Collecting Duct Function in Deoxycorticosterone Acetate-Escaped, Normal, and Salt-Deprived Rats

Response to Hypervolemia

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SUMMARY The microcatheterization technique was used to study reabsorption of fluid, sodium, and potassium in the medullary collecting duct in chronically deoxycorticosterone acetate (DOCA)-treated and salt-loaded rats, as well as in normal and chronically salt-deprived (NaD) rats, before and after infusion of donor blood (33% of estimated circulating volume). Before expansion, urinary sodium excretion was highest in DOCA rats, intermediate in normal, and lowest in low salt rats. Significant collecting duct reabsorption was found in NaD, normal, and DOCA groups. In contrast to sodium, no net transport of potassium was found in any series. During intravascular expansion, increased renal excretion of fluid and sodium was observed uniformly in both DOCA and normal groups, whereas a diuretic response was found in five of seven rats, and a natriuretic response in four of seven rats of the NaD group. Natriuresis of DOCA rats was significantly greater than that of either normal or responding NaD rats. Diuresis and natriuresis in all three series were associated with complete inhibition of fluid and sodium reabsorption from the lumen of the medullary collecting duct, whereas such reabsorption persisted in nonresponding low salt rats. Increased sodium excretion in DOCA rats in comparison to the other two series could be explained by enhanced intratubular delivery of the ion to the medullary collecting system. I conclude that the renal response to acute blood volume expansion is due primarily to complete inhibition of both fluid and sodium reabsorption in the medullary collecting duct, but that differences in tubular delivery may modify the resulting diuresis and natriuresis.

THE MECHANISM of renal escape from the salt-retaining effects of chronic mineralocorticoid administration is thought to involve alteration of sodium transport in some part of the nephron.[1, 2] Although reduction of proximal tubular reabsorption was found in an earlier investigation,[3] recent studies in the dog[4, 5] and rat[6] failed to detect significant inhibition of proximal transport. In addition, it was shown that distal tubular Na reabsorption of deoxycorticosterone acetate (DOCA) escaped rats was greater than that of salt-deprived (NaD) rats, although urinary sodium excretion was much less in the low salt group.[6] It was suggested, therefore, that the mechanism of DOCA escape included inhibition of transport downstream to the end of the distal tubule.

Body fluid volumes of DOCA-escaped rats are increased relative to those of chronically salt-deprived (NaD) rats.[7] When an acute intravascular expansion was superimposed in such rats by infusing donor blood, the resulting "volume natriuresis" was greater than that of either normal or NaD rats.[8] The renal response was not associated with inhibition of reabsorption in the proximal tubule,[9] in the loop of Henle, or in the distal tubule[10] of either DOCA or NaD rats. These data led to the conclusion that the medullary collecting duct is the site for renal regulation of blood volume during both chronic and acute imbalance. An alteration of intratubular delivery of salt and water from juxtamedullary nephrons inaccessible to micropuncture could not be excluded, however.

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To obtain direct information on collecting duct transport, the microcatheterization technique[11] was used to compare duct function in DOCA-escaped, in normal, and in NaD rats before and during acute intravascular expansion.

Methods

Male Sprague-Dawley rats (weight range, 172–385 g) were divided into three groups of seven rats each. NaD rats received the "salt-deficient-diet-modified" diet (Nutritional Biochemicals Corp.) and distilled water; DOCA rats were maintained on Purina rat chow and Ringer's solution while receiving DOCA acetate in oil (2.5 mg) subcutaneously on 5 consecutive days per week. Both groups were studied during the 3rd week of the regimen. Rats maintained on Purina rat chow and water served as normal controls. All groups were allowed food and water until the time of the experiment. The rats were anesthetized with sodium ethyl(1-methylpropyl)-malonylthiourea (Inactin), 10 mg/100 g of body wt, and kept at a body temperature of 38 ± 0.5°C on an electrically heated operating table.

Ringer's solution (0.5 ml/100 g of body wt per hour) was infused into a jugular vein; a femoral arterial catheter served for blood sampling and pressure measurement. Both ureters and femoral veins were cannulated and the left kidney was prepared for microcatheterization as described previously.[12, 13] At the end of the operative procedures a priming dose of ^{3}H-inulin (15 μCi) was injected and additional isotopically labeled inulin was added to the intravenous infusion to deliver 30 μCi/hour. After 1 hour of equilibration, urine was collected for 4–6 consecutive 20-minute periods; arterial blood samples (50 μl) were taken in the middle of each period. Using apparatus and techniques described earlier,[12, 13] samples of medullary collecting duct

fluid were collected into fine (outer diameter = 15–35 μm) polyethylene catheters, inserted via the exposed papilla tip. Sampling depth was varied to cover a range from corticomedullary border to papilla tip.

Following this control period, each rat was infused intravenously with fresh blood drawn from an anesthetized donor rat which had received the same dietary treatment as the recipient. Blood volume of the recipient rat was estimated as 7% of body weight, and donor blood equivalent to ⅓ of this volume was infused. Urine from the right kidney was returned continuously to the circulation by connecting right ureteral and femoral catheters. Urine from the left experimental kidney was collected during consecutive 20-minute periods. Using a continuously variable Sage pump, Ringer's solution was infused into the left femoral vein at a rate equivalent to experimental urine flow. Return of excreted volume by intravenous infusion and ureterovenous shunt thus allowed maintenance of volume expansion with minimal alteration of blood composition. After 20-minute infusion and equilibration periods, the rats were studied for a further 1–2 hours. Samples of plasma, urine, and duct fluid were analyzed for sodium, potassium, and ^{3}H-inulin concentration, using the same criteria as previously described.[12, 13] Clearance of inulin [glomerular filtration rate (GFR)] and excretion of sodium ($U_{Na}V$) and potassium (U_KV) were calculated for each 20 minute urine collection period. For each tubular fluid sample the fluid to plasma concentration ratio of inulin (TF/P_{In}), as well as the fractions of filtered sodium (TF/P_{Na}:TF/P_{In}) and potassium (TF/P_K:TF/P_{In}) remaining at the collection site, were calculated. The site of collection was identified in relation to total length of the medullary duct system. Linear regression and *t*-test analyses were used for statistical evaluation of data.

Results

Data for experimental kidneys were averaged for control and expansion periods for each rat and are shown in Table 1. As observed earlier,[6] in the control period NaD rats excreted significantly less sodium than DOCA-escaped rats ($P < 0.01$). Following blood infusion, all measurements showed significant increases ($P < 0.01$) over the control state, with the exception of filtration rate in NaD rats. In addition, both diuresis and natriuresis in DOCA rats were significantly greater ($P < 0.001$) than in NaD rats. The natriuresis also was greater than that of normal rats ($P < 0.05$). It is obvious from Table 1 that three of the seven rats in the low

TABLE 1 *Average Kidney Function in Deoxycorticosterone Acetate (DOCA)-Treated, Normal, and Salt-Deprived (NaD) Rats before and after Blood Infusion*

V (μl/min per g KW)		$U_{Na}V$ (nEq/min per g KW)		U_KV (nEq/min per g KW)		GFR (ml/min per g KW)	
Control	Expansion	Control	Expansion	Control	Expansion	Control	Expansion
			DOCA				
8.41	78.5	646	9747	358	1302	0.76	1.02
7.10	69.2	606	6165	395	1233	0.81	1 07
2.46	76.1	159	12010	150	2044	0.69	1.19
3.45	67.1	259	8568	415	2014	0.65	1.29
3.29	31.9	396	3992	324	1193	0.57	0.78
5.00	49.6	480	6673	364	1455	0.68	1.01
10.09	54.0	893	8217	520	1214	0.85	0.96
$\bar{X}$ 5.69	60.9	491	7910	361	1494	0.72	1.05
SE ±1.10	±6.3	±94	±893	±42	±142	±0.04	±0.06
			Normal				
7.58	50.4	72	5169	1115	4196	0.91	1.30
8.78	50.2	488	6908	1131	3248	0.83	1.03
5.14	24.9	378	2697	758	2124	0.99	1.07
7.14	28.8	102	2470	865	2760	0.89	1.03
5.57	33.8	124	2570	617	3090	0.85	1.12
10.80	85.8	556	9440	1311	1955	0.97	1.29
2.92	29.8	57	2187	573	2691	1.05	1.30
$\bar{X}$ 6.85	43.4	254	4492	910	2866	0.93	1.16
SE ±0.98	±8.1	±81	±1059	±106	±284	±0.03	±0.05
			NaD				
7.11	19.6	68	268*	655	2100	0.72	0.75
2.28	24.7	30	2232	327	2078	1.00	1.05
1.52	5.9*	20	117*	72	937*	0.60	0.89
2.17	8.5*	43	165*	32	708*	0.60	0.78
2.32	39.2	160	4125	366	1293	0.86	0.99
4.09	30.7	200	3566	460	2458	1.36	1.08
3.13	35.6	162	2713	734	1960	0.99	1.05
$\bar{X}$ 3.12	23.5	98	1884	364	1648	0.89	0.94
SE ±0.75	±4.9	±28	±643	±103	±252	±0.11	±0.05

Measurements are exposed in minutes per gram of kidney weight (KW). V = volume excretion; $U_{Na}V$ = sodium excretion; U_KV = potassium excretion; GFR = glomerular filtration rate (inulin clearance).

* NaD rats considered as having quantitatively insignificant renal responses to blood volume expansion.

TABLE 2 *Summary of Average Blood Values in Deoxycorticosterone Acetate (DOCA)-Treated, Normal, and Salt-Deprived (NaD) Rats before and after Blood Infusion*

	Blood pressure (mm Hg)		Hematocrit (%)		P_{Na} (mEq/liter)		P_K (mEq/liter)	
	Control	Expansion	Control	Expansion	Control	Expansion	Control	Expansion
DOCA (n = 7)								
$\bar{X}$	120	140	48.8	55.1	148	148	2.83	2.52
SE	±8	±7	±0.8	±1.0	±3	±3	±0.11	±0.09
Normal (n = 7)								
$\bar{X}$	116	123	48.0	54.4	139	142	4.99	4.52
SE	±3	±4	±0.9	±1.4	±2	±2	±0.16	±0.20
NaD (n = 7)								
$\bar{X}$	123	124	50.5	55.2	141	142	5.14	4.66
SE	±4	±3	±1.0	±1.0	±1	±1	±0.17	±0.19

P_{Na} and P_K = sodium and potassium plasma concentration, respectively.

salt group did not respond to expansion with a homeostatically effective natriuresis, the sodium excretion after expansion remaining in the control range for the whole group. However, even after excluding these nonresponders, sodium excretion of the remaining four rats was less than that of DOCA rats ($P < 0.05$).

Average arterial blood pressures, hematocrits, and plasma concentration of sodium and potassium are given in Table 2. Plasma sodium of DOCA rats was higher, and potassium concentration lower, than either of the other two groups, both before and during expansion. Blood infusion raised the hematocrit in all groups, presumably by translocation of infused fluid but not of red cells into the interstitium.[14] Arterial pressure also tended to rise.

The change in inulin concentration along the medullary collecting duct for the control period is shown in Figure 1. A statistically significant increase of concentration ($P < 0.01$) was found in DOCA (A), normal (B), and NaD (C) series, indicating net fluid reabsorption from this nephron segment in all three groups. The steeper slope of the regression line in salt-deprived rats is in agreement with the reduced urinary volume excretion in this series (Table 1). This difference was not statistically significant, however.

The fraction of filtered sodium remaining in the duct was calculated for each collection in the control period and related to medullary distance. Each rat of every group showed a negative slope of fractional Na remainder toward the papillary tip, indicating sodium reabsorption from the collecting duct. Regression analysis of the pooled, linearized data (Fig. 2) showed significant ($P < 0.01$) reabsorption of sodium in DOCA (r = 0.585), normal (r = 0.654), and NaD (r = 0.621) series. The calculated slopes of the regression lines, while increasing somewhat in steepness from DOCA to normal and NaD groups, were not statistically different. (A statistically significant difference ($P < 0.05$) between the slopes from DOCA and NaD groups may be obtained if the data are linearized graphically; in view of the large scatter of points in each group, however, the more usual calculation based on logarithms[12] was retained.)

A considerable range of sodium excretion was observed among rats of the same series (Table 1) and even within some individual rats. Since a reduction of fractional sodium reabsorption in the collecting duct might well be associated with increased excretion of the ion, the lack of significant difference between the slopes of the regression lines of the three groups (Fig. 2) could be due to partial overlap in the ranges of natriuresis within groups. Individual tubular fluid collections were divided arbitrarily into three approximately equal groups according to simultaneous Na excretion. Group 1 contained those samples with excretions of more than 300 nEq/min per g of kidney wt g KW (average = 632); group 2, those between 100 and 200 (average = 175); and

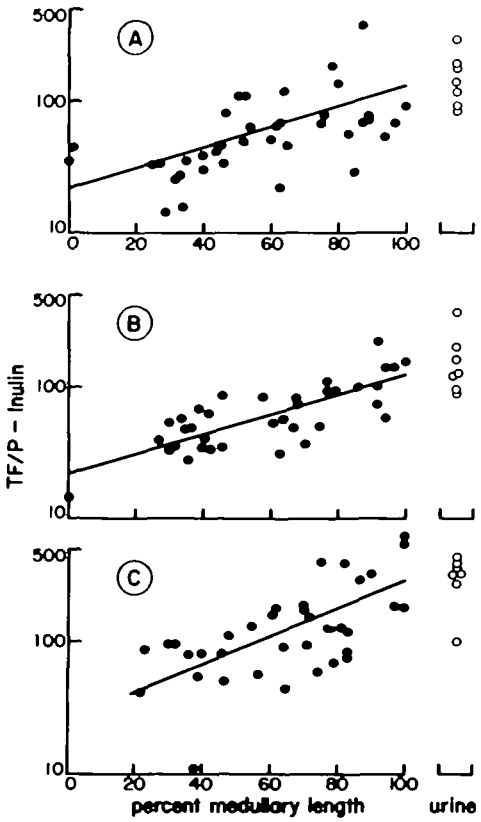

FIGURE 1 *Change of collecting duct fluid to plasma concentration ratio of inulin (TF/P-inulin) with medullary length in deoxycorticosterone acetate (DOCA)-treated rats (A), normal rats (B), and salt-deprived rats (C) during antidiuresis. Average urinary values from experimental kidneys of individual rats in each group are given (open circles). Regression lines of log of concentration ratio with length are indicated.*

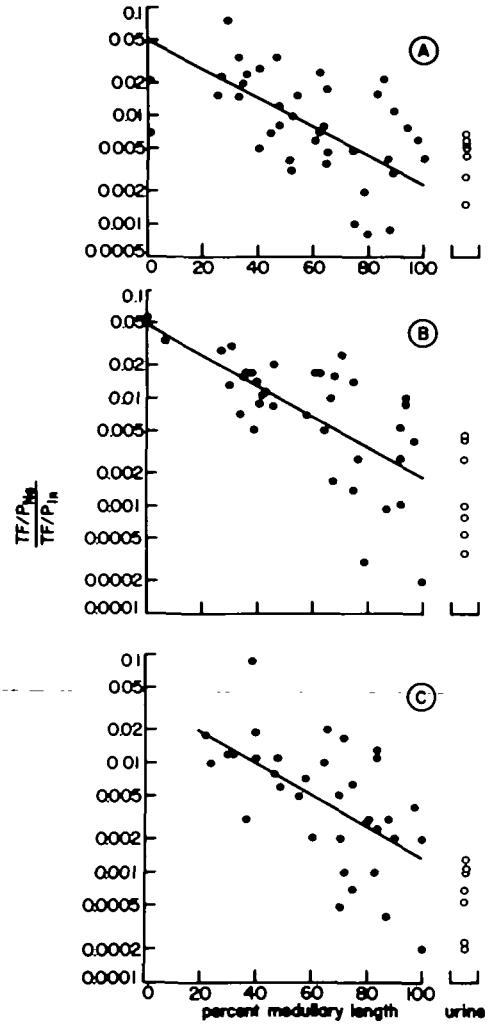

FIGURE 2 *Fraction of filtered sodium remaining at different levels of medullary collecting duct during antidiuresis. Symbols and explanations as in Figure 1.*

group 3, those below 100 (average = 55). Regression analysis of fractional Na remainder in these three groups (Fig. 3) clearly demonstrated reduced sodium reabsorption in the collecting duct when urinary excretion was high (group 1), compared to reabsorption in either group 2 or 3 ($P < 0.01$). The slightly steeper slope of group 3 samples was not statistically different from that of group 2. The zero intercepts of the three regression lines were not statistically different.

In contrast to the observed fluid and sodium reabsorption, no net transport of potassium was evident in the collecting duct of any of the three series. The fraction of filtered potassium remained constant from corticomedullary border to papillary tip, although the average value for NaD rats was significantly ($P < 0.01$) lower (0.077 ± 0.011 SE) than that for either DOCA (0.233 ± 0.30) or normal series (0. 169 ± 0.018).

Collecting duct function during the expansion period is analyzed in Figures 4-7. Inulin concentration ratios for each tubular fluid collection were plotted against medullary duct length in Figure 4 for DOCA (A), normal (B), and those NaD rats (C) responding to the expansion with a diuresis (Table 1). In contrast to the increase in concentration in the nonexpanded state (Fig. 1), no significant change in inulin concentration with length was observed during blood volume expansion, indicating complete inhibition of normal fluid reabsorption form the medullary duct system.

The fraction of filtered sodium remaining at each collection site is shown in Figure 5. Points from nonresponding NaD rats again were excluded (Table 1). The lack of correlation between fractional sodium remainder and duct length demonstrates complete inhibition of Na reabsorption during hypervolemia in all three groups. Since there was no significant change along the collecting duct, the fractional

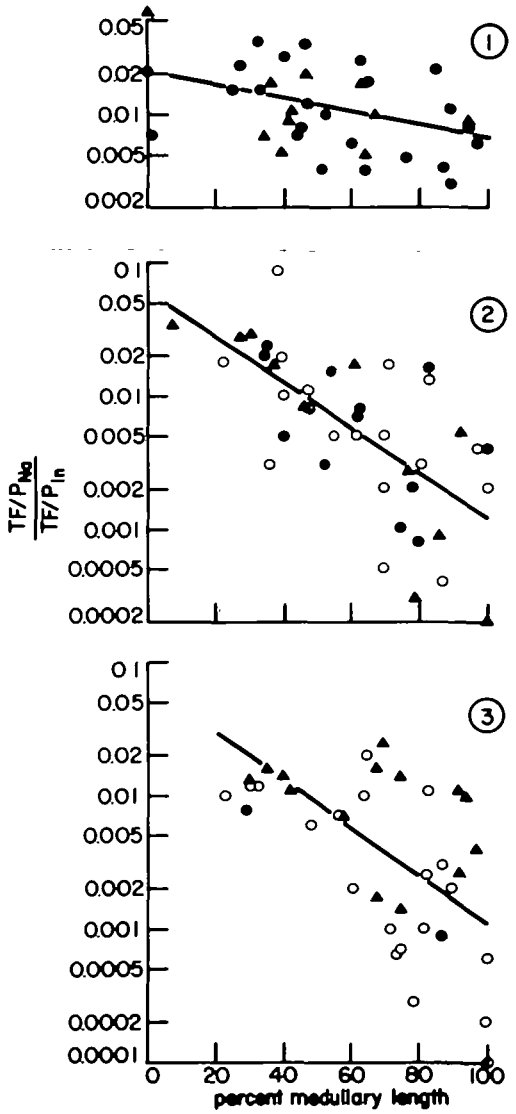

FIGURE 3 *Fraction of filtered sodium remaining at different levels of medullary collecting duct during antidiuresis: variation with sodium excretion. Group 1: Na excretion > 300 nEq/min per g of kidney wt. Group 2: Na excretion < 300 > 100. Group 3: Na excretion < 100. Filled circles represent samples from deoxycorticosterone acetate (DOCA) rats; open circles, those from salt-deprived (NaD) rats; and filled triangles, those from normal rats.*

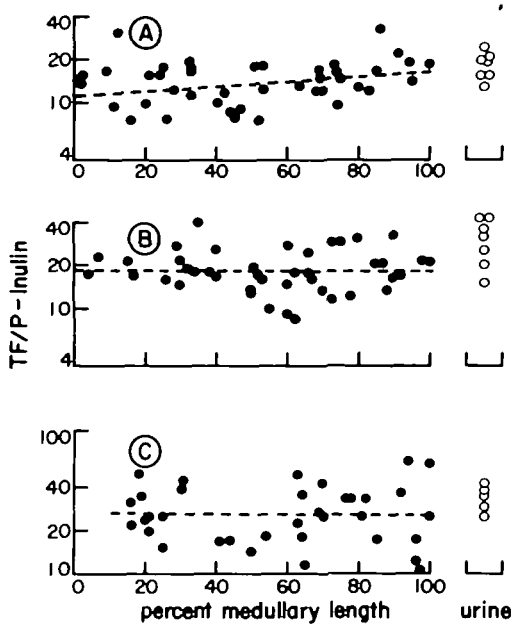

FIGURE 4 *Collecting duct fluid to plasma concentration ratio of inulin (TF/P-Inulin) vs. medullary duct length in expanded deoxycorticosterone acetate (DOCA) rats (A), normal rats (B), and responding salt-deprived (NaD) rats (C). Symbols as for Figure 1.*

amount of sodium entering the medullary collecting system was calculated as the mean of all the points in each series. DOCA rats had a significantly higher fraction (average = 0.056) than either of the other two series ($P < 0.001$). Significant difference ($P < 0.01$) was also found between normal (average = 0.039) and responding NaD rats (average = 0.025).

A plot for potassium (Fig. 6) showed no significant change of the ion in the medullary collecting system during volume expansion, independent of pretreatment of the experimental rats.

Data from nonresponding salt-deprived rats (no diuresis or kaliuresis = two rats, no natriuresis = three rats; see Table 1) are given in Figure 7. Statistically significant increase in inulin concentration ($r = 0.717$, $P < 0.05$) and decrease of fractional remainder of sodium ($r = 0.553$, $P < 0.05$) from corticomedullary border to papilla tip were observed. Again, no significant change in potassium was found. This continued medullary reabsorption of fluid and sodium in nonresponding NaD rats was not associated with differences in plasma sodium or potassium concentration, or in arterial blood pressure, compared to responding rats of the same group. Average filtration rates in the three nonnatriuretic rats were, however, significantly lower ($P < 0.01$) than those in the four natriuretic rats.

Discussion

The observation that fractional reabsorption of sodium by the medullary collecting duct is reduced when sodium excretion is increased (Fig. 3), is in agreement with the earlier conclusion, reached on the basis of distal micropuncture studies,[6] that the increased sodium excretion of DOCA rats was due to relative inhibition of Na transport downstream to the distal tubule. However, mineralocorticoid treatment per se is unlikely to be responsible for the reduction in collecting duct reabsorption. Depending on simultaneous sodium excretion, collections from DOCA rats may show essentially normal reabsorption, whereas those from normal rats may show reduced transport (Fig. 3). The results of Stein and co-workers[15] indicate that these differences in collecting duct reabsorption may be due to preexisting differences in extracellular fluid volume. It is likely, therefore, that the phenomenon of DOCA escape depends on an induced increase of extracellular fluid volume, which in the present series was nonuniform.

The mechanism of the transport alteration in the collecting duct is not known. Neither renal nerve activity[1] nor alteration of the renin-angiotensin-aldosterone system[16] appears to be essential for the natriuresis of DOCA escape. It has been suggested[1, 2] that a natriuretic humoral factor, released as a result of DOCA-induced extracellular fluid volume expansion, causes increased sodium excretion in chronically treated animals. Studies on NaD rats, cross-circulated with DOCA-escaped partners,[8] demonstrated transfer to the NaD partner of a hormonal factor producing an enhanced diuretic and natriuretic response to subsequent blood volume expansion. These results are consistent with the interpretation that variable reduction in Na reabsorption by the medullary collecting duct of the present DOCA and salt-loaded rats during the control period is due to an as yet unidentified hormone. Regardless of the mechanism involved, however, it is obvious by associating fractional collecting duct transport of sodium with absolute urinary

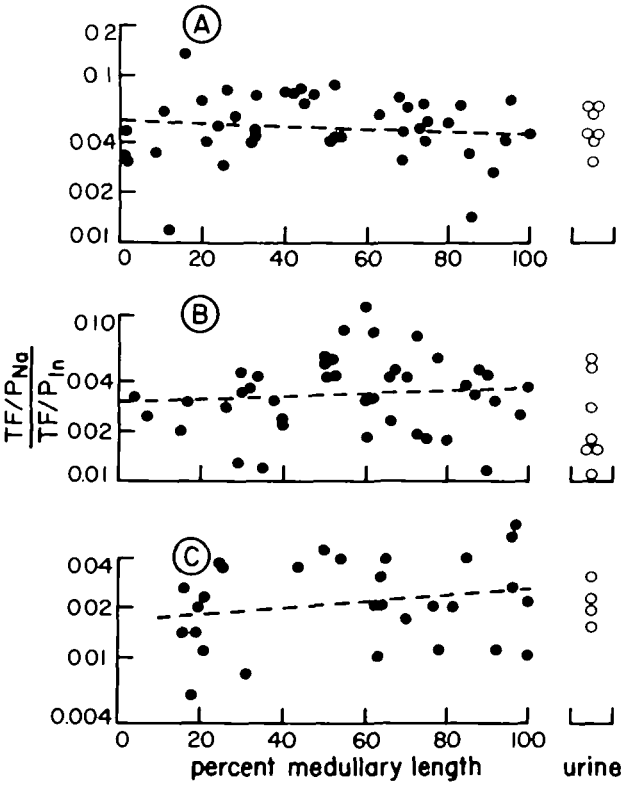

FIGURE 5 *Fraction of filtered sodium remaining along the medullary collecting duct: response to hypervolemia. Symbols and explanations as for Figure 4.*

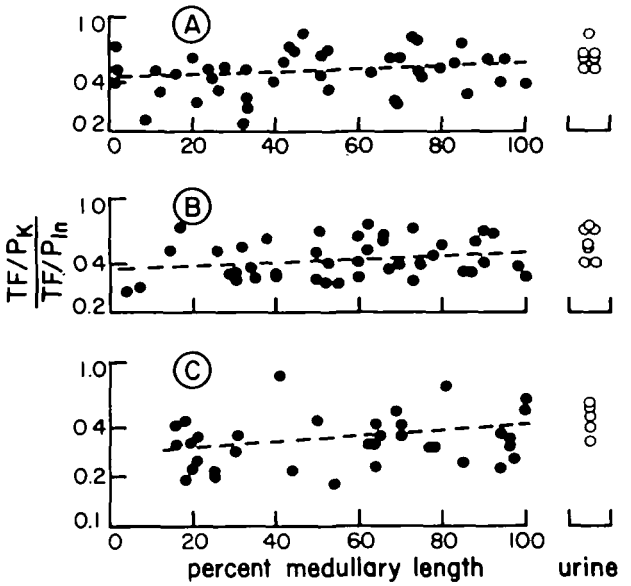

FIGURE 6 *Intratubular fractional remainder of potassium (TF/P_K) in medullary collecting duct. Symbols and explanations as for Figure 4.*

excretion (Fig. 3) that in normal, as well as in salt-loaded or salt-deprived rats, ultimate levels of excretion appear to be primarily determined by the function of the medullary collecting duct rather than by alteration in reabsorption farther upstream in the nephron.

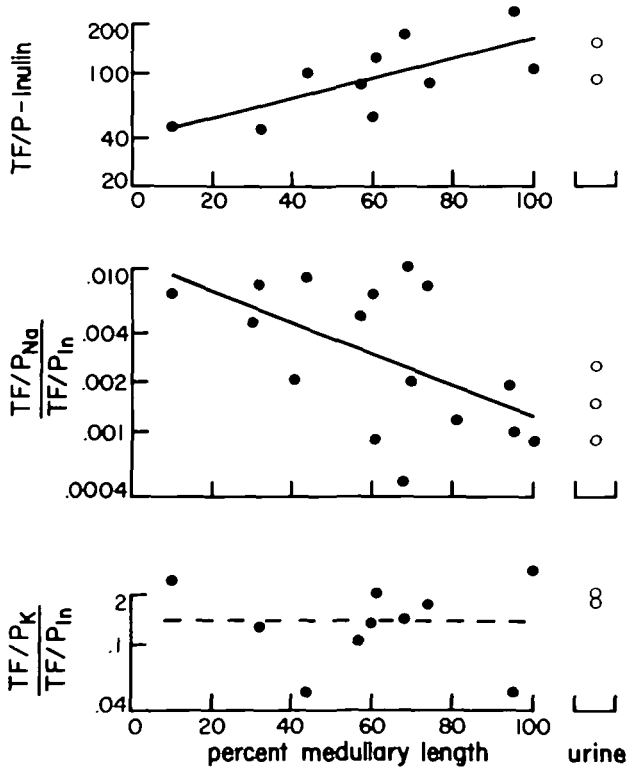

FIGURE 7 *Inulin concentration ratio and fractional remainder of Na and K in salt-deprived (NaD) rats without diuresis or natriuresis following blood volume expansion. Statistically significant regression is indicated by solid lines. Symbols and explanations as for Figure 1.*

In contrast to the variable reabsorption during antidiuresis, after blood volume expansion in each group complete inhibition of collecting duct transport of fluid and sodium was observed (Figs. 4 and 5). Infusion of blood followed by reinfusion of urine or replacement of excreted volume is associated with increases in hematocrit and plasma protein concentration[17] (Table 2). Inhibition of medullary transport therefore does not depend on dilution of either circulating protein or red cells, although such dilution was found to reduce reabsorption in the proximal tubule.[18] Similar inhibition of medullary reabsorption was observed previously in rats chronically ingesting saline followed by intravenous saline infusion during the experiment.[12] Since these rats were allowed to excrete urine freely, it is evident that urine reinfusion is not a prerequisite for the volume-induced effect on duct transport. Adrenalectomy has been shown to reduce net sodium reabsorption from the lumen of the terminal collecting duct.[19] Reduction in aldosterone levels is unlikely, however, to be the explanation for the rapidly developing inhibition seen in the present experiments, because in the rat this hormone has a latent period of at least 1 hour and a maximum effect at 3–4 hours.[20] In addition, neither aldosterone loading nor adrenalectomy can prevent the natriuresis of sustained blood volume expansion[21] (unpublished observations). Release of a blood-borne natriuretic factor has been demonstrated under these conditions,[21] however, and may indeed be the cause of the present collecting duct inhibition. An unknown humoral factor altering collecting duct reabsorption has also been suggested by Stein and coworkers[22] to explain the increased recovery, following infusion of Ringer's solution, of ^{22}Na injected into the late distal tubule.

In NaD rats, despite infusion of identical volumes of donor blood, homeostatically effective natriuresis and transport inhibition were not consistent findings (Table 1, Fig. 7). The lower filtration rate and a slightly higher control hematocrit in nonresponding rats are suggestive of a negative fluid balance. Blood infusion in such rats might result in expansion insufficient to elicit a volume response. In any case, the data show that inhibition of sodium transport in the collecting duct is a necessary requisite for the volume natriuresis.

While the effects of vascular expansion on collecting duct function were similar in DOCA, normal, and responding NaD rats, absolute levels of natriuresis were higher in the DOCA group. This difference was not due to difference in sodium delivery from the end of the superficial distal tubule.[10] Since Na load at the beginning of the medullary duct was greater in expanded DOCA rats, net addition of the ion to tubular fluid in the cortical collecting system of these rats is indicated, possibly via increased delivery from juxtamedullary nephrons. Although it is not immediately obvious why chronic mineralocorticoid administration would result in reduction of Na reabsorption from deep but not superficial nephrons following blood volume expansion, such a mechanism could explain the findings. Alternately, a difference in function of cortical collecting tubules might be postulated.

Although collecting duct transport of sodium showed large variation depending on experimental conditions, no net

potassium transport was found in either control or expanded state in any group. In contrast to the cortical collecting tubule, therefore,[23] the present experiments indicate lack of countertransport of Na and K in the medullary duct.

In summary, the results indicate that collecting duct reabsorption of sodium and water varies with body fluid balance and shows complete inhibition during acute blood volume expansion. Present and previous data are compatible with the interpretation that a humoral natriuretic factor is responsible for such transport alteration. The resulting natriuresis may be enhanced by increased delivery of sodium to the medullary system.

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