately high mineralocorticoid activity associated with placebo therapy, and failing to increase further with fludrocortisone therapy because a maximal effect had already been achieved. If the paradox was caused by failure of spironolactone to block the effects of aldosterone on the intestine, we would have expected to find that potassium output was higher on spironolactone than on placebo.

The nature of the proposed factor X is, of course, unknown. Although we will refer to it as if it were a single agent or mechanism, more than one agent or mechanism might combine to produce the observed effect. Its site of action could be either on the small intestine or colon, and its action might be mediated by increased absorption or decreased secretion. If its action is mediated by increased absorption, this could be the result of increased absorption rate by epithelial cells or by an effect on intestinal motility, which results in increased contact time of luminal fluid with absorbing mucosal cells. Factor X might be mediated by a hemodynamic or oncotic pressure change or by the sympathetic or enteric nervous system. In humans an acute reduction in circulating blood volume is associated with increased jejunal absorption of sodium (40), and it has been proposed that this effect is mediated by the sympathetic nervous system in response to an unloading of cardiopulmonary volume receptors (40, 41). Several peptides/hormones have been shown to stimulate intestinal absorption or reduce intestinal secretion in some experimental situations, including glucocorticoids, α-adrenergic agonists, somatostatin, angiotensin II, neuropeptide Y, prolactin, and opioids (9, 10, 40). Of these, angiotensin II is an attractive candidate, since the high renin activity and aldosterone concentrations associated with spironolactone therapy mean that angiotensin II levels were also elevated. In experimental animals, low doses of angiotensin II promote release of norepinephrine from sympathetic nerves, which in turn enhances sodium absorption, whereas high doses of angiotensin II inhibit absorption (42, 43). To the best of our knowledge, the effect of angiotensin II on intestinal absorption has not been studied in humans.

The mechanism of fludrocortisone-induced reduction in serum potassium concentration is of interest. Since cumulative potassium balances at the end of our experiment were similar with each of the three treatments, there was no fall in total body potassium content on fludrocortisone compared to placebo or spironolactone. This suggests that the lower serum potassium concentration on fludrocortisone was mediated by a change in internal potassium balance, ie, a shift of potassium from the extracellular to the intracellular space (44).

Two previous studies in humans yielded different results and/or were interpreted differently, and it seems appropriate to attempt a reconciliation. First, Jenkins et al reported the effect of aldosterone status on rectal absorption of sodium and secretion of potassium in children, as studied by transport of ions in and out of a dialysis bag placed in the rectum (12). They found that aldosterone had a profound effect. For example, in a patient with pseudohypoaldosteronism (where there is a defect in the response of ion-transporting epithelia to aldosterone), rectal potassium secretion was 50 times less than normal. In contrast, our results indicate that aldosterone status has a relatively modest effect on fecal cation output in people with diarrhea. This difference can be explained by postulating that the rectum is highly sensitive to aldosterone but that its surface area is small and that it therefore contributes relatively little to the ionic content of fecal fluid in people with diarrhea. In diarrhea, fecal cation output is determined mainly by the large surface area of the more proximal colon, which apparently is less sensitive to mineralocorticoids. Second, Guerrant et al (36) administered a single 100-mg oral dose of spironolactone to patients with cholera and reported that fecal sodium output increased markedly (by 74 meq/day) and potassium

output decreased by an equivalent amount. These results are quite different from ours, most notably in the direction of effect of spironolactone on fecal sodium output (an increase in their experiment, a decrease in our experiment). Their study also suggests that aldosterone mediates a 1:1 Na/K exchange, which we did not observe, and that aldosterone status has a huge rather than a modest effect on fecal cation excretion in secretory diarrhea. We have no completely satisfactory explanation for the discrepancy between our findings and those in this cholera experiment, but several partial explanations can be offered. It is conceivable that acute interruption of high aldosterone activity, with a single dose of spironolactone in cholera, might produce more pronounced and different acute effects than more gradual changes in the level of mineralocorticoid activity in our experiment. The discrepancy might be related to the fact that the diarrhea was 10 times more severe (in terms of stool weight) in the cholera patients. However, if high intestinal flow rates predispose to a high sensitivity to aldosterone, it would be hard to understand the results of colon perfusion studies (where flow rates are even higher than in cholera), which show that aldosterone has a relatively modest effect on sodium absorption with no evidence of a 1:1 Na/K exchange (45). The discrepancy might be related to differences in the mode of action of cholera toxin and phenolphthalein. Finally, in our study, spironolactone therapy was associated with development of sodium depletion, whereas in the cholera study a preexisting sodium depletion was partially or completely corrected with intravenous fluids as spironolactone was administered. If our speculations are correct, release of factor X could explain why we saw reduced fecal sodium output with spironolactone, whereas an inhibition of factor X caused by sodium repletion might explain why fecal sodium output increased so dramatically in the cholera experiment.

ACKNOWLEDGMENTS

This work was supported by U.S. Public Health Service grant 5-R01-DK37172-05 from the National Institute of Diabetes, Digestive and Kidney Diseases and the Southwest Digestive Disease Foundation. Dr. Wenzl was supported by a F. Johann Kwizda-Forschungsstipendium from the Austrian Gesellschaft für Gastroenterologie und Hepatologie; Dr. Fine was supported by an SKB Research award from the American Digestive Health Foundation. The authors wish to thank Judy Suneson for designing the study diet, George Alexander of Mission Pharmacal Co. for generously supplying the Medilax used in this study, and Diana Santa Ana for her help in preparing the manuscript.

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